

oil (10.9 mg, 0.00885 mmol, 82% yield): IR (thin film) 2937, 2867, 1738 ( $C_1$  ester), 1713 ( $C_9$ ,  $C_{10}$ ,  $C_{22}$  ketones), 1655 ( $C_8$  amide), 1462, 1383, 1252, 1140, 1109, 884, 837  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 500 MHz) 5.73–5.66 (m, 1 H), 5.36 (d,  $J = 8.7$ , 1 H), 5.24 (d,  $J = 10.1$ , 1 H), 5.21–5.18 (m, 1 H), 5.05–4.97 (m, 2 H), 4.87 (d,  $J = 10.4$ , 1 H), 4.34 (dd,  $J = 10.2$ , 3.3, 1 H), 4.28–4.25 (m, 1 H), 3.76–3.72 (br, t, 1 H), 3.57–3.52 (m, 1 H), 3.44–3.40 (m, 1 H), 3.39 (s, 3 H), 3.37 (s, 3 H), 3.28–3.21 (m, 1 H), 3.19 (s, 3 H), 3.04–2.98 (m, 1 H), 2.98–2.92 (m, 1 H), 2.48–2.42 (m), 2.38–2.31 (m), 2.30–2.17 (m), 2.05–2.00 (m), 1.98–1.88 (m), 1.80–1.50 (m), 1.76 (br s, 3 H), 1.51 (br s, 3 H), 1.18 (d,  $J = 6.8$ , 3 H), 1.10–1.05 (br s, 2  $\times$  TIPS), 0.92 (br s, *t*-BuSi), 0.90–0.80 (several Me doublets, 6 H), 0.12–0.08 (m,  $Me_2Si$ ).

The same sequence using the ( $C_8$ ,  $C_9$ - $^{13}C_2$ )-labeled diols provided the analogous ( $C_8$ ,  $C_9$ - $^{13}C_2$ )-labeled triketone **68\***: IR (thin film) 2937, 2867, 1734 ( $C_1$  ester), 1713 ( $C_{10}$ ,  $C_{22}$  ketones), 1676 ( $^{13}C_9$  ketone), 1617 ( $^{13}C_8$  amide), 1458, 1252, 1140, 1107, 884, 837  $cm^{-1}$ ;  $^{13}C$  NMR ( $CDCl_3$ , 125 MHz)  $C_8$  (two rotamers) 166.5 (d,  $J_{CC} = 64.2$  Hz, major), 166.0 (d,  $J_{CC} = 60.3$  Hz, minor);  $C_9$  188.4 (d,  $J_{CC} = 64.6$  Hz, minor), 186.6 (d,  $J_{CC} = 64.6$  Hz, major).

**FK506 (1)**. Triketone **68** (10.9 mg, 0.00885 mmol) was treated with 1.5 mL of a 3.0 N aqueous HF/ $CH_3CN$  solution (prepared by diluting 11 mL of 48% aqueous HF with  $CH_3CN$  to a total volume of 100 mL) in a polypropylene (Eppendorf-like) tube. The resulting solution was stirred at ambient temperature for 18 h, then neutralized with aqueous  $NaHCO_3$ , and extracted with several portions of  $CH_2Cl_2$ . The combined organic extracts were washed with 2 portions of aqueous  $NaHCO_3$  and dried over  $Na_2SO_4$ . Filtration, concentration, and flash chromatography (1:1 to 2:3 hexane/ethyl acetate) provided FK506 (**1**) as a white powder (5.2 mg, 0.0065 mmol, 73% yield).  $^1H$  NMR, IR, and TLC behavior of synthetic **1** in several solvent systems (2:1  $CH_2Cl_2/CH_3CN$ , 1:1 THF/hexane, 100% EtOAc, 5:2 benzene/acetone, 10:1  $CH_2Cl_2/MeOH$ ) were indistinguishable from a sample of the natural material:  $[\alpha]_D^{25}$   $-85^\circ$  (c 0.20,  $CHCl_3$ ); lit.  $[\alpha]_D^{25}$   $-84.4^\circ$  (c 1.02,  $CHCl_3$ );<sup>2b</sup> IR (thin film) 3494 (br), 2937, 2874, 2826, 1744 ( $C_1$  ester), 1717 ( $C_9$  ketone), 1705 ( $C_{22}$  ketone), 1651 ( $C_8$  amide), 1451, 1381, 1350, 1327, 1285, 1196, 1173, 1102, 1036, 990, 914, 733  $cm^{-1}$ ;  $^{13}C$  NMR ( $CDCl_3$ , 125 MHz)

(The signal for the  $C_{22}$  ketone at 212.7 ppm in the spectrum of natural FK506 was not observed in the spectrum of our synthetic FK506 due to the inadvertent use of a sweep width that did not collect data above 200 ppm. The spectra were identical in all other respects, however.) 196.1, 169.0, 164.6, 139.0, 135.6, 135.4, 132.4, 131.8, 129.7, 122.5, 116.7, 98.7, 97.0, 84.2, 77.9, 75.2, 73.7, 72.8, 72.2, 70.0, 68.9, 57.6, 57.0, 56.6, 56.3, 56.1, 52.8, 48.6, 43.9, 40.5, 39.4, 39.3, 35.6, 35.1, 34.9, 34.8, 34.7, 34.6, 33.6, 32.9, 32.7, 31.2, 30.6, 27.7, 26.3, 24.6, 24.5, 21.1, 20.9, 20.4, 19.4, 16.3, 16.0, 15.8, 14.3, 14.1, 9.8, 9.5;  $^1H$  NMR ( $CDCl_3$ , 500 MHz) 5.76–5.67 (m, 1 H), 5.33 and 5.20 (rotamers, d,  $J = 2.1$ , 1 H), 5.10 (br d,  $J = 9.0$ , 1 H), 5.05 (br d,  $J = 12.3$ , 1 H), 5.01 (br d,  $J = 10.1$ , 1 H), 4.88 and 4.26 (rotamers, br s, 1 H), 4.63 (br d,  $J = 5.2$ , 1 H), 4.44 and 3.72 (rotamers, m, 1 H), 3.97–3.90 (m, 1 H), 3.89 and 3.70 (rotamers, m, 1 H), 3.61–3.58 (m, 1 H), 3.49–3.40 (m, 3 H), 3.419, 3.417, 3.399, 3.390, 3.347, and 3.309 (rotamers of 3 methoxys, s, total of 9 H), 3.05–3.00 (m, 3 H), 2.81 and 2.74 (rotamers, dd,  $J = 16.1$ , 2.8, 1 H), 2.52–2.44 (m, 1 H), 2.38–2.26 (m, 3 H), 2.23–2.14 (m, 3 H), 2.12–1.99 (m, 4 H), 1.94–1.88 (m, 2 H), 1.83–1.72 (m, 4 H), 1.65–1.30 (m, 10 H), 1.67 and 1.65 (rotamers, br s, 3 H) 1.65 and 1.61 (rotamers, br s, 3 H), 1.10–1.03 (m, 2 H), 1.01, 0.97, 0.94, 0.93, 0.88, 0.83 (rotamers of 3 methyls, d,  $J = 6.4$ , 6.6, 6.5, 7.2, 7.1, 6.5, total of 9 H).

