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TOTAL SYNTHESIS OF (±)-8S, 14-CEDRANEDIOL

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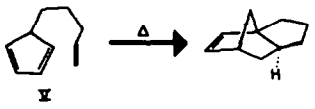
Abstract—A total synthesis of (±)-8s, 14-cedranediol (I) is described. The synthesis employed the intramolecular Diels–Alder reaction of an alkenylcyclopentadiene prepared *in situ* through the retro Diels–Alder reaction of the corresponding alkenyldicyclopentadiene. Regiospecific ring expansion of the cyclization product provided access to the natural product.

The cedrane sesquiterpenes have been the object of numerous synthetic studies since Stork's original synthesis of cedrol in 1955 for the purpose of structure elucidation.[1] Subsequent investigators[2,3] have found the natural products of this class to be challenging objectives against which to refine synthetic strategy and develop synthetic methods. Their reports detail a wide variety of approaches, and these have been directed toward the simplest cedranoids.[4] Reported herein is a total synthesis of (±)8S,14-cedranediol[5] (I) that employs intramolecular Diels–Alder strategy and that should be applicable to the most highly functionalized members of the cedrane class.

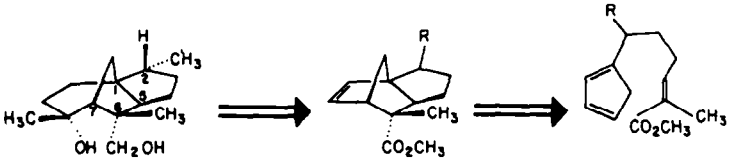
The synthetic analysis began with recognition of a structural similarity between the carbon framework of the cedranoids and that of the simple norbornenes (Scheme 1). By analogy to the established route[6] to the norbornenes (e.g. II), a Diels–Alder approach to the tricyclic intermediate III was postulated. Expansion of the ring and suitable reorganization of functional groups would yield the natural product I.[7] The stereochemical relationships as written for the Diels–Alder reaction were anticipated according to the well-known preference of ester groupings for *endo* orientation and through estimation *via* Dreiding models of steric constraints on the transition state. This approach would orient the asymmetric centers at C_1, C_5, C_6, and C_7 in the relative configuration of the natural product.

A solution to the synthesis of the requisite alkylcyclopentadiene IV entailed special considerations. First, the 1-alkyl isomer was specifically required, but alkylcyclopentadienes undergo facile sigmatropic hydride shifts at elevated temperatures.[8] Thus, exposing any one of the three possible isomeric alkylcyclopentadienes to temperatures greater than 70° soon results in an equilibrium mixture of the 1-alkyl, 2-alkyl and 5-alkyl isomers. However, steric constraints on the intramolecular reaction of the 2-alkyl isomer,[9] together with the thermodynamic unfavorability of the 5-alkyl isomer,[10] obviated this difficulty, as demonstrated in the reported cyclization of V through the 1-substituted isomer

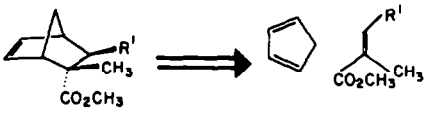


V

exclusively.[11] Second, cyclopentadienes polymerize with great facility, so late introduction of this grouping was sought. However, the standard displacement of a leaving group by a metallo cyclopentadienide[10] was inapplicable due to the presence of the α,β-unsaturated ester. An



I III IV



II

Scheme 1.

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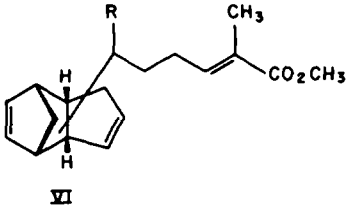
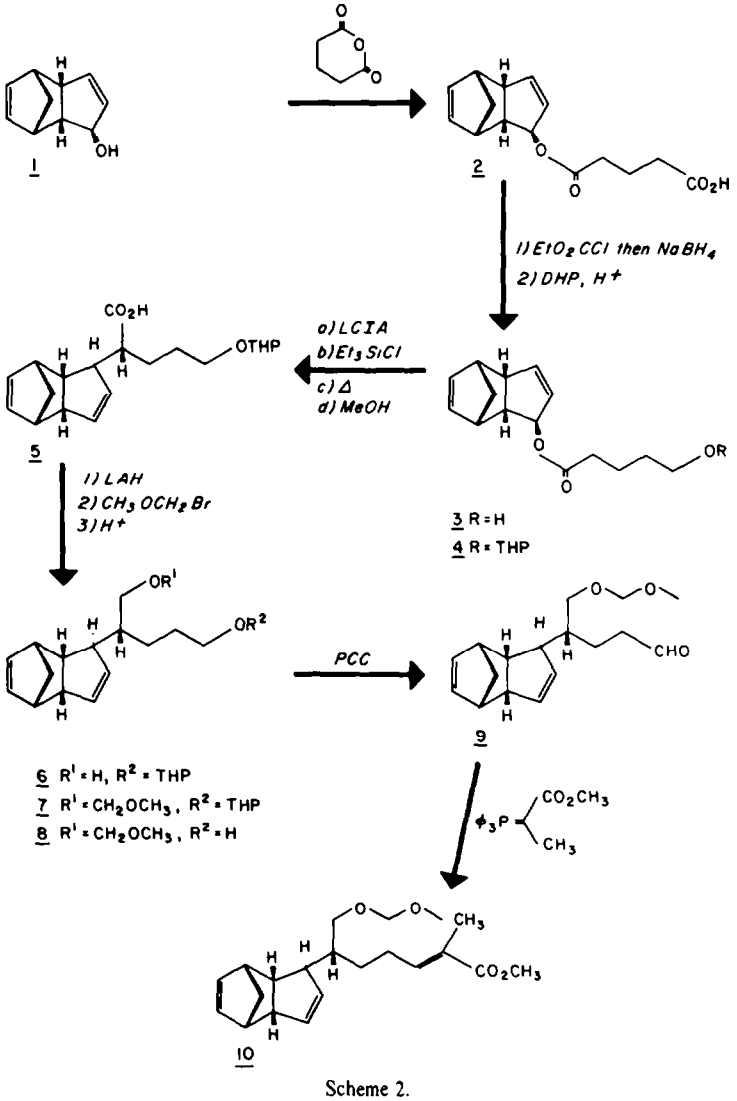
alternative was to introduce the grouping early but in a masked, stable form: a dicyclopentadienyl moiety. *Endo*-dicyclopentadiene monomerizes at an appreciable rate at temperatures in excess of 170°, and the presence of an alkyl substituent does not substantially alter the course or ease of the cycloreversion.[12] Therefore, since any of the monoalkyl isomers of cyclopentadiene would effectively provide the 1-alkyl isomer and since a dicyclopentadienyl moiety could function as a protected cyclopentadienyl grouping, a structure of type VI was equivalent to the Diels–Alder substrate IV.



