DOI: 10.1002/ejoc.200600429

Synthetic Studies on Cyathin Terpenoids: Enantioselective Synthesis of the Tricyclic Core of Cyathin through Intramolecular Heck Cyclisation

Emmanuelle Drège,[a] Cyrille Tominiaux,[a][‡] Georges Morgant,[a,b] and Didier Desmaële*[a]

Keywords: Terpenoids / Heck reaction / Palladium / Ring enlargement / Michael addition / Enantioselectivity

An enantioselective synthesis of the tricyclic ketone (+)-**5**, which displays the carbon core of NGF-inducing cyathane diterpenes, has been completed according to a strategy in which the key step was the intramolecular Heck reaction of the AC subunit **49** establishing the crucial *anti* stereochemical relationship between the two angular substituents. The C-9 quaternary centre was set up by taking advantage of the enantioselective Michael addition involving chiral imines providing keto ester (*R*)-**10** in 91 % *ee*. After incorporation of the isopropyl group and iododecarboxylation of the propionate side chain, the iodo ketone **39** was condensed with the lithium enolate of methyl dihydrobenzoate to give the AC subunit **43** which was further elaborated to triflate (–)-**22**. While direct Heck cyclisation of **22** was ineffective, oxidation of the bis(allylic) position of the 1,4-cyclohexadiene moiety enhanced the reactivity, allowing the stereoselective formation of the hexahydro-cyclopenta[*a*]naphthalene (+)-**50a**. A key element of the construction was the final C ring enlargement, involving trimethylaluminum-promoted one-carbon expansion of ketone **52** with trimethylsilyldiazomethane which provided the tricyclic ketone (+)-**5**. Furthermore, epoxidation of trienone (+)-**50a** was shown to occur exclusively on the β face, giving rise to the C-14 functionalised advanced intermediate **51** which has considerable potential for the synthesis of natural cyathins and analogues.

Introduction

Cyathane diterpenes possess an unusual angularly fused 5–6–7 tricyclic framework with 1,4-*anti* quaternary methyl groups. Ayer and coworkers isolated the first natural product of this class in 1971 from *Cyathus helenae* and several additional members of this family were discovered from a variety of fungal sources throughout the 1970's.[1] Other cyathane congeners were isolated from the mycelia of the fungus *Hericium erinaceum* and were termed erinacines A-F. These compounds are essentially D-xylose conjugates of cyathins. In the simplest case of erinacine A (**1**), the D-xylose moiety is anchored to the 14β position of allocyathin B_2 (**2**).[2] More recently Kawagishi isolated scabronines[3] and sarcodonins[4] [exemplified by scabronine B (**3**) and sarcodonin A (**4**)] from *Sarcodon scabrosus*. The initial members of this diterpenoid class were isolated because of significant antibiotic properties. However, a renewed interest in these natural products was initiated by the discovery that members of the erinacine and scabronine classes stimulate the biosynthesis of the nerve growth factor (NGF) and other neurotrophic agents.[2–5] Neurotrophic factors are key players in the early developments of the embryonic central nervous system. Although expressed at much lower concentrations in adults, these factors still play an important role in phenotypic maintenance and cell regulation. Despite the exciting biological profile of NGF and encouraging results obtained in cell culture as treatments for neurodegenerative disorders, clinical applications of NGF have failed due mainly to its inability to cross the blood-brain barrier.[6] Since NGF is an endogenous compound that is synthesised in vivo, it was reasoned that if the regulatory mechanisms controlling its expression could be stimulated, a method of controlling the endogenous production might be found. The search for compounds that could stimulate the basal production of NGF has led to the isolation of a dozen structurally unique natural products with this function.[7] Owing to their lipophilic nature and small size, cyathins seemed promising candidates for crossing the blood-brain barrier. The potential therapeutic relevance and the unique synthetic challenges provided by these molecules attracted intense efforts from a number of research teams since the disclosure of their structures. However, only few total syntheses of natural cyathins have been completed, namely (±)-allocyathin B_2 and (+)-erinacine A by the groups of Snider[8] and Tori[9] in 1996 and 1998, (±)-sarcodonin G by Piers's team,[10] (±)-allocyathin B_3 by the group of Ward in

[a] Unité de Chimie Organique Associée au CNRS, Centre d'Etudes Pharmaceutiques, Université Paris Sud,
5 rue J.-B. Clément, 92296 Châtenay-Malabry, France
Fax: +33-1-46-83-57-52
E-mail: didier.desmaele@cep.u-psud.fr
[b] Laboratoire de Cristallographie Bioinorganique, Centre d'Etudes Pharmaceutiques, Université Paris Sud,
5 rue J.-B. Clément, 92296 Châtenay-Malabry, France
[‡] Present address: Service Hospitalier Frédéric Joliot, Département de Recherche Médicale, CEA/DSV, 4 place du Général Leclerc, 91401 Orsay, France

2000,[11] (+)-allocyathin B_2 (**2**) by the groups of Nakada[12] in 2004 and Trost in 2005[13] and finally (–)-scabronine G by Danishefsky[14] in 2005. Besides these successful syntheses, a large number of approaches have been proposed over the past decade.[15]

The central synthetic challenge in designing a route to cyathins is the control of the relative *anti* stereochemistry between the A and C rings. We have previously reported a simple solution to this problem based on the intramolecular Heck cyclisation of an A-C subunit, culminating in the synthesis of ketone (+)-**5**.[16] In this paper we wish to give a full account of this work detailing the final synthetic approach and some alternative strategies which, while unsuccessful, provided a valuable learning process for structuring our later work (Figure 1).

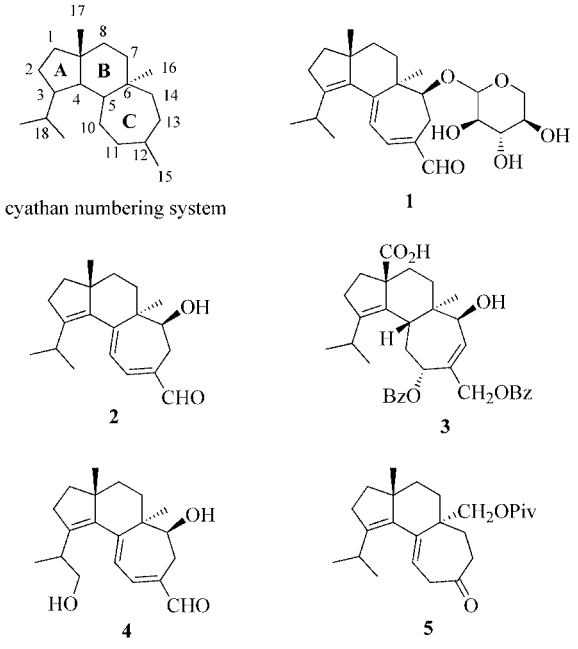
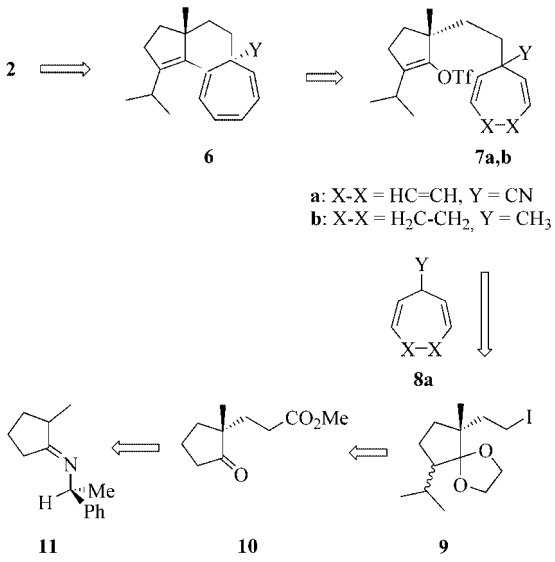


Figure 1. Structures of cyathin derivatives.

Results and Discussion

Our initial synthetic plan was based on the belief that the cycloheptatriene tethered alkenyl triflate **7a** could be converted into cyathin diterpenoids via the tricyclic tetraene **6** through an intramolecular Heck-type cyclisation. It was hoped that **7a** could be prepared by alkylation of cyclohepta-2,4,6-trienecarbonitrile **8a** with iodide **9**. The latter could be derived from the known keto ester (*R*)-**10** which is easily available in high optical purity by a deracemising Michael addition involving the chiral imine **11** derived from 2-methylcyclopentanone and (*S*)-1-phenylethylamine[17] (Scheme 1).



Scheme 1. Retrosynthetic analysis leading to the cyclohepta[*e*]indene nucleus used in our early approach.

Although the Heck cyclisation was a tempting and potentially expedient entry to systems such as **6**, one question associated with this plan was would the interaction between the two angular groups be large enough to favour a transition state leading to the proper relative *anti* stereochemistry? An investigation of the literature revealed that *cis* fused bicyclic systems are usually produced during intramolecular Heck reactions using prochiral dienes tethered to vinylic halides or triflate moieties.[18] However, the influence of an additional control element in the vicinity of the enol triflate moiety on the stereochemical outcome was only scarcely reported.[19] Furthermore, to the best of our knowledge, cycloheptatriene derivatives appear to have never been used as substrates in Heck-type processes.

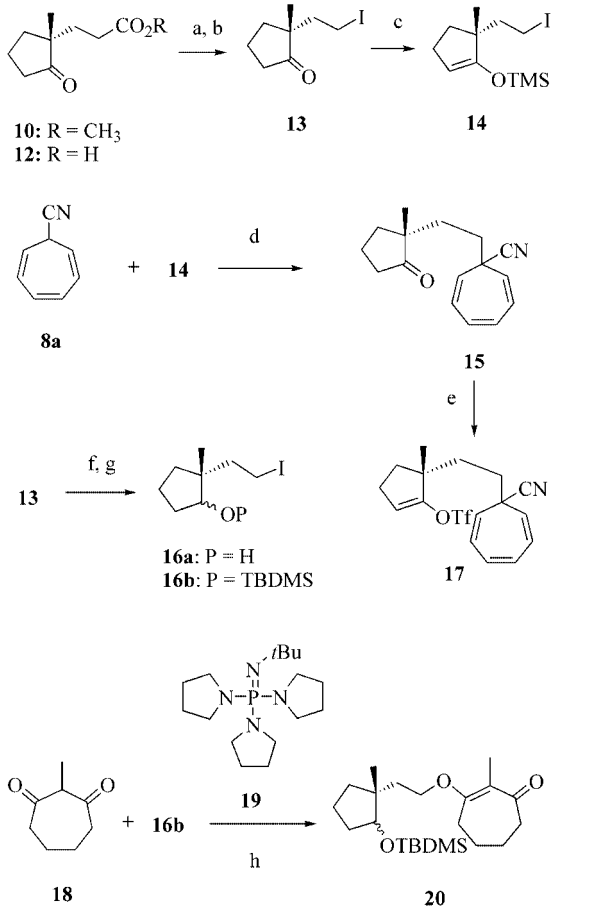
Our initial goal was to demonstrate that the Heck reaction would provide the ABC ring system with the requisite relative stereochemistry. To this end, iodide (*R*)-**13** was synthesised as a model system because it could be easily prepared from the readily available keto ester (*R*)-**10** (*ee* = 91%).[17a] Thus, saponification of **10** followed by iododecarboxylation of acid **12** according to the Barton modification of the Kochi reaction[20] gave rise to iodo ketone **13** in 81% overall yield. After the protection of the carbonyl of **13** as a trimethylsilyl enol ether using TMSOTf, the iodide **14** was condensed with cyclohepta-2,4,6-trienecarbonitrile **8a**[21] using LDA as a base. Cleavage of the enol ether with TBAF, followed by enol triflate formation provided the desired alkenyl triflate **17** in 67% overall yield from **14**. Having the required AC subunit in hand, we next turned our attention to its conversion into the tricyclic system. Unfortunately, when **17** was treated with palladium acetate under standard Heck conditions the starting material was recovered unchanged. Attempts at adding phosphane ligands, varying the catalyst or the reaction conditions met with failure.

Assuming that the poor complexing ability of the conjugated triene would account for the lack of reactivity of **17**,

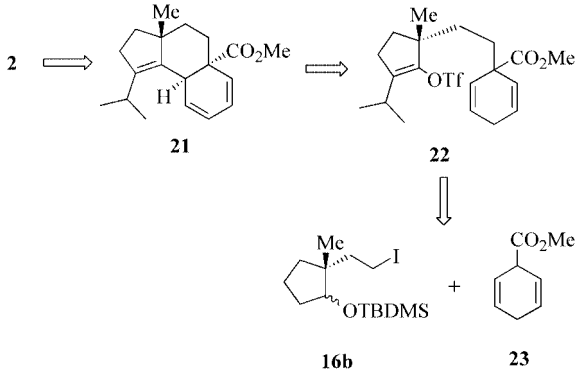
we decided to replace the cycloheptatriene moiety by a 1,3-cycloheptadiene ring as in **7b** in which the unconjugated double bonds were expected to be more reactive. This decision was based primarily on the potential availability of **7b** using 2-methylcyclohepta-1,3-dione **18**[22] as a C ring progenitor. However, alkylation of **18** with iodide **14** under a variety of conditions gave multiple by-products. Although disappointing from a practical standpoint, the desired alkylation adduct could be generated by simply switching the enol ether to another protecting group. Since attempts to prepare the dioxolane directly from iodo ketone **13** failed, the temporary shielding of the keto group by reduction was undertaken. To this end, ketone **13** was reduced with sodium borohydride and the mixture of epimeric alcohols **16a** obtained was protected as *tert*-butyldimethysilyl ether to deliver iodide **16b** in 68% overall yield. When the dione **18** was condensed with iodide **16b**, using sodium hydride as base, a complex mixture was produced. On the other hand, the use of caesium carbonate or the P_1-phosphazene base **19**[23] as base gave the *O*-alkylated derivative **20** in low yield (14% and 22%, respectively) (Scheme 2).

Since we were unable to overcome this second deviation from our original plan, we therefore designed an alternative strategy targeting a C-nor-cyathane derivative such as the ester **21**. The seven-membered C ring would ultimately be obtained from this material using a one-carbon ring enlargement reaction as the key step. This strategy was first tested in the synthesis of the model system lacking the isopropyl group. Accordingly, the crucial coupling of the chiral A-subunit with the C ring synthon could simply be performed by alkylation of the enolate of cyclohexa-2,5-dienecarboxylic acid methyl ester **23** with iodide **16b** (Scheme 3).

The coupling between the lithium enolate of methyl dihydrobenzoate **23**[24] and the iodo derivative **16b** required heating for several hours at 50 °C in the presence of DMPU. Under such conditions, the diene ester **24** was obtained in 83% yield. Removal of the *tert*-butyldimethylsilyl group with tetra-*n*-butylammonium fluoride in THF at reflux, followed by Swern oxidation of the alcohol **25** led to the ketone (+)-**26** which was taken through alkenyl triflate (+)-**27** by using triflic anhydride in the presence of 2,6-di-*tert*-butylpyridine.[25] At this point, we were prepared to check the crucial palladium-catalysed cyclisation. In the event, treatment of triflate (+)-**27** under standard Heck conditions [$Pd(OAc)_2$ cat., K_2CO_3] was disappointing, giving rise to an inseparable mixture of trienes **28a**–**c** in low yield (< 30%), along with a minute amount of allylic acetate **29** (< 10%). Although the overall yield increased to 70% when the reaction was conducted with $Pd(PPh_3)_4$ in toluene, we failed to avoid the double migration by the use of various additives such as silver[26] or thallium[27] salts. Since acetate **29** was formed by addition of acetate ions from $Pd(OAc)_2$ to the intermediate η^3-palladium complex, we anticipated that adding acetate ions might drive the reaction course toward acetate **29**.[28] Pleasingly, treatment of alkenyl triflate **27** with Pd_2dba_3 as a catalyst (5%) in the presence of 3 equiv. of tetrabutylammonium acetate in DMSO at 60 °C provided tricyclic acetate **29** in 85% yield. The stereochemical assignment of **29** was inferred from ^1H NMR spectroscopy including NOESY experiments of the corresponding alcohol (–)-**30**. The pseudo-axial configuration of the cyathin hydrogen at C9a (δ = 3.44 ppm) with respect to the C ring, was deduced from the coupling constants (J = 14.5 and 3.5 Hz) with the vicinal 9-H_{ax} and 9-H_{eq} protons,



Scheme 2. Attempts to condense various A-ring synthons with a seven- membered C ring system. (a) aq. KOH, MeOH, 16 h, 20 °C, 97%; (b) $Pb(OAc)_4$, I_2, CCl_4, visible light, 500 W, 1 h, 80 °C, 84%; (c) TMSOTf, Et_3N, CH_2Cl_2, 0 °C, 3 h, 86%; (d) *i*: LDA, **8a**, –78 °C, 10 min, *ii*: **14**, HMPA, –20 °C, 16 h, *iii*: nBu_4NF, THF, 20 °C, 1 h, 71%; (e) $(CF_3SO_2)_2O$, 2,6-di-*t*Bu-C_5H_3N, CH_2Cl_2, 20 °C, 20 h, 95%; (f) $NaBH_4$, EtOH, 20 °C, 3 h, 65%; (g) TBDMSOTf, CH_2Cl_2, 20 °C, 4 h, 96%; (h) 1 equiv. of **19**, THF, 70 °C, 24 h, 22%.

