Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 5620

www.rsc.org/obc

PAPER

Synthesis of CDE molecular fragments related to sendanin mediated by titanocene(III)†

A. Fernández-Mateos,*[a] A. I. Ramos Silvo,[a] R. Rubio González[a] and M. S. J. Simmonds[b]

Received 12th March 2012, Accepted 30th May 2012
DOI: 10.1039/c2ob25538c

A practical, brief, and diastereoselective synthesis of limonoid CDE fragments from a readily available starting material is described. The key step was the titanocene(III)-promoted cyclization of unsaturated epoxylactones, readily prepared from α-cyclocitral. In this way, we confirm the viability of our procedure for the synthesis of a limonoid model with different functionalization patterns. We also report the antifeedant activity of epoxylactones **18** and **19**, which show significant antifeedant activity against *Spodoptera littoralis* and *Spodoptera frugiperda*, two insect species with different feeding ecologies.

Introduction

Limonoids are degraded triterpenoids occurring in the Meliaceae plant family, used in popular medicine with a wide range of biological properties.[1] The 12-oxygenated derivatives of limonoids, such as sendanin and toosendanin (Fig. 1), are promising compounds of interest because of their multiple bioactivities: anticancer, antibotulinum, antiparasitic, antihelmintic, and antifeedant.[2] Moreover, the 12-oxygenated limonoid derivatives are potential precursors of the C-seco limonoids: salannin and azadirachtin, considered the most active of the limonoid family (Scheme 1).[2]

Despite their significant bioactivity, little synthetic effort has been invested in these natural products.[3] Studies directed towards the synthesis of related model compounds have been conducted to find simple analogues that display similar biological activities.[4] Most limonoids contain a structural unit of hydrindane bonded to a heterocycle, constituting the C, D and E rings. Work aimed at the hydrindane angular methyl group is limited, with few ways of accessing a functionalized C ring.

In previous papers, we described the synthesis of model insect antifeedants related to toosendanin and trichilins, with oxygenated functions at C-11/C-12 position, with the aim of finding simple analogues with similar biological activity to that of the archetype.[5] We have developed several procedures aimed at the synthesis of molecular fragments and analogues, based on the construction of the pentagonal D ring of limonoids by cationic electrocyclization,[5a–l] dipolar cycloaddition,[4j–l] and radical cascade reactions.[5m]

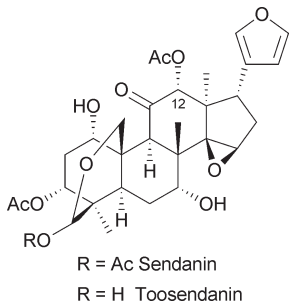


Fig. 1 Bioactive limonoids.

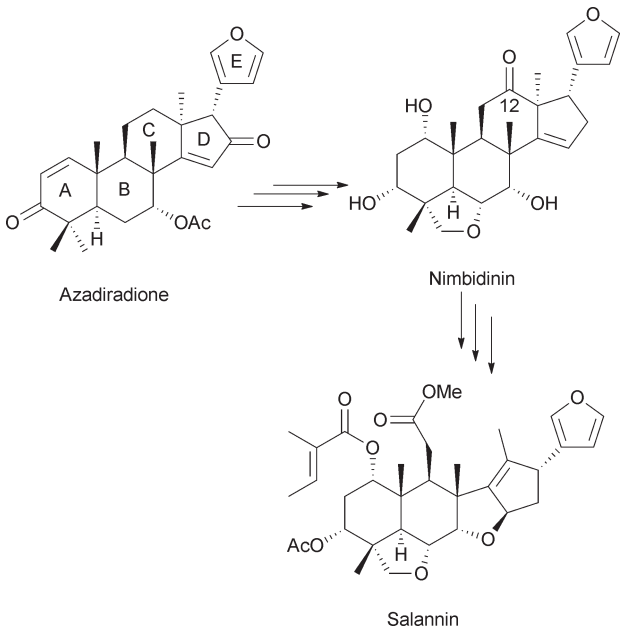
Results and discussion

In connection with these synthetic studies directed towards the CDE structural fragments of limonoids with functionalization patterns on C-12, we have designed a new approach with a view to confirming the viability of the titanocene(III)-based procedure.[6]

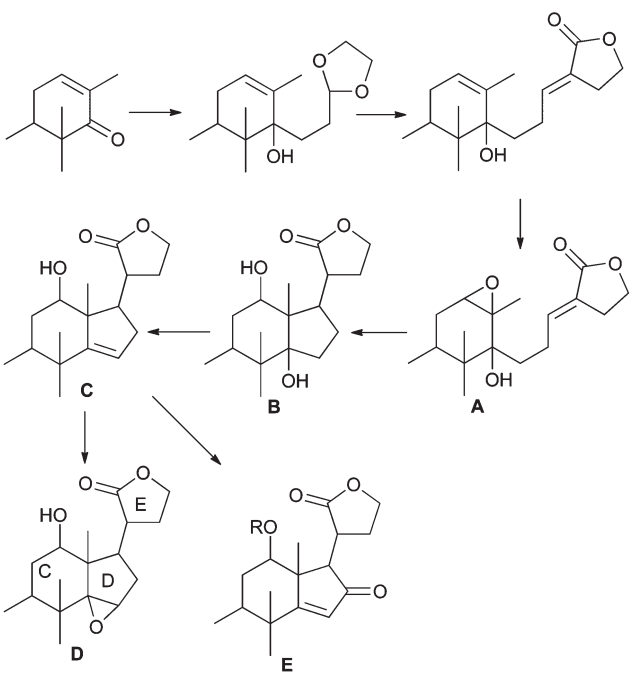
Our strategy is based on a stereoselective construction of ring D by a radical cyclization from epoxy lactone **A** to hydroxy lactone **B**, induced by titanocene chloride, in which the oxygenated functions are situated in the correct position and the relative orientation of the methyl and γ-lactone substituents is the same (*cis*) as in natural limonoids. The replacement of the characteristic furan (ring E) of limonoids by a γ-lactone, is to confer a more versatile functionality, and for SAR studies.

We carried out a synthesis of several limonoid fragment analogues, that differ in the functionalization of rings C and D, following the sequence in Scheme 2.

[a]*Departamento de Química Orgánica, Facultad de CC. Químicas, Universidad de Salamanca, Plaza de los Caídos 1–5, 37008 Salamanca, Spain. E-mail: afmateos@usal.es; Fax: (+34) 923294574; Tel: (+34)923294481*
[b]*Jodrell Laboratory, Royal Botanic Garden, Kew, Richmond, Surrey, UK*
†Electronic supplementary information (ESI) available: ^{1}H and ^{13}C spectra of all compounds are given as supplementary information. See DOI: 10.1039/c2ob25538c



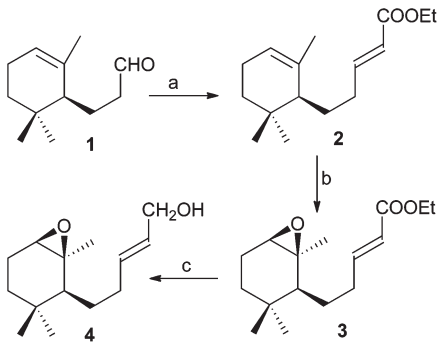
Scheme 1 Limonoid biogenetic relationship.



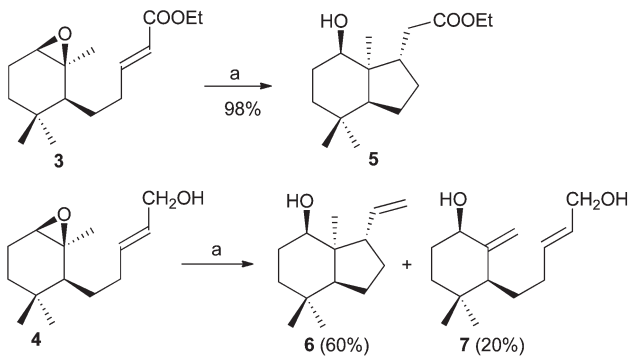
Scheme 2 C-12 Oxygenated CDE limonoid fragment synthetic plan.