VI

Based on this analysis, four objectives were defined for the successful completion of this synthesis: (i) preparation of an alkyldicyclopentadiene suitable according to the criteria above; (ii) exploration of the proposed pericyclic transformation; (iii) ring expansion of the Diels–Alder product; and (iv) reorganization of functional groups to the natural product.

(i) *Preparation of alkyldicyclopentadiene* **10**. The synthesis of an equivalent to IV of type VI was accomplished in nine steps (Scheme 2). Hydroxylation of *endo*-dicyclopentadiene by the procedure of Woodward and Katz[13] provided alcohol **1** in 49% yield. Acylation of **1** with glutaric anhydride in pyridine gave crystalline acid **2** in 99% yield. Selective reduction of the carboxylic acid group, through its ethyl carbonic anhydride, with sodium borohydride afforded alcohol **3** in 92% yield. Protection of this alcohol as a tetrahydropyranyl ether with dihydropyran under acid catalysis provided **4** in 79% yield. Ester **4** in tetrahydrofuran was deprotonated with lithium cyclohexylisopropylamide at −78° and O-silylated with triethylsilyl chloride[14] at −45°. The resulting allyl



Scheme 2.

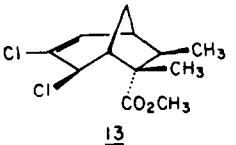
siloxyvinyl ether was refluxed to effect [3,3]-sigmatropic rearrangement,[15] and the silyl ester product was hydrolyzed with aqueous methanol to afford a carboxylic acid in 58% yield. In the absence of unusual steric constraints all variety of [3,3]-sigmatropic rearrangements, including those of allyl siloxyvinyl ethers, proceed through a chair-like conformation, and Ireland[16] has demonstrated that monoalkyl siloxyvinyl ethers possess the *E*-configuration (*E*:*Z*::9:1) when prepared from an enolate quantitatively generated with a lithium dialkylamide in THF at −78°. From these precedents, which define olefin geometry and conformation of reaction, structure **5** was assigned to the carboxylic acid product.

Due to its rapid decomposition on standing, acid **5** was reduced immediately after preparation to alcohol **6** with LAH in 94% yield. Bromomethyl methyl ether converted **6** to its methoxymethyl ether **7** in 90% yield, and selective hydrolysis of the tetrahydropyranyl ether **7** with acidic methanol afforded alcohol **8** in 86% yield. Oxidation of **8** with a 10-fold excess of Collins' reagent provided aldehyde **9** in 71% yield. Finally, reaction of **9** with α-carbomethoxyethylidenetriphenylphosphorane[18] gave the desired *E*-α,β-unsaturated ester **10** in 83% yield [NMR($CDCl_3$)δ6.76(1H, tq, J = 8, 1 Hz, H_β), 5.8–6.1 (4 H, m, olefin)]. The *Z*-isomer **10a** was also isolated in 3% yield [NMR($CDCl_3$) δ5.8–6.1 (5 H, m, olefin)].

(ii) *Intramolecular Diels–Alder synthesis of* **11**. Acquisition of ester **10** provided a substrate for the postulated pericyclic reaction. A toluene solution of **10** in a sealed tube was heated to 180° for 18 hr in order to effect the thermal transformations (a) retro Diels–Alder reaction; (b) [1,5]-sigmatropic rearrangement; and (c) intramolecular Diels–Alder reaction (Scheme 3). Chromatography under a variety of conditions suggested formation of a single product, but ^{1}H NMR analysis indicated a mixture (~1:1) of C_2 diastereomers **11**. The structure assigned to the C skeleton of the thermolysis product was supported by various spectral data [NMR($CDCl_3$)δ6.3–6.0 (2 H, olefin), 4.55 (2 H, O–CH_2–O), 3.53 (3 H,–CO_2CH_3), 3.29 (3 H,–CH_2OCH_3); IR (neat) 1740 cm^{-1} unconjugated ester; *m/e*280M$^+$]. Literature precedent[11] and the nature of the product of the next transformation supported the stereochemical assignments.

The ratio of the two epimers was not appreciably altered by replacing the methoxymethyl group of the substrate with trimethylsilyl, t-butyldimethylsilyl, or *p*-anisoyl groups. An analytical separation was accomplished by high performance liquid chromotography using three Corasil II analytical columns connected in series. However, preparative separation was postponed since the epimers were found to be easily separable after the next transformation.

(iii) *Ring expansion of* **11**. In order to devise a method for controlling the regiochemistry of the ring expansion of **11** to the cedranoid skeleton, the study of a model system was undertaken.[19] In that study, dichlorocarbene addition to **12** under phase-transfer conditions[20] (chloroform, 50% KOH aq, benzyltriethylammonium chloride)



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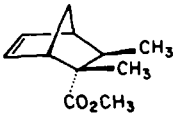

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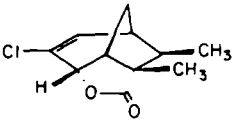

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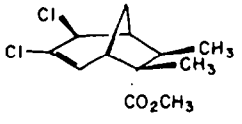

