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TOTAL SYNTHESIS OF (±)-SILPHIPERFOL-5-EN-3-OL

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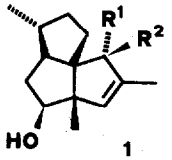
Abstract: Silphiperfol-5-en-3-ol (1) has been synthesized in five steps starting with enone 4 in an overall yield of 30%. Key step is a TMSCl assisted 1,4-addition of the Grignard reagent of acetal 5 to 4.

Within a screening program of odoriferous plants from wild sources of the Kashmir region of India[1] we recently isolated the new sesquiterpene alcohol (-)-silphiperfol-5-en-3-ol (1a) as a constituent (~3%) from the essential oil of Artemisia laciniata together with small amounts of its epimer 1b.[2,3] Since the isolated sample showed a very pleasant odour we were interested in a synthesis of 1a to find out whether the observed odour really belongs to 1a or to any unseparated concomitant.



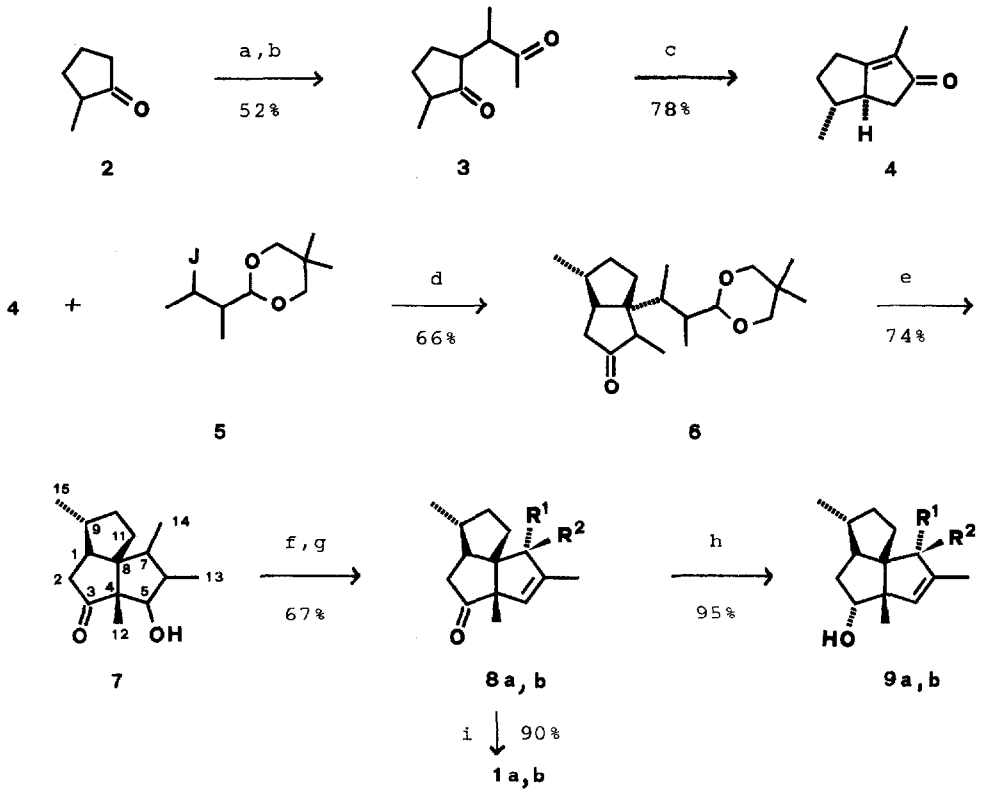
1

a: R^1 = Me, R^2 = H

b: R^1 = H, R^2 = Me

A convenient starting material is the enone 4, also used in the synthesis of silphiperfol-6-ene[4] and retigeranic acid.[5] The shortest way to obtain racemic 4[6] consists in alkylation of the pyrrolidine enamine prepared from 2-methylcyclopentanone (2) with 3-bromobutanone[7] to give diketone 3. Subsequent treatment with KOH/EtOH results in cyclization and double bond migration to furnish a mixture of 4 and its epimer (85:15) separable by flash chromatography.

