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TOTAL SYNTHESIS OF (±)-SILPHINENE

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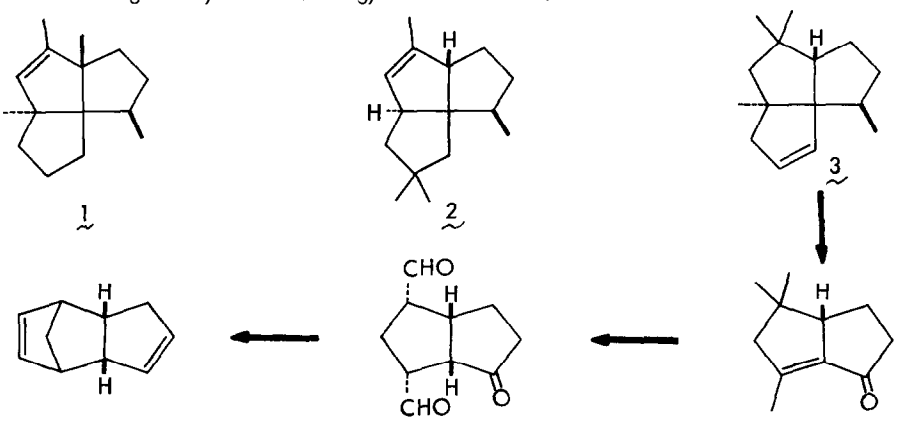
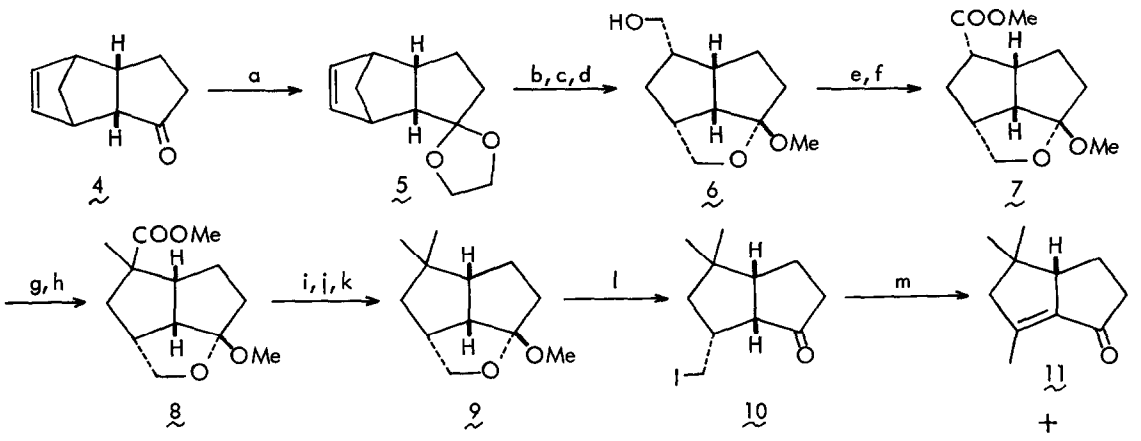
Abstract The regio- and stereoselective total synthesis of (±)-silphinene, an angular tricyclopentanoid sesquiterpene, was achieved starting from dicyclopentadiene.

Recently sesquiterpenes having a carbon skeleton of three angularly-fused cyclopentanes have attracted much attention of synthetic chemists because of their unique structures and successful syntheses of two members, isocomene (1)[1] and pentalenene (2)[2], have been reported. Silphinene (3)[3] first isolated by Bohlmann from Silphium perfoliatum belongs to this group, but has different substitution pattern from 1 and 2, which necessitates completely different synthetic strategy from those for these compounds. We wish to describe herein a regio- and stereoselective total synthesis of silphinene, starting from readily available dicyclopentadiene and following the synthetic strategy shown below[4].



