Diastereoselective Synthesis of a Limonoid Model Related to the Insect Antifeedant Genudin

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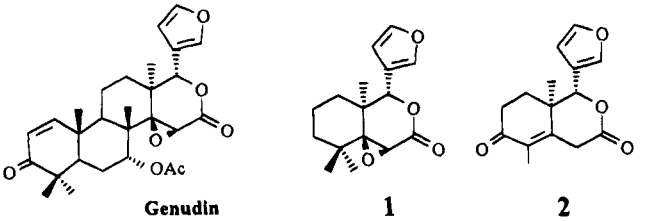
Limonoid model **1**, a substructure related to insect antifeedant genudin, was synthesized. A pinacolic rearrangement followed by a Baeyer–Villiger oxidation were the two key steps of our approach, which is totally stereocontrolled and amenable to asymmetric synthesis.

Recent years have witnessed a significant increase in the search of new powerful, selective, and biodegradable pest control agents. Of particular importance in this connection are natural substances, among which limonoids (tetranortriterpenoids) have emerged as promising insecticides owing to their marked antifeedant and growth regulating activity.[1] Despite their growing biological interest, there are few approaches to the synthesis of limonoids[2] and related degraded structures.[3] We were therefore interested in developing a new synthetic strategy toward the epoxy D-*seco* moiety commonly found in limonoids such as limonin or genudin (Chart 1) and known to be of importance for the insecticide activity.[1,4] We report herein a diastereoselective synthesis of racemic **1** which has been recently prepared by Mateos *et al.*[5]

As previously reported for our attempted synthesis of compound **2**,[6] our strategy involved (i) the construction of a [4.3.0] bicyclic skeleton, (ii) the introduction of the β-furyl substituent, (iii) a pinacolic rearrangement, and (iv) the formation of the β-lactone moiety by Baeyer–Villiger oxidation of the key β-furyl cyclopentanone **3**. The Wieland–Miescher diketone analog **6** was recognized as a convenient starting material in this strategy. It allowed indeed a ready access to the nonanolide ring of ketone **5** which in turn was a precursor of compound **3** via diol **4** (Scheme 1). One of the main advantages of this approach compared to the previously reported strategy[5] relied upon the availability of dione **6** in optically pure form,[7] thus paving the way to a subsequent asymmetric synthesis for **1** or related compounds.

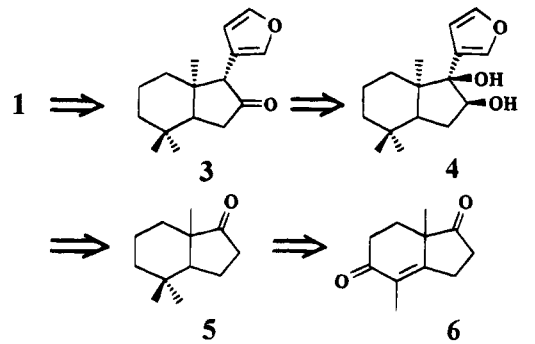
The racemic synthesis of **1** proceeded from the known, readily available tetrahydroindenedione **6**, obtained in 85% yield by a Robinson annelation between 1-chloropentan-3-one and 2-methylcyclopentan-1-3-dione in water.[8] Selective protection of the saturated ketone was achieved by transketalization between **6** and 2-ethyl-2-

Chart 1



Genudin **1** **2**

Scheme 1



3 **4**

5 **6**

methyl-1,3-dioxolane (EMD) at room temperature giving compound **7** in 85% yield. In order to obtain the *gem*-dimethyl compound **8a**, we undertook initially the direct methylation of **7** with methyl iodide in the presence of lithium in anhydrous ammonia, as previously described for octalin analogues.[9] This procedure afforded the expected product **8a** in 62% yield along with a mixture 1:1 of diastereoisomers resulting from the simple reduction of the double bond. The separation of these compounds by flash chromatography or even preparative HPLC turned out to be particularly difficult, and thus we opted for a two-step procedure. First, the catalytic hydrogenation of compound **7** over 10% Pd/C yielded ketone **9** (95%) as the major product. The latter was pure enough to be used in the next step without further purification. Subsequent alkylation in refluxing THF in the presence of 1.5 equiv of sodium hydride and methyl iodide gave rise to the expected ketone **8a** in 72% yield (70.5% for the two steps) along with its regioisomer **8b** (28%) readily separable from the latter by column chromatography (Scheme 2). In order to secure the stereochemistry of carbon C-3a, X-ray analysis of the intermediate **9** was performed.[10] The

