



Enantioselective Synthesis of the Tricyclic Furan Moiety of Azadirachtin, a Potent Insect Antifeedant.

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Abstract: A synthesis of the enantiomerically pure right-hand part (2) of an insect antifeedant, azadirachtin, is described. Reduction with baker's yeast was demonstrated to be efficient for kinetic resolution of racemic diketone (4) to give 3 of ~75% e.e., from which was derived 2 in 11 steps.
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Azadirachtin (1) is a *C-seco*-limonoid which possesses potent antifeedant and growth inhibitory activities.¹ Its complicated structure as well as its activities fascinates synthetic chemists, and up to the present, some syntheses of both highly oxygenated decalin skeletons and the tricyclic dihydrofuran portions toward the total synthesis of 1 were achieved.² Herein we would like to report a enantioselective synthesis of the right-hand moiety (2) of azadirachtin (1).

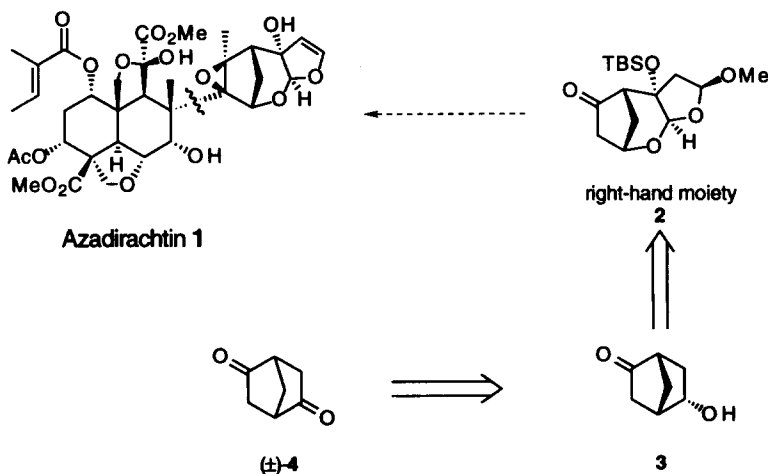


Fig. 1. Structure of Azadirachtin (1) and Synthetic Strategy for the Right-hand Moiety (2).

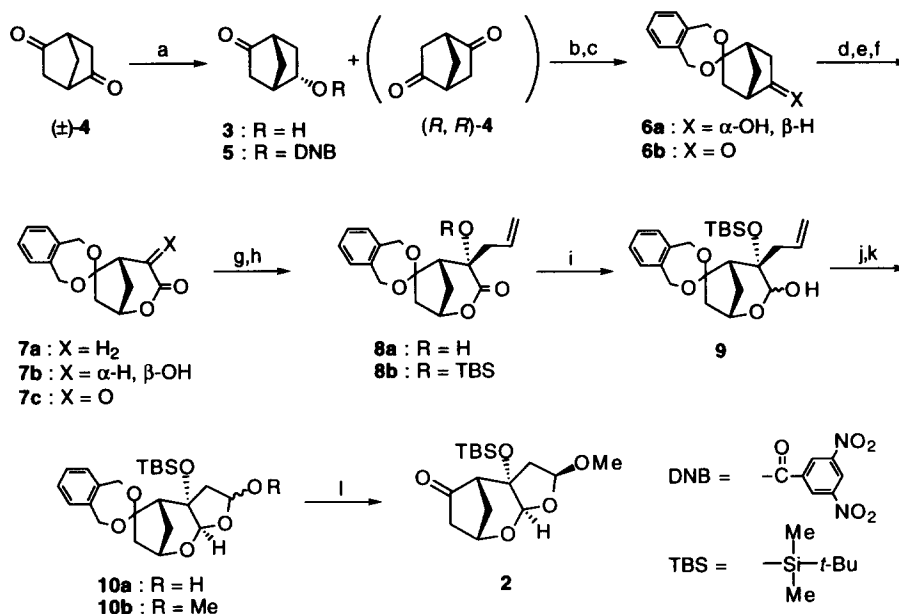
Our synthetic strategy is shown in Fig. 1. We planned to prepare the chiral starting material (**3**) by kinetic resolution of 1,4-diketone [(±)-**4**]³ with baker's yeast.⁴ We have already investigated the yeast reductions of bicyclic 1,3-diketones and shown their utility in natural product syntheses.⁵ In all of those cases, reduction took place predominantly from the less hindered *exo*-face to afford (*S*)-*endo*-alcohols without exception. According to this rule, (*S,S*)- and (*R,R*)-**4** are matched and mismatched substrate, respectively, because (*S,S*)-**4** can be reduced to (*S*)-*endo*-alcohol, while the reduction product of (*R,R*)-**4** should be (*S*)-*exo*- or (*R*)-*endo*-alcohol. The transformation of **3** to **2** was thought to be possible mainly according to the method reported by Ley *et al.*⁶

First, the kinetic resolution by yeast reduction was investigated (Fig. 2). For a large-scale preparation of **3**, we adopted the simple and convenient procedure reported by Smallridge *et al.*⁷ with minor modification. Reduction was performed in hexane with yeast and wet Celite, the latter of which heightened the efficiency of stirring and filtration. In addition to that, reduction product (**3**) and unreacted (*R,R*)-**4** can easily be separated by decantation, since the most part of **3** was absorbed in yeast, while unreacted (*R,R*)-**4** existed as a hexane solution. After stirring for 20 h at room temperature, the alcohol **3** was obtained as a solid in 21–28% [42–56% based on (*S,S*)-**4**] yield after SiO₂ purification. The enantiomeric purity was estimated to be 70–82% e.e. by HPLC analysis of the corresponding 3,5-dinitrobenzoate (**5**) using a chiral stationary phase. The optical purity could be enhanced by recrystallizing **5**, on the other hand, recrystallization of **3** decreased its e.e. The absolute configuration of **3** was confirmed by comparing the sign of the specific rotation of the reoxidized (*S,S*)-**4** with that reported in ref. 4c (see Experimental).

Since it was found that the optical purity could be enhanced more easily by recrystallizing advanced intermediates (e.g. **7a**), we started from **3** of 73% e.e. The carbonyl group of **3** was protected as *o*-xylidenedioxy acetal to give **6a** in 91% yield. Owing to an advantage of the highly crystalline nature of *o*-xylidenedioxy acetal,⁸ all the intermediates except **10a** and **10b** were crystalline. Swern oxidation⁹ of **6a** to **6b** (82% yield) was followed by Baeyer-Villiger oxidation (*m*CPBA, NaHCO₃ / CH₂Cl₂) to afford a lactone (**7a**, in 89% yield, along with 5.9% of the regioisomer). At this stage, the enantiomeric purity was enhanced to 97% e.e. by recrystallization (5 times, 57%). In contrast, recrystallization of the former intermediates (**6a** and **6b**) decreased their e.e.

