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(1a*R*,5a*R*)1a,3,5,5a-Tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic Acid (MK-1903): A Potent GPR109a Agonist that Lowers Free Fatty Acids in Humans

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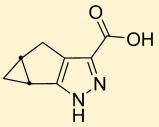
ABSTRACT: G-protein coupled receptor (GPCR) GPR109a is a molecular target for nicotinic acid and is expressed in adipocytes, spleen, and immune cells. Nicotinic acid has long been used for the treatment of dyslipidemia due to its capacity to positively affect serum lipids to a greater extent than other currently marketed drugs. We report a series of tricyclic pyrazole carboxylic acids that are potent and selective agonists of GPR109a. Compound *R*,*R*-**19a** (MK-1903) was advanced through preclinical studies, was well tolerated, and presented no apparent safety concerns. Compound *R*,*R*-**19a** was advanced into a phase 1 clinical trial and produced a robust decrease in plasma free fatty acids. On the basis of these results, *R*,*R*-**19a** was evaluated in a phase 2 study in humans. Because *R*,*R*-**19a** produced only a weak effect on serum lipids as compared with niacin, we conclude that the beneficial effects of niacin are most likely the result of an undefined GPR109a independent pathway.



R,R-19a

INTRODUCTION

Worldwide, coronary heart disease and stroke remain the leading causes of death and disability. A recent case-control study in 52 countries, INTERHEART, identified that high ratios of apolipoprotein B to apolipoprotein A, the major lipoproteins of low-density lipoprotein cholesterol (LDL-c) and high-density lipoprotein cholesterol (HDL-c), respectively, accounted for more than half of the population-attributable risk for a first myocardial infarction.[1] The management of associated risk factors and the widespread use of statins to lower plasma LDL-c levels, thereby improving the LDL-c/HDL-c ratio, have contributed to an overall decrease in morbidity and mortality in many developed countries.[2] Niacin (niacin) has been used for over 50 years for the treatment of dyslipidemia due to its capacity to lower very-low-density lipoprotein cholesterol (VLDL-c), LDL-c, and lipoprotein (a) (Lp(a)) and, most importantly, to increase HDL-c to a greater extent than other currently marketed drugs. A recent meta-analysis of clinical use of niacin alone or in combination with statins concluded that the use of niacin decreased major coronary events by 25%, stroke by 26%, and all cardiovascular events by 27%.[3] Despite the therapeutic advantages of niacin treatment, its use is less widespread than statins for the treatment lipid disorders mainly due to limited patient compliance because of adverse side effects that are associated with its use, most notably an uncomfortable cutaneous flushing effect.[4] Although the mechanism by which niacin raises HDL-c is not clear, niacin has been shown to cause a rapid, robust decrease in plasma free fatty acids (FFA). It has been hypothesized that this decrease in the concentration of free fatty acids available to the liver attenuates triglyceride synthesis and VLDL-c production. The reduced synthesis of triglyceride-rich VLDL-c particles in the liver leads to a decreased rate of HDL-c metabolism by limiting the cholesterol ester transfer protein (CETP)-mediated exchange of cholesterol from HDL-c to VLDL-c and triglyceride from VLDL-c to HDL-c.[5]

Since the identification of the G-protein coupled receptor (GPCR) GPR109a as a molecular target for niacin (niacin), interest in developing new therapeutic agents with the lipid modulating properties of niacin but with a reduced flushing effect has intensified.[6] GPR109a is expressed in adipocytes, spleen, and immune cells, including macrophage and Langerhans cells, and shares 95% identity with GPR109b and 52% identity with GPR81, two GPCRs which are also found in adipose and have been identified as hydroxycarboxylic acid receptors.[7] The flush side effect of niacin has been attributed to a GPR109a-dependent vasodilation resulting from a combination of effects on both Langerhans cells and keratinocytes.[8,9] Various strategies have been employed to separate the beneficial effects on lipids from flush induced by niacin such as sustained release formulations and combinations of niacin with aspirin or prostaglandin D_2 receptor antagonists to suppress the contribution of vasodilation following prostaglandin release from

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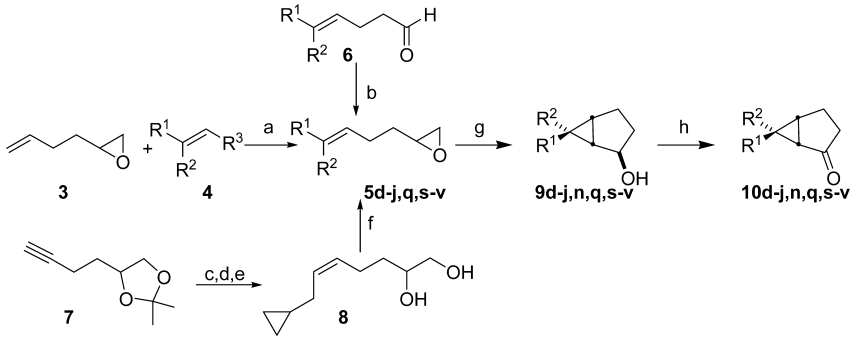
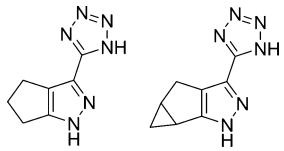
Scheme 1[a]



[a]Reagents and conditions: (a) Zhan catalyst or second-generation Grubbs' catalyst; (b) *n*-BuLi, CH_2Br_2, THF; (c) *n*-BuLi, DMPU, THF, $(CH_2)_2CHCH_2Br$; (d) Pd/$BaSO_4$, quinoline, H_2; (e) AcOH, H_2O; (f) TrisIm, NaH; (g) LiTMP, MTBE; (h) cat. TPAP, NMO, 4 Å MS, DCM.

Langerhans cells.[10] The discovery of ligand biased signaling mediated via GPR109a, whereby agonists differentially activate downstream signaling pathways, led to the development of **1** (MK-0354).[11] Compound **1** is a GPR109a agonist that activates the antilipolytic pathways in adipose cells but does not signal via the ERK 1/2 pathway that leads to prostaglandin production and vasodilation.[12] Thus, **1** produced a decrease in plasma free fatty acids in mice but did not induce the vasodilation associated with flushing. In humans, **1** behaved similarly, reducing plasma FFAs acutely without a significant associated flushing response but did not have a statistically significant effect on HDL, LDL, or triglycerides after 28-days dosing.[13] The failure of **1** to increase HDL cholesterol in the clinic led us to three alternative hypotheses. The first of these was that more potent analogues with a similar biased signaling profile to **1** would result in beneficial effects on serum lipids and triglycerides as relatively high doses of **1** were required to see any effect on FFA in humans. The second hypothesis was that the separation of signaling pathways that inhibit cAMP production from those that activate MAP kinase influences both the effects on lipids and the flushing side effect. The third is that the therapeutic effects of niacin are not entirely mediated via GPR109a.



1 (MK-0354) **2**

A number of more potent analogues of **1** were synthesized and evaluated. From these, compound **2** was identified as a potent agonist of GPR109a which lowered free fatty acids in mice and did not induce flush.[14] However, to evaluate the second hypothesis, compounds with profiles more like niacin, i.e., compounds that activate both antilipolytic and vasodilation pathways, were required. During the studies that led to the discovery of **2**, it was observed that the tricyclic pyrazole system generally provided potent GPR109a agonists. Importantly, it was also determined that in contrast to the tetrazole analogues, carboxylic acids based on this scaffold retained efficacy equal to that of niacin and were shown to activate both the antilipolytic and vasodilation pathways. These agonists appeared ideal for examination of the first two hypotheses: that increased agonist potency and that both antilipolytic and vasodilation effects are required to affect serum HDL-c levels. The synthesis and evaluation of these GPR109a full agonists is described here.

RESULTS AND DISCUSSION

Chemistry. A straightforward route to the key bicyclo[3.1.0]hexan-2-one intermediates involved the preparation of a number of 1,2-epoxy-5-alkenes (Scheme 1). Cross metathesis of 2-(but-3-enyl) oxirane (**3**) with various alkenes promoted by second-generation Grubbs' catalyst or Zhan catalyst gave epoxyolefins **5** (Scheme 1), generally as mixtures of *E*/*Z* isomers. Alternatively, addition of in situ generated (bromomethyl)lithium to commercially available *cis*- and *trans*-4-decenal to gave the epoxyolefins **5f** as individual isomers. Because of the lack of a readily available aldehyde or olefin precursor to prepare epoxy olefin **5n**, an alternate route was developed. Alkynylation of cyclopropylmethyl bromide with alkyne **7**,[15] followed by hydrogenation of the resulting alkyne with Lindlar catalyst and subsequent hydrolysis of the acetonide, produced diol **8**. Closure to the oxirane was accomplished using triisopropylsulfonylimidazole (TrisIm) to give alkene **5n**. Stereospecific intramolecular carbenoid ring closure of the epoxyalkenes,[16] followed by oxidation of the resultant alcohols, provided bicyclo[3.1.0]hexan-2-one intermediates **9**. In cases where mixtures of *E*/*Z* isomers were used, the resultant mixture of R^1 (*exo*)- and R^2 (*endo*)-substituted bicyclo[3.1.0]hexan-2-one diastereomers were carried through the synthesis and separated via chromatography after conversion to the tricyclic pyrazoles.

A more versatile cyclopropyl ketone intermediate was obtained from reaction of dichlorocarbene with commercially available 2-cyclopenten-1-one ethylene ketal **11** to give 6,6-dichlorospiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane (**12**) (Scheme 2). Stereoselective introduction of the *exo*-methyl group in **13** was accomplished by lithium halogen exchange with *t*-butyllithium followed by quenching with methyl iodide. A second lithium halogen exchange using lithium 4,4′-di-*tert*-butyl-biphenyl (LiDBB) and quenching of the anion with ethanol gave *exo*-**6b** with >95% d.e. Alternatively, reduction of **12** with zinc dust gave the monochlorocyclopropyl derivative **14** as a separable mixture of diastereomers. Lithium halogen exchange of either diastereomer, or as a mixture, and quenching with an alkyl halide (CH_3I or CH_3CH_2I), yielded only substitution on the *endo*-face. This remarkable stereoselectivity may be attributed to chelation of lithium by the ketal oxygen on the endoface. Finally, hydrolysis of the ketal gave the requisite

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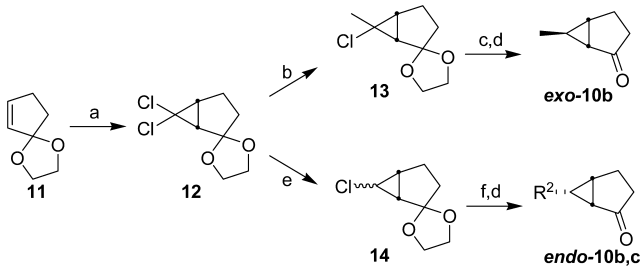
Scheme 2[a]

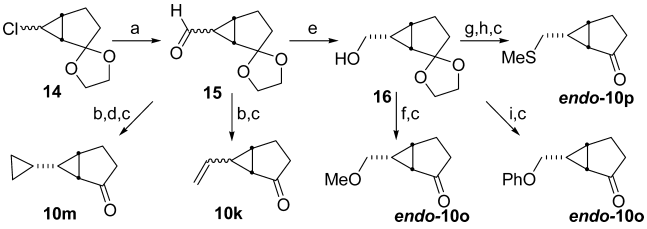


[a]Reagents and conditions: (a) 50% NaOH, $CHCl_3$, DCM, cat. triethylbenzylammonium chloride, 45 °C; (b) (1) *t*-BuLi, THF, −100 °C, (2) MeI, −100 °C to rt; (c) (1) LiDBB, THF, −78 °C, (2) EtOH; (d) cat. TsOH, acetone, H_2O, rt; (e) Zn dust, KOH, EtOH, 80 °C; (f) (1) LiDBB, THF, −78 °C, (2) R^2I, rt.

ketones *endo*-**6b** and *endo*-**6c**, which were then elaborated to the final pyrazoles.

Multiple functionalities were introduced on the apex of the cyclopropane using chlorocyclopropane intermediate **14** as a precursor (Scheme 3). Generation of the lithium anion with

Scheme 3[a]

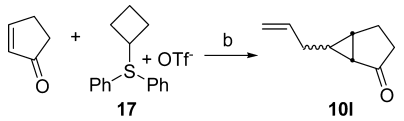


[a]Reagents and conditions: (a) (1) LiDBB, THF, −78 °C, (2) DMF, rt; (b) $[(Ph_3)PCH_3]^+Br^-$, *n*-BuLi, THF, rt; (c) cat. TsOH, acetone, H_2O, rt; (d) $Pd(OAc)_2$, CH_2N_2, Et_2O, rt; (e) $NaBH_4$, EtOH, rt; (f) NaH, MeI, THF, 0 °C to rt; (g) MsCl, Et_3N, DCM, 0 °C to rt; (h) NaSMe, DMF; (i) PhOH, D*t*-BAD, $PyPh_2P$, THF.

LiDBB and reaction with dimethylformamide gave aldehyde **15** as a separable mixture of diastereomers (*exo*:*endo* = 7:1) after aqueous workup. The lack of stereocontrol in this addition is likely due to epimerization of the chiral center adjacent to the aldehyde. Vinyl analogues *endo*-**10k** and *exo*-**10k** were prepared by Wittig olefination of the aldehyde followed by removal of the acetonide. A cyclopropanation of the vinyl group using palladium acetate and diazomethane was used to prepare *endo*-**10 m**. Reduction of the *endo*-aldehyde **15** with sodium borohydride gave the alcohol **16**, which was alkylated with methyl iodide to produce the methyl ether *endo*-**10o**. The endothiomethyl ether **10p** was also prepared from alcohol **16** by mesylation and displacement with sodium thiomethoxide. Phenyl ether **10o** was also prepared from alcohol **16** using Mitsonobu conditions.

The spirocyclic cyclohexyl- and cyclopentycyclopropanes were synthesized via the olefin cross metathesis route, however, no appropriate starting material was available to synthesize a spiro cyclobutyl cyclopropane in this manner. In an attempt to prepare a spiro-fused cyclobutyl cyclopropane, cyclobutyldiphenylsulfonium trifluoromethanesulfonate (**17**) was reacted with *t*-BuLi followed by cyclopentenone (Scheme 4). The only product isolated from the reaction mixture, however, was the allyl substituted cyclopropane **10l** resulting from ring-opening

Scheme 4[a]

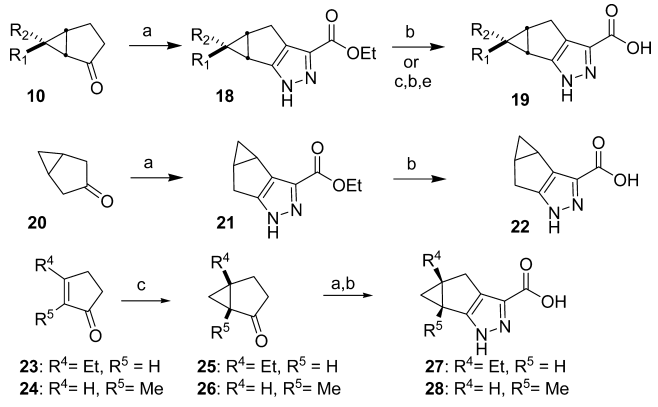


[a]Reagents and conditions: (a) $(CH_3)_3S(O)I$, NaH, THF; (b) *t*-BuLi, THF.

of the cyclobutyl ring. This mixture of ketone diastereomers was used to prepare the allyl substituted analogues.

Ketones **10** were converted to the tricyclic pyrazole esters **18** by Claisen condensation of the ketones with diethyl oxalate followed by condensation of the resulting diketones with hydrazine (Scheme 5). Hydrolysis of the esters **18** gave the

Scheme 5[a]



[a]Reagents and conditions: (a) (1) KO*t*-Bu, EtOH, $(EtO_2C)_2$, 0 °C to rt, (2) hydrazine monohydrochloride, H_2O, rt; (b) LiOH, dioxane, H_2O; (c) benzyl bromide, K_2CO_3, DMF; (d) NaI, MeI, THF; (e) KO*t*-Bu, DMSO, air; (f) $(CH_3)_3SOI$, NaH.

corresponding carboxylic acids, **19**. In cases where diastereomeric mixtures were present, separation of the isomers was accomplished by HPLC at either the ester or acid stage. The cyclopropane regioisomer **22** was prepared in analogous fashion from the symmetrical bicyclo[3.1.0]hexan-3-one **20**. To synthesize the *exo*-methyl ester of **19o** (R1 = CH_2OMe, R2 = H), the pyrazole of intermediate **17** (R1 = CH_2OH, R2 = H) was selectively benzylated and the free hydroxyl was alkylated by deprotonation with sodium hydride and followed by addition of methyl iodide. Debenzylation and ester hydrolysis were both accomplished by treatment with potassium *tert*-butoxide and dimethyl sulfoxide in the presence of air to give *endo*-**18x**. To probe substitutions at the ring fused positions of the cyclopropane, ketones **25** and **26** were prepared by direct cyclopropanation of cyclopentenones **23**[17] and **24**, respectively, with the sulfonium ylide derived from trimethylsulfoxonium iodide deprotonated by sodium hydride (Scheme 4).

To determine if any stereochemical bias for activation of GPR109a by the pyrazole acids existed, all four stereoisomers of compound **19b** were synthesized by the route shown in Scheme 6. Starting from enantiopure lactols *R*-**29** and *S*-**29**,[18] Wittig reaction with ethyltriphenylphosphonium bromide and lithium hexamethyldisilazide proceeded with concomitant epoxide ring closure to give both enantiomers of epoxide *R*-**5b** and *S*-**5b** as mixtures of olefin isomers (*E*:*Z* = 2.3:1). Intramolecular carbenoid cyclization and oxidation provided (1*R*,5*S*)-6-

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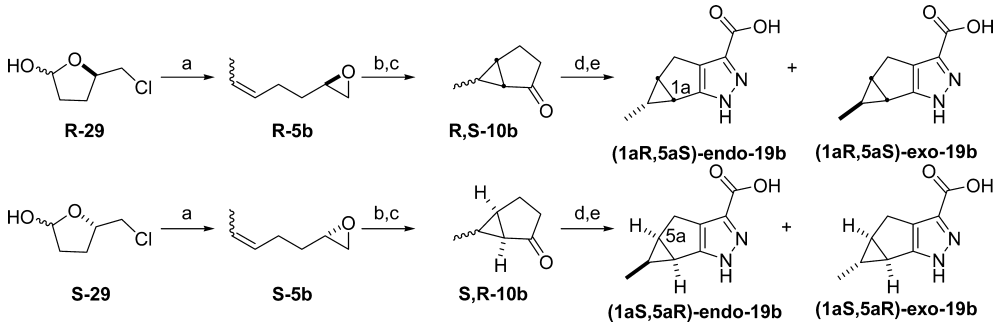
Scheme 6[a]

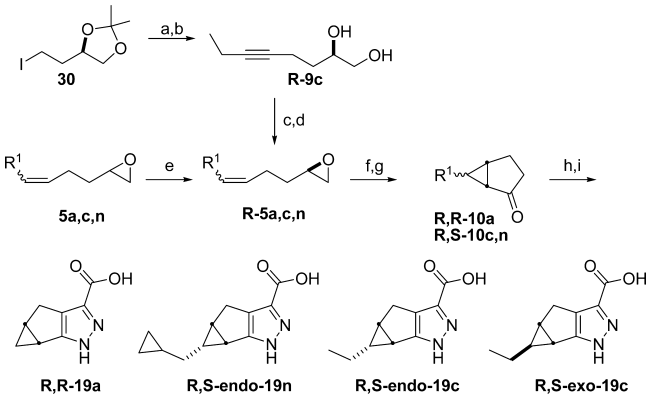


[a]Reagents and conditions: (a) $[(Ph_3)PCH_2CH_3]^+Br^-$, LiHMDS, THF, 0 °C to rt; (b) LiTMP, MTBE; (c) cat. TPAP, NMO, 4 Å MS, DCM; (d) (1) KO*t*-Bu, EtOH, $(EtO_2C)_2$, 0 °C to rt, (2) hydrazine monohydrochloride, H_2O, rt, (3) HPLC separation; (e) LiOH, dioxane, H_2O.

methylbicyclo[3.1.0]hexan-2-one (*R,S*-**10b**) and (1*S*,5*R*)-6-methylbicyclo[3.1.0]hexan-2-one (*S,R*-**10b**) as mixtures of *endo*- and *exo*-isomers. These mixtures were converted to the tricyclic pyrazole esters as described above, and the diastereomers were separated by HPLC. Ester hydrolysis of the individual enantiomers provided all four pyrazole acid stereoisomers.

The examples above established that the 1a*R*,5a*S* stereoisomers provided the greatest GPR109a agonist potency (see below). To confirm this observation, other examples with the same stereochemical orientation were synthesized (Scheme 7).

Scheme 7[a]



[a]Reagents and conditions: (a) 1-butyne, *n*-BuLi, THF, DMPU, −78 °C to rt; (b) AcOH, H_2O; (c) TrisIm, NaH; (d) Pd/$BaSO_4$, quinoline, H_2; (e) Jacobsen HKR; (f) LiTMP, MTBE; (g) cat. TPAP, NMO, 4 Å MS, DCM; (h) (1) KO*t*-Bu, EtOH, $(EtO_2C)_2$, 0 °C to rt, (2) hydrazine monohydrochloride, H_2O, rt; (i) LiOH, dioxane, H_2O, rt.

Synthesis of the ethyl substituted *R,S-endo*-**19c** and *R,S-exo*-**19c** isomers started via addition of butynyllithium to the readily available optically pure iodide **30** to give alkyne *R*-**9c** following hydrolysis of the acetal. Conversion of diol **30** to the epoxide by treatment with TrisIm and sodium hydride was accompanied by some loss of optical purity (86% e.e.) due to lack of selectivity for activation of the primary alcohol. Therefore, the epoxide was resolved using a hydrolytic kinetic resolution described by Jacobsen[19] to regain optical purity. Hydrogenation of the alkyne catalyzed by palladium on barium sulfate in the presence of quinoline gave epoxide *R*-**5c** as a mixture of olefin isomers (*E*:*Z* = 11.5:1).

The unsubstituted analogue **18a** and the cyclopropylmethyl analogue *endo*-**18n** were synthesized as single enantiomers employing Jacobsen's hydrolytic kinetic resolutions (HKR) of epoxyolefins **3** and **5n**. The chiral epoxides were used in the synthesis described in Scheme 1 to produce chiral ketones that were elaborated to the final products *R,R*-**18a**, *R,S-endo*-**5n** and *R,S-endo*-**5c** with the stereochemical orientations shown in Scheme 7.

In Vitro Studies. All compounds were assayed for GPR109a agonist activity using a homogeneous time-resolved fluorescence (HTRF) cAMP assay in cells stably transfected with GPR109a. The cells were stimulated to produce cAMP by treatment with 5 μM forskolin, and a dose response of the capacity of each compound to decrease cAMP production was generated. The tricyclic pyrazole acid **22** and the tricyclic acids **27** and **28** with substitution at the bridgehead positions produced no response in this assay. The results of the HTRF-cAMP assays for the remaining compounds are summarized in Table 1.

The tricyclic pyrazole acids were generally potent full agonists of GPR109a. The cyclopropyl ring imparts additional agonist potency over the unsubstituted bicyclic pyrazolecarboxylic acid (EC_{50} = 0.86 μM in a Flashplate cAMP assay).[20] As with the tetrazole series, agonist potency is very sensitive to substitution on the cyclopropane ring. The unsubstituted derivative **19a** is slightly more potent than niacin and was equally as effective at decreasing cAMP production (Table 2). That compounds **27** and **28**, with substituents at the ring junctions, were completely inactive in this assay demonstrated that substitution around the cyclopropane was only tolerated at the apex of the ring.

The syntheses of compounds that generated mixtures of diastereomers afforded the opportunity to investigate the stereochemical requirements for agonism of GPR109a by these tricyclic pyrazole carboxylic acids. From the assay results of compounds *endo*-**19b** and *exo*-**19b**, it is clear that the *endo*-diastereomers show a propensity toward higher agonist potencies than the *exo*-diastereomers. This was found to be the case for every *endo*/*exo* pair that was synthesized other than *endo*- and *exo*-**19d**, which were both weak agonists of GPR109a. Within the *endo*-substituted series, there is a clear trend toward decreasing potency with increasing substituent size. Whereas the endomethyl substitution gives a compound that is nearly equipotent to the unsubstituted **19a**, the ethyl analogue *endo*-**19c** is slightly less potent and the *n*-propyl analogue *endo*-**19d** is considerably less potent. It is interesting that agonist potency improves in the *endo-n*-butyl *endo*-**19e** relative to *endo-n*-propyl *endo*-**19d**. Likewise, the endoisobutyl substituent in *endo*-**19h** was much more potent than the *endo-n*-propyl, whereas the *endo*-isopentyl derivative *endo*-**19i** was much less active than either. A similar SAR pattern was observed in a series of bicyclic

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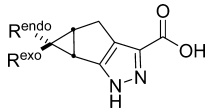
Table 1. Agonist Activity of Tricyclic Pyrazolecarboxylic Acids in the Whole Cell HTRF Assay at the hGPR109a Receptor



compd	R	*endo* EC_{50} (nM)[a]	efficacy[b]	*exo* EC_{50} (nM)[a]	efficacy[b]
niacin		51	95	NA	
1		286	96		
19a	H	27.5	95	NA	
19b	methyl	37	94	573	104
19c	ethyl	43.4	98.5	ND	
19d	*n*-propyl	1770	89	1630	83
19e	*n*-butyl	225	85	5450	88
19f	*n*-pentyl	1120	87	>10000	
19g	*i*-propyl	NA		>10000	99
19h	*i*-butyl	81	85	5330	95
19i	*i*-pentyl	>10000		>10000	
19j	dimethyl	1024	91	NA	
19k	vinyl	1290	94	>10000	
19l	allyl	28	98	227	96.4
19m	cyclopropyl	1980	90	ND	
19n	cyclopropylmethyl	85	93	ND	
19o	methoxymethyl	141	97	2470	91.5
19p	methylthiomethyl	83	97	857	96
19q	ethoxymethyl	192	92	>10000	112
19r	CH_2OPh	>10000	76.4	ND	
19s	spiro cyclopentyl	14	101	NA	
19t	spiro cyclohexyl	>10000		NA	
19u	phenyl			>10000	
19v	benzyl[c]			>10000	93

[a] EC_{50} values are the average of three determinations. [b] Efficacy is expressed as a % of the signal produced by 100 μM niacin as positive control. NA; not applicable, only one isomer is possible. ND; not determined, only one of the two possible isomers was isolated. [c] Tested as a mixture of isomers (5:1, *exo*:*endo*).

