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TOTAL SYNTHESIS OF "(±)-SENOXYDENE"

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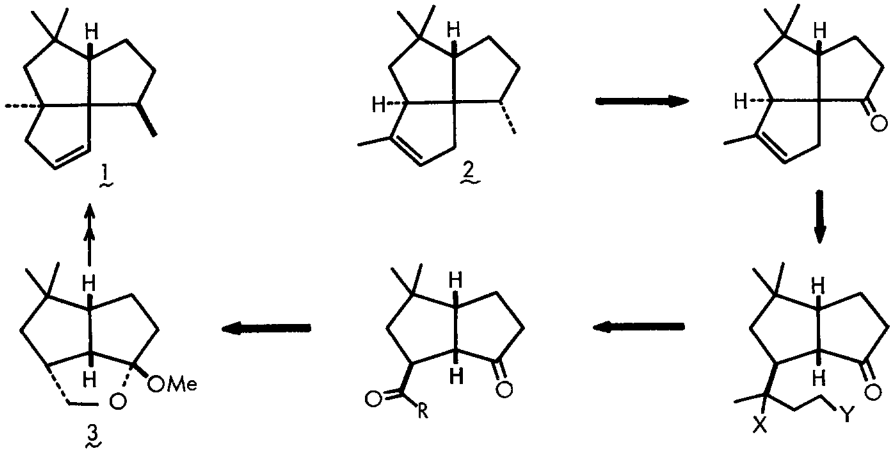
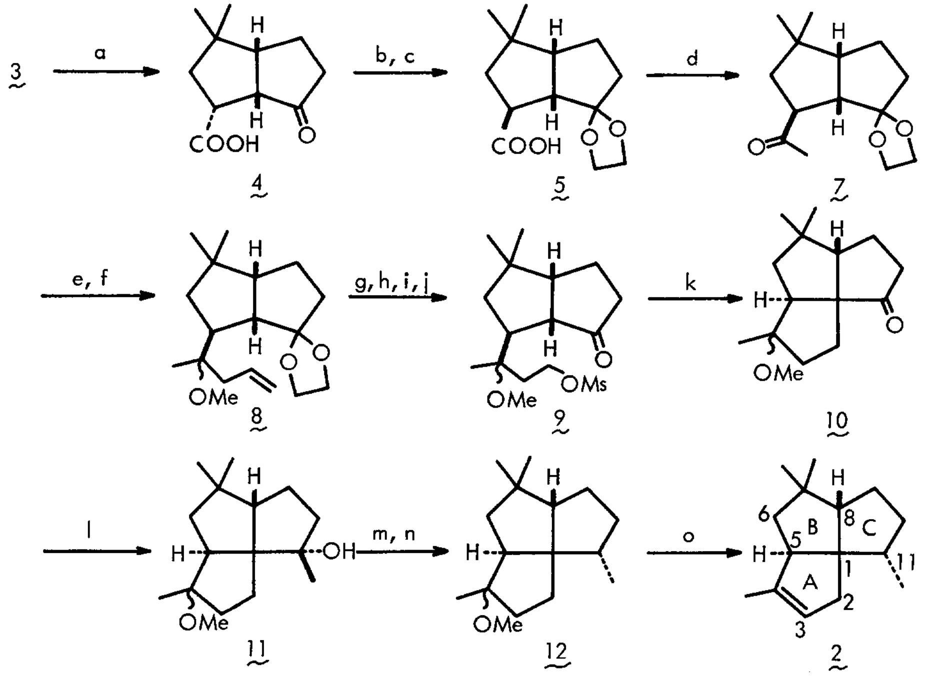
Abstract: A triquinane having the structure proposed for senoxydene has been synthesized in a regio- and stereoselective manner. However, the difference in their spectral data suggests that the structure of the natural senoxydene is incorrect and requires revision.