The same sequence using **68\*** provided ( $C_8$ ,  $C_9$ - $^{13}C_2$ )-labeled FK506 (**2**): IR (thin film) 3484 (br), 2932, 2869, 1744 ( $C_1$  ester), 1705 ( $C_{22}$  ketone), 1684 ( $^{13}C_9$  ketone), 1611 ( $^{13}C_8$  amide), 1451, 1379, 1196, 1171, 1103, 1053, 1036, 988, 912  $cm^{-1}$ ;  $^{13}C$  NMR ( $CDCl_3$ , 125 MHz)  $C_9$  major rotamer 196.1 (d,  $J_{CC} = 62.9$ ), minor rotamer 192.6 (d,  $J_{CC} = 60.8$ );  $C_8$  minor rotamer 165.8 (d,  $J_{CC} = 62.4$ ), major rotamer 164.6 (d,  $J_{CC} = 63.0$ ).

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## Sequential Radical Cyclization Approach to Propellane Triquinanes. Total Synthesis of ( $\pm$ )-Modhephene

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**Abstract:** Modhephene (**1**) was synthesized in >21% yield from the  $\alpha,\beta$ -unsaturated  $\beta$ -stannyl enoate **24**. The key steps were the radical addition–fragmentation reaction of vinylstannane **25**, which was endo stereoselective and occurred in 90% yield, and the radical cyclization of the iodovinyl ketone **52**, which occurred in 88% yield. The high stereoselectivity in the cyclization of **25** is due in part to the  $Me_3Sn$  substituent; the destannylated analogue **29** cyclized to give a 3:1 endo/exo mixture. The radical cyclization of bromoalkene **16** gave desmethylmodhephene (**19**), while the cyclization of bromoalkene **36** gave propellane **37**, which was nonselectively converted to modhephene (**1**) and isomodhephene (**39**) by Reetz dimethylation. The radical cyclization of cyclopentenyl bromide **8** gave a 5:1 mixture of stereoisomers **10** but only a 3:1 mixture of cyclized (**10**)/uncyclized (**11**) isomers. A new retrosynthetic notation for use in synthetic planning with radical reactions is also described.

We have previously demonstrated the efficiency of using sequential radical cyclizations for the synthesis of linear (hirsutene,<sup>2</sup> capnellene,<sup>3</sup> hypnophillin,<sup>4</sup> and coriolin<sup>4</sup>) and angular (silphiperfolene<sup>5</sup>) triquinanes.<sup>6</sup> Modhephene (**1**), 13-acetoxy-

modhephene (**2**), and modhephene epoxide (**3**) are members of a very small class of triquinane sesquiterpenes, the propellanes, that have been isolated from a variety of natural sources (Figure 1).<sup>7–9</sup> Modhephene's unusual [3.3.3]propellane structure has

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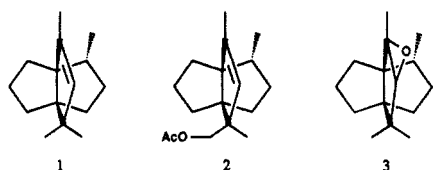


Figure 1. Structures of propellane triquinanes.

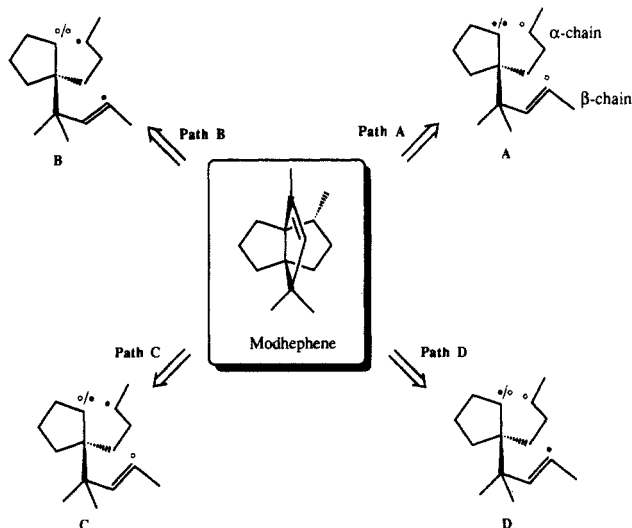


Figure 2. Strategies for modhephene.

made it a popular target for synthesis.<sup>10</sup> We now report an efficient synthesis of the fused triquinane modhephene that further extends the generality of the sequential radical cyclization strategy for the preparation of triquinane natural products.

The principal problems in the synthesis of modhephene are the formation of the three contiguous quaternary centers and the control of relative stereochemistry at the stereocenter bearing the methyl group. Free radical cyclization reactions seemed capable of addressing these problems. The early transition states of hexenyl radical cyclizations make them ideally suited for the synthesis of congested 5-membered rings, and 5-hexenyl radical cyclizations are known to proceed with high regiocontrol and sometimes high stereocontrol.<sup>11</sup>

The general plan for the synthesis of triquinanes by the sequential radical cyclization strategy<sup>6</sup> calls for the construction of a central cyclopentene ring bearing two side chains that are appropriately located and functionalized to construct the remaining

two rings by radical cyclizations. For linear and angular triquinanes, tandem radical cyclizations are possible. That is, the radical that is generated in the first cyclization becomes the precursor for the second cyclization. For modhephene, we envisioned an approach in which increasingly complex second and third rings would be fused to an original ring. Because the architecture of the propellane ring system does not permit tandem radical cyclizations in such a plan, two separate radical cyclizations are necessary.

In Figure 2 we analyze the modhephene problem in the context of a new retrosynthetic notation for radical reactions.<sup>11a</sup> In this notation, closed dots (•) represent sites where radicals are generated, and open dots (◦) represent sites that accept radicals. This new notation alleviates some of the difficulties with current retrosynthetic notations of radical reactions but still maintains harmony with the popular +/– notation for retrosynthesis involving ionic reactions.<sup>12</sup> Path A represents a sequence of diverging radical cyclizations in which radical sites are generated twice on the ring and cyclize to acceptors on the chain. In the converging route, path B, both radicals are generated on the chains and cyclize to the ring. Paths C and D depict the two possible criss-cross routes in which one radical cyclization goes from chain to ring and the other from ring to chain. Because each pair of cyclizations can be conducted in either of two possible orders, this analysis identifies eight different approaches to modhephene. Several of these eight approaches have been investigated, and we describe herein our most significant results.

