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Synthesis of limonoid CDE fragments related to limonin and nimbinim

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ABSTRACT

A practical, brief and selective synthesis of limonoid CDE fragments from a readily available starting diketone is described. The key step is a cationic electrocyclization promoted by strong acids. In general the methodology has been demonstrated for compounds with sensitive furane and thiophene substituents to obtain diverse substituted indenones. Several of the compounds obtained show significant antifeedant activity against *Spodoptera littoralis*.

1. Introduction

The limonoids are a family of natural products that have been used in folk and popular medicine for centuries.[1]

Prominent members of this family are limonin, nomilin, obacunone and gedunin, which share a common CDE ring system and have shown multiple bioactivities; among others, they have anticancer, cholesterol-lowering, antiviral and antimalarial properties.[2] Moreover limonin, nomilin and clausenolide with a C-11 oxygenated function have shown anti-HIV activity[3] (Fig. 1).

Related to them structurally are their potential biogenetic precursors: azadiradione, nimbocinol and nimbinim, with proven insect antifeedant activity.[1] Despite the significant bioactivity, little synthetic effort has been invested in these natural products.[4] Studies directed to the synthesis of related model compounds have been conduced to find simple analogues that display similar biological activities.[5] A successful example is the CDE structural fragment of the limonoid nimbinim, which has been shown to be a potent antifeedant and also to have anti-HIV properties[6] (Fig. 2).

Over the past few years we have developed a procedure aimed at the synthesis of model limonoids, based on D ring construction by cationic electrocyclization of dienones.[7] The method can be adapted by tuning the vicinal function to the synthesis of the CDE structural fragments of limonoids with an oxygenated function at the position C-11/C-12. Limonoids with this functionality are among the most active of this family of naturally occurring compounds.[1,2]

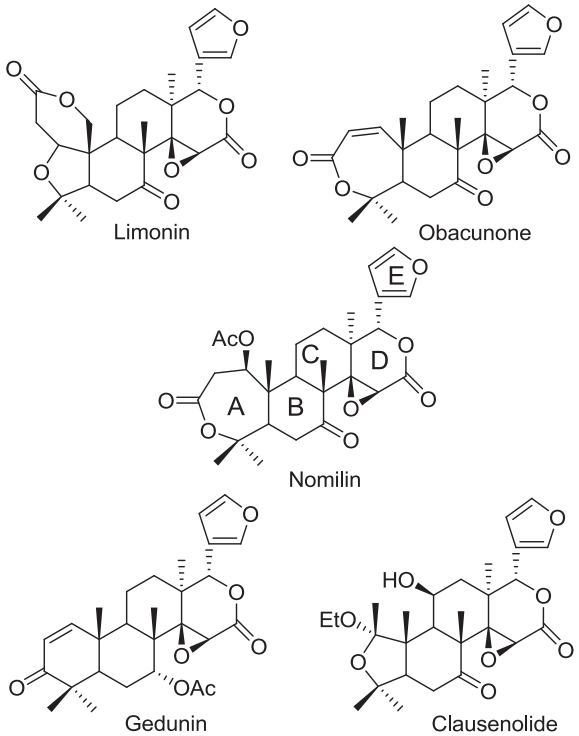

Figure 1. Structures of limonoids.

