Reactions of bridgehead halides. A synthesis of modhephene, isomodhephene, and epi-modhephene

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Abstract
A Synthesis of modhephene has been achieved, the key feature of which is the use of a novel nucleophilic addition/rearrangement reaction to develop the carbon framework. Stereochemical control of the stereogenic center bearing the methyl group was accomplished by variation of the hydrogenation conditions. As a byproduct of this work, we have clarified structural assignments of intermediates from previous syntheses.

Disciplines
Chemistry | Organic Chemistry | Other Chemistry | Polymer Chemistry

Comments
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70 eV) m/e 198.1517 (198.1494 calcd for C11H13NO2 + H).

-re[2R,5S,α]-6-Cyano-6-methyl-α-(1-methylthyl)-tetrahydro-2H-pyrimidin-2-one (17). A solution of bromoacrylonitrile 2 (0.34 mg, 0.2 mmol) in 2 mL of CH2Cl2 was stirred and cooled at −78 °C as TMSCN (0.08 mL, 0.6 mmol) and BF3•OEt2 (0.06 mL, 0.5 mmol) were added. The temperature was maintained at −78 °C for ca. 8 h and then slowly warmed to −19 °C (in a cold room) over 40 h. Ether and saturated NaHCO3 were added, and the crude product was isolated by the standard method. 1H NMR spectrum of the isolate indicated that <5% of cis diasteromer 17a was present in the crude product. Trans diasteromer 17b was isolated in 87% yield (34 mg, 0.17 mmol) using RC (6.5:1 and then 1:1 pentane–ether, pretreated plate with 7% triethylamine in 3:5:1 pentane–ether): 1H NMR (500 MHz, CDCl3) δ 3.62 (1 H, ddd, J = 8.5 Hz, H-4), 2.02 (1 H, d, H-3), 1.83 (3 H, s, H-5), 1.69 (1 H, m, H-2), 1.43 (1 H, d, H-1), 1.38 (1 H, t, J = 7 Hz, H-6), 1.12 (3 H, t, J = 7 Hz).}

Acknowledgment. This research was supported by the National Science Foundation (CHE-8713080) to which we express our gratitude. We also wish to thank ICN Pharmaceuticals for a generous gift of flash chromatography silica gel.

Supplementary Material Available: Experimental procedures for the synthesis of compounds 1–4 along with the 1H and 13C NMR spectra for all new compounds and DNGE data and 2-D homonuclear decoupling spectra (74 pages). Ordering information is given on any current masthead page.

Reactions of Bridgehead Halides. A Synthesis of Modephene, Isomodephene, and epimodephene

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A synthesis of modephene has been achieved, the key feature of which is the use of a novel nuclophilic addition/rearrangement reaction to develop the carbon framework. Stereoregularitly of the stereochemical center bearing the methyl group was accomplished by variation of the hydrogenation conditions. As a byproduct of this work, we have clarified structural assignments of intermediates from previous syntheses.

The discovery of the novel sesquiterpene modephene (1) has led to a renewed interest in the synthesis of propellanes. Total syntheses of this naturally occurring hydrocarbon have been recorded by a number of researchers.1
We recently discovered a novel rearrangement in the course of our studies on the generation and reactions of bridgehead radicals. This rearrangement, which is depicted below, transforms the readily available azabicyclo[3.3.1]nonane skeleton 2 into an azabicyclo[3.3.0]octane skeleton of general structure 3, a bicyclic ring system for which very few synthetic routes have been reported. The rearrangement is reasonably general in that alkyllithium reagents, enolate anions, and phosphonate anions all react with ketone 2 to generate 3–6. Interestingly, Grignard reagents afforded only the unrearranged alcohol. The results are collated in Table I.

In view of the successful rearrangements of 2, we decided to examine the chemistry of bicyclo[3.3.1]nonene 9, a potential precursor to 1. This compound was prepared by the reaction of keto ester 8 with methyl vinyl ketone (MVK) in the presence of concentrated sulfuric acid. The reaction conditions were very critical. The optimal conditions involved the slow dropwise addition of sulfuric acid to a mixture of 8 and MVK at −78 °C. If the reaction was conducted at higher temperatures or if the addition of sulfuric acid was too fast, dark polymeric byproducts were formed. These unusual conditions were dictated because the use of solvents such as benzene, methylene chloride, or acetonitrile led only to recovered 8.

With gram quantities of 9 in hand, the nuclophilic addition/ring contraction sequence was studied. The reaction of 9 with the anions of acetophenone and dimethyl methylphosphonate led to esters 10 and 11 in 41% and 70% yields, respectively.