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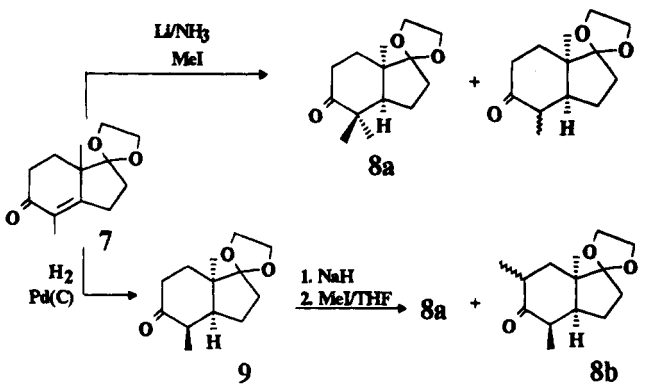
(10) The authors have deposited atomic coordinates for **9** with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ,UK.

0022-3263/94/1959-3902$04.50/0

Scheme 2



results established the cis nature of the junction of the hexahydroindene bicyclic moiety, the cis-hydrogenation proceeding on the same face as the angular methyl group.[11]

Finally, the expected ketone precursor **5** was obtained through a two-step sequence: Huan–Milong reduction of ketone **8** afforded compound **10** in 92% yield, and subsequent acid hydrolysis of the ketal group (95%) led to **5**.[12]

The required ketone was then reacted with 3-furyllithium in THF at −78 °C to give alcohol **11** as a single isomer (60–70%). Yield was enhanced by substituting the organolithium reagent for a dichlorocerate (90%). The stereochemistry of compound **11** was assigned based on previous results on analogous compounds[6] and steroids:[13] the trans relationship between the angular methyl and the furyl groups stemed from the preferential attack of the organometallic reagent from the less sterically hindered β-face of the starting ketone.

Dehydration of alcohol **11** was achieved by treatment with mesyl chloride in the presence of an excess of triethylamine to give rise directly to alkene **12** in 80% yield. The latter was then subjected to dihydroxylation with OsO_4 under catalytic conditions,[14] leading to diol **4** as a single diastereoisomer in 72% yield. Once again, the attack of the reagent was assumed to proceed from the β less hindered face of the starting molecule. Consistent with this assignment were the observed ^1H chemical shifts of the angular methyl group attached to C-7a for alcohols **11** and **4** at 0.93 and 0.85 ppm, respectively, *i.e.*, downfield and upfield relative to the *gem*-dimethyl signals. These figures reflected the different relative positions of the furan ring and the methyl group in each compound. For **4**, the cis configuration of the two substituents induced a diamagnetic shielding effect, as previously observed in similar series.[3e] This result was corroborated by NOE experiments: the existence of a NOE of the furyl protons resonances upon irradiation of the angular 7a-methyl resonance (and reciprocally) of compound **4** was in favor of a *cis* relationship between these two substituents, whereas no such effect was observed for compound **11**.

Diol **4** was next subjected to pinacolic rearrangement in the presence of *p*-toluenesulfonic acid in refluxing benzene. During the course of the reaction, we observed the formation of a mixture of two diastereoisomers whose ratios, determined by means of analytical capillary GC, evolved as heating proceeded, *i.e.*, 6:4 after a 2-h reflux, 9:1 after 4 h. Finally, after 6 h, only one compound could be isolated in 93% yield. As previously observed for compound **2**,[6] the product was shown by NMR spectroscopy to be the cis isomer **3**: irradiation on H-1 resonance resulted in NOE only of the furyl hydrogens and of H-3. We assumed that pinacolic rearrangement afforded initially the trans isomer as expected, which upon the reaction conditions slowly isomerized to the more thermodynamically stable cis compound through enolization.