Hydroxylation at the α-position of the lactone carbonyl was performed by the reaction between lithium enolate of **7a** and MoO₅·py·HMPA,¹⁰ to give **7b** as a single isomer in 86% yield. Although the use of Davis reagent (2-benzenesulfonyl-3-phenyloxaziridine)¹¹ as an alternative oxidant gave better yield of **7b** (94%), chromatographic removal of the impurities arising from Davis reagent was difficult, and we adopted MoO₅·py·HMPA for a large-scale preparation of **7b**.

The compound **7b** was oxidized to an α-ketolactone (**7c**) in 81% yield, which was then treated with 1.1 eq. allyllithium at –78°C–room temperature to give tertiary alcohol (**8a**) as a single isomer (79% yield). Protection of the hindered OH group as a TBS ether was accomplished by heating **8a** with TBSOTf and 2,6-lutidine in CH₂Cl₂ for 2 days and **8b** was obtained in 93% yield after recrystallization [m.p. 148–149°C, [α]_D²³ +170 (CHCl₃)]. By recrystallizing all the intermediates (**7b–8a**) in each steps, the optical purities were enhanced further and enantiomeric excess of **8b** determined by HPLC was *ca.* 100% (see Experimental).



a) baker's yeast, Celite, H_2O / hexane, rt, 15–20 h, 21–28% (73–78% ee); b) 1,2-benzenedimethanol, TsOH / benzene, Δ ($-\text{H}_2\text{O}$), 91%; c) Swern oxid'n, 94%; d) (i) *m*CPBA, NaHCO_3 / CH_2Cl_2 , $0^\circ\text{C} \rightarrow \text{r.t.}$; (ii) recryst'n (5 times), 57% (97% ee); e) LDA / THF, $\text{MoO}_5 \cdot \text{py} \cdot \text{HMPA}$, $-78^\circ\text{C} \rightarrow -20^\circ\text{C}$, 86%; f) Swern oxid'n, 81%; g) allyllithium / THF, -78°C , 79%; h) (i) TBSOTf, 2,6-lutidine / CH_2Cl_2 , Δ , 2 days; (ii) recryst'n, 93% (~100% ee); i) DIBAL, TMSCl / toluene, -78°C , 12 h, 84%; j) O_3 , NaHCO_3 / CH_2Cl_2 , -78°C ; Ph_3P , $-78^\circ\text{C} \rightarrow \text{r.t.}$, quant.; k) MeI, Ag_2O / MeCN, 30 h, 93%; l) H_2 , Pd-C / EtOAc, 30 min, 91%.

Fig. 2. Synthesis of 2

Unexpectedly, troublesome was the next half-reduction of **8b** to a lactol (**9**). Reduction of **8b** under usual conditions (1 eq. of DIBAL in CH_2Cl_2 or toluene at -78°C or higher temperature) mainly gave overreduced diol and unreacted **8b**, and desired **9** was obtained only in low yield (30–45%). The slow addition of DIBAL, which was reported to be effective for reducing the similar substrate,⁶ also gave poor result. After several attempts, we found TMSCl as an additive worked quite effectively to stop the reduction at the stage of lactol. Actually, treatment of **8b** with 2 eq. of DIBAL in the presence of TMSCl (2.5 eq.) at -78°C for 12 h gave **9** in 84% yield.¹²

Ozonolysis of **9** and subsequent treatment with Ph_3P gave **10a** in a quantitative yield, whose OH group was then protected as methyl ether. Acid catalyzed acetalization [HC(OMe)_3 , PPTS in CH_2Cl_2] was first investigated and **10b** was obtained in 63% yield as an about 1:1 mixture of diastereomers. On the other hand, when **10b** was treated with MeI and Ag_2O in acetonitrile, β -MeO isomer was obtained as a single isomer in higher yield (93%). The stereochemistry of methyl acetal was assigned on the analogy of the reported data.⁶ Selective deprotection of the *o*-xylidenedioxy acetal of **10b** was accomplished successfully by hydrogenolysis (H_2 , Pd-C in EtOAc) to give the target compound (**2**), the key intermediate for azadirachtin synthesis, in 91% yield as

crystals; m.p. 103–104°C, $[\alpha]_D^{24} +86.4$ (CHCl_3), [lit.⁶: m.p. 70–72°C (1:3 diastereomeric mixture)]. Its IR and ^1H NMR spectra showed good accordance with those reported by Ley *et al.*⁶

The compound **2** in hand, we synthesized some analogues for insect antifeeding assay. The carbonyl group of **2** was first reduced and dehydrated to afford an olefin (**11**), which was converted to **12**, **13** and **14** according to the reported procedure⁶ as shown in Fig. 3.

Bioassay of **12–14** were carried out by Dr. A. J. Mordue (University of Aberdeen, U.K.) by employing the fifth-instar males of the desert locust (*Schistocerca gregaria*), which is known to be sensitive to the structural changes in the azadirachtin-type molecules. The azadirachtin results showed the standard effects under the assay conditions with 100% antifeeding at 0.04 ppm. The samples **13** and **14** began to show some antifeeding at 0.4 ppm (weaker than the activity of azadirachtin at 0.004 ppm), and were no different from each other. The sample **12** showed no antifeedant activity at the concentration tested. Accordingly, the compounds **12–14** were less than 1/100 as active as azadirachtin itself.^{13–15}

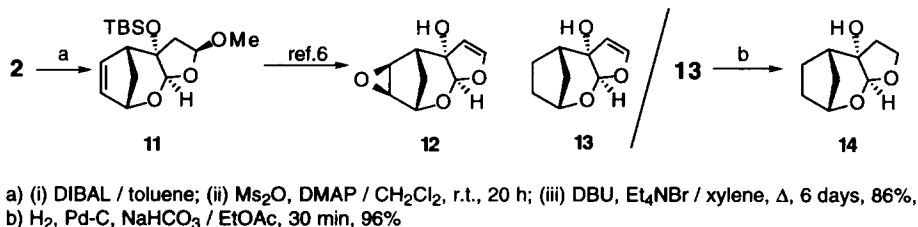


Fig. 3. Synthesis of Samples for Bioassay (**12–14**)

In conclusion, we synthesized optically pure **2**, a key intermediate of our synthetic study toward azadirachtin, in 5.0% overall yield in 12 steps from (\pm)-**4**. The construction of the decalin moiety incorporating **2** is now in progress.