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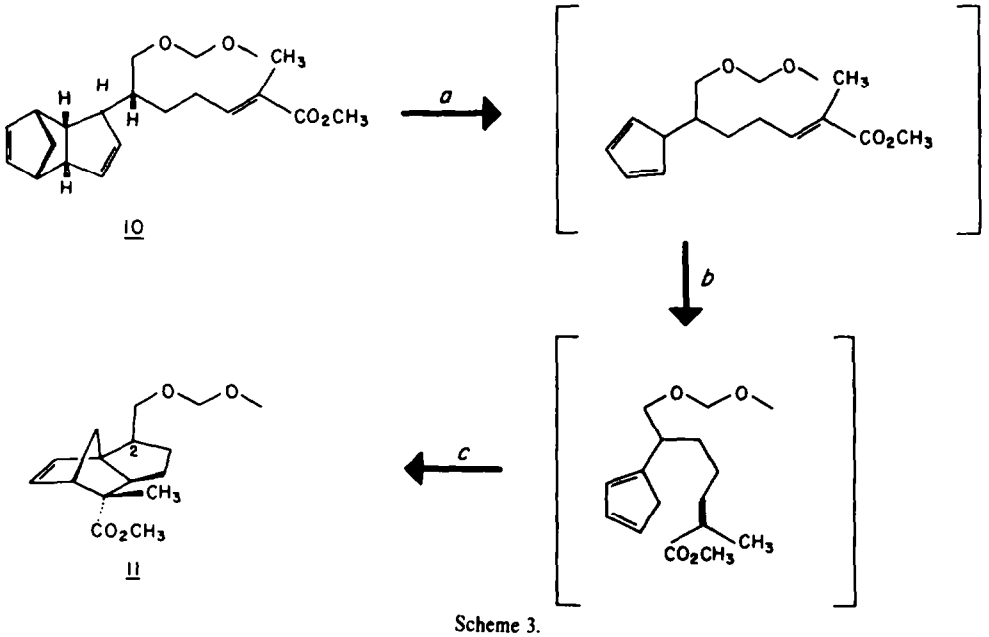
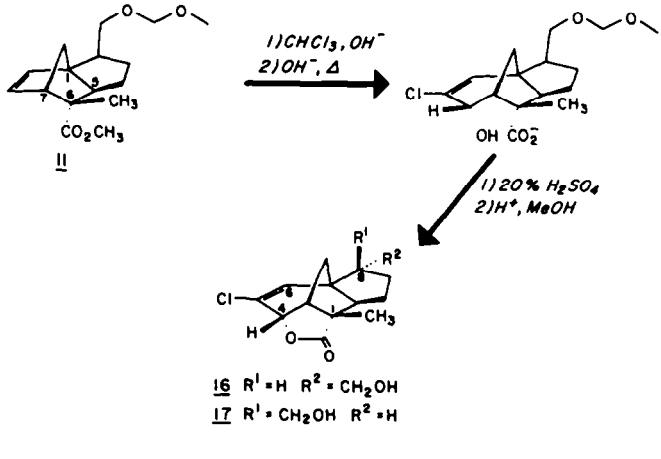


Scheme 3.

provided a mixture of allylic chlorides **13** and **14** and unreacted starting material **12**. Refluxing these chlorides with 10% KOHaq provided the regiochemically unambiguous lactone **15**. Attempts to drive the carbene addition reaction to completion through extended reaction times resulted in direct formation of lactone **15** in addition to chlorides **13** and **14**. Progressively greater proportions of **15** were obtained by extending the duration of this addition reaction, but it proved most expedient to reflux the crude product, obtained after several days, with KOHaq. The resulting base-soluble carboxylate lactonized upon simple acidification and so a high degree of purification was accomplished merely by extraction.

Thus, ester **11** was subjected to dichlorocarbene under phase-transfer conditions. After two days' exposure, the crude product was isolated and refluxed with 10% KOHaq to complete lactonization and effect hydrolysis. Acidification with excess 20% H_2SO_4, to close the lactone ring, and exposure to acidic methanol, to complete hydrolysis of the methoxy methyl ether, afforded hydroxymethyl lactones **16** and **17** in 55% yield. Easily separable by TLC on silica gel, the mixture provided **16** (R_f 0.41) in 20% yield and **17** (R_f 0.22) in 22% yield.



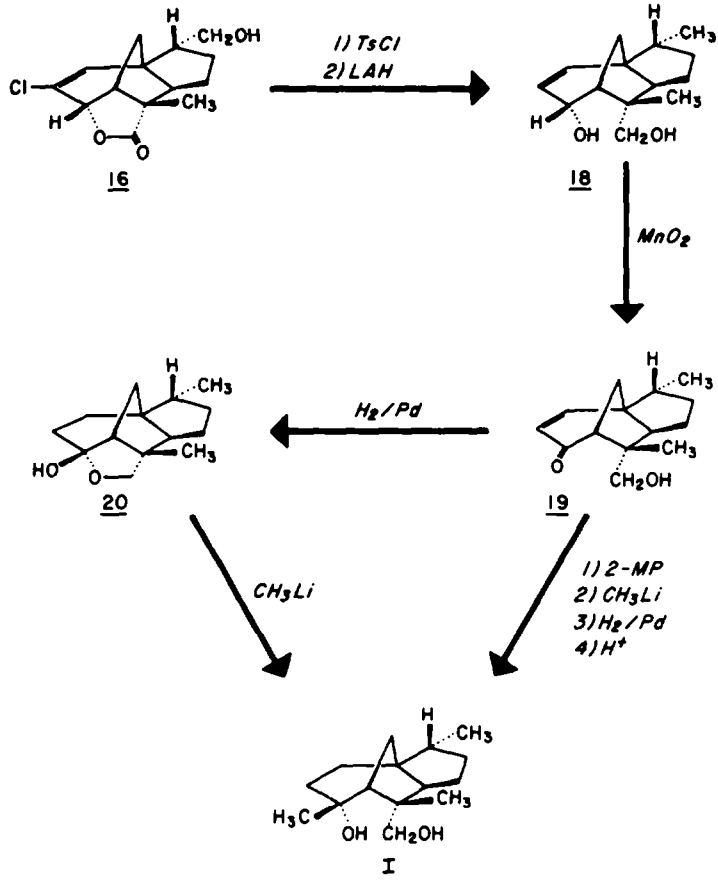
Given the C framework, the transformation of ester **11** into a lactone supported the relative stereochemical assignments at C_1, C_6, and C_7 of **11**. Since the stereochemical relationship between C_5 and C_6 was defined by the concerted nature of the Diels–Alder reaction and the *E*-configuration of the dienophile, formation of a lactone linkage also supported the assignment at C_5 of **11**.

The relative stereochemistry at the epimeric center of the lactones (C_8) was assigned on the basis of a NOE experiment in which the methylene hydrogens of the hydroxymethyl group were irradiated and the effect of this irradiation on the H_6 integral was monitored. The less polar epimer experienced a 20% enhancement of the integral over H_6; the more polar epimer displayed only a 4% increase. Dreiding models showed the methylene hydrogens to be much closer to H_6 in the α epimer (i.e., **16**), and the assignments were made accordingly.