With ketone **3** in hand, we were ready to investigate the key Baeyer–Villiger oxidation which had met with failure in the synthesis of **2**. We were delighted to find that upon treatment with anhydrous *m*-CPBA in the presence of sodium hydrogen carbonate in CH_2Cl_2, **3** led to the expected lactone **13** as the only detectable product in 60% yield. Compound **13** was next transformed into α-phenylselenide lactone by action of diphenyl diselenide in the presence of t-BuLi. Further oxidation with *m*-CPBA or H_2O_2 afforded directly the unsaturated lactone **14**[3e] in 80% yield (Scheme 3). Finally, epoxidation of **14** with H_2O_2–NaOH[15] led to the diastereofacially selective formation of the target compound **1** in 79% yield. The physical and NMR data of the two latter compounds are in agreement with the values reported by Mateos *et al.*[3e,5] for the same compounds. Furthermore, their stereochemistry was supported by NOE experiments. For both compounds, irradiation of the angular 8a-methyl resonance resulted in NOE of the furyl hydrogens resonances, while irradiation of H-1 resonance only induced a NOE of the furyl hydrogens. Moreover, a NOE of H-4 resonance upon irradiation of the angular 8a-methyl signal of compound **1** was observed.

The synthesis of compound **1**, a substructure unit of genudin, was achieved in 18% overall yield from bicyclic ketone **5**, featuring a pinacolic rearrangement followed by a Baeyer–Villiger oxidation as the two key steps. Our approach is relatively short, totally stereocontrolled, and amenable to asymmetric synthesis. Further applications of this strategy to the preparation of more complex limonoid model molecules is in progress in our laboratory.

Experimental Section[16]

1,1-(Ethylenedioxy)-4,7a-dimethyl-2,3,6,7-tetrahydroinden-5-one (7). Diketone **6** (5.42 g, 30 mmol) dissolved in 2-ethyl-2-methyl-1,3-dioxolane (50 mL) containing 2% ethylene glycol was stirred in the presence of *p*-toluenesulfonic acid (0.4 g, 2.1 mmol) at room temperature for 48 h. The reaction was quenched by the addition of a few drops of triethylamine. Benzene (50 mL) was then added, and the solution was washed with water (20 mL). The organic layer was dried ($MgSO_4$). Evaporation of the solvent left crude product (7.2 g) which was chromatographed on alumina (Et_2O–cyclohexane (8:2)) to give the expected compound as a crystalline solid (5.7 g, 85%): mp 48–49 °C (EtOAc–cyclohexane (35:65)); IR ($CHBr_3$) 1660 cm^{-1}; ^1H NMR δ 1.22 (s, 3 H), 1.53 (s, 3H), 1.54–2.6 (m, 8H), 3.93 (s, 4H); ^{13}C NMR δ 10.66, 20.33, 25.84, 26.65, 31.77, 33.08, 47.53, 64.89, 65.77, 117.88, 128.78, 166.96, 198.44. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.33; H, 8.16.

(3a*S,4*R**,7a*R**)-1,1-(Ethylenedioxy)-4,7a-dimethylhexahydroinden-5-one (9).** Ketone **7** (4g, 18 mmol) dissolved in anhydrous methanol (400 mL) was subjected to hydrogenation (1 atm) in the presence of 10% Pd/C (0.6 g) at room temperature.