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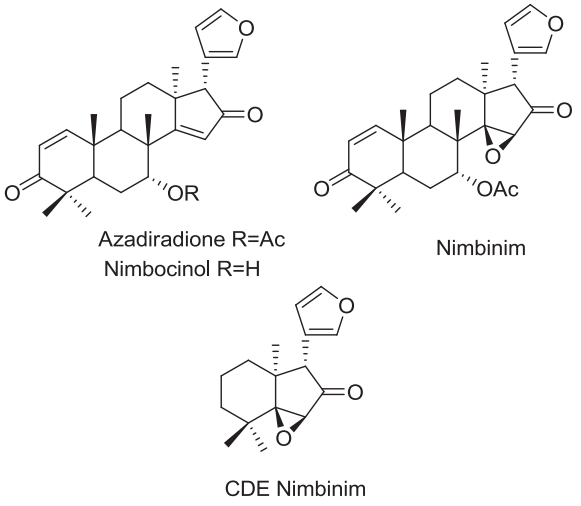
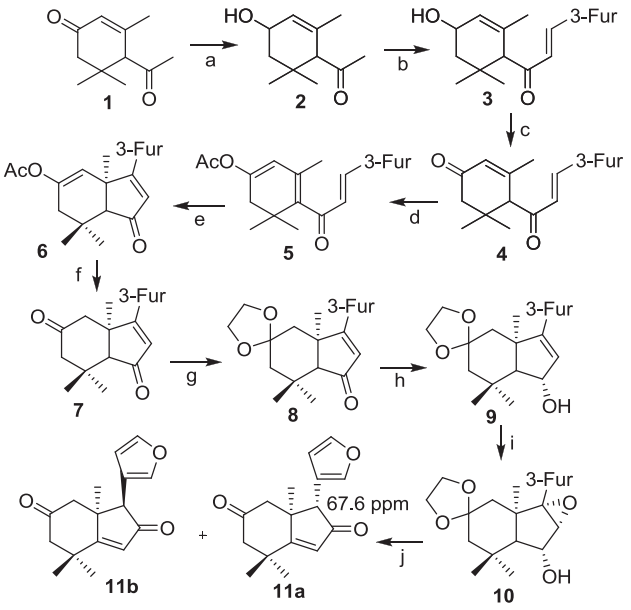


Figure 2. Structures of limonoids and CDE fragment.

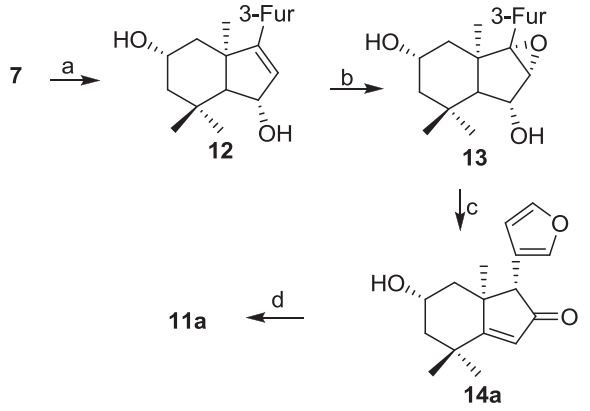
2. Results and discussion

2.1. Synthesis of furyl derivatives

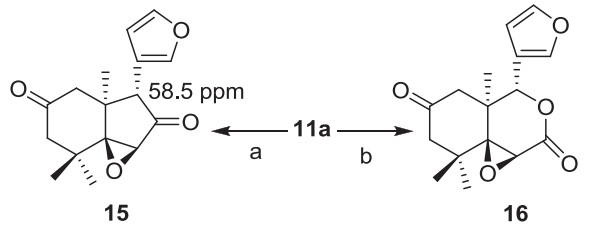
Here we describe the synthesis of CDE fragments related to the above limonoids by a route, that is, both short and stereocontrolled. The most important step of the synthesis rely on a Nazarov type reaction used by us with analogues aryl substrates[7d,e] (Schemes 1–4). Our synthesis starts with a four-step sequence to assemble all the carbons required for the construction of the limonoid fragment D ring. The readily available ketoenone **1**[7d] underwent sequential chemoselective reduction, aldolic condensation with 3-furaldehyde, oxidation and enol-acetylation to give the trienone **5** in good yield. This compound has the structure and functionalization required to provide the cationic electrocyclization, which will afford the CDE ring system.



