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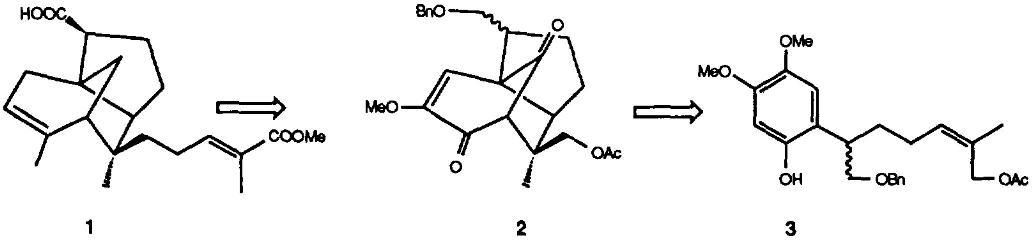
The First Synthesis of a 2-*Epi*-cedrene Isoprenologue by Means of an Electrochemical Method in the Key Step

Hiroyuki Takakura, Kunihiro Toyoda, and Shosuke Yamamura*

Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Yokohama 223, Japan

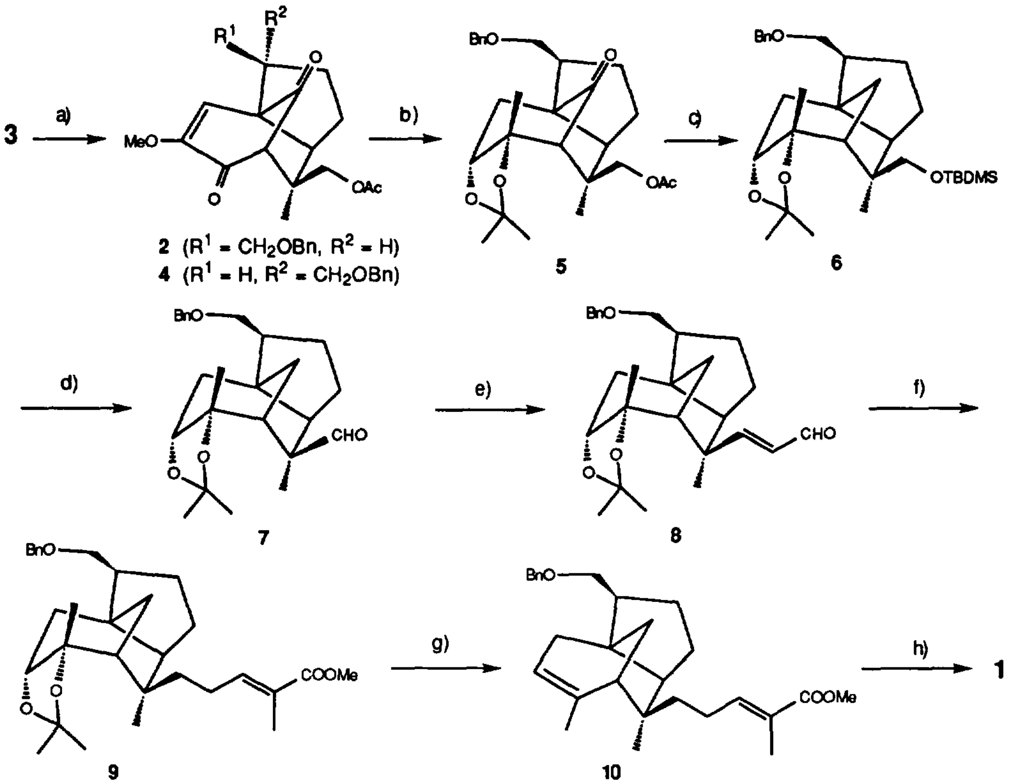
Abstract: Synthesis of a 2-*epi*-cedrene isoprenologue is described. The key step is construction of a tricyclo[5.3.1.$0^{1,5}$]undec-9-en-8,11-dione by means of electrochemical oxidation of the corresponding phenol. Copyright © 1996 Elsevier Science Ltd