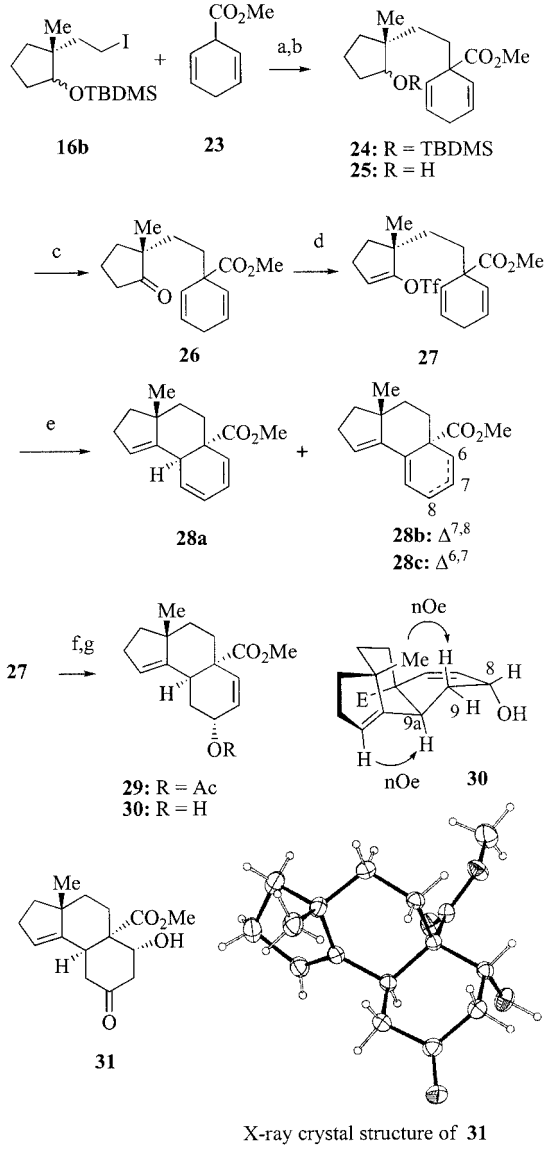


Scheme 3. Retrosynthetic analysis leading to cyathin terpenoid **2**.

respectively. Furthermore, a strong correlation between the 9-H_{ax} proton (δ = 1.92 ppm) and the angular methyl group in the NOESY chart are consistent only with the *anti-cis* configuration. This assignment was subsequently confirmed by X-ray crystallography of the β-hydroxy ketone **31**, derived from (–)-**30** through a three-step sequence.[16a,29] Interestingly, while the formation of the *cis* BC ring junction could be anticipated in view of the known steric course of such intramolecular Heck reactions,[18] the influence of the quaternary stereogenic centre in directing the reaction onto the face opposite to the methyl group seemed unprecedented. This high stereoselectivity in the ring-closure reaction could be related to steric interactions and/or the introduction of conformational strain in the tether, which does not favour a transition state that leads the angular substituents to be on the same side of the molecule. Thus, the tandem Heck reaction-acetate ion capture process[28] appears to be a viable method for establishing the crucial *anti* relationship of the A and C rings of the cyathane diterpenoids family. We therefore elected to use this method to assemble the more challenging isopropyl-substituted substrate (Scheme 4).

To implement this synthetic plan, we required a viable, large-scale preparation of the keto ester **35a**. Thus, treatment of (*R*)-**10** with TMSOTf led to the expected silylated enol ether **32**. Mukaiyama condensation with acetone using $TiCl_4$ as a Lewis acid failed to give the expected product. On the other hand acetaldehyde reacted smoothly giving rise to the ketol **33** in 89% yield. Sequential mesylate formation and β elimination with DBU produced enone **34** as a 5:1 *E*/*Z* mixture in 71% overall yield from **10**. This compound was converted into the desired keto ester **35a** (as a 1:1 diastereomeric mixture at C5) upon treatment with lithium dimethylcuprate.

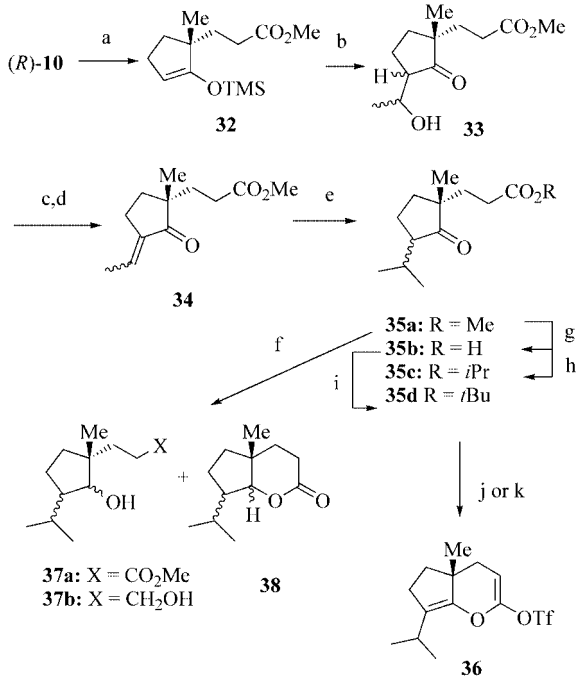
The next task was to further functionalise compound **35a** to allow the connection with the C ring synthon **23**. We chose to first incorporate the required enol triflate assuming it might offer suitable protection for the carbonyl group during the anionic condensation. However, to our surprise, when **35a** was subjected to Tf_2O in the presence of 2,6-di-*tert*-butylpyridine the main product was not the expected triflate but instead the bicyclic enol trifluoromethanesulfonate **36**. Despite a number of attempts using more bulky ester groups (**35c** or **35d**) or trying to quench the lithium enolate from **35c** with the Comins's reagent,[30] under no circumstances could we produce the required alkenyl triflate needed for the projected Heck cyclisation. We therefore returned to the reduction of the keto group and protection of the resultant alcohol as previously done with model compound **15**. Unfortunately, due to the severe hindrance of the carbonyl group, complete recovery of the starting material was routinely observed using a standard reducing procedure [$Zn(BH_4)_2$, $LiAl(tBuO)_3H$, H_2/PtO_2/AcOH]. On the other hand, subjecting **35** to sodium borohydride gave a mixture of alcohol **37a**, lactone **38** and diol **37b**. Only a marginal improvement was observed using Luche's conditions[31] which provided **37a** and **37b** in yields of 50% and 30%, respectively (Scheme 5).



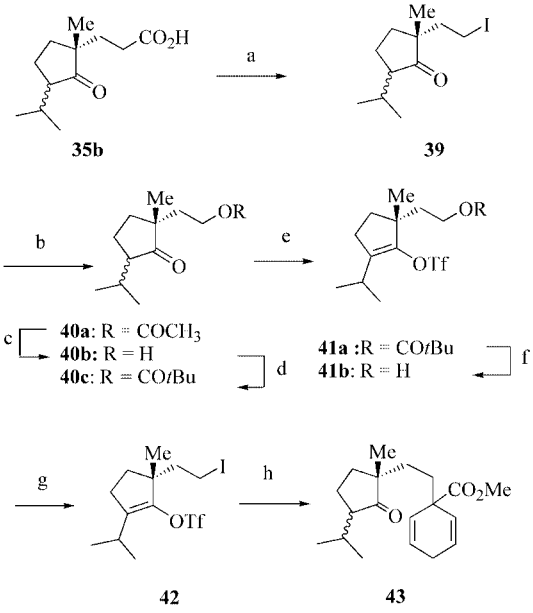
X-ray crystal structure of **31**

Scheme 4. (a) *i*: LDA, **23**, THF, –78 °C, 15 min, *ii*: DMPU, –78 °C to 50 °C, then 50 °C, 3 h, 83%; (b) nBu_4NF, THF, 60 °C, 5 h, 78%; (c) $(ClCO)_2$, DMSO, CH_2Cl_2, –78 °C, 1 h, then Et_3N, 20 °C, 16 h, 95%; (d) $(CF_3SO_2)_2O$, 2,6-di-*t*Bu-C_5H_3N, $(CH_2Cl)_2$, 20 °C, 15 h, 79%; (e) 10 mol-% $Pd(PPh_3)_4$, nBu_4NBr, K_2CO_3, toluene, 110 °C, 16 h, **28a**/**28b**/**28c** = 2:1:1, 70%; (f) 5 mol-% $Pd_2dba_3.CHCl_3$, 3 equiv. nBu_4NOAc, DMSO, 60 °C, 3 h; (g) K_2CO_3, MeOH, 3 h, 20 °C, 85% overall yield from **27**.

We therefore decided to convert the propionate side chain into an iodoethyl appendage before activating the carbonyl group. Thus saponification of **35a** followed by the Kochi reaction [$Pb(OAc)_4/I_2$, CCl_4 at reflux][20] produced the iodo ketone **39** in 65% overall yield. Unfortunately, attempts to introduce the required enol triflate on this sensitive material using Tf_2O met with failure. It was felt that it would be best to temporarily replace the iodine atom by a more stable group. At this stage new difficulties arose in what was anticipated to be a straightforward transformation. Thus S_N2 displacement of the iodide group with sodium acetate gave the acetate **40a** but, once again, this ma-



Scheme 5. (a) TMSOTf, Et_3N, CH_2Cl_2, 4 h, 20 °C, 89%; (b) 4 equiv. CH_3CHO, 4 equiv. $TiCl_4$, CH_2Cl_2, –78 °C, 2 h, 89%; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min, then 1 h 20 °C, (d) DBU, toluene, 110 °C, 1 h, 90% overall from **33**; (e) Me_2CuLi, Et_2O, –30 °C, 1 h, 70%; (f) $NaBH_4$, $CeCl_3$, MeOH, 40 °C, 3 h, **37a** 50%, **37b** 30%; (g) 3 N KOH, MeOH, 20 °C, 4 h, 75%; (h) $Ti(OiPr)_4$, *i*PrOH, 80 °C, 4 h, 70%; (i) $(tBuO)_2CHNMe_2$; toluene, 110 °C, 90 min, 60%; (j) $(CF_3SO_2)_2O$, 2,6-di-*t*Bu-C_5H_3N, $(CH_2Cl)_2$, 90 °C, 90 min, 65% from **35a**, 80% from **35d**; (k) *i*: LDA, –78 °C, 1 h, *ii*: 5-Cl(C_5H_3N)NTf_2, –78 °C to 20 °C, 2 h, 70% from **35c**.



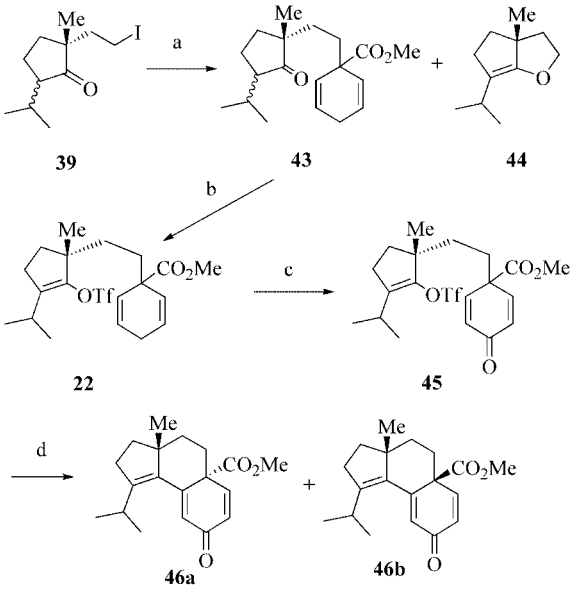
Scheme 6. (a) $Pb(OAc)_4$, I_2, CCl_4, reflux, *hv*, 65%; (b) AcONa, DMF, 110 °C, 3 h, 70%; (c) K_2CO_3, MeOH, 20 °C, 5 h, 80%; (d) PivCl, py, 20 °C, 4 h, 73%; (e) $(CF_3SO_2)_2O$, 2,6-di-*t*Bu-C_5H_3N, $(CH_2Cl)_2$, 90 °C, 15 h, 65%; (f) DIBAL-H, CH_2Cl_2, –78 °C, then –20 °C 4 h, 70%; (g) PPh_3, I_2, Im, CH_2Cl_2, 25 °C, 2 h, 70%; (h) *i*: **23**, LDA, THF, –78 °C, 15 min, *ii*: DMPU, –78 °C to 50 °C, 90 min, 65%.

terial gave a complex mixture when subjected to Tf_2O. Conversely, the corresponding pivaloyl ester **40c** prepared from **40a** through a saponification and esterification two-step sequence was more compliant affording the expected enol triflate **41** when treated with Tf_2O in the presence of 2,6-di-*tert*-butylpyridine. DIBAL-H reduction of the pivalate group and iodation using the Corey iodination procedure[32] produced iodo triflate **42** in 49% overall yield from **41**. Although this material might potentially be used as fragment A in the synthesis, the extra protection and deprotection steps required did not make this sequence very attractive. Nevertheless, we decided to continue the synthesis with this material. Thus, condensation of the lithium enolate of methyl dihydrobenzoate **23** with **42** in the presence of DMPU gave rise to a 65% yield of adduct **43**, in which the enol triflate moiety was cleaved back to the carbonyl group (Scheme 6). This disappointing result definitively thwarted this synthetic route and forced us to find a more suitable alternative method for accessing alkenyl triflate **22**.

The complications outlined above compelled us to investigate the direct coupling of iodo ketone **39** with the enolate of methyl dihydrobenzoate **23**. At the outset of the work, this straightforward procedure was rejected because we suspected that the proton transfer between the ester enolate of **23** and the free ketone group would thwart the alkylation process. Contrary to our expectations, however, treatment of the lithium enolate of **23** with iodo ketone **39** provided the desired keto ester **43** in 60% yield along with a small amount of the volatile ether **44**, arising from the aforementioned proton transfer followed by intramolecular *O*-alkylation of the ketone enolate. Therefore, the presence of the *unprotected keto group* in **39** was not prejudicial to the efficiency of the alkylation step, hence considerably improving access to the AC fragment.

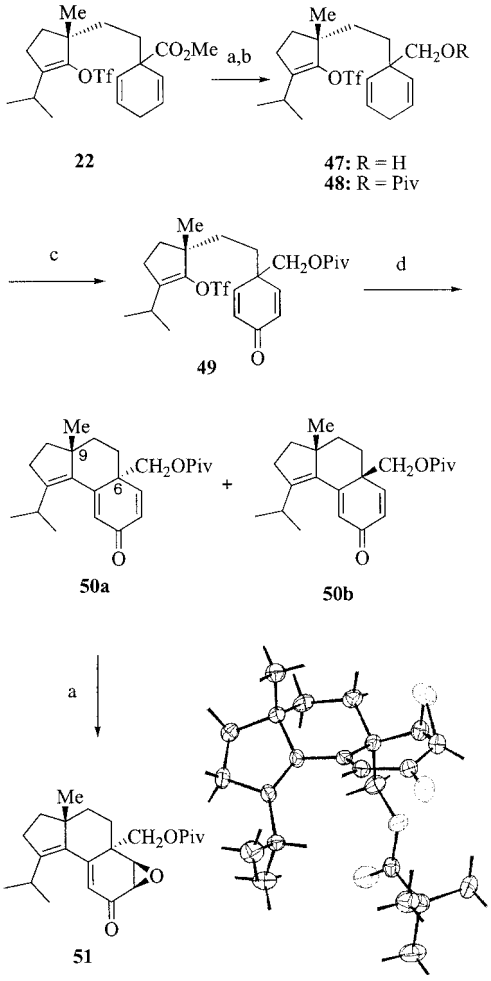
Having thus secured the critical union of subunits A and C, we turned our attention to the closing of the tricyclic ring system through the Heck reaction/acetate anion capture process we previously employed to prepare the model compound **39**. Preparation of the alkenyl triflate (–)-**22** occurred smoothly by treatment of **43** with triflic anhydride in the presence of 2,6-di-*tert*-butylpyridine in 1,2-dichloroethane at reflux. However, the presence of the bulky isopropyl group deeply affected the reactivity of triflate **22**. For example, treatment of **22** with $Pd_2(dba)_3{\cdot}CHCl_3$ in the presence of *n*-tetrabutylammonium acetate left the starting material unchanged. All attempts at improving this result using various palladium catalysts and reaction conditions failed. We speculated that the lack of reactivity of **22** might be overcome by adding a carbonyl group at the C4 position of the cyclohexadienyl appendage.[33] Allylic oxidation of (–)-**22** with $CrO_3{\cdot}$3,5-DMP[34] gave the expected dienone **45**, albeit in low yield, along with products with an aromatic C ring the structures of which were not readily formulated. Despite this drawback, it turned out that use of the dienone C ring was beneficial to the critical Heck cyclisation in view of the fact that treatment of **45** with $Pd(OAc)_2$ in toluene at reflux gave a 4:1 mixture of trienones **46a** and **46b** in

74% yield. The stereochemistry of the major diastereomer was assigned by analogy with other results obtained in the series (vide infra) (Scheme 7).



Scheme 7. (a) *i*: LDA, **23**, THF, –78 °C, 20 min, *i*: DMPU, –78 °C to +50 °C, 1 h, 60%; (b) $(CF_3SO_2)_2O$, 2,6-di-*t*Bu-C_5H_3N, $(CH_2Cl)_2$, 90 °C, 6 h, 71%; (c) CrO_3.3,5-DMP, CH_2Cl_2, 25 °C, 4 h, 40%; (d) 20 mol-% $Pd(OAc)_2$, PPh_3, *n*Bu_4NBr, toluene, 120 °C, 1 h, 74%.

Due to the low yield of the allylic oxidation of **22**, the approach was revised in such a way as to avoid decarboxylation and aromatisation of the C ring. Thus it was hoped that reduction of the ester group and protection of the resultant alcohol would improve this step. In the event, when the pivalate ester **48** [obtained in 72% yield upon treatment of (–)-**22** with DIBAL-H, followed by esterification with *t*BuCOCl] was subjected to CrO_3·3,5-DMP, the desired dienone (*S*)-**49** was obtained in 60% yield. Treatment of alkenyl triflate **49** with $Pd(OAc)_2$/PPh_3/*n*Bu_4NBr in toluene at 110 °C proceeded smoothly affording trienone (+)-**50a** (73% isolated yield) with good diastereoselectivity (95:5). The assignment of the relative configuration between rings A and C in the main isomer was first investigated by ^1H NMR spectroscopy. Significantly, the absence of a correlation between the methylene bearing the pivalate ester group and the methyl at C9 in the NOESY chart strongly suggested that this compound possessed the desired *anti* stereochemistry. In search of an unambiguous determination of the stereochemistry, we chose to prepare the epoxide **51**, since such a transformation was found to produce crystalline material in the nor-isopropyl series.[16a] Accordingly, epoxidation of (+)-**50a** was carried out with 50% hydrogen peroxide in the presence of sodium hydroxide. To our delight, epoxide **51** gave satisfactory single-crystals. The X-ray crystallographic analysis shown in Scheme 8 confirmed the *trans* relationship between the two angular groups at C6 and C9.[16b,35] In contrast to the model devoid of the isopropyl group, the epoxidation reaction had taken place exclusively on the less hindered face of the molecule, namely on the face opposite the bulky pivaloyl group.[16a] Although we had not anticipated exclusive epoxidation from the β face, we were very pleased with this favourable outcome which would prove to be of great value in the completion of the synthesis since this protocol allows the direct introduction of the oxygen functionality with the proper configuration at the C14 centre of natural cyathins (Scheme 8).