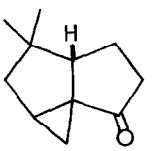
The acetal 5 prepared from the known ketone 4[5] was converted to the hydroxy-acetal 6 in three steps (73% yield) and then to the acetal-ester 7 (76%)[6]. The methylation of 7 to 8 (86%) and subsequent conversion of the ester group to methyl group (72%) afforded the tricyclic acetal 9. Although the acetal 9 failed to give the corresponding keto-alcohol as itself or as its protected forms, it was conveniently converted to the iodo-ketone 10 by trimethylsilyl iodide[7] in 99% yield. The reaction of 10 with 1,8-diazabicyclo-

[5.4.0]-7-undecene (DBU) in ether at room temperature resulted in the formation of the enone 11 in 87% yield along with the tricyclic ketone 12 (12%)[8].



4 5 6 7 8 9 10 11 +

a: $HOCH_2CH_2OH$, p-TsOH; b: $NaIO_4$, cat. OsO_4, $NaHCO_3$; c: $NaBH_4$; d: MeOH, HCl; e: Jones oxid. f: CH_2N_2; g: LDA; h: MeI; i: LAH; j: PCC; k: N_2H_4, KOH; l: Me_3SiCl, NaI/CH_3CN; m: DBU



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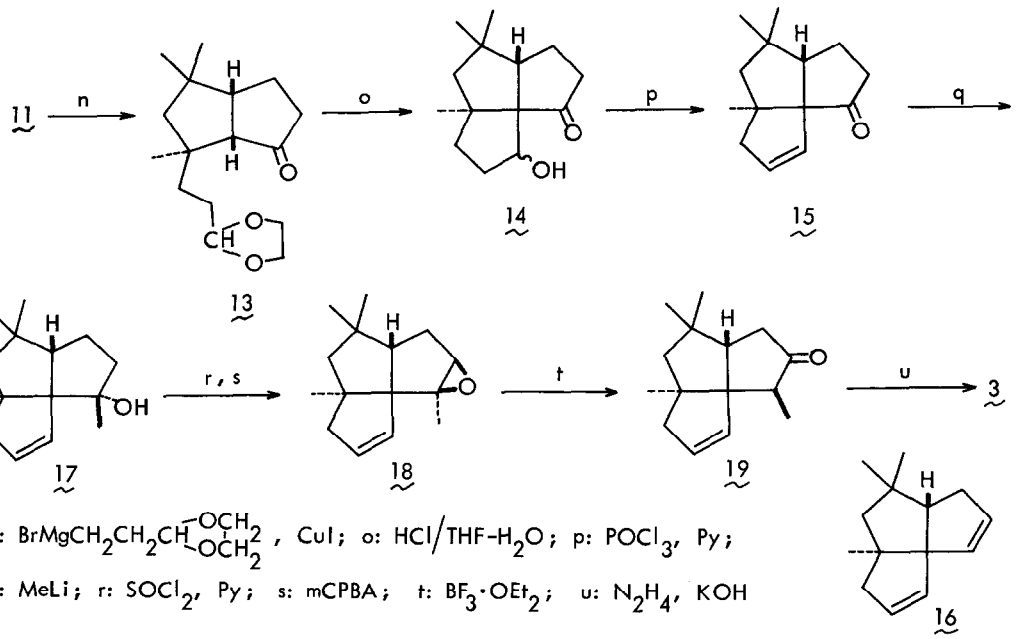
With the synthesis of the key intermediate 11 achieved, the 3rd 5-membered ring was constructed as follows. Conjugate addition of Grignard reagent prepared from β-bromopropionaldehyde ethylene acetal to 11 occurred smoothly in the presence of CuI and afforded the keto-acetal 13 (70%). Deprotection and cyclization of the resulted keto-aldehyde was accomplished by acid in one step to yield the aldol 14[9] (98%), and subsequent dehydration afforded the unsaturated ketone 15 (81% yield).

Because direct replacement of the oxygen function in 15 by methyl group, that is, the reaction of $LiCuMe_2$ on tosylate of the corresponding alcohol, gave the diene 16 as the major product, the methyl group had to be introduced indirectly. Thus methylation of 15 with methyllithium[10] afforded the methyl carbinol 17 and its dehydration and subsequent epoxidation gave β-epoxide 18 exclusively. The controlled isomerization of 18 with BF_3 etherate (0°C) yielded the methyl-ketone 19 (33% overall yield from 15). Huang-Minlon reduction of 19 afforded the hydrocarbon 3 after silica-gel column chromatography. IR and PMR spectra of 3 were identical with those of the natural silphinene.

