Total Synthesis of (±)-Modhephene

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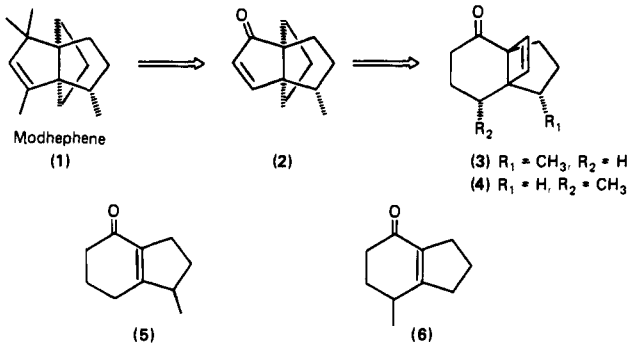
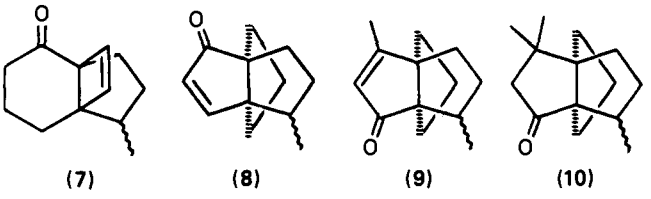
We wish to report here the first total synthesis of modhephene (**1**),[1] a sesquiterpene isolated in 1978 by Zalkow[2] from Rayless Goldenrod (*Isocoma wrightii*), a plant also known to produce caryophyllene[3a] and isocomene,[3b] which is indigenous to the Southwestern United States. Our interest in modhephene as a synthetic target was prompted by its unique[4] carbocyclic [3.3.3]propellane skeleton, the latter including absolute configuration secured through agency of an X-ray crystallographic analysis of the readily derived diol. We note in advance that we have developed two synthetic routes to modhephene which converge upon elaboration of the requisite propellane skeleton. Both routes are short and highly efficient (i.e., proceed in 10% and 7% yield overall); however, only the latter demonstrated, at best, modest stereoselectivity.



The cornerstone of our synthetic strategy derives from the pioneering observations of Cargill on the acid-catalyzed rearrangements of highly strained β,γ-unsaturated ketones.[5] In particular, we envisioned construction of the required propellane skeleton via an acid-catalyzed rearrangement of an appropriately substituted tricyclo[4.3.2.0^{1,6}]undec-10-en-2-one (e.g., **3** or **4**), which in turn was anticipated to be readily available via [2 + 2] photocycloaddition of the elements of acetylene to an appropriate enone (e.g., **5** and **6**).[5,6] Of particular note here is the fact that either enone **3** or **4**, upon execution of the Cargill rearrangement, would afford the desired propellane **2** possessing the requisite stereochemical disposition of the seconary methyl substituent.

Central to this strategy is the requirement that addition of acetylene or its equivalent takes place anti to the secondary methyl substituent in **5** and/or in **6**. While the Wiesner model[7] governing the stereoselectivity of enone–olefin cycloaddition suggested that the desired stereochemical outcome might prove problematic, the recent observation[8] that ethylene adds predominantly anti to the *tert*-butyl group of 4-*tert*-butyl-2-cyclohexenone, as required by our strategy for modhephene, was taken as encouraging.

We initiated study by examining the photocycloaddition of acetylene to enone **5**.[9] Unfortunately, the yield of tricyclic material was poor (ca. 30%); furthermore, the addition proved to be totally nonstereoselective. We therefore decided to follow a somewhat less direct approach, employing 1,2-dichloroethylene as an acetylene equivalent. It was our expectation that the steric bulk of the chloro substituents would aid in directing the addition to the face opposite the secondary methyl group of enone **5**. Toward this end, irradiation of enone **5** in hexane (0.3 M) through Pyrex in the presence of 3 equiv of 1,2-dichloroethylene (mixture of isomers) afforded after 5.5 h a 67% yield[10] of tricyclic material which after distillation was readily converted to **7**[10] in three steps [(a) ketalization (ethylene glycol, TsOH/C_6H_6, $-H_2O$), (b) reductive elimination of the vicinal chlorides (Na, liquid NH_3), and (c) hydrolysis (2% aqueous H_2SO_4 in acetone)]. Tricyclic ketone



7 proved to be a 2:1 mixture of epimers which could be cleanly separated by preparative vapor phase chromatography (VPC) (25% Carbowax, 20 M, 20 ft). Although each isomer was fully characterized, it was not possible at this point to assign the relative stereochemical disposition of the secondary methyl subsitution.