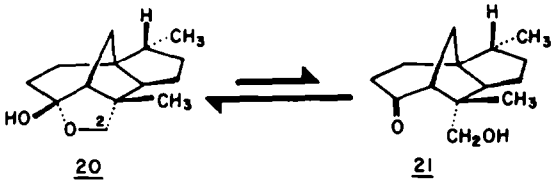
(iv) *Synthesis of* (±)-8S, 14-*cedranediol*(I). Lactone **16** possessed the tricyclic C framework and the proper stereochemical relationships for direct access to the natural product (Scheme 4).[a] Intermediate **16** was tosylated with *p*-toluenesulfonyl chloride in 92% yield and reduced with LAH. In addition to the anticipated reductions of the tosylate and lactone groupings, the vinyl chloride was reduced, all in 82% yield. Selective oxidation of diol **18** with manganese dioxide prepared according to the Attenburrow procedure[21] afforded enone **19** in 79% yield. Completion of this work required only reduction of the olefin and Me anion addition to the CO function from the less hindered β face. Enone **19** was catalytically hydrogenated on 10% Pd-C and the product was isolated in 89% yield. An IR spectrum of the product in a KBr matrix displayed no absorption in the CO region, and lactol structure **20** was assigned to this material. Solution spectra showed an equilibrium between the lactol (**20**) and hydroxyketone (**21**) forms, with the former predominating [IR($CHCl_3$ or THF) 1700 cm^{-1} weak absorption; NMR($CDCl_3$) δ3.68 (1.8H, AB, J = 1.8 Hz, $\Delta\delta$18 Hz, H_2 of lactol), 3.39 (0.2H, bs, $-CH_2-O-$of ketone)].

Addition of several equivalents of MeLi to a tetrahydrofuran solution of the hydrogenation product followed by aqueous quenching resulted in only minor conversion. However, application of MeLi and quenching, repeated twice more, followed by chromatography afforded (±)-8S,14-cedranediol I in 43% yield together with 15% recovered starting material. The need for repeated cycling was attributed either to enolization or to a slow equilibration of the deprotonated lactol with the keto-alkoxide. In an effort to circumvent either possibility, the OH function of **19** was protected with 2-methoxypropene and MeLi was added across the CO of the enone. Despite the potential for hydrogenolysis of the allylic alcohol grouping, catalytic hydrogenation proceeded smoothly and, after brief application of acid to free the protected alcohol, (±)-8S, 14-cedranediol was isolated in 71% yield from enone **19**.

[a] Lactone **17** possessed the β configuration at C_8 of jalaric and shellolic acids. Of note for the syntheses of these natural products: pyridinium chlorochromate oxidation of **16** and **17** yielded the corresponding α aldehyde [NMR($CDCl_3$) δ9.69 (1H, d, J = 2 Hz, CHO), 6.91 (1H, s, H_6), 4.91 (1H, d, J = 7 Hz, H_4)] and β aldehyde, respectively, [NMR($CDCl_3$) δ9.66 (1H, d, J = 2 Hz, CHO), 6.58 (1H, s, H_6), 4.91 (1H, d, J = 7 Hz, H_4)]. Exposure of either of these aldehydes to diazabicycloundecane in methylene chloride resulted in epimerization to an equilibrium mixture $\beta:\alpha :: > 95:5$ by NMR.



Scheme 4.



Natural 8S,14-cedranediol[22] and the synthetic material were identical by IR, NMR and mass spectral comparisons.

EXPERIMENTAL

General information. M.ps were determined on a Kofler hot-stage instrument and are uncorrected. With one exception, elemental analyses were performed by Scandinavian Microanalytical Laboratories, Herlev, Denmark. The combustion analysis of **16** was performed by Galbraith Laboratories, Knoxville, Tennessee. Dry ether and THF were distilled under N_2 from potassium-benzophenone ketyl. Methylene chloride was distilled under N_2 from calcium hydride. Toluene was distilled under N_2 from Na. Concentration of solns involved removal of solvent on a rotary evaporator followed by standing at 0.3 to 0.05 mm Hg for 24 hr. Analytical and preparative TLC was performed on precoated commercial (Analtech) silica gel plates. Column chromatography was accomplished on activity I Woelm silica gel.

IR spectra were obtained on a Perkin–Elmer Model 13F instrument. NMR spectra were recorded on a Varian XL-100 instrument in the Fourier transformation mode. Mass spectra were measured on an AEI MS-9 double focusing instrument at 70 eV and inlet temperature of 200–300°.

Glutaric acid mono (1SR, 2SR, 5SR, 6SR, 7RS-tricyclo[5.2.1.$0^{2,6}$] *deca* - 3, 8 - *dien* - 5 - *yl*) *ester* (**2**). To a soln of **1** (56.0 g, 0.370 mol) in dry pyridine (400 mL) was added glutaric anhydride (44.5 g, 0.381 mol). The soln was stirred under argon at 90° for 48 hr. The mixture was cooled to room temp, diluted with ether (800 mL) and washed with 20% HCl until the washings were acidic. The ethereal soln was washed with water and brine, dried with $MgSO_4$, and concentrated to a dark brown oil. Filtration through a silica gel column (200 g) with 20% ether-hexane as eluent afforded, after concentration, a light yellow oil which crystallized on standing at −20° to yield acid **2** (96.1 g, 0.365 mol, 99%). An analytical sample was prepared by recrystallization from hexane, m.p. 53.7–54.7°. NMR ($CDCl_3$) δ1.46 (2H, AB, J = 8 Hz, Δδ = 20 Hz), 2.58 (1H, ddd, J = 2, 4, 6 Hz), 2.83 (1H, m), 3.10 (1H, m), 3.38 (1H, m), 4.97 (1H, m), 5.56 (1H, ddd, J = 2, 2.5, 6 Hz), 5.88 (2H, m), 6.04 (1H, dd, J = 3, 6 Hz), 7.82 (1H, bs); IR[KBr] 3600–2600, 1710 cm^{-1}; *m/e* (rel-intensity) 262(1), 129(100)(Found: C68.74, H7.00. Calc. for $C_{15}H_{18}O_4$: C68.68, H6.92).