**Synthesis of Desmethylmodhephene by Path D.** The four approaches to modhephene identified by paths C and D all require a cyclopentenyl reagent capable of both generating a radical and accepting a radical. An obvious choice is a cyclopentenyl halide. This choice orders the sequence of the two radical cyclizations, the ring-to-chain cyclization necessarily preceding the chain-to-ring cyclization (if the chain-to-ring cyclization were to occur first, the halide would be lost by a fragmentation from the intermediate radical). Thus the four choices from paths C and D are reduced to two. The remaining decision was whether to use the  $\alpha$ -oriented side chain in the first cyclization as the radical acceptor (path D) or in the second cyclization as a radical site itself (path C). We chose to use path D in order to control the stereochemistry of the methyl group. Cyclopentenyl bromide **8**, precursor to the vinyl radical **9**, became our reagent equivalent to the imaginary synthon **D**. In addition to the stereoselectivity in the ring-to- $\alpha$  chain cyclization, we were also concerned about the ultimate  $\beta$  chain-to-ring cyclization (see **16**  $\rightarrow$  **19**). Such radical additions to the disubstituted termini of double bonds can be slow,<sup>11a,b</sup> and no propellanes had been synthesized by radical cyclization prior to our investigation.

The requisite vinyl bromide **8** was prepared in 50% overall yield as shown in eq 1. The key step was the Ireland–Claisen rearrangement<sup>13</sup> of **7** in which two of the contiguous quaternary centers needed for modhephene were formed simultaneously. The use of  $\text{RMgX/CeCl}_3$ <sup>14</sup> for the alkylation of ketone **5** was crucial; in the absence of the lanthanide, yields were less than 40%.

Radical cyclization of **8** by standard catalytic tin hydride reduction<sup>15</sup> gave a 5:1 mixture of diastereomers **10**, but only a 3:1 ratio of cyclized to uncyclized products (eq 2). Although the stereoselectivity of the cyclization was satisfactory, and presumably gave the isomer **10 $\alpha$**  as the major product (see below), the formation of significant amounts of the uncyclized isomer **11** was disappointing and rather surprising. Vinyl radicals are known to cyclize with greater efficiency than analogous alkyl radicals, and hydrogen transfer to vinyl radicals rarely competes with 5-exo cyclizations.<sup>16</sup> Stork has shown, for example, that even in *neat*

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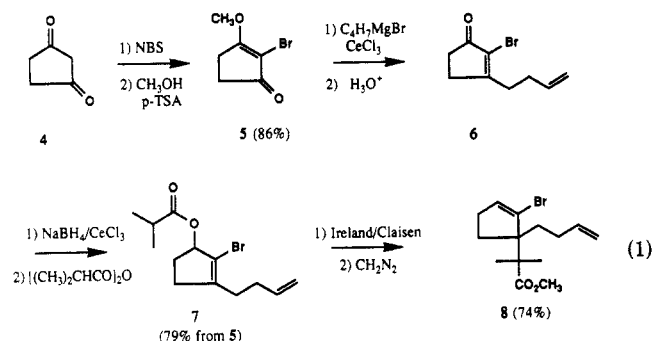
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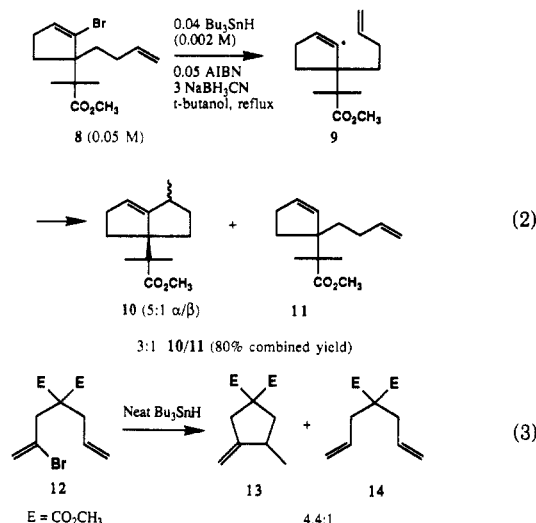
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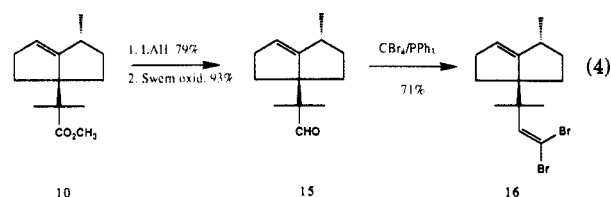
tin hydride the vinyl bromide **12** gives a 4.4:1 ratio of cyclized to uncyclized products (eq 3).<sup>17</sup>



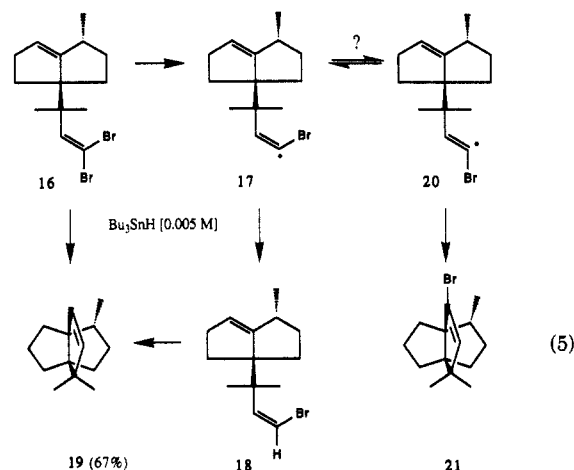
By contrast, the cyclization in eq 2 shows inferior selectivity despite the use of a minimum concentration of catalytic tin hydride (0.002 M). When higher concentrations of tin hydride were used, the ratio of **10/11** decreased, indicating that direct reduction occurred (at least in part) by intermolecular hydrogen transfer to radical **9**.<sup>18</sup> At lower tin hydride concentrations, the reaction became prohibitively slow. The ratio of cyclization to reduction also deteriorated when either Bu<sub>3</sub>GeH<sup>19</sup> or SmI<sub>2</sub><sup>20</sup> was used as the reducing agent. Although we are not certain why the cyclization of cyclopentenyl radical **9** is slow relative to reduction, we surmise that the ring strain energy of the cyclization product may be manifested to some extent in the transition state.

The selectivity problem was exacerbated by the fact that neither the three isomeric esters **10α**, **10β**, and **11** nor the corresponding alcohols (formed by LAH reduction) could be separated on preparative scale. Therefore, the mixture of esters **10** and **11** was carried on in three steps to the dibromoalkene **16** (eq 4).<sup>21</sup> Preparative separation of **16** from its isomers was still not possible, and we were forced to evaluate radical cyclizations on a mixture of isomers rich in **16**.