To examine the possibilities of the synthetic project, in particular the transformation of the epoxy alcohol **A** into the diol **B**, two simple model compounds were selected as substrates: the epoxy ester **3** and the epoxy alcohol **4** (Scheme 3). Both compounds were obtained, in two and three steps respectively, from the aldehyde **1**, readily available in turn from α-cyclocitral.[4j]

Olefination of **1** to the conjugated ester **2** and further epoxidation afforded, chemo- and stereoselectively, the epoxy ester **3**, which after selective reduction with lithium aluminium hydride afforded the epoxy alcohol **4**. In both epoxides, the oxirane is *cis*



Scheme 3 *Reagents and conditions*: (a) $(EtO)_2POCHCOOEt$, toluene, 96%. (b) *m*-CPBA, CH_2Cl_2, 87%. (c) $LiAlH_4$, ether, 75%.



Scheme 4 *Reagents and conditions*: (a) Cp_2TiCl, THF, 25 °C.

with respect to the side chain. The stereochemistry of **3** and **4** was assigned by analogy with a similar epoxysulfone, whose structure has been determined by X-ray.[7]

The radical cyclization of the epoxy ester **3** was carried out by reaction with two equivalents of titanocene chloride generated *in situ* in THF at room temperature (Scheme 4). The hydroxy ester **5** was obtained as the only product in quantitative yield. In the same way, the treatment of the epoxy alcohol **4** with titanocene afforded the unsaturated alcohol **6**, in 60% yield, as a result of the radical cyclization.[6]

In both radical cyclizations two stereocentres are created with absolute stereoselectivity; the ring fusion is *cis* and the cyclopentane substituent orientation is *exo*. The stereochemistry of the bicyclic products **5** and **6** was determined by NOE experiments (Fig. 2).

We suggest the mechanism shown in Scheme 5 to account for the regio- and stereochemical outcome of this reaction. An epoxide reductive opening regioselectively originates the tertiary radical (**F**, **G**), the stable chair conformation of this intermediate determining the stereoselectivity of the cyclization. The radical thus generated (**F**, **G**) is trapped by the double bond *via* a 5-*exo*-trig process. The stereochemistry of the interannular junction, which proved to be *cis*, is in accordance with the general guideline formation of 6,5-ring fusions by radical cyclization, which typically proceed with good to excellent *cis* selectivity. The *exo* selectivity found for the cyclopentane ring substituent is apparently in disagreement with the studies reported by RajanBabu and Fukunaga, which showed that the direction of selectivity in

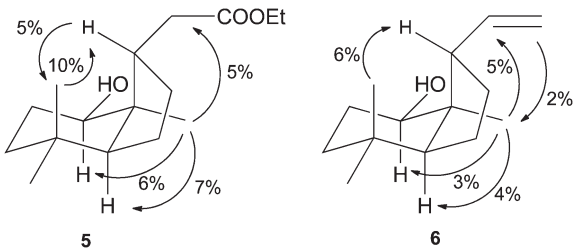
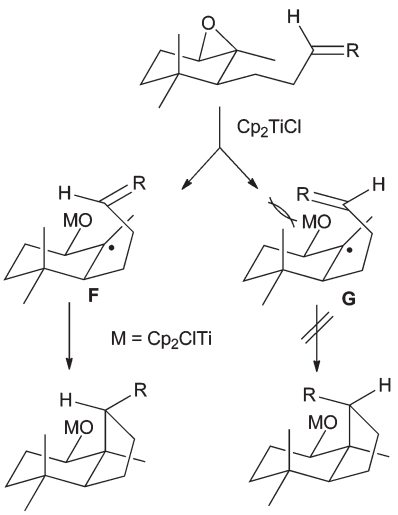
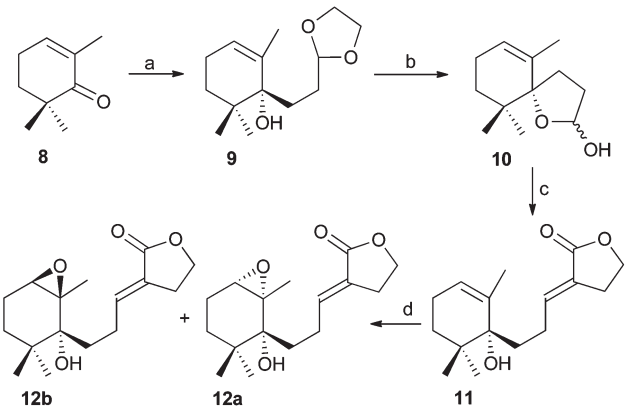


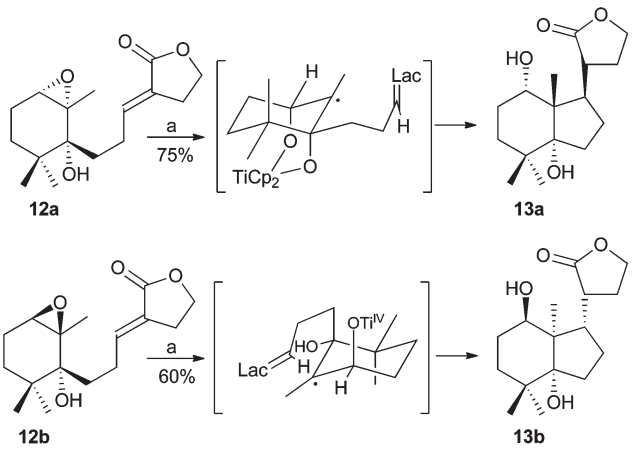
Fig. 2 NOE values of compounds **5** and **6**.



Scheme 5 Stereochemistry of cyclizations.



Scheme 6 *Reagents and conditions*: (a) 2-(2-bromoethyl)-1,3-dioxolane, Li, THF, 65%. (b) AcOH–THF–H_2O, reflux, 100%. (c) γ-butyro lactonylidene triphenyl phosphorane, DME, 41%. (d) *m*-CPBA, CH_2Cl_2, 89%.



Scheme 7 *Reagents and conditions*: (a) Cp_2TiCl, THF, 25 °C.

the reactions of cyclohexyl radicals with alkenes with a chain substituent depends on the orientation of the alkenyl side chain. For rigid cyclohexyl conformers with an equatorial acceptor side chain, the *endo* product isomer predominates, while the *exo* product is the major isomer with an axial acceptor side chain.[8]

In our case, the side chain acceptor is equatorial, but the *exo* selectivity is evident from Scheme 5, which clearly shows that the intermediate **G**, which would afford the *endo* product, is disfavoured with respect to the intermediate **F**, due to the severe non-bonded interaction between the side chain and the axial methyl group.

The success of radical cyclization experiments with models **3** and **4** from the regio- and stereochemical points of view is suitable for the construction of a hydrindane with substituents in the correct place, and the same relative orientation of the angular methyl group and the cyclopentane side chain as in limonoid CDE structural fragments. It is worth noting that the cyclization of the ester **3** is a better model for synthesis than that of alcohol **4**, because the yield of cyclic product is higher. This must be due to the nucleophilic character of the initial radical. The addition of this radical to the allylic alcohol system of **4** is slower because the non-cyclic side product **7** was obtained in 20% yield.

The next target in our approach to the synthesis of a limonoid model was the epoxy lactone **12**. The structural features of this cyclization substrate include the conjugated double bond in the side chain as a radical acceptor, the γ-lactone as an E ring precursor, and the hydroxyl group geminal to the side chain as a precursor of the cyclopentane double bond present in limonoid models.

The preparation of epoxy lactone **12** was achieved in four steps from the readily available trimethylcyclohexenone **8**, as depicted in Scheme 6: the Barbier reaction to introduce the side chain was followed by ketal deprotection, olefination and epoxidation. While the olefination only afforded one isomer, the hydroxy lactone **11**, oxidation with *m*-CPBA gave a mixture of two epoxide isomers α/β, **12a/12b**, in a 3 : 1 ratio respectively; the structural assignation is based on the *syn* director effect of the hydroxyl group and the stereochemistry of the subsequent reaction products.

