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Studies culminating in the total synthesis and determination of the absolute configuration of (−)-saudin

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ABSTRACT

A full account of studies that culminated in the total synthesis of both antipodes and the assignment of its absolute configuration of Saudin, a hypoglycemic natural product. Two approaches are described, the first proceeding though bicyclic lactone intermediates and related second monocyclic esters. The former was obtained via asymmetric Diels–Alder cycloaddition and the latter by an asymmetric annulation protocol. Both approaches employ a Lewis acid promoted Claisen rearrangement, with the successful approach taking advantage of bidentate chelation to control the facial selectivity of the key Claisen rearrangement.

1. Introduction

Saudin (**1**) was isolated by Mossa et al. in 1985 from *Clutya Richardiana*, and its structure and relative stereochemistry was elucidated by X-ray crystallography.[1] However, the absolute stereochemistry remained unknown.[1] Saudin (**1**) was presumed to be a member of the *Labdane* class of diterpenes.[1,2] Based upon biogenetic considerations, the configuration shown in Fig. 1 was tentatively assumed, although *Labdane* terpenes of both enantiomeric series have been found in nature.[3] In Saudin (**1**), the *Labdane* skeleton has been highly modified by late stage biogenetic oxidation and rearrangement.[1,2] The skeleton is highly oxygenated and presents five contiguous stereogenic centers, three of which (C_{13}, C_9, and C_{16}) are contiguous quaternary centers, two of which are all carbon and 1,3-disposed on a six-membered ring. The natural product was found to exhibit interesting biological activity. Treatment of laboratory animals that had been rendered chemically hyperglycemic resulted in lowering blood sugar levels although the mechanism of action remains unknown. Based on these studies, Saudin (**1**) was thought to have possible therapeutic value or serve as a lead structure in the development of treatments for diabetes.[1,2]

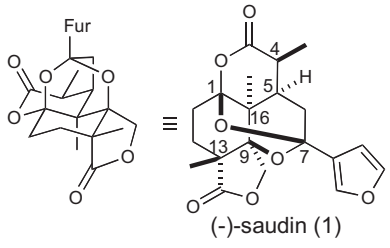

Fig. 1. (-)-Saudin.

Several groups have investigated the preparation of this interesting and challenging natural product. Initial model studies followed by a concise total synthesis of the racemate were reported by Winkler in 1998–1999.[3,4] In 2002, we reported the first enantioselective total synthesis of both antipodes, firmly establishing the absolute stereochemistry of natural (−)-saudin, as the structure depicted in Fig. 1.[5] Subsequent to that publication, several additional synthetic approaches have appeared including the studies of Labadie[6–8] and Stoltz.[9,10] Herein we wish to report the details of our studies that established a strategy and culminated in the total synthesis of natural (−)-saudin (**1**) and its antipode.

2. Results and discussion

2.1. Retrosynthetic analysis

Our retrosynthetic analysis, arbitrarily directed to what is now recognized as the antipode of natural (−)-Saudin (**1**), began with

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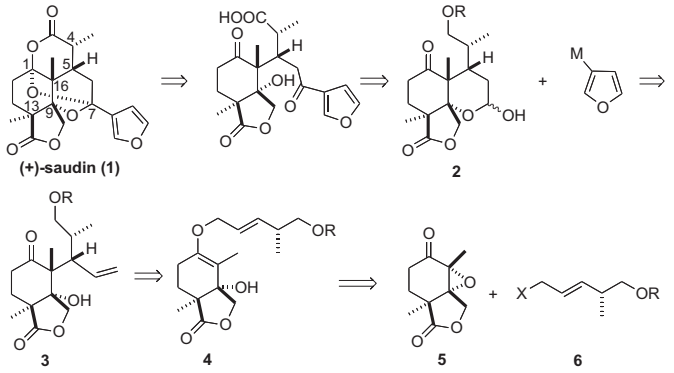
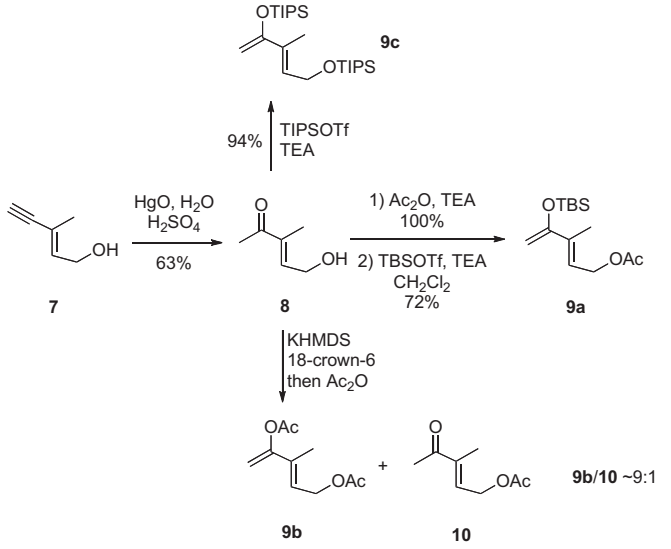
the sequential disconnection of the internal ketal unit and the furan revealing lactol **2**. Functional group modifications of **2** revealed γ,δ-enone **3**, the product of a putative Claisen rearrangement of bicyclic allyl vinyl ether **4**. Enol ether **4** was expected to be available by O-alkylation of the enolate dianion derived from enantiomerically pure epoxylactone **5** and an enantiomerically pure allyl electrophile (halide, sulfonate, or triflate) as shown in Scheme 1. The Claisen rearrangement was identified as the key transformation in this sequence owing to the expected large driving force for rearrangement permitting the stereoselective creation of the required 1,3-disposed quaternary carbon centers at C_{13} and C_{16} of Saudin (**1**).



Scheme 1.

2.2. Assembly of epoxy ketone 5

A route to epoxy ketone **5** employing an asymmetric Diels–Alder reaction was first investigated.[11,12] A chiral auxiliary was employed to afford control over the absolute configuration of the quaternary center eventually residing at C_{13}. Three dienes of general structure **9**, bearing both silicon and ester protecting groups (TBS acetate **9a**, bis-acetate **9b**, and bis-OTIPS **9c**) were prepared from common intermediate **8**, itself derived from commercially available alkyne **7** by mercury catalyzed hydration (Scheme 2). Formation of bis-acetate **9b** was incomplete affording a small amount (10%) of **10**.



Scheme 2.

Attempted cycloaddition of dienophile **11** with **9a**–**c** in the presence of a variety of Lewis acids and also under thermal conditions failed repeatedly, probably resulting from steric hindrance owing to the presence of the vinylic methyl group, which disrupted orbital overlap (Fig. 2). To overcome these problems a different camphor-derived dienophile **12** was designed. Chelated **12** should exist in the conformation depicted in Fig. 3, avoiding steric interactions between the vinylic methyl substituent and the angular proton. The β face of the complex appears congested by the *gem*-dimethyl bridge and by interaction with the bridgehead proton. Thus attack of the diene should occur primarily from the bottom α face of the dienophile complex. This assumption was confirmed by NOE experiments in the presence of $TiCl_4$.

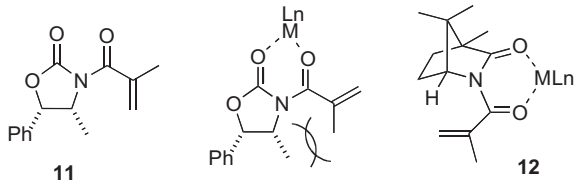


Fig. 2. Destabilizing allylic strain.

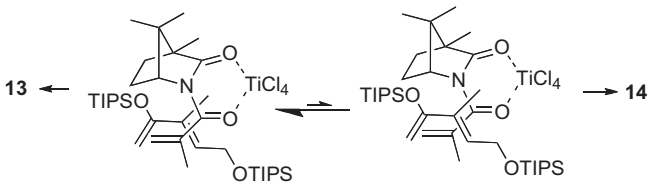
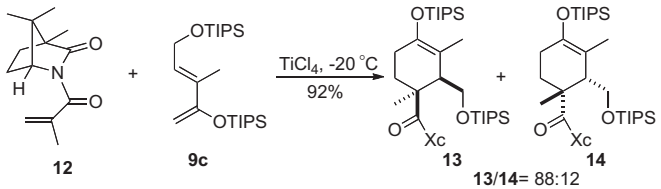


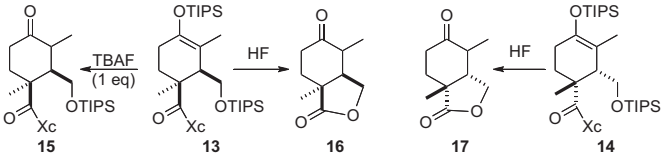
Fig. 3. Transition states for enantioselective Diels Alder reaction.

The reaction was carried out in the presence of $TiCl_4$. Bis triisopropyl ether derivative **9c** gave best results and adducts **13** and **14** (Scheme 3) were isolated in 92% yield (ratio **13**/**14**=88:12). The temperature proved to be critical since no reaction took place at −40 °C while hydrolysis of the diene occurred at −10 to 0 °C.



Scheme 3.

The stereochemistry of major isomer **13** was elucidated by X-ray analysis after cleavage of the silyl enol ether to afford crystalline ketone **15** (Scheme 4).[11] The observed stereochemistry is in agreement with the expected transition state wherein the diene approaches the imide in an *endo* orientation from the less hindered α face (Fig. 3).

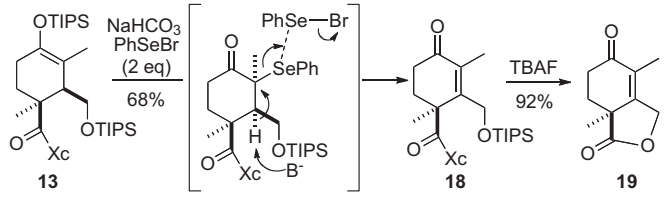


Scheme 4.

Both silyl groups of adduct **13** could be cleaved with HF affording directly keto lactone **16** (Scheme 4). Similar deprotection of the minor adduct **14** afforded lactone **12**, spectroscopically identical to **16** but exhibiting equal and opposite optical rotation, confirming

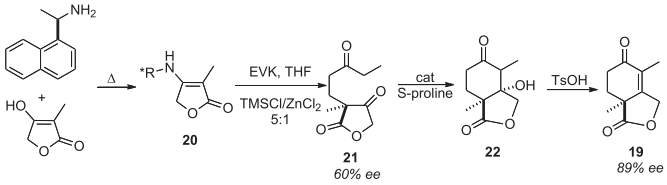
that **16** and **17** were enantiomeric and that both **16** and **17** were *endo* adducts derived from approach of the diene from the α and β face of the dienophile-LA complex, respectively (Fig. 3).

Major isomer **13** was transformed into the desired enone **19** using a two-step sequence. Although attempted Saegusa reaction on the silyl enol ether failed, treatment with 2 equiv of phenyl selenyl bromide afforded the unsaturated derivative **18** (a second molecule of PhSeBr probably reacts with the corresponding α-seleno derivative with elimination of diphenyldiselenide, making the oxidation step unnecessary). Subsequent deprotection of the primary silyl ether with TBAF, with concomitant lactonization, gave **19** in optically pure form (Scheme 5).[12b,13]



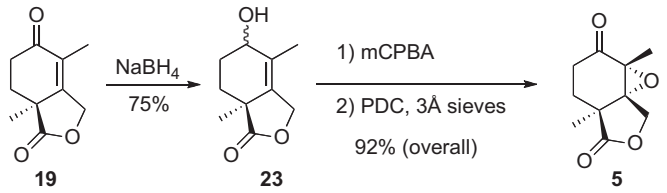
Scheme 5.

Alternatively, lactone **19** could be obtained by Michael addition of chiral vinylogous carbamates **20** derived from methyl tetronic acid to ethyl vinyl ketone affording Michael adduct **21** after hydrolytic workup. The enantiomeric excesses were modest (60% ee as illustrated for α-methyl naphthyl amine) but employing *S*-proline in the cyclization of diketone **21** to hydroxy ketones **22** allowed us to enhance the ee to an acceptable 89% (Scheme 6).[12b] Several chiral imines and Lewis acids were examined in an attempt to improve the selectivity in the Michael addition but all efforts were unsuccessful.



Scheme 6.

With enone **19** in hand we explored epoxidation of **19** to epoxy ketone **5** (Scheme 7). The lability of the γ-lactone ring under basic conditions precluded the use of the usual methods for nucleophilic epoxidation of **19**. Alternatively, reduction of **19** with $NaBH_4$ afforded a mixture of allylic alcohols **23** in 75% yield. Epoxidation of the mixture **23** with *m*-CPBA afforded the expected intermediate epoxy alcohols, which were directly reoxidized with PDC to afford epoxy ketone **5** as a single diastereomer in 92% overall yield.[12,13] Apparently, the concave surface of **23** is sufficiently congested that approach of *m*-CPBA is precluded in spite of the well-known directing effects of allylic hydroxyl groups on the stereochemistry of epoxidation.[14]



Scheme 7.

2.3. Preparation of the enantiomerically pure sidechain triflate 6 (X=OTf)

The alkenyl sidechain was prepared using the conventional sequence depicted in Scheme 8, starting from commercially available Roche ester **24**.[15] Protection of the primary alcohol as TBDPS ether followed by reduction of the carboxylic ester with DIBAl-H, gave alcohol **25**. Oxidation of **25** to the unstable aldehyde and direct reaction with isopropyl diethylphosphonoacetate afforded unsaturated ester **26** in 69% yield from **24**. Reduction of **26** with DIBAl-H afforded the allylic alcohol **27** in 90% overall yield. The corresponding triflate **6** (X=OTf) was prepared in situ by deprotonation with *n*-BuLi and reaction with triflic anhydride in an estimated >90% yield by NMR.[12,13] The allylic triflate proved to be too reactive to be isolated, thus it was generated and used in situ at low temperature.

To assure that the optical purity was maintained during preparation of **6** (X=OTf), the Mosher ester of **27** was prepared, but the resolution of the signals for the two isomers was insufficient for NMR analysis. Thus, ester **26** was degraded (ozonolysis followed by reduction) to alcohol **25** and esterification gave a single isomer of the corresponding Mosher ester (similar derivatization of racemic **25** gave a mixture of two isomers that showed different spectroscopic properties).[12]

An analogous, simpler alkenyl sidechain, lacking the secondary methyl group, was also prepared starting with **28** using the sequence depicted in Scheme 9. The alkynol **28**, after protection of the primary alcohol, was alkylated with *para*-formaldehyde to afford **29** in 85% overall yield. The triple bond was then reduced with LAH and EtOH in THF to give exclusively the *E* allylic alcohol **30** in 96% yield that was similarly activated in situ as the triflate **31** (>90%).[12]

2.4. Reductive coupling of epoxy ketone 5 and triflate 6

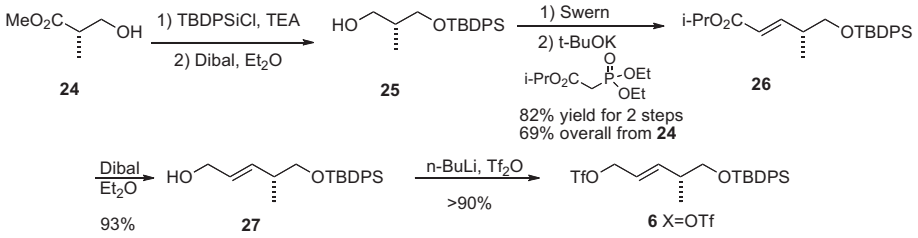
Preliminary studies of the reduction and concomitant trapping of epoxy ketone **5** with electrophiles established that the usual one electron reductants, such as Li/NH_3,[16] Li napthalenide,[17] and Li di-*tert*-butylbiphenylide[18] were too basic and/or nucleophilic, resulting in either degradation of **5** or reduction/elimination back to the enone **19**.

Examination of the literature revealed a little used one electron reductant, Li or Na trimesitylborylide (Li^+ or Na^+ TMB), originally developed by Darling, based on early work of Brown and others, as an alternative to Li/NH_3 for reduction of enones and related unsaturated compounds.[19,20] Although Darling envisioned trimesitylborane (TMB) more as a medium supporting such reductions, we found that Na^+ TMB can be generated stoichiometrically by stirring of Na metal (5 equiv) with TMB (2.0 equiv) in anhyd THF at rt for 8 h producing an intensely blue colored solution. Addition of epoxy ketone **5** (1 equiv) to this solution at −78 °C and stirring at −78 °C for 24 h followed by quenching with aq NH_4Cl afforded the hydroxy ketone **22**. Alternatively, quenching with TBDMSCl (5 equiv) afforded hydroxy silyl enol ether **32** upon workup in 71% yield (Scheme 10).[12b]

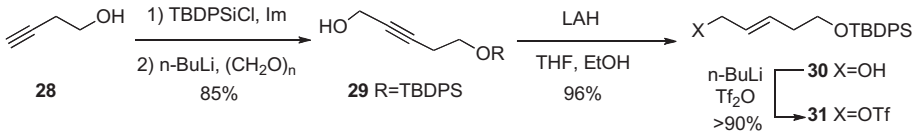
O-Allylation of hydroxyenol dianion could also be effected by quenching with allyl bromide/HMPA then pH=7 phosphate buffer affording the corresponding *O*-allyl hydroxyenol ether in 64% yield. Analogously, in situ mono trapping of the presumed enolate alkoxide dianion with triflate **6** in the presence of HMPA proceeded to afford allyl hydroxyenol ether **33** in 52% yield (unoptimized), as depicted in Scheme 10.[12b]

2.5. Introduction of the C_{16} quaternary carbon via Claisen rearrangement

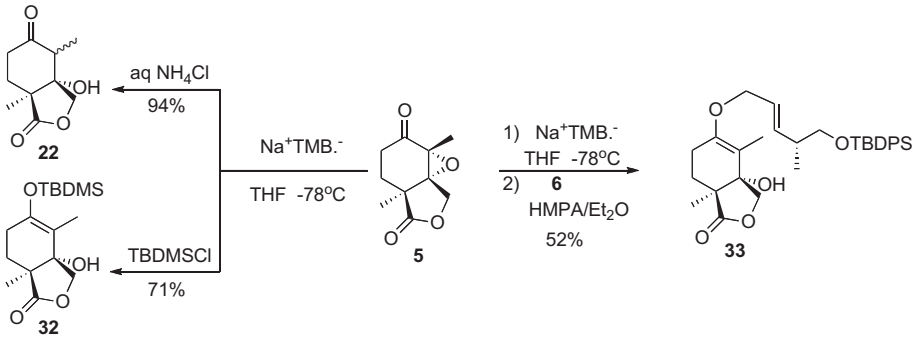
Regrettably, no reliable conditions were found to effect the desired thermal or Lewis acid promoted Claisen rearrangement of **33**. The principal products resulted from degradation back to enone **19** and allylic alcohol **27**. This outcome likely results from autocatalytic



Scheme 8.



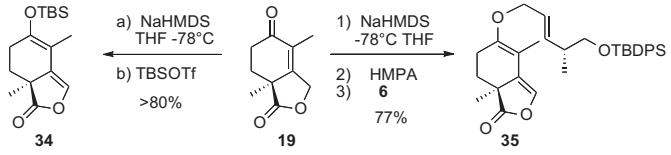
Scheme 9.



Scheme 10.

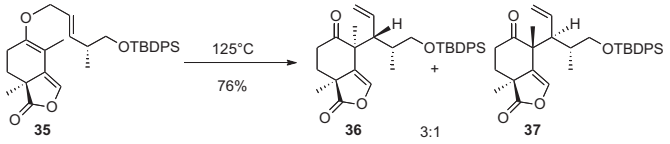
decomposition of **33** initiated by elimination of a catalytic amount of water from **33** and hydrolysis of the remaining **33** to **22** and alcohol **27** and subsequent elimination of water from **22** to afford **19** and regenerate the catalytic amount of water.

As a result, the sequence was modified by use of an allyl dienol ether lacking the labile C_9 hydroxyl group. The linearly conjugated enolate was smoothly generated by slow addition of NaHMDS in THF to enone **19** in THF at −78 °C, as demonstrated by trapping with TBSOTf affording **34**, exclusively, in good yield (Scheme 11).[12a,13]



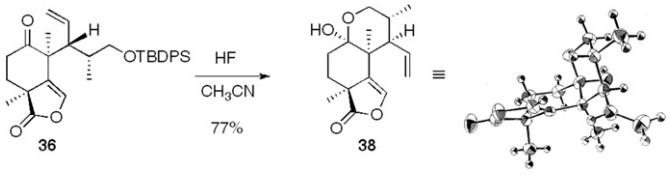
Scheme 11.

Having confirmed the exclusive formation of the linearly conjugated dienolate from **19**, treatment of that linear Na enolate derived from **19** with HMPA followed by allylic triflate **6** at −78 °C afforded the *O*-allylated dienol ether **35** in 77% yield. We were pleased to see that the desired thermal Claisen rearrangement of **35** now proceeded smoothly upon heating **35** for 2 h at 125 °C providing a 3:1 mixture of diastereomeric Claisen rearrangement products **36** and **37** in 76% yield (Scheme 12). Since the ketones **36** and **37** are substrates for a Cope rearrangement, prolonged heating or higher temperatures had to be avoided to prevent the undesired tandem



Scheme 12.

Claisen–Cope rearrangement of **35**.[21] Indeed, when Claisen rearrangement was conducted at temperatures exceeding 125 °C variable amounts of the product(s) of tandem Claisen–Cope rearrangement were isolated. At temperatures exceeding 150 °C, the product(s) of tandem Claisen–Cope rearrangement became predominant or exclusive as the temperature was increased. After chromatographic separation of **36** and **37**, the structure and relative stereochemistry of **36** was confirmed by single crystal X-ray analysis of crystalline ketol **38**, obtained by desilylation of **36** with HF in acetonitrile in 77% yield (Scheme 13). Unfortunately, the Claisen rearrangement of **35** had afforded as the major diastereomer **36**, the undesired diastereomer for conversion to Saudin (**1**). We reasoned



Scheme 13.

that steric interactions involving the methyl substituent of the allylic chain could be held responsible for this preference (Fig. 4).[12a,13]

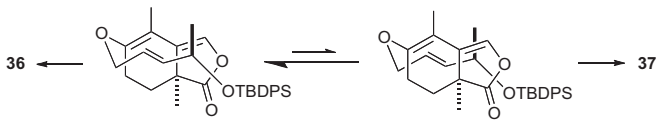
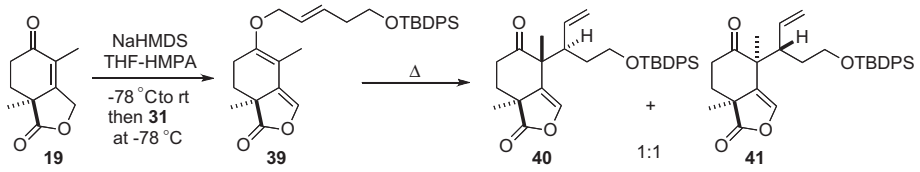


Fig. 4. Transition states for thermal Claisen rearrangement of **35**.

Assuming that introduction of the methyl group by alkylation at C_4 would not be problematic at a later stage, we reasoned that this steric interaction should be minimized when **31** was utilized as electrophile. The O-alkylation of **19** was done under the same conditions specified above. Subsequent thermal rearrangement of **39**, unfortunately, did not markedly improve the observed diastereoselectivity for the desired diastereomer **40** affording a 1:1 mixture of **40** and **41** (Scheme 14). Again, high temperatures had to be avoided to prevent formation of the products of the competing tandem Claisen–Cope process.[21] Adducts **40** and **41** were deprotected as before with HF in acetonitrile and readily separated chromatographically to provide free hydroxy ketone **42** and an uncharacterized desmethyl analog of **42** whose configurations were assigned by analogy to **36** and **37**. The direction in the change in the observed facial selectivity (from 1:3 to 1:1) was in agreement with our reasoning, but the magnitude was less than anticipated, revealing the primary controller of the stereoselectivity was the C_{13} quaternary center with a lesser contribution from the sidechain stereocenter.[13]



Scheme 14.

