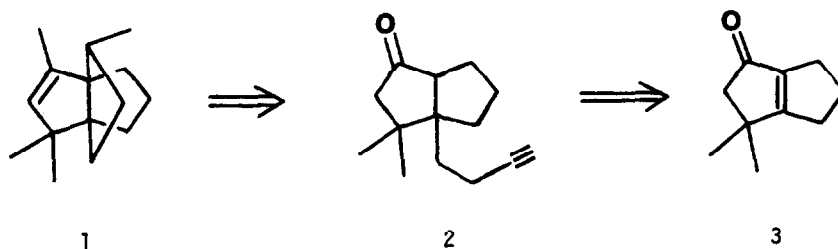


HOMOCHIRAL KETALS IN ORGANIC SYNTHESIS. ENANTIOSELECTIVE PREPARATION OF
(+)-MODHEPHENE

Eugene A. Mash*, Shivanand K. Math, and Christopher J. Flann
Department of Chemistry, University of Arizona, Tucson, Arizona 85721

Abstract. An efficient, enantioselective synthesis of the title compound 1 via diastereoselective cyclopropanation is described.

Modhephene 1 is an unusual sesquiterpene possessing a carbocyclic [3.3.3] propellane skeleton.¹ Several syntheses of racemic modhephene have been reported² but no enantioselective approach has yet been disclosed. The synthesis due to Paquette and Schostarez proceeds to



racemic modhephene via racemic bicyclic ketone 2, which can be prepared from enone 3 in two steps (42% yield).^{2b,2c} Our recently developed methodology for diastereoselective cyclopropanation of bicyclic enone 1,4-di-O-alkylthreitol ketals³ presented an opportunity for an enantioselective approach to 2 from 3. We have reduced this approach to practice as outlined in Scheme I and described below.

Ketalization of 3^{2b,c} using 1,4-di-O-methyl-2,3-di-O-trimethylsilyl-D-threitol under the conditions of Noyori⁴ gave ketal 4 in 70% yield. Simmons-Smith cyclopropanation^{3,5} of 4 provided, in 84% chemical yield, an inseparable 8:1 mixture of cyclopropyl ketals 5a and 5b as determined by 62.9 MHz ¹³C NMR spectroscopy.⁶

Ketal hydrolysis (HCl, H₂O, CH₃OH, room temperature) gave enantiomerically enriched ketone 6, mp 48-50 °C, [α]_D²⁵ -31.5° (c 3.9, CHCl₃), in 94% yield. Assignment of the (3a_S, 6a_S) absolute stereochemistry to 6 was based upon application of the "reversed octant rule" in interpreting the CD spectrum of 6.⁷ This assignment was in accord with all previously examined cyclopropyl ketones.^{3,7}

Treatment of 6 with iodotrimethylsilane (2.1 equiv, CCl_4 , -10°C , 3h) produced, via regio-selective cyclopropane ring opening,⁸ iodomethyl ketone 7, mp $38-40^\circ\text{C}$, $[\alpha]_D^{25} -33.1^\circ$ (c 3.2, CHCl_3), in 85% yield. Ketalization of 7 using bis-trimethylsilyl ethylene glycol⁴ gave iodomethyl ketal 8, $[\alpha]_D^{25} +21.7^\circ$ (c 5.5, CHCl_3) in 96% yield. Displacement of iodide by the lithium salt of 1-trimethylsilyl-1-propyne⁹ (2 equiv, $\text{Et}_2\text{O}/\text{TMED}/\text{HMPA}$, -25°C , 1 h) gave crude acetylenic ketal 9 which was hydrolyzed (HCl , CH_3OH , H_2O , room temperature) and desilylated ($n\text{Bu}_4\text{N}^+\text{F}^-$, THF , H_2O , room temperature) to give enantiomerically enriched ketone 2, $[\alpha]_D^{25} -117.9^\circ$ (c 3.5, CHCl_3), in 82% yield from 8. This material exhibited spectroscopic characteristics consistent with those published^{2b,2c} for racemic 2. Note that although the sequence outlined for preparation of enantiomerically enriched 2 is longer than the synthesis of racemic 2, it is comparably efficient (37% overall yield from 3 over eight steps).