Synthesis of the α/β isomers **12a** and **12b** allowed us to observe their different behaviour against titanocene chloride. The reaction of each isomer was carried out separately (Scheme 7). The major isomer **12a**, which features a *trans* relationship between the oxirane and the side chain, reacts with Cp_2TiCl in THF at room temperature to afford exclusively the bicyclic diol lactone **13a**, with B/C junction rings in *trans* orientation, in 75% yield. This is a rare and relevant stereoselective *5-exo* cyclization of a cyclohexyl radical to afford a 6,5-*trans* ring fusion.[9] The

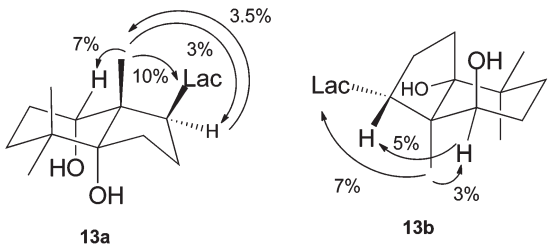
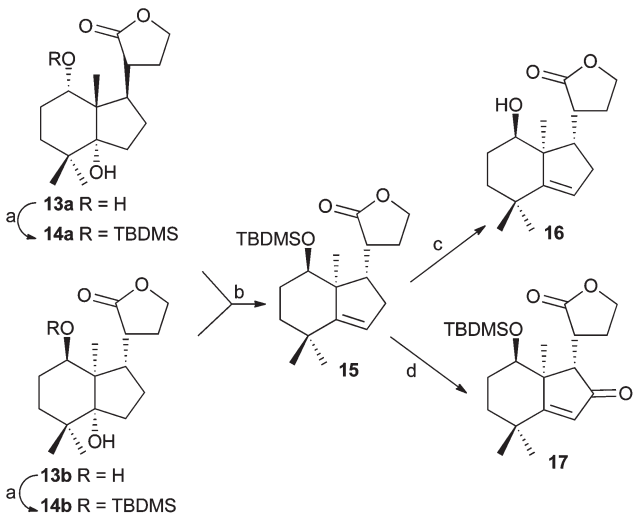


Fig. 3 NOE values of lactones **13a** and **13b**.

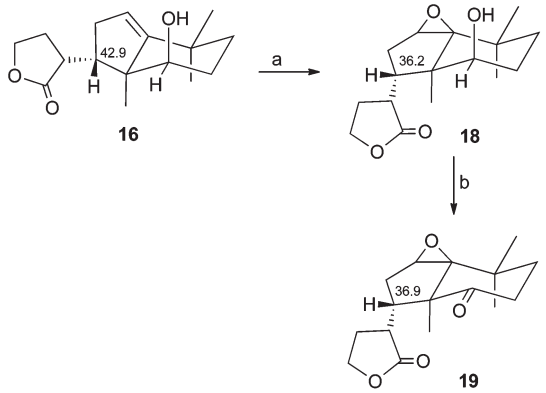


Scheme 8 *Reagents and conditions*: (a) TBDMSCl, imidazole, DME, 85%. (b) $SOCl_2$, pyr, 90%. (c) PPTS, EtOH, 98%. (d) , CH_2Cl_2, 68%.

minor isomer **12b**, which matches the *cis* relationship between the oxirane and the side chain in the former models **3** and **4**, reacts with Cp_2TiCl in THF at room temperature to afford exclusively the bicyclic diol lactone **13b**, with the B/C junction rings in *cis* orientation, in 70% yield. Stereochemical assignments were based on NOE studies. Some representative data are shown in Fig. 3.

Within the whole plan for the limonoid fragment synthesis, lactones **13a** and **13b** are very important intermediates. The lactone ring, which constitutes the E limonoid ring, is likely to be converted into unsaturated lactone, lactol, and furan, all present in certain natural limonoids. The steps required to obtain the limonoid fragments from **13a–b** are a selective dehydration of the tertiary alcohol, followed by epoxidation to afford compounds related to sendanin, or by allylic oxidation to obtain compounds related to azadiradione.

The dehydration step was carried out on **14a–b** with thionyl chloride in almost quantitative yield, after protection of the secondary alcohol using the corresponding *t*-butyl dimethyl silyl ether. The sequence was accomplished separately for **13a** and **13b**, as shown in Scheme 8. The only product obtained from either **14a** or **14b** was the unsaturated lactone **15**. It should be noted that although so far only one enantiomer has been drawn for convenience for each compound, it is really a racemic mixture. Therefore in this situation we have represented lactone **15** as an enantiomer, when it is really a racemic mixture. We chose the enantiomer most similar to the target natural limonoid.



Scheme 9 *Reagents and conditions*: (a) *m*-CPBA, CH_2Cl_2, 98%. (b) Dess–Martin reagent, CH_2Cl_2, 90%.

Desilylation of compound **15** with PPTS afforded the hydroxy lactone **16** in quantitative yield.

Fragment **17**, related to azadiradione, was obtained through the allylic oxidation of **15** with chromium trioxide–dimethylpyrazole. The δ values in the ^{13}C NMR of compound **17** are in agreement with those described by us for related compounds.[5j]

The epoxy alcohol **18** was obtained quantitatively by reaction of the unsaturated hydroxy lactone **16** with *m*-chloroperbenzoic acid (Scheme 9). The oxidation is endocyclic and directed by the hydroxyl group. Dess-Martin oxidation of **18** afforded the ketone **19** in 90% yield.

The structural assignation of the epoxides was based on experience gained with analogous compounds described by us elsewhere, in which oxidation with *m*-CBPA always afforded the *endo*-epoxide isomer **18**.[4d,h,k,n,5d,i,j] Additionally, the γ-effect in the ^{13}C NMR was considered.[4d,h,k,n,5d,i,j] The difference in the chemical displacement of the γ-carbon between **18** and **16** was as expected (6.7 ppm) for these compounds. The shielding effect of the lactone ring on the protons of the angular methyl group confirmed the *cis* relationship between both groups in epoxy lactones **18** and **19**, which appear in ^1H NMR at 0.82 and 0.90, respectively. The δ values in the ^{13}C NMR of compounds **18** and **19** are in agreement with the *endo*-epoxides described by us elsewhere.[4d,h,k,n,5d,i,j]

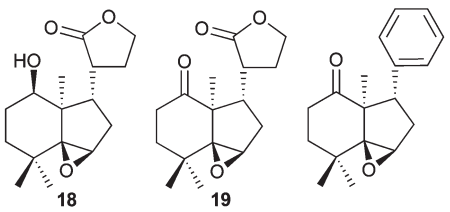
Both hydroxy lactone **18** as **19** are structural fragments related to the limonoids sendanin and toosendanin.

Biological results

Larvae of the African leafworms *Spodoptera littoralis* and *Spodoptera frugiperda* were used to assess the antifeedant activity of our molecular fragments.[10] In the series of model compounds related to toosendanin, the racemic epoxy lactones **18** and **19** exhibited similar antifeedant values when compared with the phenyl (ring E) fragment (Fig. 4).[4n]

Conclusions

A new synthetic approach to **18** and **19**, CDE fragments of limonoids related to sendanin, has been achieved from trimethylcyclohexenone in nine and ten steps, with overall yields of 14%



S. littoralis	23 (6.9)	21 (4.6)	30 (3.6)
S. frugiperda	24 (4.9)	25 (6.7)	21 (5.4)

Fig. 4 Antifeedant index of the compounds tested in choice bioassays at 100 ppm. [Antifeedant index = [(C − T)/(C + T)]% of compounds tested in choice bioassavs with glass discs (control (C) *vs.* treatment (T), $n = 20$].

and 12.5% respectively. The required D ring was formed by the titanocene(III)-promoted cyclization of unsaturated epoxy lactones, with total stereoselectivity. The versatility of the method allows it to be applied to the synthesis of more complicated limonoids. The racemic lactones **18** and **19** showed significant antifeedant activity against larvae of the African leafworms *Spodoptera littoralis* and *Spodoptera frugiperda*.

Experimental section

General methods

Melting points are uncorrected. ^{1}H NMR spectra were measured at either 200 or 400 MHz, and ^{13}C NMR were measured at 50 or 100 MHz in $CDCl_3$ and referenced to TMS (^{1}H) or solvent (^{13}C), except where indicated otherwise. IR spectra were recorded for neat samples on NaCl plates, unless otherwise noted. Standard mass spectrometry data were acquired using a GC-MS system in EI mode with a maximum *m*/*z* range of 600. When required, all solvents and reagents were purified by standard techniques: tetrahydrofuran (THF) was purified by distillation from sodium and benzophenone and was degassed before use. All reactions were conducted under a positive pressure of argon, using standard benchtop techniques for the handling of air-sensitive materials. Chromatographic separations were carried out under pressure on silica gel, using flash column techniques on Merck silica gel 60 (0.040–0.063 mm). The yields reported are for chromatographically pure isolated products unless otherwise mentioned.

General procedure 1 (GP1)

A mixture of Cp_2TiCl_2 (2.20 mmol) and Zn (6.60 equiv) in strictly deoxygenated THF (10 mL) was stirred at room temperature until the red solution turned green. In a separate flask, the epoxy compound (1 mmol) was dissolved in strictly deoxygenated THF (10 mL). The green Ti(III) solution was slowly added *via* cannula to the epoxide solution. After 30 min, an excess of saturated NaH_2PO_4 was added, and the mixture was stirred for 20 min. The mixture was filtered to remove insoluble titanium salts. The product was extracted into ether, and the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and filtered. After removal of the solvent, the crude product was purified by flash chromatography.

