Tetrahedron Letters,Vol.28,No.52,pp 6661-6664,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

EFFICIENT SYNTHESIS OF (±)-8,14-CEDRANOXIDE USING ELECTROCHEMICAL METHOD AS A KEY STEP

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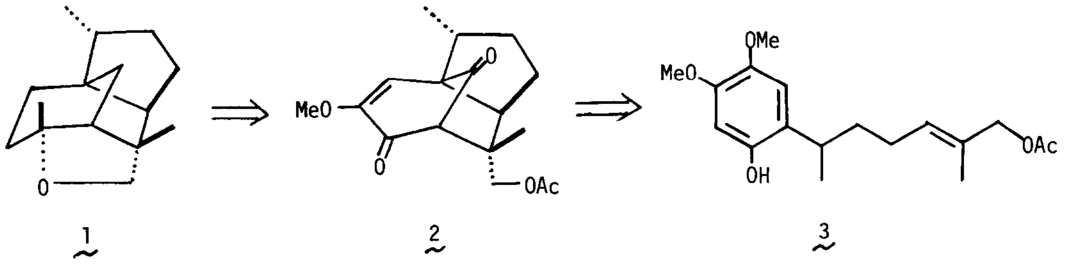
Summary: (±)-8,14-Cedranoxide has been synthesized starting from 3,4-dimethoxyphenol, wherein 6-acetoxymethyl-2,6-dimethyl-9-methoxytricyclo[5.3.1.$0^{1,5}$]undec-9-en-8,11-dione as a key intermediate has been produced efficiently by means of electrochemical methods.

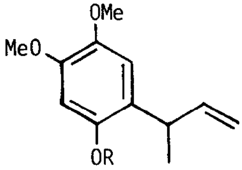
In connection with our synthetic work on bioactive substances using electrochemical methods, helminthosporal, a toxic sesquiterpene, has been synthesized in racemic form starting from the bicyclo[3.2.1]oct-3-en-2,8-dione which is formed electrochemically.[1] We describe herein a total synthesis of (±)-8,14-cedranoxide (1),[2,3] a constituent of the plant Juniperus foetidissima Willd, whose retrosynthesis is shown in Scheme 1, wherein 6-acetoxymethyl-2,6-dimethyl-9-methoxytricyclo[5.3.1.$0^{1,5}$]undec-9-en-8,11-dione (2) as a key intermediate must be produced on anodic oxidation of the corresponding phenol (3) derivable from 3,4-dimethoxyphenol.



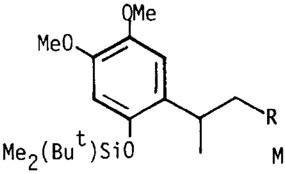
Scheme 1. Retrosynthesis of 8,14-cedranoxide

On treatment with crotyl chloride (2 equiv.) - K_2CO_3 (2 equiv.) in acetone (refluxing temp., 2 days) followed by Claisen rearrangement (200 °C, 2 h, under argon), 3,4-dimethoxyphenol was quantitatively converted into the corresponding phenol (4),[4] which was further treated with t-butyldimethylsilyl chloride (1.2 equiv.) - imidazole (2.4 equiv.) in DMF under argon (room temp., 18.5 h) to afford a silyl ether (5)[4] in quantitative yield. The compound (5) was subjected to hydroboration [$BH_3 \cdot Me_2S$ (1.5 equiv.) in THF under argon (0 °C, 30 min and then room temp., 2 h)] followed by oxidation with 30% H_2O_2 - aq.NaOH (0 °C, 1.5 h) to afford a hydroxy compound (6),[4] in 66% yield, which was further oxidized with DMSO (16 equiv.) - DCC (4 equiv.) - pyridine (1.5 equiv.) - TFA (catalytic amount) in benzene under argon (room temp., 2.5 h) to give rise to the corresponding aldehyde (7)[4] in 93% yield. This aldehyde was further subjected to Wittig reaction [Ph$_3$P$^+$CH$_2$OMe·Cl$^-$(1.5 equiv.) - MeLi (1.5 equiv.) in THF under argon (room temp., 20 min)] followed by hydrolysis with *p*-TsOH in acetone under argon (room temp., 1.3 h) to give another aldehyde (8)[4] with one more methylene group at the side chain, in 60% yield. On Wittig reaction [Ph$_3$P=C(Me)COOMe (2 equiv.) in benzene under argon (room temp., 18 h)], this compound (8) was readily converted into an α,β-unsaturated ester (9),[4] in 92% yield, which was reduced with Bu$^i_2$AlH (4 equiv.) in THF under argon (-70 °C, 2.8 h) and then acetylated with Ac$_2$O - pyridine to afford the corresponding acetate (10)[4] in 99% yield. Finally, the acetate (10) was deprotected with Bu$^n_4$NF (1.5 equiv.) in THF under argon (room temp., 15 min) to give rise to the desired phenol (3)[4], in quantitative yield, anodic oxidation of which was carried out under various conditions.