Recently, sesquiterpenes which have the tricyclo[6,3,0,$0^{1,5}$]undecane (angular triquinane) ring system have attracted much attention of synthetic chemists. We have reported[1] the synthesis of (±)-silphinene (**1**)[2] starting from dicyclopentadiene. Since very similar structure **2** was proposed by Bohlmann for senoxydene isolated from *Senecio Oxyodontus*[3], we have undertaken its synthesis utilizing the intermediate **3** used for the former synthesis. However, the product **2** derived by the synthetic strategy shown below has different spectral properties from those reported for senoxydene. As the structure of the synthetic product is established beyond any doubt (*vide infra*), that of natural senoxydene has to be revised.



Direct chromic acid oxidation of **3**[1] gave the keto acid **4** in 90% yield. Acetalization of **4** and subsequent saponification of the resulted ester proceeded with epimerization of the carboxyl group to yield **5** (70%)[4]. Deacetalization of **5** yielded the keto acid **6** isomeric with **4**. Treatment of **5** with methyl lithium afforded the methyl ketone **7** (91%). The Grignard reaction of **7** with allylmagnesium chloride followed by methylation of the hydroxy group produced gave a mixture **8** of two epimers in

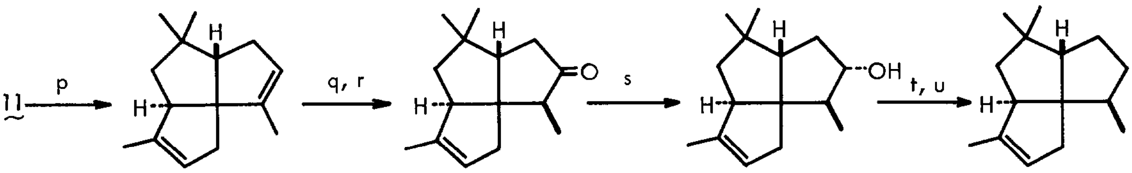


a: $CrO_3/AcOH-H_2O$, b: $\left[\begin{smallmatrix}OH\\OH\end{smallmatrix}\right./H^+$, c: $LiOH/THF-H_2O$, d: MeLi, e: $\diagup\!\diagdown\!\diagup$MgCl, f: NaH/MeI/HMPA,
g: O_3, h: $NaBH_4$, i: H^+/H_2O, j: MsCl/Py, k: t-BuOK/THF, l: MeLi, m: $MsCl/Et_3N$,
n: H_2/PtO_2/AcOH-ether, o: $BF_3 \cdot OEt_2$

72% yield. Since the methoxyl group was to be eliminated in a later stage, the mixture was used without separation. 8 was converted to the mesylate 9 in 76% yield in four steps (ozonization, reductive decomposition, deacetalization and mesylation). Treatment of 9 with potassium *t*-butoxide at room temperature resulted in formation of the 3rd 5-membered ring by intramolecular alkylation to give 10 in 93% yield. At this stage, the mixture 10 was easily separated into the epimers 10a and 10b by silica gel column chromatography.

The major ketone 10a was converted to the carbinol 11a by treatment of methyl lithium (82%), and subsequent dehydration followed by hydrogenation gave 12a in 86% yield. Finally, reaction of 12a with BF_3 etherate in dichloromethane afforded quantitatively the hydrocarbon 2 which is also obtained from the minor ketone 10b by the same reaction sequence5). However, the spectral data of 2 4) are different from those reported for natural senoxydene6). The structure of 2 is ascertained on the following bases, 1) sequence of hydrogens on ring A and B was established by a series of homonuclear decoupling experiments using 400 MHz PMR, 2) configuration of the secondary methyl group was confirmed by NOE experiment (large NOE between sec. Me and H_5, and small one between sec. Me and one of H_2) and 3) 5-membered ring ketone is present in 10a and 10b and the skeletal rearrangement is unlikely in subsequent steps7). Therefore the structure of senoxydene must be erroneous.

Considering the possibility that senoxydene has the structure 13, with the sec. methyl group in β-configuration, synthesis of 13 was carried out employing the reaction sequence similar to that used for



14 15 16 13

p: $BF_3 \cdot OEt_2$/p-TsOH, q: MCPBA, r: $BF_3 \cdot OEt_2$, s: LAH, t: MsCl/Et_3N, u: LAH

the synthesis of silphinene (1)[1].