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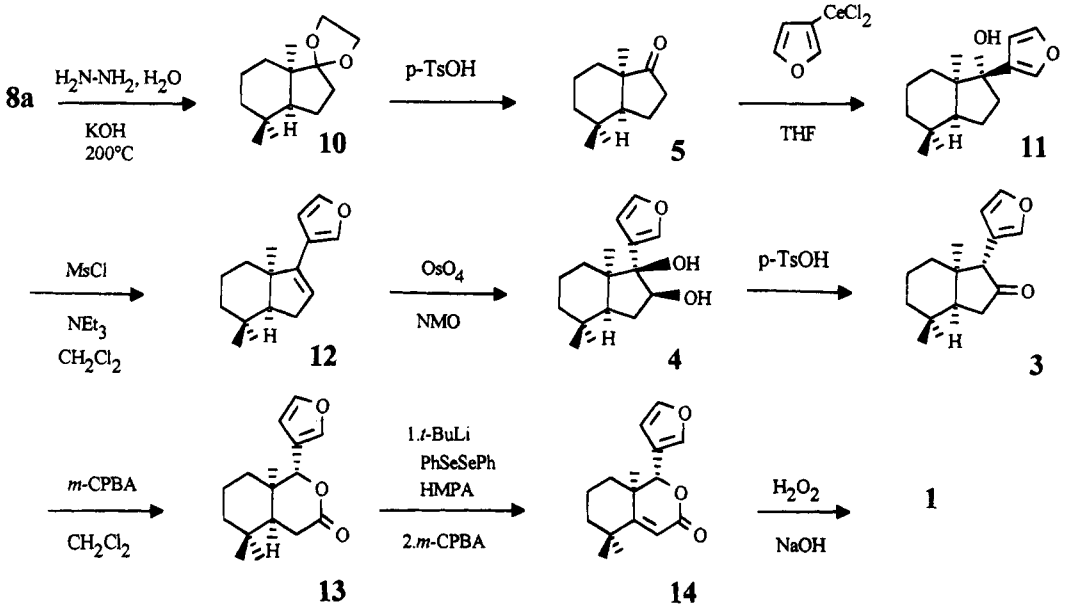
(16) The general experimental procedures are the same as those described in ref 6.

Scheme 3



After absorption of the theoretical amount of hydrogen, the mixture was filtered and the solvent was evaporated under reduced pressure to yield the expected compound **9** as a colorless oil (4.1 g, 100%), which recrystallized upon standing and was pure enough to be used in the next step: mp 24–25 °C (Et_2O–cyclohexane (1:4)); IR (neat) 1700 cm^{-1}; ^1H NMR δ 0.95 (d, J = 6 Hz, 3H), 1.07–1.26 (m, 1H), 1.20 (s, 3H), 1.74–1.92 (m, 5H), 2.26–2.3 (m, 3H), 2.70 (m, 1H), 3.92 (s, 4H); ^{13}C NMR δ 11.6, 16.9, 21.6, 31.3, 32.5, 37.6, 42.95, 45.73, 51.7, 64.4, 65.5, 119.6, 213.8. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.73; H, 8.85.

(3a*S,7a*R**)-1,1-(Ethylenedioxy)-4,4,7a-trimethylhexahydroinden-5-one (8a). A. From Enone 7.** A solution of enone **7** (1.2g, 5.4 mmol) dissolved in anhydrous THF (13 mL) was added dropwise to a solution of Li (0.12 g, 17.4 mmol) in distilled anhydrous NH_3 (76 mL) at −78 °C. After the solution was stirred for 1 h, CH_3I (1.8 mL, 28.9 mmol) was added dropwise, and the medium soon turned from dark blue to white. After 3 h at −78 °C, the dry ice–acetone bath was removed, and stirring was continued overnight. Then water (15 mL) was added and the mixture extracted with Et_2O. The combined organic extracts were washed twice with water (50 mL) and brine (20 mL) and then dried and evaporated to give a crude yellow oil (1.1 g). Purification by chromatography on silica gel (cyclohexane–Et_2O (70:30)) yielded the expected ketone **8a** (0.8 g, 62%) along with a mixture of reduced compounds. For compound **8a**: mp 46–48 °C (Et_2O–cyclohexane (1:4)); IR ($CHBr_3$) 1700 cm^{-1}; ^1H NMR δ 0.92 (s, 3H), 1.16 (s, 3H), 1.2 (s, 3H), 1.22–2.64 (m, 9H), 3.86 (s, 4H); ^{13}C NMR δ 21.06, 23.14, 24.23, 27.23, 30.55, 31.76, 34.6, 44.9, 47.15, 55.67, 64.05, 65.3, 119.82, 217.07. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.52; H, 9.28.