EXPERIMENTAL

Infra-red spectra were recorded on a Jasco IRA-102 or FT/IR-230 spectrometer. ^1H NMR spectra were recorded in CDCl_3 on a Jeol JNM EX-90, Bruker AC 300 or Jeol JNM GSX-500 nmr spectrometer, using TMS (0 ppm) or CHCl_3 (7.26 ppm) as an internal reference. Mass spectra were recorded using a Hitachi M-80 mass spectrometer. Optical rotations were measured using a Jasco DIP-371 polarimeter. HPLC analyses were performed using Shodex DS-4 instruments, detected at 254 nm. Column chromatography was performed on Merck Kieselgel 60, Art.-Nr. 7734. All melting points are uncorrected values.

(1S, 4S, 5S)-5-Hydroxybicyclo[2.2.1]heptan-2-one (3). Bicyclo[2.2.1]heptane-2,5-dione³ [(\pm)-**4**] (36.6 g, 295 mmol) was added to a suspension of dry baker's yeast (180 g, Oriental Yeast Co., Ltd.), Celite (360 g) and water (300 mL) in hexane (3 L). The mixture was mechanically stirred at room temperature in air. After

20 h the solvent was removed by decantation, and the viscous mass was suspended in acetone (1 L \times 3) and filtered through a pad of Celite. Then the combined filtrates were concentrated *in vacuo*. The residue was diluted with EtOAc, dried over MgSO_4 , and concentrated *in vacuo*. The residue was chromatographed over silica gel (150 g; hexane/EtOAc, 2.5:1) to yield 10.6 g (28 %) of **3** as a colorless solid. Since it was impossible to remove the impurities originated from baker's yeast by chromatography and recrystallization was not effective, the analytical data were not measured at this stage.

(1'S,2'S,4'S)-(5'-Oxobicyclo[2.2.1]hept)-2'-yl 3,5-Dinitrobenzoate (5). To a stirred and ice-cooled solution of **3** (400 mg, 3.17 mmol) in CH_2Cl_2 - pyridine (1:1, 4 mL) was added 3,5-dinitrobenzoyl chloride (1.10 g, 4.76 mmol). Then the mixture was stirred under argon and allowed to warm to room temperature overnight. The mixture was diluted with water and extracted with EtOAc. The extracts were washed with dil HCl, saturated NaHCO_3 and brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 and filtered through a pad of silica gel. HPLC analysis was carried out at this stage and its ee value was estimated to be 73 %. This solution was concentrated *in vacuo* to give the crude product as a colorless solid which was recrystallized from 2-propanol-EtOH (1:1) to yield 442 mg of **5** (44 %), m.p. 156°C (as needles). Its ee value was estimated to be 93 % by HPLC analysis; HPLC: Daicel Chiralcel OB ϕ 4.6 mm \times 25 cm, eluent: hexane/EtOH 1:1, 38°C, flow rate: 0.5 mL/min, t_R : 31.7 min for (*S,S,S*)-isomer and 38.0 min for (*R,R,R*)-isomer. $[\alpha]_D^{22} = -29.3$ ($c = 1.00$, CHCl_3). – IR (Nujol): $\nu = 3075\text{ cm}^{-1}$ (m, =C–H), 1748 (s, C=O), 1722 (s, C=O), 1600 (m, C=C), 1546 (s, NO_2), 1346 (s, NO_2), 1168 (s, C–O), 724 (s). – ^1H NMR (90 MHz): $\delta = 1.45\text{--}2.85$ (m, 7H), 3.14 (m, 1H, 3'-H), 5.51 (m, 1H, 2'-H), 9.09 (d, $J = 1.8\text{ Hz}$, 2H, Ar- H_2), 9.23 (t, $J = 1.8\text{ Hz}$, 1H, Ar- H_1). – Anal. calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_7$ (320.3): C 52.51, H 3.78, N 8.75; found C 52.35, H 3.86, N 8.72.

(1S,4S,5S)-5-Hydroxybicyclo[2.2.1]heptan-2-one (3). To a stirred solution of **5** (420 mg, 1.35 mmol) in MeOH (5 mL) was added K_2CO_3 (9.3 mg, 0.068 mmol) at room temperature. After 5 min, the reaction mixture was concentrated *in vacuo* and the residue was chromatographed over silica gel (10 g; eluent: CH_2Cl_2 then hexane/EtOAc, 1:1) to yield 147 mg of **3** (86 %) as a solid, m.p. 103–105°C. This compound is so hygroscopic that satisfactory elemental analytical data could not be obtained; $[\alpha]_D^{22} = -23.6$ ($c = 1.05$, CHCl_3). – IR (Nujol): $\nu = 3420\text{ cm}^{-1}$ (s, OH), 1740 (s, C=O), 1044 (s, C–O). – ^1H NMR (90 MHz): $\delta = 1.27$ (dt, $J = 13.3, 3.3\text{ Hz}$, 1H, 6- H_1), 1.50–2.45 (m, 6H, 3- H_2 , 6- H_1 , 7- H_2 , OH), 2.52 (m, 1H, 4-H), 2.70 (m, 1H, 1-H), 4.46 (m, 1H, 5-H). – HRMS calcd. for $\text{C}_7\text{H}_{10}\text{O}_2$: 126.0681; found 126.0682.

(1S,4S)-Bicyclo[2.2.1]heptane-2,5-dione [(S,S)-4]. To a stirred solution of **3** (100 mg, 0.793 mmol) in CH_2Cl_2 (20 mL) were added MS 4A (1 g) and pyridinium dichromate (880 mg, 2.34 mmol). Then the mixture was vigorously stirred at room temperature. After 2 h the mixture was diluted with ether and filtered through a pad of Celite. Then the filtrate was washed with dil HCl, water, saturated NaHCO_3 and brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was chromatographed over silica gel (5 g; hexane/ether, 1:1) and sublimed at 80°C/2.0 Torr to yield 30.6 mg of (*S,S*)-**4** (31 %) as a colorless solid, m.p. 141–143°C (ref.^{4c} 140–141°C, 99

% ee); $[\alpha]_D^{23} = -12.3$ ($c = 1.53$, EtOH) {ref.^{4c} $[\alpha]_D^{21} = -4.5$ ($c = 2.44$, EtOH), 99 % ee (crude products)}. – IR (Nujol): $\nu = 1752\text{ cm}^{-1}$ (s, C=O). – ¹H NMR (90 MHz): $\delta = 1.80\text{--}2.70$ (m, 6H), 3.05 (m, 2H, 1-H, 4-H).