Table 2. Agonist Activity of Enantiopure Tricyclic Pyrazolecarboxylic Acids in the Whole Cell HTRF-cAMP Assay at the hGPR109a Receptor

compd	EC_{50} (nM)[a]	efficacy[b]
R,S-endo-**19b**	16.4	111
R,S-exo-**19b**	311	96
S,R-endo-**19b**	1170	107
S,R-exo-**19b**	21280	100
R,R-**19a**	12.9	102
R,S-endo-**19c**	22.5	101
R,S-exo-**19c**	276	93
R,S-endo-**19n**	7.4	101

[a] EC_{50} values are the average of three determinations. [b] Efficacy is expressed as a % of the signal produced by 100 μM niacin as positive control.

pyrazole GPR109a agonists in which compounds with an ethyl substituent had low activity (4.6 μM) in a niacin binding assay, whereas the *n*-propyl and *n*-butyl substitutions resulted in higher potency (0.69 and 0.34 μM, respectively).[21] All compounds were evaluated in a similar assay for GPR109b, and all produced no response other than the spirocyclic which were nearly equipotent agonists of GPR109a and GPR109b.

The unexpected synthesis of the allyl compounds produced a highly potent analogue in the *endo*-allyl compound *endo*-**19l**. This is remarkable in that the chain length is the same as *n*-propyl, however, compound *endo*-**19l** is approximately 75-fold more potent than *endo*-**19d**. Because terminal double bonds are often metabolized in vivo, the cyclopropyl methyl analogue *endo*-**19n** was synthesized as an allyl surrogate to investigate this improvement in activity further. Although slightly less potent than *endo*-**19l**, compound *endo*-**19n** was among the most potent compounds synthesized. Reasoning that an increase in electron density resulting from introduction of the double bond and cyclopropane improved binding of these compounds to the receptor, compounds **19o−q** were synthesized, which incorporated ether and thioether linkages. Compounds *endo*-**19o**, *endo*-**19p**, and *endo*-**19q** were all more potent than the corresponding *n*-propyl derivatives, but none was as potent as the *endo*-allyl derivative *endo*-**19l**.

Having established from the racemic *endo*- and *exo*-substituted compounds that *endo*-substituents provided superior agonist potency, all four stereoisomers of the methyl substituted compound **19b** were synthesized. A bias for agonism of GPR109a by one enantiomer was strongly favored over the others just as is observed for the pairs of diastereomers. For the methyl substituted compounds, the preferred stereoisomer was (1*R*,1a*R*,5a*S*)-1-methyl-1a,2,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]pentalene-4-carboxylic acid (*R,S-endo*-**19b**), which had an EC_{50} of 16 nM and was approximately twice as potent as the racemate and 20-fold more potent than any of the other stereoisomers. This stereochemical orientation of the cyclopropyl was confirmed as an element of good agonist potency, as demonstrated by the unsubstituted cyclopropyl derivative *R,R*-**19a**, which was a highly potent agonist of GPR109a. The enantiomerically pure unsubstituted and *endo*-ethyl analogues *R,S-endo*-**19c** and *R,S-exo*-**19c** were both twice as potent as their corresponding racemates, and the *endo*-cyclopropylmethyl *R,S-endo*-**19n** was highly potent.

Although the most potent of the chiral compounds was the *endo*-cyclopropyl methyl, *R,S-endo*-**19n**, compounds *R,R*-**19a** and *R,S-endo*-**19b** were evaluated further because both exhibited good receptor potency and could be scaled up via more straightforward synthetic routes than a number of other analogues.

Compounds *R,R*-**19a** and *R,S-endo*-**19b** were screened against a standard panel of GPCRs and ion channels (PanLabs) and were found to have IC_{50} values of >10 μM for inhibition of binding of the paradigm ligands at any receptor or ion channel. The compounds were also not substrates for cytochrome P_{450} (CYP) isoforms 2D6, 2C8, 2C9, or 3A4 nor were they time-dependent inhibitors of CYP 3A4 at concentrations of 10 and 50 μM.

Preclinical Studies. Pharmacokinetic properties of compounds *R,R*-**19a** and *R,S-endo*-**19b** were evaluated in several species, and the data are summarized in Table 3. The pharmacokinetic parameters of *R,R*-**19a** and *R,S-endo*-**19b** were good, with somewhat variable but acceptable oral absorption, clearance, and half-lives in all species.

The capacity of *R,R*-**19a** and *R,S-endo*-**19b** to lower free fatty acids in vivo was tested in fasted, Sprague−Dawley rats by administration of the compound via oral gavage followed by the serial collection of plasma samples after dosing (Figure 1). Both *R,R*-**19a** and *R,S-endo*-**19b** lowered free fatty acids by approximately 90% of baseline levels at all doses tested except for the lowest dose (0.001 mg/kg), which was indistinguishable from the vehicle dose. At higher doses, the decrease was more sustained.

Measurement of changes in cutaneous blood flow in the exposed ear of anesthetized mice using a laser Doppler instrument has been established as a surrogate for flushing and the propensity

Table 3. Pharmacokinetics of Compounds *R,R*-19a and *R,S-endo*-19b in Several Species[a]

	Cl_p (mL/min/kg)		V_d (L/kg)		$t_{1/2}$ (h)		C_{max}/dose (μM·kg/mg)		AUCNpo (μM·h·kg/mg)		*F* (%)	
compd	*R,R*-**19a**	*R,S-endo*-**19b**	*R,R*-**19a**	*R,S-endo*-**19b**	*R,R*-**19a**	*R,S-endo*-**19b**	*R,R*-**19a**	*R,S-endo*-**19b**	*R,R*-**19a**	*R,S-endo*-**19b**	*R,R*-**19a**	*R,S-endo*-**19b**
mouse	10	35	0.75	0.61	8.7	0.3	3.5	1.5	4.1	1.4	40	51
rat	17	17	0.53	0.53	2.4	2.4	3.7	5	5.1	5.1	83	90
dog	3.1	2.4	0.41	0.22	3.4	2.1	17.5	26	33.3	44.4	100	100
rhesus	5.1	ND	0.21	ND	1.1	ND	5.1	ND	8.5	ND	39	ND

[a] Cl_p, plasma clearance (blood clearance for mice); V_d, volume of distribution; $t_{1/2}$, terminal half-life; C_{max}, observed maximal plasma concentration following oral dosing; T_{max}, time to reach the C_{max}; *F*, oral bioavailability.

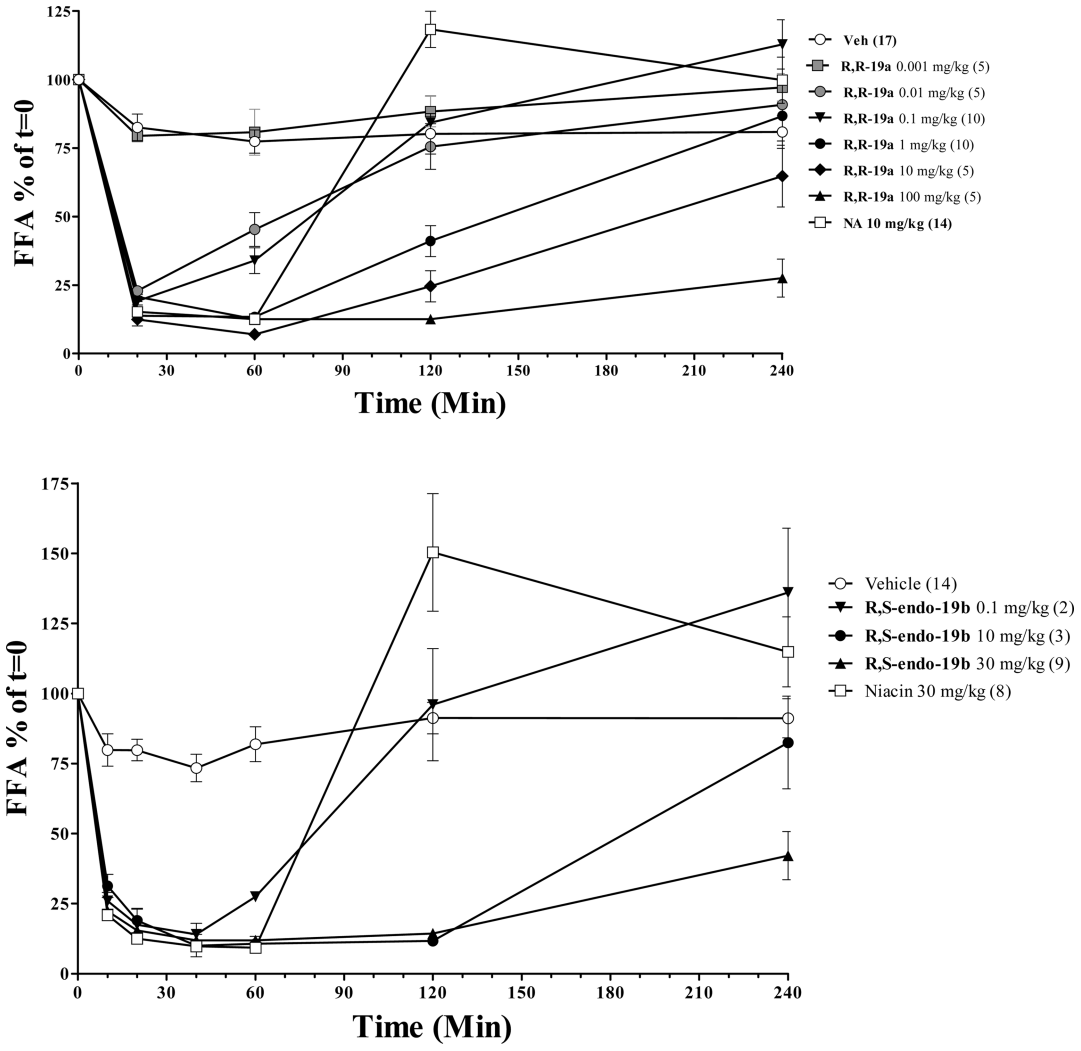


Figure 1. Time course of the effect of *R,R*-**19a** and *R,S-endo*-**19b** on plasma FFA in male Sprague–Dawley rats after oral administration. *N* (animal number) is indicated in parentheses.

of compounds *R,R*-**19a** and R,S-*endo*-**19b** to induce flush was quantified using this model (Figure 2).[22] In this model, niacin has been shown to produce a 60–100% peak increase over baseline blood flow compared to vehicle treated mice after a 100 mg/kg dose. When anesthetized mice were give a 100 mg/kg dose of either *R,R*-**19a** or *R,S-endo*-**19b**, a peak increase of approximately 30% in blood flow over baseline was observed after 5 min.

Seeing no pharmacological or toxicological signals that would distinguish *R,R*-**19a** from *R,S-endo*-**19b**, it was decided to advance *R,R*-**19a** through the remaining preclinical testing because the synthesis of *R,S-endo*-**19b** required more steps and is less stereochemically controlled.

Human Clinical Studies. On the basis of the noteworthy preclinical data, compound *R,R*-**19a** (MK-1903) was advanced into a phase 1 safety and tolerability study (Table 4).[23] Compound *R,R*-**19a** was administered orally to healthy volunteers at single doses of 5, 10, 25, 50, 100, 150, and 200 mg. Flushing was the only major adverse effect and was observed at all doses, with 200 mg determined as the maximum tolerated dose. Plasma samples obtained from subjects following doses of 50, 150, and 200 mg and were analyzed for FFA levels. *R,R*-**19a** produced a decrease in FFA by approximately 90% relative to placebo at all doses examined by 1–2 h post dose. FFA levels remained suppressed for about 8 h

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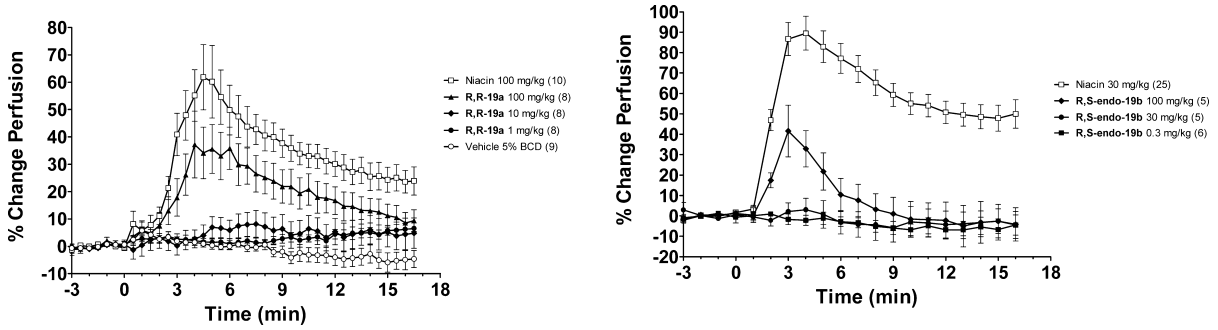

Figure 2. Quantification of the flushing response of niacin, *R,R*-**19a** and *R,S-endo*-**19b** as measured by laser Doppler recordings of cutaneous blood flow in the ear of male C57/bl6 mice.

Table 4. Pharmacokinetics Parameter Values from the Multiple Rising Dose Study in Humans

R,R-**19a** dose	panel	day	*N*	$AUC_{0-\tau}$ [a,e] (nM·h)	C_{max} [a] (nM)	C_{trough} [a,f] (nM)	T_{max} [b] (h)	apparent $t_{1/2}$ [c] (h)
50 mg BID	A	1	6	29.4 ± 6.6	12.3 ± 3.6	BLOQ	1.0 (0.5−2.0)	
		4		26.1 ± 5.7	12.3 ± 3.1	0.023 ± 0.026	1.25 (1.0−2.0)	
		11		25.4 ± 5.0	16.2 ± 2.3	0.045 ± 0.038	0.5 (0.5−1.5)	1.9 ± 0.9
		GMR[d]		0.975	1.34			
100 mg BID	B	1	6	72.8 ± 11.6	31.5 ± 4.2	0.124 ± 0.81	1.0 (0.5−2.0)	
		4		65.7 ± 9.6	33.1 ± 6.2	0.083 ± 0.063	1.0 (0.5−1.0)	
		11		61.1 ± 9.0	32.5 ± 2.5	0.104 ± 0.042	0.5 (0.5−1.0)	2.2 ± 0.9
		GMR[d]		0.929	0.993			
150 mg BID	C	1	6	97.7 ± 12.9	41.2 ± 12.8	0.316 ± 0.342	1.25 (1.0−2.0)	
		4		80.3 ± 22.9	31.7 ± 20.6	0.241 ± 0.187	1.5 (1.0−4.0)	
		11		78.8 ± 20.8	27.7 ± 13.8	0.208 ± 0.116	1.0 (1.0−2.0)	8.9 ± 4.1
		GMR[d]		0.989	0.921	0.909		
150 mg TID	D	1	6	101.8 ± 13.4	48.4 ± 15.9	0.869 ± 0.642	0.5 (0.5−2.0)	
		4		88.5 ± 4.0	52.6 ± 23.6	0.583 ± 0.343	0.5 (0.5−2.0)	
		11		87.9 ± 3.1	44.9 ± 17.5	0.708 ± 0.179	1.0 (0.5−1.5)	11.0 ± 4.6
		GMR[d]		1.00	0.888	1.33		
200 mg QD	E	4	6	113.7 ± 17.5	56.3 ± 31.6	0.244 ± 0.088	1.5 (0.5−2.0)	
		11		119.2 ± 12.3	49.8 ± 15.8	0.273 ± 0.151	1.25 (0.5−2.0)	4.6 ± 4.0
		GMR[d]		1.05	0.963	1.04		
175 mg QID	F	1	6	129.8 ± 22.3	52.6 ± 13.9	4.01 ± 0.31	1.25 (1.0−2.0)	
		4		113.0 ± 13.9	49.9 ± 9.7	2.92 ± 1.21	1.0 (0.5−2.0)	
		11		122.8 ± 19.2	56.0 ± 14.3	2.86 ± 1.55	0.75 (0.5−1.5)	6.0 ± 3.4
		GMR[d]		1.08	1.11	0.91		

[a]Mean ± standard deviation. [b]Median (min − max). [c]Harmonic mean ± pseudo standard deviation. [d]Geometric mean ratio (GMR) = day 11/day 4, calculated by DMPK. [e]τ: 12 h for 50, 100, 150 mg BID doses; 24 h for 200 mg QD dose; 8 h for 150 mg TID dose; 6 h for 175 mg QID dose. [f]C_{trough}: $C_{12\ h}$ for 50, 100, 150 mg BID, and 200 mg QD doses; $C_{8\ h}$ for 150 mg TID dose; $C_{6\ h}$ for 175 mg QID dose

before they began to return to baseline. The decrease in FFA and safety profile in humans was nearly identical to those observed in the animal models described above, confirming that the models were predictive of effects in humans. These data strongly suggest target engagement of GPR109a on adipocytes. GPR109a engagement on cells in the macrophage lineage results in the production of PGD_2, which is responsible for vasodilation.[24,25] To assess the effect of *R,R*-**19a** on GPR109a on immune cells in humans more quantitatively, urine was assessed for a PGD_2 metabolite (PGD-M, Figure 3). The production of PGD-M was approximately dose linear and doses of 10 mg and greater resulted in production of more PGD-M than a 1 g dose of Niaspan, suggesting that higher doses of *R,R*-**19a** delivered more receptor activation on immune cells than a therapeutic dose of niacin. On the basis of these observations, *R,R*-**19a** was advanced to more extensive evaluation in humans.

A double-blind, placebo-controlled, randomized, dose-escalation study was conducted to define the effects of *R,R*-**19a** on FFA levels, safety, tolerability, and pharmacokinetics following multiple oral doses for seven days to healthy male subjects. Volunteers were randomized into six cohorts each containing eight subjects (six on active treatment and two on placebo). Oral doses of *R,R*-**19a** were 50 mg bid, 100 mg bid, 150 mg bid, 150 mg tid, 200 mg qd, 175 mg qid, or placebo. Drug or placebo was administered on day 1, followed by a two-day washout period, after which dosing continued from day 4 through day 11. For the 200 mg qd dose, subjects were titrated

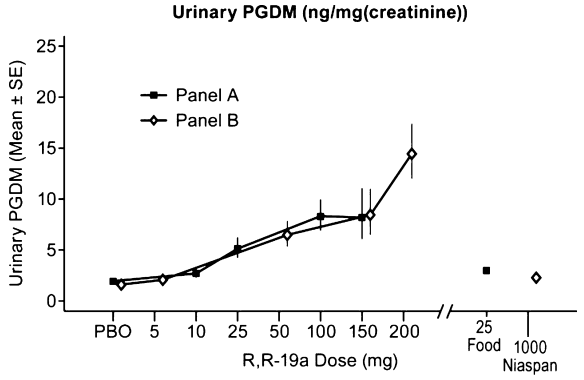

Figure 3. Human urinary prostaglandin D metabolite in urine following an oral dose of *R,R*-**19a**.

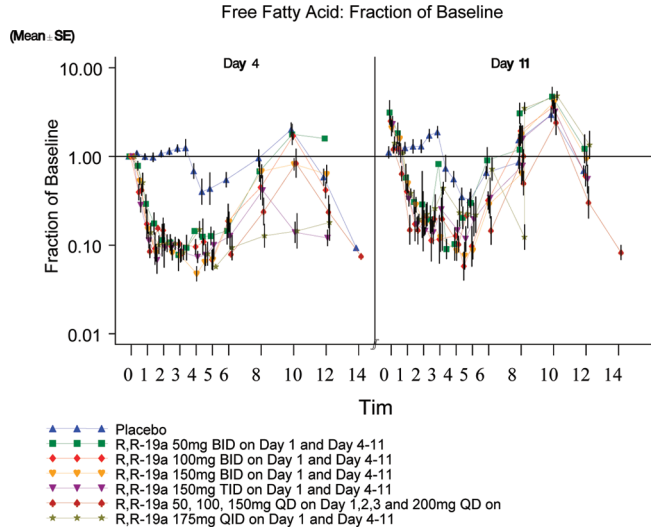

Figure 5. Plasma free fatty acid levels of *R,R*-**19a** on days 4 and 11 in humans.

to this dose over days 1−4 then dosed qd through day 11. Venous blood samples were collected predose and at 0.5, 1, 1.5, 2, 4, 6, 8, 10, and 12 h postdose on day 1, 4, and 11 and analyzed for concentrations of plasma *R,R*-**19a** and FFA. Additionally, venous blood samples were collected predose on days 5 through 10 for plasma trough level determinations.

Compound *R,R*-**19a** was rapidly absorbed at all doses with T_{max} ranging from 0.5 to 1.5 h (Figure 4). Pharmacokinetic parameter values are shown in tabular form in the Experimental section. The apparent half-life on day 11 increased from 1.9 to 11 h as total dose increased. There was little or no accumulation of drug after repeat dosing for 7 days. Analysis of urine samples indicated that 70−80% of drug was excreted intact.

Compound *R,R*-**19a** significantly lowered free fatty acids at all doses tested (Figure 5). The extent of the free fatty acid lowering was more variable on day 11 than on day 4 but statistically different from placebo. Baseline FFA levels were also higher than placebo on day 11 for all doses except the 200 mg qd dose, however, the relative decrease in FFA was equivalent on all days, indicating that *R,R*-**19a** does not cause significant tachyphylaxis of GPR109a. Compared to **1** and a 1 g dose of Niaspan, *R,R*-**19a** resulted in more durable FFA suppression.[13]

Unlike **1**, which was a partial and selective "biased" GPR109a agonist, *R,R*-**19a** induced considerable dose-dependent subject reported flushing after single doses. Using a flushing symptoms questionnaire (see ref 13), doses of 10 mg and greater were associated with flushing that was qualitatively more severe than a 1 g dose of Niaspan. Repeat dosing resulted in rapid and marked attenuation of flushing, and volunteers generally reported no flushing on questionnaires after 1−2 days of dosing with divided daily dosing regimens.

On the basis of these data, a dose of 150 mg TID was selected for future human clinical trials. This dose was expected to provide nearly continuous and profound FFA suppression and GPR109a activation on adipocytes and immune cells greater than that of therapeutic doses of niacin. On the basis of these results, it was determined that *R,R*-**19a** warranted further clinical evaluation and it was advanced into a phase 2a study in humans.[26] Briefly, the above dose of *R,R*-**19a** produced the expected suppression of FFA and a robust flush in a four-week study in dyslipidemic patients. However, the effects on triglyceride (Tg) and HDL-c were modest (−10.3% and +4.6%, respectively), whereas the corresponding changes expected in Tg and HDL-c from a therapeutic 2 g dose of niacin are approximately −26% and +20%, respectively.

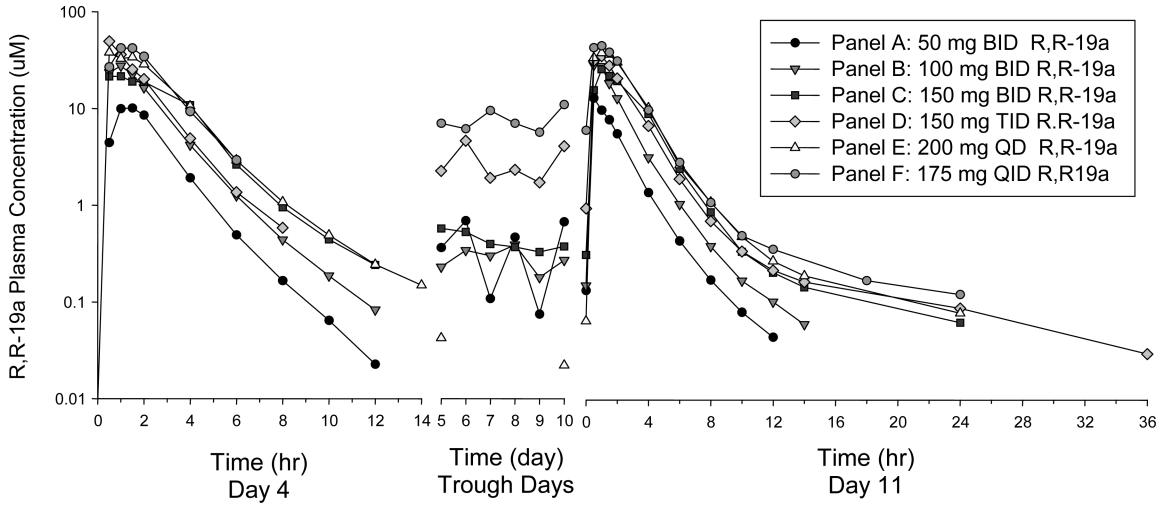

Figure 4. Plasma concentrations of *R,R*-**19a** in humans after oral administration on days 4 and 11 and trough levels on days 5 through 10.

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CONCLUSION

A series of tricyclic pyrazolecarboxylic acids has been identified as potent agonists of GRP109a and have been shown to activate both the antilipolytic and vasodilation pathways in rodents. *R,R*-**19a** is a much more potent agonist than **1** (12.9 vs 283 nM, respectively) and is more potent than niacin (51 nM) in the cell based assays employed. Compound *R,R*-**19a** was advanced through preclinical studies, was shown to be selective for GPR109a, well tolerated in several species, and presented no apparent safety concerns. On the basis of this remarkable preclinical profile, compound *R,R*-**19a** was advanced into clinical trials to assess the safety, tolerability, and ability of the compound to lower free fatty acid levels in humans. Administration of *R,R*-**19a** to humans resulted in a robust decrease in plasma free fatty acids and produced the expected flush response as predicted by the preclinical data but no other adverse effects. Thus, unlike **1**, which differed from niacin in its receptor activating properties (no flushing or activation of GPR109a on immune cells), *R,R*-**19a** closely resembled the actions of niacin on GPR109a in that it was a full agonist and activated the receptor both on adipocytes and immune cells. Using the criteria of FFA suppression, PGD-M release and qualitative assessment of flushing, doses of *R,R*-**19a** were identified that would be expected to produce niacin-like changes in serum lipids if GPR109a agonism is the mechanism by which niacin produces these changes.

That *R,R*-**19a** produced only a weak effect on HDL-c and Tg vs niacin in a phase 2 study in humans suggests that the hypothesis that GPR109a activation on adipocytes is sufficient to raise HDL-c is likely groundless. Likewise, that *R,R*-**19a** produced flush effects and production of prostaglandin D metabolites that were equivalent to or greater than those produced by Niaspan indicate that the activation of both GPR109a signaling pathways is also not sufficient to raise HDL-c. On the basis of these studies, we conclude that the contribution of GPR109a agonism toward the beneficial effects on serum lipids produced by niacin treatment is questionable. From the human data, we conclude that the beneficial effects are most likely the result of niacin acting on a GPR109a independent pathway that has yet to be defined.

EXPERIMENTAL SECTION

Chemistry. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Mercury Vx-400 equipped with a four-nucleus auto switchable probe and *z*-gradient or a Bruker Avance-400 equipped with a QNP (Quad Nucleus Probe) or a BBI (Broad Band Inverse) and *z*-gradient. Chemical shifts are given in parts per million (ppm), with the residual solvent signal used as reference. NMR abbreviations are used as follows: s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublets, dt = doublet of triplet, t = triplet, tt = triplet of triplets, q = quartet, m = multiplet, br = broad. Microwave irradiations were carried out using the Emrys synthesizer (Personal Chemistry). Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} (Merck), preparatory thin-layer chromatography (prep TLC) was preformed on PK6F silica gel 60 A 1 mm plates (Whatman), and column chromatography was carried out on a silica gel column using Kieselgel 60, 0.063−0.200 mm (Merck). Evaporation was done in vacuo on a Buchi rotary evaporator. Celite 545 was used during palladium filtrations.