B. From Ketone 9. A solution of ketone **9** (3g, 13.4 mmol) dissolved in dry THF (30 mL) was added dropwise to a suspension of NaH (1g at 50%, 20 mmol) in refluxing THF (10 mL). The reaction mixture was refluxed for 10 h, and MeI (1.25 mL, 20 mmol) was then added dropwise. The reflux was continued for one night, and then the reaction mixture was cooled to room temperature and carefully hydrolyzed. Extraction with Et_2O followed by drying and evaporation of the solvent left a crude yellow oil. Purification by flash chromatography on silica gel (cyclohexane–EtOAc (85:15)) allowed the separation of the expected ketone **8a** (2.3g, 72%) and its regioisomer **8b** (0.9 g, 28%). For compound **8b**: ^1H NMR δ 0.97 (s, 3H), 1.01 (d, J = 6 Hz, 3H), 1.31 (d, J = 6 Hz, 3H), 1.22–2.22 (m, 6H), 3.93 (s, 4H); ^{13}C NMR δ 14.91, 20.11, 23.58, 23.7, 24.61, 27.66, 31.37, 34.32, 40.39, 56.37, 63.99, 65.47, 120.02, 218. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.55; H, 9.33.

(3a*S,7a*R**)-1,1-(Ethylenedioxy)-4,4,7a-trimethyloctahydroinden-1-one (10).** A mixture of ketone **8a** (1.3 g, 5.46 mmol), KOH (2.82 g, 43.2 mmol), and hydrazine hydrate (3.1 mL, 55 mmol) in diethylene glycol (31 mL) was heated at 210 °C for 2 h. Excess hydrazine was removed by distillation, and the reaction mixture was heated for an additionnal 12 h. After dilution by water (100 mL), extraction with ether, and drying, the solvent was evaporated under reduced pressure to give a colorless oil which was filtered on silica gel (EtOAc–cyclohexane (1:5)) to give pure compound **10** (1.16 g, 92%): ^1H NMR δ 0.80 (s, 3H), 0.98 (s, 3H), 1.1 (s, 3H), 1.15–1.9 (m, 11H), 3.9 (s, 4H); ^{13}C NMR δ 18.68, 19.55, 21.99, 28.52, 29.16, 29.80, 30.51, 31.55, 33.72, 45.63, 51.61, 65.46, 63.83, 81.68. Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.23; H, 10.7.

(3a*S,7a*R**)-4,4,7a-Trimethyloctahydroinden-1-one (5).** Ketal **10** (1.4 g, 6.3 mmol) dissolved in acetone (100 mL) was refluxed in the presence of *p*-toluenesulfonic acid (0.1 g, 0.52 mmol) for 1.5 h. The solvent was evaporated under reduced pressure, and the resulting residue was dissolved in EtOAc (50 mL). The organic layer was successively washed with 10% aqueous $NaHCO_3$ solution (50 mL) and water (50 mL) and then dried and evaporated to give a crude yellow oil which was chromatographed on silica gel (cyclohexane–EtOAc (5:3)) to give the expected ketone[12] (1.1 g, 95%): ^1H NMR δ 0.83 (s, 3H), 1 (s, 3H), 1.15 (s, 3H), 1.17–2.48 (m, 11 H); ^{13}C NMR δ 17.99, 21.1, 22.52, 29.3, 28.46, 28.99, 29.98, 31.28, 34.79, 48.18, 53.04, 219.9. Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.11; H, 11.30.