Completion of the first enantioselective synthesis of modhephene 1 from optically enriched ketone 2 paralleled the route previously outlined by Paquette and Schostarez.^{2b,c} Thermolysis¹⁰ of 2 (decalin, 360°C) provided tricyclic ketone 10, $[\alpha]_D^{25} +107^\circ$ (c 2.67, CHCl_3) in 57% yield.¹¹ Olefination¹² of 10 (CH_2I_2 , Zn , TiCl_4) gave diene 11, $[\alpha]_D^{25} +40^\circ$ (c 4.0, CHCl_3), in 52% yield (81% based on unrecovered ketone). Regio- and stereoselective monoepoxidation of diene 11 (MCPBA , Na_2HPO_4 , CH_2Cl_2) produced the desired epoxide 12, $[\alpha]_D^{25} +26^\circ$ (c 3.53, CHCl_3), in 50% yield. Epoxide 12 was isomerized to ketone 13, $[\alpha]_D^{25} +10.3^\circ$ (c 2.5, CHCl_3), in 43% yield using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in CH_2Cl_2 . Double bond migration (12, C_6H_6 , heat) converted 13 into a separable 2:1 mixture of 13 and 14, $[\alpha]_D^{25} +77^\circ$ (c 1.26, CHCl_3). Finally, deoxygenation of 14 (K_2CO_3 , NH_2NH_2 , $\text{HOCH}_2\text{CH}_2\text{OH}$, heat) provided (+)-modhephene 1 $[\alpha]_D^{25} +4.5^\circ$ (c 0.13, CHCl_3) contaminated with approximately 15% of epimodhephene 15.