Key step of the synthesis is the 1,4-addition of the Grignard reagent of 5 to enone 4. The Grignard compound can be prepared from the corresponding iodo acetal 5, usual Mg turnings and 1,2-dibromoethane as entrainer.[8] Since the yield is modest (30-40%) due to radical coupling (Wurtz) and disproportionation, a large excess of 5 is needed. However, this disadvantage is compensated by the fact that the required iodo acetal 5 can be prepared (yield 92%) easily from commercially available tiglic aldehyde by a one-pot procedure.[9]



a) pyrrolidine, benzene, Dean-Stark trap, 16 h; b) MeCOCHBrMe, toluene, 2 h reflux; then H_2O, 2 h reflux; c) KOH, EtOH, H_2O, 2 h reflux; d) 7.7 eq. of 5, Mg/$BrCH_2CH_2Br$, ether, HMPA or TMEDA, TMSCl, CuBr.Me_2S, -78°C, 20 h; e) HCl, acetone, r.t., 5 d; f) p-$MeC_6H_4OC(S)Cl$, pyridine, THF, r.t., 16 h; g) 190°C, 18 Torr; h) LAH, r.t., 30 min; i) L-Selectride®, -78°C → r.t.; NaOH, H_2O_2.

Our first attempts to effect the conjugate addition were disappointing. Under usual conditions (CuBr.Me_2S, ether/Me_2S, -78°C → 0°C) we obtained exclusively 1,2-addition followed by spontaneous dehydration. In the last years several groups reported a drastically improved efficiency of conjugate addition in the presence of TMSCl and nucleophilic addends such as HMPA[10] or TMEDA.[11] Under such conditions we obtained the 1,4-adduct 6 together with varying amounts of its silyl enol ether, but without 1,2-adduct. In the best run we were able to isolate 66% of 6 as a complex mixture of diastereoisomers. Acidic hydrolysis of this product with concomitant cyclization led to the aldol 7, which was dehydrated by thermolysis of the corresponding p-tolyl thionocarbonate[4] to give the two epimeric ketones 8a,b.[12]

Now, the last step was to achieve stereoselective reduction. The use of LAH afforded the undesired thermodynamically more stable alcohol 9a,b[13] predominantly (selectivity 95:5). But reduction with L-selectride® occurred

from the less hindered α-face exclusively (selectivity 99:1) to provide **1a** along with its epimer **1b**, identical in all spectral data[14] with the natural compounds.

In summary, the total synthesis of silphiperfol-5-en-3-ol (**1**) has been accomplished in 30% overall yield from the known enone **4**. The olfactive properties of **1** and related compounds are currently under investigation and will be reported elsewhere. An enantioselective synthesis of (-)-**1a** is in progress.

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References and Notes

1. P. Weyerstahl, H. Marschall-Weyerstahl, M. Schröder and V. K. Kaul, Liebigs Ann. Chem. **1988**, 917.
2. a) First isolation of the parent hydrocarbons 7α- and 7β-silphiperfol--5-ene: F. Bohlmann and J. Jakupovic, Phytochemistry **1980** (19) 259, and b) synthesis: P. A. Wender and S. K. Singh, Tetrahedron Lett. **1985** (26) 5987.
3. P. Weyerstahl, M. Schröder and V. K. Kaul, lecture presented at the 19th International Symposium on Essential Oils and Other Natural Products, Dübendorf-Greifensee, Switzerland, September 7-10, 1988.
4. L. A. Paquette, R. A. Roberts and G. J. Drtina, J. Am. Chem. Soc. **1984** (106) 6690.
5. a) J. Wright, G. J. Drtina, R. A. Roberts and L. A. Paquette, J. Am. Chem. Soc. **1988** (110) 5806. b) T. Hudlicky, L. Radesca-Kwart, L.-q. Li and T. Bryant, Tetrahedron Lett. **1988** (29) 3283.
6. L. A. Paquette in "Topics in Current Chemistry", Vol. 119, ed. F. L. Boschke, Springer, Berlin 1984, p. 129.
7. J. R. Catch, D. F. Elliot, D. H. Hey and E. R. H. Jones, J. Chem. Soc. **1948**, 272.
8. Y.-H. Lai, Synthesis **1981**, 585.
9. Analogous to the procedure used for acrolein by G. L. Larson and R. Klesse, J. Org. Chem. **1985** (50) 3627.
   $MeCH{=}C(Me)CHO$ —— 1. TMSCl, NaI, MeCN, r.t., 15 min; 2. $HOCH_2CMe_2CH_2OH$, r.t., 30 min ⟶ **5**
10. Y. Horiguchi, S. Matsuzawa, E. Nakamura and I. Kuwajima, Tetrahedron Lett. **1986** (27) 4025.
11. C. R. Johnson and T. J. Marren, Tetrahedron Lett. **1987** (28) 27.
12. The silphiperfol-5-en-3-ones **8a,b** have also been isolated from the essential oil of *A. laciniata* as trace components. The ^1H NMR spectra of the natural and synthesized ketones are identical.