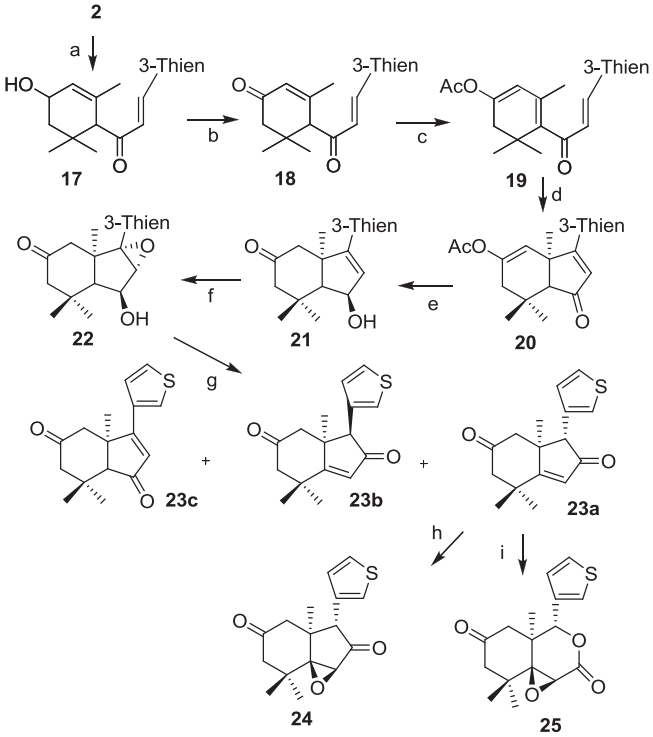
Scheme 1. Synthesis of enones **11a**/**11b** from diketone **1**.Reaction conditions: (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −40 °C; (b) Fur-CHO, NaOH, EtOH, −20 °C; (c) Jones, CH_3COCH_3, 0 °C; (d) (i) NaH, DMPU, THF, rt; (ii) Ac_2O, THF, rt; (e) $HClO_4\,10^{-2}$ M, Ac_2O, AcOEt; (f) KOH, MeOH, 0 °C; (g) $(CH_2OH)_2$, TsOH, Benzene, reflux.; (h) $LiAlH_4$, ether, 0 °C; (i) *m*-CPBA, CH_2Cl_2, −40 °C; (j) *p*TsOH, toluene, reflux.



Scheme 2. Synthesis of **11a** from diketone **7**. Reaction conditions: (a) $LiAlH_4$, THF, −78 °C; (b) *m*-CPBA, CH_2Cl_2, −40 °C; (c) *p*TsOH, toluene, reflux; (d) PCC, CH_2Cl_2, rt.



Scheme 3. Oxidation of enone **11a**. Reaction conditions: (a) UHP, NaOH, MeOH, −20 °C; (b) H_2O_2, NaOH, MeOH, 0 °C.



Scheme 4. Synthesis of CDE fragments **24** and **25** from ketone **2**. Reaction conditions: (a) Thienyl/CHO, NaOH, EtOH, −20 °C; (b) Jones, CH_3COCH_3, 0 °C; (c) (i) NaH, DMPU, THF, rt; (ii) Ac_2O, THF, rt; (d) $HClO_4\times10^{-2}$ M, Ac_2O, AcOEt; (e) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C; (f) *m*-CPBA, CH_2Cl_2, rt; (g) *p*-TsOH, toluene, reflux.; (h) UHP, NaOH, MeOH, −20 °C; (i) H_2O_2, NaOH, MeOH, 0 °C.

Although the furane ring in enone **5** is extremely sensitive to the very strong acidic conditions required to carry out the Nazarov cyclization, we will demonstrate in this paper that this type of

reaction is viable, using as reagent a dilute solution of perchloric acid in a mixture of acetic anhydride and ethyl acetate, that we have used successfully in precedent works.[7d,e,l] In these conditions, the cyclization is sufficiently fast to prevent the damage to the furane. The reaction of enol acetate **5** with a 10^{-2} M perchloric acid solution was instantaneous, giving the ketoester **6** in 60% yield. This result is somewhat lower compared with the analogue phenyl derivative, which yield the Nazarov product quantitatively.[7d] After the quantitative acetate hydrolysis of **6** we obtained the ketoenone **7**. We next turned our attention to the efficient functionalization of the D ring. First, diketone **7** was selectively protected to provide the monoketal enone **8** in 86% yield. This transformation is done to direct[7d] the reduction of the carbonyl group, stereoselectively by the *endo* face of the molecule, by coordination of the reagent ($LiAlH_4$) to the acetal oxygen. Reduction of ketone **8** with $LiAlH_4$ in ether at 0 °C afforded the unsaturated alcohol **9** quantitatively. The next step towards the limonoid functionalization of the D ring was the obtention of an epoxy-alcohol, which by rearrangement would provide the desired enone system. Thus, treatment of **9** with *m*-chloroperoxybenzoic acid gave in an *exo* stereoselective manner[7d] the epoxy-alcohol **10**. The subsequent treatment of **10** with TsOH in degassed toluene under reflux afforded a 2:1 epimeric mixture of the unsaturated diketones **11a** and **11b** in 76% overall yield.