Since our own development of the phenolic oxidation methodology employing electrolysis,[1] a number of natural products including 8,14-cedrenoxide,[1a] silphinene,[2a] pentalenene[2b] and others[3] have been extensively synthesized. A part of our continuous investigation has been focused on the new 2-epi-cedrene isoprenologues, first isolated from *Eremophila georgei* Diels,[4] which constitute a new class of diterpenes bearing a tricyclic cedrane-type skeleton in their molecule. We describe herein a total synthesis of one of these diterpenes (1), whose retrosynthesis is shown in Scheme 1, wherein the requisite key intermediate, 6-acetoxymethyl-2-benzyloxymethyl-6-methyl-9-methoxytricyclo[5.3.1.$0^{1,5}$]undec-9-en-8,11-dione (2), is obtained by means of anodic oxidation of the corresponding phenol (3).[1]



Scheme 1.

According to essentially the same procedure as described in the 8,14-cedranoxide synthesis,[1a] 3,4-dimethoxyphenol was readily converted into the desired phenol (3),[5] which was subjected to anodic oxidation [10.8 mA (+750 - 1150 mV *vs.* SCE; *ca.* 2 F/mol)][6] in acetic anhydride containing $^{n}Bu_4NBF_4$ as a supporting electrolyte to afford a mixture of two tricyclo[5.3.1.$0^{1,5}$]undec-9-en-8,11-diones (2 and 4)[7] in 68% yield (relative ratio **2**/**4** = 2/5), wherein their stereochemistry of the benzyloxymethyl group at C_2-position was unambiguously determined by ^1H NMR spectral data: particularly, the two double doublets of the benzyloxymethyl group [δ 3.94 (1H, dd, J = 6.6, 8.8 Hz) and 4.22 (1H, dd, J = 6.6, 8.8 Hz)] in **2** are observed in lower magnetic field as compared with the corresponding doublet [δ 3.67 (2H, J = 4.6 Hz)] in **4**, because of an anisotropic effect of the carbonyl group at C_{11}-position. The β-stereoisomer (**2**) was carefully treated with Grignard reagent at -78 °C and then hydrolyzed with oxalic acid to afford an α-hydroxyketone which was further subjected to $NaBH_4$ reduction in MeOH at 0 °C followed by ketalization to give **5**.,[7] which was also derived from the α-stereoisomer (**4**).[8] The ketal (**5**) was successively subjected to DIBAL reduction, selective silylation, and then Barton deoxygenation to afford the corresponding deoxy compound (**6**),[7] in high overall yield.[9]



a) Electrolysis at 10.8 mA (ca. 2 F / mol) / $^nBu_4NBF_4$ / Ac_2O (68%; 2/4 = 2/5). b) i) MeMgBr / THF (-78 °C, 1 h) (70%), ii) aq $(COOH)_2$/MeOH (60 °C, 12 h) (88%), iii) $NaBH_4$/MeOH (0 °C, 15 min) (100%), iv) p-TsOH/acetone (room temp, 12 h) (81%). c) i) DIBAL (5 equiv.) / toluene (-78 °C - room temp, 30 min), ii) TBDMSCl / imidazole/DMF (room temp, 12 h) (91% in 2 steps), iii) NaH / CS_2 / MeI / THF (0 °C, 3 h), iv) Bu_3SnH / AIBN / toluene (64% in 2 steps). d) i) TBAF / THF (room temp, 12 h), ii) SO_3 / pyridine /DMSO / Et_3N (room temp, 1 h) (62% in 2 steps). e) i) AllylMgCl / THF (-78 °C, 15 min - room temp, 45 min), ii) Ac_2O / pyridine (room temp, 8 h) (100% in 2 steps), iii) OsO_4 / NMO / acetone / H_2O (room temp, 16 h), iv) $NaIO_4$ / THF/H_2O (0 °C, 10 min - room temp, 2 h) (98% in 2 steps). f) i) H_2 / Pd-C / EtOAc (room temp, 3 h), ii) $Ph_3P{=}C(Me)COOMe$ / benzene (room temp, 1 h) (93% in 2 steps). g) i) 80% AcOH (room temp, 10 h), ii) $CH(OMe)_3$ / PPTS / CH_2Cl_2 (40 °C, 10 h), iii) Ac_2O (155 °C, 6 h) (79% in 3 steps). h) i) BCl_3 / Me_2S / CH_2Cl_2 (0 °C, 15 min - room temp, 2 h) (99%), ii) Jones oxidation (0 °C, 1 h) (55%).