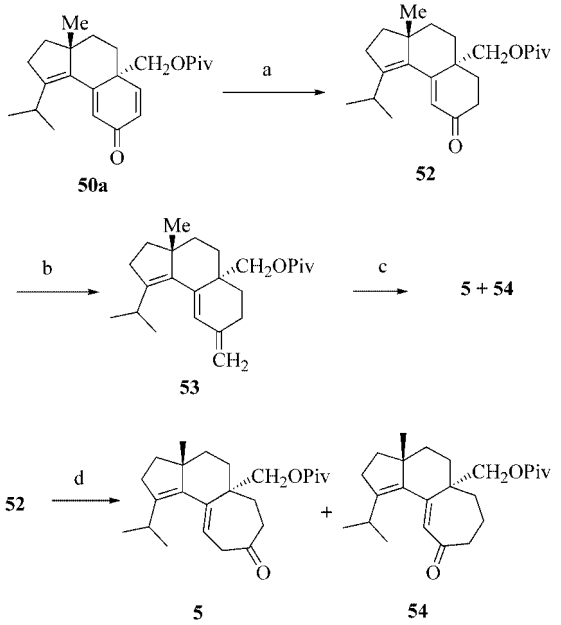


Crystal structure of epoxide **51**

Scheme 8. (a) DIBAL-H, CH_2Cl_2, –78 °C, 1 h, 90%; (b) PivCl, Et_3N, DMAP, CH_2Cl_2, 20 °C, 4 h, 71%; (c) CrO_3, 2,5-dimethylpyrazole, 4 h, 20 °C, 60%; (d) 20 mol-% $Pd(OAc)_2$, PPh_3, *n*Bu_4NBr, toluene, 120 °C, 2 h, 73%; (e) 50% H_2O_2, NaOH cat, MeOH, 25 °C, 24 h, 50%.

At this point it was considered timely to investigate the one-carbon expansion of the C ring. However, the densely functionalised materials **50a** and **51** were found to have a tendency to give aromatic decomposition products with a variety of reagents, presumably through cleavage of the pivaloyl ester group followed by a retro-aldol type process. To overcome this trend we decided to reduce the less hindered double bond of **50a** before addressing the crucial ring enlargement. Thus, homogeneous hydrogenation of the trienone (+)-**50a** using Wilkinson's catalyst[36] furnished the desired dienone (+)-**52** in 75% yield. With this compound in hand, we initially sought to accomplish ring expansion

through cyclopropanation or halocyclopropanation of the corresponding silyloxydiene[37] derived from **52**. However, this possibility was skirted because we failed to prepare the required silyl enol ether. A revised strategy was designed to circumvent the problematic enolisation step. We postulated that an *exo* methylene group, such as found in **53**, could be of value in a modified route using a thallium nitrate mediated ring expansion reaction.[38] Standard Wittig condensation of dienone (+)-**52** with the ylide derived from methyltriphenylphophonium bromide and *n*-butyllithium failed to give the desired triene **53**. The reaction of **52** with the Tebbe reagent[39] was more rewarding providing **53** in 20% yield but, finally, a 60% yield was achieved using *t*-AmONa in toluene[40] as a base in the Wittig reaction. When **53** was exposed to thallium nitrate, a 2:1 mixture of ketones **54** and **5** was obtained in a disappointing yield of 30%. Moreover, the yield was found to decrease on scaling up. It was thus deemed unlikely that we could achieve the synthesis according to this protocol. Accordingly, we examined the aluminium-catalysed carbenoid insertion of **52**. To our delight, condensation of dienone (+)-**52** with trimethylsilyldiazomethane in the presence of trimethylaluminium followed by hydrolysis of the resultant enol ether, according to Yamamoto's procedure,[41] provided the ring-expanded ketone (+)-**5** obtained in 60% isolated yield along with 10% of the regioisomeric enone **54** (Scheme 9). To the best of our knowledge, the preferential migration of the unsaturated α side of enones in such a process is unprecedented, although a similar trend was previously observed with 1-tetralone derivatives.[42]



Scheme 9. (a) $Rh(PPh_3)_3Cl$ 20 mol-%, EtOH, 25 °C, 60 h, 75%; (b) *t*-AmONa, CH_3PPh_3Br, toluene, 25 °C, 5 h, 60%; (c) $Tl(NO_3)_3$, MeOH, CH_2Cl_2, 2 min, 20 °C, 30%; (d) *i*: $TMSCHN_2$, Me_3Al, CH_2Cl_2, 20 °C, 4 h, *ii*: 3 N HCl, acetone, 20 °C, 2 h, 70% **5**/**54** = 6:1.

In summary we have successfully assembled, in optically active form, the tricyclic carbon core of the cyathin terpenoids in 18 steps from 2-methylcyclopentanone. The key steps of our synthesis were the enantioselective Michael addition to settle the absolute configuration, an intramolecular Heck reaction to establish the crucial *anti* stereochemistry of the C-nor-cyathane (+)-**50a** and the organoaluminium-promoted diazoalkane mediated ring expansion of the C ring. Further elaboration of ketone (+)-**5** into erinacine A and other cyathin diterpenes requires the reduction of the angular hydroxymethyl group to a methyl group, manipulation of the C12 carbonyl to introduce the requisite carbaldehyde and functionalisation at C14. Epoxide (+)-**51**, which displays an oxygen atom with the correct β configuration at the future C14 centre of natural cyathins, might serve as a suitable starting material to this purpose.

Experimental Section

General: Melting points: Büchi capillary tube melting point apparatus, uncorrected. IR spectra were obtained on solids or neat liquids on a Fourier Transform Bruker Vector 22 spectrometer. Only significant absorptions are listed. Optical rotations were measured on a Perkin–Elmer 241 Polarimeter at 589 nm. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 P (200 MHz and 50 MHz, for ^1H and ^{13}C, respectively), a Bruker Avance-300 (300 MHz and 75 MHz, for ^1H and ^{13}C, respectively) or a Bruker ARX 400 (400 MHz and 100 MHz, for ^1H and ^{13}C, respectively) spectrometer. Recognition of methyl, methylene, methine and quaternary carbon nuclei in ^{13}C NMR spectra rests on the *J*-modulated spin-echo sequence. Mass spectra were recorded on a Hewlett–Packard G 1019 A (70 eV) or on a Bruker Esquire-LC instrument. Analytical thin-layer chromatography was performed on Merck silica gel $60F_{254}$ glass precoated plates (0.25 mm layer). Column chromatography was performed on Merck silica gel 60 (230–400 mesh ASTM). Diethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methanol and ethanol were dried with magnesium and distilled. Benzene, toluene, DMF and CH_2Cl_2 were distilled from calcium hydride under a nitrogen atmosphere. All reactions involving air- or water-sensitive compounds were routinely conducted in glassware which had been flame-dried under a positive pressure of nitrogen. Chemicals obtained from commercial suppliers were used without further purification. Elemental analyses were performed by the Service de microanalyse, Centre d'Etudes Pharmaceutiques, Châtenay-Malabry, France with a Perkin–Elmer 2400 analyser.

Methyl (1*R*)-3-(1-Methyl-2-oxocyclopentyl)propanoate (10): In a round-bottom flask equipped with a Dean–Stark apparatus was placed 2-methylcyclopentanone, (24.6 g, 0.25 mol), (*S*)-1-phenylethylamine (30.0 g, 0.25 mol) and *p*-toluenesulfonic acid (50 mg) in toluene (150 mL). The reaction mixture was heated at reflux for 16 h and concentrated under reduced pressure. The residue was distilled (b.p. 92 °C, 0.2 Torr) to give imine **11** as a colourless oil (1:1 diastereomeric mixture, 42.0 g, 87%). IR (film): $\tilde{\nu}$ = 1673 cm^{-1} (C=N). To the imine **11** (41.7 g, 0.22 mol) was added freshly distilled methyl acrylate (89.4 g, 1.04 mol) and hydroquinone (0.05 g). The mixture was stirred at 50 °C for 48 h and concentrated under reduced pressure. To the residue was added 20% aqueous acetic acid (70 mL) and THF (120 mL). After being stirred for 3 h at 20 °C, the mixture was concentrated in vacuo and 3 N hydrochloric acid (40 mL) was added. The mixture was extracted with diethyl ether (4 × 100 mL) and the collected organic phases were washed with brine, dried with $MgSO_4$ and concentrated. Distillation af-

forded (+)-**10** as a colourless oil (27.8 g, 70% overall yield from 2-methylcyclopentanone), b.p. 110 °C/0.05 Torr. $[\alpha]_D^{20}$ = +35.5 (*c* = 1.7, EtOH). IR (film): $\tilde{\nu}$ = 2957, 1731 (C=O, CO_2Me), 1436, 1374, 1199, 1164 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.62 (s, 3 H, OCH_3), 2.36–2.12 (m, 4 H, $CH_2CO_2CH_3$ and 3-H), 1.93–1.63 (m, 6 H, $CH_2CH_2CO_2CH_3$, 4-H and 5-H), 0.97 [s, 3 H, $C(CH_3)$-CO] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 222.4 (C, *C*O), 173.6 (CO_2Me), 51.4 (CH_3, OCH_3), 47.2 (C, *C*1), 37.2 (CH_2, *C*3), 35.8 (CH_2, *C*5), 31.2 (CH_2, CH_2CO_2Me), 29.0 (CH_2, $CH_2CH_2CO_2Me$), 21.1 (CH_3), 18.3 (CH_2, *C*4) ppm. $C_{10}H_{16}O_3$ (184.2): calcd. C 65.19, H 8.75; found C 65.03, H 8.89.

Methyl (1*R*)-3-(1-Methyl-2-oxocyclopentyl)propanoate (12): To a solution of ester (+)-**10** (29.9 g, 0.16 mol) in methanol (200 mL) was added potassium hydroxide (200 mL, 2 N, 0.4 mol) and the mixture was stirred at 20 °C for 16 h. The reaction mixture was concentrated under reduced pressure and the residue extracted with diethyl ether. The organic layer was discarded and 5 N hydrochloric acid was added to the aqueous layer until a pH of 2 was obtained. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure to leave (+)-**12** as a pale yellow oil (26.7 g, 97%). $[\alpha]_D^{20}$ = +14 (*c* = 1.7, EtOH). IR (film): $\tilde{\nu}$ = 3600–2400 (OH), 1730 (C=O), 1705 (CO_2H), 1459, 1406, 1291, 1200, 1165 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.0–6.0 (br. s, CO_2H), 2.50–2.15 (m, 4 H, 3-H, CH_2CO_2H), 1.99 –1.60 (m, 6 H, 4-H, 5-H, $CH_2CH_2CO_2H$), 1.02 [s, 3 H, $C(CH_3)$] ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 222.1 (C, *C*O), 179.0 (C, CO_2H), 47.5 (C, *C*1), 37.5 (CH_2, *C*3), 36.0 (CH_2, *C*5), 31.3 (CH_2, $CH_2CH_2CO_2H$), 29.1 (CH_2, $CH_2CH_2CO_2H$), 21.3 (CH_3), 18.6 (CH_2, *C*4) ppm. $C_9H_{14}O_3$ (170.2): calcd. C 63.51, H 8.29; found C 63.29, H 8.54.

(2*R*)-2-(2-Iodoethyl)-2-methylcyclopentanone (13): A solution of crude acid (+)-**12** (2.20 g, 13 mmol) in CCl_4 (160 mL) was placed in a round-bottomed flask equipped with a dropping funnel, surmounted with a condenser and charged with solid iodine (3.40 g, 13.4 mmol) set down on a glass-wool plug sealing the stopcock. Lead(IV) acetate (6.50 g, 14.5 mmol) was added to the solution in one portion. The apparatus was illuminated with a 500 W visible light lamp set 15 cm from of the flask while the mixture was heated to reflux in such way that the condensed solvent slowly dragged iodine into the reaction flask. After stirring for 1 h all the iodine had been consumed and the milky solution was cooled to room temperature. The reaction mixture was filtered through celite and the solid was washed thoroughly with CH_2Cl_2. The organic layer was sequentially washed with aqueous potassium thiosulfate (20 mL), 2 N potassium hydroxide (20 mL) and brine (20 mL). The organic phases were dried with $MgSO_4$ and concentrated in vacuo to give an oil which was chromatographed on silica gel (cyclohexane/ethyl acetate, 4:1) to give iodide (+)-**13** as a colourless, light-sensitive oil (2.74 g, 84%) $[\alpha]_D^{20}$ = +12 (*c* = 1.1, EtOH). IR (film): $\tilde{\nu}$ = 2960, 1731 (C=O), 1456, 1404, 1373, 1319, 1269, 1201, 1161 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.19 (ddd, *J* = 11.4, 9.4, 5.8 Hz, 1 H, CH_2I), 3.05 (ddd, *J* = 11.4, 9.4, 6.3 Hz, 1 H, CH_2I), 2.34–2.16 (m, 2 H, 5-H), 2.16–2.00 (m, 2 H, CH_2CH_2I), 1.95–1.68 (m, 4 H, 3-H, 4-H), 1.00 [s, 3 H, $C(CH_3)CO$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 221.4 (C, *C*O), 50.1 (C, *C*1), 41.7 (CH_2, CH_2CH_2I), 37.3 (CH_2, *C*5), 35.6 (CH_2, *C*3), 20.9 (CH_3), 18.6 (CH_2, *C*4), –0.9 (CH_2, CH_2CH_2I) ppm. $C_8H_{13}IO$ (252.1): calcd. C 38.12, H 5.20; found C 38.23, H 5.21.

(1*R*)-1-[2-(1-Methyl-2-oxocyclopentyl)ethyl]cyclohepta-2,4,6-triene-1-carbonitrile (15): To a solution of iodo ketone **13** (150 mg, 0.60 mmol) in CH_2Cl_2 (6 mL) was added, at 0 °C, triethylamine (225 mg, 2.24 mmol) and TMSOTf (450 mg, 1.6 mmol). After being stirred at 0 °C for 3 h, the mixture was poured into pentane (15 mL) and washed with cold brine. The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to give 160 mg of crude silyl ether **14** (86%) as a yellow oil, which was used directly for the next steps.

A solution of *n*-butyllithium (2.5 M in hexane, 0.55 mL, 1.37 mmol) was added to a solution of diisopropylamine (162 mg, 1.6 mmol) in THF (4 mL) at –5 °C. The mixture was stirred at –5 °C for 15 min and cooled to –78 °C. A solution of cyclohepta-2,4,6-triene-carbonitrile **8a**[21] (160 mg, 1.35 mmol) in THF (0.5 mL) was added dropwise. The resultant mixture was stirred at –78 °C for 10 min and a solution of iodide **14** (160 mg, 0.50 mmol) in a mixture of THF (1 mL) and HMPA (2 mL) was then added. The reaction mixture was stirred while the temperature was gradually raised to –20 °C. After 16 h at –20 °C, saturated aqueous ammonium chloride was added and the mixture was extracted with diethyl ether (4 × 15 mL). The collected organic phases were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The residue was taken up in THF (2 mL) and nBu_4NF (1.5 mL, 1 M, 1.5 mmol) was added. After 1 h at 20 °C, water was added (10 mL) and the mixture was extracted with diethyl ether (4 × 15 mL). The combined organic phases were dried with $MgSO_4$ and concentrated. Purification by silica gel chromatography (cyclohexane/ethyl acetate, 7:1) gave 86 mg of (+)-**15** as a colourless oil (71% yield). $[\alpha]_D^{20}$ = +33 (*c* = 0.4, EtOH). IR (neat): $\tilde{\nu}$ = 3031, 2966, 2220 (CN), 1731 (C=O), 1638 (C=C), 1461, 1406, 1373, 1063 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.73 [m, 2 H, (CN)CCH=CH–C*H*=], 6.31 [m, 2 H, (CN)CCH=C*H*–CH=], 4.76 [dd, *J* = 14.1, 9.8 Hz, 2 H, (CN)CC*H*=CH–CH=], 2.42–2.17 (m, 2 H, 3-H), 1.96–1.71 (m, 8 H), 1.06 [s, 3 H, $C(CH_3)$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 221.9 (C, *C*O), 129.7 [2 CH, (CN)CCH=CH–*C*H=], 125.9 [2 CH, (CN)CCH=*C*H–CH=], 118.9 (CN), 106.3 [2 CH, (CN)C*C*H=CH–CH=], 47.2 (C, *C*1), 37.0 (CH_2, *C*3), 35.3 (CH_2), 34.1 [C, (CN)*C*CH=], 31.4 (CH_2), 30.7 (CH_2), 21.1 (CH_3), 18.1 (CH_2, *C*4) ppm. MS (ESI, MeOH): *m*/*z* (%): 264 (100) $[M + Na]^+$. $C_{16}H_{19}NO$ (241.3): calcd. C 79.63, H 7.94, N 5.80; found C 79.44, H 7.96, N 5.88.

***tert*-Butyl-{[(1*R*,2*R*)- and (1*S*,2*R*)-2-(2-iodoethyl)-2-methylcyclopentyl]oxy}dimethylsilane (16b):** To a solution of iodo ketone **13** (3.53 g, 14 mmol) in dry EtOH (40 mL) was added, in portions, $NaBH_4$ (300 mg, 7.9 mmol) and the mixture was stirred under nitrogen for 3 h at 20 °C. The reaction mixture was concentrated under reduced pressure, brine (10 mL) was added and the mixture was extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure to give iodo alcohol **16a** (2.34 g, 65%) as a yellow oil which was used directly for the next steps without further purification. To the crude alcohol **16a** (2.34 g, 9.2 mmol) in CH_2Cl_2 (30 mL) was added *tert*-butyldimethylsilyl chloride (3.0 g, 19.9 mmol) and imidazole (2.0 g, 29.4 mmol). After being stirred at 20 °C for 16 h, water was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were dried with $MgSO_4$ and concentrated in vacuo. Purification by chromatography on silica gel (cyclohexane/ethyl acetate, 7:1) gave **16b** as a colourless oil (3.04 g, 96%). IR (film): $\tilde{\nu}$ = 2963, 2932, 2860, 1464, 1382, 1257, 1146, 1112 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.67 (t, *J* = 7.0 Hz, 1 H, C*H*OSi), 3.30–3.00 (m, 2 H, CH_2CH_2I), 2.05 (td, 1 H, *J* = 13.1, 5.0 Hz, 1 H), 1.92–1.30 (m, 7 H), 0.88 [s, 9 H, $Si(CH_3)_2C(CH_3)_3$], 0.86 [s, 3 H, $C(CH_3)$], 0.04 [s, 3 H, $Si(CH_3)_2C(CH_3)_3$], 0.03 [s, 3 H, $Si(CH_3)_2C(CH_3)_3$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 80.0 (CH, *C*HOSi), 47.3 [C, $C(CH_3)$], 46.4 (CH_2, CH_2CH_2I), 34.9 (CH_2, *C*3), 32.3 (CH_2, *C*5), 25.9 [3 CH_3, $SiCH_2C(CH_3)_3$], 19.2 (CH_2, *C*4), 17.7 [CH_3 and C, $C(CH_3)$

and $Si(CH_3)_2C(CH_3)_3$], 1.48 (CH_2, CH_2CH_2I), –4.2 [CH_3, $Si(CH_3)_2C(CH_3)_3$], –4.8 [CH_3, $Si(CH_3)_2C(CH_3)_3$] ppm. $C_{14}H_{29}IOSi$ (368.4): calcd. C 45.65, H 7.94; found C 45.71, H 7.87.