An alternative and more stereoselective route to the fragment **11a** were devised from diketone **7**. The sequence consists of four steps: stereoselective reduction of **7** with $LiAlH_4$ in THF at −78 °C to give the diol **12**; subsequent stereoselective epoxidation to epoxydiol **13**, followed by rearrangement with *p*-TsOH to the enone **14a** and further oxidation with PCC to afford the diketone **11a** 74% overall yield.

The target compounds, the CDE fragment of nimbinim and relatives **15**, and CDE limonin fragment of **16**, were obtained selectively by oxidation of enone **11a** with urea-hydrogen peroxide complex at −20 °C, and hydrogen peroxide at 0 °C, respectively, in good yields. In both cases, a trans configuration was assigned to the oxiranic oxygen with respect to the angular methyl group, after the usual endocyclic attack, and on the basis of the upfield shift of the ^{13}C NMR signal for the homoallylic carbon bearing an axial hydrogen cis to the oxirane.

2.2. Synthesis of thienyl derivatives

The methodology employed for the synthesis of CDE limonoid fragments **15** and **16** was applied to the thienyl analogues, in which the furane is substituted by the thiophene ring.

Thus, a synthetic sequence parallel to the one described above was developed from hydroxyketone **2** to indenone **20**, with an overall yield of 42%. The electrocyclization step, **19**–**20**, took place in better yield (85%), than for the furyl derivative (60%). This result could be explained by the more robust character against strong acids of the thienyl derivative. The reduction of indenone **20** was done with sodium borohydride and cerium trichloride at 0 °C to afford, after hydrolysis, the unsaturated alcohol **21**, with the hydroxyl group trans respects the angular methyl group.[7d] The oxidation of **21** afforded only the *exo*-epoxide **22**. It is worth noting that reduction and epoxidation occurred by the same *exo* face of molecules **20** and **21**, while the reduction of related **7** and **8** took place by the *endo* face. Brief exposure of epoxide **22** to *p*-TsOH at 100 °C provided three isomeric tricyclic ketones at a 79:7:14 ratio, with ketone **23c** as the major component. The predominating diastereomer in the other two products mixture was **23a** in which the furane is cis respect to the angular methyl group. The trans isomer **23b** could be isomerized to **23a** by treatment of the crude mixture with acid or base. The thienyl derivatives of CDE nimbinim fragment **24**, and CDE limonin fragment **25** was obtained from the thienyl azadiradione fragment **23a** by the same methods as the furyl derivatives.

3. Biological activity

Larvae of the African cotton leafworm *Spodoptera littoralis* were used to assess the antifeedant activity of our racemic CDE limonoid fragments of nimbinim **15** and **24**, which show an antifeedant index of 45 and 24, respectively.[8] The furyl **15** exhibited the best antifeedant value when compared with the thienyl or phenyl fragments.[7d]

4. Experimental section

4.1. General methods

Melting points are uncorrected. ^1H 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 (^1H) 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 by using 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 ketyl and degassed before use. Dimethylformamide (DMF) was dried over CaH_2, distilled. Under reduced pressure and degassed before use. All reactions were conducted under a positive pressure of argon, utilizing standard bench-top 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). Yields reported are for chromatographically pure isolated products unless otherwise mentioned.