1SR, 2SR, 5SR, 6SR, 7RS-*Tricyclo*[5.2.1.$0^{2,6}$] *deca*-3, 8-*dien*-5-*yl* 5'-*hydroxypentanoate* (**3**). A soln of ethyl chloroformate (8.42 g, 78 mmol) in dry THF (20 mL) was added to a soln of **2** (19.55 g, 75.0 mmol) and Et_3N (8.08 g, 80 mmol) in dry THF (120 mL) at 0° in the course of 30 min. The mixture was stirred for 1 hr at the same temp. A copious white ppt (triethylammonium chloride) was filtered off and washed with dry THF (35 mL). The combined filtrate and washings were added over 40 min to a soln of $NaBH_4$ (6.4 g, 200 mmol) in water (75 mL) maintained at 10–15° by external cooling. A substantial exotherm and violent evolution of gas accompanied the addition. The

mixture was stirred vigorously at room temp. for 60 min after the addition was complete, then water (400 mL) was added and the mixture was extracted with ether (3 × 200 mL). The combined ether extracts were washed with water and brine, dried with Na_2SO_4, and concentrated to a viscous oil. This crude product was applied to a silica gel column (100 g), eluted with 20% ether–hexane, and concentrated to yield **3** (17.08 g, 68.9 mmol, 92%). An analytical sample was prepared by preparative TLC (PTLC) on silica gel with 50% ether-hexane as eluent. NMR($CDCl_3$) δ2.53 (1H, ddd, J = 2, 4, 6 Hz), 2.78 (1H, m), 3.06 (1H, m), 3.34 (1H, m), 3.59 (2H, m), 4.92 (1H, m), 5.53 (1H, ddd, J = 2, 2.5, 6 Hz), 5.85 (2H, m), 6.00 (1H, J = 3, 6 Hz); IR(neat) 3380, 1725 cm^{-1}; *m/e* (rel intensity) 248(5), 130(100). (Found: C72.25, H8.22. Calc. for $C_{15}H_{20}O_3$: C72.55, H8.12).

1SR, 2SR, 5SR, 6SR, 7RS-*Tricyclo* [5.2.1.$0^{2,6}$] *deca* - 3, 8 - *dien*- 5 - yl 5' - (2''-*tetrahydropyranyloxypentanoate* (**4**). To a soln of **3** (11.0 g, 44.4 mmol) and freshly distilled dihydropyran (4.43 g, 48.8 mmol) in dry CH_2Cl_2 (50 mL) was added a small crystal of *p*-toluenesulfonic acid. The soln was stirred under argon at room temp. for 2 hr. The mixture was then filtered through Florisil (15 G) with CH_2Cl_2 as eluent and concentrated. The resulting oil was purified by filtration through a column of silica gel (120 g) with 10% ether–hexane as eluent to yield **4** (11.6 g, 34.9 mmol, 77%). An analytical sample was prepared by PTLC on silica gel with 20% ether-hexane as eluent. NMR($CDCl_3$) δ2.56 (1H, m), 2.80 (1H, m), 3.08 (1H, m), 4.55 (1H, m), 4.94 (1H, m), 5.55 (1H, ddd, J = 2, 2.5, 6 Hz), 5.85 (2H, m), 6.00 (1H, dd, J = 3, 6 Hz); IR(neat) 1730 cm^{-1}; *m/e* (rel intensity) 332(1) 130(100). (Found: C72.28, H8.49. Calcd for $C_{20}H_{28}O_4$: C72.26, H8.49).

1RS, 2SR, 5SR, 6SR, 7SR-5- (1'RS-1' - *carboxy* - 4' - (2'' - *tetra* - *hydropyranyloxy*) - 1' - *butyl*) *tricyclo* [5.2.1.$0^{2,6}$] *deca* - 3, 8 - *diene* (**5**). A soln of lithium cyclohexylisopropylamide was prepared from cyclohexylisopropylamine (3.7 g, 4.3 mL, 26.3 mmol) and nBuLi (2.6M in hexane, 10.1 mL, 26.3 mmol) in dry THF (50 mL) at 0°. The soln under argon was cooled at −78°, and a soln of **4** (5.60 g, 16.9 mmol) in dry THF (5 mL) was added dropwise with stirring over a period of 10 min. Triethylsilyl chloride (7.0 g, 8.1 mL, 46.5 mmol) was syringed into a 20 mL test tube containing dry Et_3N (7 mL) under argon. The resulting light ppt, triethylammonium chloride, was centrifuged, thus freeing the silyl chloride of acidic impurities. After the lithium amide – ester mixture had stirred for 30 min at −78°, the silyl chloride-amine soln was added dropwise (90% of the silyl chloride was delivered based on the weight of the residue). The mixture was stirred at −45° for 30 min, warmed over the course of 1 hr to 75°, stirred for 6 hr, and then cooled to room temp. MeOH (5 mL) was added and the soln was stirred for 10 hr, diluted with ether (100 mL), and extracted with 1N NaOH (3 × 50 mL). The combined basic aqueous solns were washed with ether and then mixed with ether (150 mL). The two-phase mixture was acidified by dropwise addition of 6N HCl until no further transient cloudiness was evident. The ether phase was separated and the aqueous layer was extracted with ether (2x). The combined ethereal solns were washed with brine, dried over $MgSO_4$, and concentrated to yield crude acid (3.24 g, 9.76 mmol, 58%) as a colorless oil. NMR ($CDCl_3$) δ2.50 (1H, m), 2.80 (1H, m), 2.88 (1H, m), 4.60 (1H, bs), 5.47 (2H, AB, J = 6 Hz, Δδ = 23 Hz), 5.96 (2H, m), 7.92 (1H, bs); IR (neat) 2400–3400, 1745, 1705 cm^{-1}; *m/e* (rel intensity) 332(1), 182 (100), 164(99). Precise mass. Calcd for $C_{20}H_{28}O_4$: 332.1987; Found: 332.1985.

1RS, 2SR, 5SR, 6SR, 7SR - 5 - (2'RS - 1' *Hydroxy* - 5' - (2'' - *tetra* - *hydropyranyloxy*) - 2' - *pentyl*) *tricyclo* [5.2.1.$0^{2,6}$] deca - 3, 8 - diene (**6**). To a soln of **5** (3.25 g, 9.79 mmol) in dry ether (45 mL) was added LAH (1.20 g, 353 mmol) in three equal portions. The mixture was stirred under argon at room temp for 8 hr. After cooling to 0°, MeOH was added dropwise until evolution of H_2 subsided. The mixture was diluted with ether (150 mL), washed with 30% NaOH (3 × 100 mL), H_2O(3x) and brine, dried with $MgSO_4$, and concentrated to yield 3.1 g of pale yellow oil. This crude product was applied to a column of silica gel (50 g) and eluted with 15% ether–hexane to yield **6** as a colorless oil (2.92 g, 9.18 mmol, 94%). An analytical sample was prepared by PTLC on silica gel with 50% ether–hexane as eluent. NMR($CDCl_3$) δ2.39 (1H, m), 2.73 (1H, m), 2.83 (1H, m), 3.54 (2H, bd), 4.46 (1H, bs), 5.50 (2H, m), 5.93 (2H, m); IR (neat) 3400 cm^{-1}; *m/e* (rel intensity 318(9), 234(100). (Found: C75.38, H9.48. Calc. for $C_{20}H_{30}O_3$: C75.43, H9.50).