Analytical HPLC/MS was conducted on a PE Sciex API 150EX mass spectrometer with an electrospray source, using a Shimadzu Inc. LC-10A VP UV detector monitoring at 214 nm, Analyst 1.2 software, and either (a) a Gilson 215 autosampler and an Alltech Prevail C18 column (5 μm, 250 mm × 4.6 mm), using a gradient of 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) (t = 0.0 min) gradient to 95% v/v CH_3CN in H_2O (t = 6.0 min), 3.5 mL/min or (b) a PE 200 autosampler and a Supelco Discovery C18 column (5 μm, 50 mm × 2.1 mm), using a gradient of 5% v/v CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) (t = 0.0 min) gradient to 95% v/v CH_3CN in H_2O (t = 5.0 min), 0.75 mL/min. Preparative HPLC was conducted on a Varian Prostar reverse phase HPLC using either (a) a Phenomenex Luna C18 column (10 μm, 250 mm × 21.2 mm), 5% (v/v) CH_3CN (containing 0.1% v/v TFA) in H_2O (containing 0.1% v/v TFA) gradient to 95% CH_3CN, 20 mL/min, λ = 220 nm or (b) a Phenomenex Luna C18 column (10 μm, 250 mm × 50 mm), 5% (v/v) CH_3CN (containing 0.1% v/v TFA) in H_2O (containing 0.1% v/v TFA) gradient to 95% CH_3CN, 50 mL/min, λ = 220 nm. Purity of the tested compounds was ≥95% based on LCMS and/or ^{1}H NMR data unless stated otherwise.

*(±)-2-(Hept-3-enyl)oxirane (**5d**).* To a solution of 2-(but-3-enyl)-oxirane (**3**, 5.00 g, 50.9 mmol) in pent-1-ene (40.0 mL, 366 mmol) at rt was added Grubbs catalyst, second generation (1.08 g, 1.27 mmol). The mixture was stirred at for 48 h and concentrated in vacuo. Purification by column chromatography (0−10% EtOAc/hexanes, silica) gave 2-(hept-3-enyl)oxirane (**5d**, 915 mg, ca. 75% purity by ^{1}H NMR, 4.90 mmol, 10% yield), an inseparable mixture of *E* and *Z* isomers (ratio not determined), as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60−5.53 (m, 2H), 2.92 (m, 1H), 2.75 (m, 1H), 2.49 (dd, J = 5.0, 2.7 Hz, 1H), 2.15 (m, 2H), 1.98 (m, 2H), 1.60 (m, 2H), 1.35 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H).

*(±)-2-(Oct-3-enyl)oxirane (**5e**).* To a solution of 2-(but-3-enyl)-oxirane (**3**, 5.00 g, 50.9 mmol) in hex-1-ene (50.0 mL, 403 mmol) at rt was added Grubbs catalyst, second generation (1.08 g, 1.27 mmol). The mixture was stirred at for 72 h and concentrated in vacuo. Purification by column chromatography (0−10% EtOAc/hexanes, silica) gave the title compound (**5e**, 2.04 g, ca. 65% purity by ^{1}H NMR, 8.60 mmol, 17% yield), an inseparable mixture of *E* and *Z* isomers (ratio not determined), as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60−5.53 (m, 2H), 2.90 (m, 1H), 2.72 (m, 1H), 2.45 (m, 1H), 2.13 (m, 2H), 1.97 (m, 2H), 1.56 (m, 2H), 1.30 (m, 4H), 0.87 (t, J = 7.4 Hz, 3H).

*(±)-(Z)-2-(Non-3-enyl)oxirane (Z-**5f**).* To a solution of (*Z*)-dec-4-enal (*Z*-**6**, 2.50 g, 13.0 mmol) and dibromomethane (2.31 g, 13.3 mmol) in THF (60 mL) at −78 °C under N_2 atmosphere was added *n*-butyllithium (7.38 mL of a 1.6 M solution in hexanes, 11.8 mmol) slowly over 10 min. The mixture was warmed to rt, stirred for an additional 15 h, and poured into a NH_4Cl (satd aq, 60 mL). The mixture was extracted with MTBE (2 × 60 mL), and the organics were dried over $MgSO_4$, filtered, and concentrated. Column chromatography (0−5% EtOAc/hexanes, silica) gave the title compound (*Z*-**5f**, 1.28 g, 7.61 mmol, 59% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45−5.32 (m, 2H), 2.93 (m, 1H), 2.76 (dd, J = 5.0, 4.1 Hz, 1H), 2.49 (dd, J = 5.0, 2.7 Hz, 1H), 2.22 (q, J = 7.5 Hz, 2H), 2.04 (q, J = 6.9 Hz, 2H), 1.59 (m, 2H), 1.37−1.24 (m, 6H), 0.89 (t, J = 7.1 Hz, 3H).

*(±)-(E)-2-(Non-3-enyl)oxirane (E-**5f**).* Prepared from (*E*)-dec-4-enal (*E*-**6**, 3.37 g, 21.8 mmol) in a similar manner as described for the synthesis of *Z*-**5f**. Column chromatography (0−5% EtOAc/hexanes, silica) gave the title compound (*E*-**5f**, 2.35 g, 14.0 mmol, 64% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51−5.37 (m, 2H), 2.93 (m, 1H), 2.76 (dd, J = 5.0, 4.1 Hz, 1H), 2.49 (dd, J = 5.0, 2.7 Hz, 1H), 2.16 (m, 2H), 1.98 (q, J = 7.0 Hz, 2H), 1.59 (m, 2H), 1.38−1.22 (m, 6H), 0.89 (t, J = 7.1 Hz, 3H).

*(±)-2-(5-Methylhex-3-enyl)oxirane (**5g**).* To a solution of 2-(but-3-enyl)oxirane (**3**, 4.50 g, 45.8 mmol) in (*Z*)-4-methylpent-2-ene (10.0 g, 119 mmol) at rt was added Grubbs catalyst, second generation (973 mg, 1.15 mmol). The mixture was stirred at for 24 h and concentrated in vacuo. Purification by column chromatography (0−10% EtOAc/hexanes, silica) gave the title compound (**5g**, 2.92 g, ca. 70% purity by ^{1}H NMR, 14.6 mmol, 32% yield), an inseparable mixture of *E* and *Z* isomers (ratio not quantified), as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47−5.30 (m, 2H), 2.90 (m, 1H), 2.72 (m, 1H), 2.45 (m, 1H), 2.20 (m, 1H), 2.13 (m, 2H), 1.59 (m, 2H), 0.94 (d, J = 6.8 Hz, 6H).

*(±)-2-(6-Methylhept-3-enyl)oxirane (**5h**).* To a solution of 2-(but-3-enyl)oxirane (**3**, 5.00 g, 50.9 mmol) in 4-methylpent-1-ene (25.0 g, 297 mmol) at rt was added Grubbs catalyst, second generation (2.00 g, 2.36 mmol). The mixture was stirred at for 20 h and concentrated in vacuo. Purification by column chromatography (0−10% EtOAc/hexanes,

silica) gave the title compound (**5h**, 2.02 g, ca. 60% purity by ^{1}H NMR, 7.60 mmol, 15% yield), an inseparable mixture of *E* and *Z* isomers (ratio not quantified), as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50−5.38 (m, 2H), 2.95 (m, 1H), 2.74 (dd, *J* = 4.8, 4.3 Hz, 1H), 2.48 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.18 (m, 2H), 1.87 (m, 2H), 1.60 (m, 3H), 0.90 (m, 6H).

*(±)-2-(7-Methyloct-3-enyl)oxirane (**5i**).* To a solution of 2-(but-3-enyl)oxirane (**3**, 25.0 g, 255 mmol) and 5-methylhex-1-ene (25.1 g, 256 mmol) in DCM (50 mL) was added Zhan cat-1 (Zaanan Pharma Ltd. Cat. RC-301, 320 mg, 0.485 mmol). The mixture was stirred at rt for 20 h and concentrated in vacuo. Purification by column chromatography (0−10% EtOAc/hexanes, silica) gave the title compound (**5i**, 4.53 g, ca. 60% purity by ^{1}H NMR, 16.1 mmol, 6% yield), an inseparable mixture of *E* and *Z* isomers (ratio not quantified), as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59−5.36 (m, 2H), 2.94 (m, 1H), 2.75 (m, 1H), 2.48 (dd, *J* = 5.0, 2.8 Hz, 1H), 2.15 (m, 2H), 2.00 (m, 2H), 1.59 (m, 2H), 1.29 (m, 3H), 0.88 (m, 6H).

*(±)-2-(4-Methylpent-3-enyl)oxirane (**5j**).* A solution of 2-(but-3-enyl)oxirane (**3**, 1.00 g, 10.2 mmol) in 2-methylbut-2-ene (10.0 g, 102 mmol) containing Zhan cat-1 (57.0 mg, 0.086 mmol) at rt was stirred for 20 h and concentrated in vacuo. Purification by column chromatography (0−10% EtOAc/hexanes, silica) gave the title compound (**5j**, 1.20 g, 9.51 mmol, 93% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (m, 1H), 2.92 (m, 1H), 2.75 (dd, *J* = 5.0, 4.1 Hz, 1H), 2.48 (dd, *J* = 5.0, 2.8 Hz, 1H), 2.15 (q, *J* = 7.5 Hz, 2H), 1.70 (s, 3H), 1.60 (s, 3H), 1.54 (m, 2H).

*(E)-tert-Butyldimethyl(5-(oxiran-2-yl)pent-2-enyloxy)silane (E-**5o**).* To a solution of 2-(but-3-enyl)oxirane (**3**, 16.0 g, 163 mmol) and *cis*-1,4-bis(*tert*-butyldimethylsilyloxy)-2-butene (127 g, 326 mmol) in DCM (1.6 L) was added Grubbs catalyst, second generation (3.46 g, 4.08 mmol). The mixture was stirred for 20 h and concentrated in vacuo. Purification by column chromatography (1−10% EtOAc/hexanes, silica) gave the title compound (*E*-**5o**, 15.0 g, 61.9 mmol, 38% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (dt, *J* = 15.3, 6.2 Hz, 1H,), 5.57 (dt, *J* = 15.3, 4.9 Hz, 1H), 4.11 (m, 2H), 2.91 (m, 1H), 2.73 (m, 1H), 2.46 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.19 (m, 2H), 1.61 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H).

*(±)-(E)-2-(5-Methylsulfanyl-pent-3-enyl)-oxirane (**5p**).* To a solution of 2-(but-3-enyl)oxirane (**3**, 5.57 g, 56.7 mmol) and allyl methyl sulfide (1.00 g, 11.3 mmol) in DCM (115 mL) was added Zhan cat-1 (150 mg, 0.227 mmol). The mixture was stirred for 20 h and concentrated in vacuo. Purification by column chromatography (0−10% EtOAc/hexanes, silica) gave the title compound (**5p**, 600 mg, 3.79 mmol, 34% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60−5.43 (m, 2H), 3.07 (d, *J* = 7.2 Hz, 2H), 2.93 (m, 1H), 2.76 (m, 1H), 2.49 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.28−2.19 (m, 2H), 2.02 (s, 3H), 1.70−1.57 (m, 2H).

*(±)-2-(5-Ethoxypent-3-enyl)oxirane (**5q**).* To a solution of 2-(but-3-enyl)oxirane (**3**, 5.00 g, 50.9 mmol) and ethyl allyl ether (13.2 g, 153 mmol) in DCM (350 mL) was added Zhan cat-1 (673 mg, 1.02 mmol). The mixture was stirred for 20 h and concentrated in vacuo. Purification by column chromatography (3−20% EtOAc/hexanes, silica) gave the title compound (**5q**, 2.44 g, ca. 60% purity by ^{1}H NMR, 11.2 mmol, 21% yield), an inseparable mixture of olefin isomers (*E*:*Z* = 10:1), as a clear oil. *E*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (m, 1H), 5.63 (m, 1H), 3.98 (m, 1H), 3.91 (m, 1H), 3.48 (q, *J* = 7.0 Hz, 2H), 2.93 (m, 1H), 2.75 (m, 1H), 2.48 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.22 (m, 2H), 1.63 (m, 2H), 1.21 (t, *J* = 7.0 Hz, 3H). *Z*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (m, 2H), 4.04 (m, 2H), 3.48 (q, *J* = 7.0 Hz, 2H), 2.93 (m, 1H), 2.75 (m, 1H), 2.49 (m, 1H), 2.22 (m, 2H), 1.63 (m, 2H), 1.22 (t, *J* = 7.0 Hz, 3H).

*(±)-2-(3-Cyclopentylidenepropyl)oxirane (**5s**).* To a solution of 2-(but-3-enyl)oxirane (**3**, 5.00 g, 50.9 mmol) in methylenecyclopentane (20.0 g, 244 mmol) at rt was added Grubbs catalyst, second generation (600 mg, 0.707 mmol). The mixture was stirred at for 72 h and concentrated in vacuo. Purification by column chromatography (0−10% EtOAc/hexanes, silica) gave the title compound (**5s**, 572 mg, 3.76 mmol, 7% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (m, 1H), 2.93 (m, 1H), 2.75 (dd, *J* = 4.9, 4.1 Hz, 1H), 2.48 (dd, *J* = 5.0, 2.8 Hz, 1H), 2.25−2.10 (m, 6H), 1.70−1.55 (m, 6H).

*(±)-2-(3-Cyclohexylidenepropyl)oxirane (**5t**).* A solution of 2-(but-3-enyl)oxirane (**3**, 6.00 g, 61.1 mmol) in methylenecyclohexane (20.0 g, 208 mmol) containing Zhan cat-1 (400 mg, 0.605 mmol) at rt was stirred for 20 h and concentrated in vacuo. Purification by column chromatography (0−10% EtOAc/hexanes, silica) gave the title compound (**5t**, 950 mg, ca. 30% purity by ^{1}H NMR, 1.71 mmol, 3% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (m, 1H), 2.93 (m, 1H), 2.75 (m, 1H), 2.48 (m, 1H), 2.20−2.04 (m, 6H), 1.66−1.45 (m, 8H).

*(±)-(E)-2-(4-Phenylbut-3-enyl)oxirane (**5u**).* A solution of 2-(But-3-enyl)oxirane (**3**, 8.60 g, 87.6 mmol) in styrene (45.0 g, 432 mmol) containing Grubbs catalyst, second generation (1.10 g, 1.29 mmol) at rt was stirred for 20 h and concentrated in vacuo. Purification by column chromatography (0−20% EtOAc/hexanes, silica) gave the title compound (**5u**, 3.13 g, ca. 30% purity by ^{1}H NMR, 11.7 mmol, 13% yield) as a light brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.25 (m, 4H), 7.20 (tt, *J* = 7.1, 1.4 Hz, 1H), 6.44 (dd, *J* = 15.8 Hz, 1H), 6.24 (dt, *J* = 15.8, 6.9 Hz, 1H), 2.99 (m, 1H), 2.78 (dd, *J* = 5.0, 4.1 Hz, 1H), 2.52 (dd, *J* = 5.0, 2.8 Hz, 1H), 2.49 (m, 2H), 2.38 (m, 2H).

*(±)-2-(5-Phenylpent-3-enyl)oxirane (**5v**).* To a solution of 2-(But-3-enyl)oxirane (**3**, 1.97 g, 21.1 mmol) and allylbenzene (10.2 g, 86.0 mmol) in DCM (30 mL) was added Grubbs catalyst, second generation (220 mg, 0.259 mmol). The mixture was heated to reflux, stirred for 20 h, and concentrated in vacuo. Purification by column chromatography (0−10% EtOAc/hexanes, silica) gave the title compound (**5v**, 2.01 g, ca. 30% purity by ^{1}H NMR, 6.40 mmol, 30% yield), an inseparable mixture of *E* and *Z* isomers (ratio not quantified) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 3H), 7.18 (m, 2H), 5.63 (m, 1H), 5.53 (m, 1H), 3.33 (d, *J* = 6.6 Hz, 2H), 2.92 (m, 1H), 2.75 (dd, *J* = 4.9, 4.2 Hz, 1H), 2.47 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.20 (m, 2H), 1.62 (m, 2H).

*(±)-4-(5-Cyclopropylpent-3-ynyl)-2,2-dimethyl-1,3-dioxolane (**8**).* To a solution of TMS-acetylene (8.01 mL, 56.7 mmol) in anhydrous THF (50 mL) containing DMPU (27.0 mL, 222 mmol) was slowly added *n*-BuLi (38.7 mL of a 1.6 M soln in hexanes, 61.9 mmol) at −78 °C over 5 min. The mixture was stirred at −78 °C for 30 min, at which time (±)-4-(2-iodoethyl)-2,2-dimethyl-1,3-dioxolane (**7**, 13.2 g, 51.5 mmol) was added. The mixture was slowly warmed to rt, and stirring was continued for 4 h, at which time the reaction mixture was quenched with water followed by extraction with EtOAc. The combined organics were washed with H_2O and brine. The organics were dried over $MgSO_4$, filtered, and concentrated. Column chromatography (0−5% EtOAc/hexanes, silica) gave (±)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)but-1-ynyl)trimethylsilane (8.78 g, 38.8 mmol, 75% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19−4.12 (m, 1H), 4.07 (dd, *J* = 8.0, 6.0 Hz, 1H,), 3.57 (dd, *J* = 8.0, 6.9 Hz, 1H), 2.39−2.26 (m, 2H), 1.86−1.79 (m, 1H), 1.76−1.68 (m, 1H), 1.39 (s, 3H), 1.34 (s, 3H), 0.13 (s, 9H).

To a solution of (±)-4-(2, 2-dimethyl-[1,3]dioxolan-4-yl)-but-1-ynyl]-trimethylsilane (10.0 g, 44.2 mmol) in MeOH (40 mL) was added K_2CO_3 (7.00 g, 50.6 mmol). The mixture was stirred at rt for 4 h and concentrated in vacuo to remove MeOH. The crude material was partitioned between NH_4Cl (satd aq) and EtOAc. The layers were separated, and the organics were dried over $MgSO_4$, filtered, and concentrated. Column chromatography (5−15% EtOAc/hexanes, silica) gave afforded 4-(but-3-ynyl)-2,2-dimethyl-1,3-dioxolane (5.00 g, 32.4 mmol, 73% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21−4.15 (m, 1H), 4.05 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.55 (dd, *J* = 8.0, 6.9 Hz, 1H), 2.31−2.26 (m, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.80 (m, 1H), 1.70 (m, 1H), 1.38 (s, 3H), 1.33 (s, 3H).

To a solution of (±)-4-(but-3-ynyl)-2,2-dimethyl-1,3-dioxolane (3.88 g, 25.2 mmol) in anhydrous THF (100 mL) containing DMPU (9.10 mL, 75.5 mmol) was slowly added *n*-BuLi (14.0 mL of a 2.5*M* soln in hexanes, 35 mmol) at −78 °C over 5 min. The mixture was stirred at −78 °C for 30 min, at which time (bromomethyl)-cyclopropane (4.40 g, 32.6 mmol) was added. The mixture was slowly warmed to rt, and stirring was continued for 48 h. The reaction mixture was quenched with NH_4Cl (satd aq) and extracted with hexanes. Dried organics over $MgSO_4$, filtered, and concentrated. Column

chromatography (2−10% EtOAc/hexanes, silica) gave (±)-4-(5-cyclopropylpent-3-ynyl)-2,2-dimethyl-1,3-dioxolane (**8**, 2.60 g, 12.5 mmol, 50% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (m, 1H), 4.07 (dd, J = 8.0, 6.0 Hz, 1H), 3.57 (dd, J = 7.9, 7.1 Hz, 1H), 2.29−2.23 (m, 2H), 2.18 (m, 2H), 1.80 (m, 1H), 1.67 (m, 1H), 1.40 (s, 3H), 1.35 (s, 3H), 0.88 (m, 1H), 0.43 (m, 2H), 0.19 (m, 2H).

*(±)-(Z)-2-(5-Cyclopropylpent-3-enyl)oxirane (**5n**).* To a solution of (±)-4-(5-cyclopropyl-pent-3-ynyl)-2, 2-dimethyl-[1,3] dioxolane (**8**, 2.50 g, 12.0 mmol) in hexane (100 mL) was added quinoline (155 mg, 1.20 mmol), followed by addition of 5% Pd on $BaSO_4$ (250 mg). The mixture was stirred at room temperature under H_2 atmosphere for 4 h. The mixture was filtered through Celite and concentrated. The filtrates were diluted with hexanes and washed with NH_4Cl (satd aq) and brine. Dried organics over $MgSO_4$, filtered, and concentrated. Column chromatography (2−10% EtOAc/hexanes, silica) gave (±)-(Z)-4-(5-cyclopropylpent-3-enyl)-2,2-dimethyl-1,3-dioxolane (2.20 g, 10.5 mmol, 88% yield) as clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (m, 1H), 5.37 (m,1H), 4.08 (m, 1H), 4.02 (dd, J = 8.0, 6.0 Hz, 1H), 3.51 (t, J = 7.5 Hz, 1H), 2.17−2.04 (m, 2H), 1.97 (t, J = 7.0 Hz, 2H), 1.74−1.66 (m, 1H), 1.58−1.49 (m, 1H), 1.41 (s, 3H), 1.35 (s, 3H), 0.70 (m, 1H), 0.41 (m, 2H), 0.06 (m, 2H).

(±)-(Z)-4-(5-Cyclopropylpent-3-enyl)-2,2-dimethyl-1,3-dioxolane (2.00 g, 9.51 mmol) in AcOH/H_2O (4:1, 50 mL) was stirred overnight at rt. The mixture was concentrated and purified by column chromatography (70−90% EtOAc/hexanes, silica) to give (±)-(Z)-7-cyclopropylhept-5-ene-1,2-diol (1.45 g, 8.52 mmol, 90% yield) as clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (m, 1H), 5.37 (m, 1H), 3.73 (m, 1H), 3.66 (d, J = 11.2 Hz, 1H), 3.46 (dd, J = 11.2, 7.7 Hz, 1H), 2.19−2.10 (m, 2H), 1.97 (t, J = 7.1 Hz, 2H), 1.53−1.46 (m, 2H), 0.71 (m, 1H), 0.42 (m, 2H), 0.06 (m, 2H).

To a solution of 7-cyclopropyl-hept-5-ene-1,2-diol (1.45 g, 9.28 mmol) in THF (80 mL) was added sodium hydride (60 wt % dispersion oil, 1.11 g, 27.8 mmol) at 0 °C. The mixture was slowly warmed to room temperature and stirred for 1 h. TrisIm (3.41 g, 10.2 mmol) was added in one portion at 0 °C. The mixture was warmed to rt and stirred for 1.5 h. The mixture was quenched with water and extracted with Et_2O. The organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (7−15% EtOAc/hexanes, silica) gave the (±)-(Z)-2-(5-cyclopropylpent-3-enyl)oxirane (**5n**, 1.20 g, 8.68 mmol, 94% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (m, 1H), 5.40 (m, 1H), 2.93 (m, 1H), 2.75 (dd, J = 4.9, 4.1 Hz, 1H), 2.48 (dd, J = 5.0, 2.7 Hz, 1H), 2.19 (q, J = 7.3 Hz, 2H), 1.98 (t, J = 7.0 Hz, 2H), 1.62−1.56 (m, 2H), 0.70 (m, 1H), 0.41 (m, 2H), 0.07 (m, 2H).

*Representative Procedure for Intramolecular Cyclopropanation to Prepare Alcohols **9d−j,n−q,s−v**. Synthesis of (±)-(1R,2R,5S)-6-Propylbicyclo[3.1.0]hexan-2-ol (exo-**9d**/endo-**9d**).* To a solution of tetramethylpiperidine (1.85 g, 13.1 mmol) in MTBE (75 mL) at −78 °C under N_2 was added *n*-butyllithium (8.17 mL of a 1.6 M solution in hexanes, 13.1 mmol) dropwise over 5 min. After the addition was complete, the flask was stirred at −78 °C for 30 min and warmed to 0 °C for 10 min. The LiTMP solution was added via cannula to a solution of (±)-2-(hept-3-enyl)oxirane (**5d**, 915 mg, 6.54 mmol) in MTBE (20 mL) at 0 °C over 30 min. The reaction was slowly warmed to rt and stirred overnight. The mixture was quenched with MeOH (2 mL), and the mixture was washed with 1N HCl (100 mL) and brine. The aqueous phase was back-extracted with DCM (50 mL), and the combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (1−25% EtOAc/hexanes, silica) gave the title compound (*exo*-**9d**:*endo*-**9d** = 4.2:1, 515 mg, 3.67 mmol, 56% yield), an inseparable mixture of diastereomers, as a clear oil. *Exo*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (d, J = 4.8 Hz, 1H), 1.89 (m, 1H), 1.67 (dd, J = 12.5, 8.2 Hz, 1H), 1.53 (dd, J = 14.2, 8.3 Hz, 1H), 1.48−1.28 (m, 4H), 1.20−1.08 (m, 4H), 0.88 (t, J = 7.3 Hz, 3H), 0.37 (m, 1H). *endo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$, partial spectra of distinguishable peaks) δ 4.18 (d, J = 4.8 Hz, 1H), 2.07 (1H, m), 1.74 (m, 1H), 0.75 (m, 1H).

*(±)-(1R,2R,5S)-6-Butylbicyclo[3.1.0]hexan-2-ol (exo-**9e**/endo-**9e**).* Prepared from (±)-2-(oct-3-enyl)oxirane (**5e**, 2.04 g, 13.2 mmol) in a similar manner as described for the synthesis of *exo*-**9d**/*endo*-**9d** to give the title compound (*exo*-**9e**:*endo*-**9e** = 3.3:1, 1.20 g, 7.79 mmol, 59% yield), an inseparable mixture of diastereomers, as a clear oil. *exo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (d, J = 4.8 Hz, 1H), 1.89 (m, 1H), 1.69 (dd, J = 12.6, 8.0 Hz, 1H), 1.54 (dd, J = 11.6, 5.7 Hz, 1H), 1.48−1.25 (m, 6H), 1.25−1.08 (m, 3H), 0.89 (m, 3H), 0.36 (m, 1H). *endo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$, partial spectra of distinguishable peaks) δ 4.18 (d, J = 4.8, 1H), 2.07 (1H, m), 1.75 (m, 1H), 0.75 (m, 1H).