Scheme 2.

In order to construct the α,β-unsaturated ester side-chain of **1**, **6** was readily converted into an aldehyde (**7**) in 2 steps, as shown in Scheme 2. Further chain elongation at the CHO position of **7** was attempted under various conditions using Wittig and related reactions , but failed because of steric hindrance. However, successful conversion of **7** to the desired α,β-unsaturated aldehyde (**8**)[7] was effected by successive treatments with allyl magnesium chloride, acetic anhydride in pyridine, OsO_4 - NMO and $NaIO_4$ in almost quantitative yield. On catalytic hydrogenation followed by Wittig reaction, **8** was readily converted into the corresponding aldehyde (**9**),[7] which was further converted into a tri-substituted olefin (**10**)[7] in 79% overall yield, [10] as shown in Scheme 2. Finally, debenzylation[11] of **10** with BCl_3 - Me_2S followed by Jones oxidation gave rise to the target diterpene (**1**),[12] the spectral data of which were identical to those reported by Forster *et al.*[4b] This is the first synthesis of the naturally occurring 2-epi-cedrene isoprenoloque, although synthetic studies have been made on the rather simple cedrane-type sesquiterpenes, including 8S,14-cedranediol,[13a] which have been synthesized since Stork's original synthesis of cedrol.[1a, 13b]

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References and Notes

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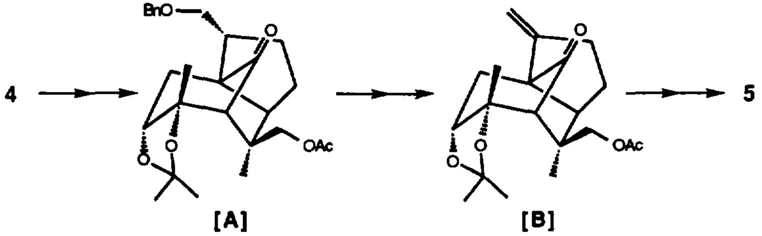
5. The synthetic procedure of **3** will be reported elsewhere in detail; its structure is based on the spectral data : $C_{23}H_{32}O_6$ [m/z 428.2188 (M$^+$)]; IR (film) 3450, 1740, 1610, 1510 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.73 (3H, s), 1.74 - 2.00 (4H, complex), 2.04 (3H, s), 2.83 (1H, m), 3.68 (1H, dd, J = 8.6, 5.6 Hz), 3.78 (1H, dd, J = 8.6, 5.6 Hz), 3.80 (3H, s), 3.82 (3H, s), 4.47 (2H, s), 4.53 (1H, d, J = 11.9 Hz), 4.61 (1H, d, J = 11.9 Hz), 5.34 (1H, t, J = 7.3 Hz), 6.51 (2H, s), 7.27 - 7.34 (5H, complex).
6. The anodic oxidation of **3** was carried out at room temperature under an argon atmosphere using a 200 ml glassy carbon beaker [GC-20, Tokai Carbon Co. Ltd.] and a platinum wire tip as an anode and a cathode, respectively. On electrolysis under aerobic condition, the total yield of **2** and **4** was very low.
7. The spectral data for the new compounds were in accord with the structures assigned, and only selected data are cited: **2** as an oil: $C_{24}H_{28}O_6$ [m/z 412.1860 (M$^+$)]; IR (film) 1740, 1690, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (3H, s), 2.05 (3H, s), 3.47 (1H, s), 3.58 (3H, s), 3.82 (1H, d, J = 11.7 Hz), 3.94 (1H, dd, J = 8.8, 6.6 Hz), 4.19 (1H, d, J = 11.7 Hz), 4.22 (1H, dd, J = 8.8, 6.6 Hz), 4.50 (1H, J = 11.7 Hz), 4.54 (1H, d, J = 11.7 Hz), 6.48 (1H, s), 7.25 - 7.34 (5H, complex); ^{13}C NMR ($CDCl_3$) δ 20.6, 23.9, 24.4, 30.0, 38.6, 47.1, 55.6, 57.6, 63.4, 68.9, 69.4, 73.2, 73.4, 125.9, 127.5, 127.6, 127.7, 128.2, 138.3, 153.2, 170.5, 191.3, 202.0. **4** as an oil: $C_{24}H_{28}O_6$ [m/z 412.1854 (M$^+$)]; IR (film) 1750, 1690, 1600 cm^{-1}; ^{1}H