We then investigated Lewis acid promoted rearrangements of both substrates (**35** and **39**) with the hope that coordination with a Lewis acid would favorably alter the stereochemical outcome of the Claisen rearrangements of these substrates. The results of these studies are summarized in Table 1.[13]

Table 1
Evaluation of Lewis Acid promoters of the Claisen rearrangement of **35**.

Entry	Substrate	Lewis acid (equiv)	Time (h)	Temp (°C)	**36**/**41**:**37**/**40**[a] (yield)
1	**39**	None	2	105	1:1 (81%)
2	**39**	*i*-Bu_3Al (2)	18	25	2:1 (33%)[b]
3	**39**	Me_3Al (2)	0.9	25	3:1 (90%)
4	**39**	MAD* (4)	2	25	2.5:1 (88%)
5	**39**	$Et_2AlCl{\cdot}Ph_3P$ (2)	1.5	−50	4:1 (57%)[c]
6	**39**	$Et_2AlCl{\cdot}Ph_3P$ (2)	0.5	25	5:1 (94%)
7	**35**	None	2	125	3:1 (76%)
8	**35**	Me_3Al (2)	0.2	45	24:1 (60%)[d]
9	**35**	MAD* (4)	2	25	24:1 (43%)[d]
10	**35**	$Et_2AlCl{\cdot}Ph_3P$ (2)	0.5	25	24:1 (39%)[d]

[a] Total yield of isolated chromatographically pure materials.
[b] Yield adjusted for conversion of 67%.
[c] Yield adjusted for conversion of 30%.
[d] Yields unoptimized for these cases.

The optimal Lewis acid for rearrangement of **35** and **39** was found to be the 1:1 complex of Et_2AlCl and Ph_3P, which provided high yields and clean products at rt. The stereoselectivity in the rearrangement of **39** appears to increase both with increasing steric bulk of the ligands on the Lewis acid, and with increasing electron deficiency of the Lewis acidic center. Under optimal conditions, using $Et_2AlCl{\cdot}PPh_3$, the selectivity rises to 1:5 (**40**/**41**). In the case of **35** the synergism of the two asymmetric centers combine to overwhelm the magnitude of the effects owing to the nature of the Lewis acid affording a remarkable enhancement from 3:1 to 24:1 (**36**/**37**) in all cases. However, in all cases the effect of the Lewis acid promotion is to increase the selectivity toward the undesired diastereomers rather than reverse the diastereoselectivity as hoped.A plausible mechanistic rationale is shown in Fig. 5. As illustrated, these results do not invalidate the previous mechanistic hypotheses, however they do indicate that kinetic and irreversible complexation of the Lewis acid is unlikely. These results further demonstrate that the interaction of the allylic sidechain with the C_{13} methyl group dominates the diastereoselectivity in the rearrangements of **35** and **39**, regardless of the presence or absence of the secondary methyl group or the use of Lewis acid promoters.[13]

2.6. Elaboration of Claisen adduct 40 toward saudin (1)

Based on the idea that increasing the diastereoselectivity of the Claisen rearrangement could be deferred until evidence was accrued that the synthetic approach was likely to afford Saudin (**1**), further elaboration of ketone **40** was then undertaken. Ketone **42** was obtained in 43% yield by deprotection of the **40**/**41** mixture with HF in CH_3CN. After Jones oxidation of **42** to the corresponding acid and iodolactonization, iodolactone **43** was rearranged in two steps to afford tricyclic intermediate **44** in 35% overall yield. Epoxidation with *m*-CPBA unexpectedly gave the undesired β isomer **45**, whose structure was corroborated by X-ray crystallographic analysis (Scheme 15).[12a]

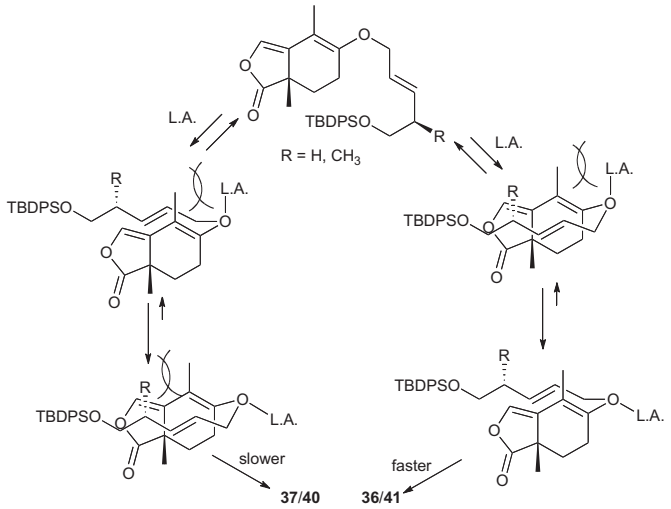
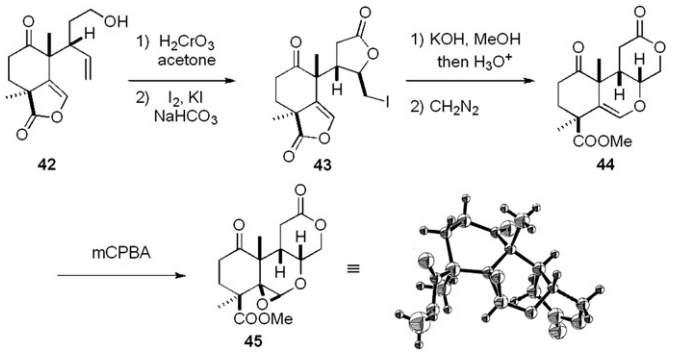


Fig. 5. Transition states for Lewis acid promoted Claisen rearrangement of **35**.

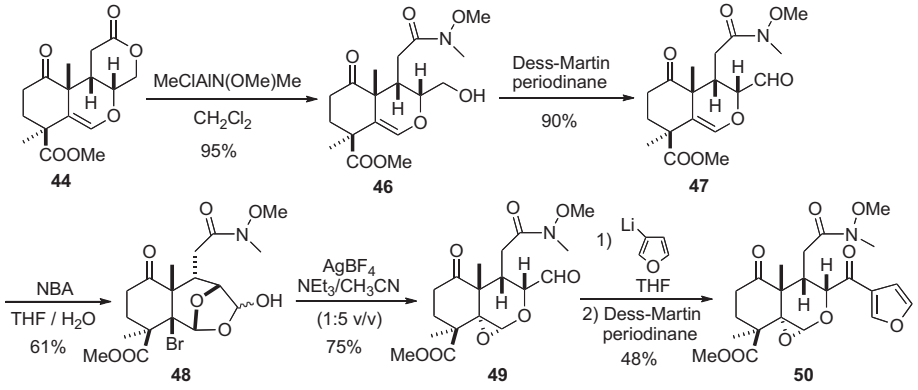
A less direct route was then devised to install the oxygen function at C_9, a fully substituted position, with the correct stereochemistry in a substrate suitable for the incorporation of the furan ring (Scheme 16). The sequence begins with conversion of enol lactone **44** to Weinreb amide **46** in 95% yield.[22] Oxidation of **46** with Dess–Martin periodinane[23] provided aldehyde **47** in 90%



Scheme 15.

To implement this approach, we required the monocyclic enone **51** rather than **19**. To assess the viability of the new route, early intermediates were initially prepared in racemic form (Scheme 17).[26] Michael addition of ethyl 2-methylacetoacetate to ethyl vinyl ketone, catalyzed by NaOMe, afforded diketone **52**, that was converted without purification to the desired **53** along with its regiosiomer **54** (**53**/**54** ~4:1) by treatment with pyrrolidinium acetate. Since keto esters **53** and **54** were inseparable, basic hydrolysis and neutralization during which the undesired beta-keto acid derived from **54** underwent decarboxylation, afforded only the pure acid **55**, which was then re-esterified under basic conditions to afford enone **51** in 50% overall yield from ethyl 2-methylacetoacetate (Scheme 17).[26c]

Highly enantiomerically enriched (−)-**51** was obtained using chiral vinylogous carbamate (+)-**56** as starting material.[27] Michael



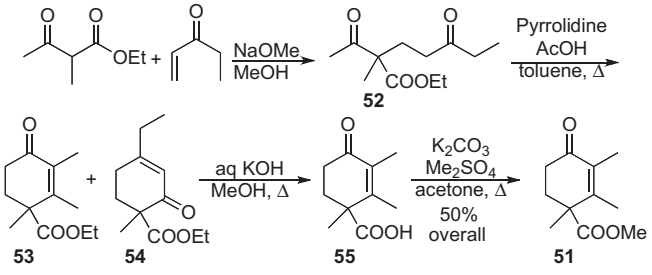
Scheme 16.

yield. Exposure of aldehyde **47** to *N*-bromoacetamide in aq THF affords a mixture of bromo hemiacetals **48** (6:1 α:β) in 61% yield via addition of the electrophilic bromine from the β face as expected based upon the observed stereochemistry of epoxidation of **44**.[24] Exposure of **48** to $AgBF_4$ in the presence of Et_3N then provided the desired α-epoxy aldehyde **49** by silver induced ionization and concomitant epoxide formation with inversion at C_9. Addition of 3-lithio furan[25] to aldehyde **49** affords, again after oxidation of the intermediate mixture of alcohols with Dess–Martin periodinane,[23] the desired 3-furyl ketone **50** in 48% overall yield (unoptimized) from **49**.

Unfortunately efforts to further elaborate furyl ketone **50** by initial reductive deoxygenation of the α-keto ether linkage were unsuccessful. Although cleavage of the desired C–O bond could be successfully accomplished, the resulting ketone enolate underwent undesired intramolecular aldol processes more rapidly than quenching of the enolate by protonation occurred leading to indane derivatives. Attempts to effect reductive scission of the C–O bond under acidic conditions were also unsuccessful.

2.7. A revised synthetic approach utilizing precursors lacking the γ-lactone

In order to better control the diastereoselectivity of the key Claisen rearrangement, a modified retrosynthetic analysis was then devised that retained a Claisen rearrangement as the key step but employed substrates with more conformational freedom by removal of the fused γ-lactone ring. It was hoped that the increased conformational freedom would permit alteration of the reactive conformation of the enol ring by use of a Lewis acid capable of chelation between the enol oxygen and the carbonyl of the ester group at C_{13}.

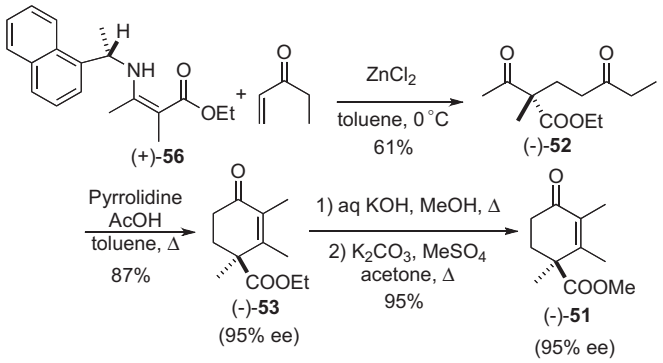


Scheme 17.

addition of (+)-**56** to ethyl vinyl ketone in toluene at 0 °C in the presence of $ZnCl_2$ afforded diketone (−)-**51** in 61% yield. Diketone (−)-**51** (>90% ee) was purified prior to cyclization. As a result, treatment of (−)-**51** with pyrrolidinium acetate under reflux afforded principally (−)-**53** (95% ee) with improved regioselectivity (**53**/**54** ~18:1) in 87% yield.[26c] Although the saponification–reesterification steps were unnecessary, the methyl ester (−)-**51** was prepared for ease in NMR analysis (Scheme 18).[26c]

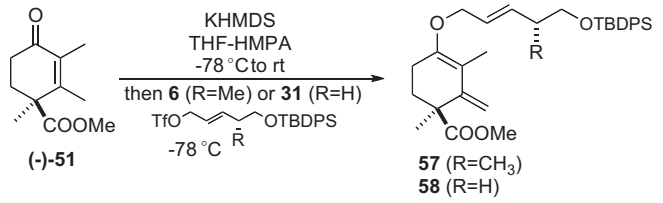
The absolute configuration of (−)-**51** was deduced from the mechanism of the Michael addition, since the sense of the chiral induction is well known. Furthermore, it was confirmed by transformation of lactone (+)-**19** (Scheme 5) into ethyl ester (−)-**53**. Also by derivatization of carboxylic acid *R*-(+)-**52** with *R*-(+)-α-methyl benzyl amine, which afforded a crystalline amide whose structure was corroborated by single crystal X-ray analysis.

By analogy to the enolization of enone **19**, the thermodynamic enolate derived from (−)-**51** was *O*-alkylated with allylic triflate **6** to afford Claisen precursor **57** (40% isolated yield) along with *C*-



Scheme 18.

alkylated by-products. When **31** was used as electrophile the corresponding enol ether **58** was obtained in 65% yield (Scheme 19).



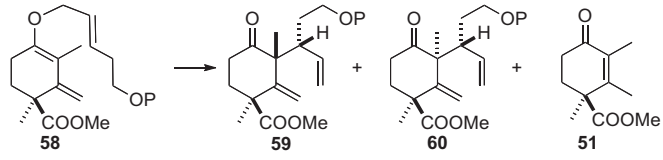
Scheme 19.

2.8. Claisen rearrangement of monocyclic substrates

We envisioned that use of a bidentate Lewis acid to promote the Claisen rearrangement of **57** and **58** would allow coordination of both oxygens (those of the vinyl ether and the ester) forcing the six-membered ring into a boat conformation, favoring the axial approach from the bottom face as required.[28]

Initial experiments were conducted using both substrates (**57** and **58**) to identify the best conditions for the [3,3]-sigmatropic rearrangement. $TiCl_4$ was employed as the Lewis acid. The results in terms of reactivity and diastereoselectivity were in agreement with those obtained previously (see Table 1).[13] Methylated analog **57** afforded mixtures of isomers along with several by-products including large amounts of enone (+)-**51**. This decomposition pathway could not be avoided by introducing additives such as bases, Ph_3X (X=P, As, Sb), R_3Al, etc. or by use of less reactive Ti(IV) Lewis acids.

In contrast, the desmethyl analog, allyl enol ether **58**, upon treatment with 2.5 equiv of $TiCl_4$, was cleanly converted into Claisen adducts **59** and **60** with very good facial selectivity (**59**/**60** ~10:1 at −78 °C) along with (+)-**51** (Scheme 20). We then attempted optimization of this transformation. We noted that addition of Me_3Al as proton scavenger minimized decomposition to the enone without interfering with the stereochemical outcome as did increasing the reaction temperature, but, in the latter case, the diastereoselectivity exhibited in formation of **59** and **60** was adversely affected (**59**/**60** ~5:1 at −30 °C). The influence of the solvent was also examined resulting in the finding that less polar solvents (such as hexanes or toluene) retarded the Claisen reaction, promoting the formation of



Scheme 20.

51 and **22**, while the use of THF inhibited both processes, leading to recovery of starting ether **58**. To our delight, our studies led to optimized conditions involving the use of 2.5 equiv of $TiCl_4$ and 2.5 equiv of Me_3Al in CH_2Cl_2 at −65 °C that permitted rearrangement of (−)-**58** cleanly affording a 75% isolated yield of the desired isomer (−)-**59**, having the correct relative stereochemistry between the two quaternary centers C_{13} and C_{16}, and a sidechain sufficiently functionalized for further elaboration.

The observed facial selectivity can be rationalized by invoking bidentate coordination of Ti(IV) to the oxygen atoms of the starting material, stabilizing a boat conformation in which the reaction leading to the major isomer takes place axially, as preferred stereoelectronically, and from the less hindered α face (**TS I** vs **TS II**, Fig. 6).[28]

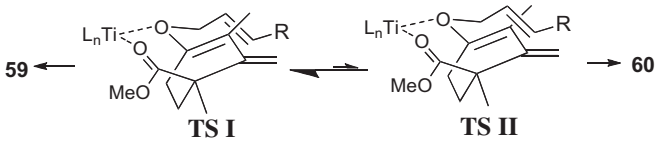
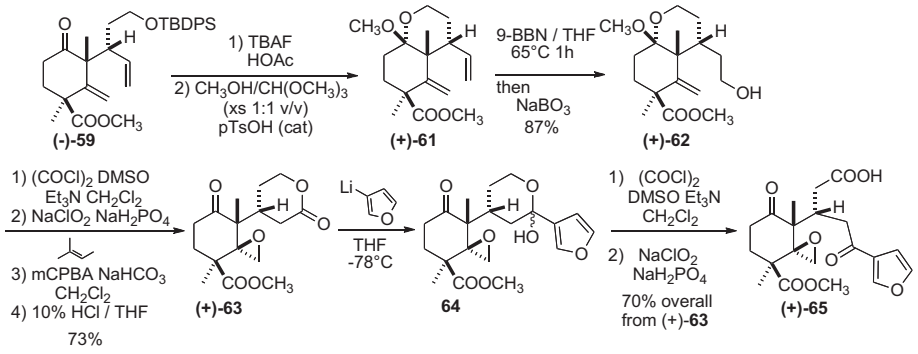


Fig. 6. Transition states for $TiCl_4$ promoted Claisen rearrangement of **57** and **58**.

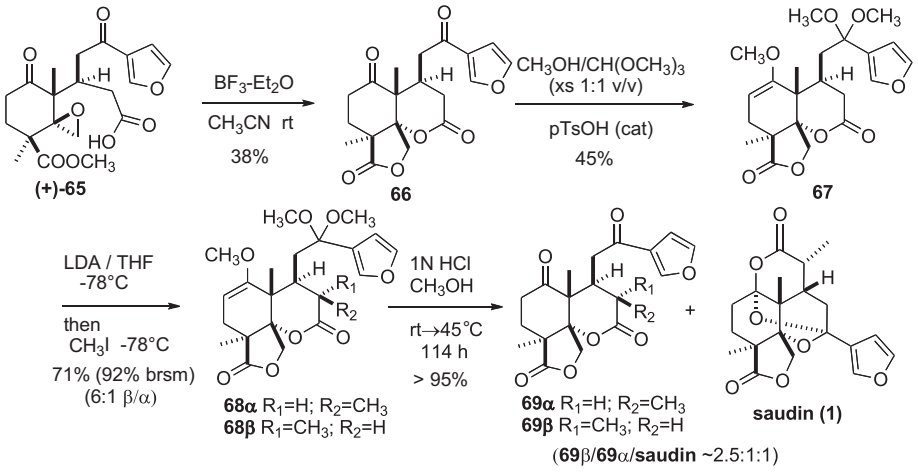
2.9. Elaboration of ketone (−)-59

Deprotection of silyl ether (−)-**59** with 2.5 equiv of TBAF in the presence of 1 equiv of HOAc spontaneously led to a mixture of hemiketals (~1:1) that were directly converted to single methyl ketal (+)-**61** in 99% yield upon treatment with excess $CH_3OH/CH(OCH_3)_3$ (1:1 v/v) in the presence of pTsOH hydrate (Scheme 21). Hydroboration of the less hindered, monosubstituted olefin with 9-BBN selectively afforded the expected primary alcohol (+)-**62** in 87% yield. Alcohol (+)-**62** was then oxidized in two steps to the corresponding carboxylic acid by sequential Swern and Pinnick oxidations (Scheme 21).[29,30] Direct oxidation of (+)-**62** using PDC[31] also proceeded efficiently (75% yield) but purification of the resulting product more problematic. Thus, the two-step sequence was employed since it proved to be higher yielding and does not require purification as well as avoiding the use of heavy metals. Direct epoxidation of the aforementioned carboxylic acid with *m*-CPBA followed by acid treatment afforded lactone (+)-**63** as a single diastereomer in 73% overall yield from (+)-**62**. Steric congestion around the ketone carbonyl in (+)-**63** resulted in complete chemoselectivity during the addition of 3-lithiofuran[25] affording a δ-lactol **64**. No products of addition to the other potentially electrophilic centers were observed. The crude lactol **64** was directly oxidized to acid (+)-**65** in 70% overall yield over three steps, via the corresponding primary alcohol tautomer of **64**, using successive Swern[29] and Pinnick[30] oxidations thus avoiding undesired internal ketalization (Scheme 21).

Opening of the epoxide group of (+)-**65** was promoted by $BF_3 \cdot Et_2O$. The intermediate carbenium ion underwent immediate intramolecular trapping by the free carboxylic acid, and the newly formed primary alcohol underwent concomitant lactonization affording as the final result of this reaction cascade bis-lactone **66** that was isolated in an unoptimized 38% yield (Scheme 22).[32] In order to introduce the methyl group at the α C_4 position of the δ-lactone (Saudin numbering), both ketone functions had to be protected. This protection operation, which required high temperatures and prolonged reaction times, was accomplished by treatment of **66** with TsOH in $CH_3OH/(CH_3O)_3CH$ affording ketal enol ether **67** in a mediocre 45% yield. The reaction is likely sluggish as a result of steric hindrance at the neopentyl carbonyl carbon of the cyclohexanone ring. Alkylation of **67** by treatment with LDA at −78 °C and quenching with CH_3I under kinetic conditions afforded an isomeric mixture of alkylation products **68** (**68β**/**68α** ~6:1) in 71% yield (92% bsrm) resulting from mainly axial methylation in



Scheme 21.



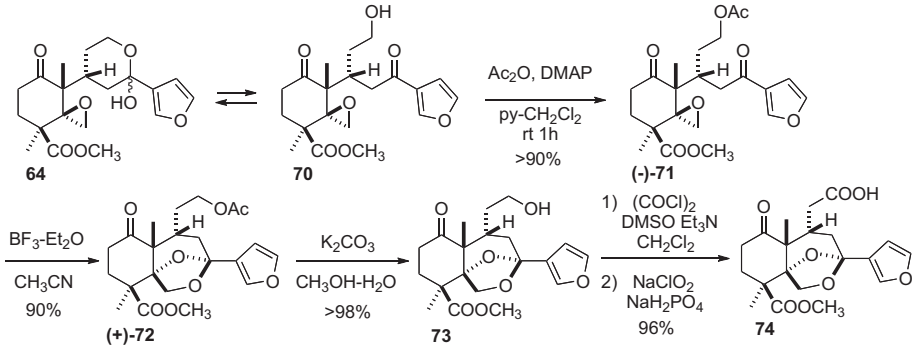
Scheme 22.

which the major isomer was confirmed to possess the desired stereochemistry at C_4 (Saudin numbering) by NOE measurements. Small amounts of saudin (**1**) were obtained from **68β** via sequential deprotection with concomitant lactone hydrolysis and cyclization. We later observed that Saudin formed directly during the deprotection step as shown in Scheme 22. However, after attempts at optimization, the yield could be improved only modestly to 25%. Epimerization at the newly formed 2° methyl chiral center at C_4 during deprotection is most likely responsible since lactone **69α** was obtained as a major by-product when starting with near homogenous **68β**.

2.10. Final elaboration of (−)-saudin (1) from lactone (+)-63

During the final conversion to Saudin, in order to avoid the evident thermodynamic preference for the wrong epimer at the eventual C_4 position (Saudin numbering) in lactones **68** and **69**, the order of ring formation had to be modified. To accomplish this change, the lactol **64**, in equilibrium with the ring opened primary alcohol **70**, was protected as the acetate (−)-**71** in >90% yield (81% overall directly from (+)-**63** by in situ trapping with Ac_2O), to avoid its participation in the opening of the epoxide. Subsequent treatment of (−)-**71** with BF_3-Et_2O as before afforded the internal ketal (+)-**72** in 90% yield.[32] The acetate group present in (+)-**72** was saponified in near quantitative yield and the corresponding alcohol **73** was oxidized by successive Swern[28] and Pinnick[29] oxidations to carboxylic acid **74** in 96% yield over two steps. Direct transformation of **73** into **74** was successful in 65% yield using catalytic TEMPO/NaOCl and $NaClO_2$ as co-oxidant,[33] although the yield was lower owing to competing oxidation of the furan ring (Scheme 23).