Catalytic Hydrogenation Route to epi-Modhephene. Ester 11 contains two of the three rings of modhephene. We subjected ester 11 to catalytic hydrogenation with hydrogen and Pd/C. A single stereoisomer was obtained which we initially assigned to be isomer 13 derived from the catalytic hydrogenation product or the regiochemistry of the phosphonate cyclic system. The possibility that the hydrogenation reaction had produced isomer 12 could more readily be tested. Although the production of 12 necessitated a hydrogenation from the crowded endo face of the bicyclo[3.3.0]octane system, approach from the exo face was hindered by both the ester and keto phosphonate groups at the bridgehead carbons. As subsequent discussion will clarify, the actual structures of the Pd/C hydrogenation product and the vinylogous ester are 12 and 14, respectively.

Iridium Catalyst Route to Modhephene and Isomodhephene. Recently, both Stork8 and Crabtree8 re-

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(3) For a related procedure, see: Hesther, C. H.; Ellis, J. E.; McMurry, J. E.; Coppolino, A. Tetrahedron Lett. 1971, 4985. The solvent used in the sulfuric acid reaction was methylene chloride.


ported the use of an iridium catalyst for directed hydrogenation of alkenes. Since they demonstrated that carbonyl groups exerted a strong directing effect, we employed this catalyst for the hydrogenation of keto phosphonate 11. The iridium-mediated reduction afforded 13 which was different from 12. Cyclization with KH (tBuOK afforded much lower yields in this case) in boiling benzene afforded a vinylogous ester 15 whose 300-MHz NMR spectrum was quite different from that of 14. Reaction of 15 with methyllithium in hot THF followed by hydrolysis of the alcohol with sulfuric acid produced 16. The 300-MHz NMR spectrum of ketone 16 was identical with the 300-MHz NMR spectrum provided by Curran. This comparison established the structure of the iridium-mediated reduction product which we had tentatively assigned as 15 and also established the structure of the vinylogous ester as 15. Since Curran has converted 16 into a mixture of 1 and isomodhephene 17, the preparation of 16 constitutes a formal synthesis of 1.

Structural Assignments in Previous Modhephene Syntheses. The major clue to resolving the stereochemical misassignments was found in a footnote in Curran's paper, which mentions a reversal of proton NMR assignments for some compounds in the modhephene series and the epimodhephene series in a full paper by Smith and co-workers detailing their clever synthesis of modhephene.13 Unfortunately, the structural assignment for the key Mundy intermediate 18 was based on a proton NMR comparison with one of these inadvertently misassigned compounds.

Interestingly, the stereogenic center bearing the methyl group in the Mundy synthesis had been introduced by catalytic hydrogenation of diester 19 using Pd/C as the catalyst. Additionally, it is now clear why diketone 20, an intermediate in the Mundy synthesis, afforded such high regioselectivity in the formation of a vinylogous ester.

Conclusions

Our synthesis represents a direct synthetic application of a novel nucleophilic addition/rearrangement sequence of bicyclic bridgehead bromides. We have also shown that either isomer can be obtained by the appropriate choice of hydrogenation conditions. Additionally, this approach has helped to clarify unresolved stereochemical assignments from prior modhephene syntheses.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. H:EA refers to hexanes-ethyl acetate solvent mixtures for TLC and chromatography. The purity of all title compounds was determined to be >90% by proton NMR and/or elemental analysis.

Ethyl 5-Bromo-5-ethyl-3-oxo-5-azabicyclo[3.3.1]nonane-carboxylate (2). To a solution of ethyl 5-bromo-2-oxocyclohexanecarboxylate (4.98 g, 20 mmol) in 120 mL of MeOH at 25 °C was added formaldehyde (37% in H2O, 3.24 g, 40 mmol) and ethanolamine (70% in H2O, 1.29 g, 20 mmol). The solution was stirred at 25 °C for 48 h. The methanol was removed in vacuo and the product was taken up in CH2Cl2. The solvent was removed in vacuo. The residue was purified by silica gel (5% diethylether in hexane) chromatography using 15:1:1:1 H:EA

by proton NMR and/or elemental analysis. The purity of all title compounds was determined to be >90% by proton NMR and/or elemental analysis. The purity of all title compounds was determined to be >90% by proton NMR and/or elemental analysis. The purity of all title compounds was determined to be >90% by proton NMR and/or elemental analysis.