Methyl (1*R*,2*R*)- and (1*S*, 2*R*)-1-[2-(2-Hydroxy-1-methylcyclopentyl)-ethyl]cyclohexa-2,5-diene-1-carboxylate (25): To a solution of diisopropylamine (605 mg, 6.0 mmol) in dry THF (3 mL) was added, at –5 °C, a hexane solution of *n*-butyllithium (2.5 M, 2.0 mL, 5.0 mmol). The mixture was stirred at –5 °C for 15 min and cooled to –78 °C. A solution of cyclohexa-2,5-dienecarboxylic acid methyl ester **23** (550 mg, 4 mmol) in dry THF (3 mL) was added dropwise with a syringe. The resultant mixture was stirred at –78 °C for 15 min and iodide **16b** (740 mg, 2.00 mmol) in DMPU (3 mL) was added. The reaction mixture was stirred while the temperature was gradually raised to 50 °C. After 3 h at 50 °C, water (3 mL) was added and the mixture was extracted with diethyl ether (3 × 10 mL). The collected organic phases were washed with brine, dried with $MgSO_4$ and concentrated. Purification by silica gel chromatography (cyclohexane/Ethyl acetate, 4:1) gave 630 mg of **24** (83% yield). To a solution of silyl ether **24** (630 mg, 1.67 mmol) in THF (2 mL) was added a solution of *n*-tetrabutylammonium fluoride (1.0 M in THF, 8.0 mL, 8 mmol). The mixture was stirred at 20 °C for 5 h. Water (6 mL) was added and the mixture was extracted with diethyl ether (3 × 10 mL). The collected organic phases were washed with brine, dried with $MgSO_4$ and concentrated. Purification by silica gel chromatography (cyclohexane/ethyl acetate, 2:1) gave 342 mg of alcohol **25** as a yellow oil (78% yield). IR (neat): $\tilde{\nu}$ = 3600–3100 (OH), 3032, 2953, 2872, 1729 (CO_2Me), 1637 (weak, C=C), 1452, 1434, 1234, 1201 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) the presence of two diastereomers induced the splitting of some signals, δ = 5.90–5.70 (m, 2 H, HC=C*H*CH_2C*H*=CH), 5.62 (d, *J* = 11.0 Hz, 2 H, *H*C=CHCH_2CH=C*H*), 3.67 (br. s, 4 H, C*H*OH and CO_2CH_3), 2.52 (br. s, 2 H, =CHCH_2CH=), 2.08–1.87 (m, 1 H), 1.81–0.93 (m, 10 H), 0.86 [s, 3 H, C(CH_3)] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.3 (C, *C*O_2Me), 127.1 (2 CH, *C*=CHCH_2CH=*C*), 125.5 (2 CH, C=*C*HCH_2*C*H=C), 80.0 (CH, *C*HOH), 51.9 (CH_3, O*C*H_3), 47.6 (C, *C*CO_2Me), 44.0 (C, *C*1), 35.6 (CH_2), 34.7 (CH_2), 34.2 (CH_2), 32.3 (CH_2), 26.0 (CH_2, C=CH*C*H_2CH=C), 19.2 (CH_2, *C*4), 18.1 [CH_3, (CH_3)C] ppm. MS (ESI, CH_3CN): *m*/*z* (%): 287 (100) [*M* + Na]$^+$. $C_{16}H_{24}O_3$ (264.4): calcd. C 72.69, H 9.15; found C 72.58, H 9.30.

Methyl (1*R*)-1-[2-(1-Methyl-2-oxocyclopentyl)ethyl]cyclohexa-2,5-diene-1-carboxylate (26): To a solution of oxalyl chloride (240 mg, 1.9 mmol) in CH_2Cl_2 (2 mL) was added dropwise, at –78 °C, anhydrous DMSO (156 mg, 2 mmol). The mixture was stirred at –78 °C for 20 min and a solution of alcohol **25** (342 mg, 1.3 mmol) in dry CH_2Cl_2 (2 mL) was added. After 1 h at –78 °C, Et_3N (710 mg, 7.0 mmol) was added and the reaction mixture was stirred for 5 min and then warmed to room temperature. After being stirred 8 h at 20 °C, water (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated in vacuo. Purification by silica gel chromatography (cyclohexane/ethyl acetate, 4:1) gave 323 mg of (+)-**26** as a yellow oil (95% yield). $[\alpha]_D^{20}$ = +36.2 (*c* = 1.3, EtOH). IR (neat): $\tilde{\nu}$ = 3032, 2954, 1727 (C=O, CO_2Me), 1637 (weak, C=C), 1458, 1433, 1406, 1231, 1201 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 5.89 (dt, *J* = 12.7, 2.9 Hz, 2 H, HC=C*H*CH_2C*H*=CH), 5.66 (d, *J* = 12.7 Hz, 2 H, *H*C=CHCH_2CH=C*H*), 3.66 (s, 3 H, OCH_3), 2.63 (br. s, 2 H, =CHCH_2CH=), 2.53–2.06 (m, 2 H, 3-H), 1.99–1.42 (m, 6 H, CH_2), 1.34–1.20 (m, 2 H, CH_2), 0.96 [s, 3 H, C(CH_3)] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 221.3 (C, *C*O), 175.2 (C, *C*O_2Me), 126.8 (CH, *C*=CHCH_2CH=*C*), 126.0 (CH, C=*C*HCH_2*C*H=C), 52.0 (CH_3, O*C*H_3), 47.7 (C, *C*CO_2Me), 41.9 [C, *C*(CH_3)CO], 37.5 (CH_2, *C*3), 35.6 (CH_2), 33.8 (CH_2), 30.8 (CH_2), 26.1 (CH_2, C=CH*C*H_2CH=C), 21.5 [CH_3, (CH_3)C], 18.6 (CH_2, *C*4) ppm. $C_{16}H_{22}O_3$ (262.3): calcd. C 73.25, H 8.45; found C 72.24, H 8.48.

Methyl (1*R*)-1-[2-(1-Methyl-2-{[(trifluoromethyl)sulfonyl]oxy}-cyclopent-2-en-1-yl)ethyl]cyclohexa-2,5-diene-1-carboxylate (27): Trifluoromethanesulfonic anhydride (3.35 g, 11.9 mmol) was added dropwise with a syringe to a mixture of 2,6-di-*tert*-butylpyridine (1.87 g, 9.8 mmol) and keto ester (+)-**26** (2.35 g, 9.0 mmol) in dry dichloromethane (40 mL). The resultant mixture was stirred for 15 h at 20 °C. Water was added (40 mL) and the mixture was extracted with dichloromethane (3 × 15 mL). The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate, 4:1) to give triflate (+)-**27** as a yellow oil (2.80 g, yield 79%). $[\alpha]_D^{20}$ = +34.6 (*c* = 2.1, EtOH). IR (neat): $\tilde{\nu}$ = 3030, 2954, 1730 (CO_2Me), 1656 (C=C), 1419, 1202, 1139 1045 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.91 (dt, *J* = 11.8, 3.1 Hz, 2 H, HC=C*H*CH_2C*H*=CH), 5.68 (dddd, *J* = 11.8, 5.8, 2.3, 1.5 Hz, 2 H, *H*C=CHCH_2CH=C*H*), 5.57 [t, *J* = 2.7 Hz, 1 H, C*H*=C(OTf)], 3.59 (s, 3 H, OCH_3), 2.68 (ddt, *J* = 23.2, 3.5, 2.1 Hz, 1 H, =CHCH_2CH=), 2.61 (d, *J* = 23.2, 3.5, 2.1 Hz, 1 H, =CHCH_2CH=), 2.36 (ddt, *J* = 16.4, 5.6, 2.7, Hz, 1 H, 4-H), 2.29 (ddt, *J* = 16.4, 5.8, 2.6 Hz, 1 H, 4-H), 1.89 (ddd, *J* = 13.6, 8.4, 5.8 Hz, 1 H, 5-H), 1.75–1.54 [m, 3 H, CH_2C*H*$_2$(C)CO_2Me, 5-H], 1.31 [t, *J* = 8.6 Hz, 2 H, CH_2CH_2(C)CO_2Me], 1.11 [s, 3 H, C(CH_3)] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.1 (C, *C*O_2Me), 154.0 (C, *C*2), 126.8 (2 CH, *C*=CHCH_2CH=*C*), 126.1 (2 CH, C=*C*HCH_2*C*H=C), 118.5 (q, *J* = 320 Hz, C, *C*F_3SO_2), 113.2 (CH, *C*3), 52.1 (CH_3, O*C*H_3), 47.5 (C, *C*CO_2Me), 46.1 (C, *C*1), 34.0 (CH_2), 33.8 (CH_2), 32.6 (CH_2), 26.1 (CH_2, C=CH*C*H_2CH=C), 25.5 (CH_2, *C*5), 24.4 [CH_3, (CH_3)C] ppm. ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –74.1 (s) ppm. MS (ESI, MeOH) *m*/*z* (%): 412 (100) [*M* + Na]$^+$, 395 (70) [*M* + H]$^+$, 245 (12).

Methyl (3a*R*,5a*R*,8*R*,9a*S*)-8-Hydroxy-3a-methyl-2,3,3a,4,5,8,9,9a-octahydro-5a*H*-cyclopenta[*a*]naphthalene-5a-carboxylate (30): To a mixture of triflate (+)-**27** (2.8 g, 7.1 mmol), *n*-tetrabutylammonium acetate (6.3 g, 21.0 mmol) and lithium chloride (600 mg, 14.2 mmol) in DMSO (10 mL) was added tris(dibenzylideneacetone) dipalladium–chloroform adduct (370 mg, 0.4 mmol). The mixture was stirred at 60 °C for 3 h. After cooling, water (10 mL) was added and the reaction mixture was extracted with diethyl ether (3 × 20 mL). The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure to leave a brown oil (3.0 g) which was taken up in dry methanol (50 mL). Potassium carbonate (1.1 g, 8.0 mmol) was added and the mixture was stirred at 20 °C for 3 h. The reaction mixture was concentrated under reduced pressure, 1 N HCl (10 mL) was added and the mixture was extracted with diethyl ether (3 × 15 mL). The combined organic phases were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate, 4:1) to give alcohol (–)-**30** as a colourless oil (1.6 g, yield 85% from **27**). $[\alpha]_D^{20}$ = –4.4 (*c* = 2.3, EtOH). IR (neat): $\tilde{\nu}$ = 3500–3000 (OH), 2947, 2852, 1726 (CO_2Me), 1638 (C=C), 1454, 1431, 1265, 1202 1146 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.92 (ddd, *J* = 9.9, 5.5, 1.4 Hz, 1 H, 7-H), 5.76 (d, *J* = 9.9 Hz, 1 H, 6-H), 5.46 (dd, 1 H, *J* = 2.8, 2.0 Hz, 1-H), 4.11 (ddd, *J* = 5.6, 3.9, 2.0 Hz, 1 H, 8-H), 3.65 (s, 3 H, CO_2CH_3), 3.44 (dd, *J* = 14.3, 3.5 Hz, 1 H, 9a-H), 2.35–2.25 (m, 1 H, 2-H), 2.15 (dddd, *J* = 15.9, 9.1, 3.1, 1.3 Hz, 1 H, 2-H), 2.05 (ddd, *J* = 14.5, 3.8, 1.4 Hz, 1 H, 5-H), 2.00–1.90 (br. s, OH), 1.92 (td, *J* = 14.3, 3.9 Hz, 1 H, 9-H_{ax}), 1.76–1.69 (m, 2 H, 3-H, 9-H_{eq}), 1.64 (dt, *J* = 13.4, 3.2 Hz, 1 H, 5-H), 1.62 (dt, *J* = 14.3, 3.4 Hz, 1 H, 4 -H_{eq}), 1.59–1.52 (m, 1 H, 3-H), 1.21 (td, *J* = 14.2, 3.5 Hz, 1 H,

4-H_{ax}), 1.06 [s, 3 H, C(CH_3)] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.1 (C, CO_2CH_3), 149.4 (C, C9b), 134.7 (CH, C6), 128.1 (CH, C7), 124.1 (CH, C1), 63.1 (CH, C8), 52.2 (CH_3, CO_2CH_3), 50.7 (C, C5a), 44.5 (C, C3a), 43.2 (CH_2, C3), 37.9 (CH_2, C4), 35.5 (CH_2, C9), 32.5 (CH, C9a), 29.1 (CH_2, C2), 27.5 (CH_2, C5), 25.1 [CH_3, C(CH_3)] ppm. $C_{16}H_{22}O_3$ (262.3): calcd. C 73.25, H 8.45; found C 73.27, H 8.61.

Methyl (1*R*)-3-{1-Methyl-2-[(trimethylsilyl)oxy]cyclopent-2-en-1-yl}propanoate (32): To an ice-cooled solution of keto ester (+)-**10** (2.0 g, 10.9 mmol) in dry CH_2Cl_2 (15 mL) were sequentially added Et_3N (1.65 g, 16.3 mmol) then trimethylsilyl(trifluoromethane)sulfonate (2.90 g, 13.0 mmol). The mixture was warmed to 20 °C and stirred for 4 h. The solution was diluted with pentane (120 mL), washed with cold water (2 × 10 mL) dried with $MgSO_4$ and concentrated under reduced pressure to leave a yellow oil (2.47 g, 89%) which was used directly for the next steps. IR (film): $\tilde{\nu}$ = 2957, 2854, 1740 (CO_2Me), 1643 (C=C), 1449, 1436, 1376, 1342, 1251, 1194 cm^{-1}. ^{1}H NMR (200 MHz, C_6D_6): δ = 4.41 (t, J = 2.4 Hz, 1 H, 3-H), 3.37 (s, 3 H, OCH_3), 2.28 (t, J = 8.1 Hz, 1 H, C$H_2CO_2CH_3$), 2.15–2.00 (m, 2 H, 4-H), 1.75–1.27 (m, 4 H, C$H_2CH_2CO_2CH_3$ and 5-H), 1.02 [s, 3 H, C(CH_3)]. 0.10 [s, 9 H, Si(CH_3)$_3$] ppm. ^{13}C NMR (50 MHz, C_6D_6): δ = 173.4 (CO_2Me), 158.9 (C, C2), 99.1 (CH, C3), 50.5 (CH_3, OCH_3), 45.7 (C, C1), 34.1 (CH_2, C5 or $CH_2CH_2CO_2Me$), 33.8 (CH_2, C5 or $CH_2CH_2CO_2Me$), 29.7 (CH_2, CH_2CO_2Me), 25.3 (CH_2, C4), 24.5 (CH_3), –0.5 [3 CH_3, Si(CH_3)$_3$] ppm.

Methyl (1*R*,*E*)- and (1*R*,*Z*)-3-(3-Ethylidene-1-methyl-2-oxocyclopentyl)propanoate (34): To a solution of silyl enol ether **32** (2.40 g, 9.37 mmol) and acetaldehyde (1.65 g, 37.5 mmol) in CH_2Cl_2 (20 mL) was added dropwise, at –78 °C, $TiCl_4$ (1.80 g, 9.61 mmol). The reaction mixture was stirred at –78 °C for 2 h and then aqueous $NaHCO_3$ (10 mL) was added. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried and concentrated under reduced pressure to leave the cetol **33** as a 4:4:1:1 mixture of stereomers which was used directly for the next steps (2.02 g, 89%). Methanesulfonyl chloride (1.15 g, 10.4 mmol) was added to a solution of ketol **33** (2.0 g, 8.42 mmol), triethylamine (1.27 g, 12.6 mmol) and DMAP (75 mg) in CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. then warmed to 20 °C. After being stirred for 1 h at 20 °C, aqueous ammonium chloride was added. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried and concentrated under reduced pressure to leave a yellow oil which was dissolved in toluene (20 mL). DBU (1.92 g, 12.7 mmol) was added and the reaction mixture was heated at reflux for 1 h. After cooling, HCl 1 N was added until a pH of 7 was reached and the mixture was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried and concentrated under reduced pressure. Chromatography (cyclohexane/ethyl acetate, 4:1) gave enone **34** as a 5:1 *E*/*Z* mixture (1.35 g, 90%). Only the major *E* isomer is described, $[\alpha]_D^{20}$ = +4.9 (c = 5, EtOH). IR (film): $\tilde{\nu}$ = 2953, 2869, 1754 (CO_2Me), 1716, (C=O), 1649, (C=C), 1436, 1374, 1288, 1198, 1170 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.55 (m, 1 H, CH_3CH=C), 3.62 (s, 3 H, CO_2CH_3), 2.56–2.42 (m, 2 H, C$H_2CO_2CH_3$), 2.40–2.20 (m, 2 H, 4-H), 1.82–1.62 (m, 7 H, CH_3CH=C, C$H_2CH_2CO_2CH_3$), 1.02 [s, 3 H, C(CH_3)] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 208.6 (C, CO), 173.6 (CO_2CH_3), 137.5 (C, CH_3CH=C), 132.3 (CH, CH_3CH=C), 51.2 (CH_3, OCH_3), 47.9 (C, C1), 32.7 (CH_2), 31.1 (CH_2), 29.0 (CH_2), 22.5 (CH_2), 21.2 [CH_3, C(CH_3)], 14.9 (CH_3, CH_3CH=C) ppm. $C_{12}H_{18}O_3 \cdot \frac{1}{6}$ H_2O (213.3): calcd. C 67.58, H 8.66; found C 67.67, H 8.69.