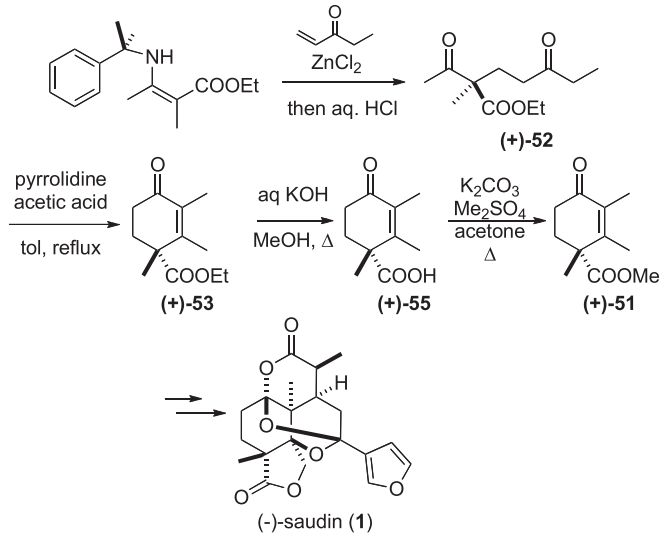
Formation of the key δ-lactone ring was then effected by conversion of acid **74** into the crystalline enol lactone (−)-**75** upon



Scheme 23.

treatment of **74** with TFAA in the presence of NaOAc, in 67% overall yield from **73** over three steps. The structure and stereochemistry of (−)-**75** were confirmed by single crystal X-ray analysis (Scheme 24). The creation of the enol lactone ring overcame the difficulties encountered during protection of the hindered carbonyl group. Attempted alkylation of (−)-**75** with LDA followed by addition of excess MeI, under a variety of reaction conditions, led to mixtures of **76α** and **76β** and **74** along with unreacted (−)-**75**, even when excess of LDA was used. Reasoning that diisopropyl amine could enhance the proton exchange between the starting lactone enolate and **76α**/**β** leading to epimerization and polyalkylation,[34] we decided to use the more hindered and stronger base Li-TMP, which is known to reduce the formation of aggregates.[35] Our hypothesis was confirmed when complete conversion of **75** was observed and a kinetically controlled mixture of **76** (**76α**/**76β** ~1:1.5) was isolated in 75% yield accompanied by only traces of **77**. In contrast to **68α**/**β** and **69α**/**β**, the desired isomer was now thermodynamically preferred. Thus, after chromatographic separation of **76α** and **76β**, the undesired isomer **76β** was epimerized to **76α** by treatment with a substoichiometric amount of LDA in 88% yield providing **76α** in 70% total yield.[36]

With the successful assembly of **76α**, having the correct stereochemistry and oxidation state at all positions, it only remained to assemble the bis ketal structure of Saudin. Our first attempts involved mild selective hydrolysis of the enol lactone and treatment of the intermediate methyl ester with TMSOTf. Under these conditions, saudin was isolated in 50% overall yield from **76α**. However, a by-product, containing two methoxy groups, was also obtained when the reaction was quenched before completion. Thus, in order to avoid the presence of methanol in the reaction mixture, harsher hydrolysis conditions were employed to afford the intermediate bis carboxylic acid **78**. Direct treatment of the crude diacid **78** with TMSOTf afforded saudin (**1**) in 70% isolated yield (Scheme 24).

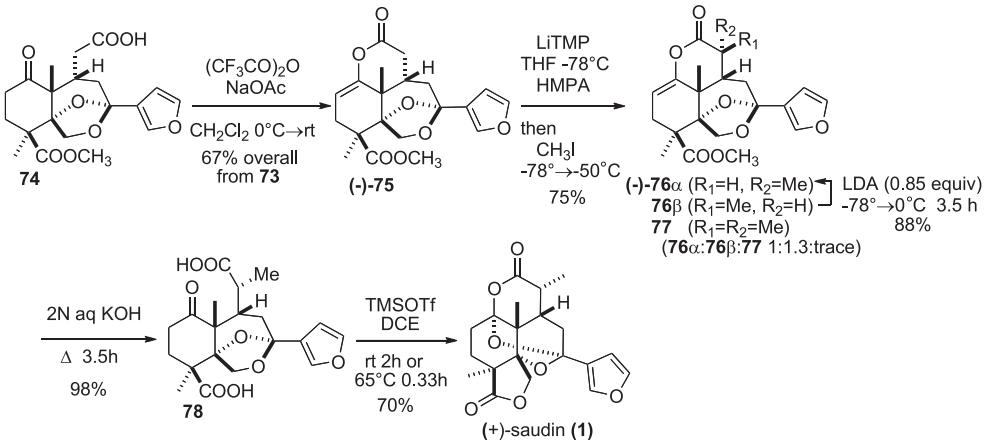


Scheme 25.

enantioselective synthesis of (−)-Saudin (**1**). The synthetic (−)-Saudin (**1**) had identical spectroscopic properties and melting point (204–206 °C) to both natural (−)-Saudin (**1**), and synthetic (+) Saudin (**1**) except for optical rotation ($[\alpha]_D^{22}$ −14; *c* 0.460, $CHCl_3$), which was equal and opposite in sign.[1,2]

3. Conclusion

The studies described herein resulted in the successful total synthesis of both natural (−)-Saudin (**1**) and its antipode (+)-Saudin (**79**), thus enabling the assignment of the absolute configuration of natural (−)-Saudin as that depicted in Fig. 1 and Scheme 25. During the course of this work, novel asymmetric Diels–Alder methodology developed in our laboratory was employed. Basic studies of the effect of Lewis acid promoters on the stereochemistry of the Claisen rearrangement were undertaken resulting in the novel application of $TiCl_4$, a bidentate chelating promoter, to control the facial selectivity in the key Claisen rearrangement step that established the relative stereochemistry of the 1,3-disposed quaternary centers present in Saudin.



Scheme 24.

The spectroscopic properties of the synthetic saudin were identical to those reported for the natural product, and as was the melting point (mp 204–206 °C).[1,2] However, the optical rotation, had opposite sign ($[\alpha]_D^{22}$ +14; *c* 0.460, $CHCl_3$) to that of natural (−)-Saudin (**1**) confirming that the synthetic material was (+)-Saudin (**1**). The absolute configuration of natural (−)-saudin (**1**) can then be assigned as shown in Fig. 1 and Scheme 25.

We then applied the above described sequence, beginning with *R*-(+)-α-methyl benzyl amine as chiral auxiliary, to achieve the first

4. Experimental section

4.1. General methods

All non-aqueous reactions were conducted in flame or oven-dried glassware under an argon atmosphere and were stirred magnetically unless otherwise noted. Air-sensitive reagents and solutions were transferred via syringe (unless noted otherwise) and were introduced to the apparatus through rubber septa. Solids were introduced under a positive pressure of argon. Temperatures, other than rt, refer to bath temperatures unless otherwise indicated. All distillations were performed under an argon atmosphere or at reduced pressure attained by either a water aspirator (15–30 mmHg) or an oil pump (<1 mmHg).

The phrase 'concentrated in vacuo' refers to removal of solvents by means of a Büchi rotary-evaporator attached to a water aspirator (15–30 mmHg) followed by pumping to constant weight (<1 mmHg).

Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on EM Reagents silica gel 60 (230–400) mesh. Acid sensitive compounds were chromatographed on EM Reagents silica gel 60 (230–400) mesh, which had been deactivated by stirring with 5% triethylamine/hexanes then equilibrated in the flash column with the indicated solvent system. The Waters Prep 500 system equipped with a refractive index detector was employed for preparative scale separations.

Analytical thin layer chromatography (TLC) was performed using EM silica gel 60 F-254 pre-coated glass plates (0.25 mm). Visualization was effected by either short-wave UV illumination, or by dipping into a solution of ceric ammonium molybdate (0.2 g $Ce(SO_4)_2$, 4.8 g $(NH_4)_6Mo_7O_{24}$, 10 mL concd H_2SO_4, 90 mL H_2O) or *p*-anisaldehyde (0.5 mL *p*-anisaldehyde, 0.5 mL concd H_2SO_4, 9 mL 95% EtOH, 2 drops HOAc) followed by heating on a hot plate.

Reagent grade solvents were used without purification for all extractions and workup procedures. Deionized water was used for all aqueous reactions and for the preparation of all aqueous solutions. Reaction solvents and reagents were dried and purified according to published literature procedures by distillation under argon or vacuum from the appropriate drying agent: Distilled from sodium/benzophenone ketyl: tetrahydrofuran, diethyl ether. Distilled from calcium hydride: hexamethylphosphoramide, methylene chloride, toluene, triethylamine. Distilled from phosphorous pentoxide/trifluoromethanesulfonic anhydride. Recrystallized from ethanol: triphenylphosphine, 2,6-di-*tert*-butyl-4-methylphenol (BHT). Other reagents and solvents were used as received.

Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained on a General Electric/Nicolet QE-300 (300 MHz), Bruker Avance 400 MHz or Bruker Avance 500 MHz spectrometers. In some cases, quaternary carbons could not be observed in the ^{13}C spectra or peaks were insufficiently resolved resulting in fewer carbon resonances than expected. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane and are internally referenced to the deuterated solvent. ^1H NMR data are reported as follows: chemical shift (multiplicity, coupling constant (Hz), number of hydrogens). Multiplicities are denoted accordingly: s (singlet), br s (broad signal), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets), tt (triplet of triplets), dq (doublet of quartets), t (triplet), q (quartet), p (pentuplet), m (multiplet). Infrared spectra (IR) were acquired on a Shimadzu FT-IR taken neat and are reported in wavenumbers (cm^{-1}) with polystyrene as a standard. Low resolution mass spectra (LRMS) were obtained using either a VG-7035 spectrometer, a Hewlet–Packard 5970 Mass selective detector coupled to an HP 5890 gas chromatograph, or a Shimadzu LCMS-2010 mass spectrometer. High resolution mass spectra were obtained at the Department of Chemistry at the State University of New York at Buffalo or the nation mass spectrometry facility at the Department of Chemistry University of California, Riverside. Ionization techniques consisted of electron impact (EI) and chemical ionization (CI). Optical rotation values were measured on a Perkin–Elmer-241 polarimeter. Samples were inserted into a cell with a path length of 1 dm. Melting points were determined using a Thomas–Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were obtained from Galbraith Laboratories. X-ray structural determinations were performed using an Enraf–Nonius CAD4 diffractometer with calculations performed with the Molecular Structures Corporation TEXAN crystallographic software package.

4.2. Synthesis and characterization

*4.2.1. 4-Keto-3-methyl-2-penten-1-ol (**8**)*[37]. To a suspension of mercuric oxide (red) (2.5 g, 12 mmol) in water (250 mL) was added sulfuric acid (~2 mL). The mixture was heated to 60 °C and then commercially available *trans*-3-methyl-2-pentene-4-yn-1-ol (**7**) (22 g, 0.23 mol) was added dropwise over 20 min. The resulting mixture was stirred at 60 °C for 1 h, then cooled to ambient temperature. The mixture was vacuum filtered through a pad of Celite, which was washed thoroughly with methylene chloride, and then the organic layer was separated from the biphasic filtrate. The aqueous layer was then extracted with methylene chloride (2×150 mL). The organic layers were combined, washed with brine (200 mL), dried over sodium sulfate, and concentrated in vacuo. Chromatography (1:1 ether/hexane) gave 16.5 g (63%) of keto alcohol **8** as an amber liquid having ^1H NMR (300 MHz, $CDCl_3$): δ 6.70 (t, 1H, *J*=4.7 Hz), 4.43 (d, 2H, *J*=4.7 Hz), 2.56 (s (br), 1H), 2.33 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.3, 142.8, 136.7, 59.7, 25.3, 11.2; IR (film): 3600–3100 (br), 2928, 1662, 1432 cm^{-1}; EIMS: 114 (M^+).

*4.2.2. 3-Methyl-2,5-triisopropylsiloxy-1,3-butadiene (**9c**)*[38]. To a solution of hydroxy ketone **8** (19 g, 0.17 mol) in CH_2Cl_2 (1 L) was added triethylamine (98 mL, 0.71 mol) followed by triisopropylsilyl triflate (108 g, 0.35 mol). The reaction mixture was stirred at 25 °C for 16 h, poured into satd aq $NaHCO_3$ (500 mL), and extracted with CH_2Cl_2 (2×500 mL). The organic layer was dried over sodium sulfate and concentrated in vacuo. Chromatography (100% hexanes) on silica gel deactivated with 5% triethylamine/hexanes provided 68 g (94%) of diene **16** as an oil: ^1H NMR (300 MHz, $CDCl_3$): δ 6.24 (t, 1H, *J*=5.8 Hz), 4.44 (s, 1H), 4.42 (s, 2H), 4.29 (s, 1H), 1.76 (s, 3H), 1.34–1.22 (m, 3H), 1.16–1.09 (m, 39H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 130.5, 128.6, 90.5, 61.0, 18.1, 17.9, 13.5, 12.8, 12.0; IR (film): 2943, 2892, 2866, 1593, 1463 cm^{-1}; EIMS: 269 (M^+–TIPS), 253 (M^+–OTIPS).

*4.2.3. (1R,4S)-2-((3′R,4′S)-2′4′-Dimethyl-1′-triisopropylsiloxy-3′-triisopropylsiloxymethyl-cyclohexene-4′-carbonyl)-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptan-3-one (**13**).* To a solution of imide **12** (29 g, 0.13 mol) and diene **9c** (68 g, 0.16 mol) in methylene chloride (800 mL) cooled to −25 °C was added titanium tetrachloride (1.0 M in methylene chloride, 180 mL, 0.13 mol) dropwise (~17 h) via syringe pump. Upon completion of the addition, the mixture was stirred an additional 1 h at −20 °C. Pyridine (25 mL) was added, the mixture warmed to 25 °C, and filtered through a silica gel pad (200 g) with elution by ether, and then the filtrate was concentrated in vacuo. The crude mixture was first purified by flash chromatography (1% ether/hexanes) on silica gel deactivated with 5% triethylamine/hexanes and then further purified by MPLC (1% ether/hexane) to provide 67 g (80%) of major cycloadduct **13** as a colorless oil and 9.3 g (11%) of minor cycloadduct **14** as an oil. Major cycloadduct **13** had: $[\alpha]_D^{22}$ −112 (*c* 1.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.23 (s, 1H), 3.69 (dd, *J*=10, 4.1 Hz, 1H), 3.46 (dd, *J*=10, 5.1 Hz, 1H), 3.31 (s (br), 1H), 2.51 (m, 1H), 2.13 (m, 2H),

2.03 (m, 1H), 1.82–1.43 (m, 4H), 1.71 (s, 3H), 1.29 (s, 3H), 1.07 (m, 21H), 1.03 (s, 3H), 0.99 (m, 21H), 0.93 (s, 3H) 0.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.0, 176.7, 143.0, 109.3, 66.5, 56.8, 47.2, 44.8, 30.8, 29.1, 27.0, 26.5, 18.8, 18.5, 18.1, 18.0, 17.8, 16.8, 13.2, 11.9, 9.9; IR (film): 2943, 2866, 1746, 1681, 1463 cm^{-1}; FAB MS: 648 (M^+). Anal. Calcd for $C_{37}H_{69}NO_4Si_2$: C, 68.56; H, 10.73. Found: C, 68.18; H, 10.96.

Minor cycloadduct **14** had: $[\alpha]_D^{22}$ +3.4 (*c* 16, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.46 (s, 1H), 3.83 (dd, *J*=10.2, 3.5 Hz, 1H), 3.62 (dd, *J*=10.2, 4.2 Hz, 1H), 3.29 (s (br), 1H), 2.50 (m, 1H), 2.11 (m, 2H), 1.98 (m, 2H), 1.83–1.50 (m, 3H), 1.71 (s, 3H), 1.17 (s, 3H), 1.07 (m, 21H), 1.03 (s, 3H), 0.99 (m, 21H), 0.91 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=177.0, 176.8, 143.2, 108.3, 65.7, 64.6, 56.6, 46.4, 46.3, 45.7, 30.1, 29.4, 27.0, 26.9, 18.9, 18.1, 17.9, 16.3, 13.3, 11.9, 9.8; IR (film): 2943, 2892, 2866, 2724, 1746, 1678, 1463 cm^{-1}; EIMS: 495 (M^+–chiral auxiliary), 460 (M^+–CH_2OTIPS).

*4.2.4. (1S,5R,6R) and (1S,5S,6R)-2,5-Dimethyl-4,9-dioxo-8-oxabicyclo[4.3.0]nonane (**16**).* To a solution of enol ether **13** (0.29 g, 0.45 mmol) in acetonitrile (5 mL) at rt was added hydrofluoric acid (48%, ~0.5 mL). The reaction mixture was capped and stirred for 3 h. At this time, 10% sodium bicarbonate (10 mL) was added, and extracted with methylene chloride (3×10 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Chromatography (1:1 ether/hexanes) afforded 70 mg (85%) of keto lactones (5*R*)-**16** and (5*S*)-**16** in ~1:1 mixture of epimers as a colorless oil having $[\alpha]_D^{22}$ +90 (*c* 5.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.50 (dd, *J*=10, 5.5 Hz, 1H), 4.36 (t, *J*=9.3 Hz, 1H), 4.15 (dd, *J*=10, 1.9 Hz, 1H), 3.74 (t, *J*=9.3 Hz, 1H), 2.81 (m, 2H), 2.60–1.80 (m, 10H), 1.49 (s, 3H), 1.33 (s, 3H), 1.11 (d, *J*=6.5 Hz, 3H), 1.05 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.2, 210.0, 180.6, 180.0, 69.4, 67.1, 50.2, 47.6, 43.9, 42.0, 41.4, 41.2, 36.3, 36.1, 31.1, 30.9, 22.7, 22.6, 12.6, 10.8; IR (film): 2971, 2934, 2875, 1770, 1716, 1486, 1455 cm^{-1}; EIMS: 182 (M^+).

*4.2.5. (1R,4S)-2-((2′R,3′R,4′S)-2′4′-Dimethyl-3′-triisopropylsiloxymethyl cyclohexanone-4′-carbonyl)-4,7,7-trimethyl-2-azabicyclo [2.2.1]heptan-3-one (**15**).* To a solution of enol ether **13** (0.24 g, 0.37 mmol) in tetrahydrofuran (4 mL) at rt was added tetrabutylammonium fluoride (1 M in THF, 0.37 mL, 0.37 mmol). The reaction mixture was stirred for 15 min before being quenched with satd NH_4Cl solution and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Chromatography (4:1 hexanes/ether) afforded 0.14 g (80%) of ketone **15** as a crystalline solid. Ketone **15** could be further purified by recrystallization from heptane and had: mp 79–81 °C; $[\alpha]_D^{22}$ −45 (*c* 5.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.35 (s, 1H), 3.81 (dd, *J*=11, 4 Hz, 1H), 3.41 (d *J*=11 Hz, 1H,), 3.21 (s (br), 1H), 2.94 (td, *J*=13, 8 Hz, 1H), 2.66 (m, 1H), 2.38 (m, 2H), 2.00 (m, 1H), 1.81 (m, 2H), 1.58 (m, 5H), 1.20–1.00 (m, 27H), 0.95 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.6, 176.2, 175.7, 65.8, 61.3, 56.2, 47.4, 46.3, 44.8, 39.9, 36.2, 31.5, 30.0, 26.0, 18.2, 17.7, 17.3, 17.1, 11.4, 11.2, 9.1; IR (film): 2963, 2943, 2867, 1743, 1716, 1674, 1458 cm^{-1}; EIMS: 448 (M^+–^{i}Pr).

*4.2.6. (1R,5R,6S) and (1R,5S,6S)-2,5-Dimethyl-4,9-dioxo-8-oxabicyclo[4.3.0]nonane (**17**).* To a solution of enol ether **14** (97 mg, 0.15 mmol) in acetonitrile (3 mL) at rt was added hydrofluoric acid (48%, ~0.3 mL). The reaction mixture was capped and stirred for 24 h. At this time the mixture was quenched with 10% sodium bicarbonate (15 mL), and extracted with methylene chloride (3×8 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Chromatography (1:1 ether/hexanes) afforded 22 mg (81%) of ~1:1 mixture of keto lactone epimers (5*S*)-**17** and (5*R*)-**17** as a colorless oil that had: $[\alpha]_D^{22}$ −96.9 (*c* 1.96, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.50 (dd, *J*=10, 5.5 Hz 1H), 4.36 (t, *J*=9.3 Hz, 1H), 4.15 (dd, *J*=10, 1.9 Hz, 1H), 3.74 (t, 9.3 Hz, 1H), 2.81 (m, 2H), 2.60–1.80 (m, 10H), 1.49 (s, 3H), 1.33 (s, 3H), 1.11 (d, *J*=6.5 Hz, 3H), 1.05 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.3, 210.0, 180.6, 179.9, 69.4, 67.2, 50.3, 47.7, 43.9, 41.2, 36.4, 36.1, 31.1, 31.0, 22.7, 22.6, 12.6, 10.9; IR (film): 2971, 2934, 2875, 1769, 1715, 1486, 1453 cm^{-1}; EIMS: 182 (M^+).

*4.2.7. (1R,4S)-2-((3′R,4′S)-2′4′-Dimethyl-3′-triisopropylsiloxymethylcyclohex-2′-ene-1′-one-4′-carbonyl)-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptan-3-one (**18**).* To a solution of enol ether **13** (63 g, 0.097 mol) in methylene chloride (60 mL) and methanol (600 mL) was added $NaHCO_3$ (82 g, 0.97 mol), followed by phenylselenenyl bromide (48 g, 0.20 mol). The resulting mixture was stirred at 25 °C for 3 h. The reaction mixture was concentrated to remove methanol, diluted with methylene chloride (700 mL) and poured into H_2O (900 mL). The layers were separated and the aqueous layer was extracted with methylene chloride (2×500 mL). The organic layers were combined, dried over sodium sulfate, and concentrated in vacuo. Chromatography (elution by 8:1 hexane/ether) provided 32 g (68%) of enone **18** as an oil having: $[\alpha]_D^{22}$ −66.0 (*c* 15.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.16 (dd, *J*=10, 8.7 Hz, 1H), 4.06 (d, *J*=1 Hz, 1H), 3.92 (dd, *J*=10, 2.8 Hz, 1H), 3.16 (m, 2H), 2.42 (m, 2H), 2.04 (m, 1H), 1.96 (s, 3H), 1.91–1.52 (m, 3H), 1.36 (s, 3H), 1.07 (s, 24H), 0.96 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=203.7, 177.4, 176.2, 67.6, 64.8, 57.0, 56.2, 47.2, 47.0, 33.6, 31.1, 29.7, 29.1, 26.4, 21.5, 18.7, 18.1, 17.9, 17.7, 11.8, 9.7; IR (film) 2943, 2866, 1739, 1717, 1676, 1462 cm^{-1}; EIMS: 489 (M^+), 446 (M^+–^{i}Pr). This material was used as obtained in the next transformation.

*4.2.8. (1S)-1,5-Dimethyl-4,9-dioxo-8-oxabicyclo[4.3.0]non-5-ene (**19**).* To a solution of enone **18** (32 g, 66 mmol) in tetrahydrofuran (300 mL) was added tetra-*n*-butylammonium fluoride (1.0 M in THF, 69 mL, 69 mmol) The resulting solution was stirred at 25 °C for 16 h. The reaction mixture was poured into 1 M hydrochloric acid (500 mL) and extracted with methylene chloride (3×400 mL). The organic layers were combined, dried over sodium sulfate, and concentrated in vacuo. Chromatography (elution by 2:1 hexane/ethyl acetate) provided 11 g (92%) of enone lactone **19** as a solid. Enone **19** was further purified by recrystallization from toluene affording **19** as a white solid with mp 97–98 °C and having $[\alpha]_D^{22}$ +186 (*c* 1.61, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.01 (s, 2H), 2.60 (m, 2H), 2.24 (ddd, *J*=13.2, 5, 2.2 Hz, 1H), 2.1 (m, 1H), 1.76 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.5, 178.3, 154.5, 128.8, 67.2, 41.3, 32.4, 29.5, 21.2, 10.7; IR (film): 2975, 2936, 1780, 1712, 1672, 1450 cm^{-1}; EIMS: 180 (M^+); Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.93; H, 6.94.