Prolonged reduction of dibromide **16** with catalytic tin hydride provided desmethylmodhephene (**19**) in 67% yield (eq 5). This is the first example in which a propellane has been generated by



radical cyclization. Unfortunately, controlled reduction of dibromide **16** with 1 equiv of tin hydride gave only *cis*-vinyl bromide **18**. None of the desired propellane **21** was formed. Only upon further reduction of monobromide **18** did cyclization to **19** occur. Vinyl radicals normally have low barriers to inversion,<sup>22</sup> so we had hoped that **17** would equilibrate with **20** and give bromopropellane **21** directly. It is possible that equilibration does occur and that **20** does not cyclize because the radical is stabilized by bromine. However, it is more likely that the less hindered bromine is selectively abstracted by tin radical to give exclusively **17**, and that the bromine substituent imposes configurational stability on the *Z*-isomer **17** and prevents it from interconverting with the *E*-isomer **20**.<sup>23</sup>



We attempted to circumvent this problem by selectively substituting a methyl group for one of the bromines prior to radical cyclization, but preliminary attempts to monomethylate dibromide **16** were unsuccessful.<sup>24</sup> Various attempts to directly alkylate the aldehyde **15** by suitable two-carbon reagents were also unsuccessful. The extremely hindered nature of aldehyde **15** made it impervious to reagents (for example, Ph<sub>3</sub>P=CBrMe) that alkylated trimethylacetaldehyde without difficulty.<sup>25</sup>

**Synthesis of Modhephene and Isomodhephene by Path B.** Although there is little doubt that we could have solved the problem of introducing the vinyl methyl group, the practical problems encountered in separation of isomers provided a strong incentive to develop a more selective route. We turned to a different approach to modhephene in which both radical cycli-

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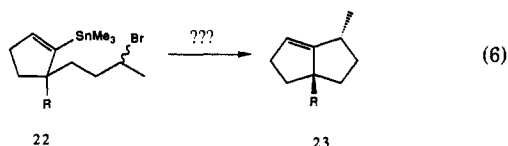
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(24) (a) Smithers, R. H. *J. Org. Chem.* **1983**, *48*, 2095. Law, K. S. Y.; Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595. Kobrich, G.; Heinemann, H.; Zundorf, W. *Tetrahedron* **1967**, *23*, 565. Masure, D.; Chuit, C.; Sauvetre, R.; Normant, J. F. *Synthesis* **1978**, 458. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769. (b) Murahashi, S.-I.; Yamamura, M.; Yanagisawa, K.-I.; Mita, N.; Kondo, K. *J. Org. Chem.* **1979**, *44*, 2408. (c) Posner, G. H.; Loomis, G. L.; Sawaya, H. S. *Tetrahedron Lett.* **1975**, 1373.

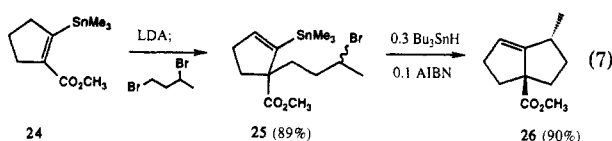
(25) (a) Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 2833. Smithers, R. H. *J. Org. Chem.* **1980**, *45*, 173. (b) Petraghini, N.; Rodrigues, R.; Comasseto, J. V. *J. Organomet. Chem.* **1976**, *114*, 281. (c) Reich, H. J.; Chow, F.; Shah, S. K. *J. Am. Chem. Soc.* **1979**, *101*, 6638, 6648. (d) Dumont, W.; Sevrin, M.; Krief, A. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 541.

zations converged on to the ring from the chains (Figure 2, path B). We again felt that the  $\alpha$ -oriented chain needed to cyclize first in order to control stereochemistry, so we sequenced accordingly. This strategy requires a cyclopentene ring suitably functionalized to accept two radicals. The most straightforward double radical acceptor, an alkyne, cannot be used in a small ring, and we chose to use the cyclopentenyl stannane **22** as an appropriate reagent (eq 6) equivalent to the synthon **B**.<sup>26,27,28</sup>



We were again concerned about the reactivity of the radical derived from **22** toward cyclization. As mentioned above, substitution at the 5-position of hexenyl radicals decelerates 5-exo cyclizations. Before our work, there were no known examples of cyclization reactions of radicals to unactivated vinylstannanes,<sup>29</sup> and the only precedented radical cyclizations (which appeared during the course of our work) employed activated (ester-substituted) vinyl stannanes.<sup>27</sup> The issue of regioselectivity in the cyclization of **22** was only a minor concern. Although substitution at the 5 position degrades the regioselectivity of hexenyl radical cyclizations by retarding 5-exo closure,<sup>30</sup> we expected that the relative strain required to make a bridged rather than a fused bicycle would ensure formation of the latter. A more interesting question involved the stereochemistry; the endo product **23** was required for the synthesis of modhephene.

The preparation of the precursor **25** is shown in eq 7. The known cyclic vinyl stannane **24** was prepared in large scale from inexpensive, commercially available carbomethoxycyclopentanone by a small modification of the procedure reported by Piers and Tse.<sup>31</sup> Alkylation of **24** with 1,3-dibromobutane in THF/HMPA gave **25** in 89% yield as a 1:1 mixture of diastereomers. To our delight, radical cyclization of compound **25** proceeded with spectacular efficiency and selectivity. Bicyclic ester **26** was isolated in 90% yield when **25** was treated with a catalytic amount of tributyltin hydride (0.1–0.3 equiv added slowly by syringe pump). Analysis of the crude reaction mixture by <sup>1</sup>H NMR, GC, and GC–MS showed **26** as the only detectable product aside from trialkyltin bromide.



The stereochemistry of **26** was initially established by NMR spectroscopy. Rhodium-catalyzed hydrogenation of **26** provided the cis-fused bicycle **27** (eq 8), which exhibited a methyl resonance

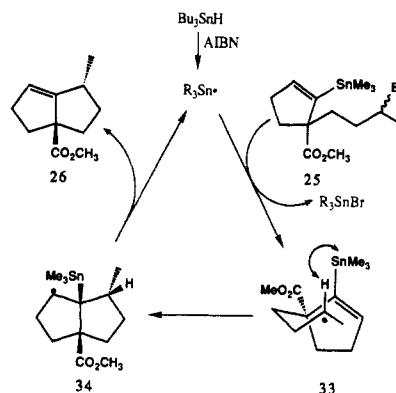
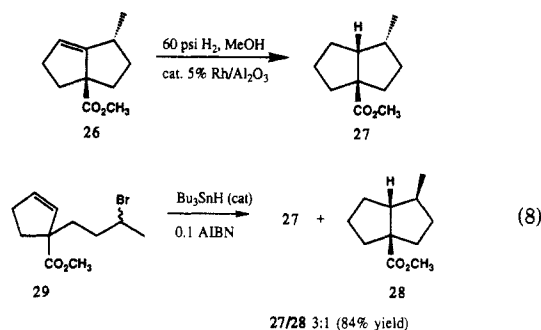


Figure 3. Mechanism and stereoselectivity.

at  $\delta$  14.8 in the <sup>13</sup>C NMR spectrum. This is within the expected range for *endo*-methyl groups on related diquinanes.<sup>32,33</sup> However, to be certain of our assignment, we cyclized the protiodestannylated alkene **29** (obtained by treatment of **25** with CF<sub>3</sub>COOH) to give a 3/1 mixture of **27** and the *exo* isomer **28**. As expected, the methyl group in the *exo* isomer **28** resonated significantly further downfield ( $\delta$  19.2) than its counterpart in **27**.