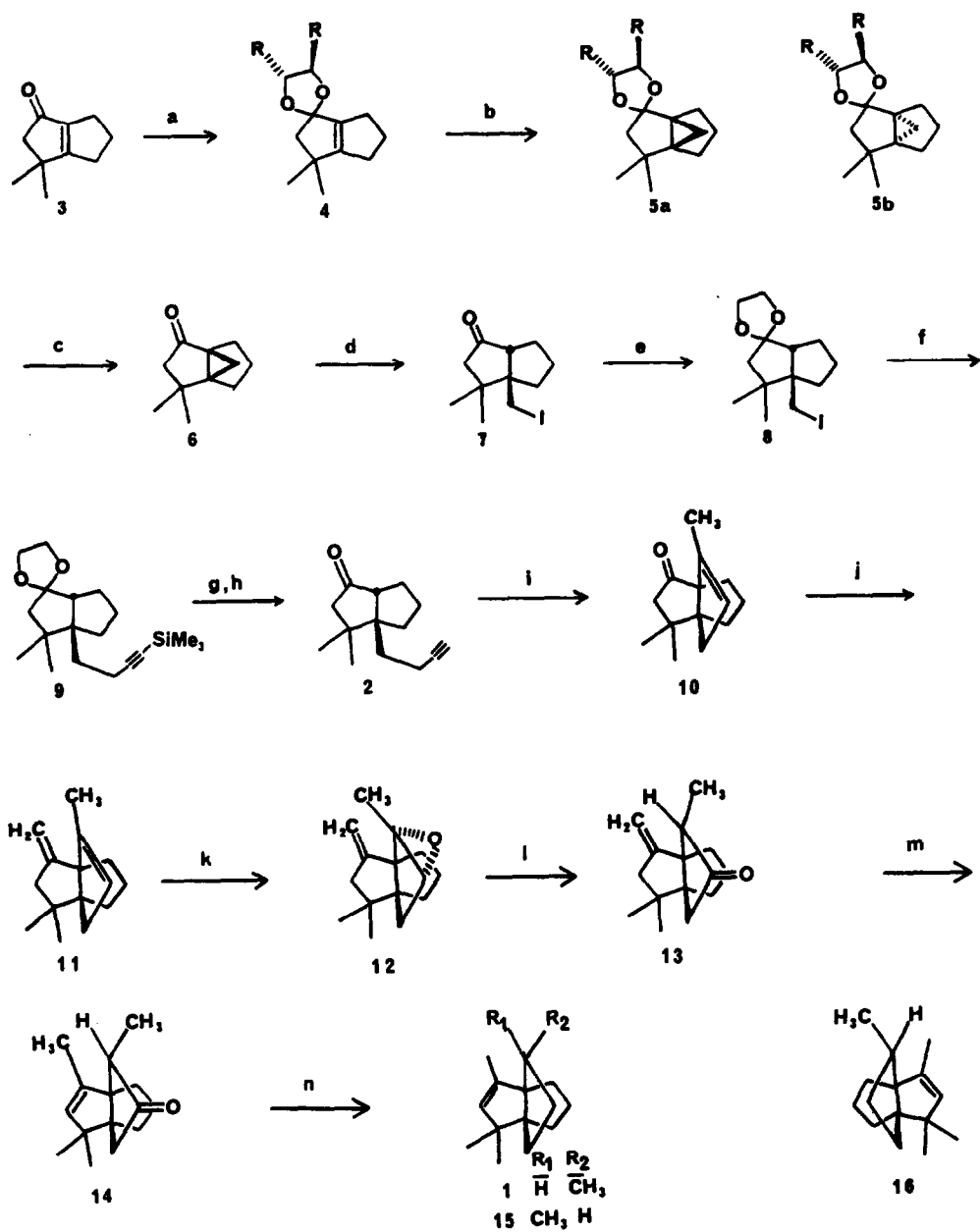
The rotation of natural modhephene, calculated¹³ from the reported ORD data,¹⁴ is -4.2° (c 1.5, CHCl_3). Thus, the absolute stereochemistry of the natural product should be formulated as 16.¹⁵ This formulation is in keeping with the postulated biosynthetic route to modhephene from (1R, 9S) caryophyllene.^{14,16,17}

REAGENTS FOR SCHEME 1:

- (a) 1,4-Di-O-methyl-2,3-di-O-trimethylsilyl-D-threitol, TMS-OTf
- (b) $\text{Zn}(\text{Cu})$, CH_2I_2 , Et_2O , heat
- (c) Aq. HCl , CH_3OH
- (d) TMS-I , CCl_4
- (e) $\text{TMSOCH}_2\text{CH}_2\text{OTMS}$, TMS-OTf , CH_2Cl_2
- (f) $\text{Li}^+ \ominus \text{CH}_2\text{C}\equiv\text{CTMS}$, TMED , HMPA , Et_2O
- (g) Aq. HCl , CH_3OH

- (h) $n\text{Bu}_4\text{N}^+\text{F}^-$, THF , H_2O
- (i) 360°C , decalin
- (j) CH_2I_2 , Zn , TiCl_4 , THF
- (k) MCPBA , Na_2HPO_4 , CH_2Cl_2
- (l) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2
- (m) I_2 , C_6H_6 , heat
- (n) NH_2NH_2 , K_2CO_3 , $\text{HOCH}_2\text{CH}_2\text{OH}$, heat

SCHEME I. Enantioselective Synthesis of (+)-Modhephene 1.