*4.2.9. (R)-(−)-4-Hydroxy-2-methyl-3-[1′(1″-naphthyl)ethylamino]-butenoic acid γ-lactone (**20**).* A 250-mL pressure bottle, charged with *R*-(+)-α-naphthyl ethyl amine (27.1 g, 0.158 mol), α-methyltetronic acid (18.0 g, 0.158 mol), and toluene (50 mL), was sealed and heated to 150 °C. After 40 h, the reaction mixture was cooled, unsealed and diluted with CH_2Cl_2 (2 L) and filtered through Buchner funnel to remove some undissolved solid. The filtrate was washed with satd. aq $NaHCO_3$ (2×200 mL), H_2O (100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated in vacuo to afford the crude yellowish solid. The crude solid was suspended in Et_2O (100 mL), filtered through a Buchner funnel, rinsed with Et_2O (3×50 mL), and concentrated in vacuo to afford 34.0 g (90%) of product **20** as a white crystalline solid. An analytical sample had: $[\alpha]_D^{22}$ −196 (*c* 1.18, 1:1 $CH_3OH/CHCl_3$); ^{1}H NMR (1:1 $CD_3OD/CDCl_3$): δ 7.78 (d, *J*=8.4 Hz, 1H), 7.67 (d, *J*=7.9 Hz, 1H), 7.56 (d, *J*=7.3 Hz, 1H), 7.36–7.20 (m, 4H), 5.10 (q, *J*=7.8 Hz, 1H), 4.42 (d, *J*=15.3 Hz, 1H), 4.29 (s, 1H), 3.96 (d, *J*=15.3 Hz, 1H), 1.45 (d, *J*=7.8 Hz, 6H); ^{13}C NMR (1:1 $CD_3OD/CDCl_3$): δ 178.2, 163.5, 139.0, 133.8, 129.6, 128.8, 127.8, 126.2, 125.5, 125.3, 121.7, 121.6, 88.6, 65.9, 49.8, 22.5, 6.0; IR ($CHCl_3$): 3374, 3017, 2944, 2833, 1635, 1448 cm^{-1}; EIMS: 267 (M^+); HRMS

calcd for $C_{17}H_{17}NO_2$: *m*/*z* 267.1259. Found: 267.1237. Crude **20** was used without further purification.

*4.2.10. (4RS,8S)-Dimethyl-1,5-dioxo-(9S)-hydroxy-2-oxabicyclo [4.3.0]nonane (**22**).* To a solution of $ZnCl_2$ (4.24 g, 31.1 mmol) in THF (50 mL) were added TMSCl (20.0 mL, 156 mmol) and lactone **20** (8.30 g, 31.1 mmol). The mixture was cooled to −78 °C, and a solution of ethyl vinyl ketone (5.59 g, 66.5 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 20 h, then the reaction was quenched by addition of 2 N HCl (5 mL) at −78 °C. The reaction mixture was allowed to warm to rt and continue to stir for 2 h. The aqueous layer was extracted with Et_2O (3×10 mL), and the combined organic layer was washed with satd aq $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, concentrated in vacuo, and purified by chromatography by silica gel column (elution by 9:1 then 4:1 hexanes/EtOAc) to afford 4.52 g (73%, 60% ee) of pure Michael adduct **21** having ^{1}H NMR: δ 4.69 (d, *J*=16.9 Hz, 1H), 4.58 (d, *J*=16.9 Hz, 1H), 2.48 (t, *J*=7.2 Hz, 2H), 2.35 (q, *J*=7.3 Hz, 2H), 1.95 (q, *J*=7.2 Hz, 2H), 1.25 (s, 3H), 0.95 (t, *J*=7.3 Hz, 3H); IR ($CHCl_3$): 2978, 2938, 1803, 1757, 1713, 1454 cm^{-1}; EIMS: 198 (M^+). Diketo lactone **21** (3.30 g, 16.7 mmol) and (*S*)-proline (0.115 g, 1.00 mmol) were stirred in DMF (20 mL) at rt for 48 h. The brown-colored reaction mixture was filtered and the filtrate was diluted with H_2O (50 mL) and EtOAc (100 mL). The aqueous layer was extracted with EtOAc (3×50 mL), and the combined organic layer was washed with H_2O (2×20 mL) and brine (10 mL), dried over Na_2SO_4, concentrated in vacuo, and chromatographed by silica gel column (4:1 then 1:1 hexanes/EtOAc) to afford 1.50 g (55%, 89% ee) of β-hydroxy keto lactone **22** and 1.50 g (45%) of unreacted starting diketo lactone **21**. Lactone **22** had ^{1}H NMR: δ 4.10 (d, *J*=10.5 Hz, 1H), 4.00 (d, *J*=10.5 Hz, 1H), 2.70 (q, *J*=6.7 Hz, 1H), 2.59–2.52 (m, 1H), 2.44–2.32 (m, 1H), 2.18 (s, 1H), 2.05–2.02 (m, 1H), 1.88–1.82 (m, 1H), 1.49 (s, 3H), 1.16 (d, *J*=6.7 Hz, 3H); ^{13}C NMR: δ 207.8, 179.9, 82.7, 73.4, 49.4, 47.1, 35.9, 30.9, 13.8, 7.0; IR ($CHCl_3$): 3413, 2977, 2941, 1779, 1720 cm^{-1}; EIMS: 198 (M^+); HRMS calcd for $C_{10}H_{14}O_4$: *m*/*z* 198.0892. Found: 198.0889.

*4.2.11. (4S,8S)-Dimethyl-1,5-dioxo-2-oxabicyclo[4.3.0]non-4(9)-ene (**19**)[26b].* A solution of β-hydroxy keto lactone **22** (0.430 g, 2.17 mmol) in toluene (50 mL) was refluxed for 2 h with azeotropic water removal via a Dean–Stark trap. Et_2O (100 mL) was added to the cooled solution which was washed with satd aq $NaHCO_3$ (2×20 mL), and brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo to afford 0.391 g (100%, 89% ee) of enone lactone **19** as a white solid after recrystallization from toluene having mp 95–96 °C and $[\alpha]_D^{22}$ +181 (*c* 6.1, $CHCl_3$) or 94% ee; ^{1}H NMR: δ 5.00 (s, 2H), 2.70–2.53 (m, 2H), 2.27–2.05 (m, 2H), 1.75 (s, 3H), 1.52 (s, 3H); IR ($CHCl_3$): 2975, 2936, 1780, 1712, 1672, 1450 cm^{-1}; EIMS: 180 (M^+).

*4.2.12. (4R,8S)-Dimethyl-4(9)-epoxy-1,5-oxo-2-oxabicyclo[4.3.0] nonane (**5**).* To a cold (0 °C) solution of enone lactone **19** (1.50 g, 8.33 mmol) in EtOH (100 mL) was added $NaBH_4$ (0.315 g, 8.33 mmol) with stirring. The resulting suspension was allowed to warm to rt and stirred for 20 h when TLC showed almost complete consumption of starting material **19**. The reaction was quenched by addition of 1 N HCl (15 mL) dropwise at 0 °C. The reaction mixture was concentrated to remove EtOH as much as possible and the residue was diluted with CH_2Cl_2 (50 mL), washed with satd aq $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, concentrated in vacuo, and purified by silica gel chromatography (elution by 4:1 then 1:1 hexanes/EtOAc) to afford 1.13 g (75%) of allylic alcohols **23** having ^{1}H NMR: δ 4.77 (d, *J*=13.4 Hz, 1H), 4.72 (d, *J*=13.4 Hz, 1H), 4.07 (t, *J*=7.5 Hz, 1H), 2.75 (s, br, 1H), 2.17–2.10 (m, 1H), 1.85–1.80(m, 1H), 1.80–1.52 (m, 2H), 1.66 (s, 3H), 1.31 (s, 3H); ^{13}C NMR: δ 180.6, 132.4, 131.5, 70.3, 68.1, 41.0, 29.0, 28.8, 21.9, 14.7; IR ($CHCl_3$): 3468, 2974, 1771 cm^{-1}; EIMS: 182 (M^+). To a cold (0 °C) suspension of allylic alcohols **23** (0.700 g, 3.85 mmol) and finely ground NaH_2PO_4 (1.60 g, 11.0 mmol) in CH_2Cl_2 (20 mL) was added solid 80% *m*-CPBA (1.24 g, 5.77 mmol) portionwise in small portions. The mixture was stirred at 0 °C for 10 h before quenched with satd aq $Na_2S_2O_5$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL), and the combined organic layer was washed with satd aq $NaHCO_3$ (2×5 mL), H_2O (5 mL) and brine (10 mL), dried over Na_2SO_4, concentrated in vacuo to afford 0.543 g (71%) of epoxy alcohol**s** pure enough to be used for subsequent reaction without further purification. For spectroscopic analysis, a sample of the epoxy alcohols was purified by silica gel chromatography (elution by 4:1 then 1:1 hexanes/EtOAc) to afford the epoxy alcohols having ^{1}H NMR: δ 4.26 (s, 2H), 3.80 (dd, *J*=10.0 Hz, 5.6 Hz, 1H), 1.84–1.67 (m, 2H), 1.52–1.18 (m, 2H), 1.47 (s, 3H), 1.34 (s, 3H); ^{13}C NMR: δ 179.3, 97.3, 76.2, 71.2, 64.7, 37.3, 28.7, 24.6, 18.0, 16.1; IR ($CHCl_3$): 2940, 1777, 1379 cm^{-1}; EIMS: 198 (M^+). To a stirring suspension of freshly activated molecular sieves 3 Å (2.2 g) and the epoxy alcohols (0.512 g, 2.59 mmol) in CH_2Cl_2 (20 mL), was added finely ground PDC[31] (1.54 g, 4.09 mmol). The reaction mixture was stirred at rt for 2 h when TLC analysis (silica gel, 1:1 hexanes/EtOAc) showed the absence of the starting material. Celite (1.3 g) was added and the reaction mixture was stirred for another 20 min, then filtered through a column of silica gel, eluted with Et_2O and concentrated in vacuo to afford 0.468 g (92%) of pure epoxy ketone **5** as white crystals $[\alpha]_D^{22}$ +26.3 (*c* 6.85, $CHCl_3$) ^{1}H NMR: δ 4.33 (d, *J*=10.8 Hz, 1H), 4.28 (d, *J*=10.8 Hz, 1H), 2.72 (dt, *J*=14.5, 5.8 Hz, 1H), 2.25 (dt, *J*=14.5, 3.2 Hz, 1H), 2.05–1.99 (m, 2H), 1.52 (s, 3H), 1.42 (s, 3H); ^{13}C NMR: δ 204.3, 177.7, 74.6, 64.0, 62.5, 37.5, 31.9, 31.1, 18.0, 12.1; IR ($CHCl_3$): 2937, 2834, 1782, 1720, 1464 cm^{-1}; EIMS (M^+): 196; HRMS calcd for $C_{10}H_{12}O_4$: *m*/*z* 196.0736. Found: 196.0748.

*4.2.13. (R)-(+)-3-(tert-Butyldiphenylsilyloxy)-2-methylpropanol (**25**)[15].* To a solution of 5.00 g (42.3 mmol) of (*S*)-(+)-Methyl-3-hydroxy-2-methylpropanoate (**24**) in dry DMF (40 mL) was added imidazole (6.34 g, 93.1 mmol), *tert*-butyldiphenylchlorosilane (12.8 g, 46.5 mmol) and a catalytic amount of DMAP (0.129 g, 1.06 mmol). The reaction mixture was stirred for 2 h when TLC (silica gel, 1:1 hexanes/EtOAc) showed the absence of the starting material. The reaction mixture was diluted with EtOAc (300 mL), the organic layer was washed with water (3×50 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo to afford 15.1 g (100%) of practically pure silyloxy ester as a colorless oil. For spectroscopic analysis, a sample of the silyloxy ester was prepared by silica gel column chromatography (9:1 hexanes/EtOAc): $[\alpha]_D^{22}$ +13.1 (*c* 4.58, $CHCl_3$); ^{1}H NMR: δ 7.78–7.69 (m, 4H), 7.47–7.41 (m, 6H), 3.91–3.68 (m, 2H), 3.72 (s, 3H), 2.80–2.73 (m, 1H), 1.20 (d, *J*=6.9 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR: δ 175.4, 135.6, 133.5, 129.7, 127.7, 65.9, 51.5, 42.4, 26.7, 19.2, 13.5; IR (neat): 3071, 3049, 2931, 2857, 1960, 1891, 1742, 1428 cm^{-1}; EIMS: 325 (M−OCH_3), 299 (M−*t*-Bu). To a cold (−78 °C) solution of silyloxy ester (15.0 g, 42.1 mmol) in Et_2O (160 mL) was added dropwise 1 M DIBAl-H in hexanes (84 mL, 84 mmol). The reaction mixture was warmed to rt and stirred for 10 h when no starting material was left by TLC (silica gel, 4:1 hexanes/EtOAc). The clear solution was cooled to 0 °C and quenched by dropwise addition of MeOH (25 mL) followed by addition of a saturated aqueous solution of Rochelle's salt (sodium potassium tartrate) (80 mL). The reaction mixture was allowed to warm to rt and stirred vigorously until two homogeneous layers resulted. The separated aqueous layer was extracted with Et_2O (2×50 mL), the combined organic layer was washed with brine (30 mL), dried over Na_2SO4, concentrated in vacuo and chromatographed (silica gel, 9:1 hexanes/EtOAc) to afford 13.8 g (100%) of pure alcohol **25** as a colorless oil: $[\alpha]_D^{22}$ +7.1 (*c* 3.49, $CHCl_3$); ^{1}H NMR (400 MHz): δ 7.75–7.73 m, 4H), 7.50–7.42 (m, 6H), 3.80–3.63 (m, 4H), 2.76 ((t, *J*=5.0 Hz 1H), 2.07–2.01 (m, 1H), 1.12 (s, 9H), 0.89 (d, *J*=6.9 Hz, 3H); ^{13}C NMR: δ 135.6, 133.3, 129.8, 127.8, 68.5, 67.4, 37.4,

26.9, 19.2, 13.2; IR (neat): 3358 (br), 3071, 3049, 2998, 2930, 2858, 1958, 1888, 1824, 1772 cm^{-1}; EIMS: 271 (M−*t*-Bu), 269 (M−CH_3CHCH_2OH).

*4.2.14. (R)-(E)-(+)-Ethyl-5-(tert-butyldiphenylsilyloxy)-4-methyl-2-pentenoate (**26**).* To a cold (−78 °C) solution of oxalyl chloride (7.0 mL, 10.3, 81.5 mmol) in CH_2Cl_2 (200 mL) was added dropwise a solution of DMSO (11.6 mL, 163 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred for another 15 min at −78 °C after addition and then a solution of alcohol **26** (13.8 g, 38.7 mmol) in CH_2Cl_2 (100 mL) was added dropwise with stirring. After stirring for 1 h at −78 °C, Et_3N (27.3 mL, 195.6 mmol) was added dropwise and stirring was continued for 15 min at this temperature. The reaction mixture was allowed to warm to 0 °C for ca. 30 min with stirring and diluted with satd aq NH_4Cl (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3×50 mL), the combined organic layer was washed with satd aq NH_4Cl (2×100 mL), H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo to afford 13.6 g (100%) of practically pure aldehyde (*S*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanal[15] having ^1H NMR: δ 9.80 (d, J=1.3 Hz, 1H), 7.77–7.67 (m, 4H), 7.47–7.39 (m, 6H), 3.95–3.85 (m, 2H), 2.66–2.58 (m, 1H), 1.13 (d, J=6.9 Hz, 3H), 1.08 (s, 9H). ^{13}C NMR: δ 204.5, 135.6, 133.2, 129.8, 127.8, 64.1, 48.8, 26.8, 19.2, 10.3. IR (neat): 2958, 2931, 2858, 2712, 1961, 1890, 1824, 1737, 1427 cm^{-1}. EIMS: 269 (M−*t*-Bu), 239 (M−$OCH_2CH(CH_3)CHO$). The aldehyde was immediately used in the next step without further purification. To a cold (0 °C) solution of ethyl diisopropylphosphonoacetate (14.7 g, 54.1 mmol) in THF (100 mL) under argon was added a filtered solution of *t*-BuOK (5.62 g, 50.1 mmol) in THF (300 mL). After stirring for 1 h at rt, the reaction mixture was cooled to −78 °C. To the stirred solution, crude (*S*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanal (27.9 g, 134 mmol) in THF (100 mL) was added dropwise. The reaction mixture was slowly warmed to rt, stirred for 7 h at rt, and quenched with satd aq NH_4Cl (80 mL) and H_2O (50 mL). The separated aqueous layer was extracted with Et_2O (2×100 mL) and the combined organic layer was washed with H_2O (100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography (silica gel, 9:1 then 4:1 hexanes/EtOAc) to afford 30.6 g (82%) of *trans*-α,β-unsaturated ester **26** (trans/cis >95:5) as a pale yellow oil having: $[\alpha]_D^{22}$ +13.5 (*c* 2.44, $CHCl_3$); ^1H NMR: δ 7.77–7.68 (m, 4H), 7.46–7.39 (m, 6H), 7.01 (dd, J=15.8, 7.2 Hz, 1H), 5.88 (d, J=15.8 Hz, 1H), 4.23 (q, J=7.0 Hz, 2H), 3.62 (d, J=6.4 Hz, 2H), 2.61–2.55 (m, 1H), 1.32 (t, J=7.0 Hz, 3H), 1.09 (s, 12H); ^{13}C NMR: δ 166.6, 151.3, 135.6, 133.6, 129.7, 127.7, 121.2, 67.6, 60.1, 39.1, 26.9, 19.3, 15.6, 14.3; IR (neat): 3071, 3049, 2959, 2930, 2857, 1960, 1888, 1825, 1721, 1651, 1427 cm^{-1}; EIMS: 351 (M^+−OEt), 339 (M^+−*t*-Bu). HRMS calcd for $C_{20}H_{23}O_3Si$: m/z 339.1416. Found: 339.1387.

*4.2.15. (R)-(E)-(+)-5-(tert-Butyldiphenylsilyloxy)-4-methyl-2-penten-1-ol (**27**).* A solution of *trans*-α,β-unsaturated ester **26** (7.6 g, 19.2 mmol) in Et_2O (400 mL) was cooled to −78 °C. To the solution, 1 M DIBAL in hexanes (48 mL, 48 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 5 h until no starting material remained by TLC (silica gel, 1:1 hexanes/EtOAc). The clear solution was quenched by dropwise addition of MeOH (60 mL) at −78 °C followed by addition of a saturated aqueous solution of Rochelle's salt (sodium potassium tartrate) (200 mL). The reaction mixture was allowed to warm to rt and stir vigorously until two homogeneous layers resulted (ca. 2 h). The separated aqueous layer was extracted with Et_2O (2×100 mL), and the combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography (silica gel, elution by 4:1 then 1:1 hexanes/EtOAc) to afford 22.0 g (93%) of allylic alcohol **27** as a colorless oil exhibiting $[\alpha]_D^{22}$ +4.6 (*c* 1.00, $CHCl_3$); ^1H NMR: δ 7.77–7.75 (m, 4H), 7.51–7.43 (m, 6H), 5.71–5.69 (m, 2H), 4.12 (d, J=4.9 Hz, 2H), 3.69–3.57 (m, 2H), 2.54–2.46 (m, 1H), 1.16 (s, 9H), 1.13 (d, J=6.8 Hz, 3H); ^{13}C NMR: δ 135.7, 135.3, 134.0, 129.7, 128.9, 127.7, 68.6, 63.7, 39.0, 27.0, 19.4, 16.5; IR (neat): 3351 (br), 3071, 3049, 2959, 2930, 2857, 1958, 1888, 1824, 1427 cm^{-1}; EIMS: 355 (M^++1), 297 (M^+−*t*-Bu). HRMS calcd for $C_{18}H_{21}O_2Si$: m/z 297.1311. Found: 297.1283.

*4.2.16. (R)-(E)-5-(tert-Butyldiphenylsilyloxy)-4-methyl-2-pentenyl trifluoromethane sulfonate (**6**).* To a solution of allylic alcohol **27** (500 mg, 1.41 mmol) in Et_2O (1.0 mL) was added 1.43 M solution of *t*-BuLi in hexanes (0.986 mL, 1.41 mmol) at −78 °C. After stirring for 10 min, the reaction mixture was transferred by cannula to a solution of Tf_2O (0.237 mL, 1.41 mmol) in Et_2O (0.5 mL). The reaction mixture was stirred at −78 °C for 30 min, and used immediately for the alkylation reaction.

4.2.17. 4-tert-Butyldiphenylsiloxy-1-butyne[39]. To a solution of 8.4 g (0.12 mol) of 3-butyn-1-ol (**28**) in 200 mL of anhyd THF was added 16 g (0.24 mol) of imidazole and 33 g (0.12 mol) *tert*-butyldiphenylsilyl chloride. The reaction mixture was stirred at rt for 18 h, and then concentrated in vacuo. The crude residue was partitioned between ether and water and the phases were separated. The aqueous phase was then further extracted twice with 200 mL portions of ether. The combined organic phases were dried over Na2SO4 and the solvent removed in vacuo to provide 38 g (>99%) of alkynol silyl ether as an oil which was used without further purification: ^1H NMR (300 MHz, $CDCl_3$): δ 7.71 (m, 4H), 7.44 (m, 6H), 3.81 (t, J=7.0 Hz, 2H), 2.48 (dt, J_1=7.0, J_2=2.5 Hz, 2H), 1.97 (t, J=2.6 Hz, 1H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.3, 133.5, 129.3, 127.3, 81.1, 68.9, 62.2, 26.6, 22.3, 18.9; IR (film): 3307, 3071, 3050, 2958, 2931, 2880, 2857, 2121, 1960, 1892, 1822, 1589, 1472, 1427 cm^{-1}; EIMS: 251 (M^+−*t*-Bu), 221 (M^+−Ph).

*4.2.18. 5-tert-Butyldiphenylsilyloxy-2-pentyn-1-ol (**29**)[40].* A solution of 38 g (0.12 mol) of 4-*tert*-butyldiphenylsiloxy-1-butyne in 800 mL of anhyd THF was cooled to −78 °C and 110 mL of a 1.48 M solution of *n*-butyllithium in hexane (0.16 mol) was added dropwise. The resulting solution was stirred at −78 °C for 1 h, warmed to ambient temperature over 2.5 h, and then recooled to −78 °C. A 9.3 g (0.31 mol) sample of solid dry *para*-formaldehyde was added in one portion and the resulting suspension was allowed to warm to rt over 16 h. The mixture was concentrated in vacuo and then partitioned between 400 mL of ether and 400 mL of water. The phases were separated and the aqueous phase was further extracted twice with 300 mL portions of ether. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Chromatography (with elution by 4:1 hexane/ether) provided 36 g (85%) of 5-*tert*-Butyldiphenylsiloxy-2-pentyn-1-ol (**29**) as an oil: ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (m, 4H), 7.44 (m, 6H), 4.22 (m, 2H), 3.82 (t, J=7 Hz, 2H), 2.52 (m, 2H), 1.92 (s (br), 1H), 1.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 133.6, 129.7, 127.7, 83.3, 79.6, 62.4, 51.2, 26.8, 22.9, 19.2; IR (film): 3583–3389 (br), 3072, 3048, 2931, 1590, 1963, 1894, 1830, 1471, 1428 cm^{-1}; EIMS: 281 (M^+−*t*-Bu), 251 (M^+−Ph). This material was used as obtained for further transformations.