Later in the synthesis, we had reason to question the spectroscopic analysis in eq 8 (see below); however, a rigorous chemical correlation (eq 9) confirmed the assignment. Samarium(II) iodide promoted reductive cyclization of the ketone **30** provided the known bicyclic alcohol **31** as a single diastereomer.<sup>34–37</sup> Dehydration of **31** with thionyl chloride in pyridine gave a 2:1 mixture of the trisubstituted olefin **26** and the tetrasubstituted olefin **32**. The preparation of **26** by the route outlined in eq 9 does not compare to the original route (eq 7) in efficiency, but it rigorously establishes that the methyl group is *endo*.

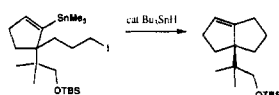
A reasonable pathway for the cyclization of vinyl stannane **22** is illustrated in Figure 3. The cyclization–fragmentation of the vinyl stannane has a 2-fold advantage: the fragmentation of radical **34** regenerates the double bond for further synthetic use, and it regenerates a tin radical for chain propagation.<sup>38</sup> A small amount of tributyltin hydride is used, not as a chain-transfer agent

(26) Bimolecular additions to vinyl stannanes: Russell, G. A.; Tashtoush, H.; Ngoviwatchai, P. *J. Am. Chem. Soc.* **1984**, *106*, 4622. Baldwin, J. E.; Kelly, D. R.; Ziegler, C. B. *J. Chem. Soc., Chem. Commun.* **1984**, 133. Baldwin, J. E.; Kelly, D. R. *J. Chem. Soc., Chem. Commun.* **1985**, 682. Keck, G. E.; Byers, J. H.; Tafesh, A. J. *Org. Chem.* **1988**, *53*, 1127.

(27) Harris, F. L.; Weiler, L. *Tetrahedron Lett.* **1987**, *28*, 2941.

(28) Concurrent with this work, we also developed new radical annulations in which cyclizations to unactivated vinyl stannanes were key steps. Curran, D. P.; van Elburg, P. A. *Tetrahedron Lett.* **1989**, *30*, 2501.

(29) The first successful model reaction (shown below) was conducted by Dr. Rajendra Deshpande in our laboratories.



(30) For example the 5-methyl-5-hexenyl radical gives only a 1:2 5-exo/6-endo ratio: Beckwith, A. L. J.; Blair, I. A.; Phillipou, G. *Tetrahedron Lett.* **1974**, 2251. Julia, M.; Descoins, C.; Baillarge, M.; Jacquet, B.; Uguen, D.; Groeger, F. A. *Tetrahedron* **1975**, *31*, 1737.

(31) Piers, E.; Tse, H. L. A. *Tetrahedron Lett.* **1984**, *25*, 3155.

(32) Whitesell, J. K.; Matthews, R. S. *J. Org. Chem.* **1977**, *42*, 3878.

(33) A recent paper suggests that a bridgehead methyl ester has a significant effect on the conformation of [3.3.0] bicycles, such that the difference in chemical shifts between an *exo* and an *endo* methyl group is not always large: Cossy, J.; Bouquant, J.; Dauphin, G.; Belotti, D. *Bull. Soc. Chim. Fr.* In press.

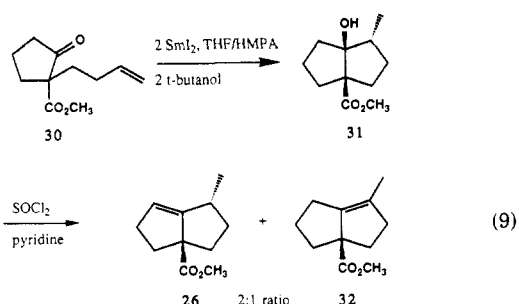
(34) Molander, G. A.; Kenny, C. *Tetrahedron Lett.* **1987**, *28*, 4367. See also ref 4.

(35) The same cyclization has been executed previously by Corey using Zn/TMSCl, which gave **31** in a 83:17 *endo/exo* ratio (ref 36), and by Cossy using photolysis, which gave **31** in an 97:3 *endo/exo* ratio (ref 37). Both diastereomers have been thoroughly characterized by Cossy, and the <sup>1</sup>H and <sup>13</sup>C NMR spectrum for our product are identical with those reported by Cossy for the *endo*-methyl diastereomer of **31** shown.

(36) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821.

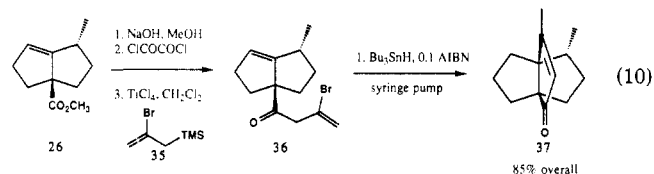
(37) Belotti, D.; Cossy, J.; Pete, J. P.; Portella, C. *J. Org. Chem.* **1986**, *51*, 4196.

(38) An added practical advantage of the fragmentation method is that reduced, uncyclized byproducts are not isomeric with cyclized products, so that desired products are more easily purified. The problems encountered in separating isomers **10** and **11**, for example, are avoided by use of the fragmentation method.



but only as an initiator. Because the tin hydride concentration is very low, radical **33** has a long lifetime within which to cyclize. The stereoselectivity of the cyclization is consistent with a chair-like transition-state **33**, in which the methyl substituent on the radical is pseudoequatorial. A comparison of the cyclization of vinyl stannane **25** with that of the destannylated analogue **29** in eq 8 shows that both **25** and **29** cyclize to give the endo products but that the  $\text{Me}_3\text{Sn}$  substituent intensifies the endo stereoselectivity. It is not clear whether the exo diastereomer formed from **29** in eq 8 results primarily from a chair-like transition state with a pseudoaxial methyl group or from a boat-like transition state with a pseudoequatorial methyl group, but the  $\text{Me}_3\text{Sn}$  substituent should destabilize both conformations for steric reasons.<sup>39,40</sup> The endo selectivity in the cyclization of **29** itself is in keeping with the known cis stereoselectivity in the cyclization of the 1-alkyl-5-hexenyl radicals<sup>41</sup> and is reminiscent of the endo selectivity observed when bicyclooctanes are formed by radical cyclizations in the reverse direction (radical in ring, alkene on chain).<sup>42</sup>