Treatment of 11 with BF_3 etherate and p-TsOH in dichloromethane yielded the diene 14 in 82% yield. Epoxidation (-10°C)[8] of 14 followed by isomerization with BF_3 etherate yielded the methyl-ketone 15 in 50% yield. Subsequent reduction of the carbonyl group in 15 in three steps to methylene group afforded the desired hydrocarbon 13 (40% yield) along with some 16[9]. However, 13 was again not identical with senoxydene[6].

On the basis of the present synthetic studies, the structure of senoxydene is concluded to be in error and has to be revised. On the other hand, a compound having the structures 2 or 13 may well be found some day in nature since their biogenesis is straightforward from humulene.

References and Notes

1) T. Tsunoda, M. Kodama and S. Itô, Tetrahedron Letters, 24, 83 (1983).

2) F. Bohlmann and J. Jakupovic, Phytochemistry, 19, 259 (1980).

3) F. Bohlmann and C. Zdero, Phytochemistry, 18, 1747 (1979).

4) Spectral properties of selected intermediate are listed.

4: m.p. 100°C (subl.), m/e 196 (M^+), 96 (b.p.), ν 3400, 1765 (sh), 1745 cm^{-1}, PMR (CCl_4) δ 0.98 (3H, s), 1.02 (3H, s), 1.0-2.0 (5H, m), 2.0-2.5 (2H, m), 2.9-3.5 (2H, sextet), 5.96 (1H, m).

5: m.p. 84-85°C, m/e 240 (M^+), 99 (b.p.), ν 3000, 1680 cm^{-1}, PMR (CCl_4) δ 0.99 (6H, s), 1.1-2.0 (6H, m), 2.25 (1H, m), 2.93 (2H, q like), 3.84 (4H, m), 11.63 (1H, m).

6: ν 3000, 1740, 1705 cm^{-1}, PMR (CCl_4) δ 0.81 (3H, s), 1.04 (3H, s), 1.3-2.7 (7H, m), 2.7-3.3 (2H, m), 11.17 (1H, m).

7: m/e 238 (M^+), 99 (b.p.), ν 1705 cm^{-1}, PMR (CCl_4) δ 0.93 (3H, s), 0.97 (3H, s), 1.3-2.0 (6H, m), 2.07 (3H, s), 2.2 (1H, m), 2.7-3.1 (2H, m), 3.6-4.0 (4H, m).

8: major component, m/e 294 (M^+), 253 (b.p.), PMR (CCl_4) δ 0.86 (3H, s), 0.96 (3H, s), 1.02 (3H, s), 1.2-1.9 (6H, m), 1.9-2.8 (5H, m), 3.13 (3H, s), 3.80 (4H, m), 4.95 (2H, ABC type), 5.7 (1H, m).

10a: m/e 236 (M^+), 206 (b.p.), ν 1730 cm^{-1}, PMR ($CDCl_3$) δ 0.69 (3H, s), 1.02 (3H, s), 1.16 (3H, s), 1.3-2.2 (9H, m), 2.2-2.7 (3H, m), 3.22 (3H, s).

10b: m/e 236 (M^+), 85 (b.p.), ν 1730 cm^{-1}, PMR ($CDCl_3$) δ 0.69 (3H, s), 1.04 (3H, s), 1.38 (3H, s), 1.1-2.5 (12H, m), 3.20 (3H, s).

11a: m/e 252 (M^+), 162 (b.p.), ν 3450 cm^{-1}, PMR ($CDCl_3$) δ 0.98 (3H, s), 1.04 (3H, s), 1.18 (3H, s), 1.24 (3H, s), 1.2-2.2 (11H, m), 2.57 (1H, br.t, J=9.3), 3.16 (3H, s).

12a: m/e 236 (M$^+$), 86 (b.p.), PMR (CDCl$_3$) δ 0.78 (3H, s), 0.95 (3H, s), 1.01 (3H, d, J=6.3), 1.15 (3H, s), 1.1-2.0 (11H, m), 2.31 (1H, dd, J=11.3, 7.5), 3.13 (3H, s).