*4.2.19. 5-tert-Butyldiphenylsiloxy-2-penten-1-ol (**30**)[41].* Ethanol (2.4 g, 53 mmol) was added dropwise to a suspension of 1.1 g of 95% LAH (27 mmol) in 80 mL of anhyd THF at 0 °C under Ar. A solution of 8.46 g 5-*tert*-butyldiphenylsiloxy-2-pentyn-1-ol (25 mmol) in 50 mL of anhyd THF was then added dropwise. Upon completion of the addition, the 0 °C bath was removed and the reaction mixture was warmed to rt then heated to reflux for 1 h. The mixture was quenched carefully with water and NaOH, and the resulting white aluminum salts were vacuum filtered through a sinter glass funnel. The salts were washed repeatedly with hot ether, and the combined filtrates were dried over Na_2SO_4 and concentrated in vacuo.

Chromatography (with elution by 3:1 hexanes/ether) provided 8.2 g (96%) of 5-*tetr*-Butyldiphenylsiloxy-2-penten-1-ol as a colorless oil having: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (m, 4H), 7.40 (m, 6H), 5.68 (m, 2H), 4.08 (s(br), 2H), 3.72 (t, J=8 Hz, 2H), 2.32 (m, 2H), 1.50 (s (br), 1H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 133.9, 131.1, 129.7, 129.3, 127.7, 63.6, 63.5, 35.6, 26.9, 19.3; IR (film): 3331, 3070, 3048, 2930, 2857, 1963, 1894, 1830, 1472, 1428 cm^{-1}; EIMS: 283 (M^+-t-Bu), 253 (M^+-Ph).

*4.2.20. 5-tert-Butyldiphenylsiloxy-1-trifluoromethanesulfonyl-2-pentene (**31**).* To a solution of alcohol **30** (9.9 g, 29 mmol) in Et_2O (25 mL) cooled to −78 °C was added *n*-BuLi (1.5 M in hexane, 19 mL, 29 mmol) dropwise. The resulting solution was stirred for 0.5 h, then slowly added dropwise via cannula to neat, freshly distilled triflic anhydride (8.2 g, 29 mmol) at −78 °C. The solution was stirred at −78 °C for 0.5 h, then used immediately in subsequent reactions.

*4.2.21. (4R,8S)-Dimethyl-1,5-dioxo-(9S)-hydroxy-2-oxabicyclo[4.3.0] nonane and (4S,8S)-dimethyl-1,5-dioxo-(9S)-hydroxy-2-oxabicyclo [4.3.0]nonane (**22**).* To a solution of trimesitylborane (TMB) (130 mg, 0.353 mmol) in THF (1 mL) was added freshly cut sodium chips (35 mg, 1.52 mmol). The resulting blue colored solution was stirred at rt for 8 h and cooled to −78 °C. To it was added a solution of epoxy ketone **5** (33.0 mg, 0.168 mmol) in THF (0.5 mL) dropwise. Stirring was continued at −78 °C for 3 h quenched with 1 mL of satd aq NH_4Cl at −78 °C. After warming to rt, the mixture was extracted with EtOAc (3×10 mL), and the combined organic layers were washed with H_2O (2×5 mL) and brine (5 mL), dried over Na_2SO_4, concentrated in vacuo and chromatographed on silica gel (elution by 9:1 then 4:1 hexanes/EtOAc) to afford 31.4 mg (94%) of lactone **22** as a colorless oil having: ^{1}H NMR: δ 4.10 (d, J=10.5 Hz, 1H), 4.00 (d, J=10.5 Hz, 1H), 2.70 (q, J=6.7 Hz, 1H), 2.59–2.52 (m, 1H), 2.44–2.32 (m, 1H), 2.18 (s, 1H), 2.05–2.02 (m, 1H), 1.88–1.82 (m, 1H), 1.49 (s, 3H), 1.16 (d, J=6.7 Hz, 3H); ^{13}C NMR: δ 207.8, 179.9, 82.7, 73.4, 49.4, 47.1, 35.9, 30.9, 13.8, 7.0; IR ($CHCl_3$): 3413, 2977, 2941, 1779, 1720 cm^{-1}; EIMS: 198 (M^+); HRMS calcd for $C_{10}H_{14}O_4$: m/z 198.0892. Found: 198.0889.

*4.2.22. (4,8S)-Dimethyl-5-(dimethyl-tert-butylsilyloxy)-(9S)-hydroxy-1-oxo-2-oxa bicyclo[4.3.0]non-4(5)-ene (**32**).* To a solution of trimesitylborane (TMB) (190 mg, 0.515 mmol) in THF (2 mL) was added freshly cut sodium chips (30 mg, 1.30 mmol). The resulting blue colored solution was stirred at rt for 8 h and cooled to −78 °C. To it was added a solution of epoxy ketone **5** (50.0 mg, 0.255 mmol) in THF (0.5 mL) dropwise. Stirring was continued at −78 °C for 24 h followed by addition of a solution of TBDMSCl (192 mg, 1.28 mmol) in THF (0.5 mL). The reaction mixture was slowly warmed to −40 °C, stirred at that temperature for 3 h and quenched with phosphate buffer (KH_2PO_4/Na_2HPO_4, pH=7.5) (3 mL) at −40 °C. After warming to rt, the aqueous layer was extracted with EtOAc (3×10 mL), and the combined organic layer was washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, concentrated in vacuo, and chromatographed by silica gel column (9:1 then 4:1 hexanes/EtOAc) to afford 56.2 mg (71%) of pure silyl enol ether **32** as a colorless oil having: ^{1}H NMR: δ 4.23 (d, J=9.3 Hz, 1H), 4.17 (d, J=9.3 Hz, 1H), 2.11–2.09 (m, 2H), 1.98–1.91 (m, 1H), 1.82 (s, 1H), 1.69 (s, 3H), 1.65–1.60 (m, 1H), 1.24 (s, 3H), 0.94 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR: δ 179.8, 149.2, 110.9, 78.3, 73.6, 45.5, 27.4, 26.8, 25.7, 18.1, 17.4, 10.3, −3.7, −3.9; IR ($CHCl_3$): 3596 (br), 2956, 2931, 2858, 1771, 1667, 1472 cm^{-1}; EIMS: 312 (M^+). HRMS calcd for $C_{16}H_{28}O_4Si$: m/z 312.1757. Found: 312.1742.

*4.2.23. (+)-5-[(E)-5′-tert-Butyldiphenylsilyloxy-4′-methyl-2′-pentenyloxy]-(4,8S)-dimethyl-(9S)-hydroxy-1-oxo-2-oxabicyclo[4.3.0]non-4(5)-ene (**33**).* To a solution of TMB (130 mg, 0.353 mmol) in THF (1 mL) was added freshly cut sodium chips (35 mg, 1.52 mmol). The resulting blue colored solution was stirred at rt for 8 h and cooled to −78 °C. To it was added a solution of epoxy ketone **5** (33.0 mg, 0.168 mmol) in THF (0.5 mL) dropwise. Stirring was continued at −78 °C for 24 h followed by addition of HMPA (0.2 mL) and a solution of allylic triflate **6** (236 mg, 0.485 mmol, prepared in situ, see **31** above) in Et_2O (1 mL) via cannula. The reaction mixture was stirred at −78 °C for 45 min and quenched with phosphate buffer (KH_2PO_4/Na_2HPO_4, pH=7.5) (3 mL) at −78 °C. After warming to rt, the aqueous layer was extracted with EtOAc (3×10 mL), and the combined organic layer was washed with H_2O (2×5 mL) and brine (5 mL), dried over Na_2SO_4, concentrated in vacuo, and chromatographed on silica gel (elution with 9:1 then 4:1 hexanes/EtOAc) to afford 46.7 mg (52%) of O-alkylation product **33** as a colorless oil having: $[\alpha]_D^{22}$ +66.0 (*c* 0.90, $CHCl_3$); ^{1}H NMR: δ 7.66 (d, J=7.6 Hz, 4H), 7.46–7.36 (m, 6H), 5.72–5.52 (m, 2H), 4.23–4.14 (m, 4H), 3.58–3.47 (m, 2H), 2.47–2.38 (m, 2H), 2.23–2.19 (m, 2H), 2.00–1.92 (m, 1H), 1.71 (s, 3H), 1.66–1.57 (m, 1H), 1.23 (s, 3H), 1.06 (s, 9H), 1.05 (d, J=6.8 Hz, 3H); ^{13}C NMR: δ 179.6, 151.8, 137.0, 135.6, 133.8, 129.6, 127.6, 125.2, 111.4, 78.2, 73.6, 68.4, 68.2, 45.4, 39.0, 27.4, 26.8, 21.8, 19.3, 17.3, 16.4, 9.7; IR (neat): 3453 (br), 3071, 3048, 2931, 2858, 1769, 1673, 1589, 1471 cm^{-1}; EIMS: 534 (M^+), 477 ($M-t$-Bu); HRMS (CI) calcd for $C_{32}H_{42}O_5Si$: m/z 534.2796. Found: 534.2798.

*4.2.24. (−)-(1S)-4-((E)(4′R)-5′-tert-butylydiphenylsiloxy-4′-methyl-2′-pentenyloxy)-2,5-dimethyl-9-oxo-8-oxabicyclo[4.3.0]nona-4,6-diene (**35**).* To a solution of enone **19** (0.10 g, 0.57 mmol) in tetrahydrofuran (2 mL) cooled to −78 °C was added sodium bistrimethylsilylamide (1.0 M in THF, 0.57 mL, 0.57 mmol) dropwise via syringe pump over 0.5 h. Upon completion of the addition, hexamethylphosphoramide (HMPA) (0.50 mL) was added and the resulting dark yellow solution was stirred at −78 °C for 0.5 h. Allylic triflate **6** (0.49 g, 1.0 mmol) was added via cannula as a solution in ether (1.5 mL) and the resulting solution was stirred for 1 h at −78 °C. The mixture was poured into aqueous sodium bicarbonate (15 mL) and extracted with ether (2×25 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Chromatography (7:1 hexane/ether) provided 0.23 g (77%) of allyl dienol ether **35** as an oil having: $[\alpha]_D^{22}$ −66.5 (*c*=5.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (m, 4H), 7.42 (m, 6H), 6.50 (s, 1H), 5.74 (dd, J=16, 6.7 Hz, 1H), 5.62 (dt, J=16, 5.5 Hz, 1H), 4.30 (d, J=5.5 Hz, 2H), 3.56 (m, 2H), 2.42 (m, 3H), 2.01 (m, 2H), 1.75 (s, 3H), 1.30 (s, 3H), 1.08 (s, 9H), 1.07 (d, J=9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.5, 149.8, 137.2, 135.6, 133.8, 130.1, 129.6, 129.4, 127.6, 125.5, 107.0, 69.1, 68.3, 42.6, 39.0, 28.2, 26.8, 22.6, 21.5, 19.3, 16.4, 10.5; IR (film): 3071, 3048, 2957, 2931, 2858, 1793, 1650, 1620, 1472, 1461, 1428 cm^{-1}. This material was used as obtained in the next transformation.

*4.2.25. (+)-(1S,5R)-5-((3′R,4′R)-5′-tert-butyldiphenylsiloxy-4′-methyl-1′-penten-3′-yl)-1,5-dimethyl-4,9-dioxo-8-oxabicyclo[4.3.0] non-6-ene (**36**) and (+)-(1S,5S)-5-((3′S,4′R)-5′-tert-butyldiphenylsiloxy-4′-methyl-1′-penten-3′-yl)-1,5-dimethyl-4,9-dioxo-8-oxabicyclo [4.3.0]non-6-ene (**37**).* A solution of dienol ether **35** (0.32 g, 0.62 mmol) in toluene (5 mL) was placed in a dry, base washed sealed tube and heated at 125 °C for 2 h. The reaction mixture allowed to cool to ambient temperature and then concentrated in vacuo. Chromatography on silica gel (elution with 3:1 hexane/ether) provided 240 mg (76%) of ketones **36** and **37** as a 3:1 mixture of diastereomeric Claisen products. The mixture could be further purified by HPLC (85:15 hexane/ether), which provided pure samples of each diastereomer. Major diastereomer (**36**): $[\alpha]_D^{22}$ +39.0 (*c* 2.64, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (m, 4H), 7.41 (m, 6H), 6.74 (s, 1H), 5.56 (dt J=16.8, 10.4 Hz, 1H,), 5.17 (dd, J=10.6, 1.6 Hz, 1H), 4.93 (dd, J=16.8, 1.6 Hz, 1H), 3.28 (dd, J=10, 8 Hz, 1H), 3.16 (dd, 1H, J=10, 8 Hz), 2.72 (dd, J=9.7, 7.1 Hz, 1H), 2.56 (m, 1H), 2.27 (ddd, J=18.6, 7.8, 2.3 Hz, 1H), 2.11 (m, 1H), 1.90 (m, 1H), 1.65 (m,

1H), 1.36 (s, 3H), 1.28 (s, 3H), 1.06 (s, 9H), 0.84 (d, *J*=9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.2, 180.5, 135.6, 135.5, 134.7, 133.5, 133.4, 130.0, 129.8, 129.7, 127.7, 120.0, 67.6, 52.4, 51.2, 43.9, 35.6, 34.7, 28.0, 26.8, 26.3, 21.8, 19.2, 14.0; IR (film): 2927, 2855, 1798, 1709, 1461, 1428 cm^{-1}; EIMS: 516 (M^+), 459 (M^+-t-Bu). HRMS (CI) calcd for $C_{32}H_{40}O_4Si$: *m*/*z* 516.7549. Found: 516.7555.

Minor diastereomer (**37**): $[\alpha]_D^{22}$ +46.6 (*c* 2.36, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (m, 4H), 7.41 (m, 6H), 6.45 (s, 1H), 5.44 (dt, *J*=17.2, 10.1 Hz, 1H), 5.04 (d, *J*=17.2 Hz, 1H), 5.03 (d, *J*=10 Hz, 1H), 3.62 (dd, *J*=10, 3 Hz, 1H), 3.45 (dd, *J*=10, 2.5 Hz, 1H), 2.66 (m, 2H), 2.31 (m, 1H), 2.17 (m, 1H), 1.75 (s, 3H), 1.72 (m, 2H), 1.13 (d, *J*=9 Hz, 3H), 1.07 (s, 9H), 1.02 (s, 3H); 13C NMR (75 MHz, $CDCl_3$): δ 208.5, 181.1, 138.0, 135.7, 135.6, 134.2, 133.6, 133.5, 130.6, 129.8, 129.7, 127.8, 127.6, 118.5, 66.7, 55.7, 51.1, 44.3, 36.2, 34.3, 33.2, 26.9, 22.8, 19.2, 17.8, 14.6; IR (film):3071, 2931, 2857, 1798, 1716, 1634, 1462, 1428 cm^{-1}; EIMS: 516 (M^+), 459 (M^+-t-Bu), 429 (M^+-Ph).

Lewis acid promoted Claisen rearrangements of were also conducted using the above procedure at various temperatures from −50 °C to 125 °C by addition of **35** in toluene to a solution of the Lewis acid promoter (2–4 equiv) at the requisite temperature or at rt followed by heating. The results are described in Table 1 above.

*4.2.26. (+)-(1S,5S)-5-((3′S,4′R)-5′-Hydroxy-4′-methyl-1′-penten-3′yl)-1,5-dimethyl-4,9-dioxo-8-oxabicyclo[4.3.0]non-6-ene hemiketal (**38**).* To a solution of ketone **36** (16 mg, 0.030 mmol) in 3:1 acetonitrile/tetrahydrofuran (0.30 mL) at rt was added 48% hydrofluoric acid (~100 μL). The reaction mixture was stirred for 36 h before being diluted with methylene chloride (3 mL) and poured into 10% sodium bicarbonate solution. The aqueous layer was extracted with methylene chloride (2×5 mL) and the combined organic extracts were dried over sodium sulfate and concentrated in vacuo. Chromatography on silica gel (elution with 3:2 hexanes/ether) provided 6.4 mg (77%) of hemiketal **38** as a white crystalline solid. Hemiketal **38** could be further purified by recrystallization from toluene to mp 195–196 °C and having: $[\alpha]_D^{22}$ +81 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.69 (s, 1H), 5.57 (ddd, *J*=17, 10, 10 Hz, 1H), 5.23 (dd, *J*=10, 2 Hz, 1H), 5.15 (dd, *J*=17, 2 Hz, 1H), 3.60 (d, *J*=8 Hz, 2H), 3.32 (t, *J*=12 Hz, 1H), 2.23 (td, *J*=14, 4 Hz, 1H), 2.13 (m, 1H), 2.04 (s, 1H), 1.85 (td, *J*=13, 4 Hz, 1H), 1.72 (m, 1H), 1.60 (m, 1H), 1.47 (s, 3H), 1.23 (s, 3H), 0.74 (d, *J*=6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.4, 135.9, 135.2, 127.7, 119.7, 98.2, 66.3, 53.5, 44.6, 42.2, 32.6, 29.2, 28.7, 23.8, 23.7, 15.2; IR (film): 3426, 2953, 2873, 1786, 1639, 1463 cm^{-1}; EIMS: 278 (M^+). The structure and stereochemistry of **38** was confirmed by single crystal X-ray analysis.

*4.2.27. (−)-(1S)-4-((E)-5′-tert-Butylydiphenylsiloxy-2′-penteny-loxy)-1,5-dimethyl-9-oxo-8-oxabicyclo[4.3.0]nona-4,6-diene (**39**).* To a solution of enone **19** (4.0 g, 22 mmol) in THF (50 mL) cooled to −78 °C was added sodium bistrimethylsilylamide (1.0 M in THF, 22 mL, 22 mmol) dropwise via syringe pump over 0.5 h. Upon completion of the addition, HMPA (19 g, 0.11 mol) was added and the resulting dark yellow solution was stirred at −78 °C for 0.5 h. Allylic triflate **31** (14 g, 29 mmol) was added quickly via cannula as a solution in ether and the resulting solution was stirred for 1 h at −78 °C. The mixture was poured into aqueous sodium bicarbonate (120 mL) and extracted with ether (3×100 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Chromatography on silica gel (elution with 8:1 hexane/ether) provided 8.9 g (81%) of allyl dienol ether **39** as an oil having: $[\alpha]_D^{22}$ −70.8 (*c* 8.19, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (m, 4H), 7.42 (m, 6H), 6.51 (s, 1H), 5.79 (dt, *J*=15, 7 Hz, 1H), 5.64 (dt, *J*=15, 6 Hz, 1H), 4.29 (d, *J*=6 Hz, 2H), 3.73 (t, *J*=7 Hz, 2H), 2.41 (m, 4H), 2.02 (m, 1H), 1.76 (s, 3H), 1.74 (m, 1H), 1.30 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.5, 149.8, 135.5, 133.8, 131.2, 130.1, 129.6, 129.4127.8, 127.6, 106.8, 69.0, 63.3, 42.6, 35.6, 28.2, 26.8, 22.6, 21.5, 19.2, 10.5; IR (film): 3117, 3070, 3048, 2931, 2858, 1793, 1649, 1620, 1472, 1460, 1445, 1428 cm^{-1}; EIMS: 445 (M^+-t-Bu).

This material was used as obtained in the next transformation.

*4.2.28. (+)-(1S,5R)-5-((3′R)-5′-tert-Butyldiphenylsiloxy-1′-penten-3′-yl)-1,5-dimethyl-4,9-dioxo-8-oxabicyclo[4.3.0]non-6-ene (**40**) and (+)-(1S,5S)-5-((3′S)-5′-tert-butyl diphenylsiloxy-1′-penten-3′-yl)-1,5-dimethyl-4,9-dioxo-8-oxabicyclo[4.3.0]non-6-ene (**41**).* A solution of dienol ether **39** (8.9 g, 18 mmol) in toluene (15 mL) was placed in a dry, base washed sealed tube and heated to 105 °C for 2 h. The reaction mixture was allowed to cool to ambient temperature, transferred to a round bottomed flask and concentrated in vacuo. Chromatography on silica gel (elution with 4:1 hexane/ether) provided 7.2 g (81%) of ketones **40** and **41** as approximately a 1:1 mixture. The mixture could be further purified by HPLC (85:15 hexane/ether) to provide the pure diastereomers: (1) **40** having: $[\alpha]_D^{22}$ +14.3 (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64(m, 4H), 7.40 (m, 6H), 6.62 (s, 1H), 5.43 (dt, 1H, *J*=16.9, 9.8 Hz), 5.07 (d, 1H, *J*=10.1 Hz), 4.98 (d, 1H, *J*=16.9 Hz), 3.72 (m, 1H), 3.54 (m, 1H), 2.81 (m, 2H), 2.36 (m, 1H), 2.16 (m, 1H), 1.79 (m, 2H), 1.62 (m, 1H), 1.55 (s, 3H), 1.12 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.7, 181.2, 137.9, 135.7, 135.6, 135.5, 133.4, 130.1, 129.8, 129.7, 129.6, 127.7, 127.6, 118.6, 61.5, 55.6, 44.6, 44.1, 34.0, 32.8, 31.1, 26.8, 22.2, 19.1, 13.5; IR (film): 3071, 2930, 2856, 1798, 1716, 1471, 1462, 1456, 1428 cm^{-1}; FDMS: 445 (M^+-t-Bu). HRMS calcd for $C_{31}H_{38}O_4Si$: *m*/*z* 502.7280. Found: 502.7280.

(2) Compound **41** having: $[\alpha]_D^{22}$ +30.8 (*c* 7.26, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (m, 4H), 7.40 (m, 6H), 6.68 (s, 1H), 5.48 (dt, *J*=17, 10 Hz, 1H), 5.12 (dd, *J*=10, 1 Hz, 1H), 4.97 (d, *J*=17 Hz, 1H), 3.62 (m, 2H), 2.64 (m, 2H), 2.41 (ddd, *J*=18.4, 6.7, 2.1 Hz, 1H), 2.05 (ddd, *J*=13.2, 7.1, 2.1 Hz, 1H), 1.91 (m, 1H), 1.58 (m, 2H), 1.44 (s, 3H), 1.27 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.2, 180.8, 136.5, 135.7, 135.6, 133.8, 133.7, 129.7, 129.6, 129.4, 127.6, 119.4, 61.7, 52.2, 47.8, 44.1, 34.8, 33.0, 28.4, 26.9, 25.7, 21.7, 19.1; IR (film): 3133, 3071, 2931, 1790, 1714, 1471, 1462, 1455, 1428 cm^{-1}; FDMS: 445 (M^+-t-Bu). HRMS calcd for $C_{31}H_{38}O_4Si$: *m*/*z* 502.7280. Found: 502.7269.

Lewis acid promoted Claisen rearrangements of were also conducted using the above procedure at various temperatures from −50 °C to 125 °C by addition of **35** in toluene to a solution of the Lewis acid promoter (2–4 equiv) at the requisite temperature or at rt followed by heating. The results are described in Table 1 above.

*4.2.29. (+)-(1S,5R)-5-((3′R)-5′-Hydroxy-1′-penten-3′-yl)-1,5-dimethyl-4,9-dioxo-8-oxabicyclo [4.3.0]non-6-ene (**42**) and (+)-(1S,5S)-5-((3′S)-5′-hydroxy-1′-penten-3′yl)-1,5-dimethyl-4,9-dioxo-8-oxabicyclo[4.3.0]non-6-ene hemiketal.* To a mixture of ketones **40** and **41** (6.2 g, 12 mmol) in acetonitrile (50 mL) was added hydrofluoric acid (48–52% aqueous solution, ca. 1 mL). The mixture was stirred at rt for 2 h at which time it was poured into aqueous sodium bicarbonate (100 mL) and extracted with methylene chloride (3×80 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Chromatography on silica gel (2:1 hexanes/ethyl acetate) provided 1.4 g (43%) of keto alcohol **42** and 1.2 g (37%) of the title hemiketal as a solids. Keto alcohol **42** could be further purified by recrystallization from methylene chloride/heptane and the hemiketal could be recrystallized from toluene. Keto alcohol **42** had mp 127–128 °C, $[\alpha]_D^{22}$ +77 (*c* 6.7, $CHCl_3$) and ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.63 (s, 1H), 5.54 (dt, *J*=19, 10 Hz, 1H), 5.12 (d, *J*=10 Hz, 1H), 5.10 (d, *J*=17 Hz, 1H), 3.70 (m, 1H), 3.55 (m, 1H), 2.85 (t (br), *J*=11 Hz, 1H), 2.81 (td, *J*=15, 6 Hz, 1H), 2.39 (dm, *J*=11 Hz, 1H), 2.15 (dm, *J*=13 Hz, 1H), 1.77 (m, 2H), 1.72 (s, 3H), 1.42 (m, 2H), 1.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.8, 181.2, 138.1, 135.9, 130.1, 118.7, 60.1, 55.5, 44.7, 44.2, 34.0, 32.7, 31.1, 22.1, 13.9; IR (film): 3750, 3123, 3074, 2944, 2879, 1793, 1717, 1636, 1458,

1421 cm^{-1}; EIMS: 264 (M^+). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.15; H, 7.63. Found: C, 67.74; H, 7.81.