*4.1.1. (E)-3-(Furan-3-yl)-1-(4-hydroxy-2,6,6-trimethylcyclohex-2-enyl) prop-2-en-1-one (**3**).* To a solution of the hydroxyketone **2** (5.10 g, 28.0 mmol) and 3-furylaldehyde (2.69 g, 28.0 mmol) in ethanol (34 mL) at −20 °C was gradually added NaOH (2.24 g, 50.0 mmol) in H_2O (6 mL). The reaction was stirred vigorously for 2 h at −20 °C. The mixture was concentrated in vacuo to afford a residue, which was dissolved with water and extracted with diethyl ether. The organic layers were washed with brine, dried and filtered. The solvent was evaporated, and the residue was purified by flash chromatography using hexane/diethylether (7:3) to give a product identified as the hydroxyketone **3** as a colourless oil (5.61 g, 77%): IR, ν (liquid film) 3435, 2961, 1661, 1607 cm^{-1}; ^1H NMR (200 MHz $CDCl_3$) δ: 0.91 (s, 3H), 1.00 (s, 3H), 1.62 (m, 3H), 1.65 (s, 1H), 1.69 (s, 1H), 2.98 (br s, 1H), 4.44 (m, 1H), 5.91 (br s, 1H), 6.63 (m, 1H), 6.64 (d, J=16 Hz, 1H), 7.45 (m, 1H) 7.54 (d, J=16 Hz, 1H), 7.72 (m, 1H) ppm; ^{13}C NMR (50 MHz $CDCl_3$) δ: 23.0 (CH_3), 28.4 (CH_3), 28.7 (CH_3), 35.0 (C), 41.0 (CH_2), 62.2 (CH), 65.7 (CH), 107.7 (CH), 123.0 (C), 126.2 (CH), 128.3 (CH), 132.7 (CH), 133.1 (C), 144.5 (CH), 145.6 (CH), 201.2 (C) ppm; HRMS (ESI): MNa^+, found 283.1321. $C_{16}H_{20}O_3Na$ requires 283.1310.

4.1.2. (3aR,7aS*)-3-(Furan-3-yl)-3a,7,7-trimethyl-1-oxo-3a,6,7,7a-tetrahydro-1H-inden-5-yl acetate (**6**).* Compound **5** (2.57 g, 8.6 mmol) was dissolved in 230 mL of the 10^{-2} M $HClO_4$ reagent, and the solution was allowed to stand under argon for 18 h at room temperature. The solution was washed with saturated sodium bicarbonate solution and extracted with ethyl acetate. The combined organic layers were washed with sodium carbonate solution and brine, dried and evaporated. The remaining residue was flash chromatographed (hexane/diethylether, 7:3) to yield the acetate **6** as a colourless oil (1.54 g, 60%): IR, ν (liquid film) 3174, 2961, 1750,

1684 cm^{-1}; ^1H NMR (200 MHz $CDCl_3$) δ: 0.92 (s, 3H), 1.27 (s, 3H), 1.49 (s, 3H), 1.91 (d, J=16 Hz, 1H), 2.11 (s, 3H), 2.12 (s, 1H), 2.30 (dd, J_1=16 Hz, J_2=2 Hz, 1H), 5.70 (d, J=2 Hz, 1H), 6.08 (s, 1H), 6.58 (m, 1H), 7.49 (m, 1H), 7.80 (m, 1H) ppm; ^{13}C NMR (50 MHz $CDCl_3$) δ: 20.9 (CH_3), 23.9 (CH_3), 28.9 (CH_3), 31.1 (CH_3), 35.4 (C), 41.7 (CH_2), 48.0 (C), 63.4 (CH), 110.0 (CH), 115.2 (CH), 119.6 (C), 126.8 (CH), 142.3 (CH), 143.9 (CH), 148.3 (C), 168.8 (C), 169.8 (C), 207.4 (C) ppm; m/z (relative intensity): 300 (M^+, 5), 258 (33), 243 (100), 91 (31), 77 (10), 55 (59); HRMS (ESI): MNa^+, found 323.1268. $C_{18}H_{20}O_4Na$ requires 323.1259.