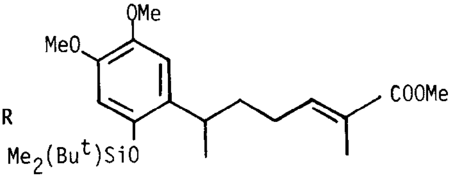
When electrolyzed at a constant current [2.5 mA (+900 - 1200 mV *vs*. SCE); *ca*. 2 F/mol][5] in acetic anhydride containing Bu$^n_4$NBF$_4$ as a supporting electrolyte, the phenol (3) was converted into an inseparable mixture of two tricyclo[5.3.1.0^{1,5}]undec-9-en-8,11-diones (2 and 11)[6] in 80% yield [relative ratio: 2/11 = 4].[7] When a mixed solvent of Ac$_2$O and AcOH (3 : 2) was used as a solvent system, the total yield of both 2 and 11 was 44%. Their



4 R = H
5 R = Si(Bu^t)Me$_2$



6 R = CH$_2$OH
7 R = CHO
8 R = CH$_2$CHO



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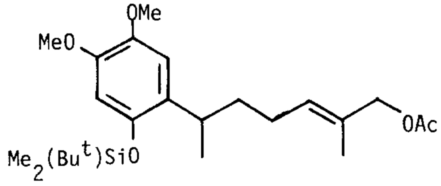

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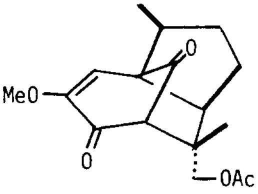
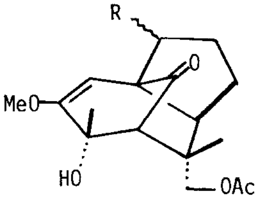
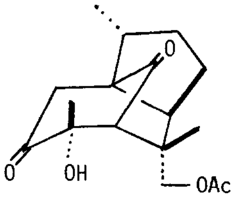


11



12a R = α-Me
12b R = β-Me



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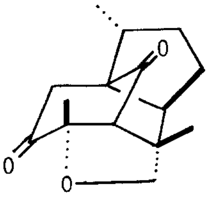

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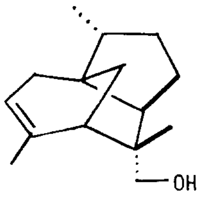

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stereostructures are based on ^1H NMR spectral data: particularly, the methyl doublet (δ 1.42) in **11** is observed in lower magnetic field as compared with the corresponding one (δ 1.15) in **2**, because of an anisotropic effect of the carbonyl group at C_{11}-position.

This mixture (**2** and **11**) so far obtained was treated with MeMgI (1.4 equiv.) in THF (-78 °C, 2.2 h) to afford an inseparable mixture of two hydroxy compounds (**12a** and **12b**),[4] in 51% yield, which was further hydrolyzed with oxalic acid in MeOH (room temp., 14 h) to give rise to the desired diketone (**13**)[4] as colorless needles, in 93% yield.[8] Furthermore, this diketone (**13**) was treated with BF_3-etherate (6 equiv.) in toluene under argon (refluxing temp., 2.7 h) to afford a tetrahydrofuran derivative (**14**)[4] in 72% yield. Finally, the compound (**14**) was subjected to Wolff-Kishner reduction [KOH (excess amount) - NH_2NH_2 (excess amount) in ethyleneglycol under argon (refluxing temp., 1.5 h)] to afford 8,14-cedranoxide (**1**)[2,9] and 8-cedren-14-ol (**15**)[2,4] in 20 and 50% yields, respectively. When treated with catalytic amount of p-TsOH in toluene under argon (refluxing temp., 1 h), the latter was readily converted into 8,14-cedranoxide (**1**) in 88% yield. Therefore, the total yield of (±)-cedranoxide (**1**) from **14** was 65%.