Methyl (1*R*,3*R*)- and (1*R*,3*S*)-3-(3-Isopropyl-1-methyl-2-oxocyclopentyl)propanoate (35a): To a suspension of anhydrous CuI (5.1 g, 30.5 mmol) in diethyl ether (40 mL) was added dropwise at –30 °C methyllithium (1.6 M in Et_2O, 37 mL, 59.4 mmol) and the mixture was stirred 5 min. To the homogeneous colourless solution obtained, enone **34** (1.6 g, 7.6 mmol) in Et_2O (10 mL) was added and the reaction mixture was stirred for 1 h. The solution was then poured into an ice-cooled saturated aqueous solution of ammonium chloride (50 mL). The resultant mixture was vigorously stirred in air for 1 h and thoroughly extracted with Et_2O (4 × 50 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated. Chromatographic purification (cyclohexane/ethyl acetate, 4:1) gave keto ester **35a** (1.20 g, 70%) as colourless oil. IR (film): $\tilde{\nu}$ = 2958, 2929, 2852, 1730 (C=O, CO_2H), 1451, 1370 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) the presence of a 2:1 mixture of diastereomers induced the splitting of some signals, only the major isomer is described, δ = 3.63 (s, 3 H, CO_2CH_3), 2.36–1.57 (m, 10 H), 0.95 [d, J = 6.3 Hz, 3 H, (CH_3)$_2$CH], 0.90 [s, 3 H, C(CH_3)], 0.79 [d, J = 6.3 Hz, 3 H, (CH_3)$_2$CH] ppm. ^{13}C NMR (75 MHz, $CDCl_3$) only the major isomer is described, δ = 222.6 (C, CO), 173.9 (CO_2CH_3), 55.7 (CH, C3), 51.6 (CH_3, CO_2CH_3), 48.1 (C, C1), 33.4 (CH_2), 32.4 (CH_2), 29.4 (CH_2), 27.2 [CH, (CH_3)$_2$CH], 21.0 [CH_3, C(CH_3) or (CH_3)$_2$CH], 20.9 [CH_3, C(CH_3) or (CH_3)$_2$CH], 20.4 (CH_2, C4), 18.3 [CH_3, (CH_3)$_2$CH] ppm. $C_{13}H_{22}O_3$ (226.3): calcd. C 68.99, H 9.80; found C 69.15, H 9.91.

(1*R*,3*R*)- and (1*R*,3*S*)-3-(3-Isopropyl-1-methyl-2-oxocyclopentyl)propanoic Acid (35b): To a solution of ester **35a** (500 mg, 2.21 mmol) in methanol (25 mL) was added 3 N sodium hydroxide (15 mL, 45 mmol). After stirring for 4 h at room temperature, 2 N hydrochloric acid was added until a pH of 2 was reached. The mixture was concentrated under reduced pressure and the residue extracted with CH_2Cl_2 (4 × 15 mL). The combined organic extracts were washed with aqueous sodium chloride, dried with $MgSO_4$, to give crude acid **35b** (350 mg, 75%) as a pale yellow oil which was used directly for the next steps without further purification. IR (film): $\tilde{\nu}$ = 3600–3400 (OH), 1728 (C=O), 1708 (CO_2H), 1459, 1415, 1386, 1369, 1295 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) the presence of a 2:1 mixture of diastereomers induced the splitting of some signals, only the major isomer is described, δ = 10.3–10.2 (br. s, 1 H, OH), 2.45–1.53 (m, 10 H), 0.94 [d, J = 6.8 Hz, 3 H, (CH_3)$_2$CH], 0.90 [s, 3 H, C(CH_3)CO], 0.76 [d, J = 6.8 Hz, 3 H, (CH_3)$_2$CH] ppm. ^{13}C NMR (50 MHz, $CDCl_3$) only the major isomer is described, δ = 222.6 (C, CO), 179.9 (CO_2H), 55.5 (CH, C3), 47.9 (C, C1), 33.3 (CH_2), 32.3 (CH_2), 29.2 (CH_2), 27.1 [CH, (CH_3)$_2$CH], 21.9 [2 CH_3, C(CH_3) and (CH_3)$_2$CH], 20.6 (CH_2, C4), 18.2 [CH_3, (CH_3)$_2$CH] ppm. $C_{12}H_{20}O_3$ (212.3): calcd. C 67.89, H 9.50; found C 67.74, H 9.45.

***tert*-Butyl (1*R*,3*R*)- and (1*R*,3*S*)-3-(3-Isopropyl-1-methyl-2-oxocyclopentyl)propanoate (35d):** To a solution of acid **35b** (100 mg, 0.47 mmol) in toluene (3 mL) was added di-*tert*-butoxymethyl-dimethylamine (450 mg, 1.88 mmol) and the mixture was heated to reflux for 90 min. After cooling, the reaction mixture was concentrated under reduced pressure and the residue purified by silica gel chromatography (cyclohexane/ethyl acetate, 4:1) to provide keto ester **35d** (75 mg, 60%) as a colourless oil. IR (film): $\tilde{\nu}$ = 2962, 2929, 2871, 1726 (C=O, CO_2tBu), 1458, 1153 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) the presence of a 2:1 mixture of diastereomers induced the splitting of some signals, only the major isomer is described, δ = 2.25–1.43 (m, 10 H), 1.36 [s, 9 H, OC(CH_3)$_3$], 0.91 [d, J = 6.7 Hz, 3 H, (CH_3)$_2$CH], 0.86 [s, 3 H, C(CH_3)], 0.78 [d, J = 6.7 Hz, 3 H, (CH_3)$_2$CH] ppm. ^{13}C NMR (50 MHz, $CDCl_3$) only the major isomer is described, δ = 222.1 (C, CO), 172.7 (CO_2tBu),

80.1 [C, O*C*(CH$_3$)$_3$], 55.6 (CH, *C*3), 48.0 (C, *C*1), 33.3 (CH$_2$), 32.5 (CH$_2$), 30.8 (CH$_2$), 28.0 [3 CH$_3$, O*C*(*C*H$_3$)$_3$], 27.6 [CH, (CH$_3$)$_2$*C*H], 20.9 [2 CH$_3$, C(*C*H$_3$) and (*C*H$_3$)$_2$CH], 20.4 (CH$_2$, *C*4), 18.3 [CH$_3$, (*C*H$_3$)$_2$CH] ppm.

7-Isopropyl-4a-methyl-4,4a,5,6-tetrahydrocyclopenta[*b*]pyran-2-yl Trifluoromethanesulfonate (36): Trifluoromethanesulfonic anhydride (172 mg, 0.61 mmol) was added dropwise with syringe to a mixture of 2,6-di-*tert*-butylpyridine (116 mg, 0.61 mmol) and keto ester **35d** (66 mg, 0.24 mmol) in 1,2-dichloroethane (3 mL). The resultant mixture was stirred for 90 min at 90 °C. After cooling, the mixture was diluted with pentane (15 mL) and filtered through celite. 3 N HCl (1 mL) was added and the mixture was extracted with dichloromethane (3×10 mL). The combined organic phases were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel. (cyclohexane/ethyl acetate, 4:1) to give 63 mg of triflate **36** as a yellow oil (yield 80%). IR (neat): $\tilde{\nu}$ = 2962, 1691, 1428, 1329, 1209, 1127 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 4.77 (dd, *J* = 5.2, 3.3 Hz, 1 H, 3-H), 2.71 [hept, *J* = 6.6 Hz, 1 H, C*H*(CH$_3$)$_2$], 2.38–2.28 (m, 1 H, 6-H), 2.24–2.17 (m, 1 H, 6-H), 2.18–2.16 (m, 2 H, 4-H), 1.92 (ddd, 1 H, *J* = 12.6, 7.8, 1.6 Hz, 5-H), 1.69–1.64 (m, 1 H, 5-H), 1.15 [s, 3 H, C(C*H*$_3$)], 1.02 [d, *J* = 6.6 Hz, 3 H, CH(C*H*$_3$)$_2$], 1.00 [d, *J* = 6.6 Hz, 3 H, CH(C*H*$_3$)$_2$] ppm. ^{13}C NMR (50 MHz, CDCl$_3$): δ = 157.4 (C, *C*7a), 146.6 (C, *C*2), 122.2 (C, *C*7), 118.4 (q, *J* = 314 Hz, C, *C*F$_3$), 87.5 (CH, *C*3), 38.8 (C, *C*4a), 36.6 (CH$_2$, *C*5), 35.1 (CH$_2$, *C*4), 25.4 (CH$_2$, *C*6), 24.9 [CH, *C*H(CH$_3$)$_2$], 23.7 [CH$_3$, C(*C*H$_3$)], 20.6 [CH$_3$, *C*H(CH$_3$)$_2$], 20.5 [CH$_3$, *C*H(CH$_3$)$_2$] ppm. ^{19}F NMR (CDCl$_3$, 188 MHz): δ = –73.6 (s) ppm.

(2*R*,5*R*)- and (2*R*,5*S*)-2-(2-Iodoethyl)-5-isopropyl-2-methylcyclopentanone (39): Treatment of acid **35b** (500 mg, 2.35 mmol) as described for acid **12** gave iodide **39** as a colourless light sensitive oil (0.45 g, 65%). IR (film): $\tilde{\nu}$ = 2555, 2872, 1730 (C=O), 1455, 1372, 1234 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$) the presence of a 2:1 mixture of diastereomers induced the splitting of some signals, only the major isomer is described, δ = 3.28–2.91 (m, 2 H, C*H*$_2$I), 2.20–1.55 (m, 8 H), 0.95 [d, *J* = 6.6 Hz, 3 H, (C*H*$_3$)$_2$CH], 0.91 [s, 3 H, C(C*H*$_3$)], 0.77 [d, *J* = 6.6 Hz, 3 H, (C*H*$_3$)$_2$CH] ppm. ^{13}C NMR (50 MHz, CDCl$_3$) only the major isomer is described, δ = 221.8 (C, *C*O), 55.5 (CH, *C*5), 50.6 (C, *C*2), 42.6 (CH$_2$, *C*H$_2$CH$_2$I), 33.0 (CH$_2$), 27.1 [CH, (CH$_3$)$_2$*C*H], 20.8 [CH$_3$, C(*C*H$_3$)], 20.6 (CH$_2$, *C*4), 18.5 [CH$_3$, (*C*H$_3$)$_2$CH], 18.3 [CH$_3$, (*C*H$_3$)$_2$CH], –0.80 [CH$_2$, CH$_2$*C*H$_2$I] ppm.

(1*R*,3*R*)- and (1*R*,3*S*)-2-(3-Isopropyl-1-methyl-2-oxocyclopentyl)-ethyl Acetate (40a): A mixture of iodide **39** (520 mg, 1.77 mmol) and sodium acetate (420 mg, 5.13 mmol) in DMF (50 mL) was stirred at 110 °C for 3 h. After cooling, the reaction mixture was concentrated in vacuo. The residue placed in water (5 mL) and extracted with diethyl ether (3×10 mL). The organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate, 4:1) to give acetate **40a** as a pale yellow oil (280 mg, yield 70%). IR (neat): $\tilde{\nu}$ = 2959, 2872, 1731, 1460, 1386, 1367, 1231 cm^{-1} ^{1}H NMR (400 MHz, C$_6$D$_6$) the presence of a 2:1 mixture of diastereomers induced the splitting of some signals, only the major isomer is described, δ = 4.13–3.88 (m, 2 H, C*H*$_2$OAc), 2.04 [m, 1 H, C*H*(CH$_3$)$_2$], 1.76–1.10 (m, 7 H, 4-H, 5-H, 3-H, C*H*$_2$CH$_2$OAc), 1.67 (s, 3 H, C*H*$_3$CO$_2$), 0.85 [d, *J* = 6.8 Hz, 3 H, CH(C*H*$_3$)$_2$], 0.71 [s, 3 H, C(C*H*$_3$)], 0.70 [d, *J* = 6.8 Hz, 3 H, CH(C*H*$_3$)$_2$] ppm. ^{13}C NMR (50 MHz, C$_6$D$_6$) only the major isomer is described, δ = 220.7 (C, *C*O), 169.9. (C, O*C*OCH$_3$), 60.9 (CH$_2$, CH$_2$*C*H$_2$OAc), 55.1 (CH, *C*3), 47.1 (C, *C*1), 36.2 (CH$_2$, *C*H$_2$CH$_2$OAc or *C*5), 33.1 (CH$_2$, *C*H$_2$CH$_2$OAc or *C*5) 27.0 [CH, *C*H(CH$_3$)$_2$], 22.6–20.5 [3 CH$_3$, *C*H$_3$CO$_2$, C(*C*H$_3$) and *C*H(CH$_3$)$_2$], 21.5 (CH$_2$, *C*4), 18.2 [CH$_3$, *C*H(CH$_3$)$_2$] ppm. C$_{13}$H$_{22}$O$_3$ (226.3): calcd. C 68.99, H 9.80; found C 68.73, H 9.96.

(2*R*,5*R*)- and (2*R*,5*S*)-2-(2-Hydroxyethyl)-5-isopropyl-2-methylcyclopentanone (40b): A mixture of acetate **40a** (120 mg, 0.53 mmol) and potassium carbonate (73 mg, 0.53 mmol) in methanol (15 mL) was stirred at 20 °C for 5 h. The reaction mixture was concentrated in vacuo and 1 N HCl was added until a pH of 7 was reached. The mixture was extracted with ethyl acetate (3×15 mL). The organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate, 4:1) to give hydroxy ketone **40b** as 3:1 mixture of diastereomers (78 mg, yield 80%). IR (neat): $\tilde{\nu}$ = 3500–3000 (OH), 3414, 1728 (C=O), 1458 cm^{-1}. ^{1}H NMR (400 MHz, C$_6$D$_6$) only the major isomer is described, δ = 3.63–3.42 (m, 2 H, C*H*$_2$OH), 2.20 [m, 1 H, C*H*(CH$_3$)$_2$], 1.93–1.81 (m, 1 H, 5-H), 1.90–1.70 (br. s, 1 H, OH), 1.70–1.50 (m, 4 H, C*H*$_2$CH$_2$OH, 4-H, 3-H), 1.45–1.30 (m, 2 H, 4-H, 3-H), 0.93 [d, *J* = 6.3 Hz, 3 H, CH(C*H*$_3$)$_2$], 0.83 [s, 3 H, C(C*H*$_3$)], 0.80 [d, *J* = 6.0 Hz, 3 H, CH(C*H*$_3$)$_2$] ppm. ^{13}C NMR (100 MHz, C$_6$D$_6$) only the major isomer is described, δ = 222.8 (C, *C*O), 59.1 (CH$_2$, CH$_2$*C*H$_2$OH), 55.2 (CH, *C*5), 47.7 (C, *C*2), 40.4 (CH$_2$, *C*H$_2$CH$_2$OH), 33.8 (CH$_2$, *C*3), 27.4 [CH, *C*H(CH$_3$)$_2$], 21.4 [CH$_3$, C(*C*H$_3$)], 21.0 [CH$_3$, CH(*C*H$_3$)$_2$], 20.8 (CH$_2$, *C*4), 18.5 [CH$_3$, CH(*C*H$_3$)$_2$] ppm. C$_{11}$H$_{20}$O$_2$·¼H$_2$O (188.8): calcd. C 69.99, H 10.95; found C 70.02, H 11.14.

(1*R*,3*R*)- and (1*R*,3*S*)-2-(3-Isopropyl-1-methyl-2-oxocyclopentyl)-ethyl 2,2-Dimethylpropanoate (40c): To a solution of alcohol **40b** (90 mg, 0.48 mmol) in pyridine (2 mL) was added at 0 °C pivaloyl chloride (117 mg, 0.97 mmol). After being stirred at 20 °C for 4 h the reaction mixture was concentrated in vacuo. The residue was taken in water (2 mL) and extracted with diethyl ether (3×15 mL). The organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate, 4:1) to give ester **40c** as a pale-yellow oil (96 mg, yield 73%). IR (neat): $\tilde{\nu}$ = 2960, 2873, 1727 (broad, CO, OCO*t*Bu), 1480, 1461, 1283, 1151 cm^{-1} ^{1}H NMR (CDCl$_3$, 200 MHz) the presence of a 2:1 mixture of diastereomers induced the splitting of some signals, only the major isomer is described, δ = 4.08 (t, *J* = 7.1 Hz, 2 H, C*H*$_2$OPiv), 2.20–1.55 (m, 8 H), 1.17 [s, 9 H, C(C*H*$_3$)$_3$], 1.06 [s, 3 H, C(C*H*$_3$)], 0.97 [d, *J* = 6.7 Hz, 3 H, CH(C*H*$_3$)$_2$], 0.80 [d, *J* = 6.7 Hz, 3 H, CH(C*H*$_3$)$_2$] ppm. ^{13}C NMR (50 MHz, CDCl$_3$) only the major isomer is described, δ = 222.9 (C, *C*O), 178.3 [C, O*C*OC(CH$_3$)$_3$], 61.0 (CH$_2$, CH$_2$*C*H$_2$OPiv), 54.0 (CH, *C*3), 47.3 (C, *C*1), 38.5 [C, OCO*C*(CH$_3$)$_3$], 34.3 (CH$_2$, *C*5 or *C*H$_2$CH$_2$OPiv), 33.6 (CH$_2$, *C*5 or *C*H$_2$CH$_2$OPiv), 27.6 [CH, *C*H(CH$_3$)$_2$], 27.0 [3 CH$_3$, OCOC(*C*H$_3$)$_3$], 22.4 [CH$_3$, C(*C*H$_3$)], 21.0 [CH$_3$, CH(*C*H$_3$)$_2$], 20.7 (CH$_2$, *C*4), 18.6 [CH$_3$, CH(*C*H$_3$)$_2$] ppm. C$_{16}$H$_{28}$O$_3$ (268.4): calcd. C 71.60, H 10.52; found C 71.32, H 10.75.

(1*R*)-2-(3-Isopropyl-1-methyl-2-{[(trifluoromethyl)sulfonyl]oxy}-cyclopent-2-en-1-yl)ethyl 2,2-Dimethylpropanoate (41a): Trifluoromethanesulfonic anhydride (905 mg, 3.2 mmol) was added dropwise with a syringe to a mixture of 2,6-di-*tert*-butylpyridine (612 mg, 3.2 mmol) and keto ester **40c** (190 mg, 0.71 mmol) in 1,2-dichloroethane (4 mL). The resultant mixture was stirred for 15 h at 90 °C. After cooling, the mixture was diluted with pentane (15 mL) and filtered through celite. 2 N HCl (2 mL) was added and the mixture was extracted with dichloromethane (3×10 mL). The combined organic phases were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (cyclohexane/ethyl

acetate, 4:1) to give triflate **41a** as a yellow oil (184 mg, yield 65%). $[\alpha]_D^{20} = -10.9$ ($c = 0.9$, EtOH). IR (film): $\tilde{\nu}$ = 2962, 2872, 1730, 1682 (C=C, weak), 1577, 1480, 1455, 1408, 1461, 1211, 1140 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.08 (m, 2 H, CH_2OPiv), 2.82 [hept, J = 6.8 Hz, 1 H, $CH(CH_3)_2$], 2.30–2.23 (m, 2 H, 4-H), 2.01 (ddd, J = 13.7, 8.2, 5.6 Hz, 1 H, 5-H), 1.78–1.71 (m, 3 H, CH_2CH_2OPiv and 5-H), 1.18 [s, 9 H, $C(CH_3)_3$], 1.17 [s, 3 H, $C(CH_3)$], 1.03 [d, J = 6.8 Hz, 3 H, $CH(CH_3)_2$], 1.01 [d, J = 6.8 Hz, 3 H, $CH(CH_3)_2$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.4 [C, $OCOC(CH_3)_3$], 144.6 (C, *C*2), 138.2 (C, *C*3), 118.6 (q, J = 319 Hz, C, CF_3), 61.2 (CH_2, CH_2CH_2OPiv), 45.2 (C, *C*1), 38.5 [C, $OCOC(CH_3)_3$], 36.8 (CH_2, CH_2CH_2OPiv), 33.7 (CH_2, *C*5), 27.1 [3 CH_3, $OCOC(CH_3)_3$], 25.7 [CH, $CH(CH_3)_2$], 24.5 [CH_3, $C(CH_3)$], 23.8 (CH_2, *C*4), 20.3 [CH_3, $CH(CH_3)_2$], 20.1 [CH_3, $CH(CH_3)_2$] ppm. ^{19}F NMR ($CDCl_3$, 188 MHz) δ = –74.2 (s) ppm.