Title hemiketal had mp 154–155 °C, $[\alpha]_D^{22}$ +19.6 (*c* 8.4, $CHCl_3$), and ^1H NMR (300 MHz, $CDCl_3$): δ=6.72 (s, 1H), 6.15 (ddd, *J*=17, 11, 5 Hz, 1H), 5.19 (d, *J*=2 Hz, 1H), 5.14 (d (broad, *J*=7 Hz), 1H), 4.07 (ddd, *J*=12, 11, 3 Hz, 1H), 3.70 (dd, *J*=11, 5 Hz, 1H), 2.78 (d(br), *J*=13 Hz, 1H), 2.26 (s(br), 1H), 2.24 (td, *J*=14, 4 Hz, 1H), 2.03 (qd, *J*=13, 6 Hz, 1H), 1.82 (td, *J*=14, 4 Hz, 1H), 1.67 (dt, *J*=13, 3 Hz, 1H), 1.55 (m, 2H), 1.45 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=182.2, 138.6, 136.4, 127.6, 115.9, 98.4, 60.2, 44.6, 43.6, 42.2, 32.5, 29.1, 25.5, 24.2, 23.8; IR (film): 3486, 3000, 2983, 2965, 2926, 2874, 1777, 1646, 1395 cm^{-1}; EIMS: 264 (M^+).

4.2.30. (1S,5R)-5-((3′R)-5′-Carboxy-1′-penten-3′-yl)-1,5-dimethyl-4,9-dioxo-8-oxa bicyclo[4.3.0]non-6-ene. To an aqueous solution of 1.5 M sulfuric acid (32.7 mL, 49.0 mmol) at 0 °C was added chromium trioxide (2.04 g, 20.4 mmol). To the resulting orange solution was added a solution of keto alcohol **42** (1.30 g, 5.54 mmol) in acetone (10 mL). The mixture was stirred for 2 h before the excess chromic acid was quenched by the addition of solid tartaric acid (~2 g). When a deep blue solution resulted, the mixture was extracted with methylene chloride (3×40 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated in vacuo to provide 1.36 g (98%) of the derived carboxylic acid as an oil: $[\alpha]_D^{22}$ +79.6 (*c* 12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 11.4 (s (broad), 1H), 6.66 (s, 1H), 5.55 (m, 1H), 5.13 (s, 1H), 5.08 (d, *J*=5 Hz, 1H), 3.23 (t, *J*=9 Hz, 1H), 2.84 (td, *J*=15, 6 Hz, 1H), 2.53 (dd, *J*=14, 2 Hz, 1H), 2.41 (dt, *J*=13, 1 Hz, 1H), 2.29 (dd, *J*=15, 1 Hz, 1H), 2.17 (dm, *J*=11 Hz, 1H), 1.79 (td, *J*=14, 4 Hz, 1H), 1.71 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.1, 180.8, 177.6, 138.7, 134.0, 129.6, 119.0, 54.8, 44.1, 44.0, 34.2, 33.9, 32.8, 22.0, 13.6; IR (film): 3260(b), 3124, 2982, 1794, 1713, 1637, 1560, 1508, 1458, 1420 cm^{-1}; EIMS: 278 (M^+).

This material was used directly in the next transformation.

*4.2.31. (1S,5R)-5-((3′R,4′R)-4′-Iodomethyl-g-lacton-3′-yl)-1,5-dimethyl-4,9-dioxo-8-oxabicyclo[4.3.0]non-6-ene (**43**).* To a solution of potassium iodide (4.7 g, 28 mmol) and sodium bicarbonate (1.2 g, 14 mmol) in water (25 mL) was added the preceding carboxylic acid (1.3 g, 4.7 mmol) as a solution in methylene chloride (5 mL). The mixture was stirred vigorously and then iodine (1.2 g, 4.9 mmol) was added. The mixture was stirred for 16 h before being extracted with methylene chloride (3×20 mL). The organic layers were combined, washed with 10% sodium thiosulfate solution until colorless, dried over sodium sulfate and concentrated in vacuo to provide 1.3 g (68%) of iodolactone **43** as an oil having $[\alpha]_D^{22}$ +65 (*c*=3.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.75 (s, 1H), 4.50 (m, 1H), 3.26 (m, 2H), 2.99 (m, 2H), 2.75 (dd, *J*=18, 10 Hz, 1H), 2.56 (ddd, *J*=16, 4, 3 Hz, 1H), 2.39 (dd, *J*=18, 3 Hz, 1H), 2.20 (ddd, *J*=13, 6, 3 Hz, 1H), 1.89 (td, *J*=14, 5 Hz, 1H), 1.66 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.0, 180.1, 174.1, 138.8, 128.4, 77.6, 52.3, 43.8, 43.2, 34.8, 31.8, 29.821.6, 13.9, 7.9; IR (film): 2935, 1786, 1712, 1636, 1458, 1419 cm^{-1}; EIMS: 404 (M^+), 277 (M^+–I). HRMS calcd for $C_{15}H_{17}IO_5$: *m*/*z* 404.2021. Found: 404.2001.

*4.2.32. (1S,4aR,4bS,8aR)-1,2,3,4,4a,4b,5,6,7,8,8a,9-Dodecahydro-1-carbomethoxy-1,4a-dimethyl-4,6-dioxo-7,9-dioxaphenanthrene (**44**).* To a solution of iodolactone **43** (1.3 g, 3.3 mmol) in tetrahydrofuran (15 mL) was added 0.5 M potassium hydroxide (13 mL, 6.6 mmol). The mixture was capped and stirred at ambient temperature for 2 h. At this time the mixture was acidified (pH <2) with concentrated hydrochloric acid, and stirred an additional 3 h. Sodium chloride (solid) was added, and the reaction mixture was extracted with tetrahydrofuran (4×10 mL). The organic layers were combined, dried over sodium sulfate, and concentrated in vacuo. An ethereal solution of diazomethane was prepared by adding an excess of *N*-nitroso-*N*-methylurea to a biphasic mixture of ether (20 mL) and 20% potassium hydroxide solution (20 mL). The resulting yellow diazomethane solution was added directly to the above residue, and the mixture was stirred vigorously overnight to ensure complete evaporation of excess diazomethane. The reaction mixture was concentrated in vacuo and then chromatographed (2:1, hexanes/ethyl acetate) to provide 0.49 g (53%) of vinyl ether **44** as a thick oil having $[\alpha]_D^{22}$ −87 (*c* 1.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.42 (s, 1H), 4.57 (dd, *J*=13, 1.3 Hz, 1H), 4.37 (dd, *J*=13, 1.3 Hz, 1H), 4.28 (m, 1H), 3.68 (s, 3H), 2.83 (ddd, *J*=15, 12, 5.3 Hz, 1H), 2.72 (dd, *J*=19, 7 Hz, 1H), 2.50 (m, 2H), 2.24 (dt, *J*=17, 5 Hz, 1H), 2.00 (dd, *J*=18, 12 Hz, 1H), 1.50 (td, *J*=13, 4 Hz, 1H), 1.36 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.6, 176.3, 169.0, 141.3, 114.0, 71.0, 65.8, 52.4, 48.9, 43.2, 35.9, 35.8, 33.1, 29.0, 28.6, 25.0; IR (film): 2971, 2921, 1735, 1725, 1644, 1460, 1435, 1407 cm^{-1}; EIMS: 308 (M^+). HRMS calcd for $C_{16}H_{21}O_6$ (M^++H): *m*/*z* 309.1334. Found: 309.1324.

*4.2.33. (−)-(1S,4aR,4bS,8aR,10S,10aR)-Tetradecahydro-1-carbomethoxy-1,4a-dimethyl-4,6-dioxo-10(10a)-epoxy-7,9-dioxaphenanthrene (**45**).* To a solution of vinyl ether **44** (87 mg, 0.28 mmol) in methylene chloride were added monobasic sodium phosphate hydrate (0.23 g, 1.7 mmol) and *m*-chloroperoxybenzoic acid (0.15 g, 0.85 mmol). The mixture was stirred at ambient temperature for 12 h before being diluted with aqueous sodium bicarbonate (5 mL) and extracted with methylene chloride (3×5 mL). The organic layers were combined, dried over sodium sulfate and concentrated in vacuo. Chromatography on silica gel (elution by 2:1 ethyl acetate/hexanes) provided 77 mg (84%) of epoxide **45** as a crystalline solid that could be further purified by recrystallization from methylene chloride/heptane to afford **45** as a white solid having mp 170 °C (dec), $[\alpha]_D^{22}$ −95.2 (*c* 1.35, $CHCl_3$), and ^1H NMR (300 MHz, $CDCl_3$): δ 5.11 (s, 1H), 4.46 (d, *J*=13 Hz, 1H), 4.32 (d, *J*=12 Hz, 1H), 3.98 (s,1H), 3.69 (s, 3H), 2.75 (m, 3H), 2.39 (m, 1H), 2.11 (dd, *J*=12, 5 Hz, 1H), 2.01 (dd, *J*=17, 12 Hz, 1H), 1.82 (m, 1H), 1.41 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.7, 172.4, 169.3, 79.6, 71.1, 62.0, 59.4, 52.4, 49.4, 45.5, 33.5, 33.4, 28.5, 26.5, 22.3, 19.7; IR (film): 2951, 1731, 1712, 1460, 1407 cm^{-1}; EIMS: 308 (M^+−16 (O)). HRMS calcd for $C_{16}H_{21}O_7$: *m*/*z* 325.3392. Found: 325.3399.

*4.2.34. (−)-(1S,2R,5S,8aR)-1,2,3,5,6,7,8,8a-Octahydro-5-carbomethoxy-5,8a-dimethyl-1-methyl-ene carbo-N-methoxy-N-methylamido-3-oxa-8-oxo-2-naphthyl alcohol (**46**).* To a suspension of methoxymethylamine hydrochloride (61 mg, 0.63 mmol) in methylene chloride (1 mL) at 0 °C was added dropwise trimethylaluminum (2.0 M in hexane, 0.32 mL, 0.63 mmol). When complete dissolution was observed, the solution was transferred via cannula to a solution of vinyl ether **44** (88 mg, 0.29 mmol) in methylene chloride (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min before being quenched with satd Rochelle's salts (10 mL) and extracted with methylene chloride (3×10 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo to provide 0.10 g (95%) of hydroxy amide **46** as an oil having $[\alpha]_D^{22}$ −53 (*c* 3.2, $CHCl_3$); ^1H NMR (300 MHz, CDCl3): δ 6.40 (s, 1H), 4.39 (m, 1H), 4.30 (m, 1H), 3.72 (m, 4H), 3.63 (s, 3H), 3.40 (t, 1H, *J*=10 Hz), 3.22 (s, 3H), 2.95 (ddd, 1H, *J*=17, 12, 5 Hz), 2.84 (d, 1H, *J*=6 Hz), 2.53 (dt, 1H, *J*=13, 5 Hz), 2.29 (m, 2H), 2.02 (d (br), 1H, *J*=17 Hz), 1.53 (td, 1H, *J*=13, 4 Hz), 1.39 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.0, 176.3, 174.2, 141.5, 115.3, 72.8, 60.7, 60.4, 52.0, 50.3, 43.0, 35.7, 34.5, 33.1, 32.0, 29.4, 28.1, 24.7; IR (film): 3396, 2949, 1723, 1711, 1641, 1434, 1390 cm^{-1}; EIMS: 308 (M^+–HN(OMe)Me). This material was of sufficient purity for use as obtained in the following transformation.

*4.2.35. (−)-(1S,2R,5S,8aR)-1,2,3,5,6,7,8,8a-Octahydro-5-carbomethoxy-5,8a-dimethyl-1-methylene carbo-N-methoxy-N-methylamido-3-oxa-8-oxo-2-naphthaldehyde (**47**).* To a solution of alcohol **46**

(0.10 g, 0.28 mmol) in methylene chloride was added Dess–Martin periodinane (190 mg, 0.44 mmol) portionwise. The reaction mixture was capped and stirred at ambient temperature for 2 h. The mixture was then quenched with 10% sodium bicarbonate (2 mL) and 10% sodium thiosulfate (2 mL). When a clear biphasic mixture was obtained, the mixture was extracted with methylene chloride (3×5 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Chromatography on silica gel (elution by 2:1 ethyl acetate/hexanes) afforded 92 mg (90%) of aldehyde **47** as a pale yellow oil having $[\alpha]_D^{22}$ −39 (*c* 1.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 9.60 (s, 1H), 6.52 (s, 1H), 4.67 (s, 1H), 3.71 (s, 3H), 3.59 (s, 3H), 3.23 (m, 1H), 3.11 (s, 3H), 2.89 (ddd, *J*=17, 12, 5 Hz, 1H), 2.51 (dt, *J*=14, 5 Hz, 1H), 2.31 (dt, *J*=17, 5 Hz, 1H), 2.23 (dd, *J*=17, 8 Hz, 1H), 2.10 (dd, *J*=17, 1 Hz, 1H), 1.57 (td, *J*=13, 4 Hz, 1H), 1.41 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.0, 196.4, 175.8, 171.8, 140.9, 116.2, 78.4, 60.7, 51.7, 49.4, 43.1, 36.3, 35.8, 32.6, 32.1, 29.6, 28.3, 24.8; IR (film): 2950, 1724, 1645, 1446, 1387 cm^{-1}; EIMS: 367 (M^+), 307 (M^+–N(OMe)Me). This material was used as obtained in the next transformation.

*4.2.36. (1R,2R,3S,7S,8S,9R,10RS)-2-Bromo-3-carbomethoxy-3,7-dimethyl-10-hydroxy-8-methylenecarbo-N-methoxy-N-methylamido-6-oxo-11,12-dioxatricyclo [6.2.1.0^{2,7}]dodecane (**48**).* To a solution of aldehyde **47** (110 mg, 0.30 mmol) in 3:1 tetrahydrofuran/water (3 mL) at rt was added *N*-bromoacetamide (43 mg, 0.30 mmol) in one portion. The reaction mixture was stirred for 4 h before being quenched with 10% sodium thiosulfate (3 mL) and extracted with methylene chloride (3×5 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Chromatography on silica gel (elution by 1:1 hexanes/ethyl acetate) provided 85 mg, (61%) of bromolactol **48** as ~6:1 mixture of lactol epimers: major epimer: $[\alpha]_D^{22}$ −4.5 (*c* 2.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.79 (s, 1H), 5.35 (d, *J*=7 Hz, 1H), 4.20 (d, *J*=3 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.42 (m, 1H), 3.20 (s, 3H), 3.05–2.82 (m, 3H), 2.36–2.18 (m, 3H), 1.82 (d (br), *J*=7 Hz, 1H), 1.52 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.2, 175.0, 173.1, 101.1, 95.1, 81.4, 77.7, 61.0, 54.7, 51.8, 49.2, 38.7, 36.1, 32.7, 32.1, 28.1, 24.2, 21.8; IR (film): 3396, 2950, 1714, 1658, 1461, 1385 cm^{-1}; FAB MS: 464 ($^{79}BrM^+$+H), 466 ($^{81}BrM^+$+H). This material was pure enough for use directly in the next transformation.

*4.2.37. (+)-(1S,2R,4R,4aS,5S,8aR)-Decahydro-5-carbomethoxy-5,8a-dimethyl-1-methylenecarbo-N-methoxy-N-methylamido-3-oxa-8-oxo-2-naphthaldehyde (**49**).* To a solution of bromolactol **48** (37 mg, 0.080 mmol) in acetonitrile (1.5 mL) was added triethylamine (0.50 mL), and the mixture was heated to 65 °C. Silver tetrafluoroborate (40 mg, 0.20 mmol) was added and the reaction mixture was stirred at 65 °C for 30 min. The mixture was cooled to rt, quenched with 10% sodium bicarbonate (3 mL) and extracted with methylene chloride (3×5 mL). The combined organic layers were filtered through a plug of Celite, dried over sodium sulfate, and concentrated in vacuo. The residue was quickly chromatographed on silica (100% ethyl acetate) to provide 23 mg (75%) of epoxy aldehyde **49** as an oil having: $[\alpha]_D^{22}$ +9.4 (*c* 1.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 9.48 (s, 1H), 5.11 (s, 1H), 4.63 (d, *J*=2 Hz, 1H), 3.81 (s, 3H), 3.74 (m, 1H), 3.63 (s, 3H), 3.21 (dd, *J*=7, 5 Hz, 1H), 3.15 (s, 3H), 2.54 (m, 1H), 2.53 (m, 3H), 1.87 (dd, *J*=13, 4 Hz, 1H), 1.46 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.7, 196.4, 175.0, 172.4, 78.9, 78.0, 65.1, 60.4, 52.3, 51.2, 44.0, 38.2, 35.5, 32.0, 30.4, 22.7, 21.9; IR (film): 2952, 1728, 1655, 1433, 1389 cm^{-1}; EIMS: 383 (M^+), 323 (M^+–N(OMe)Me).

This material was used as obtained in the following transformation.

*4.2.38. (+)-(1S,2R,4R,4aS,5S,8aR)-Decahydro-5-carbomethoxy-5,8a-dimethyl-4(4a)-epoxy-1-methylene carbo-N-methoxy-N-methylamido-3-oxa-8-oxo-2-naphthyl-3′furyl ketone (**50**).* To a solution of 3-tributylstannylfuran (35.7 mg, 0.10 mmol) in ether (0.8 mL) at −78 °C under argon was added *n*-BuLi (1.6 M in hexane, 0.16 mL, 0.10 mmol) and stirred for 1 h. At this time, a solution of epoxy aldehyde **49** (19 mg, 0.05 mmol) in toluene (0.5 mL) precooled to −78 °C was added dropwise by cannula. The reaction mixture was then stirred at −78 °C for an additional 1 h before being quenched with saturated ammonium chloride solution and extracted with methylene chloride (3×5 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo.

The resulting crude mixture of 2° alcohols was dissolved in methylene chloride (2 mL) and Dess–Martin periodinane (34 mg, 0.080 mmol) was added. The reaction mixture was stirred for 3 h before being quenched with 10% sodium bicarbonate (2 mL) and 10% sodium thiosulfate (2 mL). When a clear solution resulted the layers were separated and the aqueous phase washed with two additional portions of methylene chloride (10 mL total volume). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Chromatography on silica gel (elution with 1:1 hexanes/ethyl acetate) provided 10.5 mg (48%) of **50** as a colorless oil having: $[\alpha]_D^{22}$ +9.4 (*c* 0.64, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.43 (s, 1H), 6.77 (s, 1H), 5.17 (s, 1H), 4.98 (d, *J*=2 Hz, 1H), 3.83 (s, 3H), 3.72 (m, 1H), 3.57 (s, 3H), 3.22 (m, 1H), 3.04 (s, 3H), 2.80 (m, 1H), 2.70 (dd, *J*=19, 6 Hz, 1H), 2.54 (ddd, *J*=19, 18, 4 Hz, 1H), 2.42 (d (br), *J*=18 Hz, 1H), 1.90 (dd, *J*=13, 4 Hz, 1H), 1.53 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.5, 198.0, 190.5, 175.2, 147.4, 144.4, 143.4, 125.4, 108.8, 79.1, 65.1, 60.6, 52.4, 51.4, 44.1, 40.5, 35.6, 32.2, 30.6, 29.5, 22.7, 22.1; IR (film): 2950, 1727, 1661, 1459, 1385 cm^{-1}. EIMS: 449 (M^+), 389 (M^+–N(OMe)Me). HRMS calcd for $C_{22}H_{27}NO_9$: *m*/*z* 449.1680. Found: 449.1680.

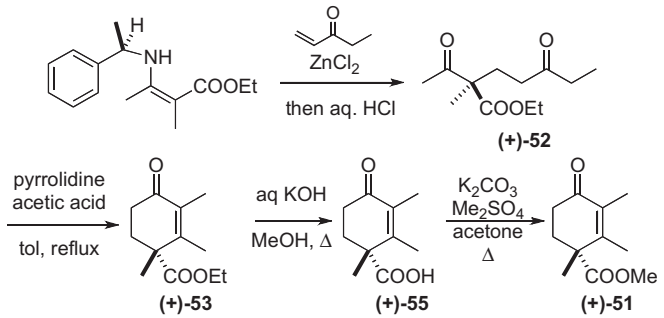
*4.2.39. (S)-(−)-Ethyl 4-oxo-1,2,3-trimethyl-2-cyclohexene-1-carboxylate [(−)-**53**]*[26b]. A mixture of 13.4 g of (*S*)-(−)-α-methylnaphthylamine (78 mmol), 11.3 g (78 mmol) of ethyl 2-methylacetoacetate and a catalytic amount (75 mg) of *p*-toluensulfonic acid in 100 mL of dry toluene was heated at reflux for 20 h with azeotropic removal of water using a Dean–Stark trap. After cooling to rt, ~200 mg of solid $NaHCO_3$ was added and the solution was filtered through a pad of silica gel using hexanes/EtOAc 4:1 containing 2% Et_3N as eluent. Evaporation of the solvent at reduced pressure afforded 20.7 g (89%) of vinylogous carbamate ($[\alpha]_D^{20}$ +299 (*c* 5.5, CH_3OH)).[26b] To a suspension of anhyd $ZnCl_2$ (11 mg) in 4 mL of dry toluene was added 0.30 mL ethyl vinyl ketone (2.73 mmol, 1.3 equiv) dropwise at 0 °C and the resulting mixture was stirred for 40 min. After cooling the reaction mixture further to −30 °C, a solution of 625 mg of carbamate (2.1 mmol) in 4 mL of dry toluene was added dropwise. The resulting reaction mixture was stirred at −30 °C for 1.5 h, then hydrolyzed by addition of 5 mL of 10% aq HOAc with stirring and warming from 0 °C to rt overnight. The aqueous phase was separated and extracted thoroughly four times with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. The residue was purified by chromatography (with elution by hexanes/EtOAc 4:1) to afford 291 mg (61%) of diketone (−)-**52**,[25] $[\alpha]_D^{22}$ −6 (*c* 5.113, $CHCl_3$), along with 49 mg of a mixture of (−)-**53** (minor amount) and its regioisomer **54** (11% combined): ^1H NMR (400 MHz, $CDCl_3$): δ 4.20 (dq, *J*=7.2, 0.9 Hz, 2H), 2.42 (q, *J*=7.3 Hz, 2H), 2.46–2.36 (m, 2H), 2.16 (ddd, *J*=14.2, 9.5, 6.0 Hz, 1H), 2.16 (s, 3H), 2.06 (ddd, *J*=14.2, 9.9. 5.9 Hz, 1H), 1.34 (s, 3H), 1.27 (t, *J*=7.2 Hz, 3H), 1.05 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.7, 205.0, 172.5, 61.2, 58.6, 37.0, 35.7, 28.4, 25.9, 19.1, 13.8, 7.6: IR (neat): 2981, 2940, 1713, 1461 cm^{-1}; APCI (+): 229 ($[M+H]^+$, 10), 211 (51), 183 (17), 145 (85), 139 (100).