4.1.3. (3a′R,7a′S*)-3′-(Furan-3-yl)-3a′,7′,7′-trimethyl-3a′,4′,7′,7a′-tetrahydrospiro[[1,3]dioxolane-2,5′-inden]-1′(6′H)-one (**8**).* The diketone **7** (483 mg, 1.8 mmol), ethyleneglycol (223 mg, 3.6 mmol) and a catalytic amount of TsOH were heated to 80 °C in anhydrous benzene (25 mL) under argon for 12 h with a Dean and Stark apparatus. Saturated sodium bicarbonate was added, and the mixture was extracted with diethyl ether. The combined ethereal layers were washed with aqueous $NaHCO_3$ (10%) and brine, dried, filtered and evaporated in vacuo to give a clear oil. Purification by flash chromatography (hexane/diethylether, 8:2) gave the compound **8** (481 mg, 86%): IR, ν (liquid film) 3148, 1684, 1607 cm^{-1}; ^1H NMR (200 MHz $CDCl_3$) δ: 0.85 (s, 3H), 1.22 (s, 3H), 1.38 (s, 3H), 1.7–2.1 (m, 5H), 3.7–4.0 (m, 4H), 6.09 (s, 1H), 6.52 (m, 1H), 7.40 (m, 1H), 7.75 (m, 1H) ppm; ^{13}C NMR (50 MHz $CDCl_3$) δ: 23.4 (CH_3), 28.8 (CH_3), 32.4 (CH_3), 33.5 (C), 41.8 (CH_2), 45.9 (C), 48.6 (CH_2), 63.5 (CH), 63.6 (CH_2), 63.8 (CH_2), 109.0 (CH), 110.0 (C), 119.7 (C), 127.1 (CH), 142.7 (CH), 143.7 (CH), 173.1 (C), 207.9 (C) ppm; MS EI, m/z (relative intensity): 302 (M^+, 24), 287 (25), 245 (7), 174 (24), 127 (100), 113 (73), 67 (8), 55 (31); HRMS (ESI): 325.1421 (M^++Na, $C_{18}H_{22}O_4Na$), calcd 325.1416.

4.1.4. (1R,6S*,7aS*)-1-(Furan-3-yl)-6-hydroxy-4,4,7a-trimethyl-5,6,7,7a-tetrahydro-1H-inden-2(4H)-one (**14**).* To a solution of epoxide alcohol **13** (52 mg, 0.19 mmol) in degassed toluene (3 mL) was added a catalytic amount of TsOH, and the mixture was heated at reflux under argon for 30 min. Then, a saturated solution of $NaHCO_3$ was added, and the mixture was extracted with diethyl ether. The extracts were washed with H_2O and brine and dried. The solvent was evaporated under reduced pressure to afford a crude oil. Purification by flash chromatography (hexane/diethylether, 6:4) gave (1*R**,6*S**,7a*S**)-1-(furan-3-yl)-6-hydroxy-4,4,7a-trimethyl-5,6,7,7a-tetrahydro-1*H*-inden-2(4*H*)-one **14** (35 mg, 71%): IR, ν (liquid film) 3430, 1699 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ: 1.02 (s, 3H), 1.29 (s, 3H), 1.31 (s, 3H), 1.4–2.3 (m, 4H), 3.49 (s, 1H), 4.21 (m, 1H), 6.01 (m, 1H), 6.23 (m, 1H), 7.42 (m, 2H) ppm; ^{13}C NMR (100 MHz $CDCl_3$) δ: 26.0 (CH_3), 28.4 (CH_3), 31.1 (CH_3), 36.4 (C), 47.7 (CH_2), 48.6 (C), 49.3 (CH_2), 60.0 (CH), 64.1 (CH), 111.1 (CH), 118.3 (C), 125.5 (CH), 141.5 (CH), 142.8 (CH), 188.9 (C), 205.7 (C) ppm; HRMS (ESI): MNa^+, found 283.1318. $C_{16}H_{20}O_3Na$ requires 283.1310.