*(±)-(1R,2R,5S,6R)-6-Pentylbicyclo[3.1.0]hexan-2-ol (endo-**9f**).* Prepared from (±)-(Z)-2-(non-3-enyl)oxirane (Z-**5f**, 1.00 g, 5.94 mmol) in a similar manner as described for the synthesis of *exo*-**9d**/*endo*-**9d** to give the title compound (*endo*-**9f**, 600 mg, 3.56 mmol, 60% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (dd, J = 5.0, 1.0 Hz, 1H), 2.08 (m, 1H), 1.75 (m, 1H), 1.70−1.49 (m, 2H), 1.40−1.25 (m, 8H), 1.18 (m, 2H), 0.88 (t, J = 6.9 Hz, 3H), 0.75 (m, 1H).

*(±)-(1R,2R,5S,6S)-6-Pentylbicyclo[3.1.0]hexan-2-ol (exo-**9f**).* Prepared from (±)-(E)-2-(non-3-enyl)oxirane (E-**5f**, 2.00 g, 11.9 mmol) in a similar manner as described for the synthesis of *exo*-**9d**/*endo*-**9d** to give the title compound (*exo*-**9f**, 950 mg, 5.64 mmol, 48% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (d, J = 4.8 Hz, 1H), 1.68 (dd, J = 12.5, 8.1 Hz, 1H), 1.54 (dd, J = 15.5, 8.5 Hz, 1H), 1.38−1.22 (m, 8H), 1.17 (m, 3H), 1.10 (m, 1H), 0.88 (t, J = 7.1 Hz, 3H), 0.37 (m, 1H).

*(±)-(1S,2R,5S,6S)-6-Isopropylbicyclo[3.1.0]hexan-2-ol (exo-**9g**).* Prepared from (±)-2-(5-methylhex-3-enyl)oxirane (**5g**, 2.04 g, 11.9 mmol) in a similar manner as described for the synthesis of *exo*-**9d**/*endo*-**9d** to give the title compound (*exo*-**9g**, 1.18 g, 8.42 mmol, 71% yield), predominately the *exo*-isomer, as a clear oil. ^{1}H NMR ($CDCl_3$) δ 4.19 (d, J = 4.8 Hz, 1H), 1.87 (m, 2H), 1.63 (dd, J = 12.5, 8.2 Hz, 1H), 1.51 (dd, J = 14.2, 8.4 Hz, 1H), 1.30 (m, 1H), 1.19 (m, 1H), 1.11 (m, 1H), 0.95−0.84 (m, 7H), 0.14 (m, 1H).

*(±)-(1S,2R,5S)-6-Isobutylbicyclo[3.1.0]hexan-2-ol (exo-**9h**/endo-**9h**).* Prepared from (±)-2-(6-methylhept-3-enyl)oxirane (**5h**, 1.21 g, 7.86 mmol) in a similar manner as described for the synthesis of *exo*-**9d**/*endo*-**9d** to give the title compound (*exo*-**9h**:*endo*-**9h** = 3.3:1, 1.21 g, ca. 70% purity by ^{1}H NMR, 5.49 mmol, 70% yield), an inseparable mixture of diastereomers, as a clear oil. *exo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (m, 1H), 1.95 (m, 1H), 1.88 (m, 1H), 1.72−1.45 (m, 2H), 1.35 (m, 2H), 1.18 (m, 1H), 1.06 (m, 2H), 0.97−0.83 (m, 6H) 0.37 (m, 1H). *endo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$, partial spectra of distinguishable peaks) δ 4.18 (d, J = 4.8 Hz, 1H), 2.07 (m, 1H), 1.75 (m, 1H), 0.75 (m, 1H).

*(±)-(1R,2R,5S)-6-Isopentylbicyclo[3.1.0]hexan-2-ol (exo-**9i**/endo-**9i**).* Prepared from 2-(7-methyloct-3-enyl)oxirane (**5i**, 2.70 g, 16.0 mmol) in a similar manner as described for the synthesis of *exo*-**9d**/*endo*-**9d** to give the title compound (*exo*-**9i**:*endo*-**9i** = 3.3:1, 3.30 g, ca. 60% purity by ^{1}H NMR, 11.8 mmol, 74% yield), an inseparable mixture of diastereomers, as a clear oil. *exo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (d, J = 4.4 Hz, 1H), 1.89 (m, 1H), 1.68 (dd, J = 12.5, 8.0 Hz, 1H), 1.60−1.49 (m, 2H), 1.40−1.15 (m, 6H), 1.10 (m, 1H), 0.86, (d, J = 6.7 Hz, 6H) 0.35 (m, 1H). *endo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$, partial spectra of distinguishable peaks) δ 4.18 (d, J = 4.8 Hz, 1H), 2.07 (m, 1H), 1.75 (m, 1H), 0.74 (m, 1H).

*(±)-(1S,2R,5R)-6,6-Dimethylbicyclo[3.1.0]hexan-2-ol (**9j**).* Prepared from (±)-2-(4-methylpent-3-enyl)oxirane (**5j**, 4.33 g, 34.3 mmol) in a similar manner as described for the synthesis of *exo*-**9d**/*endo*-**9d** to give the title compound (**9j**, 1.67 g, 13.3 mmol, 39% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (m, 1H), 2.05 (m, 1H), 1.84 (m, 1H), 1.74 (m, 1H), 1.56 (ddd, J = 12.9, 9.5, 2.9 Hz, 1H), 1.28 (m, 1H), 1.14 (dd, J = 6.3, 1.2 Hz, 1H), 0.99 (s, 3H), 0.93 (s, 3H).

*(±)-(1S,2R,5S,6R)-6-(Cyclopropylmethyl)bicyclo[3.1.0]hexan-2-ol (endo-**9n**).* Prepared from (±)-(Z)-2-(4-cyclopropyl-but-2-enyl)-oxirane (**5n**, 350 mg, 2.30 mmol) in a similar manner as described for the synthesis of *exo*-**9d**/*endo*-**9d** to give the title compound (*endo*-**9n**, 219 mg, 1.44 mmol, 63% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (d, J = 5.5 Hz, 1H), 2.10 (m, 1H), 1.75 (dd, J = 11.0, 9.7 Hz, 1H), 1.69−1.52 (m, 4H), 1.42 (dd, J = 8.1, 6.2 Hz, 1H), 0.98−0.87 (m, 2H), 0.71 (m, 1H), 0.43 (m, 2H), 0.03 (m, 2H).

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*(±)-(1S,2R,5S,6S)-6-((tert-Butyldimethylsilyloxy)methyl)bicyclo-[3.1.0]hexan-2-ol (exo-**9o**).* Prepared from (±)-(*E*)-*tert*-butyldimethyl-(5-oxiranyl-pent-2-enyloxy)-silane (*E*-**5o**, 1.80 g, 7.43 mmol) in a similar manner as described for the synthesis of *exo*-**9d**/*endo*-**9d** to give the title compound (*exo*-**9o**, 1.12 g, 4.62 mmol, 62% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25 (d, J = 4.8 Hz, 1H), 3.49 (dd, J = 10.8, 6.2 Hz, 1H), 3.44 (dd, J = 10.8, 6.4 Hz, 1H), 1.93 (m, 1H), 1.72 (dd, J = 12.6, 8.1 Hz, 1H), 1.57 (dd, J = 14.5, 8.4 Hz, 1H), 1.38−1.24 (m, 3H), 0.89 (s, 9H), 0.71 (m, 1H), 0.04 (s, 6H).

*(±)-(1S,2R,5R,6S)-6-(Methylthiomethyl)bicyclo[3.1.0]hexan-2-ol (exo-**9p**).* Prepared from (±)-(*E*)-2-(5-methylsulfanyl-pent-3-enyl)-oxirane (**5p**, 600 mg, 4.20 mmol) in a similar manner as described for the synthesis of *exo*-**9d**/*endo*-**9d** to give the title compound (*exo*-**9p**, 40 mg, 0.28 mmol, 7% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (t, J = 5.0 Hz, 1H), 2.41 (d, J = 7.0 Hz, 2H), 2.14 (s, 3H), 1.95 (m, 1H), 1.75 (dd, J = 12.7, 8.1 Hz, 1H), 1.58 (dd, J = 14.6, 8.6 Hz, 1H), 1.40−1.28 (m, 4H), 0.69 (m, 1H).

*(±)-(1S,2R,5S)-6-(Ethoxymethyl)bicyclo[3.1.0]hexan-2-ol (exo-**9q**/endo-**9q**).* Prepared from (±)-2-(5-ethoxypent-3-enyl)oxirane (**5q**, 1.76 g, 11.3 mmol) in a similar manner as described for the synthesis of *exo*-**9d**/*endo*-**9d** to give the title compound (*exo*-**9q**:*endo*-**9q** = 10:1, 298 mg, 1.91 mmol, 17% yield), an inseparable mixture of diastereomers, as a clear oil. *exo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (m, 1H), 3.47 (q, J = 7.1 Hz, 2H), 3.24 (m, 2H), 1.94 (m, 1H), 1.75 (dd, J = 12.6, 8.1 Hz, 1H), 1.56 (m, 1H), 1.40−1.28 (m, 3H), 1.20 (t, J = 7.1 Hz, 3H), 0.78 (m, 1H). *endo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$, partial spectra of distinguishable peaks) δ 3.90 (m, 1H), 2.17 (m, 1H), 1.66 (m, 1H), 1.21 (t, J = 7.1 Hz, 3H).

*(±)-(1S,2R,5R)-Spiro[bicyclo[3.1.0]hexane-6,1′-cyclopentan]-2-ol (**9s**).* Prepared from (±)-2-(3-cyclopentylidenepropyl)oxirane (**5s**, 572 mg, 3.76 mmol) in a similar manner as described for the synthesis of *exo*-**9d**/*endo*-**9d** to give the title compound (**9s**, 250 mg, 1.64 mmol, 44% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (d, J = 4.8 Hz, 1H), 2.00 (m, 1H), 1.69−1.46 (m, 8H), 1.40−1.26 (m, 5H).

*(±)-(1S,2R,5R)-Spiro[bicyclo[3.1.0]hexane-6,1′-cyclohexan]-2-ol (**9t**).* Prepared from 2-(3-cyclohexylidenepropyl)oxirane (**5t**, 950 mg, 5.71 mmol) in a similar manner as described for the synthesis of *exo*-**9d**/*endo*-**9d** to give the title compound (**9t**, 406 mg, 2.44 mmol, 43% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (m, 1H), 2.03 (m, 1H), 2.00−1.10 (m, 15H).

*(±)-(1S,2R,5S,6S)-6-Phenylbicyclo[3.1.0]hexan-2-ol (exo-**9u**).* Prepared from (±)-(*E*)-2-(4-phenylbut-3-enyl)oxirane (**5u**, 3.13 g, 18.0 mmol) in a similar manner as described for the synthesis of *exo*-**9d**/*endo*-**9d** to give the title compound (*exo*-**9u**, 2.38 g, ca. 60% purity by ^{1}H NMR, 8.88 mmol, 49% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 2H), 7.14 (m, 1H), 7.02 (m, 2H), 4.41 (d, J = 4.7 Hz, 1H), 3.58 (d, J = 6.8 Hz, 1H), 2.09 (m, 1H), 1.89 (dd, J = 12.8, 8.0 Hz, 1H), 1.77−1.64 (m, 2H), 1.54 (m, 1H), 0.79 (m, 1H).

*(±)-(1S,2R,5S)-6-Benzylbicyclo[3.1.0]hexan-2-ol (exo-**9v**/endo-**9v**).* Prepared from (±)-2-(5-phenylpent-3-enyl)oxirane (**5v**, 2.01 g, 10.7 mmol) in a similar manner as described for the synthesis of *exo*-**9d**/*endo*-**9d** to give the title compound (*exo*-**9v**:*endo*-**9v** = 4:1, 828 mg, 4.40 mmol, 41% yield), an inseparable mixture of diastereomers, as a clear oil. *exo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.25 (m, 2H), 7.25−7.15 (m, 3H), 4.25 (d, J = 4.7 Hz, 1H), 2.54 (d, J = 6.9 Hz, 2H), 1.95 (m, 1H), 1.74 (dd, J = 12.5, J = 8.0 Hz, 1H), 1.57 (m, 1H), 1.39 (m, 2H), 1.31 (m, 1H), 0.71 (m, 1H). *endo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$, partial spectra of distinguishable peaks) δ 2.57 (m, 1H), 2.19 (m, 1H), 1.81 (m, 1H), 1.67 (m, 1H), 1.14 (m, 1H).

*Representative Procedure for Alcohol Oxidation to Prepare **10d−j,n−q,s−v**. Synthesis of (±)-6-Propylbicyclo[3.1.0]hexan-2-one (exo-**10d**/endo-**10d**).* To a solution of (±)-(1*R*,2*R*,5*S*)-6-propylbicyclo[3.1.0]hexan-2-ol (*exo*-**9d**:*endo*-**9d** = 4.2:1, 515 mg, 3.68 mmol) in DCM (15 mL) containing 4 Å molecular sieves (1.0 g) at 0 °C was added 4-methylmorpholine 4-oxide (862 mg, 7.36 mmol) followed by TPAP (78 mg, 0.23 mmol). The mixture was slowly warmed to rt and stirred for 1 h. The mixture was filtered through a plug of silica gel (DCM:Et_2O, 5:1 as eluent) and concentrated to a light-yellow oil. Purification by column chromatography (10−25% EtOAc/hexanes, silica) gave the title compound (*exo*-**10d**/*endo*-**10d**, 251 mg, 1.82 mmol, 49% yield), an inseparable mixture of diastereomers (ratio not determined), as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29−1.82 (m, 5H), 1.53 (d, J = 5.0 Hz, 1H), 1.48−1.21 (m, 5H), 0.91 (t, J = 7.2 Hz, 3H).

*(±)-6-Butylbicyclo[3.1.0]hexan-2-one (exo-**10e**/endo-**10e**).* Prepared from (±)-(1*R*,2*R*,5*S*)-6-butylbicyclo[3.1.0]hexan-2-ol (*exo*-**9e**:*endo*-**9e** = 3.3:1, 1.20 g, 7.79 mmol) in a similar manner as described for the synthesis of *exo*-**10d**/*endo*-**10d** to give the title compound *exo*-**10e**/*endo*-**10e**, 664 mg, 4.37 mmol, 56% yield), an inseparable mixture of diastereomers (ratio not determined), as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29−1.82 (m, 5H), 1.53 (d, J = 5.0 Hz, 1H), 1.45−1.24 (m, 7H), 0.87 (t, J = 7.2 Hz, 3H).

*(±)-endo-6-Pentylbicyclo[3.1.0]hexan-2-one (endo-**10f**).* Prepared from (±)-(1*R*,2*R*,5*S*,6*R*)-6-pentylbicyclo[3.1.0]hexan-2-ol (*endo*-**9f**, 975 mg, 5.79 mmol) in a similar manner as described for the synthesis of *exo*-**10d**/*endo*-**10d** to give the title compound (*endo*-**10f**, 740 mg, 4.45 mmol, 77% yield) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34−2.19 (m, 2H), 2.14 (q, J = 5.9 Hz, 1H), 2.01−1.86 (m, 3H), 1.49−1.24 (m, 9H), 0.89 (t, J = 6.4 Hz, 3H).

*(±)-exo-6-Pentylbicyclo[3.1.0]hexan-2-one (**exo-10f**).* Prepared from (±)-(1*R*,2*R*,5*S*,6*S*)-6-pentylbicyclo[3.1.0]hexan-2-ol (*exo*-**9f**, 950 mg, 5.64 mmol) in a similar manner as described for the synthesis of *exo*-**10d**/*endo*-**10d** to give the title compound (*exo*-**10f**, 782 mg, 4.70 mmol, 83% yield) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15−1.98 (m, 4H), 1.87 (q, J = 4.5 Hz, 1H), 1.55 (dd, J = 5.0, 2.0 Hz, 1H), 1.42 (m, 2H), 1.34−1.22 (m, 7H), 0.89 (t, J = 6.9 Hz, 3H).

*(±)-exo-6-Isopropylbicyclo[3.1.0]hexan-2-one (exo-**10g**).* Prepared from (±)-(1*S*,2*R*,5*S*,6*S*)-6-isopropylbicyclo[3.1.0]hexan-2-ol (*exo*-**9g**, 1.18 g, 8.42 mmol) in a similar manner as described for the synthesis of *exo*-**10d**/*endo*-**10d** to give the title compound (*exo*-**10g**, 737 mg, 5.33 mmol, 63% yield) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10−1.90 (m, 4H), 1.85 (m, 1H), 1.53 (d, J = 4.4 Hz, 1H), 1.04 (m, 2H), 0.98 (d, J = 5.1 Hz, 3H), 0.93 (d, J = 5.1 Hz, 3H).

*(±)-6-Isobutylbicyclo[3.1.0]hexan-2-one (exo-**10h**/endo-**10h**).* Prepared from (±)-(1*S*,2*R*,5*S*)-6-isobutylbicyclo[3.1.0]hexan-2-ol (*exo*-**9h**:*endo*-**9h** = 3.3:1, 847 mg, 5.49 mmol) in a similar manner as described for the synthesis of *exo*-**10d**/*endo*-**10d** to give the title compound (*exo*-**10h**:*endo*-**10h** = 3:1, 723 mg, ca. 70% purity by ^{1}H NMR, 3.33 mmol, 61% yield), an inseparable mixture of diastereomers, as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (m, 1H from *endo*-isomer), 2.13−1.87 (m, 4H), 1.86 (q, J = 4.6 Hz, 1H from *exo*-isomer), 1.70 (m, 1H), 1.55 (d, J = 5.1 Hz, 1H from *exo*-isomer), 1.28 (m, 2H), 1.11 (m, 1H), 0.95 (d, J = 2.5 Hz, 3H), 0.92 (d, J = 2.5 Hz, 3H).

*(±)-6-Isopentylbicyclo[3.1.0]hexan-2-one (exo-**10i**/endo-**10i**).* Prepared from (±)-(1*R*,2*R*,5*S*)-6-isopentylbicyclo[3.1.0]hexan-2-ol (*exo*-**9i**:*endo*-**9i** = 3.3:1, 1.98 g, 11.8 mmol) in a similar manner as described for the synthesis of *exo*-**10d**/*endo*-**10d** to give the title compound (*exo*-**10i**/*endo*-**10i**, 1.71 g, 10.3 mmol, 87% yield), an inseparable mixture of diastereomers (ratio not determined), as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (m, 1H from *endo* isomer), 2.17−1.85 (m, 6H), 1.55 (m, 2H), 1.45−1.22 (m, 4H), 0.95−0.86 (m, 6H).

*(±)-6,6-Dimethylbicyclo[3.1.0]hexan-2-one (**10j**).* Prepared from (±)-(1*S*,2*R*,5*R*)-6,6-dimethylbicyclo[3.1.0]hexan-2-ol (**9j**, 1.67 g, 13.3 mmol) in a similar manner as described for the synthesis of *exo*-**10d**/*endo*-**10d** to give the title compound (**10j**, 1.49 g, 12.0 mmol, 90% yield) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35−2.16 (m, 2H), 2.04 (m, 1H), 1.94−1.86 (m, 2H), 1.65 (d, J = 4.7 Hz, 1H), 1.16 (s, 3H), 1.12 (s, 3H).

*(±)-endo-6-(Cyclopropylmethyl)bicyclo[3.1.0]hexan-2-one (endo-**10n**).* Prepared from (±)-(1*S*,2*R*,5*S*,6*R*)-6-(cyclopropylmethyl)-bicyclo[3.1.0]hexan-2-ol (*endo*-**9n**, 210 mg, 1.38 mmol) in a similar manner as described for the synthesis of *exo*-**10d**/*endo*-**10d** to give the title compound (*endo*-**10n**, 110 mg, 0.732 mmol, 53% yield) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32−2.20 (m, 2H), 2.16 (q, J = 5.4 Hz, 1H), 1.97−1.84 (m, 3H), 1.57 (m, 1H), 1.38−1.24 (m, 2H), 0.76 (m, 1H), 0.46 (m, 2H), 0.07 (m, 2H).

*(±)-exo-6-((tert-Butyldimethylsilyloxy)methyl)bicyclo[3.1.0]-hexan-2-one (exo-**10o**).* Prepared from (±)-(1*S*,2*R*,5*S*,6*S*)-6-((*tert*-butyldimethylsilyloxy)methyl)bicyclo[3.1.0]hexan-2-ol (*exo*-**9o**, 1.88 g,

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7.76 mmol) in a similar manner as described for the synthesis of *exo*-**10d**/*endo*-**10d** to give the title compound (*exo*-**10o**, 1.59 g, 6.62 mmol, 85% yield) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (dd, J = 10.8, 4.8 Hz, 1H), 3.58 (dd, J = 10.8, 5.3 Hz, 1H), 2.15 (m, 1H), 2.05 (m, 4H), 1.72 (m, 1H), 1.51 (m, 1H), 0.87 (s, 9H), 0.04 (s, 6H).

*(±)-exo-6-(Methylthiomethyl)bicyclo[3.1.0]hexan-2-one (**exo-10p**).* Prepared from (±)-(1*S*,2*R*,5*R*,6*S*)-6-(methylthiomethyl)bicyclo-[3.1.0]hexan-2-ol (*exo*-**9p**, 40 mg, 0.25 mmol) in a similar manner as described for the synthesis of *exo*-**10d**/*endo*-**10d** to give the title compound (*exo*-**10p**, 35 mg, 0.22 mmol, 89% yield) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65 (dd, J = 13.5, 5.8 Hz, 1H), 2.38 (dd, J = 13.5, 7.7 Hz, 1H), 2.18 (s, 3H), 2.16−2.03 (m, 4H), 2.00 (dd, J = 9.1, 5.1 Hz, 1H), 1.78 (dd, J = 5.3, 2.5 Hz, 1H), 1.53 (m, 1H).

*(±)-6-(Ethoxymethyl)bicyclo[3.1.0]hexan-2-one (exo-**10q**/endo-**10q**).* Prepared from (±)-(1*S*,2*R*,5*S*)-6-(ethoxymethyl)bicyclo[3.1.0]-hexan-2-ol (*exo*-**9q**:*endo*-**9q** = 10:1, 290 mg, 1.86 mmol) in a similar manner as described for the synthesis of *exo*-**10d**/*endo*-**10d** to give the title compound (*exo*-**10q**:*endo*-**10q** = 10:1, 186 mg, 0.829 mmol, 45% yield), an inseparable mixture of diastereomers, as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (dd, J = 10.8, 6.3 Hz, 1H from *endo*-isomer), 3.46 (m, 3H), 3.27 (dd, J = 10.4, 6.7 Hz, 1H), 2.19−1.97 (m, 5H), 1.77 (m, 1H from *endo*-isomer), 1.70 (dd, J = 5.2, 2.6 Hz, 1H), 1.59 (m, 1H), 1.20 (t, J = 7.0 Hz, 3H).

*(±)-Spiro[bicyclo[3.1.0]hexane-6,1′-cyclopentan]-2-one (**10s**).* Prepared from (±)-(1*S*,2*R*,5*R*)-spiro[bicyclo[3.1.0]hexane-6,1′-cyclo-pentan]-2-ol (**9s**, 266 mg, 1.74 mmol) in a similar manner as described for the synthesis of *exo*-**10d**/*endo*-**10d** to give the title compound (**10s**, 115 mg, 0.766 mmol, 44% yield) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23−2.11 (m, 2H), 2.02−1.90 (m, 3H), 1.77−1.73 (m, 3H), 1.70−1.50 (m, 5H), 1.48−1.24 (m, 1H).

*(±)-Spiro[bicyclo[3.1.0]hexane-6,1′-cyclohexan]-2-one (**10t**).* Prepared from (±)-(1*S*,2*R*,5*R*)-spiro[bicyclo[3.1.0]hexane-6,1′-cyclohexan]-2-ol (**9t**, 406 mg, 2.44 mmol) in a similar manner as described for the synthesis of *exo*-**10d**/*endo*-**10d** to give the title compound (**10t**, 244 mg, 1.49 mmol, 61% yield) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39−2.28 (m, 1H), 2.28−2.14 (m, 1H), 2.10−1.99 (m, 2H), 1.97−1.82 (m, 2H), 1.64 (d, J = 5.2 Hz, 1H), 1.60−1.44 (m, 7H), 1.33−1.25 (m, 2H).

*(±)-exo-6-Phenylbicyclo[3.1.0]hexan-2-one (exo-**10u**).* Prepared from (±)-(1*S*,2*R*,5*S*,6*S*)-6-phenylbicyclo[3.1.0]hexan-2-ol (*exo*-**9u**, 1.55 g, 8.88 mmol) in a similar manner as described for the synthesis of *exo*-**10d**/*endo*-**10d** to give the title compound (*exo*-**10u**, 351 mg, 2.04 mmol, 23% yield) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.21 (m, 1H), 7.05 (m, 2H), 2.38 (m, 2H), 2.33−2.10 (m, 4H), 2.06 (dd, J = 5.0, 2.8 Hz, 1H).

*(±)-6-Benzylbicyclo[3.1.0]hexan-2-one (exo-**10v**/endo-**10v**).* Prepared from (±)-(1*S*,2*R*,5*S*)-6-benzylbicyclo[3.1.0]hexan-2-ol (*exo*-**9v**:*endo*-**9v** = 4:1, 828 mg, 4.40 mmol) in a similar manner as described for the synthesis of *exo*-**10d**/*endo*-**10d** to give the title compound (*exo*-**10v**:*endo*-**10v** = 6:1, 641 mg, 3.44 mmol, 78% yield), an inseparable mixture of diastereomers, as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.28 (m, 2H), 7.25−7.20 (m, 3H), 2.78 (dd, J = 14.9, 6.1 Hz, 1H), 2.70 (dd, J = 15.1, 7.8 Hz, 1H from *endo*-isomer, 2.60 (dd, J = 14.9, 7.2 Hz, 1H from *exo*-isomer), 2.43−2.20 (m, 3H from *endo*-isomer), 2.16−2.00 (m, 5H), 1.73 (dd, J = 5.2, 2.4 Hz, 1H), 1.57 (m, 1H).

*(±)-6,6-Dichlorospiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane] (**12**).* To a solution of 2-cyclopenten-1-one ethylene ketal (**11**, 25.2 g, 200 mmol) in $CHCl_3$ (200 mL) and CH_2Cl_2 (200 mL) was added benzyltriethylammonium chloride (100 mg, 0.44 mmol) and 50% NaOH solution (aq, 200 mL) at rt. This solution was vigorously stirred at 45 °C over 3 d. The reaction mixture was diluted with H_2O (300 mL) and extracted with $CHCl_3$ (2 × 150 mL). The combined organics were concentrated in vacuo, and the residue was purified by column chromatography (0−50% EtOAc/hexanes, silica) to the give the title compound (**12**, 22.0 g, 105 mmol, 53% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06−3.93 (m, 4H), 2.25−2.01 (m, 5H), 1.86 (m, 1H).