(1S, 4S, 5S)-Spiro[bicyclo[2.2.1]heptan-5-ol-2,3'-(1,5-dihydro-2,4-benzodioxepin)] (6a). A solution of **3** (8.20 g, 65.0 mmol), 1,2-benzenedimethanol (9.88 g, 71.5 mmol) and *p*-toluenesulfonic acid monohydrate (247 mg, 1.30 mmol) in benzene (100 mL) was refluxed under argon for 80 min, with azeotropic removal of water. The reaction mixture was poured into saturated NaHCO₃, then the separated benzene layer was washed with water and brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was chromatographed over silica gel (100 g; hexane/EtOAc, 3:1) to yield 14.6 g of **6a** (91 %) as a solid. Since recrystallization of **6a** decreased its enantiomeric purity, only a small portion of **6a** was recrystallized for analysis, m.p. 106–107°C [α . 55 % ee, from hexane–EtOAc (1:1)]; HPLC: Daicel Chiralcel OD $\phi 4.6\text{ mm} \times 25\text{ cm}$, eluent: hexane/2-propanol 9:1, 10°C, flow rate, 0.5 mL/min, t_R : 8.6 min for (*R,R,R*)-isomer and 11.9 min for (*S,S,S*)-isomer. – $[\alpha]_D^{22} = -51.9$ ($c = 1.00$, CHCl₃) (α . 55 % ee). – IR (Nujol): $\nu = 3360\text{ cm}^{-1}$ (s, OH), 1210 (m, C–O), 1182 (s, C–O), 1116 (s, C–O), 1048 (s, C–O), 748 (s). – ¹H NMR (90 MHz): $\delta = 1.30\text{--}2.50$ (m, 9 H), 4.30 (m, 1H, 5-H), 4.67 (d, $J = 14.6\text{ Hz}$, 1H, 1'-H₁), 4.80 (s, 2H, 5'-H₂), 4.95 (d, $J = 14.6\text{ Hz}$, 1H, 1'-H₁), 6.95–7.40 (m, 4H, Ar-H₄). – Anal. calcd. for C₁₅H₁₈O₃ (246.3): C 73.15, H 7.37; found C 73.07, H 7.28.

(1S, 4S)-Spiro[bicyclo[2.2.1]heptan-5-one-2,3'-(1,5-dihydro-2,4-benzodioxepin)] (6b). To a stirred solution of oxalyl chloride (7.44 mL, 85.3 mmol) in CH₂Cl₂ (300 mL) was added dropwise DMSO (10.1 mL, 142 mmol) at –70°C under argon. After 10 min **6a** (14.0 g, 56.8 mmol) was added in one portion to the reaction mixture and the mixture was warmed gradually to –50°C during 1 h. The reaction mixture was cooled to –70°C again, then triethylamine (39.6 mL, 284 mmol) was added dropwise, and the cooling bath was removed after the addition. After the mixture had been warmed to room temperature, the solvent was evaporated *in vacuo*. The residue was diluted with EtOAc, washed with water (4 times) and brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was chromatographed over silica gel (250 g, hexane/EtOAc, 8:1→3:1) to yield 13.0 g of **6b** (94 %) as a solid. Since recrystallization of **6b** decreased its enantiomeric purity, only a small portion of **6b** was recrystallized for analysis, m.p. 99–113°C [α . 50 % ee, hexane–EtOAc (1:1)]; HPLC: Daicel Chiralcel OD $\phi 4.6\text{ mm} \times 25\text{ cm}$, eluent: hexane/2-propanol 9:1, 10°C, flow rate: 0.5 mL/min, t_R : 17.2 min for (*R,R*)-isomer and 18.2 min for (*S,S*)-isomer. – $[\alpha]_D^{24} = -29.4$ ($c = 1.00$, CHCl₃) (α . 50 % ee). – IR (Nujol): $\nu = 1754\text{ cm}^{-1}$ (s, C=O), 1216 (m, C–O), 1180 (s, C–O), 1118 (s, C–O), 1036 (s, C–O), 758 (s). – ¹H NMR (90 MHz): $\delta = 1.70\text{--}2.55$ (m, 6H), 2.68 (m, 1H, 1 or 4-H), 2.89 (m, 1H, 1 or 4-H), 4.65–5.05 (m, 4H, 1'-H₂, 5'-H₂), 6.95–7.40 (m, 4H, Ar-H₄). – Anal. calcd. for C₁₅H₁₆O₃ (244.3): C 73.75, H 6.60; found C 73.73, H 6.61.

(1'S, 5'S)-Spiro[1,5-dihydro-2,4-benzodioxepin-3,6'-(2-oxabicyclo[3.2.1]octan-3-one)] (7a). To a stirred and ice-cooled solution of **6b** (12.8 g, 52.4 mmol) in CH₂Cl₂ (250 mL) was added NaHCO₃ (8.80 g, 105 mmol) and *m*-chloroperbenzoic acid (55 % purity, 18.1 g, 57.6 mmol). The mixture was warmed to room temperature during 3 h. Then 10 % aqueous Na₂SO₃ (50 mL) and saturated NaHCO₃ (100 mL) were added and the stirring was continued for 10 min. The organic layer was separated and the aqueous layer was extracted with

CHCl₃ (3 times). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated *in vacuo* to give the crude product as a solid. The crude product was recrystallized from CH₂Cl₂–hexane (5 times) to yield 7.83 g of **7a** (57 %). Its ee value was estimated to be 97 % by HPLC analysis (Chiralcel OB-H ϕ 4.6 mm \times 25 cm, eluent: hexane/EtOH 1:1, 40°C, flow rate: 0.5 mL/min, *t_R*: 20.1 min for (*R,R*)-isomer and 22.1 min for (*S,S*)-isomer); m.p. 193–194°C [from hexane–CHCl₃ (2:1), as rods]. – [α]_D²³ = –31.6 (*c* = 1.00, CHCl₃). – IR (Nujol): ν = 1730 cm^{–1} (s, C=O), 1204 (s, C–O), 1152 (s, C–O), 1120 (s, C–O), 1080 (s, C–O), 764 (s). – ¹H NMR (90 MHz): δ = 1.90–3.20 (m, 7H), 4.70–5.10 (m, 5H, 1-H₂, 5-H₂, 1'-H), 7.00–7.40 (m, 4H, Ar-H₄). – Anal. calcd. for C₁₅H₁₆O₄ (260.3): C 69.22, H 6.20; found C 69.36, H 6.18.