1RS, 2SR, 5SR, 7SR - 5 - (2'RS-1' - *Methoxymethyloxy*-5' - (2'' - *tetrahydropyranyloxy*) - 2' - *pentyl*) *tricyclo* [5.2.1.$0^{2,6}$] *deca* - 3, 8-*diene* (**7**). To **6** (3.10 g, 9.70 mmol) and N,N-dimethylaniline (2.10 mL, 17 mmol) in CH_2Cl_2 (40 mL) at 15° was added bromomethyl methyl ether (1.88 g, 1.25 mL, 15 mmol). The soln was stirred under argon for 15 min at room temp. MeOH (2 mL) was added and the mixture was washed with 1N HCl (2x), and brine (2x), filtered through a cotton plug, and concentrated to yield **7** (3.15 g, 8.70 mmol, 90%). An analytical sample was prepared by PTLC on silica gel with 20% ether-hexane as eluent. NMR ($CDCl_3$) δ2.41 (1H, m), 2.76 (1H, m), 2.88 (1H, m), 3.35 (3H, s), 3.45 (2H, ba), 4.59 (3H, bs), 5.49 (2H, m), 5.94 (2H, m); IR(neat 1020 cm^{-1}; *m/e* (rel intensity) 362(2), 150(100). (Found: C72.88, H9.43 Calc. for $C_{22}H_{34}O_4$: C72.99, H9.45).

1RS, 2SR, 5SR, 6SR, 7SR - 5 - (2'RS - 5' - *Hydroxy* - 1' - *methoxy* - *methyloxy* - 2' - *pentyl*) *tricyclo* [5.2.1.$0^{2,6}$] *deca* - 3, 8 - *diene* (**8**). Compound **7** (2.30 g, 6.35 mmol) in MeOH (30 mL) was treated with two drops of 1 N HCl and stirred under argon for 2 hr at room temp. The mixture was diluted with ether (100 mL) and washed with water (2x), sat $NaHCO_3$aq and brine. The organic layer was dried with $MgSO_4$ and concentrated. Purification of the crude product by PTLC on silica gel with 50% ether-hexane afforded **8** (1.52 g, 5.47 mmol, 86%) as an oil. An analytical sample was prepared by PTLC on silica gel with 50% ethe-hexane as eluent. NMR ($CDCl_3$) δ1.91 (1H, s), 2.41 (1H, m), 2.77 (1H, m), 2.86 (1H, m), 3.17 (1H, m), 3.36 (3H, s), 3.62 (2H, bt), 4.60 (1H, s), 5.49 (2H, m), 5.95 (2H, m): IR (neat) 3400 cm^{-1}; *m/e* (rel intensity) 278 (1), 106(100). (Found: C73.22, H9.35. Calc. for $C_{17}H_{26}O_3$: C73.34, H9.41).

1RS, 2SR, 5SR, 6SR, 7SR - 5 - (2'RS - 1' - *Methoxymethyloxy* - 5' - *oxo* - 2' - *pentyl*) *tricyclo* [5.2.1.$0^{2,6}$] *deca* - 3, 8 - *diene* (**9**). CrO_3 (4.0 g, 40 mmol) was added to a stirred soln of dry pyridine (6.3 g, 80 mmol) in dry CH_2Cl_2 (100 mL) under argon. After stirring for 15 min, **8** (1.02 g, 3.67 mmol) in dry CH_2Cl_2(1 mL) was added in one portion, and the soln was stirred at room temp. for 20 min. The mixture was then diluted four-fold with ether and filtered through a pad of Celite. The filtrate was washed with 1N HCl, water and brine, dried with $MgSO_4$, and concentrated to a yellow oil. The crude product was purified by column chromatography on silica gel (50 g) with 10% ether-hexane elution to yield **9** (721 mg, 2.61 mmol, 71%). An analytical sample was prepared by PTLC on silica gel with 1:1 ether-hexane as eluent. NMR($CDCl_3$) δ2.88 (1 H, m), 3.19 (1 H, m), 3.36 (3 H, s), 3.47 (2 H, bd), 4.60 (2 H, s), 5.50 (2 H, m), 5.95 (2 H, m), 9.77 (1 H, t, J = 1 Hz); IR (neat) 2700, 1715 cm^{-1}; *m/e* (rel intensity) 276(5) 148 (100) 106(97) (Found C73.70, H8.73. Calc. for $C_{17}H_{24}O_3$: C73.88, H8.75).

1RS, 2SR, 5SR, 6SR, 7SR - 5 - (2'RS - E - 6' - *Carbomethoxy* - 1' - *methoxymethyloxy* - 5' - *hexen* - 2' - *yl*) *tricyclo* [5.2.1.$0^{2,6}$] *deca* - 3, 8-*diene* (**10**): *and the* Z - *isomer* **10a**. To a soln of **9** (1.79 g, 6.41 mmol) in dry CH_2Cl_2 (15 mL) was added α-carbomethoxyethylidenetriphenylphosphorane (2.44 g, 7.00 mmol). The soln was stirred at room temp under argon for 16 hr. The mixture was concentrated, applied to a column of silica gel (100 g), and eluted with 10% ether-hexane to yield **10** and **10a** as colorless oils. The *Z*-isomer **10a** was eluted first (R_f = 0.44*, 65 mg, 0.188 mmol, 3%). NMR ($CDCl_3$) δ1.88 (3 H, q, J = 1), 2.77 (1 H, m), 2.86 (1 H, m), 3.17 (1 H, m), 3.35 (3 H, s), 3.46 (2 H, d), 3.73 (3 H, s), 4.60 (2 H, s), 5.50 (2 H, m), 5.95 (3 H, m); IR (neat) 1715, 1640 cm^{-1}; *m/e* (rel intensity) 396(2), 85(100). Precise mass measurement; Calc. for $C_{21}H_{30}O_4$: 346.2145; Found: 346.2144.