*(±)-6-Chloro-6-methylspiro[bicyclo[3.1.0]hexane-2,2′-[1,3]-dioxolane] (**13**).* To a solution of (±)-6,6-dichloro-spiro-[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane] (**12**, 6.50 g, 31.1 mmol) in THF (140 mL) at −100 °C was added dropwise *tert*-butyllithium (22.0 mL of a 1.7 M solution in pentane, 37.4 mmol). After stirring for 20 min, methyl iodide (2.33 mL, 37.3 mmol) was added dropwise and the mixture was slowly warmed to rt over 2 h. The reaction was quenched with water and extracted with hexanes. The layers were separated, and the organics were dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (0−20% EtOAc/hexanes, silica) gave the title compound (**13**, 3.20 g, 17.0 mmol, 55% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01−3.91 (m, 4 H), 2.20−2.07 (m, 2H), 1.90 (m, 2H). 1.63 (dd, J = 6.8, 5.3 Hz, 1H), 1.61 (s, 3H), 1.54 (dd, J = 7.6 Hz, 1.0 Hz, 1H).

*(±)-exo-6-Chlorospiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane] (exo-14) and (±)-endo-6-Chlorospiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane] (endo-**14**).* To a solution of (±)-6,6-dichloro-spiro-[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane] (**12**, 17.0 g, 81.3 mmol) and KOH (28.0 g, 499 mmol) in EtOH (200 mL) was added Zn dust (62.8 g, 960 mmol) at rt. The reaction mixture was heated at 80 °C under vigorous stirring for 20 h. The mixture was cooled to rt and filtered through Celite. The filtrate was cooled to 0 °C and treated with acetic anhydride (47.3 mL, 500 mmol). The solution was concentrated in vacuo and partitioned between (300 mL) and H_2O (150 mL). The layers were separated, and the organics were washed with H_2O and brine (150 mL). The organics were dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (20−70% DCM/hexanes, silica) gave the *exo*-chloride (*exo*-**14**, 7.20 g, 41.2 mmol, 51% yield) followed by the *endo*-chloride (*endo*-**14**, 3.70 g, 21.2 mmol, 26% yield), both colorless oils. *exo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05−3.86 (m, 4H), 2.92 (t, J = 1.9 Hz, 1H) 1.90 (m, 2H), 1.74 (m, 2H), 1.62 (m, 1H), 1.37 (m, 1H). *endo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03−3.86 (m, 4H), 3.42 (t, J = 7.5 Hz, 1H) 2.17 (m, 1H), 2.05−1.77 (m, 3H), 1.81 (m, 1H), 1.72 (m, 1H).

*General Procedure for Lithiation/Electrophile Quench of mono-Chloride **13** or mono-Chloride **14** to Prepare exo-**10b** Ketal, endo-**10b** Ketal, endo-**10c** Ketal, endo-**15**, exo-**15**.* To a solution of 4,4′-di-*tert*-butyl-biphenyl (5.0 equiv) in THF (0.5M) under N_2 was added portionwise lithium wire (5.0 equiv). The solution was vigorously stirred at 0 °C for 6 h and cooled to −78 °C. (±)-*Endo* or *exo-mono*-chloride (**13** or **14**, 1.0 equiv) dissolved in THF (2.0M) was added to the dark-green solution. After stirring for 15 min, the electrophile (5.0 equiv) was added dropwise to the solution. The mixture was slowly warmed to rt, and the resulting solution was poured into a mixture of hexanes/NH_4Cl (satd aq) cooled at 0 °C. The phases were separated, and the organics were dried over $MgSO_4$, filtered, and concentrated. Products were purified by column chromatography (EtOAc/hexanes, silica).

*(±)-exo-6-Methylspiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane] (exo-**10b** Ketal).* Prepared from (±)-6-chloro-6-methylspiro-[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane] (**13**) using the general procedure for lithiation/electrophile quench described above where EtOH is substituted as the electrophile to give the title compound (*exo*-**10b** ketal). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05−3.87 (m, 4H), 1.85 (m, 1H), 1.76 (dd, J = 12.3, 8.0 Hz, 1H), 1.61 (dd, J = 13.8, 8.4 Hz, 1H), 1.45 (ddd, J = 13.8, 11.8, 8.2 Hz, 1H), 1.16 (m, 1H), 1.10 (ddd, J = 6.1, 2.9, 1.1 Hz, 1H), 1.00 (d, J = 6.0 Hz, 3H), 0.88 (m, 1H).

*(±)-endo-6-Methylspiro[bicyclo[3.1.0]hexane-2,2′-[1,3]-dioxolane] (endo-**10b** Ketal).* Prepared from a mixture of *exo*-**14** and *endo*-**14** (3.00 g, 17.2 mmol) by the general procedure using methyl iodide (5.36 mL, 85.9 mmol) as the electrophile to give the title compound (*endo*-**10b** ketal, 1.85 g, 12.0 mmol, 70% yield) as a clear oil after purification by column chromatography (0−20% EtOAc/hexanes, silica). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99−3.86 (m, 4H), 2.05 (m, 1H), 1.91 (m, 1H), 1.70 (ddd, J = 13.2, 9.3, 1.4 Hz, 1H), 1.56 (m, 1H), 1.48 (m, 1H), 1.38 (ddd, J = 8.6, 6.5, 1.3 Hz, 1H), 1.15 (d, J = 6.6 Hz, 3H), 0.96 (m, 1H).

*(±)-endo-6-Ethylspiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane] (endo-**10c** Ketal).* Prepared from a mixture of *exo*-**14** and *endo*-**14** by the general procedure using ethyl iodide as the electrophile to give the title compound (*endo*-**10c** ketal). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99−3.88 (m, 4H), 2.09−1.91 (m, 2H), 1.73−1.50 (m, 4H), 1.45−1.35 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H), 0.78 (m, 1H).

*(±)-endo-Spiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane]-6-carbaldehyde (endo-**15**) and (±)-exo-Spiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane]-6-carbaldehyde (exo-**15**).* Prepared by the general procedure using a mixture of *exo*-**14** and *endo*-**14** (8.00 g, 45.8 mmol) and dimethylformamide (14.2 mL, 183 mmol) as the electrophile. Purification by column chromatography (5−40% EtOAc/hexanes, silica) gave the title compound (*endo*-**15**:*exo*-**15** = 7:1, 4.10 g, 24.4 mmol, 53% yield), a clear oil, as a mixture of diastereomers. The isomers were partially separated by repeated and careful column chromatography under the same conditions to give pure fractions of the faster eluting *endo*-isomer followed by pure fractions of the *exo*-isomer. *endo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (d, J = 6.3 Hz, 1H), 4.05−3.93 (m, 4H), 2.34−2.19 (m, 2H), 2.15−2.06 (m, 3H), 1.91−1.76 (m, 2H). *exo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (d, J = 4.0 Hz, 1H), 4.05 (m, 1H), 3.99−3.91 (m, 3H), 2.13−1.99 (m, 4H), 1.90 (dd, J = 12.7, 8.0 Hz, 1H), 1.72 (dd, J = 14.0, 8.7 Hz, 1H), 1.54 (m, 1H).

*Preparation of (±)-endo-6-Vinylspiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane] (endo-**10k** Ketal).* To a solution of methyltriphenylphosphonium bromide (2.55 g, 7.14 mmol) in THF (40 mL) was added *n*-butyllithium (4.46 mL of 1.6 M solution in hexanes, 7.14 mmol) at rt. After 2 h, a solution of (±)-*endo*-spiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane]-6-carbaldehyde (*endo*-**15**, 1.00 g, 5.95 mmol) in THF (8 mL) was added and the reaction was stirred for 20 h. The mixture was treated with H_2O, and the product was extracted with hexanes. The organics were dried over $MgSO_4$, filtered, and concentrated. Column chromatography (0−20% EtOAc/hexanes, silica) gave the title compound (*endo*-**10k** ketal, 700 mg, 4.21 mmol, 71% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (ddd, J = 17.0, 10.2, 8.6 Hz, 1H), 5.30 (ddd, J = 17.0, 2.0, 1.0 Hz, 1H), 5.18 (ddd, J = 10.2, 2.0, 1.0 Hz, 1H), 4.00−3.88 (m, 4H), 2.07 (m, 1H), 1.90 (m, 1H), 1.80−1.56 (m, 5H).

*(±)-exo-6-Vinylspiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane] (exo-**10k** Ketal).* Prepared from (±)-*exo*-spiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane]-6-carbaldehyde (*exo*-**15**, 2.00 g, 11.9 mmol) in a similar manner as described for the synthesis of *endo*-**10k** ketal to give the title compound (*exo*-**10k** ketal, 1.20 g, 7.22 mmol, 61% yield) as a clear oil. δ 5.35 (ddd, J = 17.0, 10.2, 8.6 Hz, 1H), 5.05 (ddd, J = 17.0, 1.5, 0.4 Hz, 1H), 4.96 (dd, J = 10.3, 1.6 Hz, 1H), 4.03 (m, 1H), 3.99−3.88 (m, 3H), 1.93 (m, 1H), 1.84 (dd, J = 12.1, 8.1 Hz, 1H), 1.66 (dd, J = 14.2, 8.8 Hz, 1H), 1.56−1.43 (m, 4H).

*(±)-endo-Spiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane]-6-ylmethanol (**16**).* Sodium borohydride (90.0 mg, 2.38 mmol) was dissolved in MeOH (2 mL) and added dropwise to a solution of (±)-*endo*/*exo*-spiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane]-6-carbaldehyde (*endo*-**15**:*exo*-**15** = 7:1, 400 mg, 2.38 mmol) dissolved in MeOH (8 mL). Reaction was stirred at ambient temperature for 10 min and then quenched with NaOH (aq 10%). The mixture was extracted with ether, and the organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (50% EtOAc/hexanes, silica) gave the title compound (**16**, 200 mg, 1.09 mmol, 46% yield), a clear viscous oil, as a single diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07−3.88 (m, 5H), 3.64 (ddd, J = 12.5, 10.4, 2.2 Hz, 1H), 2.79 (dd, J = 11.0, 2.2 Hz, 1H), 2.18−2.05 (m, 2H), 1.82−1.60 (m, 4H), 1.35 (m, 1H).

*(±)-endo-6-(Methoxymethyl)spiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane] (endo-**10o** Ketal).* To a solution of (±)-*endo*-spiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane]-6-ylmethanol (**16**, 200 mg, 1.18 mmol) in DMF (6 mL) cooled to 0 °C was added sodium hydride (60% dispersion in mineral oil, 94.0 mg, 2.35 mmol). The mixture was stirred for 10 min, at which time methyl iodide (341 mg, 2.40 mmol) was added. The mixture was warmed to rt and stirred overnight, quenched with H_2O, and extracted with Et_2O. The organics were dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (5−25% EtOAc/hexanes, silica) gave the title compound (*endo*-**10o** ketal, 180 mg, 1.02 mmol, 87% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00−3.82 (m, 4H), 3.77 (dd, J = 10.5, 5.4 Hz, 1H), 3.44 (dd, J = 10.5, 8.5 Hz, 1H), 3.40 (s, 3H), 2.10 (m, 1H), 2.00 (m, 1H) 1.87−1.79 (m, 1H), 1.72−1.65 (m, 1H), 1.64−1.54 (m, 2H), 1.20 (m, 1H).

*(±)-endo-6-(Methylthiomethyl)spiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane] (endo-**10p** Ketal).* To a solution of (±)-*endo*-spiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane]-6-ylmethanol (**16**, 350 mg, 2.06 mmol) in DCM (12 mL) was added Et_3N (561 μL, 4.11 mmol). The flask was cooled to 0 °C, and methanesulfonyl chloride (318 μL, 4.11 mmol) was added dropwise. After stirring for 5 min, the flask was warmed to rt and stirred for 1 h. The DCM was evaporated, and the mixture was partitioned between H_2O and EtOAc. The aqueous phase was back-extracted with EtOAc, and the combined extracts were dried over $MgSO_4$, filtered, and concentrated to give (±)-*endo*-spiro[bicyclo-[3.1.0]hexane-2,2′-[1,3]dioxolane]-6-ylmethyl methanesulfonate (500 mg, 2.01 mmol, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 (dd, J = 11.2, 6.3 Hz, 1H), 4.34 (dd, J = 11.2, 9.3 Hz, 1H), 4.01−3.85 (m, 4H), 3.04 (s, 3H), 2.11 (m, 2H), 1.89 (m, 1H), 1.78 (m, 1H), 1.70 (m, 1H), 1.63 (m, 1H), 1.35 (m, 1H).

To a solution of the mesylate (250 mg, 1.01 mmol) in DMF (5.0 mL) was added sodium thiomethoxide (176 mg, 2.52 mmol). The solution became quite viscous initially and was stirred at rt overnight. The mixture was partitioned between EtOAc and H_2O. The layers were separated, and the aqueous phase was back-extracted with EtOAc. The combined organics were dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (3−12% EtOAc/hexanes, silica) gave the title compound (*endo*-**10p** ketal, 173 mg, 0.821 mmol, 81% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99−3.87 (m, 4H), 2.87 (dd, J = 13.5, 5.4 Hz, 1H), 2.54 (dd, J = 13.4, 8.8 Hz, 1H), 2.19 (s, 3H), 2.14−1.96 (m, 2H), 1.80 (m, 1H), 1.68−1.53 (m, 3H), 1.18 (qd, J = 8.6, 5.4 Hz, 1H).

*(±)-endo-6-Cyclopropylspiro[bicyclo[3.1.0]hexane-2,2′-[1,3]-dioxolane] (endo-**10m** Ketal).* To a solution of (±)-*endo*-6-vinylspiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane] (*endo*-**10k** ketal, 800 mg, 4.81 mmol) in Et_2O (15 mL) containing $Pd(OAc)_2$ (10 mg, 0.044 mmol) was added a diazomethane solution (45 mL of 1 M solution in Et_2O, 45 mmol) dropwise over 1 h. Additional $Pd(OAc)_2$ (10 mg, 0.044 mmol) and diazomethane solution (45 mL of 1 M solution in Et_2O, 45 mmol) was added four additional times until the reaction was complete by TLC. Purification by column chromatography (50−90% DCM/hexanes, silica) gave the title compound (*endo*-**10m** ketal, 680 mg, 3.77 mmol, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02−3.88 (m, 4H), 2.04 (m, 1H), 1.91−1.50 (m, 3H), 1.48−1.39 (m, 2H), 1.20 (m, 1H), 0.74 (m, 1H), 0.65−0.52 (m, 2H), 0.33−0.26 (m, 2H).

*(±)-endo-6-(Phenoxymethyl)spiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane] (endo-**10r** Ketal).* A mixture of (±)-*endo*-spiro-[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane]-6-ylmethanol (**16**, 178 mg, 0.966 mmol), phenol (141 mg, 1.50 mmol), $PyPh_2P$ (395 mg, 1.50 mmol), and D*t*-BAD (345 mg, 1.50 mmol) in THF (5 mL) was stirred at rt overnight. The mixture was partitioned between Et_2O and HCl (1N aq). The layers were separated, and the aqueous phase was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (0−25% EtOAc/hexanes, silica) to give the title compound (*endo*-**10r** ketal, 120 mg, 0.487 mmol, 50% yield) as clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.25 (m, 2H), 6.99−6.92 (m, 3H), 4.41 (dd, J = 10.6, 5.2 Hz, 1H), 4.03−3.89 (m, 5H), 2.13 (m, 1H), 2.04 (m, 1H), 1.89 (m, 1H), 1.78 (m, 1H), 1.68 (m, 1H), 1.60 (m, 1H), 1.40 (m, 1H).

General Method for Ketal Deprotection. A solution of ketal in acetone/H_2O (4/1, 0.15M) was treated with TsOH (5 mol %) at rt. The solution was stirred until reaction was complete as judged by TLC. The acetone was removed in vacuo, and the product was extracted with hexanes (2×). The combined organic layers were washed with $NaHCO_3$ (satd, aq) and brine. The organics were dried organics over $MgSO_4$, filtered, and concentrated in vacuo to afford the product ketones. All ketones obtained in ≥90% yield as clear oils.

*(±)-endo-6-Methylbicyclo[3.1.0]hexan-2-one (endo-**10b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32−2.21 (m, 2H), 2.10 (m, 1H), 1.97−1.84 (m, 3H), 1.51 (m, 1H), 1.15 (d, J = 6.6 Hz, 3H).

*(±)-exo-6-Methylbicyclo[3.1.0]hexan-2-one (exo-**10b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14−1.98 (m, 4H), 1.85 (q, J = 4.8 Hz, 1H), 1.52 (dd, J = 5.0, 2.5 Hz, 1H), 1.33 (m, 1H), 1.12 (d, J = 6.0 Hz, 3H).

*(±)-endo-6-Ethylbicyclo[3.1.0]hexan-2-one (endo-**10c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34−2.20 (m, 2H), 2.15 (q, J = 6.0 Hz, 1H), 2.00−1.87 (m, 3H), 1.48−1.36 (m, 3H), 1.04 (t, J = 6.5 Hz, 3H).

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*(±)-endo-6-Vinylbicyclo[3.1.0]hexan-2-one (endo-**10k**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (ddd, J = 17.0, 10.3, 8.5 Hz, 1H), 5.37 (dt, J = 17.0, 1.4 Hz, 1H), 5.27 (dt, J = 10.3, 1.5 Hz, 1H), 2.32−2.21 (m, 3H), 2.16 (m, 1H), 2.09 (m, 1H), 2.03−1.93 (m, 2H).

*(±)-exo-6-Vinylbicyclo[3.1.0]hexan-2-one (exo-**10k**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (ddd, J = 17.0, 10.2, 8.5 Hz, 1H), 5.15 (ddd, J = 17.0, 1.2, 0.4 Hz, 1H), 4.99 (dd, J = 10.2, 1.1 Hz, 1H), 2.20−2.05 (m, 5H), 1.93 (m, 1H), 1.83 (dd, J = 5.1, 2.4 Hz, 1H).

*(±)-endo-6-Cyclopropylbicyclo[3.1.0]hexan-2-one (endo-**10m**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32−2.09 (m, 5H), 1.84 (m, 1H), 1.16−1.09 (m, 1H), 0.68 (m, 1H), 0.61−0.56 (m, 2H), 0.39−0.29 (m, 2H).

*(±)-endo-6-(Methoxymethyl)bicyclo[3.1.0]hexan-2-one (endo-**10o**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (dd, J = 10.8, 6.4 Hz, 1H), 3.45 (dd, J = 10.8, 8.5 Hz, 1H), 3.37 (s, 3H), 2.36−2.23 (m, 3H), 2.05−1.98 (m, 3H), 1.78 (m, 1H).

*(±)-endo-6-(Methylthiomethyl)bicyclo[3.1.0]hexan-2-one (endo-**10p**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (dd, J = 13.6, 6.5 Hz, 1H), 2.53 (dd, J = 13.6 8.6 Hz, 1H), 2.32 (m, 2H), 2.24 (m, 1H), 2.17 (s, 3H), 1.99 (m, 3H), 1.75 (m, 1H).

*(±)-endo-6-(Phenoxymethyl)bicyclo[3.1.0]hexan-2-one (endo-**10r**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.25 (m, 2H), 7.00−6.94 (m, 1H), 6.92−6.88 (m, 2H), 4.19 (dd, J = 10.6, 6.1 Hz, 1H), 3.96 (dd, J = 10.6, 8.9 Hz, 1H), 2.38−2.32 (m, 3H), 2.13−1.94 (m, 4H).

*Cyclobutyldiphenylsulfonium Trifluoromethanesulfonate (**17**).* A solution of cyclobutanol (1.00 g, 13.9 mmol) in DCM (25 mL) was chilled to −20 °C and dry pyridine (1.35 mL, 16.6 mmol) was added followed by a solution of trifluoromethanesulfonic anhydride (2.33 mL, 13.9 mmol) in DCM (5 mL). The solution was allowed to warm to room temperature over 1 h. Pentane (40 mL) was added and the resulting mixture shaken and filtered. The filtrate was concentrated in vacuo. The residual oil was chilled to −20 °C, and diphenylsulfane (10.2 mL, 61.0 mmol) was added. The mixture was warmed to 25 °C and stirred for 20 h followed by heating to 45 °C for 30 min. The mixture was cooled to rt, and pentane was added. The resulting solid collected by vacuum filtration to give the title compound (**17**, 1.82 g, 4.86 mmol, 35% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (dt, J = 7.8, 3.1 Hz, 4H), 7.84−7.72 (m, 6H), 5.84 (m, 1H), 5.15 (ddd, J = 14.9, 10.3, 1.4 Hz, 2H), 4.48 (t, J = 14.2 Hz, 2H), 2.45 (dd, J = 13.8, 7.1 Hz, 2H). LCMS (ESI$^+$): m/z 241 $[C_{16}H_{17}S]^+$.

*(±)-6-Allylbicyclo[3.1.0]hexan-2-one (**10l**).* A solution of cyclobutyldiphenylsulfonium trifluoromethanesulfonate (**17**, 1.82 g, 4.86 mmol) in THF (30 mL) was chilled to −78 °C, and *tert*-butyllithium, (2.70 mL of 1.7 M soln in pentane, 4.59 mmol) was added dropwise. After 30 min, cyclopent-2-enone (0.190 mL, 2.35 mmol) in THF (3 mL) was added and the solution stirred at −78 °C for 2 h. The reaction was quenched with the addition of $NaHCO_3$ (satd aq) and warmed to room temperature. The product was extracted with DCM and the solvent removed under reduced pressure. Purification by column chromatography (0−20% EtOAc/hexanes, silica) gave the title compound (*endo*-**10l**:*exo*-**10l** = 1:1, 178 mg, 1.31 mmol, 56%), a clear oil, as an inseparable mixture of diastereomers. Isomer mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95−5.75 (m, 1H), 5.20−5.00 (m, 2H), 2.35−1.88 (m, 7.5H), 1.60 (m, 0.5 H), 1.52 (m, 0.5H), 1.36 (m, 0.5H).

*Bicyclo[3.1.0]hexan-3-one (**20**).* To a solution of cyclopentene-4-ol (5.00 g, 59.5 mmol) and Et_2Zn (12.4 mL, 121 mmol) in DCM (25 mL) under N_2 atmosphere at 0 °C was added CH_2I_2 (9.76 mL, 121 mmol) over 30 min using a syringe pump. The reaction was slowly warmed to rt and stirred overnight, at which time the mixture was opened to air and slowly quenched by the addition of dilute HCl (aq, 50 mL). The mixture was diluted with EtOAc (100 mL) and filtered. The organic layer was separated and washed with H_2O (100 mL) and brine (100 mL). The organics were dried over $MgSO_4$, filtered, and concentrated to an oil, which was purified by column chromatography (0−20% EtOAc/hexanes, silica) to give *endo*-bicyclo[3.1.0]hexan-3-ol (3.47 g, 35.4 mmol, 59% yield) as clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 (t, J = 6.5 Hz, 1H), 2.10 (m, 2H), 1.72 (d, J = 14.2 Hz, 1H, 1.39 (br s, 1H), 1.27 (m, 2H), 0.56−0.45 (m, 2H).

endo-Bicyclo[3.1.0]hexan-3-ol (3.47 g, 35.4 mmol)) was dissolved in DCM (250 mL) and treated sequentially with basic alumina (10 g) and PCC (15.2 g, 70.6 mmol) at rt. After stirring for 18 h, the solution was filtered through a pad of Celite atop silica gel using DCM/Et_2O (3:1) as eluent. The solvent was removed in vacuo (250 mbar, 20 °C bath temperature), and the product was purified by bulb-to-bulb distillation at reduced pressure (100 mbar) to give the title compound (**20**, 2.48 g, 25.8 mmol, 73% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (m, 2H), 2.16 (d, J = 20.0 Hz, 2H), 1.54 (m, 2H), 0.90 (dt, J = 6.0, 1.6 Hz, 1H), −0.05 (dt, J = 6.0, 4.0 Hz, 1H).

*(±)-5-Ethylbicyclo[3.1.0]hexan-2-one (**25**).* Sodium hydride (1.40 g of a 60% dispersion in mineral oil, 35.0 mmol) was added to DMSO (75 mL). Trimethylsulfoxionium iodide (8.21 g, 37.3 mmol) was added and the mixture was stirred for 0.5 h, at which time a solution of 3-ethylcyclopent-2-enone (**23**, 2.57 g, 23.3 mmol) in DMSO (25 zmL) was added dropwise via addition funnel. The mixture was stirred at rt for 2 h, quenched with H_2O, and extracted with EtOAc. The organics were washed with H_2O and brine. Dried organics over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (5−25% EtOAc/hexanes, silica) gave the title compound (**25**, 1.54 g, 12.4 mmol, 53% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20−2.03 (m, 3H), 1,95 (m, 1H), 1.73−1.60 (m, 2H), 1.53 (m, 1H), 1.15 (ddt, J = 9.0, 4.7, 1.1 Hz, 1H), 1.10 (m, 1H), 0.97 (t, J = 7.5 Hz, 3H).

*(±)-1-Methylbicyclo[3.1.0]hexan-2-one (**26**).* Prepared from 2-methylcyclopent-2-enone (**24**, 1.00 g, 10.4 mmol) in a similar manner as described for the synthesis of **25** to give the title compound (**26**, 492 mg, 4.47 mmol, 44% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20−2.00 (m, 3H), 1.97−1.87 (m, 2H), 1.23 (s, 3H), 1.02 (m, 2H).

*Representative Procedure for Synthesis of Pyrazole Ethyl Esters **18**. Preparation of (±)-1a,2,5,5a-Tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (**18a**).* To a solution of bicyclo[3.1.0]hexan-2-one (2.20 g, 22.9 mmol) and diethyl oxalate (3.10 mL, 22.9 mmol) in EtOH (50 mL) was added KO*t*-Bu (22.9 mL of a 1 M soln in THF, 22.9 mmol). Stirring was continued for 2.5 h, at which time hydrazine monohydrochloride (1.88 g, 27.5 mmol) was added to a solution in H_2O (10 mL). The mixture was stirred overnight and concentrated in vacuo to remove EtOH, diluted with EtOAc, and washed with H_2O and brine. The organics were dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (25−50% EtOAc/hexanes, silica) gave the title compound (**18a**, 2.44 g, 12.7 mmol, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (br s, 1H), 4.32 (q, J = 6.8 Hz, 2H), 2.96 (dd, J = 16.8, 6.0 Hz, 1H), 2.80 (d, J = 17.2 Hz, 1H), 2.23−2.13 (m, 2H), 1.35 (t, J = 7.2 Hz, 3H), 1.15 (m, 1H), 0.34 (m, 1H). ^{13}C APT NMR (100 MHz, $CDCl_3$, partial spectra) δ up, 23.0, 15.4, 14.5; down, 127.4, 61.2, 26.8, 16.8. LCMS (ESI$^+$): t_r = 1.62 min; m/z 193.1 $[M + H]^+$.

*(±)-endo-1-Methyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (endo-**18b**).* Prepared from (±)-*endo*-6-methylbicyclo[3.1.0]hexan-2-one (*endo*-**10b**, 500 mg, 4.55 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (*endo*-**18b**, 403 mg, 1.96 mmol, 43% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37−4.30 (m, 2H), 2.92 (dd, J = 17.5, 6.8 Hz, 1H), 2.65 (d, J = 17.5 Hz, 1H), 2.33 (m, 1H), 2.17 (m, 1H), 1.36 (t, J = 7.2 Hz, 3H), 1.32 (m, 1H), 0.71 (d, J = 6.5 Hz, 3H). LCMS (ESI$^+$): m/z 207.1 $[M + H]^+$, 229.2 $[M + Na]^+$.