(1'S, 4'R, 5'S)-Spiro[1,5-dihydro-2,4-benzodioxepin-3,6'-(4-hydroxy-2-oxabicyclo[3.2.1]octan-3-one)] (7b). To a stirred solution of diisopropylamine (4.55 mL, 32.5 mmol) in THF (150 mL) was added dropwise *n*-butyllithium in hexane (1.64 M, 18.3 mL, 30.0 mmol) at –78°C under argon. After 20 min, **7a** (6.5 g, 25.0 mmol) was added in one portion to the reaction mixture at –78°C, then the mixture was allowed to warm to –55°C during 70 min. After the reaction mixture had been cooled to –78°C again, MoO₅·py·HMPA (13.8 g, 31.7 mmol) was added in one portion, then the mixture was warmed to –20°C overnight. After saturated aqueous Na₂SO₃ (50 mL) had been added, the cooling bath was removed and stirring was continued for 20 min. The reaction mixture was diluted with water, and extracted twice with EtOAc. The combined organic layers were washed with dil HCl, water, saturated NaHCO₃ and brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was chromatographed over silica gel (150 g; CHCl₃/EtOAc, 100:1 \rightarrow 30:1) to yield 6.10 g of **7b** (88 %) as a solid. Recrystallization from CH₂Cl₂–hexane gave pure **7b** (5.91 g, 86 %), m.p. 166–167°C [from CH₂Cl₂–hexane (1:1), as prisms]; [α]_D²⁴ = +51.8 (*c* = 1.00, CHCl₃). – IR (Nujol): ν = 3340 cm^{–1} (s, O–H), 1746 (s, C=O), 1722 (s, C=O), 1218 (s, C–O), 1200 (s, C–O), 1118 (s, C–O), 1088 (s, C–O), 1048 (s, C–O), 760 (s). ¹H NMR (90 MHz): δ = 1.90–2.50 (m, 4H, 7'-H₂, 8'-H₂), 2.70–2.95 (m, 2H, 5'-H, OH), 4.55 (br. s, 1H, 4'-H), 4.70–5.05 (m, 5H, 1-H₂, 5-H₂, 1'-H), 6.95–7.40 (m, 4H, Ar-H₄). – Anal. calcd. for C₁₅H₁₆O₅ (276.3): C 65.20, H 5.84; found C 65.13, H 5.79.

(1'S, 5'S)-Spiro[1,5-dihydro-2,4-benzodioxepin-3,6'-(2-oxabicyclo[3.2.1]octane-3,4-dione)] (7c). To a stirred solution of oxalyl chloride (2.75 mL, 31.5 mmol) in CH₂Cl₂ (120 mL) was added dropwise DMSO (3.73 mL, 52.5 mmol) at –70°C under argon. After 10 min, **7b** (5.80 g, 21.0 mmol) was added in one portion and the mixture was warmed gradually to –30°C over 2 h. The mixture was cooled to –70°C again and triethylamine (14.6 mL, 105 mmol) was added dropwise, then the cooling bath was removed. After the mixture had been warmed to room temperature, 100 mL of water was added. The aqueous layer was extracted twice with CH₂Cl₂. The combined organic layers were washed with water (3 times) and brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was roughly chromatographed over silica gel (100 g; CH₂Cl₂:EtOAc, 10:1) and recrystallized from CH₂Cl₂–hexane to yield 4.67 g of **7c** (81 %), m.p. 227–228°C (as needles); [α]_D²⁵ = +56.0 (*c* = 1.00, CHCl₃). – IR (Nujol): ν = 1742 cm^{–1} (s, C=O), 1222 (s, C–O), 1144 (s, C–O), 1122 (s, C–O), 1102 (m, C–O), 1082 (s, C–O), 1034 (m, C–O), 764 (s). – ¹H NMR (90 MHz): δ = 2.30–2.85 (m, 4H, 7'-H₂, 8'-H₂), 3.66 (dd, *J* = 5.8, 2.5 Hz, 1H, 5'-H), 4.74 (d, *J* = 14.3 Hz, 1H, 1-H₁), 4.77 (d, *J* = 14.3 Hz, 1H, 5-

H₁), 4.93 (d, $J = 14.3$ Hz, 1H, 1 or 5-H₁), 4.99 (d, $J = 14.3$ Hz, 1H, 1 or 5-H₁), 5.13 (m, 1H, 1'-H), 6.95–7.35 (m, 4H, Ar-H₄). – Anal. calcd. for C₁₅H₁₄O₅ (274.3): C 65.69, H 5.15; found C 65.32, H 5.12.

(1'S,4'S,5'S)-Spiro[1,5-dihydro-2,4-benzodioxepin-3,6'-(4-hydroxy-4-(prop-2-enyl)-2-oxabicyclo[3.2.1]octan-3-one)] (8a). To a stirred solution of allyl tri-*n*-butyltin (1.39 g, 4.20 mmol) in anhydrous THF (10 mL) was added dropwise *n*-butyllithium (1.64 M in hexane, 2.45 mL, 4.02 mmol) at –78°C under argon. After 10 min, the resulting allyllithium solution was added dropwise, via cannular, to a stirred solution of **7c** (1.00 g, 3.65 mmol) in anhydrous THF (100 mL) at –78°C under argon over 25 min. After 30 min, the cooling bath was removed and the mixture was warmed to room temperature. The reaction was quenched by adding saturated aqueous NaHCO₃ (50 mL). Then the mixture was extracted twice with EtOAc. The combined organic layers were washed with 10 % aqueous NaF and brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was chromatographed over silica gel (50 g; hexane/EtOAc, 3:1) to yield 970 mg of **8a** (84 %) as a colorless solid. Recrystallization from CH₂Cl₂-hexane gave pure **8a** (913 mg, 79 %), m.p. 146–147°C [from hexane–EtOAc (3:1), as prisms]; $[\alpha]_D^{25} = +184$ ($c = 1.00$, CHCl₃). – IR (Nujol): $\nu = 3470$ cm^{–1} (s, O–H), 3070 (w, =C–H), 1744 (s, C=O), 1636 (w, C=C), 1210 (m, C–O), 1158 (m, C–O), 1126 (s, C–O), 1102 (s, C–O), 1082 (m, C–O), 746 (s). – ¹H NMR (90 MHz): $\delta = 1.95$ –2.90 (m, 7H, 5'-H, 7'-H₂, 8'-H₂, 9'-H₂), 4.60–5.30 (m, 8H), 5.94 (m, 1H, 10'-H), 6.90–7.40 (m, 4H, Ar-H₄). – Anal. calcd. for C₁₈H₂₀O₅ (316.4): C 68.34, H 6.37; found C 68.07, H 6.31.