Acknowledgement We thank Professor P. Teresa for a sample of silphinene and its spectra.



References and Notes

1) a. W. Oppolzer, K. Bättig and T. Hudlicky, Helv. Chim. Acta, 62, 1493 (1979); Tetrahedron, 37, 4359 (1981). b. M.C. Pirrung, J. Am. Chem. Soc., 101, 7130 (1979); ibid., 103, 82 (1981). c. L.A. Paquette and Y.K. Han, J. Org. Chem., 44, 4014 (1979); J. Am. Chem. Soc., 103, 1835 (1981). d. W.G. Dauben and D.M. Walker, J. Org. Chem., 46, 1103 (1981). e. S. Chatterjee, J.C.S. Chem. Comm., 620 (1979). f. P.A. Wender and G.B. Dreyer, Tetrahedron, 37, 4445 (1981).

2) a. Y. Ohfune, H. Shirahama and T. Matsumoto, Tetrahedron Letters, 2869 (1976). b. S. Misumi, T. Ohtsuka, Y. Ohfune, K. Sugita, H. Shirahama and T. Matsumoto, ibid., 31 (1979). c. G.D. Annis and L.A. Paquette, J. Am. Chem. Soc., 104, 4505 (1982).

3) a. F. Bohlmann and J. Jakupovic, Phytochemistry, 19, 259 (1980). b. P. Teresa, A.S. Feliciano, A.F. Barrero, M. Medarde and F. Tomé, ibid., 20, 166 (1981).

4) L.A. Paquette has mentioned the synthesis of 3 in his paper[2c], but no detail is known so far.

5) W.L. Dilling and R.A. Plepys, J. Org. Chem., 35, 2971 (1970).

6) Spectral properties of the selected intermediates are listed.

6: m/e 198 (M^+, b.p.), ν 3400 cm^{-1}, PMR ($CDCl_3$) δ 3.28 (3H, s), 3.60 (2H, d, J=7.2), 3.71 (1H, d, J=8.5), 3.92 (1H, dd, J=8.5, 4.2).

7: m/e 226 (M^+), 195 (b.p.), ν 1732 cm^{-1}, PMR (CCl_4) δ 3.15 (3H, s), 3.58 (3H, s), 3.65 (1H, d, J=8.0), 3.77 (1H, dd, J=8.0, 3.9).

8: m/e 240 (M^+), 99 (b.p.), ν 1730 cm^{-1}, PMR (CCl_4) δ 1.18 (3H, br.s), 3.16 (3H, s), 3.59 (3H, s), 3.62 (1H, d, J=8.2), 3.81 (1H, dd, J=8.2, 4.2).

9: m/e 196 (M^+), 165 (b.p.), PMR (CCl_4) δ 0.92 (3H, s), 0.94 (3H, s), 3.14 (3H, s), 3.53 (1H, d, J=8.4), 3.77 (1H, dd, J=8.4, 4.5).

10: m/e 292 (M^+), 165 (b.p.), ν 1715 cm^{-1}, PMR (CCl_4) δ 1.06 (3H, s), 1.09 (3H, s), 2.6-3.5 (3H, m), 3.61 (1H, m), CMR ($CDCl_3$) δ 10.44 (t), 23.63 (q), 24.61 (t), 29.64 (q), 40.41 (s), 40.60 (t), 43.15 (d), 47.20 (t), 53.92 (d), 54.18 (d), 220.30 (s).

11: m/e 164 (M^+), 149 (b.p.), ν 1740 (sh), 1705, 1658 cm^{-1}, PMR (CCl_4) δ 0.93 (3H, s), 1.20 (3H, s), 1.4-2.0 (2H, m), 1.96 (3H, br.s), 2.0-2.5 (3H, m), 2.74 (1H, br.d, J=18.8), 3.02 (1H, m), CMR ($CDCl_3$) δ 15.34 (q), 22.00 (t), 24.15 (q), 28.20 (q), 43.28 (s), 44.58 (t), 58.55 (d), 59.21 (d), 138.78 (s), 148.11 (s), 202.94 (s).