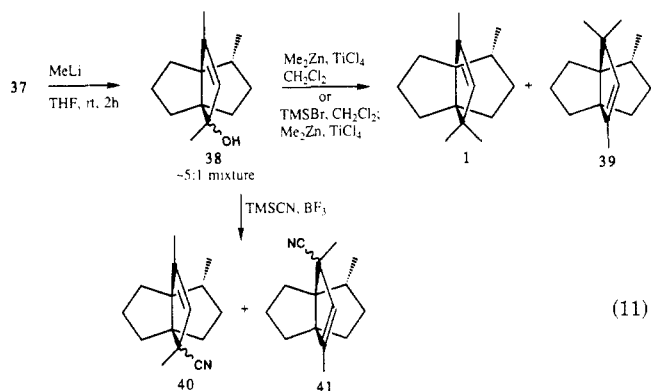
The first conversion of bicyclic ester **26** to a propellane ring skeleton is shown in eq 10. The ester was saponified and converted to an acid chloride, which was alkylated by 2-bromoallylsilane **35**.<sup>43,44</sup> As the resulting bromide **36** was sensitive to dehydrobromination, it was immediately subjected to dilute tin hydride reduction (syringe pump addition) to give the propellane **37** in 85% overall purified yield. No reduced, uncyclized material could be detected by  $^1\text{H}$  NMR, GC, or GC-MS. We believe that a  $\beta,\gamma$ -unsaturated ketone was the primary product of this reaction<sup>45</sup> but that it isomerized to the  $\alpha,\beta$  isomer **37** during heating.



In 1985, Mundy and co-workers reported that they had prepared **37** and that it could be converted directly to modhephene by using Reetz's dimethylation conditions ( $\text{Me}_2\text{Zn}/\text{TiCl}_4$ ),<sup>46</sup> albeit in only 8% yield.<sup>108</sup> However, in our hands **37** did not react with  $\text{Me}_2\text{Zn}/\text{TiCl}_4$ , even under forcing conditions. Further, when we

received copies of the original spectra from Professor Mundy, it was clear that the two samples of **37** were not identical. We are now certain that our structure assignment for **37** is correct (see below).<sup>47</sup> With our present information, we cannot assign the structure of Mundy's compound; however, this does not compromise Mundy's main synthesis of modhephene, which did not proceed through the compound that was assigned structure **37**.<sup>108</sup>

Stepwise Reetz dimethylation<sup>48</sup> of **37** via alcohol **38** was successful but gave a mixture of modhephene (**1**) and its regioisomer isomodhephene (**39**) (eq 11).<sup>49</sup> Although they were not separable by column chromatography, the regioisomers were distinguishable by GC, GC-MS, and  $^1\text{H}$  NMR, and the modhephene formed was identical with authentic material. This lack of regioselectivity was not unexpected, because Reetz has previously demonstrated that the dimethylation of  $\alpha,\beta$ -unsaturated ketones occurs by  $\text{S}_{\text{N}}1$  substitution of an allylic cation.<sup>45</sup> Cationic alkylation of propellane alcohol **38** by using  $\text{TMSCN}/\text{BF}_3$  was also nonselective, giving four regio- and stereoisomeric nitriles (**40/41**) in roughly equal quantities.



Because the synthesis of enone **37** was so efficient (65% from **24**), we invested significant effort to develop a regioselective conversion to **1**. This effort yielded some interesting transformations but was ultimately unsuccessful. Treatment of **37** with Martin's reagent  $\text{PhCHNCHLiP}(\text{O})(\text{OEt})_2$ ,<sup>50</sup> Corey's anion  $\text{Ph}_3\text{PCHLi}(\text{OMe})$ ,<sup>51</sup> the phosphorus ylide  $\text{Ph}_3\text{PCHOMe}$ , or the sulfur ylide  $\text{Me}_2\text{SCH}_2$ <sup>52</sup> resulted in decomposition of the nucleophiles without significant alkylation of the ketone, which could be recovered unchanged.<sup>53</sup> Attempted Barbier coupling of **37** with  $\text{SmI}_2$  and  $\text{CHCl}_2\text{OCH}_3$  or  $\text{CHBr}_3$  gave reduction products but no alkylation.<sup>54</sup>

(47) Although we cannot account for the discrepancy between the chemical and spectroscopic character of our propellane **37** and that reported by Mundy, the thorough characterization of the stereochemistry of our precursor **26**, the conversion of our propellane **37** to modhephene (**1**) itself, our efficient and unambiguous alternate synthesis of modhephene from the same precursor **26** (see eqs 14 and 15), the lack of regioselectivity in our dialkylation of **37**, and our thorough chemical and spectroscopic characterization of the key structures (the derived modhephene in ref 10g was characterized only by GC and MS) confirm our assignments.

(48) Reetz, M. T.; Steinbach, R.; Wenderoth, B. *Synth. Commun.* **1981**, *11*, 261. Reetz, M. T.; Westermann, J.; Steinbach, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 900, 901. Reetz, M. T.; Wenderoth, B.; Peter, R.; Steinbach, R.; Westermann, J. *J. Chem. Soc., Chem. Commun.* **1980**, 1202. (49) Although we feel that the structure assignment of isomodhephene **39** is secure, complete characterization was not possible because **1** and **39** could not be preparatively separated. The MS of **39** (GC-MS) was virtually identical **1** (see Experimental Section). In the  $^1\text{H}$  NMR, the methyl protons of **39** overlapped those of modhephene, but the vinyl proton was distinct ( $\delta$  4.78, bs).

(50) Davidsen, S. K.; Phillips, G. W.; Martin, S. F. *Org. Synth.* **1987**, *65*, 119.

(51) Corey, E. J.; Tius, M. A. *Tetrahedron Lett.* **1980**, *21*, 3535.

(52) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

(53) The failure of Corey's reagent  $\text{Ph}_3\text{PCHLi}(\text{OMe})$  is remarkable because in our hands it quantitatively adds to the doubly neopentyl ketone fenchone but gave only trace alkylation of propellane **37**. There was no indication that deprotonation of **37** by the reagent was the problem.

(54) Imamoto, T.; Takeyama, T.; Yokoyama, M. *Tetrahedron Lett.* **1984**, *25*, 3225. Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

(39) Recent calculations provide support for the chair-like transition-state model for 5-hexenyl radical cyclizations but suggest that for simple systems boat-like transition states may also contribute to formation of products: Spellmeyer, D. C.; Houk, D. N. *J. Org. Chem.* **1987**, *52*, 959. Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.

(40) Trimethyltin is not actually very large. Its  $A$  value is only 1.1, considerably smaller than that of methyl (1.7) for example.

(41) The 1-methyl-5-hexenyl radical cyclizes to give a 2:1 cis/trans mixture of 1,2-dimethylcyclopentane: See ref 30.

(42) Leading references: Burnett, D. A.; Choi, J.-K.; Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8201. Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943.