Since we were well aware that the relative configuration could not easily be established until spectral comparisons were made between synthetic and natural modhephene, the epimeric mixture was carried through the remainder of the synthesis. For the record, each epimeric pair unless otherwise indicated was separated by preparative VPC and fully characterized at each step.[10]

We next focused attention on the critical acid-catalyzed isomerization which was to establish the propellane skeleton. Toward this end, treatment of **7** with 0.6 equiv of TsOH (benzene, 80 °C/4 h) afforded an excellent yield (93%) of a 2:1 mixture of the epimeric propellanes **8**.[10] That indeed the desired propellane skeleton had been elaborated followed from the spectral data: 250-MHz NMR (ca. δ 6.0 and 7.5, 1 H each) and IR spectra (ca. 1710 and 1630–1680 cm^{-1}; cyclopentenone).[11]

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(1) A preliminary account of this paper was presented at the 179th National Meeting of the American Chemical Society, Houston, Texas, March 1980, ORGN 63.

(2) L. H. Zalkow, R. N. Harris, III, and D. Van Derveer, *J. Chem. Soc., Chem. Commun.*, 420 (1973).

(3) (a) L. H. Zalkow, R. N. Harris, III, and N. I. Burke, *J. Nat. Prod.*, **42**, 96 (1979); (b) L. H. Zalkow, R. N. Harris, III, D. Van Derveer, and J. A. Bertrand, *J. Chem. Soc., Chem. Commun.*, 454 (1977); for recent syntheses of isocomene see: W. Oppolzer, K. Bättig, and T. Hudlicky, *Helv. Chim. Acta*, **62**, 1493 (1979); L. Paquette and Y. K. Han, *J. Org. Chem.*, **44**, 4014 (1979); M. C. Pirrung, *J. Am. Chem. Soc.*, **101**, 7130 (1979).

(4) Recently an acetoxy derivative of modhephene has been isolated: see F. Bohlmann, C. Zdero, R. Bohlmann, R. M. King, and H. Robinson, *Phytochemistry*, **19**, 579 (1980).

(5) For a review of this area see R. L. Cargill, T. E. Jackson, N. P. Peet, and D. M. Pond, *Acc. Chem. Res.*, **7**, 106 (1974); also see R. L. Cargill and J. W. Crawford, *Tetrahedron Lett.*, 169 (1967); *J. Org. Chem.*, **35**, 356 (1970); R. L. Cargill, D. M. Pond, and S. O. LeGrand, *ibid.*, **35**, 359 (1970).

(6) H. O. House and T. H. Cronin, *J. Org. Chem.*, 30, 1061 (1965).

(7) For an excellent review of the Wiesner model see K. Wiesner, *Tetrahedron*, **31**, 1655 (1975); also see R. W. Guthrie, Z. Valenta, and K. Wiesner, *Tetrahedron Lett.*, 4645 (1966); G. A. Poulton and K. Wiesner, *Symp. Pap.—IUPAC Int. Symp. Chem. Nat. Prod., 11th*, **3**, 115 (1978); F. J. A. Lauman, M.Sc. Thesis, University of New Brunswick, 1969; G. R. Lenz, *Tetrahedron*, **28**, 2195 (1972); R. B. Kelly, J. Zamecnik, and B. A. Beckett, *Can. J. Chem.*, **50**, 3455 (1972); R. B. Kelly, J. Eber, and H. K. Hung, *ibid.*, **51**, 2534 (1973); F. E. Ziegler and J. A. Kloek, *Tetrahedron Lett.*, 315 (1974).

(8) R. L. Cargill, Jr., G. H. Morton, and J. Bordner, *J. Org. Chem.*, **45**, 3929 (1980). We thank Professor Cargill, University of South Carolina, for a preprint of this paper.

(9) E. Piers, C. K. Lau, and I. Nagakura, *Tetrahedron Lett.*, 3233 (1976); also see E. Piers and J. Banville, *J. Chem. Soc., Chem. Commun.*, 1138 (1979). We thank Professor Piers, University of British Columbia, for providing us with a detailed experimental procedure for the preparation of enone **5**.

(10) (a) The structure assigned to each new compound was in accord with its infrared and 250- or 360-MHz NMR spectra. Analytical samples of all new compounds, obtained by chromatography (TLC or VPC) gave satisfactory C and H combustion analysis within 0.4% and/or appropriate parent ion identification by high-resolution mass spectrometry. (b) All yields recorded here are based upon isolated material which was >97% pure.

(11) (a) L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed., Pergamon Press, Oxford, 1969, Chapters 2 and 3, and references cited therein; (b) L. H. Bellamy, "The Infrared Spectra of Complex Molecules", Matheson, London, 1958, Chapter 2; "Advances in Infrared Group Frequencies", Matheson, London, 1968, Chapter 3.