(1S,4S,5S)-Spiro[4-(tert-butyldimethylsilyloxy)-4-(prop-2-enyl)-2-oxabicyclo[3.2.1]octan-3-one-6,3'-(1,5-dihydro-2,4-benzodioxepin)] (8b). To a stirred solution of **8a** (1.80 g, 5.69 mmol) and 2,6-lutidine (2.65 mmol, 22.8 mmol) in anhydrous CH₂Cl₂ (20 mL) was added dropwise *t*-butyldimethylsilyl trifluoromethanesulfonate (2.61 mL, 11.4 mmol) under argon. Then the mixture was heated and refluxed for 2 days. The mixture was cooled in an ice-cooled bath and the reaction was quenched by adding MeOH (0.5 mL). The mixture was diluted with ether, washed with water, dil HCl, water, saturated NaHCO₃ and brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was chromatographed over silica gel (50 g; hexane/EtOAc, 5:1) to yield 2.35 g of **8b** (96 %). Recrystallization from hexane gave pure **8b** (2.29 g, 93 %), m.p. 148–149°C (as prisms). The HPLC analysis (Chiralcel OD-H, $\phi 4.6$ mm \times 25 cm, eluent: hexane/EtOH 7:3, 25°C, flow rate: 0.5 mL/min, t_R : 8.8 min for (*R,R,R*)-isomer and 10.5 min for (*S,S,S*)-isomer) revealed the compound **8b** to be enantiomerically pure; $[\alpha]_D^{23} = +170$ ($c = 1.00$, CHCl₃). – IR (Nujol): $\nu = 3080$ cm^{–1} (m, =C–H), 3030 (m, =C–H), 1750 (s, C=O), 1256 (s, Si–Me), 1166 (s, C–O), 1138 (m, C–O), 1120 (s, C–O), 1100 (s, C–O), 1080 (s, C–O), 1020 (s, Si–O), 840 (s), 802 (s), 782 (s), 758 (s). – ¹H NMR (90 MHz): $\delta = 0.08$ (s, 3H, MeSi), 0.28 (s, 3H, MeSi), 0.69 (s, 9H, *t*BuSi), 1.85–2.80 (m, 7H), 4.61 (d, 1H, $J = 14.7$ Hz, 1'-H₁), 4.69 (d, 1H, $J = 15.0$ Hz, 5'-H₁), 4.84 (m, 1H, 1-H), 4.94 (d, $J = 15.0$ Hz, 1H, 5'-H₁), 5.04 (d, $J = 14.7$ Hz, 1H, 1'-H₁), 5.18 (m, 1H, 11-H₁), 5.22 (m, 1H, 11-H₁), 5.99 (m, 1H, 10-H), 6.95–7.25 (m, 4H, Ar-H₄). – Anal. calcd. for C₂₄H₃₄O₅Si (430.6): C 66.94, H 7.96; found C 66.80, H 8.04.

(1*S*, 3*RS*, 4*S*, 5*S*)-Spiro[4-(*tert*-butyldimethylsilyloxy)-4-(prop-2-enyl)-2-oxabicyclo[3.2.1]octan-3-ol-6,3'-(1,5-dihydro-2,4-benzodioxepin)] (9).** To a stirred solution of **8b** (1.40 g, 3.25 mmol) and trimethylsilyl chloride (1.03 mL, 8.13 mmol) in anhydrous toluene (80 mL) was added dropwise diisobutylaluminium hydride (1.01 M in toluene, 6.44 mL, 6.50 mmol) at -78°C under argon. Then the mixture was stirred at -78°C for 12 h. The reaction was quenched by the slow addition of MeOH (0.3 mL) at -78°C . The reaction mixture was then treated with 4 mL of water and 2 g of NaHCO_3 and the cooling bath was removed. After warmed to room temperature the mixture was treated with MgSO_4 and stirred for 2 h. The mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was chromatographed over silica gel (70 g; hexane/EtOAc, 8:1 \rightarrow 4:1) to yield 1.18 g of **9** (84 %) as a solid; m.p. $135\text{--}136^{\circ}\text{C}$ [from hexane-EtOAc (1:1), as plates]. This products showed a complex ^1H NMR spectrum of the mixture of open chain aldehyde, α -hydroxy isomer and β -hydroxy isomer, and the ratio was about 1:1:1; IR (Nujol): $\nu = 3360\text{ cm}^{-1}$ (s, O-H), 3080 (m, =C-H), 3025 (m, =C-H), 1642 (m, C=C), 1258 (m, Si-Me), 1160 (s, C-O), 1138 (s, C-O), 1116 (s, C-O), 1100 (s, C-O), 1060 (s, Si-O), 840 (s), 808 (s), 776 (s), 756 (s). – ^1H NMR (90 MHz): $\delta = -0.13\text{--}0.22$ (s \times 6, total 6H, MeSi), 0.72–0.87 (s \times 3, total 9H, *t*BuSi), 1.70–3.00 (m, total 7H, 5-H, 7-H₂, 8-H₂, 9-H₂), 4.35–5.35 (m, total 8.7 H, 1-H, 3-H, 11-H₂, 1'-H₂, 5'-H₂, OH), 5.70–6.30 (m, 1H, 10-H), 6.90–7.30 (m, 4H, Ar-H₄), 9.87 (s, 0.3 H, CHO). – Anal. calcd. for $\text{C}_{24}\text{H}_{36}\text{O}_5\text{Si}$ (432.6): C 66.63, H 8.39; found C 66.45, H 8.36.

(1*S*, 3*R*, 5*RS*, 7*S*, 8*S*)-Spiro[7-(*tert*-butyldimethylsilyloxy)-2,4-dioxatricyclo[6.2.1.0^{3,7}]undecan-5-ol-9,3'-(1,5-dihydro-2,4-benzodioxepin)] (10a).** To a suspension of NaHCO_3 (204 mg, 2.43 mmol) in anhydrous CH_2Cl_2 (50 mL) was added **9** (1.05 g, 2.43 mmol), and the mixture was cooled to -78°C . Ozone was then bubbled through the mixture at -78°C until the mixture turned pale blue. After removing excess ozone from the mixture with oxygen purge, triphenylphosphine (1.27 g, 4.86 mmol) was added, and the mixture was warmed gradually to room temperature under nitrogen overnight. The solvent was evaporated and the residue was chromatographed over silica gel (50 g; hexane/EtOAc, 4:1 \rightarrow 3:1) to yield 1.05 g of epimeric hemiacetals **10a** (quantitative yield) as foams. This products were partially decomposed during chromatography, and satisfactory elemental analytical data could not be obtained; IR (Nujol): $\nu = 3400\text{ cm}^{-1}$ (s, O-H), 1254 (s, Si-Me), 1200 (s, C-O), 1140 (s, C-O), 1060 (s, Si-O), 1028 (s, C-O), 838 (s), 804 (s), 776 (s), 746 (s). – ^1H NMR (90 MHz) for the major isomer: $\delta = 0.03$ (s, 3H, MeSi), 0.08 (s, 3H, MeSi), 0.72 (s, 9H, *t*BuSi), 1.90–2.40 (m, 6H, 6-H₂, 10-H₂, 11-H₂), 2.65 (m, 1H, 8-H), 3.34 (d, 1H, $J = 9.3$ Hz, OH), 4.45 (m, 1H, 1-H), 4.57 (d, $J = 14.6$ Hz, 1H, 1'-H₁), 4.73 (d, $J = 14.6$ Hz, 1H, 5'-H₁), 5.02 (d, $J = 14.6$ Hz, 2H, 1'-H₁, 5'-H₁), 5.25 (s, 1H, 3-H), 5.71 (m, 1H, 5-H), 7.00–7.30 (m, 4H, Ar-H₄). – HRMS calcd. for $\text{C}_{23}\text{H}_{34}\text{O}_6\text{Si}$: 434.2125; found 434.2148.