(5*R*)-5-(2-Hydroxyethyl)-2-isopropyl-5-methylcyclopent-1-en-1-yl Trifluoromethanesulfonate (41b): To a solution of ester **41a** (168 mg, 0.42 mmol) in CH_2Cl_2 (6 mL) was added dropwise at –78 °C a toluene solution of DIBAL-H (1.5 M, 0.6 mL, 0.90 mmol). The reaction was stirred for 4 h at –20 °C and saturated aqueous tartaric acid (sodium potassium salt) was added. The mixture was vigorously stirred for 1 h and filtered through celite. The solid was thoroughly washed with CH_2Cl_2 and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, evaporated and chromatographed on silica gel (cyclohexane/ethyl acetate, 4:1) to give alcohol **41b** (94 mg, 70%) as an oil. $[\alpha]_D^{20} = -12.7$ (c = 1.1, EtOH). IR (film): $\tilde{\nu}$ = 3600–3400 (OH), 2966, 1682 (C=C, weak), 1461, 1405, 1206, 1138 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.70 (t, J = 7.2 Hz, 2 H, CH_2OH), 2.82 [hept, J = 6.7 Hz, 1 H, $CH(CH_3)_2$], 2.27 (t, J = 6.8 Hz, 2 H, 4-H), 2.06–1.92 (m, 1 H, 5-H), 1.80–1.66 (m, 3 H, CH_2CH_2OH and 5-H), 1.20 (br. s, OH), 1.16 [s, 3 H, $C(CH_3)$], 1.03 [d, J = 6.7 Hz, 3 H, $CH(CH_3)_2$], 1.01 [d, J = 6.7 Hz, 3 H, $CH(CH_3)_2$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 144.9 (C, *C*2), 137.8 (C, *C*3), 118.5 (q, J = 318 Hz, C, CF_3SO_2), 59.5 (CH_2, CH_2CH_2OH), 45.0 (C, *C*1), 41.1 (CH_2, CH_2CH_2OH), 33.8 (CH_2, *C*5), 25.6 [CH, $CH(CH_3)_2$], 24.7 [CH_3, $C(CH_3)$], 23.8 (CH_2, *C*4), 20.3 [CH_3, $CH(CH_3)_2$], 20.0 [CH_3, $CH(CH_3)_2$] ppm. ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –74.2 (s) ppm. $C_{12}H_{19}F_3O_4S$ (316.4): calcd. C 45.56, H 6.05; found C 45.84, H 6.22.

(5*R*)-5-(2-Iodoethyl)-2-isopropyl-5-methylcyclopent-1-en-1-yl Trifluoromethanesulfonate (42): A mixture of **41b** (60 mg, 0.19 mmol), triphenylphosphane (94 mg, 0.36 mmol), imidazole (25 mg, 0.36 mmol) and solid iodine (92 mg, 0.36 mmol) in dry CH_2Cl_2 (2 mL) was stirred at 25 °C for 2 h. An aqueous solution of $Na_2S_2O_3$ (2 mL) was then added and the mixture was extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (cyclohexane/ethyl acetate, 10:1) gave **42** as pale yellow oil (56 mg, 70% yield). $[\alpha]_D^{20}$ = –34.6 (c = 1.7, EtOH). IR (film): $\tilde{\nu}$ = 2966, 2873, 1681 (C=C, weak), 1460, 1405, 1241, 1207, 1138 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.14–3.07 (m, 2 H, CH_2CH_2I), 2.85 [hept, J = 6.8 Hz, 1 H, $CH(CH_3)_2$], 2.40–2.20 (m, 2 H, 3-H), 2.15–2.09 (m, 2 H, CH_2CH_2I), 1.95 (ddd, J = 13.4, 8.4, 4.6 Hz, 1 H, 4-H), 1.75 (ddd, J = 13.4, 9.3, 6.5 Hz, 1 H, 4-H), 1.17 [s, 3 H, $C(CH_3)$], 1.05 [d, J = 6.7 Hz, 3 H, $CH(CH_3)_2$], 1.03 [d, J = 6.7 Hz, 3 H, $CH(CH_3)_2$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 143.7 (C, *C*1), 138.8 (C, *C*2), 118.4 (q, J = 318 Hz, C, CF_3SO_2), 48.5 (C, *C*5), 44.0 (CH_2, CH_2CH_2I), 32.9 (CH_2, *C*4), 25.8 [CH, $(CH_3)_2CH$], 24.2 [CH_3, $C(CH_3)$], 24.0 (CH_2, *C*3), 20.4 [CH_3, $(CH_3)_2CH$], 20.1 [CH_3, $(CH_3)_2CH$], –1.3 [CH_2, CH_2CH_2I] ppm. ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –74.1 (s) ppm.

Methyl (1*R*,3*R*)- and (1*R*,3*S*)-1-[2-(3-Isopropyl-1-methyl-2-oxocyclopentyl)ethyl]cyclohexa-2,5-diene-1-carboxylate (43) and 6-Isopropyl-3a-methyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*b*]furan (44): To a solution of diisopropylamine (373 mg, 3.7 mmol) in dry THF (2 mL) was added at 0 °C a solution of *n*-butyllithium (2.5 M in hexane, 1.3 mL, 3.25 mmol). The mixture was stirred at 0 °C for 15 min then cooled to –78 °C. A solution of methyl 2,5-cyclohexadienecarboxylate (**23**) (422 mg, 3.06 mmol) in THF (3 mL) was added. The mixture was stirred 20 min at –78 °C and a solution of iodide **39** (300 mg, 1.02 mmol) in DMPU (3 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 15 min and the temperature was then gradually raised to 50 °C. After 1 h at 50 °C, the dark-red mixture was cooled to 0 °C and 1 N HCl (5 mL) was added. The mixture was extracted with diethyl ether (3 × 20 mL). The collected organic phases were washed with brine, dried with $MgSO_4$ and concentrated in vacuo. Purification by silica gel chromatography (cyclohexane/ethyl acetate, 4:1) gave ether **44** (15 mg, 10%) as a volatile colourless oil. ^1H NMR ($CDCl_3$, 200 MHz): δ = 4.50–4.40 (m, 2 H, =C–OCH_2), 2.74 (dddd, J = 14.2, 10.0, 6.1, 1.0 Hz, 1 H, 5-H), 2.45 [hept, J = 6.8 Hz, 1 H, $CH(CH_3)_2$], 2.29 (ddd, J = 14.2, 8.0, 1.5 Hz, 1 H, 5-H), 1.80–1.60 (m, 4 H, 3-H, 4-H), 1.17 [s, 3 H, $C(CH_3)$], 1.05 [d, J = 6.7 Hz, 3 H, $CH(CH_3)_2$], 1.01 [d, J = 6.7 Hz, 3 H, $CH(CH_3)_2$] ppm. Further elution gave **43** as a pale-yellow oil (186 mg, 60% yield). IR (film): $\tilde{\nu}$ = 2955, 2871, 1725 (CO, CO_2Me), 1637 (C=C, weak), 1453, 1435, 1276, 1242 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) the presence of a 2:1 mixture of diastereomers induced the splitting of some signals, only the major isomer is described, δ = 5.84 (dt, J = 11.0, 3.0 Hz, 2 H, $HC{=}CHCH_2CH{=}CH$), 5.62 (br.d, J = 11.0 Hz, 2 H, $HC{=}CHCH_2CH{=}CH$), 3.62 (s, 3 H, CO_2CH_3), 2.58 (br. s, 2 H, $=CHCH_2CH=$), 2.30–1.15 (m, 10 H), 0.92 [d, J = 6.4 Hz, 3 H, $CH(CH_3)_2$], 0.83 [s, 3 H, $C(CH_3)$], 0.74 [d, J = 6.4 Hz, 3 H, $CH(CH_3)_2$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$) only the major isomer is described, δ = 218.9 (C, *C*O), 175.1 (C, CO_2Me), 126.7 (2 CH, $C{=}CHCH_2CH{=}C$), 125.9 (2 CH, $C{=}CHCH_2CH{=}C$), 55.6 (CH, *C*3), 51.9 (CH_3, OCH_3), 48.2 (C, *C*1), 47.4 (C, CCO_2Me), 33.9 (CH_2), 33.2 (CH_2), 31.8 (CH_2), 27.0 [CH, $CH(CH_3)_2$], 26.0 (CH_2, $C{=}CHCH_2CH{=}C$), 21.1 [CH_3, $C(CH_3)$], 21.0 [CH_3, $CH(CH_3)_2$], 20.4 (CH_2, C4), 18.2 [CH_3, $CH(CH_3)_2$] ppm. MS (ESI, MeOH): *m*/*z* (%): 327 (30) $[M + Na]^+$, 305 (25) $[M + 1]^+$, 245 (100). $C_{19}H_{28}O_3$ (304.4): calcd. C 74.96, H 9.27; found C 74.69, H 9.11.

Methyl (1*R*)-1-[2-(3-Isopropyl-1-methyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclopent-2-en-1-yl)ethyl]cyclohexa-2,5-diene-1-carboxylate (22): Trifluoromethanesulfonic anhydride (160 mg, 0.57 mmol) was added dropwise with a syringe to a mixture of 2,6-di-*tert*-butylpyridine (115 mg, 0.60 mmol) and keto ester **43** (50 mg, 0.16 mmol) in 1,2-dichloroethane (1.5 mL). The resultant mixture was stirred at 90 °C for 6 h. After cooling, the mixture was diluted with pentane (15 mL) and filtered through celite. 1 N HCl (3 mL) was added and the mixture was extracted with dichloromethane (3 × 10 mL). The combined organic phases were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate, 4:1) to give triflate **22** as a yellow oil (51 mg, yield 71%). $[\alpha]_D^{20} = -22.4$ (c = 2.5, MeOH). IR (film): $\tilde{\nu}$ = 3028, 2962, 2860, 1730 (CO_2Me), 1683 (C=C, weak), 1454, 1406, 1208, 1139 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.90 (dt, J = 10.4, 3.3 Hz, 2 H, $HC{=}CHCH_2CH{=}CH$), 5.69 (dt, J = 10.4, 2.0 Hz, 2 H, $HC{=}CHCH_2CH{=}CH$) 3.70 (s, 3 H, OCH_3), 2.85 [hept, J = 6.8 Hz, 1 H, $CH(CH_3)_2$], 2.65 (br. s, 2 H, $=CHCH_2CH=$), 2.28–2.22 (m, 2 H, 4-H), 1.84 (ddd, J = 13.0, 8.2, 5.7 Hz, 1 H, 5-H), 1.59–1.56 [m, 3 H, 5-H, $CH_2CH_2C(CO_2Me)$], 1.34–1.29 [m, 2 H, $CH_2CH_2C(CO_2Me)$], 1.11 [s, 3 H, $C(CH_3)$], 1.03 [d, J = 6.8 Hz, 6

H, $CH(CH_3)_2$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.2 (C, CO_2Me), 145.1 (C, *C*2), 137.5 (C, *C*3), 126.7 (CH, *C*=CHCH$_2$CH=*C*), 126.1 (CH, C=*C*HCH$_2$*C*H=C), 118.5 (q, J = 319 Hz, C, CF_3SO_2), 52.1 (CH_3, OCH_3), 47.4 (C, *C*CO_2Me), 45.8 (C, *C*1), 33.9 (CH_2), 33.1 (CH_2), 32.8 (CH_2), 26.0 (CH_2, C=CH*C*H$_2$CH=C), 25.7 [CH, $(CH_3)_2CH$], 24.3 [CH_3, C(*C*H$_3$)], 23.7 (CH_2), 20.4 [CH_3, $(CH_3)_2$CH], 20.1 [CH_3, $(CH_3)_2$CH] ppm. ^{19}F NMR ($CDCl_3$, 188 MHz) δ = –74.3 (s) ppm. $C_{20}H_{27}F_3O_5S$ (436.5): calcd. C 55.03, H 6.23; found C 55.23, H 6.34.

Methyl (1*R*)-1-[2-(3-Isopropyl-1-methyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclopent-2-en-1-yl)ethyl]-4-oxocyclohexa-2,5-diene-1-carboxylate (45): 3,5-Dimethypyrazole (670 mg, 7.0 mmol) was added to a suspension of anhydrous chromium trioxide (700 mg, 7.0 mmol) in CH_2Cl_2 (6 mL), and the mixture was stirred at 0 °C for 20 min. Triflate **22** (300 mg, 0.7 mmol) in CH_2Cl_2 (6 mL) was added in one portion to the dark-red solution and the reaction mixture was stirred at 20 °C for 4 h. Diethyl ether (10 mL) and celite (500 mg) were added and the mixture was stirred for a further 1 h. The mixture was filtered through a short column packed with florisil and the filtrate was concentrated in vacuo. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate, 4:1) to give **45** as a pale-yellow oil (126 mg, 40% yield). $[\alpha]_D^{20}$ = –34.6 (c = 0.6, EtOH). IR (neat): $\tilde{\nu}$ = 2964, 1736 cm^{-1} (CO_2Me), 1669 (C=O), 1631 (C=C), 1475, 1403, 1207, 1138 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.96 (d, J = 10.3 Hz, 2 H, *H*C=CHCOCH=C*H*), 6.34 (d, J = 10.3 Hz, 2 H, C=C*H*COC*H*=C), 3.72 (s, 3 H, CO_2CH_3), 2.84 [hept, J = 6.7 Hz, 1 H, C*H*$(CH_3)_2$], 2.34–2.20 (m, 2 H, 4-H), 1.94–1.85 [m, 2 H, CH_2C(CO_2Me)], 1.81–1.75 (m, 1 H, 5-H), 1.71–1.66 (m, 1 H, 5-H), 1.30–1.21 [m, 2 H, CH_2CH$_2$C(CO_2Me)], 1.08 [s, 3 H C(CH_3)], 0.99 [d, J = 6.8 Hz, 6 H, CH(CH_3)$_2$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 184.9 (C, C=CH*C*OCH=C), 170.7 (C, *C*O_2CH_3), 147.4 (2 CH, *C*=CHCOCH=*C*), 144.1 (C, *C*2), 138.5 (C, *C*3), 130.4 (2 CH, C=*C*HCO*C*H=C), 118.5 (q, J = 320 Hz, C, *C*F_3SO_2), 53.0 (CH_3, CO_2CH_3), 51.8 [C, *C*(CO_2Me)], 45.9 (C, *C*1), 33.1 [2 CH_2, *C*H$_2$C(CO_2Me) and *C*5], 32.6 [CH_2, *C*H$_2$CH$_2$C(CO_2Me)], 25.7 [CH, $(CH_3)_2CH$], 24.6 [CH_3, (CH_3)C], 23.9 (CH_2, *C*4), 20.4 [CH_3, $(CH_3)_2$CH], 20.1 [CH_3, $(CH_3)_2$CH] ppm. ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –74.2 (s) ppm. $C_{20}H_{25}F_3O_6S$ (450.4): calcd. C 53.33, H 5.59; found C 53.54, H 5.75.

Methyl (3a*R*,5a*R*)-1-Isopropyl-3a-methyl-8-oxo-2,3,3a,4,5,8-hexahydro-5a*H*-cyclopenta[*a*]naphthalene-5a-carboxylate (46a): To a mixture of triflate **45** (163 mg, 0.36 mmol), triphenylphosphane (37 mg, 0.14 mmol), potassium carbonate (100 mg, 0.72 mmol) and *n*-tetrabutylammonium bromide (210 mg, 0.65 mmol) in toluene (10 mL) was added palladium acetate (16 mg, 20 mol-%, 0.07 mmol). The mixture was carefully degassed through two freeze-pump-thaw cycles and stirred at 120 °C (oil bath) for 1 h. After cooling, the reaction mixture was filtered through celite and the solid was thoroughly washed with diethyl ether. The combined organic phases were dried and concentrated under reduced pressure to give a yellow oil which was purified by flash chromatography to yield a 4:1 mixture of esters **46a** and **46b** (80 mg, 74% yield). An analytical sample of **46a** (64 mg, 65% yield) was obtained by careful chromatography on silica gel (cyclohexane/ethyl acetate, 4:1). $[\alpha]_D^{20}$ = +118 (c = 0.6, EtOH). IR (neat): $\tilde{\nu}$ = 1732, 1660, 1452 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.74 (d, J = 10.0 Hz, 1 H, 6-H), 6.34 (dd, J = 10.0, 1.6 Hz, 1 H, 7-H), 6.14 (d, J = 1.6 Hz, 1 H, 9-H), 3.62 (s, 3 H, CO_2CH_3), 2.92 [hept, J = 6.8 Hz, 1 H, C*H*$(CH_3)_2$], 2.55–2.42 (m, 1 H, 5-H$_{eq}$), 2.39–2.34 (m, 2 H, 2-H), 1.84–1.67 (m, 5 H, 5-H$_{ax}$, 3-H, 4-H), 1.04 [d, J = 6.8 Hz, 3 H, CH(CH_3)$_2$], 0.97 [d, J = 6.8 Hz, 3 H, CH(CH_3)$_2$], 0.94 [s, 3 H, C(CH_3)] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 186.4 (C, *C*O), 170.1 (C, *C*O_2CH_3), 155.0 (C, *C*9a), 147.5 (CH, *C*6), 146.4 (C, *C*1), 136.5 (C, *C*9b), 129.8 (CH, *C*7), 126.8 (CH, *C*9), 54.1 (C, *C*5a), 52.9 (CH_3, OCH_3), 49.6 (C, *C*3a), 39.6 (CH_2, C3), 36.1 (CH_2, *C*4), 33.6 (CH_2, *C*5), 28.7 (CH_2, *C*2), 26.7 [CH, $(CH_3)_2CH$], 23.1 [CH_3, C(*C*H$_3$)], 21.5 [CH_3, (CH_3)$_2$CH], 21.2 [CH_3, (CH_3)$_2$CH] ppm. $C_{19}H_{24}O_3$ (300.4): calcd. C 75.97, H 8.05; found C 75.85, H 7.98.