(1*R,3a*S**,7a*R**)-1-(3-Furyl)-4,4,7a-trimethyloctahydroinden-1-ol (11).** To $CeCl_3 \cdot 7H_2O$ (6 g, 16 mmol) previously dried overnight at 140 °C under high vacuum (1 mmHg) was added anhydrous THF (40 mL). The suspension was stirred at room temperature under nitrogen for 24 h. Meanwhile, a solution of 3-bromofuran (1.45 mL, 16 mmol) in THF (15 mL) was treated dropwise with nBuLi (2.4 M in hexane, 6.7 mL, 16 mmol) at −78 °C. After the reaction mixture was stirred for 1 h at this temperature, the $CeCl_3$–THF slurry was added via cannula and the mixture was stirred for an additionnal 30 min. A solution of ketone **5** (2.2 g, 12 mmol) in dry THF (10 mL) was then added dropwise. The mixture was stirred for 3 h at −78 °C and then treated with a saturated NH_4Cl aqueous solution, filtered through a Celite pad, and extracted with Et_2O. The combined organic layers were washed with brine and concentrated. The resulting brown oil was chromatographed on silica gel (cyclohexane–EtOAc (85:15)) to yield the expected alcohol **11** as an orange oil (2.7 g, 90%): IR (neat) 3240 cm^{-1}; ^1H NMR δ 0.83 (s, 6H), 0.93 (s, 3H), 1.1–1.8 (m, 10H), 2–2.1 (m, 2H), 6.37 (m, 1H), 7.29 (m, 1H), 7.34 (m, 1H); ^{13}C NMR δ 19.14, 22.06, 23.17, 28.40, 28.89, 30.74, 32.22, 33.72, 37.36, 45.91, 51.05, 83.90, 110.27, 132.13, 138.91, 142.07. Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74 . Found: C, 77.61; H, 9.57.

(3a*S,7a*R**)-3-(4,4,7a-Trimethyl-3a,4,5,6,7,7a-hexahydro-3*H*-inden-1-yl)furan (12).** To a solution of alcohol **11** (5 g, 20 mmol) and triethylamine (10 mL, 71.7 mmol) in anhydrous CH_2Cl_2 (100 mL) at 0 °C was added dropwise mesyl chloride (4.25 mL, 54.9 mmol). The reaction mixture was stirred at 0 °C for 2 h and then allowed to warm to room temperature. The solution was diluted with additional CH_2Cl_2 (50 mL) before washing with a saturated $NaHCO_3$ aqueous solution (100 mL) and water (100 mL), drying, and evaporation under reduced pressure. The resulting residue was chromatographed on silica gel (EtOAc–cyclohexane (1:1)) to yield the expected alkene as an orange oil (3.7 g, 80%): ^{1}H NMR δ 0.89 (s, 3H), 1.07 (s, 3H), 1.28 (s, 3H), 1.28–1.83 (m, 7H), 2.26 (ddd, J = 2.4, 4.9, and 12.4 Hz, 2H), 5.72 (t, J = 2.4 Hz, 1H), 6.43 (m, 1H), 7.36 (m, 1H), 7.39 (m, 1H); ^{13}C NMR δ 18.50, 25.23, 29.68, 31.19, 32.08, 33.49, 35.34, 35.40, 47.07, 56.76, 110.33, 124.51, 138.03, 142.41, 146.06, 121.5. Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.37; H, 9.60.