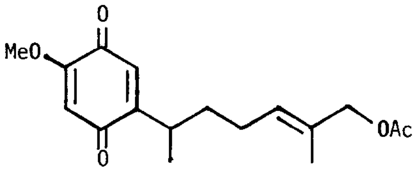
This research has been supported in part by grants from the Ministry of Education, Science and Culture as well as from the Kurata Foundation, to which grateful acknowledgment is made.

References

1. Y. Shizuri, K. Suyama, and S. Yamamura, J. Chem. Soc., Chem. Commun., 1986, 63.
2. K. H. Baggaley, H. Erdtman, and T. Norin, Tetrahedron, 24, 3399 (1968).
3. A number of synthetic studies have been carried out on α-cedrene and/or cedrol since Stork's original synthesis of cedrol [G. Stork and F. H. Clark, J. Am. Chem. Soc., 77, 1072 (1955)]. Recently, the first synthesis of a more highly functionalized cedranoid, (±)-8S,14-cedranediol, was reported by Landry [D. W. Landry, Tetrahedron, 39, 2761 (1983) and many references cited therein].
4. The spectral data for the new compounds were in accord with the structures assigned, and only selected data are cited: **4**: $C_{12}H_{16}O_3$ [m/z 208.1081(M^+)]; IR (film) 3460, 1600, and 1590 cm^{-1}; δ($CDCl_3$) 1.34(3H, d, J = 8 Hz), 3.65(1H, m), 3.77(3H, s), 3.80(3H, s), 5.0 - 5.27(2H, complex), 6.03(1H, ddd, J = 6, 11, 18 Hz), 6.41(1H, s), and 6.63(1H, s). **5**: $C_{18}H_{30}O_3Si$ [m/z 322.1945(M^+)]; IR (film) 1630 and 1600 cm^{-1}; δ($CDCl_3$) 0.21(6H, s) and 1.00(9H, s). **6**: $C_{18}H_{32}O_4Si$ [m/z 340.2072(M^+)]; IR (film) 3450 cm^{-1}; δ($CDCl_3$) 1.3 - 2.0 (2H, m) and 3.1 - 3.6(3H, complex). **7**: $C_{18}H_{30}O_4Si$ [m/z 338.1913(M^+)]; IR (film) 1720 cm^{-1}; δ($CDCl_3$) 2.5 - 2.7(2H, m), 3.5 - 4.0(1H, m), and 9.66(1H, t, J = 2 Hz). **8**: $C_{19}H_{32}O_4Si$ [m/z 352.2049(M^+)]; IR (film) 1720 cm^{-1}; δ($CDCl_3$) 9.67(1H, t, J = 1 Hz). **9**: $C_{23}H_{38}O_5Si$ [m/z 422.2465(M^+)]; IR (film) 1710, 1640, 1600 cm^{-1}; δ($CDCl_3$) 1.72(3H, br.s), 3.66(3H, s), 3.77(3H, s), 3.80(3H, s), and 6.71(1H, m). **10**: $C_{24}H_{40}O_5Si$ [m/z 436.2626(M^+)]; δ($CDCl_3$) 1.57(3H, br.s), 2.03(3H, s), 4.30(2H, br.s), and 5.43(1H, m). **3**: $C_{18}H_{26}O_5$ [m/z 322.1754 (M^+)]; IR (film) 3450, 1730, 1710sh., and 1610 cm^{-1}; δ($CDCl_3$) 1.19(3H, d, J = 7 Hz), 1.53 (3H, br.s), 1.5 - 1.8(2H, complex), 1.8 - 2.1(2H, complex), 2.03(3H, s), 2.96(1H, sextet, J = 7 Hz), 3.75(3H, s), 3.78(3H, s), 4.41(2H, s), 5.17(1H, s), 5.42(1H, br.t, J = 7 Hz), 6.40(1H, s), and 6.63(1H, s). A mixture of **12a** and **12b**: $C_{18}H_{26}O_5$ [m/z 322.1758(M^+)]; IR 3450, 1740, and 1630 cm^{-1}; the NMR signals due to **12a**: δ($CDCl_3$) 1.39(3H, s), 3.58(3H, s),