(*E*)-Ethyl 5-(2,6,6-trimethylcyclohex-2-enyl)-pent-2-enoate 2. A dry three-necked flask equipped with stirrer, condenser, and dropping funnel was purged with argon and charged with a 60% dispersion oil of sodium hydride in mineral oil (117 mg, 2.91 mmol) and dry toluene (0.9 mL). To this stirred mixture at 25 °C was added dropwise triethyl 2-phosphonoacetate (0.6 mL, 3.06 mmol), and the mixture was stirred for 30 min at room temperature to ensure complete reaction. To this nearly clear solution was added dropwise the aldehyde **1** (500 mg, 2.78 mmol) in toluene (0.6 mL). The mixture was stirred for an additional 16 h and diluted with ether, and water was then added dropwise. The organic layer was separated, and the aqueous phase was extracted with ether. The combined extracts were washed with brine and dried (Na_2SO_4), the solvent was evaporated and the residue was chromatographed on silica gel. Elution with hexane–ether (97 : 3) gave unsaturated ester **2** as a colorless oil (671 mg, 96%): ^{1}H NMR (δ): 0.87 (3H, s), 0.91 (3H, s), 1.28 (3H, t, $J = 7$ Hz), 1.4–2.1 (7H, m), 1.65 (3H, br s), 2.21 (2H, m), 4.18 (2H, q, $J = 7$ Hz), 5.31 (1H, br s), 5.80 (1H, dt, $J = 1.6$ Hz, $J' = 15.6$ Hz), 6.95 (1H, dt, $J = 6.8$ Hz, $J' = 15.6$ Hz) ppm; ^{13}C NMR (δ): 14.2, 22.9, 23.3, 27.3, 27.5, 29.4, 31.5, 32.5, 32.6, 48.9, 59.9, 120.6, 121.2, 135.9, 149.2, 166.5 ppm; IR: 2934, 1724, 1655 cm^{-1}; MS EI, *m*/*z* (relative intensity): 250 (M^+, 1), 235 (2), 204 (1), 162 (5), 137 (13), 114 (19), 95 (10), 81 (100), 67 (12), 55 (20); HRMS: for $C_{16}H_{26}O_2$ + Na: 273.1830, found. 273.1833.

(*E*)-Ethyl 5-((1*S,2*S**,6*R**)-1,3,3-trimethyl-7-oxa-bicyclo [4.1.0]-heptan-2-yl)pent-2-enoate 3.** To a stirred solution of **2** (200 mg, 0.8 mmol) in CH_2Cl_2 (6 mL) was added *m*-CPBA (138 mg, 0.8 mmol) and Na_2CO_3 (6.7 mg, 0.08 mmol). The reaction mixture was stirred under argon at room temperature for 3 h. Then, Na_2SO_3 (10%) was added and the resulting heterogeneous mixture was vigorously stirred for 15 min. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extract was washed with sat. $NaHCO_3$ and brine. Removal of the solvent afforded a crude residue, which was purified by flash chromatography. Eluting with hexane–Et_2O (90 : 10) furnished epoxide **3** (185 mg, 87%), as a colourless oil. ^{1}H NMR (δ): 0.80 (3H, s), 0.88 (3H, s), 1.28 (3H, t, $J = 7$ Hz), 1.32 (3H, s), 1.4–2.5 (9H, m), 2.94 (1H, br s), 4.17 (2H, q, $J = 7$ Hz), 5.85 (1H, dt, $J = 1.5$ Hz, $J' = 15.6$ Hz), 7.00 (1H, dt, $J = 7$ Hz, $J' = 15.6$) ppm; ^{13}C NMR (δ): 14.2, 22.0, 26.0, 26.8 (2), 27.2, 27.6, 31.4, 31. 7, 46.7, 59.1, 60.0 (2C), 121.3, 149.3, 166.6 ppm; IR: 2957, 1723, 1655, 1196 cm^{-1}; MS EI, *m*/*z* (relative intensity): 266 (M^+, 1), 251 (1), 233 (1), 205 (2), 153 (81), 125 (32), 95 (27), 81 (48), 69 (40), 55 (100); HRMS: for $C_{16}H_{26}O_3$ + Na, 289.1780, found. 289.1782.

(*E*)-5-((1*S,2*S**,6*R**)-1,3,3-Trimethyl-7-oxa-bicyclo[4.1.0] heptan-2-yl) pent-2-en-1-ol 4.** $LiAlH_4$ (17 mg, 0.4 mmol) was added to a solution of the unsaturated ester **3** (106 mg, 0.4 mmol) in diethyl ether (2.3 ml). The reaction mixture was vigorously stirred at room temperature under argon for 1 h, after which it was quenched with $Na_2SO_4{\cdot}10H_2O$. The resulting mixture was filtered, and then the filtrate was evaporated under reduced pressure to afford unsaturated alcohol **4** as a colorless oil (67 mg,

75%): ^{1}H NMR (δ): 0.80 (3H, s), 0.88 (3H, s), 1.2–2.4 (9H, m), 1.33 (3H, s), 2.93 (1H, br s), 4.08 (2H, d, J 4.8 Hz), 5.71 (2H, m) ppm; ^{13}C NMR (δ): 22.0, 26.8 (2), 27.0, 27.3, 27.7, 31.4, 31.8, 46.6, 59.5, 60.0, 63.8, 128.9, 133.6 ppm; IR: 3447, 2930, 1456 cm^{-1}; HRMS: for $C_{14}H_{24}O_2$ + Na, 247.1674, found. 247.1672.

Reaction of 3 with Cp_2TiCl

According to GP1, reaction of **3** (67 mg, 0.25 mmol) with Cp_2TiCl followed by flash chromatography (hexane 8 : 2 diethyl ether) furnished ethyl 2-((1*S**,3a*S**,7*R**,7a*S**)-7-hydroxy-4,4,7a-trimethyl-octahydro-1*H*-inden-1-yl)acetate **5** as a colorless oil (65 mg, 98%): ^{1}H NMR (δ): 0.83 (3H, s), 0.89 (3H, s), 0.99 (3H, s), 1.2–2.6 (10H, m), 1.23 (3H, t, J = 7 Hz), 2.10 (1H, dd, J = 9 Hz, J' = 15.6 Hz), 2.90 (1H, dd, J = 4 Hz, J' = 15 Hz), 3.58 (1H, dd, J = 5 Hz, J' = 11 Hz), 4.10 (2H, q, J = 7 Hz) ppm; ^{13}C NMR (δ): 14.2, 23.5, 24.3, 24.7, 27.6, 31.2, 32.7 (2C), 37.4, 38.0, 38.3, 48.1, 57.9, 60.0, 78.2, 174.7 ppm; IR: 3476, 2947, 1738, 1032 cm^{-1}; MS EI, *m*/*z* (relative intensity): 268 (M$^+$, 1), 250 (1), 235 (3), 211 (12), 168 (100), 123 (63), 93 (35), 81 (80), 69 (32), 55 (67); HRMS: for $C_{16}H_{28}O_3$ + Na, 291.1936, found. 291.1933.