NMR (CDCl$_3$) δ 1.06 (3H, s), 2.06 (3H, s), 3.50 (1H, s), 3.54 (3H, s), 3.67 (2H, d, J = 4.6 Hz), 3.79 (1H, d, J = 11.2 Hz), 4.08 (1H, d, J = 11.2 Hz), 4.56 (2H, s), 6.66 (1H, s), 7.27 - 7.34 (5H, complex); 13C NMR (CDCl$_3$) d 20.7, 23.7, 26.0, 31.3, 37.7, 38.2, 55.4, 58.9, 63.8, 68.8, 70.1, 72.5, 73.3, 122.1, 127.5, 127.7, 127.8, 128.3, 128.5, 137.8, 153.4, 170.6, 191.0, 202.0. **5** as an oil: $C_{27}H_{36}O_6$ [m/z 456.2532 (M$^+$)]; IR (film) 1750 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.39 (3H, s), 1.42 (3H, s), 1.46 (3H, s), 1.66 (3H, s),1.98 (3H, s), 4.09 (1H, d, J = 7.3 Hz). **6** as an oil: $C_{31}H_{50}O_4Si$ [m/z 514.3459 (M$^+$)]; IR (film) no CO band; ^{1}H NMR (CDCl$_3$) δ 0 .01 (6H,s), 0.88 (9H, s). **7** as an oil: $C_{25}H_{34}O_4$ [m/z 398.2449 (M$^+$)]; IR (film) 1720 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 9.51 (1H, s); ^{13}C NMR (CDCl$_3$) δ 206.4. **8** as an oil: $C_{27}H_{36}O_4$ [m/z 424.2651 (M$^+$)]; IR (film) 1690 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 6.13 (1H, dd, J = 16.0, 7.6 Hz), 6.99 (1H, d, J = 16.0 Hz), 9.49 (1H, d, J = 7.6 Hz). **9** as an oil: $C_{31}H_{44}O_5$ [m/z 496.3220 (M$^+$)]; IR (film) 1720, 1640 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.82 (3H, d, J = 1.1 Hz), 3.73 (3H, s), 6.73 (1H, tq, J = 7.3, 1.1 Hz) **10** as an oil: $C_{28}H_{38}O_3$ [m/e 422.2828 (M$^+$)]; ^{1}H NMR (CDCl$_3$) δ 1.66 (3H, d, J = 1.0Hz), 5.26 (1H, br.s).

8. The α–stereoisomer (**4**) has been converted into **5**, as shown in Scheme 3; respective reaction conditions, however, have not been optimized.



4→**[A]**: see the same procedure as shown in Scheme 2 (**2**→**5**) (50% overall yield)
[A]→**[B]**: i) H_2, $Pd(OH)_2$, EtOH; ii) ArSeCN, Bu_3P, THF; iii) H_2O_2, THF (48% overall yie
[B]→**5**: i) 9-BBN and then $NaBO_3$, THF; ii) KH, BnBr, DMF (50% overall yield)

Scheme 3.

9. Direct Wolff-Kishner reduction of the CO group at C_{11}-position did not give satisfactory results in the case of **5** bearing the β-acetoxymethyl group at C_6-position.
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12. The synthetic 2-epi-cedrene isoprenologue as colorless crystals: mp 74 - 76 °C (from pentane); ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.04 (3H, s), 1.67 (3H, d, J = 1.9 Hz), 1.85 (3H, d, J = 1.0 Hz), 2.17 (1H, m), 2.34 (1H, m), 2.43 (1H, dd, J = 10.2, 7.5 Hz), 2.71 (1H, dt, J = 14.8, 1.5 Hz), 3.75 (3H, s), 5.28 (1H, br.s), 6.77 (1H, tq, J = 6.4, 1.0 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 12.3, 23.1, 24.0, 24.5, 24.6, 29.7, 34.1, 34.9, 42.1, 48.2, 51.1, 51.6, 51.8, 54.4, 60.6, 120.2, 127.3, 140.3, 143.1, 168.7, 180.2.
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