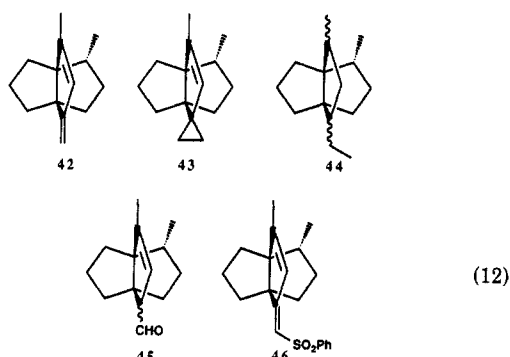
(43) Nishiyama, H.; Yokoyama, H.; Narimatsu, S.; Itoh, K. *Tetrahedron Lett.* **1982**, *23*, 1267. Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1982**, *104*, 3733.

(44) Fleming, I.; Paterson, I. *Synthesis* **1979**, 446.

(45) In one experiment, some of the  $\beta,\gamma$ -isomer was actually observed by  $^1\text{H}$  NMR and GC-MS early in the reaction. This product was quickly overwhelmed by the  $\alpha,\beta$ -isomer. There was no indication that the starting material isomerized during the reaction.

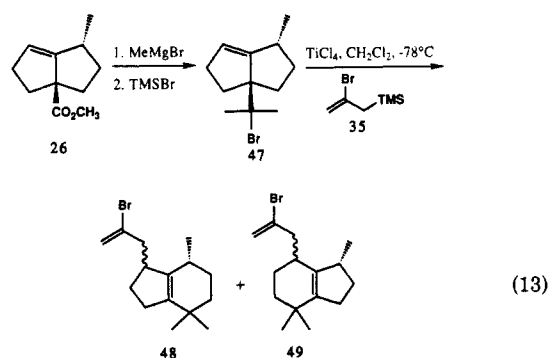
(46) Reetz, M. T.; Westermann, J.; Kyung, S.-H. *Chem. Ber.* **1985**, *118*, 1050.

Methylenation of **37** with Tebbe's reagent<sup>55</sup> or  $\text{Ph}_3\text{PCH}_2$  was slow and inefficient, even under forcing conditions, and  $\text{TMSCH}_2\text{MgCl}$ <sup>56</sup> gave no reaction at all. However, Lombardo's reagent ( $\text{CH}_2\text{Br}_2\text{-TiCl}_4\text{-Zn}$ )<sup>57</sup> quantitatively methylenated **37** within only a few hours at room temperature to provide diene **42** (eq 12).<sup>58</sup> Selective cyclopropanation of **42** by using  $\text{Et}_2\text{Zn}/\text{CH}_2\text{I}_2$ <sup>59</sup> provided the vinyl cyclopropane **43**, but we were unable to hydrogenolyze the cyclopropane with the desired regioselectivity.<sup>60</sup> Instead cleavage of the allylic cyclopropane bond occurred, and the doubly reduced ethyl propellane isomers **44** formed. Attempts to oxidize the diene **42** to the aldehyde **45** by using  $\text{CrO}_2\text{Cl}$ ,<sup>61</sup> *m*-CPBA,<sup>62</sup>  $\text{BH}_3/\text{PCC}$ ,<sup>63</sup>  $\text{BH}_3/\text{NaOH}, \text{H}_2\text{O}_2/\text{PCC}$ , or  $\text{BH}_3/\text{NaOH}, \text{H}_2\text{O}_2/\text{Swern}$  gave complex product mixtures. The diene **42** could be sulfonylated ( $\text{PhSO}_2\text{Br}, h\nu$ ),<sup>64</sup> but attempted Michael addition to the resulting sulfone **46** by using  $\text{MeMgBr}$  or  $\text{MeMgBr}/\text{CuCN}$  gave no reaction.<sup>65</sup> Addition of  $\text{MeLi}$  destroyed **46**.

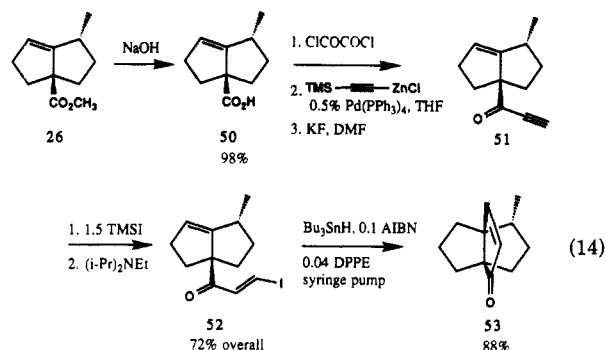


Another attractive approach to modhephene from bicyclic ester **26**, in which the geminal methyl groups were to be introduced before rather than after formation of the propellane skeleton, also failed. Dimethylation of **26** and treatment of the resulting alcohol with  $\text{TMSBr}$ <sup>66</sup> gave the tertiary bromide **47** (eq 13). Unfortunately, cationic alkylation of **47** with (2-bromoallyl)trimethylsilane (**35**)<sup>44</sup> gave a mixture of isomers **48** and **49** due to rapid cationic rearrangement of the [3.3.0] to the [4.3.0] bicyclic skeleton. Attempts to bromoallylate **47** with 2-bromoallyl phenyl sulfide under free radical conditions ( $\text{Me}_3\text{SnSnMe}_3, h\nu$ )<sup>67</sup> also failed because the tertiary bromide decomposed faster than it was al-

kylated under the reaction conditions.



**Synthesis of Modhephene.** The best route to modhephene eventually involved conversion of the bicyclic ester **26** to the propellane **53** (eq 14), an intermediate that has been used in several previous syntheses.<sup>10a,b,d</sup> Conversion of **26** to the acid chloride, alkylation according to Negishi's procedure,<sup>68</sup> and desilylation provided the unstable ynone **51**. This ynone was immediately iodinated under Kishi's conditions<sup>69</sup> to give the *trans*-iodoenone **52** in 72% overall yield from the acid **50**. Radical cyclization of **52** with dilute tributyltin hydride (syringe pump addition) gave the desired propellane **53**<sup>70</sup> in 88% purified yield provided that DPPE [1,2-bis(diphenylphosphino)ethane] was included in the reaction mixture. In preliminary experiments when DPPE was not used, little or no **53** formed; instead, reduction led to the ethyl ketone via the vinyl ketone. We believe that trace amounts of residual palladium from the Negishi coupling must have contaminated iodide **52** and catalyzed vinyl iodide reduction<sup>71</sup> and enone 1,4-reduction.<sup>72</sup> Presumably the DPPE binds and deactivates the palladium catalyst. Hart recently encountered a similar problem and devised the same solution.<sup>73</sup>