A solution 286 mg (1.25 mmol) of (−)-**52** in 15 mL dry toluene was heated to reflux and then 0.31 mL (3.7 mmol) of pyrrolidine

was added followed by addition of 0.28 mL (5 mmol) of glacial HOAc. The mixture was stirred at reflux for 3 h with azeotropic removal of water using a Dean–Stark trap. After cooling to rt and concentration at reduced pressure, the residue was purified by chromatography (with elution by hexanes/EtOAc 4:1) to afford 229 mg (87%) of (*S*)-(−)-ethyl 4-oxo-1,2,3-trimethyl-2-cyclohexene-1-carboxylate [(−)-**53**] ($[\alpha]_D^{22}$ −82 (*c* 0.989, $CHCl_3$, 95% ee)) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (dq, *J*=7.2, 1.8 Hz, 2H), 2.55–2.36 (m, 3H), 1.91 (ddd, *J*=11.8, 6.8, 3.8 Hz, 1H), 1.89 (q, *J*=0.9 Hz, 3H), 1.80 (q, *J*=0.9 Hz, 3H), 1.43 (s, 3H), 1.27 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 197.8, 180.6, 154.2, 132.7, 48.2, 33.7, 33.4, 22.2, 18.1, 11.4; IR (neat): 2940, 1729, 1666 cm^{-1}; APCI (+): 183 ($[M+H]^+$, 7), 139 (100), 111 (17).

*4.2.40. (S)-(−)-Methyl 4-oxo-1,2,3-trimethyl-2-cyclohexene-1-carboxylate (−)-(**51**)[26c].* A mixture of 10.2 g (48 mmol) of (−)-**53** in 60 mL of CH_3OH and 32 mL (62.4 mmol, 1.3 equiv) of 2 M aq KOH was heated at reflux for 3 h. After cooling to rt and acidification to pH ≤1 with 10% aq hydrochloric acid, the solution was saturated with solid NaCl and extracted thoroughly four times with EtOAc. The combined organic phases were washed once with brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. An analytical sample of acid (−)-**55** was purified by chromatography and had $[\alpha]_D^{22}$ −96 (*c* 0.989, $CHCl_3$).[26c] Crude acid (−)-**55** above was dissolved in 200 mL of acetone and 33 g (240 mmol) of K_2CO_3 and 5.4 mL (57 mmol) of $(CH_3)_2SO_4$ were added sequentially at rt and the mixture was heated at reflux with stirring for 2 h. After cooling to rt, 150 mL of 1.5 M aq NaOAc was added and stirring was continued at rt overnight. The biphasic mixture was separated and the aqueous phase was extracted thoroughly four times with EtOAc. The combined organic phases were washed once with brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. The residue was purified by chromatography (with elution by a gradient of hexanes/EtOAc 7:1 to 4:1) to afford 8.95 g of (*S*)-(−)-methyl 4-oxo-1,2,3-trimethyl-2-cyclohexene-1-carboxylate [(−)-**51**][26c] (95% from (−)-**53**) as a yellow oil: $[\alpha]_D^{22}$ −93 (*c* 1.523, $CHCl_3$): IR (neat): 2951, 1732, 1669, 1428 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.69 (3H, s), 2.49–2.32 (3H, m), 1.92–1.84 (1H, m), 1.84 (3H, q, *J*=0.9), 1.75 (3H, br s), 1.40 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.2, 175.4, 154.1, 132.3, 52.3, 48.4, 33.7, 33.3, 22.1, 17.9, 11.3. APCI (+): 197 ($[MH]^+$, 100), 169 (30), 137 (34).

*4.2.41. The R series of derivatives **51**–**53** and **55**, were prepared starting with R(+)-α-methyl benzyl amine as shown below using the procedures described for the S series above.*



*4.2.41.1. Ethyl R-(+)-2-acetyl-2-methyl-5-oxo-heptanoate (+)-**52**[26a].* $[\alpha]_D^{22}$ +6 (*c* 5.113, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20 (dq, *J*=7.2, 0.9 Hz, 2H), 2.42 (q, *J*=7.3 Hz, 2H), 2.46–2.36 (m, 2H), 2.16 (ddd, *J*=14.2, 9.5, 6.0 Hz, 1H), 2.16 (s, 3H), 2.06 (ddd, *J*=14.2, 9.9, 5.9 Hz, 1H), 1.34 (s, 3H), 1.27 (t, *J*=7.2 Hz, 3H), 1.05 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.7, 205.0, 172.5, 61.2, 58.6, 37.0, 35.7, 28.4, 25.9, 19.1, 13.8, 7.6; IR (neat): 2981, 2940, 1713, 1461 cm^{-1}; APCI (+): 229 ($[M+H]^+$, 10), 211 (51), 183 (17), 145 (85), 139 (100).

*4.2.41.2. Ethyl R-(+)-1,2,3-trimethyl-4-oxo-3-cyclohexenyl-carboxylate (+)-**53**[26c].* $[\alpha]_D^{22}$ +84 (*c* 2.155, $CHCl_3$, 95% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (dq, *J*=7.2, 1.8 Hz, 2H), 2.55–2.36 (m, 3H), 1.91 (ddd, *J*=11.8, 6.8, 3.8 Hz, 1H), 1.89 (q, *J*=0.9 Hz, 3H), 1.80 (q, *J*=0.9 Hz, 3H), 1.43 (s, 3H), 1.27 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 197.8, 180.6, 154.2, 132.7, 48.2, 33.7, 33.4, 22.2, 18.1, 11.4; IR (neat): 2940, 1729, 1666 cm^{-1}; APCI (+): 183 ($[M+H]^+$, 7), 139 (100), 111 (17).

*4.2.41.3. 1,2,3-Trimethyl-4-oxo-cyclohex-2-enecarboxylic acid (+)-**55**[26c].* $[\alpha]_D^{22}$ +96 (*c* 0.989, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.24 (s(br), 1H), 2.61–2.38 (m, 3H), 1.98–1.91 (m, 1H), 1.94 (d(br), *J*=0.7, 3H), 1.78 (d(br), *J*=0.7, 3H), 1.44 (s,3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 197.8, 180.6, 154.2, 132.7, 48.2, 33.7, 33.4, 22.2, 18.1, 11.4; IR (neat): 2940, 1729, 1666, 1452 cm^{-1}; APCI (+): 183 ($[M+H]^+$, 7), 139 (100), 111 (17).

*4.2.41.4. Methyl R-(+)-1,2,3-trimethyl-4-oxo-cyclohex-2-enecarboxylate (+)-**51**[26c].* $[\alpha]_D^{22}$ +93 (*c* 1.523, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.69 (3H, s), 2.49–2.32 (3H, m), 1.92–1.84 (1H, m), 1.84 (3H, q, *J*=0.9 Hz), 1.75 (3H, br s), 1.40 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.1, 175.4, 154.2, 132.4, 52.3, 48.4, 33.7, 33.3, 22.0, 17.9, 11.3; IR (neat): 2951, 1732, 1669, 1428 cm^{-1}; APCI (+): 197 ($[M+H]^+$, 100), 169 (30), 137 (34).

*4.2.42. 1S-(+)-4-[(E)-5′-tert-Butyldiphenylsilyloxy-4′-methyl-2′-pentenyloxy]-1,3-dimethyl-2-methylene-cyclohex-3-ene (**58**).* Allylic triflate **31** was prepared in situ as follows: (*E*) 5-*tert*-butyldiphenylsilyloxy-2-penten-1-ol (8.2 g, 24 mmol),[41] and a catalytic amount of 1,10-phenantroline were dissolved in ~60 mL of dry ether and cooled to −78 °C; *n*-BuLi was added until the equivalence point then, after 5 min, Tf_2O (4.2 mL, 25 mmol) was added quickly. After stirring for 10 min at −78 °C the reaction mixture was transferred via cannula to a solution of the enolate as described below. A solution of 4.25 g (21.7 mmol) of (−)-**51** (≥95% ee) in 40 mL of anhyd THF was added dropwise under Ar to KHMDS (4.12 g, 20.6 mmol) in anhyd THF (50 mL) at −78 °C followed by addition of anhyd HMPA (20 mL) and the mixture was stirred for 30 min at −78 °C, then warmed to rt and stirred for 2 h. After recooling the reaction mixture to −78 °C, the solution of **31**, prepared above, was added via cannula and stirring was continued for 30 min at −78 °C. The reaction mixture was then poured into satd aq $NaHCO_3$ (350 mL) containing Et_3N (10 mL) and the resulting mixture was stirred at rt for 20 min. The reaction mixture was extracted with three 200 mL portions of EtOAc, and the organic layer was washed successively with water and brine, dried over K_2CO_3, filtered, and the solvent removed in vacuo. The residue was chromatographed on silica gel (hexanes/EtOAc 30:1 to 1:1 containing 2% of Et_3N) to afford 6.90 g (65%) of (+)-**58** having $[\alpha]_D^{22}$ +37 (*c* 2.142, Et_2O) and ^{1}H NMR (400 MHz, C_6D_6): δ 7.86–7.84 (m, 4H), 7.34–7.32 (m, 6H), 5.72 (dt, J_1=15.4, J_2=6.5 Hz, 1H), 5.58 (dt, J_1=15.4, J_2=5.5 Hz, 1H), 5.15 (s, 1H), 5.06 (s, 1H), 4.09 (d(br), *J*=5.5 Hz, 2H), 3.73 (t, *J*=6.5 Hz, 2H), 3.43 (s, 3H), 2.50–2.41 (m, 1H), 2.39 (dd, J_1=12.7, J_2=6.0 Hz, 1H), 2.29 (q (br), *J*=6.5 Hz, 2H), 2.14–2.05 (m, 1H), 2.09 (s, 3H), 1.58–1.53 (m, 1H), 1.50 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6): δ 176.0, 151.4, 147.9, 136.0, 134.2, 130.1, 129.9, 128.6, 128.0, 113.4, 106.3, 68.0, 63.7, 51.5, 46.8, 36.0, 32.6, 27.1, 24.1, 23.2, 19.4, 11.7; IR (neat): 2931, 1732, 1643, 1428 cm^{-1}; APCI (+): 519 ($[M+H]^+$, 7), 441 (100), 197 (8); APIES (+): 519 ($[M+H]^+$, 85), 323 (28), 197 (100), 157 (79), 129 (42), 102 (23).

Owing to its sensitivity, this material was used as obtained for the following transformation.

*4.2.43. (−)-(4S)-2-[(E)-5′-tert-Butylydiphenylsiloxypenten-3′(R)-yl]-2,4-dimethyl-3-methylene-4-carbomethoxycyclohexanone (**59**).* Freshly distilled $TiCl_4$ (1.5 mL, 14.0 mmol) was dissolved in anhyd CH_2Cl_2 (75 mL) containing suspended powdered activated 4 Å MS, and a 2 M solution of Me_3Al in toluene (7.0 mL, 14.0 mmol) was added under Ar at −65 °C. After 10 min, a solution of **58** (2.72 g, 5.22 mmol) in 25 mL of anhyd CH_2Cl_2 containing suspended powdered activated 4 Å MS was added dropwise, and the deep purple reaction mixture was stirred for 25 min before dilution with tech Et_2O. Water was added and, after warming to rt, the salts were dissolved by addition of 1 N aq HCl. The aqueous phase was extracted three times with portions of EtOAc and the organic layer was washed successively with brine containing $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. The residue was chromatographed using a gradient of hexanes/EtOAc (6:1 to 1:1) to afford 2.03 g (75%) of (−)-**59** ($[\alpha]_D^{22}$ −26 (*c* 1.895, $CHCl_3$)); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66–7.63 (m, 4H), 7.45–7.35 (m, 6H), 5.44 (dt, J_1=17.0, J_2=10.0 Hz, 1H), 5.30 (s,1H), 5.17 (s, 1H), 5.05 (dd, J_1=10.0, J_2=1.9 Hz, 1H), 4.96 (dd, J_1=17.0, J_2=1.9 Hz, 1H), 3.68 (ddd, J_1=10.1, J_2=6.4, J_3=3.4 Hz, 1H), 3.63 (s, 3H), 3.54 (dt, J_1=10.1, J_2=4.6 Hz, 1H), 2.80 (ddd, J_1=11.8, J_2=10.0, J_3=2.2 Hz, 1H), 2.65 (ddd, J_1=18.1, J_2=12.2, J_3=7.8 Hz, 1H), 2.43 (ddd, J_1=18.1, J_2=7.3, J_3=1.9 Hz, 1H), 2.28 (ddd, J_1=14.7, J_2=12.2, J_3=7.3 Hz, 1H), 2.09 (ddd, J_1=14.7, J_2=7.8, J_3=1.9 Hz, 1H), 2.02–1.94 (m, 1H), 1.49 (s, 3H), 1.25–1.17 (m, 1H), 1.20 (s, 3H), 1.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.9, 176.3, 151.4, 137.6, 135.5, 133.7, 133.6, 129.6, 127.6, 118.0, 115.5, 61.4, 58.7, 52.1, 46.4, 45.2, 35.6, 30.4, 30.3, 27.2, 26.8, 19.1, 17.1. IR (neat): 2952, 1732, 1428 cm^{-1}; APCI (+): 519 ([M+H]+, 79), 441 (100), 395 (18), 263 (25). HRMS calcd for $C_{32}H_{43}O_4Si$ $(M+H)^+$: *m*/*z* 519.2931. Found: 519.2929.

*4.2.44. (+)-(2S,5S,7R,8R)-5-Carbomethoxy-5,7-dimethyl-8-(1-ethenyl)-2-methoxy-4-methylene-1-oxabicyclo[4.4.0^{2,7}]decane (**61**).* AcOH (0.37 mL, 6.5 mmol) and TBAF (1 M soln in THF, 16.2 mL, 16.2 mmol) were added successively at rt to a solution of **15** (3.37 g, 6.5 mmol) in THF (20 mL). After stirring for 3 h, the reaction mixture was diluted with Et_2O and EtOAc and washed with brine. The organic phase was dried over Na_2SO_4, filtered, and the solvent removed in vacuo. Chromatography (hexanes/EtOAc 5:1 to 1:1) afforded an isomeric mixture of hemiketals (1.85 g) that was directly protected by treatment with catalytic TsOH/H_2O in CH_3OH/$CH(OCH_3)_3$ (25 mL, 1:1 v/v) at rt for 1 h. After quenching with solid $NaHCO_3$ and dilution with Et_2O the organic phase was washed with water and brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo to afford (+)-**61** (1.90 g) as a single isomer. An analytical sample was purified by recrystallization in hexanes to afford pure (+)-**61** mp 76–78 °C having $[\alpha]_D^{22}$ +147 (*c* 1.347, THF); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.33 (ddd, J_1=17.3, J_2=10.8, J_3=4.5 Hz, 1H), 5.48 (1H, s), 5.21 (1H, s), 5.06 (td, J_1=4.5, J_2=2.1 Hz, 1H), 5.02 (td, J_1=10.8, J_2=2.1 Hz, 1H), 3.71–3.67 (m, 2H), 3.61 (s, 3H), 3.16 (s, 3H), 3.02–2.95 (m, 1H), 2.18–2.07 (m, 2H), 1.99 (dt, J_1=13.7, J_2=4.4 Hz, 1H), 1.80 (ddd, J_1=13.7, J_2=4.4, J_3=2.8 Hz, 1H), 1.57–1.52 (m, 1H), 1.38 (dt, J_1=13.7, J_2=4.2 Hz, 1H), 1.28 (3H, s), 1.04 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.2, 149.7, 140.9, 115.0, 113.0, 101.1, 60.9, 51.7, 47.7, 47.2, 46.8, 42.5, 31.5, 27.2, 26.5, 24.8, 23.3; IR (neat): 3078, 2950, 2879, 1728, 1634, 1460, 1435 cm^{-1}; APCI(+): 295 ($[M+H]^+$, 2), 263 (100), 233 (18), 203 (29), 173 (13); APIES (+): 317 ($[M+Na]^+$, 100).

The crude mixed ketal, which a single compound by NMR, was used as obtained for the following transformation.

*4.2.45. (+)-(2S,5S,7R,8S)-5-Carbomethoxy-5,7-dimethyl-8-(2-hydroxyethyl)-2-methoxy-4-methylene-1-oxabicyclo[4.4.0^{2,7}]decane (**62**).* A solution of **61** (1.90 g, 6.5 mmol) in anhyd THF (35 mL) was added dropwise (argon atmosphere, rt) to a solution of 9-BBN (1.60 g, 13 mmol) in anhyd THF (25 mL). The mixture was stirred while temperature was slowly raised from rt to reflux and the mixture heated at reflux 1 h. After cooling to 0 °C water was carefully added, followed by addition of $NaBO_3.4H_2O$ (8.0 g, 52 mmol) and the mixture was stirred at rt for 20 h. After dilution with water, the aqueous phase was extracted with Et_2O; the combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. The crude was purified by flash chromatography on silica gel to yield 1.76 g (87% from (−)-**59**, three steps) of (+)-**62**.having: $[\alpha]_D^{22}$ +120 (*c* 1.020, THF); ^{1}H NMR (C_6D_6, 400 MHz): δ 5.33 (s, 1H), 5.23 (s, 1H), 3.64–3.54 (m. 2H), 3.88–3.31 (m, 2H), 3.30 (s, 3H), 3.00 (s, 3H), 2.41–2.34 (m, 1H), 2.34 (ddd, J_1=13.1, J_2=4.3, J_3=2.8 Hz, 1H), 2.23 (dt, J_1=13.8, J_1=4.3 Hz, 1H), 2.15–2.04 (2H, m), 2.04–1.96 (2H, m), 1.86 (ddd, J_1=13.8, J_2=4.5, J_3=2.8 Hz, 1H), 1.65 (ddd, J_1=13.84, J_2=13.1, J_3=4.5 Hz, 1H), 1.41–1.32 (m, 2H), 1.29 (s, 1H), 1.20 (s, 1H), 1.19–1.14 (m, 2H), 0.91 (s(br), 1H); ^{13}C NMR (C_6D_6, 100 MHz): δ 176.9, 150.0, 114.9, 101.8, 63.4, 61.6, 51.3, 49.3, 47.3, 47.0, 37.3, 35.7, 32.2, 28.1, 27.6, 27.3, 22.9; IR (neat): 3440, 2951, 1727, 1634, 1436 cm^{-1}; APCI (+): 281 ($[M+H]^+$−MeOH, 100), 113 (19); APIES (+): 335 ($[M+Na]^+$, 100), 281 (18), 113 (11), 102 (43). HRMS (CI) calcd for $C_{17}H_{28}O_5$: *m*/*z* 312.1931. Found: 312.1943.

*4.2.46. (+)-(3R,4S,8R)-Methyl 4,8-dimethyl-7-oxo-8-[(4R)-tetrahydro-2-oxo-2H-pyran-4-yl]-1-oxaspiro[2.5]octane-4-carboxylate (**63**).* A solution of 2.0 mL (28 mmol) of DMSO in 60 mL of anhyd CH_2Cl_2 was treated with 7.0 mL (14 mmol) of a 2 M solution of $(COCl)_2$ in CH_2Cl_2 at −70 °C under Ar and the mixture was stirred for 30 min at −70 °C. A solution of 1.76 g (5.6 mmol) of (+)-**62** in 35 mL of anhyd CH_2Cl_2 was then added and stirring was continued at the same temperature for 30 min. A 6.2 mL portion of anhyd Et_3N (45 mmol) was then added. After stirring at 0 °C for 20 min and dilution with CH_2Cl_2, the reaction mixture was quenched with cold water and the aqueous phase was extracted four times with CH_2Cl_2. The organic phase was washed successively with 1 N aq HCl, satd $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. The residue was dissolved in a mixture of *t*-BuOH (50 mL) and 2-methyl-2-butene (6 mL) and a solution of 3.2 g of 80% $NaClO_2$ (28 mmol) and 6.4 g of $NaH_2PO_4.H_2O$ (45 mmol) in 25 mL of water was added at rt. The resulting mixture was stirred for 15 min then diluted with brine. The aqueous phase was saturated with NaCl and extracted thoroughly four times with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. The residual crude acid was dissolved in 60 mL of CH_2Cl_2 and 1.4 g of $NaHCO_3$ (17 mmol) and 2.9 g of ~85% *m*-CPBA (14 mmol) were added at rt. The resulting reaction mixture was stirred overnight at rt before quenching with satd aq $NaHSO_3$ at 20 °C (with water bath cooling). The aqueous phase was extracted thoroughly with CH_2Cl_2, and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. The residue was then dissolved in 30 mL THF and 30 mL of 10% aq HCl solution was added at 20 °C (with water bath cooling) and the resulting mixture was stirred at rt for 1.5 h. After thorough extraction of the reaction mixture four times with CH_2Cl_2, the combined organic phases were washed with satd $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. Flash chromatography (elution with a gradient of hexanes/EtOAc from 1:1 to pure EtOAc) afforded 1.26 g of **15** (73% from **12**) as a white solid having mp 174–176 °C (from heptane/CH_2Cl_2) and $[\alpha]_D^{22}$ +19 (*c* 0.975, $CHCl_3$): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.44 (dt, J_1=11.5, J_2=4.4 Hz, 1H), 4.22 (ddd, J_1=11.5, J_2=10.4, J_3=3.7 Hz, 1H), 3.70 (s, 3H), 3.09 (d, J=3.9 Hz, 1H), 2.95 (ddd, J_1=17.9, J_2=11.5, J_3=5.9 Hz, 1H), 2.75 (d, J=3.9 Hz, 1H), 2.66 (dt, J_1=14.8, J_2=5.5 Hz, 1H), 2.56 (dt, J_1=18.0, J_2=4.9 Hz, 1H), 2.51–2.40 (m, 3H), 1.99–1.76 (m, 3H), 1.43 (s, 3H), 1.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 210.2, 172.8, 170.5, 67.5, 61.1, 54.6, 52.1, 47.1, 46.6, 36.2, 33.9, 32.4, 28.1, 24.5, 24.1, 11.1. IR (neat): 2955, 1731,

1466, 1406 cm^{-1}. APCI (+): 311 ([M+H]+, 100), 293 (10), 233 (6). HRMS calcd for $C_{16}H_{23}O_6$ $(M+H)^+$: *m/z* 311.1495. Found: 311.1504.

*4.2.47. (+)-(3R,4S,8R)-Methyl 4,8-dimethyl-8-[(1R)-3-(3-furanyl)-1-(2-methylene carboxy)-3-oxopropyl]-7-oxo-1-oxaspiro[2.5]octane-4-carboxylate (**65**).* A solution of 1.50 g of 3-tributylstannylfuran[25] (4.2 mmol) in anhyd 5 mL of THF was cooled to −78 °C and 2.3 mL of a 1.6 M solution of *n*-BuLi in hexanes (3.7 mmol) was added and the resulting mixture was stirred for 1.5 h at −78 °C. At which time, a solution of (+)-**63** (501 mg, 1.6 mmol) in 15 mL of anhyd THF was added and stirring was continued at the same temperature for 15 min. The reaction mixture was then quenched with satd aq NH_4Cl, then the cold bath was removed. After warming to rt, the phases were separated and the aqueous phase was extracted thoroughly four times with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo.

Oxalyl chloride (2 M solution in CH_2Cl_2, 0.4 mL, 0.81 mmol) was added, at −70 °C and under argon atmosphere, over DMSO (0.11 mL, 1.6 mmol) in anhyd CH_2Cl_2 (2.5 mL) and the mixture was stirred for 30 min; a solution of a portion of the crude lactol/alcohol **64** (100 mg, 0.27 mmol) prepared above in anhyd CH_2Cl_2 (2.5 mL) was then added and stirring was continued at the same temperature for 30 min before Et_3N (0.34 mL, 2.43 mmol) was added. After stirring at 0 °C for 20 min and dilution with CH_2Cl_2 the reaction was quenched with cold water and the aqueous phase was extracted with CH_2Cl_2; the organic phase was washed with 1 N aq HCl, satd $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. The residue was dissolved in *t*-BuOH (7 mL) and 2-methyl-2-butene (1 mL) and an aq solution (3.5 mL) of $NaClO_2$ (80%, 209 mg, 1.8 mmol) and $NaH_2PO_4.H_2O$ (408 mg, 3.0 mmol) was added at rt; the mixture was stirred for 15 min before brine was added, the aqueous phase was saturated with NaCl and extracted with EtOAc; the organic phase was washed with brine (once), dried over Na_2SO_4, filtered, and the solvent removed in vacuo to afford 74 mg (70%) of the crude title acid **65**, which was used as obtained in the following transformation.