*(±)-exo-1-Methyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa-[a]pentalene-4-carboxylic Acid Ethyl Ester (exo-**18b**).* Prepared from (±)-*exo*-6-methylbicyclo[3.1.0]hexan-2-one (*exo*-**10b**, 88 mg, 1.25 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (*exo*-**18b**, 49 mg, 0.22 mmol, 18% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37−4.31 (m, 2H), 2.97 (dd, J = 17.1, 5.7 Hz, 1H), 2.86 (d, J = 17.1 Hz, 1H), 1.98 (m, 2H), 1.36 (t, J = 7.1 Hz, 3H), 1.13 (d, J = 6.1 Hz, 3H), 0.73 (m, 1H). LCMS (ESI$^+$): m/z 207.2 $[M + H]^+$, 229.4 $[M + Na]^+$.

*(±)-endo-1-Ethyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa-[a]pentalene-4-carboxylic Acid Ethyl Ester (endo-**18c**).* Prepared from (±)-*endo*-6-ethylbicyclo[3.1.0]hexan-2-one (*endo*-**10c**, 503 mg, 4.04 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (*endo*-**18c**, 374 mg, 1.70 mmol, 42% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39−4.27 (m, 2H), 2.90 (dd, J = 17.5,

6.9 Hz, 1H), 2.65 (d, J = 17.5 Hz, 1H), 2.33 (ddd, J = 7.6, 6.2, 1.3 Hz, 1H), 2.20 (m, 1H), 1.35 (t, J = 7.1 Hz, 3H), 1.17 (m, 1H), 1.05 (m, 1H), 0.91−0.83 (m, 4H). LCMS (ESI$^+$): m/z 221.3 $[M + H]^+$, 243.3 $[M + Na]^+$.

*(±)-exo/endo-1-Propyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (exo-**18d**/endo-**18d**).* Prepared from (±)-6-propylbicyclo[3.1.0]hexan-2-one (*exo*/*endo*-**10d**, 251 mg, 1.82 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (*exo*-**18d**:*endo*-**18d** = 3.3:1, 280 mg, 1.20 mmol, 66% yield) as a mixture of diastereomers. *exo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (q, J = 7.1 Hz, 2H), 2.91 (dd, J = 17.1, 6.2 Hz, 1H), 2.80 (d, J = 17.1 Hz, 1H), 1.98 (m, 1H), 1.88 (m, 1H), 1.42 (m, 2H), 1.37−1.17 (m, 5H), 0.90 (t, J = 7.1 Hz, 3H), 0.65 (m, 1H). LCMS (ESI$^+$): m/z 235 $[M + H]^+$, 257 $[M + Na]^+$, 189 $[M - OEt]^+$. *endo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (m, 2H), 2.89 (dd, J = 17.4, 6.9 Hz, 1H), 2.63 (d, J = 17.4 Hz, 1H), 2.32 (m, 1H), 2.18 (m, 1H), 1.48−1.16 (m, 6H), 1.02 (m, 1H), 0.81 (m, 4H).

*(±)-exo/endo-1-Butyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (exo-**18e**/endo-**18e**).* Prepared from (±)-6-butylbicyclo[3.1.0]hexan-2-one (*exo*/*endo*-**10e**, 664 mg, 4.37 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (*exo*-**18e**:*endo*-**18e** = 2.5:1, 460 mg, 1.85 mmol, 42% yield) as a mixture of diastereomers. *exo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (q, J = 7.2 Hz, 2H), 2.91 (dd, J = 17.0, 6.2 Hz, 1H), 2.79 (d, J = 17.0 Hz, 1H), 1.96 (m, 1H), 1.88 (m, 1H), 1.45−1.15 (m, 9H), 0.87 (t, J = 6.8 Hz, 3H), 0.65 (m, 1H). LCMS (ESI$^+$): m/z 249 $[M + H]^+$, 203 $[M - OEt]^+$. *endo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (m, 2H), 2.88 (dd, J = 17.4, 6.9 Hz, 1H), 2.62 (d, J = 17.4 Hz, 1H), 2.30 (m, 1H), 2.17 (m, 1H), 1.44−1.15 (m, 8H), 1.03 (m, 1H), 0.85−0.75 (m, 4H).

*(±)-endo-1-Pentyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (endo-**18f**).* Prepared from (±)-*endo*-6-pentylbicyclo[3.1.0]hexan-2-one (*endo*-**10f**, 730 mg, 4.39 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (*endo*-**18f**, 731 mg, 2.91 mmol, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40−4.30 (m, 2H), 2.90 (dd, J = 17.5, 6.8 Hz, 1H), 2.64 (d, J = 17.5 Hz, 1H), 2.33 (ddd, J = 7.7, 6.2, 1.2 Hz, 1H), 2.20 (m, 1H), 1.37 (t, J = 7.1 Hz, 3H), 1.35−1.15 (m, 7H), 1.03 (m, 1H), 0.89−0.78 (m, 4H). LCMS (ESI$^+$): m/z 263 $[M + H]^+$, 217 $[M - OEt]^+$.

*(±)-exo-1-Pentyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa-[a]pentalene-4-carboxylic Acid Ethyl Ester (exo-**18f**).* Prepared from (±)-*exo*-6-pentylbicyclo[3.1.0]hexan-2-one (*exo*-**10f**, 780 mg, 4.69 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (*exo*-**18f**, 562 mg, 2.14 mmol, 46% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (q, J = 7.1 Hz, 2H), 2.93 (dd, J = 17.1, 6.2 Hz, 1H), 2.81 (d, J = 17.1 Hz, 1H), 1.98 (ddd, J = 6.0, 2.9, 1.1 Hz, 1H), 1.90 (m, 1H), 1.88 (m, 1H), 1.47−1.23 (m, 10H), 0.87 (t, J = 6.9 Hz, 3H), 0.66 (m, 1H). LCMS (ESI$^+$): m/z 263 $[M + H]^+$, 217 $[M - OEt]^+$.

*(±)-exo-1-Isopropyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (exo-**18g**).* Prepared from (±)-*exo*-6-isopropylbicyclo[3.1.0]hexan-2-one (*exo*-**10g**, 200 mg, 1.45 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (*exo*-**18g**, 385 mg crude without purification, ca. 30% purity by ^{1}H NMR, 1.02 mmol, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (q, J = 7.2 Hz, 2H), 2.90 (dd, J = 7.1, J = 5.3 Hz, 1H), 2.77 (d, J = 17.1 Hz, 1H), 1.90 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.21 (m, 1H), 1.05 (m, 1H), 0.97 (d, J = 11.5 Hz, 6H), 0.45 (m, 1H). LCMS (ESI$^+$): m/z 235 $[M + H]^+$, 189 $[M - OEt]^+$.

*(±)-exo/endo-1-Isobutyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (exo-**18h**/endo-**18h**).* Prepared from (±)-6-isobutylbicyclo[3.1.0]hexan-2-one (*exo*-**10h**:*endo*-**10h** = 3.3:1, 200 mg, 1.31 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (*exo*-**18h**:*endo*-**18h** = 2.5:1, 330 mg crude without purification, ca. 50% purity by ^{1}H NMR, 0.66 mmol, 51% yield) as a mixture of diastereomers. *exo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (m, 2H), 2.90 (dd, J = 17.1, 6.2 Hz, 1H), 2.80 (d, J = 17.0 Hz, 1H), 1.95 (m, 1H), 1.87 (m, 1H), 1.70 (m, 1H), 1.31 (t, J = 7.1 Hz, 3H), 1.32 (m, 1H), 1.10 (m, 1H), 0.92−0.85 (m, 6H), 0.64 (m, 1H). LCMS (ESI$^+$): m/z 249 $[M + H]^+$, 203 $[M - OEt]^+$. *endo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35 (m, 2H), 2.85 (dd, J = 17.0, 6.2 Hz, 1H), 2.61 (d, J = 17.0 Hz, 1H), 2.32 (m, 1H), 2.18 (m, 1H), 1.53 (m, 1H), 1.34 (t, J = 6.9 Hz, 3H), 1.32 (m, 1H), 0.95 (m, 1H), 0.84 (d, J = 6.6 Hz, 3H), 0.78 (d, J = 6.6 Hz, 3H), 0.69 (m, 1H).

*(±)-exo-1-Isopentyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (exo-**18i**) and (±)-endo-1-Isopentyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (endo-**18i**).* Prepared from (±)-6-isopentylbicyclo[3.1.0]hexan-2-one (*exo*-**10i**:*endo*-**10i** = 3.3:1, 850 mg, 5.11 mmol) in a similar manner as described for the synthesis of **18a** with the exception that 2.20 equiv of KO*t*-Bu were used, and the hydrazine condensation step was performed at 80 °C for 24 h. Purification by reverse phase HPLC [Phenomenex Luna C18 column (10 μ, 250 mm × 100 mm), 5% (v/v) CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 50% H_2O, 60 mL/min, λ = 254 nm] gave *endo*-**18i** (24.0 mg, 0.091 mmol, 2% yield) followed by *exo*-**18i** (446 mg, 1.70 mmol, 33% yield). *exo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35 (q, J = 7.1 Hz, 2H), 2.97 (dd, J = 17.1, 5.8 Hz, 1H), 2.84 (d, J = 17.1 Hz, 1H), 2.02 (m, 2H), 1.55 (m, 1H), 1.42−1.23 (m, 7H), 0.88 (d, J = 6.6 Hz, 6H), 0.70 (m, 1H). LCMS (ESI$^+$): m/z 263 $[M + H]^+$, 285 $[M + Na]^+$, 217 $[M - OEt]^+$. *endo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (m, 2H), 2.94 (m, 1H), 2.66 (d, J = 17.0 Hz, 1H), 2.35 (m, 1H), 2.24 (m, 1H), 1.72 (m, 1H), 1.36 (t, J = 7.0 Hz, 3H), 1.30−1.00 (m, 4H), 0.81 (m, 1H), 0.76 (d, J = 6.9 Hz, 3H), 0.73 (d, J = 7.0 Hz, 3H). LCMS (ESI$^+$): m/z 263 $[M + H]^+$, 285 $[M + Na]^+$, 217 $[M - OEt]^+$.

*(±)-1,1-Dimethyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa-[a]pentalene-4-carboxylic Acid Ethyl Ester (**18j**).* Prepared from (±)-6,6-dimethylbicyclo[3.1.0]hexan-2-one (**10j**, 1.49 g, 12.0 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (**18j**, 1.32 g, 5.99 mmol, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (m, 2H), 2.89 (dd, J = 17.5, 6.9 Hz, 1H), 2.64 (d, J = 17.5 Hz, 1H), 2.07 (m, 1H), 1.94 (m, 1H), 1.37 (t, J = 7.1 Hz, 3H), 1.12 (s, 3H), 0.73 (s, 3H). LCMS (ESI$^+$): m/z 221 $[M + H]^+$, 243 $[M + Na]^+$, 175 $[M - OEt]^+$.

*(±)-endo-1-Vinyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa-[a]pentalene-4-carboxylic Acid Ethyl Ester (endo-**18k**).* Prepared from (±)-*endo*-6-vinylspiro[bicyclo[3.1.0]hexane-2,2′-[1,3]dioxolane] (*endo*-**10k**, 101 mg, 0.83 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (*endo*-**18k**, 144 mg, 0.66 mmol, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26 (m, 1H), 5.05−4.95 (m, 2H), 4.34 (m, 2H), 2.98 (dd, J = 17.5, 6.7 Hz, 1H), 2.76 (d, J = 17.5 Hz, 1H), 2.60 (ddd, J = 7.6, 6.0, 1.2 Hz, 1H), 2.42 (m, 1H), 1.98 (m, 1H), 1.36 (t, J = 7.1 Hz, 3H). LCMS (ESI$^+$): m/z 219.2 $[M + H]^+$, 241.1 $[M + Na]^+$.

*(±)-exo-1-Vinyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa-[a]pentalene-4-carboxylic Acid Ethyl Ester (exo-**18k**).* Prepared from (±)-*exo*-6-vinylbicyclo[3.1.0]hexan-2-one (*exo*-**10k**, 350 mg, 2.87 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (*exo*-**18k**, 300 mg, 1.38 mmol, 48% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (ddd, J = 17.1, 10.3, 8.6 Hz, 1H), 5.04 (dd, J = 17.1, 1.0 Hz, 1H), 4.92 (dd, J = 10.3, 1.4 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 3.02 (dd, J = 17.3, 6.1 Hz, 1H), 2.90 (d, J = 17.3 Hz, 1H), 2.32 (m, 1H), 2.19 (m, 1H), 1.34 (t, J = 7.2 Hz, 3H), 1.30 (m, 1H). LCMS (ESI$^+$): m/z 219.3 $[M + H]^+$, 241.1 $[M + Na]^+$.

*(±)-endo-1-Allyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa-[a]pentalene-4-carboxylic Acid Ethyl Ester (endo-**18l**) and (±)-exo-1-Allyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (exo-**18l**).* Prepared from (±)-6-allylbicyclo[3.1.0]hexan-2-one (*exo*-**10l**:*endo*-**10l** = 1:1, 80.0 mg, 0.587 mmol) in a similar manner as described for the synthesis of **18a**. Separation of the diastereomers was accomplished by reverse-phase HPLC [Phenomenex Luna C18 column (10 μ, 250 mm × 21.2 mm), 5% (v/v) CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 95% H_2O, 20 mL/min, λ = 214 nm] to give *endo*-**18l** (41.4 mg, 0.177 mmol, 30% yield) followed by *exo*-**18l** (17.5 mg, 0.0747 mmol, 13% yield). *endo*-Isomer: ^{1}H NMR (400 MHz,

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$CDCl_3$) δ 5.79 (m, 1H), 5.00 (dd, J = 17.2, 1.7 Hz, 1H), 4.95 (dd, J = 10.2, 1.5 Hz, 1H), 4.38 (m, 2H), 2.95 (dd, J = 17.5, 6.9 Hz, 1H), 2.70 (d, J = 17.5, 1H), 2.44 (t, J = 7.6 Hz, 1H), 2.31 (dd, J = 14.5, 6.5 Hz, 1H), 1.79−1.66 (m, 2H), 1.42−1.33 (m, 4H). LCMS (ESI$^+$): m/z 233 $[M + H]^+$, 255 $[M + Na]^+$; 187 $[M - OEt]^+$. *exo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (m, 1H), 5.02 (dd, J = 17.2, 1.6 Hz, 1H), 4.92 (dd, J = 10.3, 1.6 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 2.97 (dd, J = 17.1, 6.3 Hz, 1H), 2.86 (d, J = 17.1 Hz, 1H), 2.22−2.14 (m, 2H), 2.11−2.00 (m, 2H), 1.36 (t, J = 7.1 Hz, 3H), 0.80 (m, 1H). LCMS (ESI$^+$): m/z 233 $[M + H]^+$, 255 $[M + Na]^+$, 187 $[M - OEt]^+$.

*(±)-endo-1-Cyclopropyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (endo-**18m**).* Prepared from (±)-*endo*-6-vinylbicyclo[3.1.0]hexan-2-one (*endo*-**10m**, 220 mg, 1.62 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (*endo*-**18m**, 150 mg, 0.646 mmol, 40% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (m, 2H), 2.98 (dd, J = 17.4, 6.4 Hz, 1H), 2.88 (d, J = 17.4 Hz, 1H), 2.35 (m, 1H), 2.20 (m, 1H), 1.37 (t, J = 7.2 Hz, 3H), 0.74 (m, J = 8.4 Hz, 1H), 0.45 (m, 1H), 0.32−0.14 (m, 3H), −0.08 (m, 1H). LCMS (ESI$^+$): m/z 233.4 $[M + H]^+$, 255.4 $[M + Na]^+$.

*(±)-endo-1-Cycloproylmethyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (endo-**18n**).* Prepared from (±)-*endo*-6-(cyclopropylmethyl)bicyclo[3.1.0]-hexan-2-one (*endo*-**10n**, 500 mg, 3.40 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (*endo*-**18n**, 300 mg, 1.22 mmol, 36% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 (m, 2H), 2.94 (dd, J = 17.4, 6.8 Hz, 1H), 2.67 (d, J = 17.4 Hz, 1H), 2.45 (m, 1H), 2.31 (m, 1H), 1.42 (m, 1H), 1.37 (t, J = 7.1 Hz, 3H), 1.00 (m, 1H), 0.74 (m, 1H), 0.65 (m, 1H), 0.36 (m, 2H), −0.05 (m, 1H), −0.12 (m, 1H). LCMS (ESI$^+$): m/z 247.3 $[M + H]^+$, 269.1 $[M + Na]^+$.

*(±)-1-endo-Methoxymethyl-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (endo-**18o**).* Prepared from (±)-*endo*-6-(methoxymethyl)bicyclo[3.1.0]hexan-2-one (*endo*-**10o**, 60.0 mg, 0.428 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (*endo*-**18o**, 90.0 mg, 0.381 mmol, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.44−4.29 (m, 2H), 3.23 (s, 3H), 3.07 (m, 2H), 2.96 (dd, J = 17.6, 6.8 Hz, 1H), 2.77 (d, J = 17.6 Hz, 1H), 2.48 (m, 1H), 2.36 (m, 1H), 1.59 (m, 1H), 1.37 (t, J = 7.1 Hz, 3H). LCMS (ESI$^+$): t_r = 1.84 min; m/z 236.9 $[M + H]^+$.

*(±)-exo-1-Hydroxymethyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (exo-**18o**).* Prepared from (±)-*exo*-6-((*tert*-butyldimethylsilyloxy)methyl)bicyclo-[3.1.0]hexan-2-one (*exo*-**10o**, 7.45 g, 31.0 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (*exo*-**18o**, 5.30 g, 23.8 mmol, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (q, J = 7.1 Hz, 2H), 3.41 (dd, J = 11.4, 5.9 Hz, 1H), 3.28 (dd, J = 11.4, 6.8 Hz, 1H), 2.84 (dd, J = 16.9, 6.2 Hz, 1H), 2.69 (d, J = 16.9 Hz, 1H), 2.05 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H), 0.78 (m, 1H). LCMS (ESI$^+$): t_r = 1.54 min; m/z 223.2 $[M + H]^+$.

*(±)-endo-1-(Methylthiomethyl)-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (endo-**18p**).* Prepared from (±)-*endo*-6-(methylthiomethyl)bicyclo[3.1.0]-hexan-2-one (*endo*-**10p**, 52.0 mg, 0.333 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (*endo*-**18p**, 34.0 mg, 0.135 mmol, 41% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.2−9.4 (br s, 1H), 4.34 (m, 2H), 2.96 (dd, J = 17.7, 6.8 Hz, 1H), 2.75 (d, J = 17.7 Hz, 1H), 2.50 (m, 1H), 2.32 (m, 1H), 2.15 (m, 2H), 2.08 (s, 3H), 1.57 (m, 1H), 1.37 (t, J = 7.1 Hz, 3H). LCMS (ESI$^+$): t_r = 2.29 min; m/z 253.3 $[M + H]^+$.

*(±)-exo-1-(Methylthiomethyl)-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (exo-**18p**).* Prepared from (±)-*exo*-6-(methylthiomethyl)bicyclo[3.1.0]-hexan-2-one (*exo*-**10p**, 80.0 mg, 0.512 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (*exo*-**18p**, 40.0 mg, 0.159 mmol, 31% yield). LCMS (ESI$^+$): t_r = 2.35 min; m/z 253.1 $[M + H]^+$.

*(±)-1-endo-Phenoxymethyl-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (endo-**18r**).* Prepared from (±)-*exo*-6-(phenoxymethyl)bicyclo[3.1.0]hexan-2-one (*endo*-**10r**, 43.0 mg, 0.213 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (*endo*-**18r**, 28.0 mg, 0.084 mmol, 39% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.21 (m, 2H), 6.91 (t, J = 7.3 Hz, 1H), 6.83−6.79 (m, 2H), 4.39−4.25 (m, 2H), 3.85 (m, 1H), 3.48 (dd, J = 10.4, 8.3 Hz, 1H), 3.02 (dd, J = 17.8, 6.8 Hz, 1H), 2.84 (d, J = 17.8 Hz, 1H), 2.58 (m, 1H), 2.45 (m, 1H), 1.80 (m, 1H), 1.35 (t, J = 7.1 Hz, 3H). LCMS (ESI$^+$): t_r = 2.56 min; m/z 299.1 $[M + H]^+$.

*(±)-Spiro[1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]-pentalene-1,1′-cyclopentan]-4-carboxylic Acid Ethyl Ester (**18s**).* Prepared from (±)-spiro[bicyclo[3.1.0]hexane-6,1′-cyclopentan]-2-one (**10s**, 115 mg, 0.761 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (**18s**, 87 mg, 0.353 mmol, 46% yield). LCMS (ESI$^+$): m/z 247 $[M + H]^+$, 269.1 $[M + Na]^+$, 201 $[M - OEt]^+$.

*(±)-Spiro[1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]-pentalene-1,1′-cyclohexan]-4-carboxylic Acid Ethyl Ester (**18t**).* Prepared from (±)-spiro[bicyclo[3.1.0]hexane-6,1′-cyclohexan]-2-one (**10t**, 120 mg, 0.73 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (**18t**, 152 mg, 0.58 mmol, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35 (m, 2H), 2.93 (dd, J = 17.5, 6.9 Hz, 1H), 2.68 (d, J = 17.5 Hz, 1H), 2.15 (m, 2H), 1.59−1.24 (m, 11H), 1.08 (m, 1H), 0.98 (m, 1H). LCMS (ESI$^+$): m/z 261 $[M + H]^+$, 283 $[M + Na]^+$, 215 $[M - OEt]^+$.

*(±)-exo-1-Phenyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa-[a]pentalene-4-carboxylic Acid Ethyl Ester (exo-**18u**).* Prepared from (±)-6-phenylbicyclo[3.1.0]hexan-2-one (*exo*-**10u**, 224 mg, 1.30 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (*exo*-**18u**, 120 mg, 0.447 mmol, 34% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (br s, 1H), 7.27 (m, 2H), 7.17 (tt, J = 7.4, 1.8 Hz, 1H), 7.05 (m, 2H), 4.34 (q, J = 7.1 Hz, 2H), 3.12 (dd, J = 17.4, 6.0 Hz, 1H), 3.02 (d, J = 17.4 Hz, 1H), 2.57 (ddd, J = 6.1, 2.9, 1.0 Hz, 1H), 2.46 (m, 1H), 1.78 (t, J = 3.3 Hz, 1H), 1.35 (t, J = 7.1 Hz, 3H).

*(±)-endo/exo-1-Benzyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (exo/endo-**18v**).* Prepared from (±)-6-benzylbicyclo[3.1.0]hexan-2-one (*exo*-**10v**:*endo*-**10v** = 4:1, 641 mg, 3.44 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (*exo*-**18v**:*endo*-**18v** = 5:1, 582 mg, 2.06 mmol, 60% yield) as a mixture of diastereomers. *exo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.15 (m, 5H), 4.31 (q, J = 7.1 Hz, 2H), 2.97 (dd, J = 17.2, 6.2 Hz, 1H), 2.86 (d, J = 17.2 Hz, 1H), 2.82 (dd, J = 15.0, 6.3 Hz, 1H), 2.59 (dd, J = 15.0, 7.5 Hz, 1H), 2.18 (ddd, J = 6.0, 2.9, 1.1 Hz, 1H), 2.08 (m, 1H), 1.34 (t, J = 7.1 Hz, 3H), 0.99 (m, 1H). LCMS (ESI$^+$): m/z 283 $[M + H]^+$, 305 $[M + Na]^+$, 237 $[M - OEt]^+$. *endo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.13 (m, 5H), 4.35 (m, 2H), 3.00 (dd, J = 17.6, 6.9 Hz, 1H), 2.77 (d, J = 17.6 Hz, 1H), 2.47 (m, 1H), 2.40−2.30 (m, 2H), 2.23 (m, 1H), 1.55 (m, 1H), 1.37 (t, J = 7.1 Hz, 3H).

*(±)-3b,4,4a,5-Tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]-pyrazole-3-carboxylic Acid Ethyl Ester (**21**).* Prepared from bicyclo[3.1.0]hexan-3-one (**20**, 1.49 g, 15.5 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (**21**, 1.70 g, 8.84 mmol, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (m, 2H), 2.98 (ddd, J = 16.6, 6.4, 1.8 Hz, 1H), 2.79 (d, J = 16.6 Hz, 1H), 2.25 (m, 1H), 2.11 (m, 1H), 1.39 (t, J = 7.1 Hz, 3H), 1.20 (m, 1H), 0.30 (m, 1H).

*(±)-5a-Ethyl-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]-pentalene-4-carboxylic Acid Ethyl Ester (**27**-Et Ester).* Prepared from (±)-5-ethylbicyclo[3.1.0]hexan-2-one (**25**) in a similar manner as described for the synthesis of **18a** to give the title compound (**27**-**Et** ester). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.60 (br s, 1H), 4.33 (q, J = 7.1 Hz, 2H), 2.85 (dd, J = 17.0, 0.9 Hz, 1H), 2.78 (d, J = 17.0 Hz, 1H), 2.00 (ddd, J = 7.9, 3.3, 1.0 Hz, 1H), 1.76 (m, 1H), 1.55 (m, 1H), 1.35 (t, J = 7.1 Hz, 3H), 1.07 (dd, J = 8.0, 4.8 Hz, 1H), 1.02 (t, J = 7.4 Hz, 3H), 0.49 (m, 1H).

*(±)-1a-Methyl-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]-pentalene-4-carboxylic Acid Ethyl Ester (**28**-Et Ester).* Prepared from (±)-1-methylbicyclo[3.1.0]hexan-2-one (**26**, 492 mg, 4.47 mmol) in a similar manner as described for the synthesis of **18a** give the title compound (**28**-Et ester, 513 mg, 2.49 mmol, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (q, J = 7.2 Hz, 2H), 2.97 (dd, J = 17.1, 6.2 Hz, 1H), 2.74 (d, J = 17.1 Hz, 1H), 1.89 (m, 1H), 1.52 (s, 3H),

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1.34 (t, J = 7.2 Hz, 3H), 1.05 (dd, J = 8.2, 4.8 Hz, 1H), 0.50 (t, J = 4.5 Hz, 1H).

General Procedure for Ester Hydrolyses Prepare to Pyrazole Acids ***19***. To a solution of the corresponding ester in dioxane or THF (0.1 M) or THF/MeOH (3: 1, 0.1 M) was added a solution of LiOH, NaOH, or KOH (2N aq, 5−10 equiv) at rt. In some cases, the reaction mixtures were heated to 55 °C to facilitate the hydrolysis. The reaction was stirred until the ester was consumed and the mixture was acidified to pH = 1 with HCl (6N, aq). Purification by reverse-phase HPLC [Phenomenex Luna C18 column (10 μ, 250 mm × 21.2 mm), 5% (v/v) CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 95% H_2O, 20 mL/min, λ = 214 nm] gave the free acids white solids in high yields after lyophilization.