Reaction of 4 with Cp_2TiCl

According to GP1, reaction of **4** (52 mg, 0.23 mmol) with Cp_2TiCl followed by flash chromatography (hexane 80 : 20 diethyl ether) furnished (3*S**,3a*S**,4*R**,7a*S**)-3a,7,7-trimethyl-3-vinyl-octahydro-1*H*-inden-4-ol **6** as a colorless oil (21 mg, 60%). ^{1}H NMR (δ): 0.83 (3H, s), 0.92 (3H, s), 1.09 (3H, s), 1.2–2.0 (10H, m), 3.50 (1H, dd, J = 6 Hz, J' = 10 Hz), 4.96 (1H, dd, J = 2 Hz, J' = 9.5 Hz), 5.08 (1H, dd, J = 2 Hz, J' = 17 Hz), 5.95 (1H, ddd, J = 17 Hz, J' = 9.5 Hz, J'' = 9.6 Hz) ppm; ^{13}C NMR (δ): 23.6, 24.3, 25.2, 27.7, 30.5, 32.7 (2C), 37.9, 46.6, 49.9, 58.1, 78.6, 114.7, 143.4 ppm; IR: 3447, 2953, 1456, 1042 cm^{-1}; MS EI, *m*/*z* (relative intensity): 208 (M$^+$, 3), 194 (3), 175 (10), 139 (49), 93 (58), 69 (36), 55 (73), 41 (100). HRMS: for $C_{14}H_{24}O$ + Na, 231.1725, found. 231.1726. Eluting with hexane–Et_2O (5 : 95) furnished (1*R**,3*S**)-3-(5-hydroxypentyl)-4,4-dimethyl-2-methyl-ene-cyclohexanol **7** as a colorless oil (10 mg, 20%): ^{1}H NMR (δ): 0.69 (3H, s), 0.95 (3H, s), 1.2–1.7 (13H, m), 3.64 (2H, t, J = 6.4 Hz), 3.96 (1H, br s), 4.70 (1H, br s), 5.17 (1H, br s) ppm; ^{13}C NMR (δ): 25.4, 26.1, 28.0, 29.5, 29.6, 30.3, 32.7, 33.3, 35.7, 51.6, 63.0, 73.8, 104.6, 150. 9 ppm; IR: 3398, 2964 cm^{-1}; MS EI, *m*/*z* (relative intensity): 208 (M$^+$–H_2O, 3), 193 (4), 175 (3), 122 (52), 107 (100), 91 (30), 79 (37), 55 (57), 41 (91); HRMS: for $C_{14}H_{26}O_2$ + Na, 249.1830, found. 249.1835.

1-(2-(1,3-Dioxolan-2-yl)ethyl)-2,6,6-trimethylcyclohex-2-enol 9. To a stirred suspension of Li (1.24 g, 117 mmol) in THF (64 mL) was added a solution of 2-(2-bromoethyl)-1,3-dioxolane (1.37 mL, 76.1 mmol) and 2,6,6-trimethyl-2-cyclohexenone (7 g, 50.7 mmol). The resulting mixture was stirred under argon for 1 h at room temperature, and then 2 M HCl was added at 0 °C, and the heterogeneous mixture stirred for 5 min. The organic layer was separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with brine. Removal of the solvent afforded a crude residue, which was purified by flash chromatography. Eluting with hexane–Et_2O (80 : 20) gave the alcohol **9** as a colorless oil (7.9 g, 65%). ^{1}H NMR (δ): 0.93 (3H, s), 0.95 (3H, s), 1.1–2.1 (9H, m), 1.71 (3H, s), 3.90 (4H, m), 4.81 (1H, t, J = 3.9 Hz), 5.38 (1H, br s) ppm; IR: 3516, 2961, 1451. 1142 cm^{-1}; HRMS: for $C_{14}H_{24}O_3$ + Na, 263.1623, found. 263.1624.

(*E*)-3-(3-(1-Hydroxy-2,6,6-trimethylcyclohex-2-enyl) propylidene)-dihydrofuran-2(3*H*)-one 11. A solution of **9** (3.88 g, 16.2 mmol) in a mixture of 3 : 1 : 1 AcOH–THF–H_2O (40.4 mL) was stirred under argon at reflux for 3 h. Then, the mixture was cooled to room temperature and an aqueous solution of 5% $NaHCO_3$ was added to quench the reaction. The organic layer was separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with saturated $NaHCO_3$ and brine. Removal of the solvent afforded a mixture of lactols **10** as a colorless oil (3.16 g, 100%), which where used for further reaction without any purification; ^{1}H NMR (δ: 0.81 (3H, s), 0.89 (3H, s), 0.96 (6H, s), 1.2–2.2 (16H, m), 1.63 (3H, s), 1.76 (3H, s), 5.30 (1H, br s), 5.38 (1H, br s), 5.61 (2H, br s) ppm; IR: 3410, 2972, 2917, 1723 cm^{-1}.

A solution of lactol **10** (882 mg, 4.50 mmol), benzoic acid (112 mg, 0.92 mmol), and γ-butyro-lactonylidene triphenyl phosphorane (4.27 g, 12.35 mmol) in dry DME (40 mL) was stirred at reflux for 2 d under argon. When the reaction was complete the solvent were evaporated *in vacuo* and the residue was purified by flash chromatography (3 : 7 hexane–ethyl acetate) to give **11** as a colorless oil (487 mg, 41%), ^{1}H NMR (δ): 0.95 (3H, s), 0.97 (3H, s), 1.5–2.4 (8H, m), 1.74 (3H, br s), 2.87 (2H, dt, J = 2.7 Hz, J' = 6 Hz), 4.36 (2H, t, J = 7.4 Hz), 5.45 (1H, br s), 6.71 (1H, m) ppm; ^{13}C NMR (δ): 19.5, 22.6, 23.0, 24.3, 25.1, 26.9, 34.2, 35.8, 37. 8, 65.5, 77.1, 124.4, 125.1, 137.0, 141.5, 171.4 ppm; IR: 3511, 2922, 1751, 1678 cm^{-1}; MS EI, *m*/*z* (relative intensity): 264 (M$^+$, 3), 246 (8), 231 (6), 208 (17), 139 (92), 125 (52), 112 (74), 95 (100), 79 (34); HRMS: for $C_{16}H_{24}O_3$ + Na, 287.1623, found. 287.1624.

Epoxidation of 11

To a stirred solution of **11** (304 mg, 1.15 mmol) in CH_2Cl_2 (6 mL) was added *m*-CPBA (198 mg, 1.15 mmol) and Na_2CO_3 (1.6 mg, 0.015 mmol). The reaction mixture was stirred under argon at room temperature for 150 min. Then, Na_2SO_3 (10%) was added and the resulting heterogeneous mixture was vigorously stirred for 15 min. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extract was washed with sat. $NaHCO_3$ and brine. Removal of the solvent afforded a crude residue, which was purified by flash chromatography. Eluting with hexane–Et_2O (4 : 6) furnished (*E*)-3-(3-((1*R**,2*R**,6*R**)-2-hydroxy-1,3,3-trimethyl-7-oxa-bicyclo[4.1.0]heptan-2-yl)-propylidene)-dihydrofuran-2(3*H*)-one **12b** as a white solid (78 mg, 24%), m. p. 130 °C, ^{1}H NMR (δ): 0.80 (3H, s), 0.91 (3H, s), 1.1–2.1 (8H, m), 1.43 (3H, s), 2.63 (1H, d, J = 1.5 Hz), 2.90 (1H, m), 3.17 (1H, br s), 4.38 (2H, t, J = 7.5 Hz), 6.77 (1H, m) ppm; ^{13}C NMR (δ): 21.3, 21.5, 21. 8, 24.1, 25.1, 26.4, 28.5, 31.2, 37.2, 62.1, 65.0, 65.3, 73.1, 124.9, 141.3, 171.2; IR: 3511, 2934, 1744, 1678 cm^{-1}; MS EI, *m*/*z* (relative intensity): 280 (M$^+$, 5),

264 (6), 223 (7), 205 (9), 149 (100), 126 (29), 109 (31), 95 (37), 81 (47); HRMS: for $C_{16}H_{24}O_4$ + Na, 303.1572, found. 303.1571. Eluting with hexane–Et_2O (2 : 8) furnished a white solid identified as (*E*)-3-(3-((1*S**,2*R**,6*S**)-2-hydroxy-1,3,3-trimethyl-7-oxa-bicyclo[4.1.0]heptan-2-yl)propylidene)-dihydrofuran-2(3*H*)-one **12a** (209 mg, 65%), m.p. 100–104 °C; ^{1}H NMR (δ): 0.84 (3H, s), 0.92 (3H, s), 1.0–2.0 (8H, m), 1.38 (3H, s), 2.53 (1H, m), 2.94 (1H, m), 2.98 (1H, br s), 4.37 (2H, t, J = 7.5 Hz), 6.77 (1H, m) ppm; ^{13}C NMR (δ): 21.6, 21.9, 22.1, 23.7, 25.1, 25.6, 30.0, 33.9, 36.6, 60.8, 61.1, 65.3, 75.7, 125.3, 141.2, 171.4 ppm; IR: 3520, 1741, 1675 cm^{-1}; MS EI, *m*/*z* (relative intensity): 280 (M^+, 3), 262 (3), 219 (7), 181 (10), 153 (20), 125 (74), 112 (100), 95 (67), 81 (57); HRMS: for $C_{16}H_{24}O_4$ + Na, 303.1572, found. 303.1570.