4.1.5. (1R,3S*,3aS*,7aS*)-3,3a-Epoxy-1-(furan-3-yl)-4,4,7a-trimethyl-4,5-dihydro-1H-indene-2,6(7H,7aH)-dione (**15**).* To a stirred solution of diketone **11a** (70 mg, 0.3 mmol) in methanol (1 mL) maintained under argon at −20 °C was added UHP (51 mg, 0.5 mmol). Then a solution of NaOH (0.2 mL, 6 M, 1.2 mmol) was added. The resulting solution was stirred for 50 min at this temperature and then poured into a solution of $NaHSO_3$ (10%). The aqueous solution was extracted with diethyl ether, dried and filtered. Removal of the solvent afforded the epoxide compound **15** (60 mg, 81%): IR, ν (liquid film) 1755, 1713 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ: 0.89 (s, 3H), 1.02 (s, 3H), 1.30 (s, 3H), 2.45 (m, 2H), 2,72 (d, J=14 Hz, 1H), 2.75 (d, J=14 Hz, 1H), 3.67 (s, 1H), 4.03 (s, 1H), 6.17 (m, 1H), 7.42 (m, 1H), 7.46 (m, 1H) ppm; ^{13}C NMR (100 MHz $CDCl_3$) δ: 21.2 (CH_3), 27.0 (CH_3), 27.2 (CH_3), 37.3 (C), 45.5 (C), 49.7 (CH_2), 50.3 (CH), 54.4 (CH_2), 58.0 (CH), 73.3 (C), 110.8 (CH), 115.4 (C), 141.7 (CH), 142.9 (CH), 207.1 (C), 207.4 (C) ppm; MS EI, m/z (relative intensity): 274 (M^+, 10), 190 (37), 176 (83), 108 (100), 91 (36), 69 (53), 55 (56); HRMS (ESI): MNa^+, found 297.1112. $C_{16}H_{18}O_4Na$ requires 297.1103.

4.1.6. (1S,4S*,4aS*,8aR*)-4,4a-Epoxy-1-(furan-3-yl)-5,5,8a-trimethyl-5,6-dihydro-1H-isochromene-3,7(8H,8aH)-dione (**16**).* To a stirred solution of diketone **11a** (26 mg, 0.1 mmol) in methanol (0.5 mL) maintained under argon at 0 °C was added H_2O_2 (0.1 mL, 30%). Then a solution of NaOH (0.2 mL, 6 M, 1.2 mmol) was added dropwise. The resulting solution was stirred for 40 min at this temperature and then poured into a solution of $NaHSO_3$ (10%). The aqueous solution was extracted with diethyl ether, dried and filtered. Removal of the solvent afforded the epoxide compound **16** (22 mg, 76%): IR, ν (liquid film) 1694, 1593 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ: 0.98 (s, 3H), 1.13 (s, 3H), 1.27 (s, 3H), 2.08 (dd, J_1=2 Hz, J_2=13 Hz, 1H), 2.33 (dd, J_1=2 Hz, J_2=14 Hz, 1H), 2.53 (d, J=13 Hz, 1H), 2.64 (d, J=14 Hz, 1H), 3.81 (s, 1H), 5.77 (s, 1H), 6.30 (m, 1H), 7.40 (m, 1H), 7.42 (m, 1H) ppm; ^{13}C NMR (100 MHz $CDCl_3$) δ: 17.2 (CH_3), 25.7 (CH_3), 27.6 (CH_3), 38.4 (C), 42.6 (C), 47.5 (CH_2), 52.8 (CH_2), 53.3 (CH), 68.5 (C), 77.6 (CH), 109.6 (CH), 119.1 (C), 141.2 (CH), 143.4 (CH), 166.7 (C), 206.5 (C) ppm; MS EI, m/z (relative intensity): 290 (M^+, 4), 233 (50), 167 (78), 137 (82), 109 (100), 67 (62), 55 (62); HRMS (ESI): MNa^+, found 313.1063. $C_{16}H_{18}O_5Na$ requires 313.1052.

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Supplementary data

Experimental procedures and copies of ^1H and ^{13}C NMR spectra for all new compounds can be found. Supplementary data associated with this article can be found in online version at. doi:10.1016/j.tet.2010.07.020. These data include MOL files and InChIKeys of the most important compounds described in this article.

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