(1S*,2S*, 3a*S,7a*R**)-1-(3-Furyl)-4,4,7a-trimethyloctahydroinden-1,2-diol (4).** To an ice-cooled solution of 4-methylmorpholine *N*-oxide (0.75 g, 4.35 mmol) in water (2 mL) and acetone (0.85 mL) was added a solution of OsO_4 (1% in *t*-BuOH, 0.33 mL, 1.3 × 10^{-5} mol). Alkene **12** (1 g, 4.35 mmol) was then added, and the reaction mixture was stirred for 12 h. A 10% aqueous solution of $NaHSO_3$ (5 mL) was then added, and the organic layer was washed with water (5 mL). Evaporation of the solvent followed by chromatography on silica gel (cyclohexane–EtOAc (75:25)) yielded a colorless solid which was identified as the diol monohydrate **4** (0.88 g, 72%): mp 91–92 °C (EtOAc–hexane (1:1)); ^{1}H NMR δ 0.85 (s, 3H), 1.03 (s, 3H), 1.07 (s, 3H), 0.94–1.62 (m, 7H), 1.6 (s, 2H, H_2O), 1.87 (m, 1H), 2.14–2.17 (m, 1H), 2.18 (s, 1H), 2.92 (s, 1H), 4.52 (m, 1H), 6.35 (m, 1H), 7.41 (m, 1H), 7.47 (m, 1H); ^{13}C NMR δ 18.50, 19.74, 28.84, 30.80, 31.08, 31.97, 33.50, 33.66, 47.45, 51.42, 75.89, 84.16, 110.12, 127.01, 140.95, 142.58. Anal. Calcd for $C_{16}H_{24}O_3{\cdot}H_2O$: C, 68.05; H, 9.28. Found: C, 68.26; H, 9.11.

(1R*,3a*S,7a*R**)-1-(3-Furyl)-4,4,7a-trimethyloctahydroinden-2-one (3).** A solution of diol monohydrate **4** (0.8 g, 2.8 mmol) in benzene (40 mL) was refluxed in the presence of *p*-toluenesulfonic acid (0.05 g, 2.6 × 10^{-4} mol) for 6 h. The water was azeotropically removed using a Dean–Stark trap. The cooled solution was then washed with a saturated aqueous solution of $NaHSO_3$ (10 mL) and water (10 mL), dried, and evaporated to give an orange residue which was chromatographed on silica gel (cyclohexane–EtOAc (75:25)) to yield the expected cyclopentanone **3** as a pale orange solid (0.65 g, 93%): mp 78–79 °C (hexane); IR ($CHBr_3$) 1740 cm^{-1}; ^{1}H NMR δ 0.89 (s, 3H), 1.17 (s, 3H), 1.25 (s, 3H), 0.9–1.6 (m, 4H), 1.85 (dd, J = 6 and 8 Hz, 2H), 2.2–2.53 (m, 3H), 3.19 (s, 1H), 6.2 (m, 1H), 7.27 (m, 1H), 7.40 (m, 1H); ^{13}C NMR δ 18.28, 25.45, 28.79, 29.25, 31.34, 32.25, 33.39, 39.43, 42.83, 50.86, 62.02, 111.55, 117.07, 141.59, 142.50, 216.29. Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.03; H, 9.10.

(1R*,4a*S,8a*R**)-1-(3-Furyl)-5,5,8a-trimethyloctahydroisochromen-3-one (13).** To a suspension of ketone **3** (0.57 g, 2.31 mmol) and $NaHCO_3$ (0.2 g, 2.38 mmol) in CH_2Cl_2 (10 mL) was added a solution of *m*-CPBA (0.6 g, 3.47 mmol) in a mixture of anhydrous CH_2Cl_2 and CH_2Cl–CH_2Cl (5 mL). The reaction mixture was stirred at room temperature in the dark for 5 h and then diluted with Et_2O (15 mL) and washed successively three times with a 10% aqueous $NaHSO_3$ solution, water, and brine. The organic layer was dried and evaporated, and the resulting residue was chromatographed on silica gel ($CHCl_3$) to yield the expected lactone **13** as a yellow solid (0.36 g, 60%): mp 112–113 °C (hexane–EtOAc (7:3)); IR ($CHBr_3$) 1735 cm^{-1}; ^{1}H NMR δ 0.93 (s, 3H), 1.07 (s, 3H), 1.10 (s, 3H), 2.7 (dd, J = 6.4 and 8.8 Hz, 2H), 1.11–1.8 (m, 7H), 4.97 (s, 1H), 6.4 (m, 1H), 7.38 (m, 1H), 7.39 (m, 1H); ^{13}C NMR δ 16.63, 23.24, 25.54, 27.83, 30.39, 31.24, 33.27, 34.53, 37.47, 47.05, 81.97, 110.58, 121.00, 141.28, 142.74, 172.92. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45 . Found: C, 73.48; H, 8.69.

