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The First Synthesis of a Racemic Acourtia Isocedrene by Means of Electrochemical Methodology in the Key Step

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Abstract : A highly oxygenated isocedrene, which has been isolated from *Acourtia Nana,* has been synthesized as a racemate *via* its dial precursor. The key step is the construction of a tricyclo [5.3.1.$0^{1,5}$]undec-9-ene-8,11- dione by means of electrochemical oxidation of the corresponding phenol. © 1998 Elsevier Science Ltd. All rights reserved.

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Since our own development of the phenolic oxidation methodology employing electrolysis [1], a number of natural products including 8,14-cedrenoxide, silphinene [2], pentalenene [3] and others [4] have been extensively synthesized. A part of our continuous investigation has been focused on the highly oxygenated isocedrenes, first isolated from *Acourtia Nana* [5], which constitute a new class of sesquiterpenes bearing a tricyclic cedrane-type skeleton in their molecule. In the previous paper [6], we reported two synthetic pathways leading to the target molecule (**1**) through the corresponding dial (**2**), one of which is shown in Scheme 1, wherein the requisite key intermediate, 6,6-dimethyl-9-methoxytricyclo[5.3.1.$0^{1,5}$]undec-9-ene-8,11-dione (**3**), has been obtained by means of anodic oxidation of the corresponding phenol (**5**), and one carbon unit must be introduced at the C_{10}-position of **3**.

According to essentially the same procedure as described in the 8,14-cedranoxide synthesis [2], 3,4-dimethoxyphenol was readily converted into the desired phenol (**5**), which was subjected to anodic oxidation [9.4 mA (+1000 - 1550 mV *vs.* SCE; *ca.* 2 F/mol)] in acetic anhydride containing nBu_4NBF_4 as a supporting electrolyte to afford a mixture of two tricyclo[5.3.1.$0^{1,5}$]undec-9-ene-8,11-diones (**3** and **4**) in 70% yield (relative ratio **3**/**4** = 3/1) [6].

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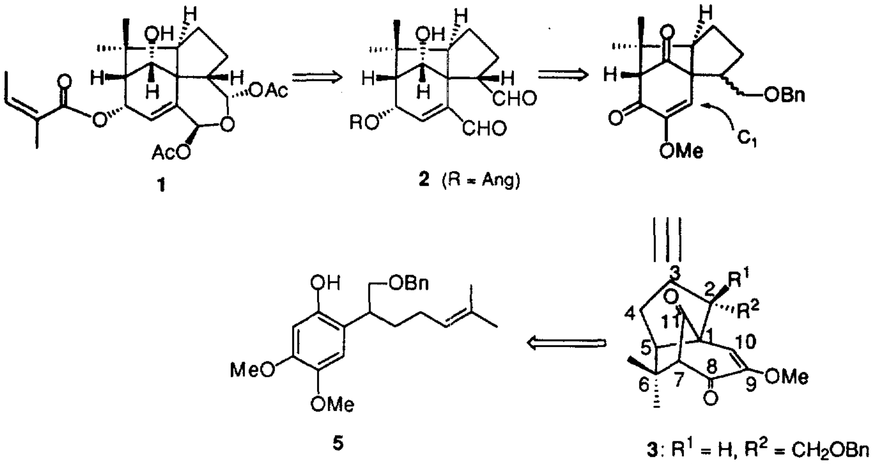
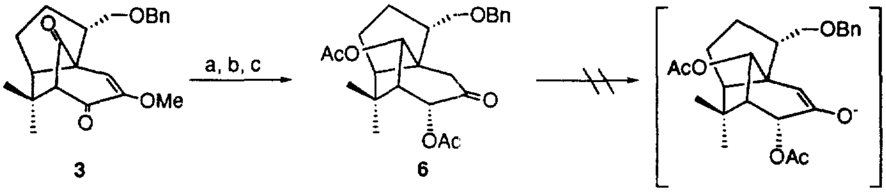


Scheme 1.