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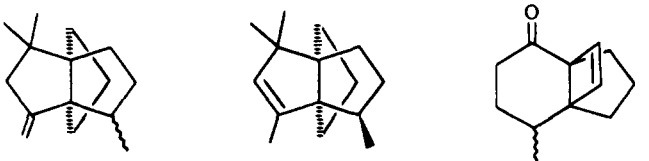
With the propellane framework constructed, all that remained to complete a total synthesis of modhephene was introduction of three methyl substituents exploiting the functionality inherent in the cyclopentenone ring. The first was introduced by way of an alkylative 1,3-ketone transposition.[12] Addition of methyllithium (−78 °C, Et_2O) to enone **8** followed by Jones oxidation[13] (0 °C, 2 h) afforded **9**[10] in 88% yield overall. The second methyl group was anticipated to be introduced via a cuprate 1,4-conjugate addition.[14] However, due to the neopentyl environment proximate to C(4), enone **9** proved to be completely unreactive under a variety of time and temperature regimes. This problem was, however, easily overcome by effecting the conjugate addition process in the presence of Lewis acid.[15] That is, addition of 1.8 equiv of $BF_3{\cdot}Et_2O$ to an ethereal solution of $LiMe_2Cu$ cooled to −78 °C followed by enone **9** afforded after one recycle saturated ketone **10**[10] in 70% yield.

With an efficient route to **10** secure, the total synthesis of modhephene appeared to be within easy grasp; only introduction of the final methyl group and elimination of water remained. In principle this transformation could be effected by either of two methods: (a) 1,2-addition of a methyl nucleophile to the carbonyl followed by dehydration, or (b) Wittig olefination and subsequent isomerization. We embarked initially on the first of these approaches, attempting to add a variety of methyl or closely related nucleophiles. To our dismay, such reagents[16] failed completely to add to ketone **10**. Even methylmagnesium bromide in toluene,[20] conditions known to enhance 1,2-addition to easily enolizable substrates, did not afford the desired adduct. Presumably the severe steric hindrance in the vicinity of the carbonyl, in conjunction with facile enolization of the cyclopentanone system, precluded 1,2-addition.

We next turned attention to Wittig-olefination avenues.[21] Frustrated initially by the lack of reactivity of methylenetriphenylphosphorane generated with dimsylsodium (Me_2SO, 3 days, 70 °C) toward **10**, we explored the high-temperature Wittig conditions of Conia[22] known to be particularly effective for olefination of hindered, enolizable ketones (e.g., camphor). To our delight, addition of **10** to a preheated (ca. 92 °C)[23] solution containing a sevenfold excess of methylenetriphenylphosphorane generated from an equimolar amount of potassium *tert*-amylate in toluene afforded an epimeric mixture of hydrocarbons **11**.[10] That olefination had proceeded derived from the observation of two sets of characteristic *exo*-methylene AB quartets in the 250-MHz NMR spectrum (integration = 2:1) as well as only C–H and C–C absorptions in the IR spectrum.[11]



(11) Epimodhephene (12) (13)

With acceptable olefination conditions established, isomerization of the *exo*-methylene group proceeded without event. Thus, without separation, the mixture of isomodhephenes (**11**) was treated with 0.4 equiv of *p*-toluenesulfonic acid in methylene chloride at room temperature for 3 h. That complete isomerization had occurred was clear from the ^1H (250 MHz) NMR spectrum. Unfortunately, all attempts to separate modhephene (**1**) from its epimer (**12**) proved fruitless. Hence, it was necessary to subject individually each epimer of ketone **10** to the olefination sequence. In that event modhephene (**1**) and epimodhephene (**12**)[10] were isolated in 43% and 56% yield overall from the respective epimers. Synthetic modhephene was demonstrated to be identical in all respects, except for rotation, with natural modhephene by direct comparison (IR, 60- and 250-MHz NMR, TLC, and VPC) with an authentic sample.[24] However, to our surprise modhephene proved to arise from the minor epimer; thus the photoaddition of dichloroethylene to enone **5** had occurred predominantly syn to the secondary methyl substituent.

Intent on achieving a stereoselective synthesis of modhephene, we explored the photoaddition of dichloroethylene with the closely related enone **6**.[25] Here, irradiation in hexane (0.3 M) through Pyrex in the presence of 3 equiv of 1,2-dichloroethylene afforded a 68% yield of tricyclic material, which was converted without event via the sequence (a) ketalization, (b) reduction, (c) hydrolysis, and (d) acid-catalyzed rearrangement to an epimeric mixture of enones **8**, the overall yield from enone **6** being 27%. While the sequence was not stereospecific, we were pleased to find that the ratio of epimers was 57:43, with the anti isomer (that leading to modhephene) predominating the mixture.