Table I. Organometallic Additions to Keto Ester 2

<table>
<thead>
<tr>
<th>RM</th>
<th>% yield</th>
<th>compd</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhOCOCH₃Li</td>
<td>60</td>
<td>3</td>
</tr>
<tr>
<td>PhLi</td>
<td>58</td>
<td>0</td>
</tr>
<tr>
<td>MeLi</td>
<td>73</td>
<td>0</td>
</tr>
<tr>
<td>Me₂MgBr</td>
<td>53</td>
<td>0</td>
</tr>
<tr>
<td>CH₂=CH₂CH₂MgBr</td>
<td>0</td>
<td>92</td>
</tr>
</tbody>
</table>

6: NMR (CDCl₃) δ 4.075 (q, J = 7.2, 2 H), 3.025 (d, J = 9.3, 1 H), 2.790 (d, J = 9.0, 1 H), 2.683 (d, J = 8.4, 2 H), 2.450 (m, 2 H), 2.286-2.167 (2 H, m), 2.104 (d, J = 0.6, 3 H), 1.921 (m, 1 H), 1.212 (d, J = 6.9, 3 H), 1.079 (t, J = 7.5, 3 H); IR (film) 2986, 2874, 2804, 1730, 1705, 1448, 1229, 1032, 932 cm⁻¹; MS m/e for C₂₄H₂₄O₄N calcd 353.15481, measured 353.15476; 13C NMR (CDCl₃) δ 209.029, 175.305, 69.483, 64.438, 64.003, 62.405, 60.564, 49.387, 39.036, 37.282, 37.267, 25.163, 13.813, 13.548; TLC (5:1 H₂:EA) R₅ = 0.28.

10: NMR (CDCl₃) δ 15.906 (1 H, s), 7.804 (2 H, d, J = 7.5), 7.555 (3 H, m), 6.065 (1 H, s), 5.572 (1 H, s), 5.397 (2 H, m), 3.438 (1 H, m), 2.311 (3 H, m), 1.849 (4 H, m), 1.579 (3 H, s), 1.093 (3 H, t, J = 6.9); MS m/e 340, 294, 296, 220, 194, 175, 141, 105, 91, 77, 65; HRMS m/e for C₁₇H₂₃O₃Br calcd 340.16771, measured 340.16772; 13C NMR (CDCl₃) δ 200.265, 179.924, 175.972, 139.505, 134.472, 131.892, 128.502, 127.292, 126.719, 94.733, 76.704, 73.057, 60.447, 43.101, 40.63, 30.302, 24.488, 13.699, 13.204.

4-Methoxy-5-methyl-9-oxobicyclo[3.3.3]limonene-3-one (15). A solution of ester 14 (0.490 g, 0.45 mmol) and [Ir(COD)](PCy₃)(py)PF₆ (0.020 g, 0.025 mmol) in 3 mL of CH₂Cl₂ was charged with an atmosphere of hydrogen. The solution was stirred for 15 h at 25 °C. The solvent was removed in vacuo and ether was added. The suspension was passed through a silica gel column with 5:1 H₂O:EtOH. The crude product had been quantitatively eluted from the column by 5:1 H₂O:EtOH to afford the product (98% yield) of ketone 15.
Concerning the Diastereofacial Selectivity of the Aldol Reactions of α-Methyl Chiral Aldehydes and Lithium and Boron Propionate Enolates

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The diastereofacial selectivity of the aldol reactions of α-methyl chiral aldehydes and propionate and ethyl ketone derived lithium and boron enolates is analyzed from the perspective of a transition state model suggested by Evans in 1982. The dominant stereocentrum element in these reactions, as in the mechanistically related reactions of alkenes, reagents and α-substituted chiral aldehydes appears to be the minimization of gauche pentane interactions in the competing transition states. Transition state 35 is viewed as the lowest energy structure in the "anti-Felkin" selective aldol reactions of Z(0)-enolates as long as the steric requirements of R are greater than that of the α-Me group. Transition state 36 is similarly the lowest energy structure available in the aldol reactions of Z(0)-enolates (Felkin selective). The model also recoules data involving the aldol reactions of Ph(Me)CHO (1a) and R=CHCH(Me)CHO (1b, 1c) that preferentially provide the 2,3-syn-3,4-syn (Felkin) diastereomers 3: the Ph or vinyl substituents are viewed as the smaller of the two α-substituents (Me > Ph or vinyl) since they expose a sterically undemanding, flat surface to the incoming nucleophile in the lowest energy transition structure 39 (for 1a) and 41 (for 1b, 1c).

Supplementary Material Available: 1H NMR spectra of compounds for which elemental analyses are not reported (5 pages). Ordering information is given on any current masthead page.