The *E*-isomer **10** followed closely (R_f = 0.41*, 1.85 g, 5.35 mmol, 83%). An analytical sample was prepared by PTLC on silica gel with 1:1 ether–hexane* as eluent. NMR ($CDCl_3$) δ1.83 (3 H, q, J = 1 Hz), 2.76 (1 H, m), 2.86 (1 H, m), 3.12 (1 H, m), 3.35 (3 H, s), 3.46 (2 H, bd), 3.17 (1H, m), 3.35 (3 H, s), 3.46 (2 H, bd), 4.60 (2 H, s), 5.49 (2 H, m). 5.94 (2 H, m), 6.76 (1 H, tq, J = 1, 8 Hz): IR (neat) 1710, 1650 cm^{-1}; *m/e* (rel intensity) 346(7) 218(100). (Found: C72.82, H8.73. Calc. for $C_{21}H_{30}O_4$: C72.80, H8.73).

1SR, 2RSSR, 5RS, 6SR, 7RS - 6 - *Carbomethoxy* - 2 - *methoxymethyl* - *oxymethyl* - 6 - *methyltricyclo* [5.2.1.$0^{1,5}$] *dec* - 8

- *ene* (**11**). The ester **10** (1.58 g, 4.57 mmol), hydroquinone (1 mg) and dry toluene (47 mL) were placed in a resealable Carius tube, and the soln was de-gassed with a stream of argon. The tube was sealed and heated in a silicon oil bath at 180° for 24 hr. The mixture was cooled and concentrated to yield a yellow oil (1.15 g). The crude product was purified by chromatography through silica gel (100 g) with 20% ether-hexane as eluent to yield **11** as a colorless oil (1.06 g, 3.79 mmol, 83%). Spectral data as in text. Precise mass: Calc. for $C_{16}H_{25}O_4$: 280.1674; Found: 280.1671.

1SR, 4SR, 7SR, 8RS, 11RS, 12RS - 5 - Chloro - 8 - hydroxymethyl - 1 - methyl - 3 - oxatetracyclo [5.4.2.$0^{4,12}0^{7,11}$] *tridec* - 5 - *en* - 2 - *one* (**16**); *and the 8SR-isomer* **17**. To **11** (1.10 g, 4.10 mmol) in benzene (5 mL) were added benzyltriethyl-ammonium chloride (85 mg, 0.37 mmol) and 50% KOHaq (30 mL). The mixture was stirred vigorously at room temp under argon, and $CHCl_3$ (8 mL) was added dropwise over a period of 2 hr. The mixture was stirred for 15 hr. The mixture was stirred for 15 hr, and then 50% KOH (10 mL), benzene (2 mL) and $CHCl_3$ (2 mL, dropwise) were added. After stirring an additional 10 hr, the mixture was diluted with ether and acidfied to pH 1 with 6N HCl. The organic layer was separated, and the aqueous layer was extracted with ether (3x). The combined ethereal solns were washed with water and brine, dried with $MgSO_4$, and concentrated to yield a yellow oil (1.5 g). A de-gassed mixture of the crude oil in 8% KOHaq (35 mL) and THF (0.2 mL) was refluxed for 12 hr. The mixture was allowed to cool to room temp and was washed with ether. The basic aqueous soln was acidified with excess 20% H_2SO_4, allowed to stand for 1 hr, and then extracted with ether (2 × 70 mL). The ether extract was washed with water, $NaHCO_3$aq and brine, dried with $MgSO_4$, concentrated, and dissolved in MeOH (30 mL). The soln was treated with conc HCl (4 drops), stirred for 6 hr at room temp, and diluted with ether. The ethereal soln was washed with water, sat $NaHCO_3$aq and brine, dried with $MgSO_4$, and concentrated to yield a mixture of **16** and **17** (607 mg, 2.26 mmol, 55.1%). The mixture was easily separated by PTLC on silica gel with 2:1 ether-hexane to yield **17** (R_f = 0.22, 233 mg, 0.883 mmol, 22%) and **16** (R_f = 0.41, 218 mg, 0.812 mmol, 20%).

An analytical sample of **17** was prepared by recrystallization from hexane as white needles, m.p. 113.0–114.5°. NMR($CDCl_3$) δ1.25 (3 H, s), 2.52 (1 H, dd, J = 8, 8 Hz), 2.88 (1H, ddd, J = 8, 4, 1 Hz), 3.67 (2 H, dd, J = 6.5, 4 Hz), 4.99 (1 H, dd, J = 8, 1 Hz), 6.52 (1 H, s); IR (KBr) 3380, 3300, 1765, 1755, 1630 cm^{-1}; *m/e* (rel intensity) 270 (4.5) 268 (14), 138 (100). (Found: C62.55, H6.31, Cl 13.31. Calc. for $C_{14}H_{17}O_3Cl$: C62.57, H6.38, Cl 13.19).

An analytical sample of **16** was prepared by recrystallization from hexane, mp 90.5–92.0°. NMR ($CDCl_3$) δ1.28 (3 H, s), 2.45 (1 H, bdd, J = 7, 11 Hz), 2.83 (1 H, ddd, J = 8, 4, 1.5 Hz), 3.72 (2 H, dd, J = 6, 4 Hz), 4.98 (1 H, dd, J = 8, 1 Hz), 6.77 (1 H, s); IR (KBr) 3250, 1765, 1630 cm^{-1}; *m/e* (rel intensity) 270(4), 268(12), 138(100). (Found: C62.57, H6.57, Cl 13.30. Calc. for $C_{14}H_{17}O_3Cl$: C62.57, H6.38, Cl 13.19).