References and Notes

1. Zalkow, L.H.; Harris, R.N., III.; Van Derueer, D. J. Chem. Soc. Chem. Commun. 1978, 420-421.
2. (a) Smith, A.B., III.; Jerris, P.J. J. Am. Chem. Soc., 1981, 103, 194-195.
 (b) Schostarez, H.; Paquette, L.A. J. Am. Chem. Soc., 1981, 103, 722-724.
 (c) Schostarez, H.J., Ph.D. Dissertation, The Ohio State University, 1982.
 (d) Karpf, M.; Dreiding, A.S. Tetrahedron Lett., 1980, 21, 4569-4570.
 (e) Oppolzer, W.; Marazza, F. Helv. Chim. Acta, 1981, 64, 1575-1578.
 (f) Oppolzer, W.; Bättig, K. Helv. Chim. Acta, 1981, 64, 2489-2491.
 (g) Smith, A.B., III.; Jerris, P.J. J. Org. Chem., 1982, 47, 1845-1855.
 (h) Wender, P.A.; Dreyer, G.B. J. Am. Chem. Soc., 1982, 104, 5805-5807.
 (i) Wrobel, J.; Takahashi, K.; Honkan, U.; Lannoye, G.; Cook, J.M.; Bertz, S.H. J. Org. Chem., 1983, 48, 139-141.
 (j) Mundy, B.P.; Wilkening, D.; Lipkowitz, K.B. J. Org. Chem., 1985, 50, 5727-5731.
3. (a) Mash, E.A.; Nelson, K.A. Tetrahedron Lett., 1986, 27, 1441-1444.
 (b) Mash, E.A.; Nelson, K.A. J. Am. Chem. Soc., 1985, 107, 8256-8258.
 (c) Mash, E.A.; Nelson, K.A. Tetrahedron, 1987, 43, 679-692.
4. Tsunoda, T.; Suzuki, M.; Noyori, R. Tetrahedron Lett., 1980, 27, 1357-1358.
5. Shank, R.S.; Shechter, H. J. Org. Chem., 1959, 24, 1825-1826.
6. An authentic diastereomeric mixture of cyclopropane ketals was prepared for spectral comparison by reketalization of ketone 6 with 1,4-di-O-methyl-DL-threitol. For previous examples of the use of ^{13}C NMR in the measurement of diastereomer ratios see: Hiemstra, H.; Wynberg, H. Tetrahedron Lett., 1977, 18, 2183-2186.
7. Lightner, D.A.; Jackman, D.E. Tetrahedron Lett., 1975, 16, 3051-3054. From the CD Spectrum of 6: $[\theta]_{308} -6230^\circ$, $[\theta]_{297} -11,220^\circ$, $[\theta]_{288} -11,220^\circ$ (c 0.009, pentane).
8. Miller, R.D.; McKean, D.R. J. Org. Chem., 1981, 46, 2412-2414.
9. Corey, E.J.; Kirst, H.A.; Katzenellenbogen, J.A. J. Am. Chem. Soc., 1970, 92, 6314-6317.
10. Drouin, J.; Leyendecker, F.; Conia, J.M. Tetrahedron, 1980, 36, 1195.
11. The ratio of enantiomers for 10, as assayed by ketalization⁴ with 1,4-di-O-benzyl-L-threitol followed by ^{13}C NMR analysis⁶ of the resulting diastereoisomeric mixture, was 8:1.
12. Hibino, J.; Okazoe, T.; Takai, K.; Nozaki, H. Tetrahedron Lett., 1985, 26, 5579-5580.
13. Lambert, J.B.; Shurvell, H.F.; Verbit, L.; Cooks, R.G.; Stout, G.H. "Organic Structural Analysis"; Macmillan Publishing Co., Inc., New York; 1976; p. 329.
14. Zalkow, L.H.; Harris, R.N.; Burke, N.I. J. Nat. Prod., 1979, 42, 96-102.
15. Our synthetic approach permits construction of either enantiomer of modhephene from the appropriate threitol enantiomer.
16. Roberts, J.S.; in "Terpenoids and Steroids"; Hanson, J.R., Ed.; The Royal Society Press, London, 1981, Vol. 10, p. 105.
17. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. Partial support of this research by the American Heart Association, Arizona Affiliate, is gratefully acknowledged.

(Received in USA 1 December 1987)