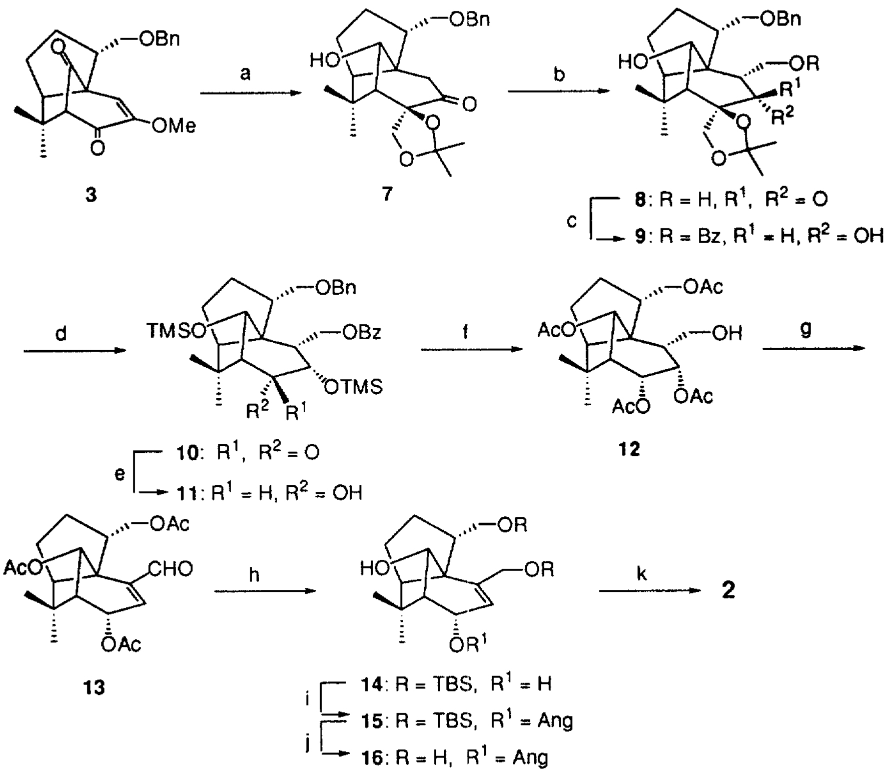
The α-stereoisomer (3) was successively treated with $NaBH_4$ in MeOH, acetic anhydride in pyridine, and then oxalic acid to afford an α-acetoxyketone (6). In order to synthesize 1, a C1 unit must be introduced at the C_{10}-position in 6. However, further experiments suggested that the carbon atom at the C_8-position adjacent to the CO group must be fully substituted, because the desired enolate was not formed, but instead the hydrogen atom attached to the C_8-position was easily removed (Scheme 2).



a) $NaBH_4$, b) Ac_2O, Py., c) $(COOH)_2$

Scheme 2.

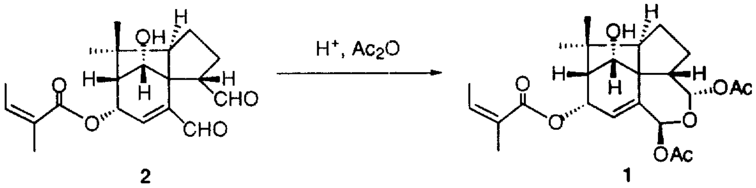
Thus, α-stereoisomer (3) was selectively reduced with $NaBH_3CN$ in AcOH- MeOH and then successively treated with the Tebbe reagent, a stoichiometric amount of OsO_4-$NaHSO_3$, and 2,2-dimethoxypropane-PPTS to afford the ketone (7). Reaction of 7 with methyl formate or a similar reagent (dimethyl carbonate, ClCOOMe, NCCOOMe and others) under basic conditions did not take place, because of highly steric hindrance. However, successful conversion of 7 to the desired aldol (8) was effected with 2 equivalents of LDA and CH_2O (gas.) in 70% yield, and then **8** was successively subjected to reduction and selective esterification to afford the corresponding benzoate (**9**). Hydrolysis of **9** followed by selective silylation and oxidative cleavage afforded the α-silyloxyketone (**10**), which was selectively reduced with $NaBH_4$ in MeOH at -23 °C to give **11** in 83% yield. This compound has the same carbon skeleton as that of the target molecule (**1**). Further deprotection of **11** followed by acetylation afforded the corresponding acetate (**12**), Swern oxidation of which gave an enal (**13**) in almost quantitative yield. Protection of the resulting aldehyde group in **13** was not possible, because of some steric hindrance. Therefore, **13** was subjected to $NaBH_4$-$CeCl_3$ reduction followed by selective silylation to afford the diol (**14**), which was readily esterified by means of Yamaguchi's method to afford angelate **15**,