12: m/e 164 (M^+), 108 (b.p.), ν 1726 cm^{-1}, PMR (CCl_4) δ 0.65-1.0 (2H, m), 1.00 (3H, s), 1.08 (3H, s), 1.1-1.4 (1H, m), 1.4-2.3 (4H, m), 2.4-2.7 (3H, m), CMR ($CDCl_3$) δ 21.87 (t), 22.59 (d), 23.63 (t), 26.83 (q), 31.20 (s), 33.16 (q), 44.85 (t), 47.26 (s), 48.70 (t), 55.88 (d), 212.47 (s).

13: m/e 266 (M^+), 165 (b.p.), ν 1725 cm^{-1}, PMR (CCl_4) δ 0.89 (3H, s), 1.02 (3H, s), 1.11 (3H, s), 3.79 (4H, AA'BB' type), 4.72 (1H, t, J=4.2).

14: m/e 222 (M^+), 194 (b.p.), ν 3440, 1720 (sh), 1710 cm^{-1}, PMR (CCl_4) δ 0.90 (3H, s), 1.09 (6H, s), 1.54 (2H, s), 4.09 (1H, dd, J=9.6, 6.0).

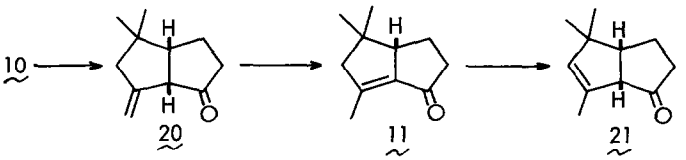
15: m/e 204 (M^+, b.p.), ν 1730 cm^{-1}, PMR (CCl_4) δ 1.01 (3H, s), 1.02 (3H, s), 1.09 (3H, s), 1.75 (2H, AB type), 2.42 (2H, AB type), 5.24 (1H, dt, J=6.0, 2.0), 5.66 (1H, dt, J=6.0, 2.7).

17: m/e 220 (M^+, b.p.), ν 3450 cm^{-1}, PMR (CCl_4) δ 1.01 (3H, s), 1.04 (3H, s), 1.19 (3H, s), 1.36 (3H, s), 1.72 (2H, s), 5.43 (2H, br.s).

19: m/e 218 (M^+), 147 (b.p.), ν 1735 cm^{-1}, PMR (CCl_4) δ 0,88 (3H, d, J=7.2), 0.98 (3H, s), 1.03 (3H, s), 1.15 (3H, s), 1.79 (2H, s), 5.47 (2H, br.s).

7) T. Morita, Y. Okamoto and H. Sakurai, J.C.S. Chem. Comm., 874 (1978); Bull. Chem. Soc. Jpn., 54, 267 (1981).

8) The reaction can be followed by G.L.C. Although the cyclopropane formation competes with the formation of double bond, the major pathway is the initial formation of the unconjugated enone 20 and subsequent isomerization to 11. Prolonged reaction gradually convert 11 to another unconjugated enone 21. 21: m/e 164 (M^+, b.p.), ν 1735 cm^{-1}, PMR (CCl_4) δ 1.04 (3H, s), 1.06 (3H, s), 1.67 (3H, t, J=1.2), 3.05 (1H, br.d, J=6.5), 5.06 (1H, m), CMR ($CDCl_3$) δ 14.49 (q), 22.06 (q), 23.83 (t), 30.03 (q), 39.56 (t), 46.35 (s), 51.24 (d), 61.49 (d), 133.30 (s), 136.95 (d), 218.09 (s).



9) A 20:1 mixture of epimeric alcohols. On the basis of PMR, the major epimer was established to have an α-hydroxyl group.

10) H. Schostarez and L.A. Paquette, J. Am. Chem. Soc., 103, 722 (1981).

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