(1R*,8a*R)-1-(3-Furyl)-5,5,8a-trimethyl-1,5,6,7,8,8a-hexahydro-3*H*-2-benzopyran-3-one (14) .** To a cooled (−78 °C) solution of lactone **13** (100 mg, 0.38 mmol) in anhydrous THF (0.75 mL) was added a 1.67 M solution of *t*-BuLi in hexane (0.23 mL, 0.38 mmol). The reaction mixture was strirred for 1 h, and then a solution of diphenyl diselenide (119 mg, 0.38 mmol) in THF (0.75 mL) containing HMPA (73 μL, 0.4 mmol) was added dropwise. After disappearance of the starting material, the temperature was raised to −40 °C and the mixture was stirred for another 45 min. The reaction was warmed to 0 °C and then quenched by addition of a 0.1 N HCl solution (0.3 mL). Extraction with Et_2O, followed by successive washing of the organic layer with water and brine, gave, after evaporation of the solvent, a residue which was dissolved in CH_2Cl_2 (1.5 mL). To this ice-cooled solution was then added a solution of anhydrous *m*-CPBA (0.86 g, 0.5 mmol) in CH_2Cl_2. The reaction mixture was subsequently stirred at 0 °C for 4 h before addition of $NaHCO_3$ (20 mg). The organic layer was washed with water and the aqueous layer extracted with Et_2O. The combined organic layers were evaporated to give an oily yellow residue wich was chromatographed on silica gel (cyclohexane–EtOAc (80:20)) to yield compound **14** as a colorless solid[3e] (78 mg, 80%): mp 139–140 °C (hexane); ^{1}H NMR δ 1.11 (s, 3H), 1.24 (s, 3H), 1.28 (s, 3H), 1.34–2.15 (m, 6H), 4.97 (s, 1H), 5.96 (s, 1H), 6.42 (m, 1H), 7.41 (m, 1H), 7.46 (m, 1H); ^{13}C NMR δ 16.71, 18.52, 29.97, 30.15, 34.51, 35.80, 38.42, 39.03, 82.51, 110.22, 113.33, 119.98, 141.18, 142.65, 166.02, 175.22. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74 . Found: C, 73.80; H, 7.70.

(1R*,4S*,4a*S,8a*S**)-1-(3-Furyl)-5,5,8a-trimethyl-4,4a-epoxyoctahydro-2-benzopyran-3-one (1).** To an ice-cooled solution of lactone **14** (250 mg, 0.96 mmol) in MeOH (10 mL) was added a 35% solution of H_2O_2 (1.42 mL, 14.6 mmol). A 6 N solution of NaOH (0.5 mL) was then added dropwise over 10 min, and the temperature was allowed to rise to 20 °C. Stirring was continued for 2 days, until GC indicated the total conversion of the starting material. The reaction mixture was poured into water, and the aqueous layer was extracted with $CHCl_3$ (75 mL) and dried over $MgSO_4$. Solvent was removed under reduced pressure to give a yellow oil. Chromatography on silica gel (hexane–EtOAc (6:4)) gave the expected product **1**[5]as a yellow solid (210 mg, 79%): mp 121–122 °C (hexane); ^{1}H NMR δ 0.84 (s, 3H), 1.08 (s, 3H), 1.18 (s, 3H), 1.27–1.98 (m, 6H), 3.68 (s, 1H), 5.63 (s, 1H), 6.35 (m, 1H), 7.39 (m, 1H), 7.40 (m, 1H); ^{13}C NMR δ 16.10, 17.70, 25.90, 26.30, 33.10, 34.70, 38.20, 39.01, 52.93, 69.80, 79.10, 110.01, 120.50, 141.50, 142.27, 168.12. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.49; H, 7.18.

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