(5*S*)-5-{2-[1-(Hydroxymethyl)cyclohexa-2,5-dien-1-yl]ethyl}-2-isopropyl-5-methylcyclopent-1-en-1-yl Trifluoromethanesulfonate (47): A 1.5 M solution of DIBAL-H in toluene (0.6 mL, 0.90 mmol) was added dropwise at –78 °C to a stirred solution of compound **22** (130 mg, 0.30 mmol) in CH_2Cl_2 (4 mL). The mixture was stirred at –78 °C for 1 h and then treated with saturated aqueous ammonium chloride (1 mL). The mixture was warmed to 0 °C and a saturated aqueous solution of sodium and potassium tartaric acid salt (4 mL) was added. The mixture was vigorously stirred at room temperature for 1 h, diluted with CH_2Cl_2 (10 mL) and filtered. The solid was abundantly washed with CH_2Cl_2. The phases of the filtrate were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried with anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate, 5:1) to give alcohol **47** as a yellow oil (110 mg, 90% yield). $[\alpha]_D^{20}$ = –31.1 (c = 2.3, EtOH). IR (neat): $\tilde{\nu}$ = 3600–3200 (OH), 1683, 1460, 1405, 1207, 1139 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ = 6.01 (dt, J = 10.6, 3.2 Hz, 2 H, HC=C*H*CH$_2$C*H*=CH), 5.34 (dt, J = 10.6, 2.1 Hz, 2 H, *H*C=CHCH$_2$CH=C*H*), 3.34 (s, 2 H, CH_2OH), 2.83 [hept, J = 6.8 Hz, 1 H, C*H*$(CH_3)_2$], 2.66 (br. s, 2 H, =CHCH_2CH=), 2.30–2.10 (m, 2 H, 3-H), 1.82 (ddd, J = 12.8, 8.6, 5.6 Hz, 1 H, 4-Hα), 1.70–1.63 (m, 1 H, 4-Hβ), 1.47 (br. s, 1 H, OH), 1.27–1.00 [m, 4 H, CH_2CH_2(C)CH$_2$OH], 1.10 [s, 3 H, C(CH_3)], 1.03 [d, J = 6.8 Hz, 3 H, CH(CH_3)$_2$], 1.02 [d, J = 6.8 Hz, 3 H, CH(CH_3)$_2$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 145.4 (C, C1), 137.4 (C, C2), 129.5 (2 CH, *C*=CHCH$_2$CH=*C*), 127.9 (2 CH, C=*C*HCH$_2$*C*H=C), 118.5 (q, J = 320 Hz, C, *C*F_3SO_2), 70.6 (CH_2, *C*H$_2$OH), 46.1 [C, *C*(CH_3)], 43.1 (C, *C*CH$_2$OH), 33.3 (CH_2), 33.2 (CH_2), 31.4 (CH_2), 26.6 (CH_2), 25.7 [CH, $(CH_3)_2CH$], 24.6 [CH_3, C(CH_3)], 23.8 (CH_2, *C*3), 20.5 [CH_3, (CH_3)$_2$CH], 20.1 [CH_3, (CH_3)$_2$CH] ppm. ^{19}F NMR ($CDCl_3$, 188 MHz) δ = –74.3 (s) ppm. $C_{19}H_{27}F_3O_4S$ (408.5): calcd. C 56.14, H 6.20; found C 56.17, H 6.31.

(1*S*)-{1-[2-(3-Isopropyl-1-methyl-2-{[(trifluoromethyl)sulfonyl]oxy}cyclopent-2-en-1-yl)ethyl]cyclohexa-2,5-dien-1-yl}methyl 2,2-Dimethylpropanoate (48): To a solution of alcohol **47** (120 mg, 0.29 mmol) in CH_2Cl_2 (3 mL) was sequentially added at 0 °C, triethylamine (52 mg, 0.51 mmol), DMAP (10 mg, 0.09 mmol) and pivaloyl chloride (40 mg, 0.33 mmol). After stirring for 4 h at 20 °C, 1 N HCl (2 mL) was added. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine, dried with anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate, 4:1) to give **48** as a colourless oil (102 mg, 71% yield). $[\alpha]_D^{20}$ = –25.4 (c = 0.6, EtOH). IR (neat): $\tilde{\nu}$ = 2962, 2929, 2872, 1732, 1460, 1407, 1365, 1211, 1140 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.84 (dt, J = 10.8, 3.1 Hz, 2 H, HC=C*H*CH$_2$C*H*=CH), 5.35 (tt, J = 10.8, 1.9 Hz, 2 H, *H*C=CHCH$_2$CH=C*H*), 3.83 (s, 2 H, CH_2OCO*t*Bu), 2.81 [hept, J = 6.8 Hz, 1 H, C*H*$(CH_3)_2$], 2.60 (br. s, 2 H, =CHCH_2CH=), 2.30–2.15 (m, 2 H, 4-H), 1.81 (ddd, J = 12.7, 8.6, 5.3 Hz, 1 H, 5-Hα), 1.68–1.63 (m, 1 H, 5-Hβ), 1.35–1.25 [m, 4 H, CH_2CH_2(C)CH$_2$OPiv], 1.16 [s, 9 H, OCOC(CH_3)$_3$], 1.09 [s, 3 H, C(CH_3)], 1.01 [d, J = 6.7 Hz, 3 H, CH(CH_3)$_2$], 0.99 [d, J = 6.7 Hz, 3 H, CH(CH_3)$_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.1 [C, *C*O_2C(CH_3)$_3$], 145.2 (C, *C*2), 137.4 (C, *C*3), 128.9 (1 CH,

C=CHCH$_2$CH=*C*), 128.8 (1 CH, *C*=CHCH$_2$CH=*C*), 126.4 (1 CH, C=*C*HCH$_2$*C*H=C), 126.2 (1 CH, C=*C*HCH$_2$*C*H=C), 118.5 (q, J = 320 Hz, C, *C*F$_3$SO$_2$), 70.8 (CH$_2$, *C*H$_2$OCO*t*Bu), 46.0 [C, *C*(CH$_3$)], 40.5 [C, *C*CH$_2$OCOC(CH$_3$)$_3$], 38.7 [C, OCO*C*(CH$_3$)$_3$], 33.2 (CH$_2$, *C*5), 33.1 (CH$_2$), 31.4 (CH$_2$), 26.7 (CH$_2$, C=CH*C*H$_2$CH=C), 26.5 [3 CH$_3$, OCOC(*C*H$_3$)$_3$], 25.5 [CH$_3$, C(*C*H$_3$)], 24.6 [CH, (CH$_3$)$_2$*C*H], 23.7 (CH$_2$, *C*4), 20.3 [CH$_3$, (*C*H$_3$)$_2$CH], 19.9 [CH$_3$, (*C*H$_3$)$_2$-CH] ppm. ^{19}F NMR (CDCl$_3$, 188 MHz) δ = –74.2 (s) ppm. C$_{24}$H$_{35}$F$_3$O$_5$S (492.6): calcd. C 58.52, H 7.16; found C 58.74, H 7.35.

(1*S*)-{1-[2-(3-Isopropyl-1-methyl-2-{[(trifluoromethyl)sulfonyl]-oxy}cyclopent-2-en-1-yl)ethyl]-4-oxocyclohexa-2,5-dien-1-yl}methyl 2,2-Dimethylpropaonate (49): 3,5-Dimethypyrazole (220 mg, 2.3 mmol) was added to a suspension of anhydrous chromium trioxide (230 mg, 2.3 mmol) in CH_2Cl_2 (3 mL) and the mixture was stirred at room temperature for 20 min. To the dark-red solution, triflate **48** (113 mg, 0.23 mmol) in CH_2Cl_2 (2 mL) was added in one portion and the reaction mixture was stirred at 20 °C for 4 h. Diethyl ether (5 mL) and celite (200 mg) were added and the mixture was stirred for one more hour. The mixture was filtered through a short column packed with florisil and the filtrate was concentrated in vacuo. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate, 4:1) to give **49** a pale-yellow oil (70 mg, 60% yield). $[\alpha]_D^{20}$ = –29.2 (c = 1.0, EtOH). IR (neat): $\tilde{\nu}$ = 2962, 2860, 1732, 1667 (C=O), 1635 (C=C), 1475, 1460, 1407 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$): δ = 6.71 (ddd, J = 10.2, 7.0, 3.2 Hz, 2 H, *H*C=CHCOCH=C*H*), 6.38 (d, J = 10.2 Hz, 2 H, HC=C*H*COC*H*=CH), 4.12 (s, 2 H, C*H*$_2$OCO*t*Bu), 2.82 [hept, J = 6.8 Hz, 1 H, C*H*(CH$_3$)$_2$], 2.36–2.12 (m, 2 H, 4-H), 1.83–1.56 (m, 4 H), 1.30–1.17 (m, 2 H), 1.12 [s, 9 H, OCOC(C*H*$_3$)$_3$], 1.08 [s, 3 H, C(C*H*$_3$)], 1.09 [d, J = 6.8 Hz, 6 H, CH(C*H*$_3$)$_2$] ppm. ^{13}C NMR (50 MHz, CDCl$_3$): δ = 185.8 (C, *C*O), 177.7 (C, O*C*O*t*Bu), 150.7 (CH, *C*=CHCOCH=*C*), 150.5 (CH, *C*=CHCOCH=*C*), 144.1 (C, *C*2), 138.4 (C, *C*3), 131.5 (CH, C=*C*HCO*C*H=C), 131.4 (CH, C=*C*HCO*C*H=C), 118.5 (q, J = 320 Hz, C, *C*F$_3$SO$_2$), 67.5 (CH$_2$, *C*H$_2$OCO*t*Bu), 46.0 [C, *C*1 or *C*CH$_2$OCOC(CH$_3$)$_3$], 45.9 [C, *C*1 or *C*CH$_2$OCOC(CH$_3$)$_3$], 38.7 [C, CO$_2$*C*(CH$_3$)$_3$], 33.2 (CH$_2$), 32.6 (CH$_2$), 29.8 (CH$_2$), 26.9 [3 CH$_3$, OCOC(*C*H$_3$)$_3$], 25.6 [CH$_3$, C(*C*H$_3$)], 24.9 [CH, (CH$_3$)$_2$*C*H], 23.9 (CH$_2$, C4), 20.4 [CH$_3$, (*C*H$_3$)$_2$CH], 20.1 [CH$_3$, (*C*H$_3$)$_2$CH] ppm. ^{19}F NMR (CDCl$_3$, 188 MHz) δ = –74.2 (s) ppm.

(3a*R*,5a*R*)-[1-Isopropyl-3a-methyl-8-oxo-2,3,3a,4,5,8-hexahydro-5a*H*-cyclopenta[*a*]naphthalen-5a-yl]methyl 2,2-Dimethylpropanoate (50a): A mixture of triflate **49** (300 mg, 0.59 mmol), triphenylphosphane (62 mg, 0.23 mmol), potassium carbonate (205 mg, 1.48 mmol) and *n*-tetrabutylammonium bromide (380 mg, 1.18 mmol) in toluene (10 mL) was added palladium acetate (26 mg, 20 mol-%, 0.11 mmol). The mixture was carefully degassed through two freeze-pump-thaw cycles and stirred at 120 °C (oil bath) for 2 h. After cooling, the reaction mixture was filtered through celite and the solid was thoroughly washed with diethyl ether. The combined organic phases were dried and concentrated under reduced pressure. Chromatography on silica gel (cyclohexane/ethyl acetate, 5:1) afforded ester **50a** (153 mg, 73% yield). $[\alpha]_D^{20}$ = +82.5 (c = 1.9, EtOH). IR (neat): $\tilde{\nu}$ = 2956, 2630, 2870, 1734 (OCO*t*Bu), 1684 (weak, CO), 1658, 1624, 1450 1405, 1239, 1209 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 6.79 (d, J = 10.1 Hz, 1 H, 6-H), 6.34 (dd, J = 10.1, 1.3 Hz, 1 H,7-H), 6.18 (d, J = 1.3 Hz, 1 H, 9-H), 4.27 (d, J = 10.5 Hz, 1 H, C*H*$_2$OCO*t*Bu), 4.05 (d, J = 10.5 Hz, 1 H, C*H*$_2$OCO*t*Bu), 2.85 [hept, J = 6.8 Hz, 1 H, C*H*-(CH$_3$)$_2$], 2.50–2.40 (m, 2 H, 2-H), 1.94 (dt, J = 12.8, 2.7 Hz, 1 H, 5-H$_{eq}$), 1.88 (ddd, J = 11.7, 6.8, 2.7 Hz, 1 H, 3-Hβ), 1.80 (m, 1 H, 5-H$_{ax}$), 1.76–1.67 (m, 3 H, 3-Hα, 4-H), 1.11 [s, 9 H, OCOC-(C*H*$_3$)$_3$], 1.05 [d, J = 6.8 Hz, 3 H, CH(C*H*$_3$)$_2$], 0.96 [d, J = 6.8 Hz, 3 H, CH(C*H*$_3$)$_2$], 0.96 [s, 3 H, C(C*H*$_3$)] ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 186.9 (C, *C*O), 177.9 [C, O*C*OC(CH$_3$)$_3$], 157.5 (C, *C*9a), 152.2 (CH, *C*6), 147.2 (C, *C*1), 136.5 (C, *C*9b), 129.7 (CH, *C*7), 127.6 (CH, *C*9), 66.2 (CH$_2$, *C*H$_2$OCO*t*Bu), 49.9 (C, *C*3a), 45.3 (C, *C*5a), 39.6 (CH$_2$, *C*3), 38.7 [C, OCO*C*(CH$_3$)$_3$], 36.1 (CH$_2$, *C*4), 31.8 (CH$_2$, *C*5), 29.0 (CH$_2$, *C*2), 27.1 [CH, (CH$_3$)$_2$*C*H], 26.9 [3 CH$_3$, OCOC(*C*H$_3$)$_3$], 23.5 [CH$_3$, C(C*H*$_3$)], 21.5 [CH$_3$, (*C*H$_3$)$_2$CH], 21.4 [CH$_3$, (*C*H$_3$)$_2$CH] ppm. MS (ESI, MeOH): m/z (%): 379 (100) [M + Na]$^+$. C$_{23}$H$_{32}$O$_3$·½H$_2$O (365.5): calcd. C 75.58, H 9.10; found C 75.25, H 9.37.

(1a*R*,1b*R*,3a*R*,8a*R*)-[6-Isopropyl-3a-methyl-8-oxo-1a,2,3,3a,4,5,8,8a-octahydro-1b*H*-cyclopenta[5,6]naphtho[1,2-*b*]oxiren-1b-yl]-methyl 2,2-Dimethylpropanoate (51): To a mixture of trienone **50a** (94 mg, 0.26 mmol) in methanol (0.4 mL) was added a solution of 50% hydrogen peroxide (0.15 mL, 0.78 mmol) in 5% aqueous sodium hydroxide (0.22 mL, 0.13 mmol). The reaction mixture was stirred for 24 h at 25 °C. Brine (2 mL) was added and the mixture was extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with saturated aqueous sodium bisulfite, brine, dried with MgSO$_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (cyclohexane/ethyl acetate, 1:4) gave epoxide **51** as colourless crystals (50 mg, 50% yield), m.p. 159 °C (*i*PrOH). $[\alpha]_D^{20}$ = +47 (c = 5.1, EtOH). IR (film): $\tilde{\nu}$ = 2958, 2927, 2856, 1727 (OCO*t*Bu), 1668, 1461, 1410, 1280, 1261, 1215, 1140 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.86 (s, 1 H, 7-H), 4.22 (d, J = 11.2 Hz, 1 H, C*H*$_2$OCO*t*Bu), 4.06 (d, J = 11.2 Hz, 1 H, C*H*$_2$OCO*t*Bu), 3.50–3.45 (m, 2 H, 1a-H and 8a-H), 2.76 [hept, J = 6.8 Hz, 1 H, C*H*(CH$_3$)$_2$], 2.45–2.40 (m, 2 H, 5-H), 2.29 (td, J = 13.8, 4.8 Hz, 1 H, 2-Hβ), 1.91 (dt, J = 13.8, 2.7 Hz, 1 H, 2-Hα), 1.86–1.60 (m, 4 H, 3-H, 4-H), 1.13 [s, 9 H, OCOC(C*H*$_3$)$_3$], 1.03 [d, J = 6.8 Hz, 3 H, CH(C*H*$_3$)$_2$], 1.02 [s, 3 H, C(C*H*$_3$)], 0.92 [d, J = 6.8 Hz, 3 H, CH(C*H*$_3$)$_2$] ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 187.5 (C, *C*O), 180.8 [C, O*C*OC(CH$_3$)$_3$], 159.6 (C, *C*6 or *C*6b), 159.2 (C, C6 or C6b), 145.8 (C, *C*6a), 123.9 (CH, *C*7), 66.8 (CH$_2$, *C*H$_2$OCO), 60.7 (CH, *C*1a), 55.3 (CH, *C*8a), 48.6 (CH, *C*3a), 46.2 (C, *C*1b), 39.0 (CH$_2$, *C*4), 38.9 [C, OCO*C*(CH$_3$)$_3$], 36.1 (CH$_2$, *C*3), 29.7 (CH$_2$, *C*2), 29.2 (CH$_2$, *C*5), 27.0 [3 CH$_3$, OCOC(*C*H$_3$)], 26.7 [CH, (CH$_3$)$_2$*C*H], 23.5 [CH$_3$, C(C*H*$_3$)], 21.5 [2 CH$_3$, (*C*H$_3$)$_2$-CH] ppm. MS (ESI, MeOH), m/z (%): 395 (6) [M + Na]$^+$, 379 (100), 357 (17).