Reaction 12a with Cp_2TiCl

According to GP1, reaction of **12a** (175 mg, 0.62 mmol) with Cp_2TiCl followed by flash chromatography (hexane 7 : 3 diethyl ether) furnished a white solid identified as ethyl 3-((1*R**,3a*R**,7*S**,7a*S**)-3a,7-dihydroxy-4,4,7a-trimethyloctahydro-1*H*-inden-1-yl)dihydrofuran-2(3*H*)-one **13a** (131 mg, 75%), m.p. 150–156 °C, ^{1}H NMR (δ): 0.95 (3H, s), 1.03 (3H, s), 1.07 (3H, s), 1.2–1.9 (7H, m), 2.08 (1H, m), 2.24 (1H, m), 2.45 (1H, m), 2.80 (1H, m), 2.89 (1H, m), 3.70 (1H, dd, J = 3 Hz, J' = 5.5 Hz), 4.14 (1H, m), 4.30 (1H, dt, J = 2.6 Hz, J' = 9 Hz) ppm; ^{13}C NMR (δ): 18.4, 23.6, 24.2, 25.7, 26.3, 27.7, 32.3, 35.8, 37.1, 41.8, 43.7, 51.0, 66.6, 75.8, 85.2, 180.8 ppm; IR: 3464, 2943, 1739, 1215 cm^{-1}; MS EI, *m*/*z* (relative intensity): 264 (M^+–H_2O, 2), 249 (8), 231 (4), 213 (7), 195 (6), 178 (21), 123 (31), 97 (100), 86 (45), 55 (52), 43 (84); HRMS: for $C_{16}H_{26}O_4$ + Na, 305.1729, found. 305.1731.

Reaction 12b with Cp_2TiCl

According to GP1, reaction of **12b** (76 mg, 0.27 mmol) with Cp_2TiCl followed by flash chromatography (hexane 7 : 3 diethyl ether) furnished ethyl 3-((1*R**,3a*R**,7*R**,7a*R**)-3a,7-dihydroxy-4,4,7a-trimethyloctahydro-1*H*-inden-1-yl)dihydrofuran-2(3*H*)-one **13b** as a colorless oil (46 mg, 60%), ^{1}H NMR (δ): 0.89 (3H, s), 1.02 (3H, s), 1.06 (3H, s), 1.3–2.5 (10H, m), 2.66 (1H, m), 3.05 (1H, m), 4.02 (1H, br s), 4.48 (1H, m), 4.84 (1H, m) ppm; ^{13}C NMR (δ): 17.5, 24.5, 25.0, 25.6, 27.2, 28.7, 29.6, 30.1, 37.9, 39.3, 40.2, 49.8, 67.5, 72.9, 87.3, 181.7 ppm; IR: 3422, 2926, 1750, 1365 cm^{-1}; MS EI, *m*/*z* (relative intensity): 264 (M^+–H_2O, 3), 246 (9), 231 (13), 203 (4), 178 (46), 161 (48), 145 (31), 123 (49), 105 (31), 86 (78), 55 (63), 41 (100); HRMS: for $C_{16}H_{26}O_4$ + Na, 305.1729, found. 305.1727.

3-((1*R,7*R**,7a*S**)-7-(*tert*-Butyldimethylsilyloxy)-4,4,7a-trimethyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-1-yl) dihydrofuran-2(3*H*)-one 15**

*From compound **13a**.* A mixture of the hydroxy ester **13a** (105 mg, 0.37 mmol), *tert*-butyldimethylsilyl chloride (231 mg, 1.49 mmol), and imidazole (209 mg, 3.07 mmol) in dry DMF (1 mL) was stirred for 7 d under argon at 25 °C, poured into ice water, and extracted with hexane. The organic layer was washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was filtered though a small pad of silica gel, and concentrated to yield silyloxy alcohol **14a** as a colorless oil (125 mg, 85%), which was used for further reaction without any purification; ^{1}H NMR (δ): 0.06 (3H, s), 0.16 (3H, s), 0.86 (9H, s), 0.93 (3H, s), 1.03 (6H, s), 1.1–2.2 (12H, m), 4.20 (3H, m) ppm.

To a stirred solution of the alcohol **14a** (123 mg, 0.31 mmol) in CH_2Cl_2 (2 mL) and pyridine (0.04 mL, 0.63 mmol), at 0 °C was added $SOCl_2$ (0.06 ml, 0.94 mmol). After 75 min at this temperature, the mixture was poured into ice water and stirred for an additional 20 min at room temperature. The two-phase system was extracted with ether. The combined ethereal extracts were washed with 2 N HCl, 5% $NaHCO_3$, water and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give the silyloxy ester **15** as a white solid (105 mg, 90%), m.p. 55 °C; ^{1}H NMR (δ): 0.02 (3H, s), 0.05 (3H,s), 0.86 (12H, s), 1.08 (3H, s), 1.11 (3H, s), 1.9–2.3 (8H, m), 2.62 (1H, dd, J = 9 Hz, J' = 18 Hz), 2.97 (1H, m), 4.22 (3H, m), 5.34 (1H, br s), ppm; ^{13}C NMR (δ): −5.0, −4.3, 16.2, 19.0, 26.0 (3C), 26.2, 28.4, 29.6, 31.5, 32.6, 33.3, 33.4, 39.7, 42.5, 52.2, 66.1, 71.7, 119.0, 155.9, 178.2 ppm; IR: 2930, 1775, 1080 cm^{-1}; MS EI, *m*/*z* (relative intensity): 363 (M^+–Me, 3), 321 (100), 246 (34), 161 (73), 119 (44), 91 (30), 75 (54), 55 (30), 41 (35); HRMS: for $C_{22}H_{38}O_3Si$ + Na, 401.2488, found. 401.2489.

*From compound **13b**.* A mixture of the hydroxy ester **13b** (28 mg, 0.10 mmol), *tert*-butyldimethylsilyl chloride (66 mg, 0.43 mmol), and imidazole (59 mg, 0.85 mmol) in dry DMF (1 mL) was stirred for 2 d under argon at 25 °C, poured into ice water, and extracted with hexane. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was filtered though a small pad of silica gel, and concentrated to yield the silyloxy alcohol **14b**, as a colorless oil (34 mg, 86%), which was used for further reaction without any purification; ^{1}H NMR (δ): 0.06 (3H, s), 0.13 (3H, s), 0.88 (9H, s), 1.01 (3H, s), 1.05 (6H, s), 1.1–2.2 (12H, m), 4.25 (3H, m) ppm.

To a stirred solution of the alcohol **14b** (34 mg, 0.09 mmol) in CH_2Cl_2 (0.5 mL) and pyridine (0.03 mL, 0.52 mmol), at 0 °C was added $SOCl_2$ (0.03 ml, 0.35 mmol). After 12 h at this temperature, the mixture was poured into ice water and stirred for an additional 20 min at room temperature. The two-phase system was extracted with ether. The combined ethereal extracts were washed with 2 N HCl, 5% $NaHCO_3$, water and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give the silyloxy ester **15** (32 mg, 95%).

3-((1*S,7*R**,7a*S**)-7-Hydroxy-4,4,7a-trimethyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-1-yl)dihydro furan-2(3*H*)-one 16.** To a solution of the silyloxy compound **15** (16 mg, 0.04 mmol) in EtOH (0.5 mL) was added PPTs (20 mg, 0.08 mmol). The reaction mixture was refluxed for 48 h under argon, and then concentrated to afford a residue, which was dissolved in H_2O and extracted with Et_2O. The combined organic extracts were washed with brine, and dried with Na_2SO_4. Removal of the solvent afforded a colorless oil identified as **16** (11 mg, 98%): ^{1}H NMR (δ): 1.06 (3H, s), 1.11 (3H, s), 1.12 (3H, s), 1.1–2.4 (9H, m), 2.77 (2H, m), 3.99 (1H, t, J = 3 Hz), 4.24 (1H, m), 4.33 (1H, dt, J = 3 Hz, J' = 8 Hz), 5.44 (1H, br s) ppm; ^{13}C NMR (δ): 18.3, 25.9, 28.9, 29.3, 31.1, 32.6, 33.0, 33.5, 39.3, 42.9, 51.4, 66.9, 70.8, 120.2, 156.4, 180.3 ppm; IR: 3511, 2930, 2857, 1750 cm^{-1}; MS EI, *m*/*z* (relative intensity): 264 (M^+, 3), 246 (21), 161 (100), 145

(51), 121 (62), 105 (52), 91 (36), 77 (29), 55 (39); HRMS: for $C_{16}H_{24}O_3$ + Na, 287.1623, found. 287.1622.