4.30(1H, d, J = 11 Hz), 4.38(1H, d, J = 11 Hz), and 4.84(1H, s). The NMR signals due to 12b: δ ($CDCl_3$) 1.40(3H, s), 3.58(3H, s), 4.27(1H, d, J = 11 Hz), 4.36(1H, d, J = 11 Hz), and 4.70(1H, s). 13: mp 142 - 145 °C; $C_{17}H_{24}O_5$ [m/z 308.1607(M^+)]; IR (film) 3500, 1740, and 1720 cm^{-1}; δ($CDCl_3$) 0.91(3H, d, J = 7 Hz), 0.93(3H, s), 1.31(3H, s), 2.05(3H, s), 2.63(1H, d, J = 16 Hz), 2.70(1H, d, J = 16 Hz), 3.61(1H, s), 4.05(1H, d, J = 11 Hz), and 4.18(1H, d, J = 11 Hz). 14: $C_{15}H_{20}O_3$ [m/z 248.1382(M^+)]; IR (film) 1760, 1740, and 1720 cm^{-1}; δ($CDCl_3$) 2.67(1H, d, J = 19 Hz), 2.99(1H, d, J = 19 Hz), 3.87(1H, d, J = 8 Hz), and 4.00(1H, d, J = 8 Hz). 15: $C_{15}H_{24}O$ [m/z 220.1832(M^+)]; IR 3400 cm^{-1}; δ($CDCl_3$) 0.85 (3H, d, J = 7 Hz), 1.03(3H, s), 1.70(3H, br.s), 3.49(1H, d, J = 10 Hz), 3.55(1H, d, J = 10 Hz), and 5.27(1H, br.s).

5. A glassy carbon beaker and a platinum wire tip were used as an anode and a cathode, respectively.
6. A mixture of 2 and 11: $C_{17}H_{22}O_5$ [m/z 306.1442(M^+)]; IR (film) 1740, 1680, and 1590 cm^{-1}; the NMR signals due to 2: δ ($CDCl_3$) 1.07(3H, s), 1.15(3H, d, J = 7 Hz), 1.53(2H, complex), 1.76(1H, m), 1.91(1H, m), 2.03(3H, s), 2.34(1H, t, J = 8 Hz), 2.68(1H, m), 3.43 (1H, s), 3.70(3H, s), 3.85(1H, d, J = 11 Hz), 3.96(1H, d, J = 11 Hz), and 6.38(1H, s). The NMR signals due to 11: δ($CDCl_3$) 1.09(3H, s), 1.42(3H, d, J = 7 Hz), 1.53(2H, complex), 1.76(1H, m), 1.91(1H, m), 2.02(3H, s), 2.34(1H, t, J = 8 Hz), 2.68(1H, m), 3.31(1H, s), 3.71(3H, s), 3.81(1H, d, J = 11 Hz), 3.95(1H, d, J = 11 Hz), and 6.25(1H, s).
7. In addition to both 2 and 11, the quinone [A] was obtained in 18% yield.



[A]

8. Fortunately, the desired diketone (13) was easily crystallized from hexane - EtOAc.
9. The synthetic sample as racemic form has the following spectral data: $C_{15}H_{24}O$ [m/z 220.1833 (M^+)]; IR (film) 1040 cm^{-1}; δ($CDCl_3$) 0.84(3H, d, J = 7 Hz), 1.00(3H, s), 1.17(3H, s), 1.2 - 1.9(13H, complex), 3.46(1H, d, J = 8 Hz), and 3.58(1H, d, J = 8 Hz). The ^1H NMR (400 MHz) spectrum of the synthetic sample is compatible with that of natural 8,14-cedranoxide (1) cited in the reference 2.

(Received in Japan 12 October 1987)