8a: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.00 (s, 4-Me), 1.01, 1.09 (2 d, J = 7 Hz, 7-, 9-Me, 1.61 (dd, J = 1.5; 1.5 Hz, 6-Me), 1.90, 2.67 (ABd, J = 17.5 and 1.5 resp. 9.5 Hz, 2-H_2), 2.75 (q, br., J = 7 Hz, 7-H), 4.94 (q, br., J = 1.5 Hz, 5-H). — ^{13}C NMR ($CDCl_3$, C-1 — C-15): δ = 44.6 (d), 42.5 (t), 221.1 (s), 62.5 (s), 129.0 (d), 145.8 (s), 52.3 (d), 64.0 (s), 43.6 (d), 34.7 (t), 33.7 (t), 15.7, 19.1, 13.3, 14.7 (4 q).

8b: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.03 (s, 4-Me), 1.00, 1.09 (2 d, J = 7 Hz, 7-, 9-Me), 1.72 (d, J = 1.5 Hz, 6-Me), 1.87, 2.74 (ABd, J = 18.5 and 6 resp. 10 Hz, 2-H_2), 2.34 (q, J = 7 Hz, 7-H), 4.98 (q, br., J = 1.5 Hz, 5-H). — ^{13}C NMR ($CDCl_3$, C-1 — C-15): δ = 54.1 (d), 44.3 (t), 221.1 (s), 63.6 (s), 127.9 (d), 147.1 (s), 55.1 (d), 65.6 (s), 43.4 (d), 34.7 (t), 28.8 (t), 18.3, 21.2, 16.0, 15.4 (4 q).

13. **9a**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.96 (s, 4-Me), 0.95, 0.98 (2 d, J = 7 Hz, 7-, 9-Me), 1.59 (dd, J = 1.5; 1.5 Hz, 6-Me), 2.60 (q, br., J = 7 Hz, 7-H), 3.73 (dd, J = 11; 6 Hz, 3-H), 5.17 (q, br., J = 1.5 Hz, 5-H). — ^{13}C NMR ($CDCl_3$, C-1 — C-15): δ = 46.8 (d), 38.9 (t), 79.9 (d), 59.1 (s), 127.1 (d), 143.4 (s), 51.4 (d), 63.5 (s), 43.3 (d), 35.3 (t), 34.8 (t), 18.3, 19.8, 13.4, 14.8 (4 q).

9b: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.01 (s, 4-Me), 0.93, 0.97 (2 d, J = 7 Hz, 7-, 9-Me), 1.70 (d, J = 1.5 Hz, 6-Me), 2.24 (q, J = 7 Hz, 7-H), 3.72 (dd, J = 11; 7 Hz, 3-H), 5.19 (q, br., J = 1.5 Hz, 5-H). — ^{13}C NMR ($CDCl_3$, C-1 — C-15): δ = 58.9 (d), 38.6 (t), 80.0 (d), 60.1 (s), 126.8 (d), 145.0 (s), 56.0 (d), 62.5 (s), 43.6 (d), 35.1 (t), 29.5 (t), 20.1, 20.9, 17.0, 15.6 (4 q).

14. **1a**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.02 (s, 4-Me), 0.97, 1.01 (2 d, J = 7 Hz, 7-, 9-Me), 1.54 (dd, J = 1.5; 1.5 Hz, 6-Me), 2.63 (q, br., J = 7 Hz, 7-H), 3.99 (d, br., J = 4.5 Hz, 3-H), 4.96 (q, br., J = 1.5 Hz, 5-H). — ^{13}C NMR ($CDCl_3$, C-1 — C-15): δ = 52.1 (d), 39.1 (t), 82.5 (d), 60.9 (s), 132.4 (d), 141.7 (s), 51.8 (d), 66.2 (s), 44.0 (d), 36.3 (t), 35.7 (t), 15.0, 19.6, 14.4, 14.6 (4 q).

1b: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.08 (s, 4-Me), 0.95, 0.98 (2 d, J = 7 Hz, 7-, 9-Me), 1.66 (d, J = 1.5 Hz, 6-Me), 2.32 (q, J = 7 Hz, 7-H), 4.00 (d, br., J = 4 Hz, 3-H), 4.97 (q, br., J = 1.5 Hz, 5-H). — ^{13}C NMR ($CDCl_3$, C-1 — C-15): δ = 64.5 (d), 39.0 (t), 83.0 (d), 61.7 (s), 132.2 (d), 143.3 (s), 55.7 (d), 65.1 (s), 44.1 (d), 36.3 (t), 30.0 (t), 18.2, 20.1, 16.9, 15.5 (4 q).

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