(1*S*, 3*R*, 5*S*, 7*S*, 8*S*)-Spiro[7-(*tert*-butyldimethylsilyloxy)-5-methoxy-2,4-dioxatricyclo[6.2.1.0^{3,7}]undecane-9,3'-(1,5-dihydro-2,4-benzodioxepin)] (10b). To a stirred solution of **10a** (450 mg, 1.04 mmol) in acetonitrile - iodomethane (1:1, 6 mL) was added silver(I) oxide (360 mg, 1.55 mmol). The mixture was stirred at room temperature under argon for 30 h, and then treated with MgSO_4 . The mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was chromatographed over silica gel (20 g; hexane/EtOAc, 3:1) to yield 430 mg of **10b** (93 %, single isomer) as forms; $[\alpha]_{\text{D}}^{22} = +146$ ($c = 1.41$,

CHCl₃). – IR (film): ν = 1254 cm⁻¹ (s, Si–Me), 1212 (s, C–O), 1136 (s, C–O), 1100 (m, C–O), 1062 (s, Si–O), 1032 (s, C–O), 836 (s), 802 (s), 772 (s), 744 (s). – ¹H NMR (90 MHz): δ = 0.03 (s, 3H, MeSi), 0.09 (s, 3H, MeSi), 0.73 (s, 9H, *t*BuSi), 1.75–2.75 (m, 7H), 3.48 (s, 3H, MeO), 4.46 (m, 1H, 1-H), 4.58 (d, J = 13.9 Hz, 1H, 1'-H₁), 4.73 (d, J = 13.9 Hz, 1H, 5'-H₁), 5.01 (d, J = 13.9 Hz, 1H, 1' or 5'-H₁), 5.04 (d, J = 13.9 Hz, 1H, 1' or 5'-H₁), 5.21 (s, 1H, 3-H), 5.32 (dd, J = 6.2, 4.9 Hz, 1H, 5-H), 6.95–7.25 (m, 4H, Ar-H₄). – Anal. calcd. for C₂₄H₃₆O₆Si (448.6): C 64.25, H 8.09; found C 63.95, H 8.04.

(1S,3R,5S,7S,8S)-7-(*tert*-Butyldimethylsilyloxy)-5-methoxy-2,4-dioxatricyclo[6.2.1.0^{3,7}]undecan-9-one (2). To a solution of **10b** (420 mg, 0.936 mmol) in EtOAc (20 mL) was added 10 % palladium on carbon (30 mg). After the reaction flask had been degassed and filled with hydrogen twice, the mixture was vigorously stirred at room temperature. After 20 min, NaHCO₃ (100 mg) was added, then the mixture was filtered through a pad of silica gel and concentrated *in vacuo* to give a solid. The solid was recrystallized from hexane to yield 280 mg of **2** (91 %), m.p. 103–104°C (as plates); $[\alpha]_D^{24}$ = +86.4 (c = 1.00, CHCl₃). – IR (Nujol): ν = 1756 cm⁻¹ (s, C=O), 1254 (s, Si–Me), 1196 (s, C–O), 1152 (s, C–O), 1140 (s, C–O), 1088 (m, C–O), 1072 (m, C–O), 1042 (s, Si–O), 1018 (s, C–O), 840 (s), 780 (s). – ¹H NMR (500 MHz): δ = 0.10 (s, 3H, MeSi), 0.17 (s, 3H, MeSi), 0.85 (s, 9H, *t*BuSi), 1.82 (ddd, J = 13.4, 5.1, 2.6 Hz, 1H, 11-H₁), 2.25 (ddd, J = 19.5, 5.1, 1.0 Hz, 1H, 10-H₁), 2.29 (dd, J = 15.0, 5.8 Hz, 1H, 6-H₁), 2.33 (dd, J = 15.0, 4.8 Hz, 1H, 6-H₁), 2.33 (ddd, J = 13.4, 4.5, 1.5 Hz, 1H, 11-H₁), 2.58 (dd, J = 19.5, 4.5 Hz, 1H, 10-H₁), 2.73 (br.d, J = 5.1 Hz, 1H, 8-H), 3.47 (s, 3H, MeO), 4.71 (m, 1H, 1-H), 5.03 (s, 1H, 3-H), 5.31 (dd, J = 5.8, 4.8 Hz, 1H, 5-H). – Anal. calcd. for C₁₆H₂₈O₅Si (328.4): C 58.52, H 8.59; found C 58.72, H 8.59.

(1S,3R,5S,7S,8R)-7-(*tert*-Butyldimethylsilyloxy)-5-methoxy-2,4-dioxatricyclo[6.2.1.0^{3,7}]undec-9-ene (11). To a stirred solution of **2** (50.0 mg, 0.152 mmol) in anhydrous toluene was added dropwise diisobutylaluminium hydride (1.01 M in toluene, 0.226 mL, 0.228 mmol) at –78°C under argon, and the mixture was gradually warmed to –50°C during 2 h. The reaction was quenched by addition of MeOH (0.025 mL) and warmed to room temperature. The mixture was treated with water (0.15 mL), NaHCO₃ (1 g), MgSO₄ (2 g) and stirred for 2 h. Then the mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was dissolved in anhydrous CH₂Cl₂ (3 mL), then 4-(*N,N*-dimethylamino)pyridine (223 mg, 1.83 mmol) and methanesulfonic anhydride (159 mg, 0.913 mmol) was added to the solution at room temperature under argon. After 20 h the mixture was treated with 3 mL of saturated NaHCO₃ for 10 min. The mixture was extracted with ether and the organic layer was washed with water and brine. The mixture was dried over MgSO₄ and concentrated *in vacuo*. The residue was dissolved in xylene (6 mL) with 1,8-diazabicyclo[5.4.0]undec-7-ene (1 mL) and tetraethylammonium bromide (320 mg, 1.52 mmol). After refluxing for 6 days under argon, the mixture was directly chromatographed over silica gel (10 g; hexane/EtOAc, 10:1) to yield 41.1 mg of **11** (86 %) as a solid, m.p. 30–31 °C; $[\alpha]_D^{22}$ = +113 (c = 1.95, CHCl₃). – IR (film): ν = 3070 cm⁻¹ (m, =C–H), 1257 (s, Si–Me), 1194 (s, C–O), 1132 (s, C–O), 1076 (s, C–O), 1028 (s, Si–O), 968 (s), 937 (s). – ¹H NMR (500 MHz): δ = 0.11 (s, 3H, MeSi), 0.14 (s, 3H, MeSi), 0.86 (s, 9H, *t*BuSi), 1.75 (ddd, J = 11.5, 4.5, 3.0 Hz, 1H, 11-H₁), 2.05 (br.d, J = 11.5 Hz, 1H, 11-H₁), 2.26 (dd, J = 15.0, 4.5 Hz, 1H, 6-H₁), 2.29 (dd, J = 15.0, 5.5

Hz, 1H, 6-H₁), 2.96 (dd, $J = 4.5, 3.0$ Hz, 1H, 8-H), 3.45 (s, 3H, MeO), 4.66 (m, 1H, 1-H), 4.80 (s, 1H, 3-H), 5.30 (dd, $J = 5.5, 4.5$ Hz, 1H, 5-H), 6.07 (dd, $J = 5.5, 2.5$ Hz, 1H, 10-H), 6.46 (dd, $J = 5.0, 3.0$ Hz, 1H, 9-H). – Anal. calcd. for C₁₆H₂₈O₄Si (312.5): C 61.50, H 9.03; found C 61.78, H 9.05.