Crystallographic Data: Crystal size 0.23 × 0.25 × 0.29 mm, orthorhombic, space group $P2_12_12_1$ (no. 19), Z = 4, a = 10.511(5), b = 12.617(5), c = 15.818(5) Å, α = β = γ = 90°, V = 2097.9(15) Å^3, d = 1.179 g cm^{-3}, F(000) = 808, λ = 0.710693 Å (Mo-K_α), μ = 0.079 mm^{-1}; 5788 reflections measured ($0 \le h \le 14$, $0 \le k \le 17$, $0 \le l \le 22$) on a Nonius CAD4 diffractometer. The structure was solved with SIR92 and refined with CRYSTALS. Hydrogen atoms riding refinement converged to $R(gt)$ = 0.0493 for the 1716 reflections having $I \ge 2\sigma(I)$, and $wR(gt)$ = 0.1041, goodness-of-fit S = 0.9117, residual electron density –0.25 and 0.29 e Å^{-3}, CCDC-267231.[35]

(3a*R*, 5a*R*)-[1-Isopropyl-3a-methyl-8-oxo-2,3,3a,4,6,7,8-octahydro-5a*H*-cyclopenta[*a*]naphthalene-5a-yl]methyl 2,2-Dimethylpropanoate (52): A solution of trienone **50a** (206 mg, 0.58 mmol) in EtOH (10 mL) was hydrogenated over chlorotris(triphenylphosphane)rhodium(I) (100 mg, 0.11 mmol) at atmospheric pressure for 60 h at 25 °C. The mixture was filtered through celite and the filtrate was concentrated in vacuo. Chromatography of the crude residue (cyclohexane/ethyl acetate, 4:1) gave dienone **52** (155 mg, 75%) as a yellow oil. $[\alpha]_D^{20}$ = +448 (c = 0.7, EtOH). IR (film): $\tilde{\nu}$ = 2961, 2931, 1729 (OCO*t*Bu), 1707 (C=O), 1673 (C=C), 1459, 1281, 1146,

1034 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.89 (s, 1 H, 9-H), 4.17 (d, J = 11.5 Hz, 1 H, $CH_2OCOtBu$), 4.01 (d, J = 11.5 Hz, 1 H, $CH_2OCOtBu$), 2.81 [hept, J = 6.8 Hz, 1 H, $CH(CH_3)_2$], 2.64 (ddd, J = 11.8, 5.6, 2.1 Hz, 1 H, 7-Hβ), 2.45–2.30 (m, 3 H, 2-H, 7-Hα), 2.10 (ddd, J = 11.8, 5.4, 2.1 Hz, 1 H, 6-Hβ), 1.85–1.78 (m, 3 H, 6-Hα, 5-H, 3-H), 1.75–1.60 (m, 4 H, 4-H, 5-H, 3-H), 1.21 [s, 9 H, $OCOC(CH_3)_3$], 1.03 [d, J = 6.8 Hz, 3 H, $CH(CH_3)_2$], 1.01 [s, 3 H, $C(CH_3)$], 0.96 [d, J = 6.8 Hz, 3 H, $CH(CH_3)_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.1 (C, *C*O), 178.0 [C, $OCOC(CH_3)_3$], 157.9 (C, C9a), 149.2 (C, *C*1), 136.8 (C, *C*9b), 127.2 (CH, *C*9), 64.0 (CH_2, $CH_2OCOtBu$), 49.5 (C, *C*3a), 40.3 (C, *C*5a), 39.2 (CH_2, *C*3), 38.8 [C, $OCOC(CH_3)_3$], 36.1 (CH_2, *C*4), 34.0 (CH_2, *C*7), 33.4 (CH_2, *C*6), 32.6 (CH_2, *C*5), 29.2 (CH_2, *C*2), 27.2 [3 CH_3, $OCOC(CH_3)_3$], 26.9 [CH, $(CH_3)_2CH$], 23.8 [CH_3, $C(CH_3)$], 21.3 [CH_3, $(CH_3)_2CH$], 21.2 [CH_3, $(CH_3)_2CH$] ppm. MS (EI = 70 eV), *m*/*z* (%): 358 (49) [$M^{+\cdot}$], 343 (17), 271 (14), 259 (43), 257 (100). $C_{23}H_{34}O_3$ (358.5): calcd. C 77.05, H 9.56; found C 76.71, H 9.79.

(3a*R*,5a*R*)-[1-Isopropyl-3a-methyl-8-oxo-3,3a,4,5,6,7,8,9-octahydrocyclohepta[*e*]inden-5a(2*H*)-yl]methyl 2,2-Dimethylpropanoate (5): A solution of Me_3Al (2 M in heptane, 0.5 mL, 1 mmol) was added to dry CH_2Cl_2 (6 mL). The mixture was cooled to –78 °C and a solution of dienone **52** (80 mg, 0.22 mmol) in dry CH_2Cl_2 (2 mL) was added followed by a solution of $TMSCHN_2$ (2 M in hexane, 0.5 mL, 1 mmol). The reaction mixture was warmed to room temperature for 4 h. After diluting with CH_2Cl_2 (20 mL), an ice-cooled aqueous solution of $NaHCO_3$ (3 mL) was slowly added at 0 °C and stirring was continued for 5 min. The organic layer was separated and the aqueous phase extracted with diethyl ether (2 × 10 mL). The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. The residue was dissolved in acetone (3 mL) and 3 N HCl (1.5 mL) was added. The mixture was stirred for 2 h at room temperature. Solid K_2CO_3 (330 mg, 2.4 mmol) was then added and the mixture was concentrated under reduce pressure. The residue was extracted with diethyl ether (2 × 10 mL). The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. Purification by silica gel chromatography (cyclohexane/ethyl acetate, 10:1) gave ketone **5** as colourless oil (50 mg, 60% yield) and **54** (8 mg, 10% yield). Only the major isomer **5** is described. $[\alpha]_D^{20}$ = +225 (*c* = 0.8, EtOH). IR (film): $\tilde{\nu}$ = 2957, 2934, 2865, 1727 (C=O, OC-O*t*Bu), 1667 (C=C), 1479, 1458, 1397, 1281, 1150 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 5.30 (t, J = 6.5 Hz, 1 H, 10-H), 3.97 (d, J = 11.2 Hz, 1 H, $CH_2OCOtBu$), 3.93 (d, J = 11.2 Hz, 1 H, CH_2OC-O*t*Bu), 3.48 (dd, J = 14.4, 6.2 Hz, 1 H, 9-H), 3.18 (dd, J = 14.4, 6.7 Hz, 1 H, 9-H), 2.73 [hept, J = 6.8 Hz, 1 H, $CH(CH_3)_2$], 2.69 (ddd, J = 18.8, 9.8, 2.7 Hz, 1 H, 7-H), 2.52 (ddd, J = 18.8, 8.9, 2.3 Hz, 1 H, 7-H), 2.35–2.25 (m, 3 H, 2-H, 6-H), 1.95–1.85 (m, 1 H, 4-Hax), 1.80–1.50 (m, 5 H, 6-H, 3-H, 5-H), 1.38 (dt, J = 13.8, 3.3 Hz, 1 H, 4-Heq), 1.19 [s, 9 H, $OCOC(CH_3)_3$], 0.94 [d, J = 6.8 Hz, 3 H, $CH(CH_3)_2$], 0.92 [s, 3 H, $C(CH_3)$], 0.90 [d, J = 6.8 Hz, 3 H, $CH(CH_3)_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 209.2 (C, *C*O), 178.2 [C, $OCOC(CH_3)_3$], 142.3 (C, *C*10b), 139.9 (C, *C*1 or *C*10a), 139.7 (C, *C*1 or *C*10a), 117.8 (CH, *C*10), 66.8 (CH_2, CH_2O-CO*t*Bu), 48.7 (C, *C*3a), 44.8 (C, *C*5a), 41.6 (CH_2, *C*9), 38.9 [C, $OCOC(CH_3)_3$], 38.7 (CH_2, *C*3), 37.9 (CH_2, *C*7), 36.4 (CH_2, *C*5), 31.7 (CH_2, *C*4), 30.6 (CH_2, *C*6), 28.4 (CH_2, *C*2), 27.2 [3 CH_3, OC-$OC(CH_3)_3$], 26.4 [CH, $(CH_3)_2CH$], 23.4 [CH_3, $C(CH_3)$], 21.6 [CH_3, $(CH_3)_2CH$], 21.3 [CH_3, $(CH_3)_2CH$] ppm. $C_{24}H_{36}O_3$ (372.5): calcd. C 77.38, H 9.74; found C 77.15, H 9.84.

Acknowledgments

We gratefully acknowledge Dr. Jacqueline Mahuteau and Dr. Michèle Ourevitch for the NMR experiments, Mrs Michèle Danet for the MS spectra and Mrs. S. Mairesse-Lebrun for the elemental analyses.

[1] a) A. D. Allbutt, W. A. Ayer, H. J. Brodie, B. N. Johri, H. Taube, *Can. J. Microbiol.* **1971**, 1401–1407; b) W. A. Ayer, H. Taube, *Tetrahedron Lett.* **1972**, 1917–1920; c) W. A. Ayer, H. Taube, *Can. J. Chem.* **1973**, *51*, 3842 –3854; d) W. A. Ayer, L. L. Carstens, *Can. J. Chem.* **1973**, *51*, 3157–3160; e) W. A. Ayer, L. M. Browne, J. R. Mercer, D. R. Taylor, D. E. Ward, *Can. J. Chem.* **1978**, *56*, 717–721; f) W. A. Ayer, T. Yoshida, D. M. J. van Schie, *Can. J. Chem.* **1978**, *56*, 2113–2120; g) W. A. Ayer, T. T. Nakashima, D. E. Ward, *Can. J. Chem.* **1978**, *56*, 2197–2199; h) H.-J. Hecht, G. Höfle, W. Steglich, T. Anke, F. Oberwinkler, *J. Chem. Soc., Chem. Commun.* **1978**, 665–666; i) D. Green, I. Goldberg, Z. Stein, M. Ilan, Y. Kashman, *Nat. Prod. Lett.* **1992**, *4*, 193–199.

[2] a) H. Kawagishi, A. Shimada, R. Shirai, K. Okamoto, F. Ojima, H. Sakamoto, Y. Ishiguro, S. Furakawa, *Tetrahedron Lett.* **1994**, *35*, 1569–1572; b) H. Kawagishi, A. Shimada, K. Shizuki, H. Mori, K. Okamoto, H. Sakamoto, S. Furukawa, *Heterocycl. Commun.* **1996**, *2*, 51–54; c) H. Kawagishi, A. Shimada, S. Hosakawa, H. Mori, H. Sakamoto, Y. Ishiguro, S. Sakemi, J. Bordner, N. Kojima, S. Furukawa, *Tetrahedron Lett.* **1996**, *37*, 7399–7402.

[3] a) T. Ohta, T. Kita, N. Kobayashi, Y. Obara, N. Nakahata, Y. Ohizumi, Y. Takaya, Y. Oshima, *Tetrahedron Lett.* **1998**, *39*, 6229–6232; b) T. Kita, Y. Takaya, Y. Oshima, T. Ohta, K. Aizawa, T. Hirano, T. Inakuma, *Tetrahedron* **1998**, *54*, 11877–11886; c) Y. Obara, N. Nakahata, T. Kita, Y. Takaya, H. Kobayashi, S. Hosoi, F. Kiuchi, T. Ohta, Y. Oshima, Y. Ohizumi, *Eur. J. Pharmacol.* **1999**, *370*, 79–84.

[4] H. Shibata, T. Tokunaga, D. Karasawa, A. Hirota, M. Nakayama, H. Nozaki, T. Tada, *Agric. Biol. Chem.* **1989**, *53*, 3373–3375.

[5] Y. Obara, H. Kobayashi, T. Ohta, Y. Ohizumi, N. Nakahata, *Mol. Pharmacol.* **2001**, *59*, 1287–1297.

[6] a) S. Carswell, *Exp. Neurol.* **1993**, *124*, 36–42; b) S. S. Riaz, D. R. Tomlinson, *Prog. Neurobiol.* **1996**, *49*, 125–143; c) J. M. Conner, M. H. Tuszynski, *Ment. Retard Dev. Dis.* **1998**, *4*, 212–222; d) D. Kirik, B. Georgievska, A. Bjorklund, *Nat. Neurosci.* **2004**, *7*, 105–110.

[7] S. J. Pollack, S. J. Harper, *Curr. Drug Targets CNS & Neurol. Disord.* **2002**, *1*, 59–80.

[8] a) B. B. Snider, N. H. Vo, S. V. O'Neil, B. M. Foxman, *J. Am. Chem. Soc.* **1996**, *118*, 7644–7645; b) B. B. Snider, N. H. Vo, S. V. O'Neil, *J. Org. Chem.* **1998**, *63*, 4732–4740.

[9] M. Tori, N. Toyoda, M. Sono, *J. Org. Chem.* **1998**, *63*, 306–313.

[10] E. Piers, M. Gilbert, K. L. Cook, *Org. Lett.* **2000**, *2*, 1407–1410.

[11] a) W. A. Ayer, D. E. Ward, L. M. Browne, L. T. J. Delbaere, Y. Hoyano, *Can. J. Chem.* **1981**, *59*, 2665–2672; b) D. E. Ward, *Can. J. Chem.* **1987**, *65*, 2380–2384; c) D. E. Ward, Y. Gai, Q. Qiao, *Org. Lett.* **2000**, *2*, 2125–2127; d) D. E. Ward, Y. Gai, Q. Qiao, J. Shen, *Can. J. Chem.* **2004**, *82*, 254–267.

[12] M. Takano, A. Umino, M. Nakada, *Org. Lett.* **2004**, *6*, 4897–4900.

[13] B. M. Trost, L. Dong, G. M. Schroeder, *J. Am. Chem. Soc.* **2005**, *127*, 2844–2845.

[14] S. P. Waters, Y. Tian, Y.-M. Li, S. J. Danishefsky, *J. Am. Chem. Soc.* **2005**, *127*, 13514–13515.

[15] For a review see: a) D. L. Wright, C. R. Whitehead, *Org. Prep. Proced. Int.* **2000**, *32*, 307–330. For more recent approaches see; b) K. Takeda, D. Nakane, M. Takeda, *Org. Lett.* **2000**, *2*, 1903–1905; c) P. A. Wender, F. C. Bi, M. A. Brodney, F. Gosselin, *Org. Lett.* **2001**, *3*, 2105–2108.

[16] a) C. Thominiaux, A. Chiaroni, D. Desmaële, *Tetrahedron Lett.* **2002**, *43*, 4107–4110; b) E. Drège, G. Morgant, D. Desmaële, *Tetrahedron Lett.* **2005**, *46*, 7263–7266.

[17] a) M. Pfau, G. Révial, J. d'Angelo, A. Guingant, *J. Am. Chem. Soc.* **1985**, *107*, 273–274. For a review, see; b) J. d'Angelo, D. Desmaële, F. Dumas, A. Guingant, *Tetrahedron: Asymmetry* **1992**, *3*, 459–505; c) J. d'Angelo, C. Cavé, D. Desmaële, F. Dumas, *Trends in Organic Synthesis* (Ed.: S. G. Pandalai), Trivandrum, India, **1993**, vol. 4, pp. 555–616.
[18] J. T. Link, *Org. React.* **2002**, *60*, 157–534.
[19] For some examples, see: a) A. Brown, R. Grigg, T. Ravishankar, M. Thornton-Pett, *Tetrahedron Lett.* **1994**, *35*, 2753–2756; b) S. Honzawa, T. Mizutani, M. Shibazaki, *Tetrahedron Lett.* **1999**, *40*, 311–314.
[20] D. H. R. Barton, H. P. Faro, E. P. Serebryakov, N. F. Woosley, *J. Chem. Soc.* **1965**, 2438–2443.
[21] a) W. von E. Doering, L. H. Knox, *J. Am. Chem. Soc.* **1954**, *76*, 3203–3207; b) E. Vedejs, R. A. Gabel, P. D. Weeks, *J. Am. Chem. Soc.* **1972**, *94*, 5842–5845.
[22] S. Lewicka-Piekut, W. H. Okamura, *Synth. Commun.* **1980**, *10*, 415–420.
[23] a) R. Schwesinger, *Chimia* **1985**, *39*, 269–272; b) R. Schwesinger, H. Schlemper, *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1167–1169; c) T. Pietkonza, D. Seebach, *Chem. Ber.* **1991**, *124*, 1837–1843; d) R. Schwesinger, J. Willaredt, H. Schlemper, M. Keller, D. Schmitt, H. Fritz, *Chem. Ber.* **1994**, *127*, 2435–2454.
[24] P. W. Rabideau, D. M. Wetzel, D. M. Young, *J. Org. Chem.* **1984**, *49*, 1544–1549.
[25] a) P. J. Stang, W. Treptow, *Synthesis* **1980**, 283–284; b) P. J. Stang, M. Hanack, L. R. Subramanian, *Synthesis* **1982**, 85–126.
[26] M. M. Abelman, T. Oh, L. E. Overman, *J. Org. Chem.* **1987**, *52*, 4130–4133.
[27] R. Grigg, V. Loganathan, V. Santhakumar, V. Sridharan, A. Teasdale, *Tetrahedron Lett.* **1991**, *32*, 687–690.
[28] a) K. Kagechika, M. Shibasaki, *J. Org. Chem.* **1991**, *56*, 4093–4094; b) X. Han, R. C. Larock, *Synlett* **1998**, 748–750.
[29] Crystallographic results for compound **31** have been deposited (CIF file) in the Cambridge Crystallographic Data Centre, U. K., and allocated the deposition number CCDC-179328.
[30] D. L. Commins, A. Dehghani, *Tetrahedron Lett.* **1992**, *33*, 6299–6302.
[31] A. L. Gemal, J.-L. Luche, *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.
[32] E. J. Corey, S. G. Pyne, W.-G. Su, *Tetrahedron Lett.* **1983**, *24*, 4883–4886.
[33] K. Kondo, M. Sodeoka, M. Mori, M. Shibasaki, *Synthesis* **1993**, 920–930.
[34] E. J. Corey, G. W. J. Fleet, *Tetrahedron Lett.* **1973**, *14*, 4499–4501.
[35] CCDC-267231 (for **51**) and CCDC-179328 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[36] J. F. Young, J. A. Osborn, F. H. Jardine, G. Wilkinson, *J. Chem. Soc., Chem. Commun.* **1965**, 131–132.
[37] a) Y. Ito, S. Fujii, T. Saegusa, *J. Org. Chem.* **1976**, *41*, 2073–2074; b) T. Hirao, T. Masunaga, K.-i. Hayashi, Y. Ohshiro, T. Agawa, *Tetrahedron Lett.* **1983**, *24*, 399–400.
[38] E. C. Taylor, C.-S. Chiang, A. McKillop, *Tetrahedron Lett.* **1977**, *18*, 1827–1830.
[39] a) F. N. Tebbe, G. W. Parshall, G. S. Reddy, *J. Am. Chem. Soc.* **1978**, *100*, 3611–3613; b) S. H. Pine, G. S. Shen, H. Hoang, *Synthesis* **1991**, 165–167.
[40] J. Conia, *Bull. Soc. Chim. Fr.* **1955**, 301–302.
[41] a) K. Maruoka, A. B. Concepcion, H. Yamamoto, *J. Org. Chem.* **1994**, *59*, 4725–4726; b) K. Maruoka, A. B. Concepcion, H. Yamamoto, *Synthesis* **1994**, 1283–1290; c) S. Yang, B. Hungerhoff, P. Metz, *Tetrahedron Lett.* **1998**, *39*, 2097–2098.
[42] T. L. Smalley Jr, *Synth. Commun.* **2004**, *341*, 1973–1980.

Received: May 16, 2006
Published Online: September 5, 2006