3-((1*S,7*R**,7a*S**)-7((*tert*-Butyldimethylsilyl)oxy)-4,4,7a-trimethyl-2-oxo-2,4,5,6,7,7a-hexahydro-1*H*-inden-1-yl) dihydrofuran-2(3*H*)-one 17.** A suspension of CrO_3 (107 mg, 1.07 mmol) in CH_2Cl_2 (1 ml) was added 3,5-dimethylpyrazole (107 mg, 1.07 mmol) under argon at −25 °C. After 15 min, a solution of the compound **15** (32 mg, 0.09 mmol) in CH_2Cl_2 (1 ml) was added dropwise. The reaction mixture was stirred for a further 3 h, and 2 M NaOH (0.8 ml, 1.6 mmol) was added, and stirring was continued for a further 10 min at 0 °C. Then, it was allowed to warm to room temperature, the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined extracts were washed with 2 M HCl, water, dried (Na_2SO_4) and filtered. Removal of the solvent afforded a crude residue, which was purified by flash chromatography. Eluting with hexane–Et_2O (4 : 6) furnished ketone **17** as a colorless oil (24 mg, 68%), ^{1}H NMR (δ): 0.06 (3H, s), 0.08 (3H, s), 0.86 (9H, s), 1.20 (3H, s), 1.24 (3H, s), 1.30, (3H, s), 1.6–2.6 (7H, m), 3.63 (1H, d, J = 4.5 Hz), 3.96 (1H, d, J = 3.8 Hz), 4.20 (1H, dd, J = 2.1 Hz, J' = 8.3 Hz), 4.40 (1H, dt, J = 2.8 Hz, J' = 8.9 Hz), 5.89 (1H, s) ppm; ^{13}C NMR (δ): −5.3, −4.3. 18.0, 23.4, 25.4, 25.8 (3C), 26.7, 28.3, 31.2, 33.3, 35.4, 36.6, 52.7, 53.2, 66.5, 71.6, 126.5, 178.2, 191.4, 206.8 ppm; IR: 2926, 1778, 1690 cm^{-1}; MS EI, *m*/*z* (relative intensity): 392 (M^+, 6), 355 (100), 263 (6), 177 (38), 75 (43); HRMS: for $C_{22}H_{36}O_4Si$ + Na, 415.2281, found. 415.2283.

3((1a*R,3*S**,3a*R**,4*R**,7a*S**)-4-Hydroxy-3a,7,7-trimethyloctahydroindeno[1,7a-b]oxiren-3-yl)-dihydrofuran-2(3*H*)-one 18.** To a stirred solution of **16** (11 mg, 0.04 mmol) in CH_2Cl_2 (1 mL) was added *m*-CPBA (7 mg, 0.04 mmol). The reaction mixture was stirred under argon at room temperature for 120 min. Then, Na_2SO_3 (10%) was added and the resulting heterogeneous mixture was vigorously stirred for 15 min. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extract was washed with sat. $NaHCO_3$ and brine. Removal of the solvent afforded a crude residue, which was purified by flash chromatography. Eluting with hexane–Et_2O (4 : 6) furnished epoxide **18** as a colorless oil (11 mg, 98%), ^{1}H NMR (δ): 0.82 (3H, s), 1.10 (3H, s), 1.19 (3H, s), 1.6–2.5 (11H, m), 3.35 (1H, br s), 4.17 (1H, br s), 4.19 (1H, m), 4.34 (1H, dt, J = 2.5 Hz, J' = 8.3 Hz), ppm; ^{13}C NMR (δ): 17.4, 26.3, 26.5, 27.6, 28.7, 31.0, 31.7, 33.2, 36.2, 38.8, 45.8, 54.5, 66.4, 71.6, 73.2, 178.5; IR: 3505, 2928, 1763, 1458 cm^{-1}; MS EI, *m*/*z* (relative intensity): 280 (M^+, 2), 262 (7), 247 (18), 229 (14), 177 (58), 139 (53), 119 (37), 95 (44), 86 (47), 55 (100), HRMS: for $C_{16}H_{24}O_4$ + Na, 303.1572, found. 303.1575.

(1a*R,3*S**,3a*S**,7a*S**)-3a,7,7-Trimethyl-3-(2-oxotetrahydrofuran-3-yl)hexahydroindeno[1,7a-b]oxiren-4(5*H*)-one 19.** To a solution of the epoxy-alcohol **18** (11 mg, 0.04 mmol) in CH_2Cl_2 (0.6 mL) were added Dess–Martin reagent (20 mg, 0.05 mmol). The reaction mixture was stirred under argon at room temperature for 20 h, after which it was diluted with CH_2Cl_2. The solution was washed with 5% $NaHCO_3$, 10% Na_2SO_3, and brine, dried (Na_2SO_4). Removal of the solvent afforded a crude residue, which was purified by flash chromatography. Eluting with hexane–Et_2O (2 : 8) furnished ketone **19** as a colorless oil (10 mg, 90%), ^{1}H NMR (δ): 0.90 (3H, s), 1.31 (3H, s), 1.33 (3H, s), 1.5–2.7 (10H, m), 2.98 (1H, dt, J = 5 Hz, J' = 9 Hz), 3.44 (1H, br s), 4.20 (1H, dd, J = 7 Hz), 4.31 (2H, dt, J = 3.8 Hz, J' = 8.2 Hz), ppm; ^{13}C NMR (δ): 17.5, 26.7, 27.3, 28.1 (2C), 32.4, 36.2, 36.6, 36.9, 38.9, 54.1, 55.7, 65.8, 73.5, 178.1, 213.5 ppm; IR: 2928, 2857, 1771, 1717 cm^{-1}; MS EI, *m*/*z* (relative intensity): 278 (M^+, 4), 263 (6), 249 (18), 223 (19), 207 (32), 177 (99), 149 (24), 133 (38), 91 (45), 77 (40), 55 (100), HRMS: for $C_{16}H_{24}O_4$ + Na, 301.1416, found. 301.1418.

References

1 (*a*) D. L. Dreyer, *Prog. Chem. Org. Nat. Prog.*, 1968, **26**, 190–244; (*b*) J. D. Connolly, K. H. Overton and J. Polonsky, *Prog. Phytochem.*, 1970, **2**, 385–455; (*c*) D. A. H. Taylor, *Prog. Chem. Org. Nat. Prod.*, 1984, **45**, 1–102; (*d*) D. E. Champagne, O. Koul, M. B. Isman, G. G. E. Scudder and G. H. N. Towers, *Phytochemistry*, 1992, **31**, 377–394; (*e*) A. Akhila and K. Rani, *Prog. Chem. Org. Nat. Prod.*, 1999, **78**, 48–149.

2 (*a*) G. Brahmachari, *ChemBioChem*, 2004, **5**, 408–421; (*b*) A. Roy and S. Saraf, *Biol. Pharm. Bull.*, 2006, **29**, 191–201; (*c*) S. Ejaz, A. Ejaz, K. Matsuda and C. W. Lim, *J. Sci. Food Agric.*, 2006, **86**, 339–345; (*d*) G. D. Manners, *J. Agric. Food Chem.*, 2007, **55**, 8285–8294; (*e*) S. J. Uddin, L. Nahar, J. A. Shilpi, M. Shoeb, T. Borkowski, S. Gibbons, M. Middleton, M. Byres and S. D. Sarker, *Phytother. Res.*, 2007, **21**, 757–761; (*f*) G. E. L. Brandt, M. D. Schmidt, T. E. Prisinzano and B. S. J. Blagg, *J. Med. Chem.*, 2008, **51**, 6495–6502; (*g*) S. E. Lee, M. R. Kim, J. H. Kim, G. R. Takeoka, T. W. Kim and B. S. Park, *Phytomedicine*, 2008, **15**, 533–535; (*h*) T. Qin-Gang and L. Xiao-Dong, *Chem. Rev.*, 2011, **111**, 7437–7522.