(1R, 3S, 7S, 8S)-2,4-Dioxatricyclo[6.2.1.0^{3,7}]undecan-7-ol (14). To a solution of (1R,3S,7R,8S)-2,4-dioxatricyclo[6.2.1.0^{3,7}]undec-5-en-7-ol (**13**) (3.2 mg, 0.019 mmol) in EtOAc (2 mL) was added NaHCO₃ (10 mg) and 10 % palladium on carbon (3.0 mg). After the reaction flask had been degassed and filled with hydrogen twice, the mixture was vigorously stirred at room temperature. After 30 min the mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was chromatographed over silica gel (5 g; hexane/EtOAc, 1:1) to yield 3.1 mg of **14** (96 %) as a solid, m.p. 86–87 °C (needles from hexane). – $[\alpha]_D^{23} = +16$ ($c = 0.50$, CHCl₃). – IR (film): $\nu = 3425$ cm⁻¹ (s, O-H), 2960 (s, C-H), 2920 (s, C-H), 1132 (s, C-O), 1164 (m, C-O), 1122 (m, C-O), 1110 (m, C-O), 1048 (m, C-O). – ¹H NMR (300 MHz): $\delta = 1.39$ (ddd, $J = 12.5, 5.1, 2.7$ Hz, 1H, 11-H₁), 1.69 (tt, $J = 12.3, 5.3$ Hz, 1H, 9-H₁), 1.72–1.86 (m, 3H, 6-H₁, 10-H₁, OH), 1.90–2.02 [m, 2H (includes br.d, $J = 12.5$ Hz, 11-H₁), 10-H₁], 2.16 (dddd, $J = 12.3, 8.7, 3.9, 2.6$ Hz, 1H, 9-H₁), 2.42 (dt, $J = 13.5, 8.1$ Hz, 1H, 6-H₁), 2.51 (br.t, $J = 5.3$ Hz, 1H, 8-H₁), 4.20 (dd, $J = 8.1, 6.8$ Hz, 2H, 5-H₂), 4.36 (m, 1H, 1-H), 4.88 (s, 1H, 3-H). – HRMS calcd. for C₉H₁₄O₃: 170.0943; found 170.0929.

(1R, 3S, 7R, 8S)-2,4-Dioxatricyclo[6.2.1.0^{3,7}]undec-5-en-7-ol (13). Foams. – $[\alpha]_D^{23} = -195$ ($c = 0.55$, CHCl₃) {ref.⁶ $[\alpha]_D^{20} = -193$ ($c = 1.13$, CHCl₃)}. – IR (film): $\nu = 3410$ cm⁻¹ (s, O-H), 3100 (w, =C-H), 2950 (s, C-H), 1612 (s, C=C). – ¹H NMR (500 MHz): $\delta = 1.41$ (ddd, $J = 12.4, 5.5, 3.0$ Hz, 1H, 11-H₁), 1.66 (dddd, $J = 13.0, 12.5, 6.5, 5.5$ Hz, 1H, 9-H₁), 1.71 (br.s, 1H, OH), 1.79 (br.d, $J = 12.4$ Hz, 1H, 11-H₁), 1.81 (ddt, $J = 14.5, 12.5, 4.5$ Hz, 1H, 10-H₁), 1.92 (dddd, $J = 14.5, 9.0, 5.5, 2.5$ Hz, 1H, 10-H₁), 2.24 (dddd, $J = 13.0, 9.0, 4.5, 1.6$ Hz, 1H, 9-H₁), 2.47 (dd, $J = 6.5, 5.5$ Hz, 1H, 8-H), 4.31 (m, 1H, 1-H), 5.12 (d, $J = 2.8$ Hz, 1H, 6-H), 5.27 (s, 1H, 3-H), 6.50 (d, $J = 2.8$ Hz, 1H, 5-H).

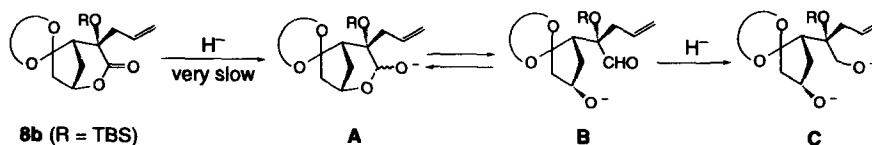
(1S, 3R, 7S, 8R, 9S, 11S)-2,4,10-Trioxatetracyclo[6.3.1.0^{3,7}.0^{9,11}]dodec-5-en-7-ol (12). m.p. 150–151 °C (plates from hexane). – $[\alpha]_D^{23} = -145$ ($c = 0.44$, CHCl₃) {ref.⁶ $[\alpha]_D^{20} = -146.4$ ($c = 0.80$, CHCl₃)}. – IR (film): $\nu = 3480$ cm⁻¹ (s, O-H), 2940 (s, C-H), 1618 (s, C=C), 1176 (s, C-O), 1142 (s, C-O), 1086 (s, C-O), 1060 (s, C-O), 1004 (s, C-O). – ¹H NMR (500 MHz): $\delta = 1.35$ (d, $J = 13.3$ Hz, 1H, 12-H), 1.53 (ddd, $J = 13.3, 5.3, 3.3$ Hz, 1H, 12-H), 1.89 (s, 1H, OH), 2.67 (d, $J = 5.3$ Hz, 1H, 8-H), 3.53 (d, $J = 2.5$ Hz, 1H, 9 or 10-H), 3.84 (d, $J = 2.5$ Hz, 1H, 9 or 10-H), 4.36 (d, $J = 3.3$ Hz, 1H, 1-H), 5.13 (d, $J = 2.8$ Hz, 1H, 6-H), 5.49 (s, 1H, 3-H), 6.52 (d, $J = 2.8$ Hz, 1H, 5-H).

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- See refs. 1b and refs. cited therein.
- Ley *et al.* reported **13** and **14** to have shown almost the same and a half anifeedant activity of azadirachtin against *Spodoptera littoralis* (Boisduval), respectively. See ref. 1a and refs. cited therein.
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