*(±)-1a,2,5,5a-Tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (**19a**).* Prepared from ester **18a** by the general procedure. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.84 (m, 1H), (d, J = 16.8 Hz, 1H), 2.13 (m, 2H), 1.09 (m, 1H), 0.19 (q, J = 4.1 Hz, 1H). LCMS (ESI$^+$): t_r = 1.09 min; m/z 165.3 $[M + H]^+$.

*(±)-endo-1-Methyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid (endo-**19b**).* Prepared from *endo*-**18b** by the general procedure. ^{1}H NMR (400 MHz, CD_3OD) δ 2.89 (dd, J = 17.3, 6.7 Hz, 1H), 2.64 (d, 1H, J = 17.2 Hz), 2.30−2.18 (m, 2H), 1.34 (m, 1H). 0.69 (d, J = 6.4 Hz, 3H). LCMS (ESI$^+$): t_r = 1.54 min; m/z 179.1 $[M + H]^+$.

*(±)-exo-1-Methyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa-[a]pentalene-4-carboxylic Acid (exo-**19b**).* Prepared from *exo*-**18b** by the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02 (dd, J = 18.5, 6.3 Hz, 1H), 2.91 (d, J = 18.5 Hz, 1H), 2.09 (m, 1H), 1.78 (m, 1H), 1.17 (d, J = 6.0 Hz, 3H), 0.74 m, 1H). LCMS (ESI$^+$): m/z 179.1 $[M + H]^+$, 201.5 $[M + Na]^+$.

*(±)-endo-1-Ethyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa-[a]pentalene-4-carboxylic Acid (endo-**19c**).* Prepared from *endo*-**18c** by the general procedure. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.80 (dd, J = 17.2, 6.8 Hz, 1H), 2.49 (d, J = 17.2 Hz, 1H), 2.24 (ddd, J = 7.6, 6.2, 1.0 Hz, 1H), 2.15 (m, 1H), 1.14 (m, 1H), 0.97 (m, 1H), 0.81 (t, J = 6.9 Hz, 3H), 0.73 (m, 1H). LCMS (ESI$^+$): m/z 193.0 $[M + H]^+$, 215.0 $[M + Na]^+$.

*(±)-endo-1-Propyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid (endo-19d) and (±)-exo-1-Propyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]-pentalene-4-carboxylic Acid (exo-**19d**).* Prepared from a mixture of *exo*-**18d** and *endo*-**18d** (3.3:1 respectively) by the general procedure. Separation by reverse-phase HPLC [Phenomenex Luna C18 column (10 μ, 250 mm × 21.2 mm), 5% (v/v) CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 95% H_2O, 20 mL/min, λ = 214 nm] gave pure *endo*-**19d** followed by pure *exo*-**19d**. *endo*-Isomer: ^{1}H NMR (400 MHz, CD_3OD) δ 2.87 (dd, J = 17.1, 6.6 Hz, 1H), 2.63 (d, J = 17.1 Hz, 1H), 2.26 (m, 2H), 1.40−1.32 (m, 2H), 1.09 (m, 1H), 0.91 (m, 1H), 0.84 (t, J = 7.2 Hz, 3H), 0.76 (m, 1H). LCMS (ESI$^+$): m/z 207 $[M + H]^+$, 229 $[M + Na]^+$, 189 $[M - OH]^+$. *exo*-Isomer: ^{1}H NMR (400 MHz, CD_3OD) δ 2.91 (m, 1H), 2.79 (d, J = 16.8 Hz, 1H), 1.95 (m, 2H), 1.47 (m, J = 7.1 Hz, 2H), 1.32 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H), 0.63 (m, 1H).

*(±)-endo-1-Butyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa-[a]pentalene-4-carboxylic Acid (endo-19e) and (±)-exo-1-Butyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid (exo-**19e**).* Prepared from a mixture of *exo*-**18e** and *endo*-**18e** (2.5:1 respectively) by the general procedure. Separation by reverse-phase HPLC [Phenomenex Luna C18 column (10 μ, 250 mm × 21.2 mm), 5% (v/v) CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 95% H_2O, 20 mL/min, λ = 214 nm] gave *endo*-**19e** followed by *exo*-**19e**. *endo*-Isomer: ^{1}H NMR (400 MHz, CD_3OD) δ 2.88 (dd, J = 17.1, 6.7 Hz, 1H), 2.63 (d, J = 17.1 Hz, 1H), 2.27 (m, 2H), 1.40−1.13 (m, 4H), 1.10 (m, 1H), 0.91 (m, 1H), 0.83−0.74 (m, 4H). LCMS (ESI$^+$): m/z 221 $[M + H]^+$, 203 $[M - OH]^+$. *exo*-Isomer: ^{1}H NMR (400 MHz, CD_3OD) δ 2.90 (m, 1H), 2.78 (d, J = 16.9 Hz, 1H), 1.95 (m, 2H), 1.48−1.25 (m, 6H), 0.93 (t, J = 7.0 Hz, 3H), 0.62 (m, 1H). LCMS (ESI$^+$): m/z 221 $[M + H]^+$, 203 $[M - OH]^+$.

*(±)-endo-1-Pentyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid (endo-**19f**).* Prepared from ester *endo*-**18f** by the general procedure. ^{1}H NMR (400 MHz, CD_3OD) δ 2.86 (dd, J = 17.2, 6.7 Hz, 1H), 2.40 (d, J = 17.2 Hz, 1H), 2.30 (m, 1H), 2.24 (m, 1H), 1.40−1.15 (m, 7H), 1.09 (m, 1H), 0.86 (m, 3H), 0.78 (m, 1H). LCMS (ESI$^+$): t_r = 2.38 min; m/z 235.3 $[M + H]^+$, 217.4 $[M - OH]^+$.

*(±)-exo-1-Pentyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa-[a]pentalene-4-carboxylic Acid (exo-**19f**).* Prepared from *exo*-**18f** by the general procedure. ^{1}H NMR (400 MHz, CD_3OD) δ 2.91 (m, 1H), 2.79 (d, J = 16.8 Hz, 1H), 1.95 (m, 2H), 1.46 (m, 2H), 1.40−1.28 (m, 6H), 0.92 (t, J = 5.8 Hz, 3H), 0.61 (m, 1H). LCMS (ESI$^+$): t_r = 2.59 min; m/z 235.3 $[M + H]^+$, 217.4 $[M - OH]^+$.

*(±)-exo-1-Isopropyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid (exo-**19g**).* Prepared from *exo*-**18g** by the general procedure. ^{1}H NMR (CD_3OD) δ 2.95−2.93 (m, 1H), 2.90 (d, J = 16.7 Hz, 1H), 2.00 (m, 2H), 1.08−1.03 (m, 7H), 0.43 (m, J = 4.1, 1H). LCMS (ESI$^+$): m/z 207 $[M + H]^+$, 189 $[M - OH]^+$.

*(±)-endo-1-Isobutyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid (endo-**19h**) and (±)-exo-1-Isobutyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]-pentalene-4-carboxylic Acid (exo-**19h**).* Prepared from a mixture *exo*-**18g** and *endo*-**18g** (2.5:1 respectively) by the general procedure. Separation by reverse-phase HPLC [Phenomenex Luna C18 column (10 μ, 250 mm × 21.2 mm), 5% (v/v) CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 95% H_2O, 20 mL/min, λ = 214 nm] gave *endo*-**19h** followed by *exo*-**19h**. *endo*-Isomer: ^{1}H NMR (400 MHz, CD_3OD) δ 2.91 (dd, J = 6.7 Hz, 1H), 2.65 (d, J = 17.5, 1H), 2.33 (m, 1H), 2.26 (m, 1H), 1.58 (m, 1H), 1.30 (m, 1H), 1.03 (m, 1H) 0.90 (d, J = 6.6 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H), 0.66 (m, 1H). LCMS (ESI$^+$): m/z 221 $[M + H]^+$, 203 $[M - OH]^+$. *exo*-Isomer: ^{1}H NMR (400 MHz, CD_3OD) δ 2.93 (m, 1H), 2.80 (d, J = 16.9 Hz, 1H), 1.96 (m, 2H), 1.75 (m, 1H), 1.24 (m, 2H), 0.98−0.94 (m, 6H), 0.62 (m, 1H). LCMS (ESI$^+$): m/z 221 $[M + H]^+$, 203 $[M - OH]^+$.

*(±)-endo-1-Isopentyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid (endo-**19i**) and (±)-exo-1-Isopentyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]-pentalene-4-carboxylic Acid (exo-**19i**).* Compounds were isolated as side products during HPLC separation of the corresponding esters *endo*-**18i** and *exo*-**18i** without the need for an additional hydrolysis step. *endo*-**19i** eluted prior to *exo*-**19i**. *endo*-Isomer: ^{1}H NMR (400 MHz, CD_3CN) δ 2.92 (dd, J = 18.5, 6.9 Hz, 1H), 2.66 (d, J = 18.5 Hz, 1H), 2.32 (m, 1H), 2.00 (m, 1H), 1.46 (m, 1H), 1.31−1.10 (m, 4H), 0.93 (m, 1H), 0.78 (d, J = 6.7 Hz, 3H), 0.76 (d, J = 6.7 Hz, 3H). *exo*-Isomer: ^{1}H NMR (400 MHz, CD_3CN) δ 2.92 (dd, J = 18.1, 6.4 Hz, 1H), 2.77 (d, J = 18.1 Hz, 1H), 2.03 (m, 1H), 1.76 (m, 1H), 1.56 (m, 1H), 1.38−1.24 (m, 4H), 0.87 (d, J = 6.6 Hz, 6H), 0.64 (m, 1H).

*(±)-1,1-Dimethyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa-[a]pentalene-4-carboxylic Acid (**19j**).* Prepared from **18j** by the general procedure. ^{1}H NMR (CD_3CN) δ 2.91 (dd, J = 17.4, 6.8 Hz, 1H), 2.66 (d, J = 17.4 Hz, 1H), 2.11 (dd, J = 6.3, 1.2 Hz, 1H), 2.00 (m, 1H), 1.19 (s, 3H), 0.77 (d, J = 2.0 Hz, 3H). LCMS (ESI$^+$): m/z 193 $[M + H]^+$, 215 $[M + Na]^+$, 175 $[M - OH]^+$.

*(±)-endo-1-Vinyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa-[a]pentalene-4-carboxylic Acid (endo-**19k**).* Prepared from *endo*-**18k** by the general procedure (90% purity by ^{1}H NMR). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.25 (dd, J = 16.9, 2.3 Hz, 1H), 4.99 (dd, J = 10.4, 2.4 Hz, 1H), 4.85 (ddd, J = 16.9, 10.4, 9.2 Hz, 1H), 2.88 (dd, J = 17.3, 6.6 Hz, 1H), 2.57−2.50 (m, 2H), 2.39 (m, 1H), 1.94 (m, 1H). LCMS (ESI$^+$): m/z 191.2 $[M + H]^+$.

*(±)-exo-1-Vinyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa-[a]pentalene-4-carboxylic Acid (exo-**19k**).* Prepared from *exo*-**18k** by the general procedure. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.53 (m, 1H), 5.13 (dd, J = 17.1, 1.6 Hz, 1H), 4.97 (dd, J = 10.3, 1.7 Hz, 1H), 2.98 (dd, J = 18.2, 6.3 Hz, 1H), 2.80 (d, J = 18.2 Hz, 1H), 2.36 (dd, J = 6.1, 2.6 Hz, 1H), 2.05 (m, 1H), 1.37 (dt, J = 8.8, 3.1 Hz, 1H). LCMS (ESI$^+$): m/z 191.3 $[M + H]^+$.

*(±)-endo-1-Allyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa-[a]pentalene-4-carboxylic Acid (endo-**19l**).* Prepared from *endo*-**18l** by the general procedure. ^{1}H NMR (CD_3CN) δ 5.68−5.56 (m, 1H), 4.81 (dq, J = 15.5, 1.7 Hz, 1H), 5.03 (dq, J = 10.2, 1.4 Hz, 1H), 2.68

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(dd, J = 17.4, 6.8 Hz, 1H), 2.43 (d, J = 17.3 Hz, 1H), 2.14 (m, 1H), 2.06 (m, 1H), 1.55 (m, 1H), 1.40 (m, 1H), 1.13 (m, 1H). LCMS (ESI^+): m/z 205 $[M + H]^+$, 227 $[M + Na]^+$, 187 $[M - OH]^+$.

*(±)-exo-1-Allyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]-pentalene-4-carboxylic Acid (exo-**19l**).* Prepared from *exo*-**18l** by the general procedure (90% purity by ^1H NMR). ^1H NMR (CD_3CN) δ 5.94 (m, 1H), 5.13 (dq, J = 17.2, 1.7 Hz, 1H), 5.03 (dq, J = 10.3, 2.1 Hz, 1H), 2.92 (dd, J = 16.8, 5.8 Hz, 1H), 2.78 (d, J = 17.0 Hz, 1H), 2.30−2.00 (m, 4H), 0.71 (m, 1H). LCMS (ESI^+): m/z 205 $[M + H]^+$, 227 $[M + Na]^+$, 187 $[M - OH]^+$.

*(±)-endo-1-Cyclopropyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid (endo-**19m**).* Prepared from *endo*-**18 m** by the general procedure. ^1H NMR (400 MHz, $CDCl_3$) δ 3.06 (dd, J = 18.9, 5.9 Hz, 1H), 2.99 (d, J = 18.7 Hz, 1H), 2.43 (t, J = 8.2 Hz, 1H), 2.05 (q, J = 6.1 Hz, 1H), 0.85 (q, J = 8.3 Hz, 1H), 0.52 (m, 1H), 0.38 (m, 1H), 0.29−0.21 (m, 2H), 0.04 (m, 1H). LCMS (ESI^+): m/z 205.3 $[M + H]^+$.

*(±)-endo-1-Cyclopropylmethyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid (endo-**19n**).* Prepared from *endo*-**18n** by the general procedure. ^1H NMR (400 MHz, CD_3OD) δ 2.95 (dd, J = 18.5, 6.9 Hz, 1H), 2.69 (d, J = 18.5 Hz, 1H), 2.40 (t, J = 6.9 Hz, 1H), 2.17 (dd, J = 14.0, 6.7 Hz, 1H), 1.44 (m, 1H), 1.13 (m, 1H), 0.84 (m, 1H), 0.72 (m, 1H), 0.44−0.36 (m, 2H), 0.00 (m, 1H), −0.06 (m, 1H). MS m/z (ES^+): 219.3 $[M + H]^+$.

*1-endo-Methoxymethyl-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid (endo-**19o**).* Prepared from *endo*-**18o** by the general procedure (93% purity by LC/MS). LCMS (ESI^+): t_r = 1.17 min; m/z 209.1 $[M + H]^+$.

*(±)-endo-1-(Methylthiomethyl)-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid (endo-**19p**).* Prepared from *endo*-**18p** by the general procedure. ^1H NMR (400 MHz, DMSO-d_6) δ 13.6−12.1 (br s, 1H), 2.82 (dd, J = 17.4, 6.8 Hz, 1H), 2.57 (d, J = 17.4 Hz, 1H), 2.40 (m, 1H), 2.23 (m, 1H), 2.08 (dd, J = 13.4, 7.1 Hz, 1H), 1.99 (m, 4H), 1.48 (m, 1H). LCMS (ESI^+): t_r = 1.59 min; m/z 225.3 $[M + H]^+$.

*(±)-exo-1-(Methylthiomethyl)-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid (exo-**19p**).* Prepared from *exo*-**18p** by the general procedure. ^1H NMR (400 MHz, CD_3OD) δ 2.94 (dd, J = 16.9, 5.9 Hz, 1H), 2.82 (d, J = 16.9 Hz, 1H), 2.53 (m, 2H), 2.14 (s, 3H), 2.16−2.08 (m, 2H), 0.89 (m, 1H). LCMS (ESI^+): t_r = 1.64 min; m/z 225.2 $[M + H]^+$.

*(±)-1-endo-Phenoxymethyl-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid (endo-**19r**).* Prepared from *endo*-**18r** by the general procedure. LCMS (ESI^+): t_r = 2.01 min; m/z 271.0 $[M + H]^+$.

*(±)-Spiro[1a,3,5,5a-Tetrahydro-1H-2,3-diaza-cyclopropa[a]-pentalene-1,1′-cyclopentan]-4-carboxylic Acid (**19s**).* Prepared from **18s** by the general procedure. ^1H NMR (CD_3OD) δ 2.94 (dd, J = 17.1, 2.1 Hz, 1H), 2.72 (d, J = 17.1 Hz, 1H), 2.17 (s, 2H), 1.78−1.53 (m, 6H), 1.29 (m, 1H), 0.89 (m, 1H). LCMS (ESI^+): m/z 219 $[M + H]^+$, 201 $[M - OH]^+$.

*(±)-Spiro[1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]-pentalene-1,1′-cyclohexan]-4-carboxylic Acid (**19t**).* Prepared from **18t** by the general procedure. ^1H NMR (400 MHz, CD_3CN) δ 2.89 (dd, J = 18.5, 7.0 Hz, 1H), 2.65 (d, J = 18.5 Hz, 1H), 2.07 (d, J = 6.2 Hz, 1H), 1.79 (m, 1H), 1.58−1.24 (m, 8H), 1.18 (ddd, J = 13.7, 8.1, 3.8 Hz, 1H), 1.18 (ddd, J = 13.7, 7.2, 3.8 Hz, 1H). LCMS (ESI^+): m/z 233 $[M + H]^+$, 255 $[M + Na]^+$.

*(±)-exo-1-Phenyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa-[a]pentalene-4-carboxylic Acid (exo-**19u**).* Prepared from *exo*-**18u** by the general procedure. ^1H NMR (400 MHz, CD_3CN) δ 7.27 (m, 2H), 7.18 (m, 1H), 7.09 (m, 2H), 3.05 (dd, J = 17.2, 5.8 Hz, 1H), 2.95 (d, J = 17.2 Hz, 1H), 2.65−2.32 (m, 2H), 1.74 (t, J = 3.4 Hz, 1H). LCMS (ESI^+): m/z 241 $[M + H]^+$, 263 $[M + Na]^+$.

*(±)-exo/endo-1-Benzyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid (exo/endo-**19v**).* Prepared from a mixture of *exo*-**18v** and *endo*-**18v** (5:1 respectively) by the general procedure. The product was obtained as a mixture of diastereomers (*exo*-**19v**:*endo*-**19v** = 5:1). *exo*-Isomer: ^1H NMR (400 MHz, CD_3CN) δ 7.33−7.15 (m, 5H), 2.90 (dd, J = 17.0, 5.8 Hz, 1H), 2.75 (d, J = 17.0 Hz, 1H), 2.66 (m, 2H), 2.12 (m, 2H), 0.91 (m, 1H). *endo*-Isomer: ^1H NMR (400 MHz, CD_3CN) (partial spectra of distinguishable peaks) δ 2.91 (dd, J = 17.4, 6.9 Hz, 1H), 2.42−2.17 (m, 3H), 1.54 (m, 1H). LCMS (ESI^+): m/z 255 $[M + H]^+$, 277 $[M + Na]^+$, 237 $[M - OH]^+$.

*(±)-3b,4,4a,5-Tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]-pyrazole-3-carboxylic Acid (**22**).* Prepared from **21** by the general procedure. LCMS (ESI^+): t_r = 1.24 min; m/z 165.0 $[M + H]^+$.

*(±)-5a-Ethyl-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]-pentalene-4-carboxylic Acid (**27**).* Prepared from **27**-Et ester by the general procedure. ^1H NMR (400 MHz, DMSO-d_6) δ 2.74 (dd, J = 17.0, 0.7 Hz, 1H), 2.66 (d, J = 17.0 Hz, 1H), 1.92 (m, 1H), 1.71 (m, 1H), 1.51 (m, 1H), 1.04 (dd, J = 7.8, 4.4 Hz, 1H), 0.96 (t, J = 7.4 Hz, 3H), 0.34 (t, J = 3.9 Hz, 1H).

*(±)-1a-Methyl-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]-pentalene-4-carboxylic Acid (**28**).* Prepared from **28**-Et ester by the general procedure. ^1H NMR (400 MHz, CD_3OD) δ 2.94 (dd, J = 16.8, 6.1 Hz, 1H), 2.70 (d, J = 16.8 Hz, 1H), 1.92 (m, 1H), 1.49 (s, 3H), 1.07 (m, 1H), 0.44 (m, 1H).

*(±)-endo-1-Ethoxymethyl-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid (endo-**19q**) and (±)-exo-1-Ethoxymethyl-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]-pentalene-4-carboxylic Acid (exo-**19q**).* To a solution of ethoxymethyl)bicyclo[3.1.0]hexan-2-one (*exo*-**10q**:*endo*-**10q** = 10:1, 298 mg, 1.93 mmol) and diethyl oxalate (282 mg, 193 mmol) in EtOH (5 mL) was added potassium *tert*-butoxide (2.0 mL of a 1.0 M solution in THF, 2.0 mmol). The mixture was stirred for 5 h at rt, at which time hydrazine monohydrochloride (172 mg, 2.51 mmol) was added as a solution in water (1.5 mL). The mixture was stirred overnight, at which time 1N NaOH (3 mL) was added followed by stirring for an additional 2 h. The mixture was acidified with 1N HCl and purified by reverse-phase HPLC [Phenomenex Luna C18 column (10 μ, 250 mm × 21.2 mm), 5% (v/v) CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 95% H_2O, 20 mL/min, λ = 214 nm] to give *endo*-**19q** (6.0 mg, 0.027 mmol, 1% yield, 90% purity by ^1H NMR) followed by *exo*-**19q** (80.0 mg, 0.36 mmol, 19% yield), isolated as white solids after lyophilization. *endo*-Isomer: ^1H NMR ((400 MHz, DMSO-d_6) δ 3.30−3.15 (m, 2H), 3.01 (dd, J = 10.7, 6.8 Hz, 1H), 2.91 (dd, J = 10.7, 7.6 Hz, 1H), 2.80 (dd, J = 17.3, 6.8 Hz, 1H), 2.57 (d, J = 17.3 Hz, 1H), 2.35 (m, 1H), 2.24 (m, 1H), 1.45 (m, 1H), 1.00 (t, J = 7.0 Hz, 3H). LCMS (ESI^+): t_r = 1.42 min; m/z 223.2 $[M + H]^+$. *exo*-Isomer: ^1H NMR (400 MHz, DMSO- d_6) δ 13.50−12.03 (bs, 1H), 3.42 (q, J = 7.0 Hz, 2H), 3.35 (dd, J = 10.5, 6.2 Hz, 1H), 3.23 (dd, J = 10.5, 7.3 Hz, 1H), 2.84 (dd, J = 16.9, 6.2 Hz, 1H), 2.69 (d, J = 17.0 Hz, 1H), 2.09 (m, 1H), 2.03 (m, 1H), 1.11 (t, J = 7.0 Hz, 3H), 0.83 (m, 1H). LCMS (ESI^+): t_r = 1.56 min; m/z 223.2 $[M + H]^+$.

*(±)-exo-1-Methoxymethyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid (exo-**19o**).* (±)-*exo*-1-Hydroxymethyl-1a,3,5,5a-tetrahydro-1*H*-2,3-diaza-cyclopropa[*a*]-pentalene-4-carboxylic acid ethyl ester (*exo*-**18o**, 1.50 g, 6.75 mmol) was dissolved in DMF (20 mL), and K_2CO_3 (1.84 g, 13.5 mmol) was added followed by benzyl bromide (1.73 g, 10.1 mmol). The reaction stirred for 20 h at rt. The mixture was diluted with EtOAc, and the organics were washed with water and brine. The organics were dried over $MgSO_4$, filtered, and concentrated to dryness in vacuo. Purification by column chromatography (25−50% EtOAc/hexanes, silica) gave the *N*-benzylated product (300 mg, 1.04 mmol, 15% yield) as a white solid. A second slower eluting alternate *N*-benzyl regiosiomer was also isolated but not carried forward. Isomer 1: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 3H), 7.30 (m, 2H), 5.42 (d, J = 14.9 Hz, 1H), 5.29 (d, J = 14.9 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 3.14 (m, 1H), 2.91 (dd, J = 16.7, 6.3 Hz, 1H), 2.82 (d, J = 16.7 Hz, 1H), 2.03 (m, 1H), 1.67 (m, 1H), 1.37 (t, J = 7.1 Hz, 3H), 0.85 (m, 1H). LCMS (ESI^+): t_r = 2.11 min; m/z 313.2 $[M + H]^+$.

To a solution of the alcohol from above (300 mg, 1.04 mmol) in DMF (5 mL) was added NaH (88.0 mg of a 60% dispersion in mineral oil, g, 2.20 mmol) at 0 °C under N_2. The mixture was stirred for 10 min and methyl iodide (239 mg, 1.68 mmol) was added. The reaction mixture stirred at ambient temperature for 20 h, and quenched with water. The mixture was extracted with EtOAc (2 × 10 mL), and the combined organic layers were washed with water (10 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by column

chromatography (40% EtOAc/hexanes, silica) gave the corresponding methyl ether (150 mg, 0.460 mmol, 44% yield). LCMS (ESI^+): t_r = 2.65 min; m/z 327.4 $[M + H]^+$.

Air was bubbled through a stirring solution of the ether (75 mg, 0.23 mmol) and KO*t*-Bu (2.3 mL of a 1 M solution in THF, 2.3 mmol) in DMSO (2.5 mL) for 1 h at rt. The remaining THF was removed in vacuo, and the reaction was acidified by the addition of HCl (3 M aq). Purification by reverse-phase HPLC [Phenomenex Luna C18 column (10 μ, 250 mm × 21.2 mm), 5% (v/v) CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 95% H_2O, 20 mL/min, λ = 214 nm] to give title compound (*exo*-**19o**, 3.5 mg, 0.018 mmol, 8% yield, 92% purity by LC/MS) as a white solid after lyophilization. ^1H NMR (400 MHz, DMSO-d_6) δ 13.0 (br s, 1H), 3.31 (dd, J = 16.7, 6.4 Hz, 1H), 3.24 (s, 3H), 3.22 (dd, J = 10.5, 7.2 Hz, 1H), 2.84 (dd, J = 16.9, 6.2 Hz, 1H), 2.69 (d, J = 14.8 Hz, 1H), 2.09 (m, 1H), 2.04 (m, 1H), 0.84 (m, 1H). LCMS (ESI^+): t_r = 1.36 min; m/z 208.9 $[M + H]^+$.