*4.2.48. (1S,5R,6R,10S)-6,10-Dimethyl-2,12-dioxa-3,7,11-trioxo-5-[2-oxoethyl-2-(3-furanyl)]tricyclo[7.4.0^{1,6}.0^{1,10}]tridecane (**66**).* A sample of the preceding crude carboxylic acid **65** (145 mg, 0.37 mmol) was dissolved in CH_3CN (10 mL) and BF_3-Et_2O (0.27 mL, 2.1 mmol) was added at rt After stirring for 10 min the reaction was quenched with satd aq $NaHCO_3$ and the aqueous phase extracted with EtOAc; the organic phase was washed with brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. Flash chromatography (elution by hexanes/EtOAc 2:1 to 1:1) yielded 55 mg (38%) of dilactone **66** as an oil having: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (dd, J_1=1.4, J_2=0.9 Hz, 1H), 7.47 (dd, J_1=1.9, J_2=1.4 Hz, 1H), 6.72 (dd, J_1=1.9, J_2=0.9 Hz, 1H), 4.34 (d, J=10.9 Hz, 1H), 4.02 (d, J=10.9 Hz, 1H), 3.50–3.43 (m, 1H), 2.94 (dd, J_1=18.7, J_2=6.2 Hz, 1H), 2.93 (ddd, J_1=15.4, J_2=12.6, J_3=5.5 Hz, 1H), 2.69 (dd, J_1=17.9, J_2=4.1 Hz, 1H), 2.53 (dd, J_1=17.9, J_2=7.3 Hz, 1H), 2.39–2.25 (m, 3H), 1.93 (ddd, J_1=14.4, J_2=12.3, J_3=4.4 Hz, 1H), 1.66 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.7, 190.9, 177.7, 166.6, 147.5, 144.6, 126.9, 108.2, 92.7, 72.8, 50.9, 47.1, 33.3, 32.3, 30.3, 30.1, 17.6, 10.1. IR (neat): 3138, 2924, 1784, 1715, 1681, 1564, 1511 cm^{-1}; APCI (+): 361 ($[M+H]^+$, 100).

This material was used in the following transformation as obtained.

*4.2.49. (1S,5R,6R,10S)-6,10-Dimethyl-2,12-dioxa-3,11-dioxo-5-[2,2-dimethoxy ethyl-2-(3-furanyl)]-7-methoxy-tricyclo[7.4.0^{1,6}.0^{1,10}]tridec-7-ene (**67**).* Toluensulfonic acid hydrate (70 mg, 0.37 mmol) was added to a solution of bis-lactone **66** (50 mg, 0.14 mmol) in CH_3OH (8 mL) and $CH(OCH_3)_3$ (1.5 mL) at rt. The mixture was stirred at reflux (Dean–Stark system containing 3 Å MS in the trap) for 19 h. After cooling and addition of solid $NaHCO_3$ the mixture was diluted with EtOAc and water was added, the aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Chromatography of the crude product on silica gel (elution by hexanes/EtOAc 2:1 to 1:2) afforded 26.4 mg (45%) of **67** as an oil having: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (m, 2H), 6.18 (t, J=1.4 Hz, 1H), 4.55 (dd(br), J_1=7.4, J_2=2.4 Hz, 1H), 4.23 (d, J=10.4 Hz, 1H), 4.06 (d, J=10.4 Hz, 1H), 3.52 (s, 3H), 3.16 (s, 3H), 3.06 (s, 3H), 2.88 (dd, J_1=18.8, J_2=6.0 Hz, 1H), 2.54 (dd, J_1=17.4, J_2=7.4 Hz, 1H), 2.27 (dd, J_1=18.8, J_2=11.9 Hz, 1H), 2.21–2.13 (m, 1H), 1.90 (dd, J_1=17.4, J_2=2.4 Hz, 1H), 1.87 (dd, J_1=14.5, J_2=9.6 Hz, 1H), 1.80 (dd, J_1=14.5, J_2=2.2 Hz, 1H), 1.16 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.2, 168.8, 156.8, 143.7, 141.6, 126.0, 108.5, 101.5, 92.7, 91.3, 75.4, 55.0, 48.8, 48.5, 47.0, 43.2, 36.8, 32.9 (×2), 30.4, 23.0, 9.6. IR (neat): 2939, 1778, 1745, 1660 cm^{-1}; APCI (+): 389 ($[M-CH_3OH]^+$, 100), 195 (33), 151 (10); APIES (positive): 443 ($[M+Na]^+$, 99), 301(65), 233 (100), 123 (74), 102 (46).

This material was used in the following transformation as obtained.

*4.2.50. (1S,4S,5R,6R,10S)-2,12-Dioxa-3,11-dioxo-5-[2,2-dimethoxyethyl-2-(3-furanyl)]-7-methoxy-4,6,10-trimethyl-tricyclo[7.4.0^{1,6}.0^{1,10}]tridec-7-ene (**68β**) and (1S,4R,5R,6R,10S)-2,12-dioxa-3,11-dioxo-5-[2,2-dimethoxyethyl-2-furanyl]-7-methoxy-4,6,10-trimethyl-tricyclo[7.4.0^{1,6}.0^{1,10}]tridec-7-ene (**68α**).* A 0.1 M solution of LDA in THF/hexanes (1.5 mL, 3 equiv) was added at −78 °C under inert atmosphere over a stirred solution of **67** (21 mg, 0.05 mmol) in anhyd THF (1.5 mL) and anhyd HMPA (0.25 mL). After stirring for 1 h excess of CH_3I (0.75 mL, freshly filtered over Al_2O_3) was added and the mixture was stirred for 1 h while warming to rt, then quenched with satd aq NH_4Cl (3 mL). The layers were separated and the organic phase was extracted with ether; the combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent removed in vacuo. The crude material was chromatographed (elution with hexanes/EtOAc 3:1 to 2:1) to obtain 18.2 mg (84%) of **68** (**68β**/**68α** ~3:1). Alternatively the reaction was carried out at −78 °C to obtain, after chromatography, 71% of **68β**/**68α** ~6:1 and 23% of **67** as an oil having for the major isomer **68β**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (t, J=1.7 Hz, 1H), 7.34 (s(br), 1H), 6.25 (dd, J_1=1.7, J_2=0.7 Hz, 1H), 4.48 (dd(br), J_1=7.3, J_2=2.5 Hz, 1H), 4.24 (d, J=10.3 Hz, 1H), 3.48 (s, 3H), 3.25 (s, 3H), 3.18 (s, 3H), 2.82 (dt, J_1=7.6, J_2=7.6 Hz, 1H), 2.52 (dd, J_1=17.4, J_2=7.3 Hz, 1H), 2.39 (dd(br), J_1=10.2, J_2=7.6 Hz, 2H), 2.29 (dd, J_1=14.3, J_2=10.2 Hz, 1H), 1.91 (dd, J_1=17.4, J_2=2.5 Hz, 1H), 1.68 (d(br), J=14.3 Hz, 1H), 1.45 (d, J=7.6 Hz, 3H), 1.25 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.4, 178.8, 156.9, 143.4, 140.8, 126.3, 109.3, 102.2, 92.5, 91.7, 75.5, 54.8, 49.8, 48.5, 47.1, 44.1, 36.5, 33.5, 33.0, 32.6, 23.1, 17.2, 12.3; IR (neat): 2926, 1784, 1715, 1674, 1563, 1463, 1386 cm^{-1}; APCI (+): 403 ($[M+H]^+-CH_3OH$, 100), 279 (7), 195 (51), 165 (12); APIES (+): 457 ($[M+Na]^+$, 100).

This material was used in the following transformation as obtained.

*4.2.51. (1S,4S,5R,6R,10S)-6,10-Trimethyl-2,12-dioxa-5-[2-oxoethyl-2-(3-furanyl)]-3,7,11-trioxotricyclo[7.4.0^{1,6}.0^{1,10}]tridecane (**69β**), (1S,4R,5R,6R,10S)-2,12-dioxa-5-[2-oxoethyl-2-furanyl]-4,6,10-trimethyl-3,7,11-trioxotricyclo[7.4.0^{1,6}.0^{1,10}] tridecane (**69α**) and (+)saudin (**1**).* Major diastereomer **68β** was deprotected by treatment with dilute hydrochloric acid in CH_3OH, controlling the temperature to prevent epimerization at C-4 by dissolving a few mg of **68β** in CH_3OH (0.5 mL) and aq 1 N HCl (0.5 mL) was added at rt. The mixture was stirred at rt for 18 h, then at 45 °C (oil bath temperature) for 4 days. ^{1}H NMR after evaporation to dryness showed a clean mixture of **69** and (+)-saudin (**69β**/**69α**/(+)-saudin

~2.5:1:1). Spectroscopic data for the major isomer **69β**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s(br), 1H), 7.48 (s(br), 1H), 6.75 (d(br), J=1.5 Hz, 1H), 4.34 (d, J=10.9 Hz, 1H), 3.60 (ddd, J_1=9.1, J_2=7.8, J_3=3.7 Hz, 1H), 3.16 (dt, J_1=7.8, J_2=7.8 Hz, 1H), 2.95 (dd, J_1=18.1, J_2=9.1 Hz, 1H), 2.86 (ddd, J_1=15.4, J_2=12.9, J_3=6.0 Hz, 1H), 2.44 (dd, J_1=18.1, J_2=3.7 Hz, 1H), 2.39 (dt, J_1=15.4, J_2=4.6 Hz, 2H), 2.23 (ddd, J_1=14.1, J_2=6.0, J_3=4.6 Hz, 1H), 1.89 (ddd, J_1=14.1, J_2=12.9, J_3=4.6 Hz, 1H), 1.66 (s, 3H), 1.29 (d, J=7.8 Hz, 3H), 1.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.1, 191.1, 177.6, 171.3, 147.4, 144.7, 126.8, 108.3, 92.2, 72.9, 51.5, 47.0, 36.6, 34.9, 33.1, 29.9, 17.2, 15.7, 12.4; IR (neat): 2925, 1784, 1716, 1677, 1463, 1385, 1262, 1156, 1089, 1018, 970, 801 cm^{-1}. APCI (+): 375 ([M+H]$^+$, 100), 200 (13), 122 (11).

*4.2.52. (−)-(3R,4S,8R)-Methyl 8-[(1R)-1-[2-(acetyloxy)ethyl]-3-(3-furanyl)-3-oxopropyl]-4,8-dimethyl-7-oxo-1-oxaspiro[2.5]octane-4-carboxylate (**71**).* A solution of 1.50 g of 3-tributylstannylfuran[25] (4.2 mmol) in anhyd 5 mL of THF was cooled to −78 °C and 2.3 mL of a 1.6 M solution of *n*-BuLi in hexanes (3.7 mmol) was added and the resulting mixture was stirred for 1.5 h at −78 °C. At which time, a solution of (+)-**63** (501 mg, 1.6 mmol) in 15 mL of anhyd THF was added and stirring was continued at the same temperature for 15 min. The reaction mixture was then quenched with satd aq NH_4Cl, then the cold bath was removed. After warming to rt, the phases were separated and the aqueous phase was extracted thoroughly four times with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. The resulting crude alcohols **64** (and/or **70**) was dissolved in 10 mL of CH_2Cl_2 and acetylated under standard conditions by treatment with 0.4 mL of Ac_2O, a catalytic amount of DMAP, and 1 mL of pyridine at rt for 1 h. After quenching the reaction mixture with satd aq $NaHCO_3$, the aqueous phase was extracted thoroughly four times with CH_2Cl_2 and the combined organic phases were washed successively with 1 N aq HCl, satd $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. Flash chromatography (elution with a gradient of hexanes/EtOAc from 1.5:1 to 1:2) afforded 550 mg of (−)-**71** (81% overall from (+)-**63**) having $[\alpha]_D^{22}$ −4 (*c* 1.785, $CHCl_3$): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (s(br), 1H), 7.42 (s(br), 1H), 6.69 (s(br), 1H), 4.11–3.99 (m, 2H), 3.66 (s, 3H), 3.26–3.17 (m, 1H), 3.16 (dd, J_1=18.5, J_2=6.2 Hz, 1H), 3.09 (d, J=3.9 Hz, 1H), 2.93–2.81 (m, 1H), 2.75 (d, J=3.9 Hz, 1H), 2.63 (dd, J_1=18.5, J_2=3.1 Hz, 1H), 2.52–2.43 (m, 3H), 2.04–1.97 (m, 1H), 1.97 (s, 3H), 1.60 (s, 3H), 1.55–1.46 (m, 1H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 212.5, 193.1, 173.4, 170.7, 147.0, 144.2, 127.0, 108.4, 62.0, 60.8, 55.8, 51.9, 46.9 (×2), 40.3, 37.0, 31.0, 29.5, 27.8, 24.8, 20.7, 10.1; IR (neat): 3139, 2955, 1732, 1681, 1563, 1368, 1156, 1044, 954, 735 cm^{-1}; APCI (+): 421 ([M+H]$^+$, 56), 316 (100), 343 (10), 123 (9); HRMS calcd for $C_{22}H_{29}O_8$ (M+H)$^+$: *m*/*z* 421.1862. Found: 421.1877.

*4.2.53. 7-(2-Acetyloxyethyl)-2-carboxymethyl-2,6-dimethyl-9-(3-furanyl)-10,12-dioxa tricyclo [7.2.1.0^{2,6}]dodecane (+)-(**72**).* A 0.2 mL portion of $BF_3{\cdot}Et_2O$ (1.6 mmol) was added at rt to a solution of 84 mg of (−)-**71** (0.2 mmol) in 5 mL of CH_3CN. After stirring for 10 min at rt, the reaction mixture was quenched with satd aq $NaHCO_3$ and the aqueous phase extracted thoroughly four times with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. Flash chromatography on silica gel (elution with a gradient of hexanes/EtOAc from 2:1 to 1:1) provided 76 mg of (+)-**72** (90%) having $[\alpha]_D^{22}$ +46 (*c* 1.250, $CHCl_3$): ^{1}H NMR (CD_3CN, 400 MHz): δ 7.57 (s(br), 1H), 7.44 (t, J=1.8 Hz, 1H), 6.46 (d(br), J=1.8 Hz, 1H), 4.25 (d, J=9.3 Hz, 1H), 4.17 (d, J=9.3 Hz, 1H), 4.06–3.99 (m, 2H), 3.71 (s, 3H), 2.92 (dt, J_1=14.1, J_2=6.5 Hz, 1H), 2.40 (ddd, J_1=13.6, J_2=6.5, J_3=2.3 Hz, 1H), 2.14–1.80 (m, 7H), 1.98 (s, 3H), 1.31 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (CD_3CN, 100 MHz): δ 212.3, 176.1, 171.7, 144.4, 141.5, 127.5, 109.4, 105.6, 91.3, 68.9, 64.3, 56.0, 52.9, 47.4, 39.5, 37.2, 36.5, 33.7, 30.3, 22.7, 21.1, 18.9; IR (neat): 2954, 1732, 1604 cm^{-1}; APCI (+): 421 ([M+H]$^+$, 6), 361 (100), 123 (14); APIES (+): 443 ([M+Na]$^+$, 100). HRMS calcd for $C_{22}H_{29}O_8$: *m*/*z* 421.1862. Found: 421.1860.

*4.2.54. (1S,4R,6S,13S,14S)-13-Carbomethoxy-13,14-dimethyl-4-(3-furanyl)-8-oxo-3,9,15-trioxatetracyclo[8.3.1.1^{1,4}.0^{6,14}]tetradec-10-ene (−)-**75**.* Solid K_2CO_3 (800 mg, 5.8 mmol) was added at 0 °C to a solution of 485 mg of (+)-**72** (1.15 mmol) in 10 mL of CH_3OH, then 1 mL of H_2O was added and the mixture was stirred for 1 h at rt. After dilution of the reaction mixture with EtOAc, the organic phase was washed with H_2O and brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. The crude primary alcohol **73** (438 mg) was directly oxidized to carboxylic acid **74** as previously described above for the transformation of **64** into **65**.

The resulting crude acid **74** (~1.15 mmol) was dissolved in 10 mL of anhyd CH_2Cl_2 in the presence of 471 mg of anhyd NaOAc (5.7 mmol) and the mixture cooled to 0 °C. A 1 mL portion of $(CF_3CO)_2O$ (7.0 mmol) was added at 0 °C, and the reaction mixture was stirred for 1 h while warming slowly from 0 °C to rt. After quenching the reaction mixture with satd aq $NaHCO_3$, the aqueous phase was separated and extracted thoroughly four times with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. Flash chromatography (a gradient of hexanes/EtOAc from 2:1 to 1:1) yielded 289 mg of (−)-**75** (67% for four steps from (+)-**72**) as a white solid having mp 128–130 °C (from hexanes/Et_2O/CH_2Cl_2) and $[\alpha]_D^{22}$ −31 (*c* 0.995, $CHCl_3$): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51 (s(br), 1H), 7.41 (t, J=1.9 Hz, 1H), 6.45 (d(br), J=1.9 Hz, 1H), 5.35 (dd, J_1=4.6, J_2=3.2 Hz, 1H), 4.32 (d, J=9.0 Hz, 1H), 4.28 (d, J=9.0 Hz, 1H), 3.71 (s, 3H), 3.07 (dd, J_1=18.2, J_2=4.6 Hz, 1H), 3.06 (dd, J_1=18.9, J_2=6.8 Hz, 1H), 2.48–2.40 (m, 2H), 2.20 (dd, J_1=18.2, J_2=3.2 Hz, 1H), 2.09 (dd, J_1=13.0, J_2=5.7 Hz, 1H), 1.85 (t, J=13.0 Hz, 1H), 1.41 (s, 3H), 1.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.2, 165.9, 149.4, 143.4, 140.1, 125.6, 108.1, 105.5, 103.4, 85.9, 67.7, 52.3, 45.2, 40.2, 37.9, 32.0, 31.5, 22.8, 22.1; IR (neat): 2919, 1732, 1691, 1602 cm^{-1}; APCI (+): 375 ([M+H]$^+$, 100), 279 (60). HRMS calcd for $C_{20}H_{23}O_7$ (M+H)$^+$: *m*/*z* 375.1444. Found: 375.1459.

From the less polar fractions, 58 mg of the primary trifluoroacetate of alcohol **73** (12%) was also recovered which was recycled by hydrolysis to **73**.

*4.2.55. (1S,4R,6S,7R,13S,14S)-13-Carbomethoxy-4-(3-furanyl)-8-oxo-7,13,14-trimethyl-3,9,15-trioxatetracyclo[8.3.1.1^{1,4}.0^{6,14}]tetradec-10-ene (−)-(**76α**).* A 1.45 M solution of *n*-BuLi in hexane (0.56 mL, 0.81 mmol) was added dropwise at −78 °C under Ar to a solution of 0.15 mL of 2,2,6,6-tetramethylpiperidine (0.92 mmol) in 5 mL of anhyd THF and the resulting mixture was stirred for 1 h. At −78 °C, a solution of 193 mg (0.52 mmol) of (−)-**75** in 10 mL of anhyd THF was then added dropwise at such a rate that the temperature did not rise. After stirring the resulting mixture for 2.5 h at −78 °C, 0.56 mL of HMPA (3.2 mmol) was added dropwise, followed after 5 min by rapid addition of 3 mL of CH_3I (excess) via syringe. The temperature of the reaction mixture was slowly raised to −50 °C and stirring was continued for 35 min at ~ −50 °C. After quenching the reaction mixture at ~ −45 °C with 10 mL of satd aq NH_4Cl and warming to rt, the aqueous phase was separated and extracted thoroughly four times with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. Flash chromatography on silica gel (elution using a gradient of hexanes/EtOAc from 2:1 to 1:1) afforded 59 mg (29%) of **76α**, and 92 mg (46%) of **76β**. Treatment of the 92 mg (0.24 mmol) sample of **76β** in 5 mL of anhyd THF at −78 °C with 1.5 mL (0.85 equiv) of a 0.14 M solution of LDA in anhyd THF and warming with stirring to 0 °C over 1.5 h then continued stirring at 0 °C for 2 h followed by quenching, isolation, and purification as above afforded 82 mg (88%) of (−)-**76α** or a combined yield of 70%

of (−)-**76α** having $[\alpha]_D^{22}$ −14 (*c* 1.390, $CHCl_3$): ^1H NMR ($CDCl_3$, 400 MHz): δ 7.52 (s(br), 1H), 7.40 (t, *J*=1.8 Hz, 1H), 6.46 (d(br), *J*=1.8 Hz, 1H), 5.29 (dd, J_1=4.4, J_2=3.5 Hz, 1H), 4.30 (d, *J*=9.0 Hz, 1H), 4.27 (d, *J*=9.0 Hz, 1H), 3.71 (s, 3H), 3.17 (dq, J_1=7.1, J_2=6.1 Hz, 1H), 3.11 (dd, J_1=18.4, J_2=4.4 Hz, 1H), 2.32 (ddd, J_1=11.7, J_2=6.1, J_3=5.5 Hz, 1H), 2.17 (dd, J_1=18.4, J_2=3.5 Hz, 2H), 2.13 (dd, J_1=13.3, J_2=5.5 Hz, 2H), 1.56 (t(br), *J*=12.7, 1H), 1.41 (s, 3H), 1.25 (d, *J*=7.1 Hz, 1H), 1.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.3, 169.5, 149.8, 143.3, 140.0, 125.9, 108.1, 104.9, 103.5, 86.0, 67.7, 52.3, 45.1, 39.5, 37.6, 35.3, 34.6, 31.5, 23.1, 22.3, 13.0; IR (neat): 2918, 1732, 1693 cm^{-1}; APCI (+): 389 ($[M+H]^+$, 100). HRMS calcd for $C_{21}H_{25}O_7$ $(M+H)^+$: *m*/*z* 389.1600. Found: 389.1615.

Traces of *gem*-dimethyl product **77** arising from polyalkylation and minor by-products arising from an additional alkylation of a position on the furan ring were observed to be present in the crude alkylation product by ^1H NMR.

*4.2.56. (+)-Saudin (**1**).* A suspension of 56 mg of **76a** (0.14 mmol) in 10 mL of 2 N aq KOH was degassed with Ar and heated at reflux for 3.5 h. After cooling to rt and acidification with 10% hydrochloric acid to pH ≤1, the resulting aqueous phase was saturated with solid NaCl and extracted thoroughly four times with EtOAc. The combined organic phases were washed once with brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. The resulting 58 mg of crude diacid **78** was directly dissolved in 10 mL of anhyd 1,2-dichloroethane under Ar, and 0.7 mL of a 0.5 M solution of TMSOTf in 1,2-dichloroethane (0.35 mmol) was added at rt. After stirring for 1 h at rt, an additional 0.3 mL of the 0.5 M solution of TMSOTf in 1,2-dichloroethane (0.14 mmol) was added and stirring was continued for an additional 1 h. At which point, the reaction mixture was quenched with satd aq $NaHCO_3$, the phases separated, and the aqueous phase extracted thoroughly four times with EtOAc. The combined organic phases were washed once with brine, dried over Na_2SO_4, filtered, and the solvent removed in vacuo. Flash chromatography of the residue afforded 36 mg (70%) of (+)-Saudin (**1**) having mp 204–206 °C from Et_2O/EtOAc and $[\alpha]_D^{22}$ +14 (*c* 0.460, $CHCl_3$). All spectroscopic properties [IR, ^1H NMR, ^{13}C NMR, APCI (positive)] except the sign of the optical rotation were identical to those of an authentic sample of natural (−)-Saudin kindly provided by Professor Mossa.[1,2]

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.067.

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