1SR, 2RS, 5RS, 6SR, 7RS, 8SR - 2, 6 - *dimethyl* - 8 - *hydroxy* - 6 - *hydroxymethyltricyclo* [5.3.1^{1,5}] *undec* - 9 - *ene* (**18**). A soln of **16** (89 mg, 0.331 mmol) and *p* - toluene-sulfonyl chloride (98 mg, 0.509 mmol) in dry pyridine (3.8 mL) was stirred under argon at room temp for 4 days. The mixture was then diluted with CH_2Cl_2, washed with water, 1 N HCl, sat $NaHCO_3$aq and water. The organic layer was filtered through a cotton plug and concentrated to a yellow solid (128 mg, 0.304 mmol, 91.8%). The crude tosylate (124 mg, 0.292 mmol) was dissolved in dry dimethoxyethane (30 mL); LAH_4 (150 mg, 3.95 mmol) was added, and the mixture under argon was stirred at reflux for 48 hr. The mixture was cooled to room temp and quenched by addition to a 10% MeOH–CH_2Cl_2 soln. The CH_2Cl_2 soln was washed with 30% KOHaq (2x), 1N HCl, sat $NaHCO_3$aq and water, and filtered through a cotton plug. Evaporation of solvents and purification of the crude product by PTLC on silica gel with 1:1 hexane as eluent yielded **18** (53 mg, 0.239 mmol, 81.7%, 75.0% overall) as a white solid. An analytical sample was prepared by recrystallization from hexane, m.p. 92.0–93.5°. NMR ($CDCl_3$) δ0.95 (3H, d, J = 7 Hz), 1.08 (3H, s), 2.20 (1 H, bt), 3.61 (2 H, bs), 3.33 (1 H, d, J_{gem} = 12 Hz), 3.81 (1 H, d, J_{gem} = 12 Hz), 4.71 (1 H, ddd, J = 4, 2, 2), 5.41 (1 H, ddd, J = 10, 2, 2), 6.06 (1 H, ddd, J = 10, 2, 2); IR (KBr) 3380 cm^{-1}; *m/e* (rel intensity) 222(4), 147(100). (Found: C75.57, H9.95 Calc. for $C_{14}H_{22}O_2$: C75.63, H9.97).

1*SR*, 2*RS*, 5*RS*, 6*SR*, 7*RS* - 2, 6 - *Dimethyl* - 6 - *hydroxymethyl* - *tricyclo* [5.3.1.0^{1,5}] *undec* - 9 - *en* - 8 - *one* (**19**). The alcohol **18** (18 mg, 0.081 mmol) and MnO_2 (100 mg, 1.15 mmol) in ether (3 mL) were stirred under argon for 48 hr. The mixture was filtered through a Celite column (0.5 × 5 cm), eluted with CH_2Cl_2 (100 mL), and concentrated. The crude product was purified by PTLC on silica gel with 2:1 ether–hexane as eluent to yield **19** as a colorless oil (14 mg, 0.064 mmol, 79%). NMR ($CDCl_3$) δ1.12 (3 H, d, J = 7 Hz), 1.27 (3 H, s), 2.78 (1 H, m), 3.25 (3 H, m, CH_2OH), 5.96 (1 H, dd, J = 10, 2 Hz), 7.64 (1 H, dd, J = 10, 2 Hz); IR (neat) 3640, 3500, 1655; *m/e* (rel intensity) 220(15), 190 (100). Precise mass: (Calc. for $C_{14}H_{20}O_2$: 220.1463; Found: 220.1462.

1SR, 4SR, 7SR, 8RS, 11RS, 12RS - 1, 8 - *Dimethyl* - 4 - *hydroxy* - 3 - *oxatetracyclo* [5.4.2.$^{4,12}0^{7,11}$] tridecane (**20**). The enone **19** (31 mg, 0.141 mmol) in EtOH (2.8 mL) was catalytically hydrogenated over 10% Pd–C (6 mg) at room temp and under atmospheric pressure. After 18 hr, the mixture was filtered through Celite (10 g) and concentrated to yield **20** (28 mg, 0.126 mmol, 89%). An analytical sample was prepared by recrystallization from hexane, m.p. 104–106°. NMR ($CDCl_3$) lactol δ0.83 (3 H, d, J = 7), 1.01 (3 H, s), 2.44 (1 H, m), 3.59 (~0.9 H, d, J = 18 Hz), 3.77 (~0.9H, d, J = 18 Hz) keto δ3.39 (~0.2H, bs, CH_2–OH); IR(KBr) 3530 cm^{-1}; IR ($CDCl_3$) 3800, 3550, 1675 cm^{-1}; *m/e* (rel intensity) 222(10), 149(94), 99(100). (Found: C75.50, H10.01. Calcd for $C_{14}H_{22}O_2$: C75.63, H9.97).

(±) 8S, 14-*Cedranediol* (I)

Method A. To a stirred soln of **20** (13 mg, 0.059 mmol) in ether (3 mL) at −78° under argon was added MeLi (1.3 M in ether, 0.20 mL, 0.26 mmol). After 15 min at −78°, the mixture was allowed to warm to room temp and, after 2 hr, was quenched with water (4.7 μL, 0.26 mmol). This sequence—cooling to −78°, treating with MeLi, warming to room temp and quenching with water—was repeated twice more. The ethereal soln was then washed with water (2x) and brine, dried with Na_2SO_4, and concentrated to an oily solid. The crude product was purified by PTLC on silica gel with 1:1 ether-hexane as eluent to yield recovered starting material **20** (2 mg, 0.009 mmol, 15%) and the diol I (6.0 mg, 0.025 mmol, 43%). Recrystallization from hexane provided an analytical sample, m.p. 129.0–130.5°. NMR($CDCl_3$) δ0.85 (3 H, d, J = 7), 1.10 (3 H, d, J = 1), 1.81 (3 H, d, J = 1), 3.28 (1 H, d, J = 11), 4.04 (1 H, d, J = 11); IR(KBr) 3250 cm^{-1}; *m/e* (rel intensity) 238(2) 190(100) 161(59) 149(80) 119(42). Calc. for $C_{15}H_{26}O_2$: C75.58, H11.00; Found: C75.61, H10.89.

Method B. To **19** (10 mg, 0.045 mmol) and 2-methoxypropene (15 mg, 0.49 mmol) in dry CH_2Cl_2 (3 mL) was added a small crystal of *p*-toluenesulfonic acid, and the soln was stirred under argon at room temp for 1 hr. The mixture was filtered through Florisil, concentrated, and taken up in ether (3 mL). The ethereal soln under argon was cooled to −78°, and MeLi (1.3 m in ether, 0.20 mL, 0.26 mmol) was added. After stirring at room temp for 1 hr, the mixture was diluted with ether, washed with water and brine, dried with Na_2SO_4, concentrated, and dissolved in abs EtOH (4 mL). The soln was hydrogenated over 10% Pd–C (8 mg) at room temp and under atmospheric pressure. After 20 hr the mixture was filtered through Celite (1 g) with additional EtOH (20 ml) and a small crystal of *p*-toluenesulfonic acid was added. After stirring for 1 hr, the soln was diluted with ether, washed with sat $NaHCO_3$aq and brine, dried with Na_2SO_4 and concentrated. The crude product was purified by PTLC on silica gel with 1:1 ether–hexane as solvent to yield I (7.5 mg, 0.032 mmol, 71%). This material was identical to that obtained from method A.

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