*(R)-2-(Pent-3-enyl)oxirane (R-**5b**).* To a suspension of ethyltriphenylphosphonium bromide (5.57 g, 15.0 mmol) in THF (15 mL) at 0 °C was added lithium bis(trimethylsilyl)amide (15.0 mL of a 1 M solution in THF, 15.0 mmol). The solution was stirred for 0.5 h, at which time the (*R*)-5-(chloromethyl)tetrahydrofuran-2-ol (*R*-**29**, 1.00 g, 7.32 mmol) was added at 0 °C as a solution in THF (15 mL). The resulting solution was allowed to warm to rt and stirred overnight. The mixture was quenched with H_2O and extracted with Et_2O (2×), dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (1−5% Et_2O/pentane, silica) gave the title compound (*R*-**5b**, 467 mg, 4.16 mmol, 57% yield), an inseparable mixture of olefin isomers (*Z*:*E* = 2.3:1), as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.55−5.35 (m, 2H), 2.93 (m, 1H), 2.76 (m, 1H), 2.49 (dd, J = 6.0, 2.8 Hz, 1H from *Z*-isomer), 2.48 (dd, J = 6.0, 2.8 Hz, 1H from *E*-isomer), 2.21 (q, J = 7.6 Hz, 2H from *Z*-isomer), 2.14 (m, 2H from *E*-isomer), 1.67−1.53 (m, 5H).

*(1R,2R,5S)-6-Methylbicyclo[3.1.0]hexan-2-ol (1R,2R,5S-**9b**).* Prepared from (*R*)-2-(pent-3-enyl)oxirane (*R*-**5b**, *Z*:*E* = 2.3:1, 980 mg, 8.74 mmol) in a similar manner as described for the synthesis of *exo*-**9d**/*endo*-**9d** to give the title compound (1*R*,2*R*,5*S*-*endo*-**9b**:1*R*,2*R*,5*S*-*exo*-**9b** = 2:1, 647 mg, 5.77 mmol, 66% yield), an inseparable mixture of diastereomers, as a clear oil. *endo*-Isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 4.15 (d, J = 4.8 Hz, 1H), 2.08 (m, 1H), 1.75−1.25 (m, 5H), 0.92−0.85 (m, 4H). *exo*-Isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 4.21 (d, J = 4.8 Hz, 1H), 1.88 (m, 1H), 1.75−1.25 (m, 3H), 1.15 (m, 1H), 1.07 (m, 1H), 0.96 (d, J = 6.0 Hz, 3H), 0.41 (m, 1H).

*(1R,5S)-endo/exo-6-Methylbicyclo[3.1.0]hexan-2-one (1R,5S-**10b**).* Prepared from (1*R*,2*R*,5*S*)-6-methylbicyclo[3.1.0]hexan-2-ol (1*R*,2*R*,5*S*-*endo*-**9b**:1*R*,2*R*,5*S*-*exo*-**9b** = 2:1, 658 mg, 5.87 mmol) in a similar manner as described for the synthesis of *exo*-**10d**/*endo*-**10d** to give the title compound (1*R*,5*S*-*endo*-**10b**:1*R*,5*S*-*exo*-**10b** = 2:1, 580 mg, 5.26 mmol, 90% yield), an inseparable mixture of diastereomers, as a light-yellow oil. The ^1H NMR spectral data were identical to that of the racemic compounds *endo*-**10b** and *exo*-**10b** as shown previously.

*(1R,1aR,5aS)-1-Methyl-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (1aR,5aS-endo-**18b**) and (1S,1aR,5aS)-1-Methyl-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (1aR,5aS-exo-**18b**).* Prepared from 1*R*,5*S*-**10b** (1*R*,5*S*-*endo*-**10b**:1*R*,5*S*-*exo*-**10b** = 2:1, 570 mg, 5.18 mmol) in a similar manner as described for the synthesis of **18a**. Separation of the isomers was performed by reverse-phase HPLC [Phenomenex Luna C18 column (10 μ, 250 mm × 100 mm), 5% (v/v) CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 50% H_2O, 100 mL/min, λ = 254 nm] to give the *endo*-isomer (1a*R*,5a*S*-*endo*-**18b**, 211 mg, 1.02 mmol, 30% yield) followed by the *exo*-isomer (1a*R*,5a*S*-*exo*-**18b**, 78 mg, 0.38 mmol, 22% yield). The ^1H NMR spectral data for these compounds was identical to that of the racemic compounds *endo*-**18b** and *exo*-**18b** as shown previously.

*(1R,1aR,5aS)-1-Methyl-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid (1aR,5aS-endo-**19b**).* Prepared from 1a*R*,5a*S*-*endo*-**18b** by the general ester hydrolysis procedure. $[\alpha]^{25}_D$ + 67.6 (*c* 0.52, MeOH). The ^1H NMR spectral data was identical to the racemic material *endo*-**19b** shown previously. ^{13}C APT NMR (HCl salt, partial) (100 MHz, CD_3OD) δ up, 28.0, 20.4, 17.9, 7.1; down, 131.0, 22.9.

*(1S,1aR,5aS)-1-Methyl-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic acid (1aR,5aS-exo-**19b**).* Prepared from 1a*R*,5a*S*-*exo*-**18b** by the general ester hydrolysis procedure. The ^1H NMR spectral data was identical to the racemic material *exo*-**19b** shown previously.

*(1S,1aS,5aR)-1-Methyl-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (1aS,5aR-endo-**19b**) and (1R,1aS,5aR)-1-Methyl-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (1aS,5aR-exo-**19b**).* The title compounds were prepared as pure enantiomers from (*S*)-5-(chloromethyl)dihydrofuran-2(3*H*)-one (*S*-**29**) by the identical synthetic route as described for the preparation of 1a*R*,5a*S*-*endo*-**19b** and 1a*R*,5a*S*-*exo*-**19b** from *R*-**29**. Rotation data for 1a*S*,5a*R*-*endo*-**19b**: $[\alpha]^{25}_D$ − 93.0 (*c* 0.55, MeOH). Anal. Calcd for 1a*S*,5a*R*-*endo*-**19b** $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.49; H, 5.38; N, 15.57.

*(R)-4-(Hex-3-ynyl)-2,2-dimethyl-1,3-dioxolane (**30**).* To a flask cooled to −78 °C under N_2 was added 2-butyne gas via syringe needle until approximately ∼3 mL of liquid had condensed in the flask. THF (120 mL) was then added followed by DMPU (18.9 mL, 156 mmol). The flask was purged with N_2, and *n*-butyllithium (18.7 mL of a 2.5 M solution in hexanes, 46.9 mmol) was added via syringe over 5 min and stirred for an additional 15 min, at which time (*R*)-4-(2-iodoethyl)-2,2-dimethyl-1,3-dioxolane (*R*-**7**, 10.0 g, 39.1 mmol) was added as a solution in THF (30 mL). The reaction was slowly warmed to rt and stirred a total of 3 h. The mixture was quenched with satd NH_4Cl and extracted with Et_2O (2×). The organics were washed with H_2O and brine. Dried organics over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (5−15% EtOAc/hexanes, silica) gave the title compound (**30**, 5.92 g, 32.5 mmol, 83% yield) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.19 (m, 1H), 4.08 (dd, J = 8.0, 6.0 Hz, 1H), 3.58 (dd, J = 7.6, 6.8 Hz, 1H), 2.26 (m, 2H), 2.15 (qt, J = 5.2, 2.4 Hz, 2H), 1.81 (m, 1H), 1.68 (m, 1H), 1.40 (s, 3H), 1.36 (s, 3H), 1.11 (t, J = 7.6 Hz, 3H).

*(R,Z/E)-2-(Hex-3-enyl)oxirane (R-**5c**).* To a solution of (*R*)-4-(hex-3-ynyl)-2,2-dimethyl-1,3-dioxolane (**30**, 5.30 g, 29.1 mmol) in hexanes (80 mL) was added 5% palladium on $BaSO_4$ (928 mg), and quinoline (freshly distilled from Zn dust, 563 mg, 4.36 mmol). The flask was then purged with H_2 and stirred under an H_2 atmosphere for 2 h. The reaction mixture was filtered through Celite and washed sequentially with HCl (1*N* aq, 2×) and brine. The organics were dried over $MgSO_4$, filtered, and concentrated to give (*R*,*Z*/*E*)-4-(hex-3-enyl)-2,2-dimethyl-1,3-dioxolane (4.84 g, 26.3 mmol, 90% yield). This material contained approximately 8% of the inseparable *E*-isomer (data not shown). *Z*-isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 5.40 (m, 1H), 5.31 (m, 1H), 4.06 (m, 2H), 3.52 (t, J = 4.8 Hz, 1H), 2.09 (m, 4H), 1.71 (m, 1H), 1.54 (m, 1H), 1.41 (s, 3H), 1.35 (s, 3H), 0.96 (t, J = 7.6 Hz, 3H).

(*R*,*Z*/*E*)-4-(Hex-3-enyl)-2,2-dimethyl-1,3-dioxolane (4.84 g, 26.3 mmol) was stirred in AcOH/H_2O (4:1, 50 mL) at rt for 20 h. The mixture was concentrated in vacuo and purified by column chromatography (40−70% EtOAc/hexanes, silica) to give (*R*,*Z*/*E*)-oct-5-ene-1,2-diol (3.59 g, 24.9 mmol, 95% yield) as a clear oil. *Z*-isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 5.45 (m, 1H), 5.36 (m, 1H), 3.75 (m, 1H), 3.67 (dd, J = 10.8, 2.8 Hz, 1H), 3.45 (dd, J = 11.2, 7.6 Hz, 1H), 2.16 (m, 2H), 2.04 (m, 2H), 1.50 (m, 2H), 0.96 (t, J = 7.6 Hz, 3H).

To a solution of (*R*,*Z*/*E*)-oct-5-ene-1,2-diol (8.50 g, 58.9 mmol) in THF (230 mL) at 0 °C was added NaH (7.06 g of a 60% dispersion in mineral oil, 177 mmol) in portions over 5 min. The mixture was warmed to rt and stirred for 40 min. The reaction was recooled to 0 °C, and triisopropylbenzenesulfonyl imidazole (20.7 g, 61.8 mmol) was added. The reaction was warmed to rt, stirred for 1 h, and quenched H_2O. The mixture was extracted with Et_2O, and the organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (2−8% Et_2O/pentane, silica) gave the title compound (*R*-**5c**, 5.04 g, 40.0 mmol, 68% yield),[27]

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a clear oil, which contained approximately 8% of the *E*-isomer. *Z*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (m, 1H), 5.35 (m, 1H), 2.93 (m, 1H), 2.75 (dd, J = 5.2, 4.4 Hz, 1H), 2.49 (dd, J = 5.2, 2.8 Hz, 1H), 2.20 (q, J = 6.8 Hz, 2H), 2.06 (quin, J = 7.6 Hz, 2H), 1.59 (m, 2H), 0.97 (t, J = 7.6 Hz, 3H).

*Optional Enantioenrichment of (R,Z/E)-2-(Hex-3-enyl)oxirane (R-**5c**).* To (*R*,*Z*/*E*)-2-(hex-3-enyl)oxirane (*R*-**5c**, 84% *ee* material, 6.30 g, 49.9 mmol) was added THF (0.40 mL), (*R*,*R*)-Co-Salen (150 mg, 0.248 mmol), and AcOH (60 mg, 1.00 mmol). The flask was cooled to 0 °C, and H_2O (130 mg, 7.22 mmol) was added. The mixture was stirred in open air overnight, diluted with Et_2O, dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (2−10% Et_2O/pentane, silica) gave the title compound (*R*-**5c**, >96% *ee*, 3.00 g, 23.8 mmol, 48% yield).

*(1R,2R,5S)-6-Ethylbicyclo[3.1.0]hexan-2-ol (1R,2R,5S-**9c**).* Prepared from (*R*,*Z*/*E*)-2-(hex-3-enyl)oxirane (*R*-**5c**, 3.00 g, 23.8 mmol) in a similar manner as described for the synthesis of *exo*-**9d**/*endo*-**9d** to give the title compound (**1***R*,2*R*,5*S*-*endo*-**9c**:1*R*,2*R*,5*S*-*exo*-**9c** = 12:1, 647 mg, 5.77 mmol, 66% yield), an inseparable mixture of diastereomers, as a clear oil. *endo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (t, J = 5.6 Hz, 1H), 2.08 (m, 1H), 1.79−1.49 (m, 4H), 1.42 (d, J = 5.5 Hz, 1H), 1.37 (m, 1H), 1.22 (m, 2H), 0.96 (t, J = 7.6 Hz, 3H), 0.74 (1H, m). *exo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$, partial spectra of distinguishable peaks) δ 4.21 (t, J = 5.0 Hz, 1H), 1.90 (m, 1H), 0.36 (m, 1H).

*(1R,5S)-6-Ethylbicyclo[3.1.0]hexan-2-one (1R,5S-**10c**).* Prepared from (1*R*,2*R*,5*S*)-6-ethylbicyclo[3.1.0]hexan-2-ol (1*R*,2*R*,5*S*-*endo*-**9c**:1*R*,2*R*,5*S*-*exo*-**9c** = 13:1, 1.75 g, 13.9 mmol) in a similar manner as described for the synthesis of *exo*-**10d**/*endo*-**10d** to give the title compound (1*R*,5*S*-*endo*-**10c**:1*R*,5*S*-*exo*-**10c** = 12:1, 1.62 g, 13.0 mmol, 94% yield), an inseparable mixture of diastereomers, as a light-yellow oil. The ^{1}H NMR spectral data for 1*R*,5*S*-*endo*-**10c** was identical to that of the racemic compound *endo*-**10c**. The only distinguishable peak assigned to 1*R*,5*S*-*exo*-**10c** in the ^{1}H NMR (400 MHz, $CDCl_3$) spectra was a peak for the terminal methyl group at δ 0.99 (t, J = 7.4 Hz, 3H).

*endo/exo-(1aR,5aS)-1-Ethyl-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (1aR,5aS-endo/exo-**18c**).* Prepared from (*endo*-1*R*,5*S*-**10c**:*exo*-1*R*,5*S*-**10c** = 12:1, 1.62 g, 13.0 mmol) in a similar manner as described for the synthesis of **18a** to give the title compound (1a*R*,5a*S*-*endo*-**18c**:1a*R*,5a*S*-*exo*-**18c** = 12:1, 2.10 g, 9.53 mmol, 73% yield) as a mixture of diastereomers. The ^{1}H NMR spectral data for 1a*R*,5a*S*-*endo*-**18c** was identical to that of the racemic compound *endo*-**18c**. *exo*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$, partial spectra of distinguishable peaks) δ 2.95 (dd, J = 17.2, 6.2 Hz, 1H), 2.82 (d, J = 17.2 Hz, 1H), 1.99 (m, 1H), 1.91 (m, 1H), 0.65 (m, 1H).

*(1R,1aR,5aS)-1-Ethyl-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid (1aR,5aS-endo-**19c**) and (1S,1aR,5aS)-1-Ethyl-1a,2,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid Ethyl Ester (1aR,5aS-exo-**19c**).* Prepared from 1a*R*,5a*S*-*endo*/*exo*-**18c** by the general ester hydrolysis procedure. Separation of the isomers was performed by reverse-phase HPLC [Phenomenex Luna C18 column (10 μ, 250 mm × 50 mm), 5% (v/v) CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 50% H_2O, 60 mL/min, λ = 254 nm] to give gave 1a*R*,5a*S*-*endo*-**19c** followed by 1a*R*,5a*S*-*exo*-**19c**. The ^{1}H NMR and LCMS (ESI^+) data for 1a*R*,5a*S*-*endo*-**19c** was identical to that of the racemic compound *endo*-**19c**. *exo*-Isomer: ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.79 (dd, J = 17.2, 6.7 Hz, 1H), 2.48 (d, J = 17.2 Hz, 1H), 2.23 (m, 1H), 2.15 (m, 1H), 1.14 (m, 1H), 0.98 (m, 1H), 0.80 (t, J = 7.5 Hz, 3H), 0.71 (m, 1H).

*(R)-4-(5-Cyclopropylpent-3-ynyl)-2,2-dimethyl-1,3-dioxolane (R-**8**).* The title compound was prepared as a single enantiomer from (*R*)-4-(2-iodoethyl)-2,2-dimethyl-1,3-dioxolane (**R**-**7**) by the identical synthetic route as described for the preparation of **8** from racemic (±)-4-(2-iodoethyl)-2,2-dimethyl-1,3-dioxolane (**7**). The ^{1}H NMR spectral data for *R*-**8** was identical to that of the racemic compound **8**.

*(R,Z)-2-(5-Cyclopropylpent-3-enyl)oxirane (R-**5n**).* (*R*)-4-(5-Cyclopropylpent-3-ynyl)-2,2-dimethyl-1,3-dioxolane (*R*-**8**, 7.20 g, 34.6 mmol) was stirred in AcOH/H_2O (4:1, 25 mL) at rt for 20 h. The mixture was concentrated in vacuo, dissolved in THF (100 mL), and cooled to 0 °C. NaH (1.49 g of a 60% dispersion in mineral oil, 62.3 mmol) was added in portions over 5 min. The mixture was warmed to rt and stirred for 1 h. The reaction was recooled to 0 °C, and triisopropylbenzenesulfonyl imidazole (13.9 g, 41.5 mmol) was added. The reaction was warmed to rt, stirred for 1.5 h, and quenched with H_2O. The mixture was extracted with Et_2O, and the organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (7−14% EtOAc/hexanes, silica) gave (*R*)-2-(5-cyclopropylpent-3-ynyl)oxirane (4.00 g, 26.6 mmol, 77% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05 (m, 1H), 2.79 (dd, J = 5.0, 4.1 Hz, 1H), 2.54 (dd, J = 5.0, 2.7 Hz, 1H), 2.32 (tt, J = 7.1, 2.3 Hz, 2H), 2.20 (m, 2H), 1.72 (m, 2H), 0.89 (m, 1H), 0.44 (m, 2H), 0.20 (m, 2H).

To a solution of (*R*)-2-(5-cyclopropylpent-3-ynyl)oxirane (4.00 g, 26.6 mmol) in hexanes (50 mL) was added 5% palladium on $BaSO_4$ (567 mg) and quinoline (freshly distilled from Zn dust, 344 mg, 2.66 mmol). The flask was then purged with H_2 and stirred under an H_2 atmosphere for 2 h. The reaction mixture was filtered through Celite and washed sequentially with HCl (1N aq, 2×) and brine. The organics were dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (4−20% EtOAc/hexanes, silica) gave the title compound (*R*-**5n**, 3.40 g, 22.3 mmol, 84% yield) as a clear oil. The ^{1}H NMR spectral data were identical to the racemic material **5n** as shown previously.

*Enantioenrichment of (R,Z)-2-(5-Cyclopropylpent-3-enyl)oxirane (R-**5n**).* To (±)-(*Z*)-2-(5-cyclopropylpent-3-enyl)oxirane (*R*-**5n**, 2.00 g, 13.1 mmol) was added THF (0.50 mL), (*R*,*R*)-Co-Salen (11.2 mg, 0.020 mmol), and AcOH (15.7 mg, 0.26 mmol). The flask was cooled to 0 °C, and H_2O (250 mg, 13.9 mmol) was added. The mixture was stirred in open air overnight, diluted with Et_2O, dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (4−20% EtOAc/hexanes, silica) gave the title compound (*R*-**5c**, 1.50 g, 9.83 mmol, 75% yield) as a clear oil.

*(1R,1aR,5aS)-1-Cyclopropylmethyl-1a,3,5,5a-tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid (R,S-endo-**19n**).* The title compound was prepared as a single enantiomer from (*R*,*Z*)-2-(5-cyclopropylpent-3-enyl)oxirane (*R*-**5n**) by the identical synthetic route as described for the preparation of *endo*-**19n** from racemic (±)-(*Z*)-2-(5-cyclopropylpent-3-enyl)oxirane (**5n**). The ^{1}H NMR spectral data were identical to the racemic material *endo*-**19n** as shown previously.

*Multigram Scale Synthesis of (+)-(1aR,5aS)-1a,2,5,5a-Tetrahydro-1H-2,3-diaza-cyclopropa[a]pentalene-4-carboxylic Acid (R,R-**19a**).* To a solution of diethyl oxalate (71.3 mL, 525 mmol) in EtOH (1.00 L) under N_2 was added potassium *tert*-butoxide (551 mL of a 1.0 M solution in THF, 551 mmol). The mixture was cooled to 0 °C, and (1*R*,5*S*)-bicyclo[3.1.0]hexan-2-one (50.4 g, 525 mmol) was added as a solution in EtOH (150 mL) over 15 min. The mixture was warmed slowly to rt and stirred mechanically overnight. H_2O (approximately 100 mL) and HCl (6N aq, added until acidic, ~100 mL) were added followed by the addition of hydrazine monohydrochloride (39.5 g, 577 mmol). The mixture was mechanically stirred at rt for 12 h and concentrated in vacuo to approximately 300 mL in order to remove volatiles. The remaining material was partitioned between H_2O and EtOAc. The layers were separated, and the aqueous phase was back-extracted with EtOAc. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The resultant yellow solid was dissolved in dioxane (900) mL and H_2O (400 mL). Lithium hydroxide (25.1 g, 1.05 mol) was added, and the mixture was stirred overnight via mechanical stirrer and concentrated to approximately 300 mL. HCl (6N aq, added until acidic) was added, and a light-brown solid crashed out. The mixture was filtered, and the filtrate was extracted with EtOAc (2×). The filtrate was concentrated and combined with the light-brown solid. The crude solid was suspended in EtOAc/MeOH (20:1, approximately 500 mL), heated gently, and filtered to remove colored impurities. This process was repeated (2×). The remaining filtrates were combined, concentrated, and purified by reverse phase HPLC [Phenomenex Luna C18 column (10 μ, 250 mm × 100 mm), 5% (v/v) CH_3CN (containing 1% v/v TFA) in H_2O (containing 1% v/v TFA) gradient to 50% H_2O, 100 mL/min,

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λ = 254 nm]. The product was isolated by extraction from HPLC solvents with EtOAc, followed by brine wash, drying over $MgSO_4$, filtration, and concentration. In total, the pyrazole acid (*R,R*-**19a**, 53.4 g, 325 mmol, 62% yield) was obtained as a white solid (mp 238 °C). The LC/MS (ESI^+), and ^1H NMR spectral data were identical to the racemic material **19a** as shown previously. ^{13}C APT NMR (partial) (100 MHz, CD_3OD) δ up: 22.5, 14.7; down: 162.1, 161.0, 129.5, 126.2, 26.1, 16.5. IR (KBr) 3279, 3053, 2941, 2502, 1703, 1479, 1446, 1339, 1308, 1261, 1138, 1052, 1005, 943, 792 cm^{-1}. $[\alpha]^{25}_D$ + 37.5 (*c* 1.01, MeOH). Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.37; H, 4.82; N, 16.78.

Measurement of cAMP Inhibition. GPR109a with an N-terminal HA tag was cloned into pHM6 (Invitrogen) and GPR109a CHO stable cell lines were generated by G418 selection. Positive clones were selected by anti-HA immunostaining. Compound potencies were determined by the 384 well cAMP Dynamic2 homogenous time-resolved fluorescence (HTRF) assay from CisBio International as described by the manufacturer's one-step protocol. The HTRF cAMP assay was optimized for the GPR109 stable clone no. 46, 5 μM forskolin was used for stimulation, and 3700 cells were used for each well. Positive controls (200%) were defined as cAMP generated by 5 μM forskolin stimulated cells with 100 μM of niacin. Negative controls (100%) were defined as cAMP generated by 5 μM forskolin stimulated cells.

Rat Pharmacokinetics. Male Sprague–Dawley rats were dosed orally or intravenously at 10 and 2 mg/kg, respectively, in 80% PEG400 and 20% phosphate buffeted saline. Animals were fasted overnight prior to oral dose administration. Whole blood samples were collected from the jugular vein over a 24 h period postdose. Plasma was prepared from sodium heparin treated whole blood and separated by centrifugation. Plasma samples were assayed using a selective HPLC/MS/MS method. The HPLC/MS/MS was operated in multiple reaction monitoring (MRM) mode under optimized conditions for detection of selected compounds and the internal standard using positive ions formed by electrospray ionization. Quantitation was determined using a weighted regression analysis of peak area ratios of analyte and internal standard. This method provided a lower limit of quantitation of 1 ng/mL and an upper limit of quantitation of 2000 ng/mL. Serial sampling [at 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 15, 18, and 21 h post dosing] was used to define the plasma concentration vs time profile.

In Vivo Assays. Animals. Animal studies were performed according to the Guide for the Care and Use of Laboratory Animals published by the National Academy of Sciences (1996) and approved by the Arena Pharmaceuticals and Merck Research Laboratories Animal Care and Use Committees. All mice used were C57Bl/6 males, at least 8 weeks old (The Jackson Laboratories West, Sacramento, CA). Animals were housed under standard laboratory conditions with a 12 h dark, 12 h light cycle with constant temperature and humidity. Mice were fed a standard rodent diet and had ad libitum access to food and water.

In Vivo Mouse Lipolysis. Prior to study, mice were fasted for 16 h. Compound or vehicle (0.5% methylcellulose) was administered by oral gavage (po), and animals were euthanized 20 min postdose by CO_2 asphyxiation. Blood was collected via the inferior vena cava, anticoagulated in EDTA, and plasma separated by centrifugation on a tabletop microcentrifuge. Plasma was used for the measurement of FFA using an enzymatic method (NEFA C Free Fatty-Acid Assay; WAKO Chemicals USA, Richmond, VA) and for the measurement of compound levels by API-4000 LCMS/MS after acetonitrile precipitation.

In Vivo Mouse Vasodilation. Mouse vasodilation was measured by laser Doppler flowmetry as previously described.[22] Briefly, male C57/Bl6 mice (8–10 weeks old; ~25 g) were anesthetized with Nembutal via ip injection (80 mg/10 mL/kg). After 10 min, the mouse was placed under an LDPI laser Doppler (PeriScan PIM II; Perimed, Stockholm) and a needle and syringe containing vehicle (PBS; 40% hydroxypropyl-β-cyclodextrin (HPBCD) or 0.5% methylcellulose) or drug was placed in the intraperitoneal space and a slight back pressure was applied to prevent premature delivery of compound. The mouse's right ear was turned inside-out to expose the ventral side using forceps. The laser Doppler was focused in the center of the ventral right ear and adjusted as follows: repeated data collection, 15 × 15 image format, auto interval start, 20 s delay, medium resolution, very fast scan speed, and 8–9 V intensity (~4.5 cm from ear). After a 3 min baseline reading, vehicle or compound was administered into the ip space (5 mL/kg through the preinserted syringe) and readings continued for approximately 15 min. Vasodilation was expressed as "% change of perfusion over baseline values". At the end of the studies, mice were euthanized and a blood sample was collected by cardiac puncture and anticoagulated in EDTA. Plasma was obtained by centrifugation and used for determination of compound concentration by LC-MS/MS.

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Notes

The authors declare no competing financial interest.

ABBREVIATIONS USED

Tg, triglycerides; HDLc, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; VLDL-c, very low-density lipoprotein cholesterol; LiDBB, lithium 4,4′-di-*tert*-butylbiphenyl; TrisIm, triisopropylsulfonylimidazole; HKR, hydrolytic kinetic resolution

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