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

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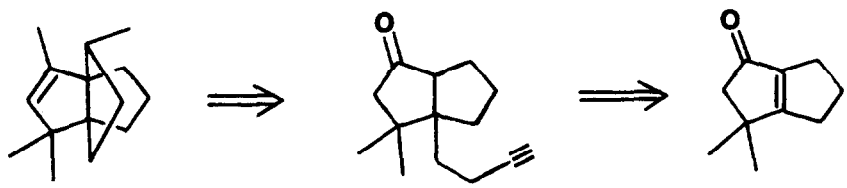
Abstract. An efficient, enantioselective synthesis of the title compound 1 via diastereoselective cyclopropanation is described.

Modhephene 1 is an unusual sesquiterpene possessing a carbocyclic [3.3.3] propellane skeleton.[1] Several syntheses of racemic modhephene have been reported[2] but no enantioselective approach has yet been disclosed. The synthesis due to Paquette and Schostarez proceeds to



1 2 3

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 ketals[3] 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 Noyori[4] 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 ^{13}C NMR spectroscopy.[6]

Ketal hydrolysis (HCl, H_2O, CH_3OH, room temperature) gave enantiomerically enriched ketone 6, mp 48-50 °C, $[\alpha]_D^{25}$ -31.5° (c 3.9, $CHCl_3$), in 94% yield. Assignment of the (3aS, 6aS) 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 regioselective cyclopropane ring opening,[8] iodomethyl ketone 7, mp 38-40 °C, $[\alpha]_D^{25}$ -33.1° (c 3.2, $CHCl_3$), in 85% yield. Ketalization of 7 using bis-trimethylsilyl ethylene glycol[4] gave iodomethyl ketal 8, $[\alpha]_D^{25}$ +21.7° (c 5.5, $CHCl_3$) in 96% yield. Displacement of iodide by the lithium salt of 1-trimethylsilyl-1-propyne[9] (2 equiv, Et_2O/TMED/HMPA, -25 °C, 1 h) gave crude acetylenic ketal 9 which was hydrolyzed (HCl, CH_3OH, H_2O, room temperature) and desilylated ($nBu_4N^+ F^-$, THF, H_2O, room temperature) to give enantiomerically enriched ketone 2, $[\alpha]_D^{25}$ -117.9° (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] Thermolysis[10] of 2 (decalin, 360 °C) provided tricyclic ketone 10, $[\alpha]_D^{25}$ +107° (c 2.67, $CHCl_3$) in 57% yield.[11] Olefination[12] of 10 (CH_2I_2, Zn, $TiCl_4$) gave diene 11, $[\alpha]_D^{25}$ +40° (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° (c 3.53, $CHCl_3$), in 50% yield. Epoxide 12 was isomerized to ketone 13, $[\alpha]_D^{25}$ +10.3° (c 2.5, $CHCl_3$), in 43% yield using $BF_3 \cdot Et_2O$ in CH_2Cl_2. Double bond migration (I_2, C_6H_6, heat) converted 13 into a separable 2:1 mixture of 13 and 14, $[\alpha]_D^{25}$ +77° (c 1.26, $CHCl_3$). Finally, deoxygenation of 14 (K_2CO_3, NH_2NH_2, $HOCH_2CH_2OH$, heat) provided (+)-modhephene 1 $[\alpha]_D^{25}$ +4.5° (c 0.13, $CHCl_3$) contaminated with approximately 15% of epimodhephene 15.

The rotation of natural modhephene, calculated[13] 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 I:

(a) 1,4-Di-O-methyl-2,3-di-O-trimethylsilyl-D-threitol, TMS-OTf

(b) Zn(Cu), CH_2I_2, Et_2O, heat

(c) Aq. HCl, CH_3OH

(d) TMS-I, CCl_4

(e) $TMSOCH_2CH_2OTMS$, TMS-OTf, CH_2Cl_2

(f) $Li^{\oplus}\ominus CH_2C{\equiv}CTMS$, TMED, HMPA, Et_2O

(g) Aq. HCl, CH_3OH

(h) $nBu_4N^{\oplus}F^{\ominus}$, THF, H_2O

(i) 360 °C, decalin

(j) CH_2I_2, Zn, $TiCl_4$, THF

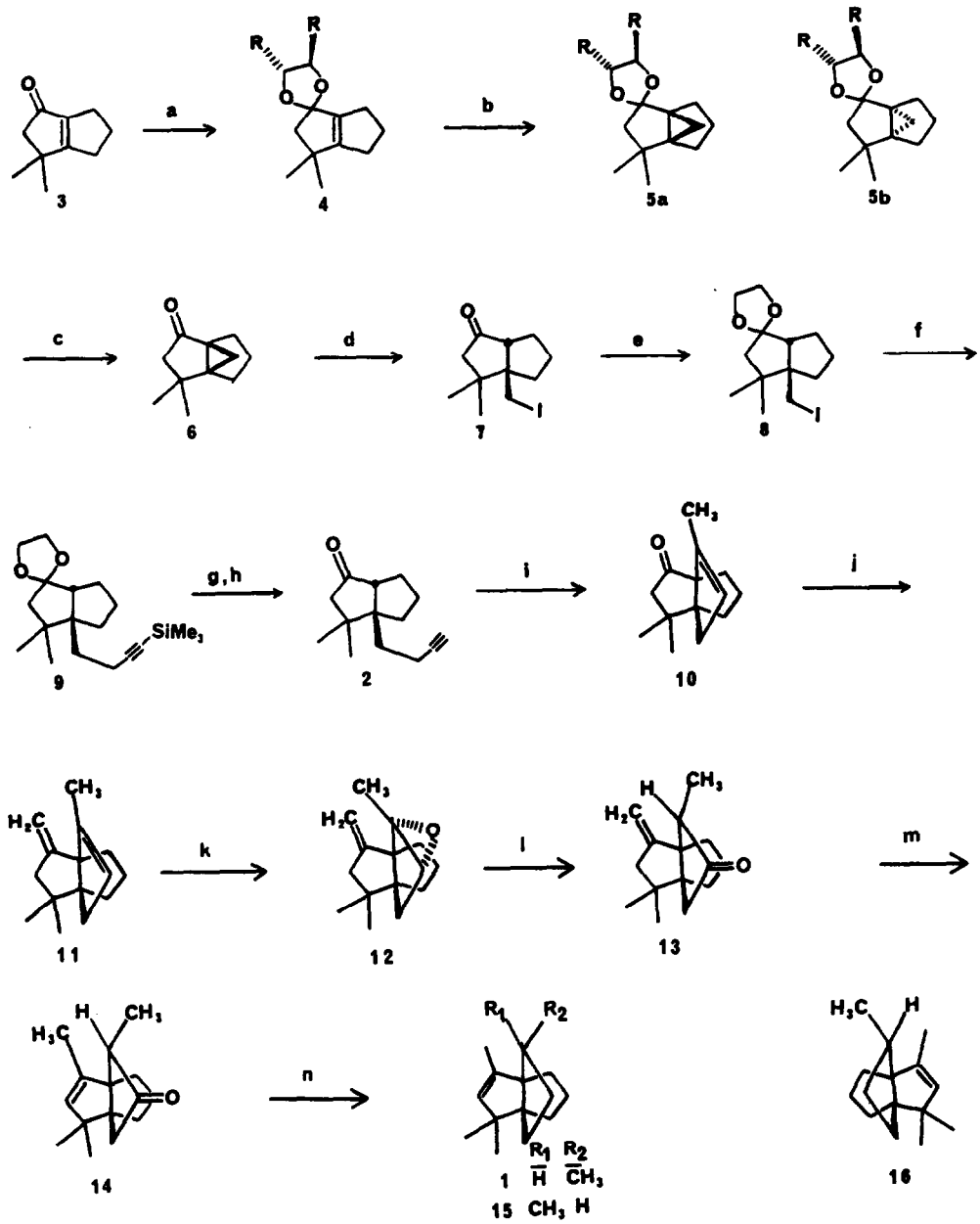
(k) MCPBA, Na_2HPO_4, CH_2Cl_2

(l) $BF_3 \cdot Et_2O$, CH_2Cl_2

(m) I_2, C_6H_6, heat

(n) NH_2NH_2, K_2CO_3, $HOCH_2CH_2OH$, heat

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



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