12b: m/e 236 (M$^+$), 204 (b.p.), PMR (CDCl$_3$) δ 0.77 (3H, s), 0.97 (3H, s), 0.98 (3H, d, J=6.8), 1.0-2.0 (11H, m), 1.25 (3H, s), 2.24 (1H, t, J=9.0), 3.20 (3H, s).

2: m/e 204 (M$^+$, 58), 189 (81), 148 (44), 147 (43), 133 (34), 123 (b.p.), 106 (30), 81 (21), ν 3040, 1460, 1445, 1385, 1375, 1365 cm^{-1}, PMR (CDCl$_3$) δ 0.85 (3H, d, J=6.8), 0.93 (3H, s), 0.99 (3H, s), 1.07 (1H, m), 1.38 (1H, dd, J=13.2, 9.3), 1.46 (1H, br.d, J=13.2), 1.5-1.65 (3H, m), 1.66 (3H, br.s), 1.77 (1H, ddq, J=12.6, 5.0, 6.8), 1.90 (1H, dd, J=2.6, 10.0), 2.36 (1H, d, J=16.6), 2.55 (1H, d, J=16.6), 2.60 (1H, br.d, J=9.3), 5.13 (1H, br.s), CMR (CDCl$_3$) δ 13.71, 15.58, 26.59, 27.42, 30.53, 34.03, 43.16, 43.44, 45.72, 46.60, 53.67, 63.33, 64.94, 123.24, 144.04.

14: m/e 202 (M$^+$, b.p.), PMR (CDCl$_3$) δ 0.75 (3H, s), 0.97 (3H, s), 1.22 (1H, dd, J=12.0, 9.3), 1.54 (3H, q like, J=1.8), 1.67 (3H, q like, J≃1.5), 1.80 (1H, dd, J=12.0, 7.5), 1.9-2.4 (5H, m), 2.68 (1H, br.t, J≈8.7), 5.06 (2H, br.s).

15: m/e 218 (M$^+$), 147 (b.p.), ν 1740 cm^{-1}, PMR (CDCl$_3$) δ 0.93 (3H, s), 0.99 (3H, d, J=7.2), 1.03 (3H, s), 1.69 (3H, br.s), 5.09 (1H, m).

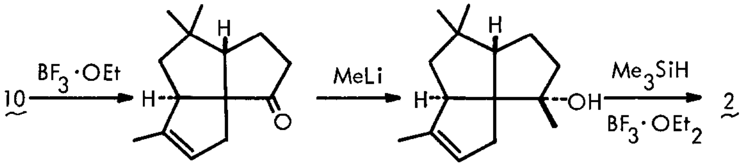
16: m/e 220 (M$^+$), 147 (b.p.), ν 3350 cm^{-1}, PMR (CDCl$_3$) δ 0.95 (3H, s), 0.96 (3H, d, J=6.8), 0.98 (3H, s), 1.66 (3H, br.s), 2.4-2.7 (3H, m), 3.58 (1H, td, J=10.4, 5.9), 5.08 (1H, br.s).

13: m/e 204 (M$^+$), 123 (b.p.), PMR (CDCl$_3$) δ 0.90 (3H, d, J=7.0), 0.92 (3H, s), 0.96 (3H, s), 1.43 (1H, dd, J=12.6, 4.6), 1.72 (1H, dd, J=12.6, 8.0), 2.02 (1H, br.d, J=17.6), 2.45 (1H, br.t like), 2.58 (1H, br.d, J=17.6), 5.08 (1H, br.s).

5) Hydrogenolysis of 11b, however, yielded also the epimer of 12b in 5% yield. This compound led to 13, the epimer of 2, by the same reaction sequence.

6) Their PMR and IR spectra were directly compared by Professor Bohlmann (private communication Nov. 14, 1983), to whom our sincere thanks are due.

7) If any skeletal rearrangement should occur in any of subsequent steps, it would change the hydrogen sequence on rings A and B. The fact that 2 was obtained also by the following sequences suggests the rearrangement unlikely.



8) A bisepoxide, the overoxidation product, was also formed in 25% yield, and separated by SiO$_2$ chromatography.

9) Walf-Kishner reduction of 15 furnished a mixture of 2 (major) and and 13 (minor).

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