In summary, we have achieved the first total synthesis of (±)-modhephene and (±)-epimodhephene in nine steps from enones **5** and **6**, with the overall yield of modhephene being 10% and 7%, respectively. The lack of marked stereospecificity detracts little from our synthetic approach in that the synthesis is direct, is highly efficient, and requires no chromatographic separations until the final olefination step.

Acknowledgment. It is a pleasure to acknowledge the support of this investigation by the National Institutes of Health (Institute of General Medical Sciences) through Grant No. GM 24680. In addition, we thank Mr. S. T. Bella of the Rockefeller University for the microanalyses and the Middle Atlantic Regional NMR Facility (NIH Grant No. RR542) at The University of Pennsylvania where the 360-MHz NMR spectra were recorded.

(12) For example see (a) G. Büchi and D. Egger, *J. Org. Chem.*, **36**, 2021 (1971); (b) P. Grieco, *ibid.*, **37**, 2363 (1972); (c) K. Oshima, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **95**, 4446 (1973); (d) P. M. McCurry, Jr., and R. K. Singh, *J. Org. Chem.*, **39**, 2316 (1974); (e) J. S. Dutcher, J. G. MacMillan, and C. H. Heathcock, *ibid.*, **41**, 2663 (1976); (f) W. G. Dauben and D. M. Michno, *ibid.*, **42**, 682 (1977).

(13) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, 1967, pp 142–144.

(14) G. H. Posner, *Org. React.*, **19**, 1 (1972).

(15) To the best of our knowledge cuprate conjugate additions have *not* previously been promoted with Lewis acid. For conjugate addition of alkyl groups to α,β- and β,β-disubstituted enoate esters employing an alkylcopper–boron trifluoride reagent, see K. Maruyama and Y. Yamamoto, *J. Am. Chem. Soc.*, **99**, 8068 (1977); **100**, 3240 (1978).

(16) We examined here methyllithium, methylmagnesium bromide, [(trimethylsilyl)methyl]magnesium chloride,[17] diethylaluminum cyanide,[18] and [(phenylthio)methyl]lithium,[19] all to no avail.

(17) D. J. Peterson, *J. Org. Chem.*, **33**, 780 (1968); T. H. Chan, E. Chang, and E. Vinokur, *Tetrahedron Lett.*, 1137 (1970); T. H. Chan and E. Chang, *J. Org. Chem.*, **39**, 3264 (1974); T.-H. Chan, *Acc. Chem. Res.*, **10**, 442 (1977).

(18) W. Nagata, M. Yoshioka, and M. Murakami, *J. Am. Chem. Soc.*, **94**, 4654 (1972); also see W. Nagata, M. Yoshioka, and M. Murakami, *Org. Synth.*, **52**, 96 (1972).

(19) I. Kuwajima, S. Sato, and Y. Kurata, *Tetrahedron Lett.*, 737 (1972); also see R. L. Sowerby and R. M. Coates, *J. Am. Chem. Soc.*, **94**, 30, 2027 (1974).

(20) E. C. Ashby and R. Reed, *J. Org. Chem.*, **31**, 971 (1966); also see P. Canone, G. B. Foscolos, and G. Lemay, *Tetrahedron Lett.*, 4383 (1979).

(21) For excellent reviews of the Wittig reagent, see A. W. Johnson, "Ylid Chemistry", Academic Press, New York, 1966; M. Scholsser, *Top. Stereochem.* **5**, 1 (1970).

(22) J. M. Conia and J.-C. Limasset, *Bull. Soc. Chim. Fr.*, 1936 (1967); also see S. R. Schow and T. C. McMorris, *J. Org. Chem.*, **44**, 3760 (1979).

(23) The success of this olefination reaction is dependent upon three critical factors. First, it is essential to use a substantial excess of Wittig reagent. Second, best results are obtained when the reagent is generated in a minimum of solvent. Finally, it is imperative that the ketone be added to a preheated solution of Wittig reagent.

(24) We are grateful to Professor L. H. Zalkow, Georgia Institute of Technology, for a generous sample of natural modhephene.

(25) Enone **6** was prepared, as illustrated below, employing i, a novel diene developed in our laboratory (unpublished results of Mr. Barry Wexler). Studies demonstrating the general utility of i, as well as analogues thereof, as efficient partners in the Diels–Alder reaction will be forthcoming in the near future.