3 Reviews on limonoid synthesis: (*a*) T. Tokoroyama, *J. Synth. Org. Chem. Jpn.*, 1998, **56**, 1014; (*b*) B. Heasley, *Eur. J. Org. Chem.*, 2011, 19. Synthesis of azadiradione: (*c*) E. J. Corey, J. G. Reid, A. G. Myers and R. W. Hahl, *J. Am. Chem. Soc.*, 1987, **109**, 918–919; (*d*) E. J. Corey and R. W. Hahl, *Tetrahedron Lett.*, 1989, **30**, 3023–3026; (*e*) D. C. Behenna and E. J. Corey, *J. Am. Chem. Soc.*, 2008, **130**, 6720–6721. Synthesis of azadirachtin: (*f*) S. V. Ley, A. A. Denholm and A. A. Wood, *Nat. Prod. Rep.*, 1993, **10**, 109–157; (*g*) G. E. Veitch, A. Boyer and S. V. Ley, *Angew. Chem., Int. Ed.*, 2008, **47**, 9402–9429; (*h*) J. Jauch, *Angew. Chem., Int. Ed.*, 2008, **47**, 34–37. Synthetic dumsin studies: (*i*) L. A. Paquette and F.-T. Hong, *J. Org. Chem.*, 2003, **68**, 6905–6918; (*j*) L. A. Paquette, Y. Hu, A. Luxenburger and R. L. Bishop, *J. Org. Chem.*, 2007, **72**, 209–222; (*k*) A. Srikrishna, V. H. Pardeshi and P. Thriveni, *Tetrahedron: Asymmetry*, 2008, **19**, 1392–1396. Synthetic Azadiradione study: (*l*) A. Fernández-Mateos, A. López Barba, E. M. Martín de la Nava, G. Pascual Coca, J. J. Pérez Alonso, R. Rubio González and C. Tapia Hernández, *Tetrahedron*, 1997, **53**, 14131–14140.

4 (*a*) S. E. Drews, P. A. Grieco and J. C. Huffman, *J. Org. Chem.*, 1985, **50**, 1309–1313; (*b*) T. Tokoroyama, Y. Fukuyama and Y. Kotsuji, *J. Chem. Soc., Perkin Trans. 1*, 1988, 445–450; (*c*) M. D. Bentley, M. S. Rajab, M. J. Mendel and A. R. Alford, *J. Agric. Food Chem.*, 1990, **38**, 1400–1403; (*d*) A. Fernández-Mateos and J. A. de la Fuente, *J. Org. Chem.*, 1990, **55**, 1349–1354; (*e*) A. Fernández-Mateos and J. A. de la Fuente, *J. Org. Chem.*, 1991, **56**, 7084–7092; (*f*) A. Fernández-Mateos, M. Grande Benito, G. Pascual Coca, R. Rubio González and C. Tapia Hernández, *Tetrahedron*, 1995, **27**, 7521–7526; (*g*) A. Fernández-Mateos and A. López Barba, *J. Org. Chem.*, 1995, **60**, 3580–3585; A. Fernández-Mateos, G. Pascual Coca, R. Rubio González and C. Tapia Hernández, *Tetrahedron*, 1996, **52**, 4817–4828; (*h*) J. A. de la Fuente, J. J. Marugán, S. S. Cross, A. Fernández-Mateos, S. García and A. Menéndez, *Bioorg. Med. Chem. Lett.*, 1995, **14**, 1471; (*i*) A. Fernández-Mateos, G. Pascual Coca, J. J. Pérez Alonso and R. Rubio González, *Synlett*, 1996, 1134–1136; (*j*) A. Fernández-Mateos, G. Pascual Coca, R. Rubio González and C. Tapia Hernández, *J. Org. Chem.*, 1996, **61**, 9097–9102; (*k*) A. Fernández-Mateos, G. Pascual Coca, J. J. Pérez Alonso, R. Rubio González, M. S. J. Simmonds and W. M. Blaney, *Tetrahedron*, 1998, **54**, 14989–14998; (*l*) A. Fernández-Mateos, G. Pascual Coca and R. Rubio González, *Tetrahedron*, 2005, **61**, 8699–9704; (*m*) S. Trudeau and J. P. Morken, *Org. Lett.*, 2005, **7**, 5465–5468; (*n*) A. Fernández-Mateos, A. I. Ramos Silvo, R. Rubio González and M. S. J. Simmonds, *Tetrahedron*, 2006, **62**, 7809–7816;

(*o*) L. A. Baker, C. M. Williams, P. V. Bernhardt and G. W. Yanik, *Tetrahedron*, 2006, **62**, 7355–7360.

5 (*a*) A. Fernández-Mateos, A. López Barba, G. Pascual Coca, R. Rubio González and C. Tapia Hernández, *Synlett*, 1995, 409–410; (*b*) A. Fernández-Mateos, A. López Barba, G. Pascual Coca, R. Rubio González and C. Tapia Hernández, *Synthesis*, 1997, 1381–1383; (*c*) A. Fernández-Mateos, E. Martín de la Nava, G. Pascual Coca, A. I. Ramos Silvo and R. Rubio González, *Synlett*, 1998, 1372–1374; (*d*) A. Fernández-Mateos, E. M. Martín de la Nava, G. Pascual Coca, R. Rubio González, A. I. Ramos Silvo and W. M. Blaney, *J. Org. Chem.*, 1998, **63**, 9440–9447; (*e*) A. Fernández-Mateos, E. M. Martín de la Nava and R. Rubio González, *Tetrahedron*, 2001, **57**, 1049–1057; (*f*) A. Fernández-Mateos, E. M. Martín de la Nava and R. Rubio González, *Synlett*, 2001, 1399–1402; (*g*) A. Fernández-Mateos, E. M. Martín de la Nava and R. Rubio González, *J. Org. Chem.*, 2001, **66**, 7632–7638; (*h*) A. Fernández-Mateos, E. M. Martín de la Nava and R. Rubio González, *Synthesis*, 2002, 1728–1734; (*i*) A. Fernández-Mateos, L. Mateos Burón, E. M. Martín de la Nava and R. Rubio González, *J. Org. Chem.*, 2003, **68**, 3585–3592; (*j*) A. Fernández-Mateos, E. M. Martín de la Nava, R. Rabanedo Clemente, R. Rubio González and M. S. J. Simmonds, *Tetrahedron*, 2005, **61**, 12264–12274; (*k*) Y. Nakai, W. H. Tepp, T. J. Dickerson, E. A. Johnson and K. D. Janda, *Bioorg. Med. Chem.*, 2009, **17**, 1152–1157; (*l*) A. Fernández-Mateos, P. Herrero Teijón, G. Pascual Coca, R. Rubio González and M. S. J. Simmonds, *Tetrahedron*, 2010, **66**, 7257–7251; (*m*) A. Fernández-Mateos, P. Herrero Teijón, R. Rabanedo Clemente, R. Rubio González and F. Sanz González, *Synlett*, 2007, 2718–2722.

6 (*a*) T. V. RajanBabu and W. A. Nugent, *J. Am. Chem. Soc.*, 1994, **116**, 986–997; (*b*) A. Fernández-Mateos, E. Martín de la Nava, G. Pascual Coca, A. I. Ramos Silva and R. Rubio González, *Org. Lett.*, 1999, **1**, 607; (*c*) A. Gansäuer and H. Bluhm, *Chem. Rev.*, 2000, **100**, 2771–2788; (*d*) A. Gansäuer and S. Narayan, *Adv. Synth. Catal.*, 2002, **344**, 465–475; (*e*) A. Gansäuer, T. Lauterbach and S. Narayan, *Angew. Chem., Int. Ed.*, 2003, **42**, 5556–5573; (*f*) J. M. Cuerva, J. Justicia, J. L. Oller-López and J. E. Oltra, *Top. Curr. Chem.*, 2006, **264**, 63–92; (*g*) A. F. Barrero, J. F. Quilez del Moral, E. M. Sánchez and J. F. Arteaga, *Eur. J. Org. Chem.*, 2006, 1627–1641; (*h*) A. Gansäuer, J. Justicia, C.-A. Fan, D. Worgull and F. Piestert, *Top. Curr. Chem.*, 2007, **279**, 25–52; (*i*) J. Justicia, L. Alvarez Cienfuegos, A. G. Campaña, D. Miguel, V. Jakoby, A. Gansäuer and J. M. Cuerva, *Chem. Soc. Rev.*, 2011, **40**, 3525–3537.

7 K. Mori, S. Aki and M. Kido, *Liebigs Ann. Chem.*, 1993, 83.

8 (*a*) T. V. RajanBabu and T. Fukunaga, *J. Am. Chem. Soc.*, 1989, **111**, 296; (*b*) T. V. RajanBabu, *Acc. Chem. Res.*, 1991, **24**, 139–145.

9 D. P. Curran, N. A. Porter and B. Giese, *Stereochemistry of Radical Reactions*, VCH, Weinheim, 1996, pp 51–63.

10 M. W. Blaney, M. S. J. Simmonds, S. V. Ley, J. C. Anderson and P. L. Toogood, *Entomol. Exp. Appl.*, 1990, **55**, 149.