a) i. $NaBH_3CN$ (91%), ii. Tebbe reagent (72%), iii. OsO_4, and then $NaHSO_3$ (82%), iv. 2,2-dimethoxypropane, PPTS (98%); b) LDA, then CH_2O (gas) (70%); c) i. NaBH4, ii. BzCl, py. (86% in 2 steps); d) i. *c*.HCl - MeOH (88%), ii. TMSOTf, 2,6-lutidine, then PPTS, MeOH (74%), iii. $Pb(OAc)_4$ (89%); e) $NaBH_4$, MeOH, -23 °C (93%); f) i. TBAF,then $Ba(OH)_2$ (83%), ii. TBSCl, Imd., then H_2, $Pd(OH)_2$ (72%), iii. Ac_2O, DMAP, then HF-Py. complex (76%); g) Swern oxidation (91%); h) i. $NaBH_4$, $CeCl_3$ (93%), ii. $Ba(OH)_2$, then TBSCl, Imd. (89%); i) Angellic acid, 2,4,6-Trichlorobenzoyl chloride, DMAP (72%); j) HF-py. complex (90%); k) $(COCl)_2$ (10eq.), DMSO(20eq.), -50°C, 2h, then TEA (40eq.) (87%).

Scheme 3

while the more hindered OH group at the C_{11}-position was not reactive. Deprotection of the TBS groups in **14** afforded the triol (**16**), which was subjected to Swern oxidation to give rise to the desired dial (**2**). The structure of the promising synthetic intermediate (**2**) was unambiguously confirmed by its spectral data: **2** as an oil: $C_{20}H_{26}O_5$ [m/z 346.1777 (M^+)]; IR (film) 3300, 1710, 1640, 1600 cm^{-1}; ^1H NMR (C_6D_6) δ 1.22 (3H, s), 1.26 (3H, s), 1.88 (3H, dq, J = 7.0, 1.62 Hz), 2.02 (3H, dq, J = 1.63, 1.62 Hz), 2.14 - 2.28 (4H, complex), 2.42 (1H, d, J = 2.8 Hz), 3.28 (1H, dd, J = 6.2, 12.0 Hz), 3.78 (1H, br.s), 5.88 (1H, br.s), 6.04 (1H, dd, J = 2.0, 4.4 Hz), 6.12 (1H, qq, J = 1.63, 7.0 Hz), 6.91 (1H, br.s), 8.96 (1H, s), 9.83 (1H, s); ^{13}C NMR (C_6D_6) δ 12.2, 14.2, 27.9, 28.8, 31.9, 42.1, 49.3, 58.9, 60.7, 68.0, 74.6, 79.1, 80.6, 128.8, 139.0, 144.9, 150.4, 166.7, 192.4, 203.0.



2 **1**

Scheme 4

Finally, the dial (**2**) was treated with a trace amount of H_2SO_4 in acetic anhydride to afford the target molecule (**1**) in 33% yield together with its stereoisomers (Scheme 4). The ^1H NMR spectrum of the synthetic compound was completely identical with that of the natural product (**1**), and its EI-MS spectral fragmentation was also in good agreement with that of **1**.

This is the first synthesis of the racemate of the naturally occurring and highly oxygenated isocedrene, although many synthetic studies have been made on the rather simple cedrane-type sesquiterpenes, including 8S,14-cedranediol, since Stork's original synthesis of cedrol. [7]

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