Conversion of propellane **53** to modhephene (**1**) is shown in eq 15.<sup>10a,b,d</sup> Alkylative 1,3-carbonyl transposition was affected by addition of  $\text{MeLi}$  and in situ treatment with Jones reagent.<sup>74</sup> A modification of Dreiding's<sup>10a</sup> and Smith's<sup>10b</sup> procedures was used to methylate **54**; the use of the higher order cuprate with  $\text{BF}_3$  allowed quantitative alkylation in a single pass.<sup>75</sup> Wittig olefi-

(55) Cannizzo, L. F.; Grubbs, R. H. *J. Org. Chem.* **1985**, *50*, 2386. Brown-Wensley, K. A.; Buchwald, S. L.; Cannizzo, L.; Clawson, L.; Ho, S.; Meinhardt, D.; Stille, J. R.; Straus, D.; Grubbs, R. H. *Pure Appl. Chem.* **1983**, *55*, 1733. Although ketones have been reported to react with excess Tebbe reagent to give titanacyclobutanes, which can be protonated to give *gem*-dimethyl compounds, we found no evidence of any modhephene upon prolonged treatment of **37** with excess Tebbe reagent. With our very hindered ketone **37** it is difficult enough to add the first methylene, and we suppose that subsequent formation of a titanacycle is both kinetically and thermodynamically unfavorable (formation of titanacyclobutanes are reversible).

(56) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780.

(57) Lombardo, L. *Org. Synth.* **1987**, *65*, 81. See also: Takai, K.; Fujimura, O.; Kataoka, Y.; Utimoto, K. *Tetrahedron Lett.* **1989**, *30*, 211 and references therein.

(58) We have observed that whereas Corey's anion  $\text{Ph}_3\text{PCHLi}(\text{OMe})$  is more reactive toward fenchone than **37**. The opposite is true for  $\text{CH}_2\text{Br}_2\text{-TiCl}_4\text{-Zn}$ . Presumably  $\text{CH}_2\text{Br}_2\text{-TiCl}_4\text{-Zn}$  is much more sensitive to the Lewis basicity of the carbonyl.

(59) Miyano, S.; Hashimoto, H. *J. Chem. Soc., Chem. Commun.* **1971**, 1418. Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53. (60) Zutterman, F.; Krief, A. *J. Org. Chem.* **1983**, *48*, 1135. Woodworth, C. W.; Buss, V.; Schleyer, P. v. R. *J. Chem. Soc., Chem. Commun.* **1968**, 569.

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(63) Brown, H. C.; Kulkarni, S. U.; Gundu Rao, C. *Synthesis* **1980**, 151. Gundu Rao, C.; Kulkarni, S. U.; Brown, H. C. *J. Organomet. Chem.* **1979**, *172*, C20.

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(65) Posner, G. H.; Brunelle, D. J. *Tetrahedron Lett.* **1973**, 935. Posner, G. H.; Brunelle, D. J. *J. Org. Chem.* **1973**, *38*, 2747. Fuchs, P. L.; Braish, T. F. *Chem. Rev.* **1986**, *86*, 903.

(66) Jung, M. E.; Hatfield, G. L. *Tetrahedron Lett.* **1978**, 4483.

(67) Keck, G. E.; Byers, J. H. *J. Org. Chem.* **1985**, *50*, 5442.

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(70) Our **53** was identical with a sample of the same material kindly provided to us by Professor A. B. Smith. Professor Smith has also confirmed that the spectra for the compounds assigned numbers **9**, **29**, and **30** in the Experimental Section of his paper (ref 10b) are reversed (spectra for the  $\alpha$ -methyl isomers are listed under the  $\beta$ -structures, and vice versa). These compounds correspond to our compound numbers **53**, **54**, and **55**. His spectra are identical with ours.

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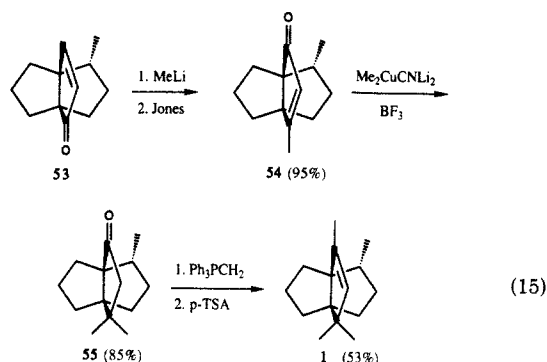
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(74) Propellane enones **37** and **54** are regioisomers; although our assembly of the former is more concise, only the latter could be regiospecifically dimethylated.



nation of **55** proceeded efficiently, as indicated by Oppolzer,<sup>10d</sup> THF proved satisfactory as solvent, and potassium *tert*-butoxide was a good base. Acid-catalyzed rearrangement of the double bond provided modhephene (**1**), whose spectra were identical with those reported by Smith.<sup>10b</sup> None of the intermediates between **53** and **1** required any purification, and the overall yield was a respectable 43%.<sup>76</sup>



### Summary

We have achieved a short, efficient synthesis of modhephene (**1**). The preparation of enone **37** (a regioisomer of **53**) required six steps from vinyl stannane **24** and proceeded in 65% yield. Two high yielding steps (>90%) completed the synthesis, but unfortunately they produced inseparable modephenene and iso-modhephene. The overall conversion from the starting stannane **24** to the known propellane **53** also required six steps and proceeded in 50% yield. Adding the known synthesis of stannane **26** from commercially available carbomethoxycyclopentanone (two steps), and adding conversion of propellane **54** to modhephene (**1**) (5 steps), the overall yield for the synthesis is still >16%, with complete control of relative stereochemistry. A practical advantage of the synthesis is that the purification of intermediates is rarely necessary; the starting keto ester could be carried to the iodoenone **53** without distillation or chromatography of intermediates, and with no reduction in overall yield compared to the purified yields listed. The synthesis demonstrates the utility of the fragmentation method for achieving both high yield and high stereoselectivity in an intramolecular 5-exo cyclization. Our synthesis for the first time demonstrates the ability to form propellanes by radical cyclizations, and both of our radical cyclizations leading to modhephene (**25** → **26** and **52** → **53**) show the ability of radical cyclization reactions to generate extremely crowded neopentyl quaternary centers.

### Experimental Section

This section describes only the reactions on the best route to modhephene. All others are described in the Supplementary Material.

**Methyl 2-(Trimethylstannyl)cyclopent-1-enecarboxylate (24).**<sup>31</sup> An oil dispersion of NaH (60%, 2 g, 42 mmol) was washed with hexane (2 × 35 mL) and was then suspended in ether (100 mL) under N<sub>2</sub> at 0 °C. Methyl 2-oxocyclopentylcarboxylate (3.97 mL, 4.54 g, 32 mmol) was added neat, dropwise, over 5 min. The addition was accompanied by vigorous effervescence. After 30 min, trifluoromethanesulfonic anhydride (6.6 mL, 11.1 g, 39 mmol) was added neat, dropwise, over 5 min. After 30 min, the solution was poured into water (200 mL), and the layers were separated. The aqueous phase was washed with CH<sub>2</sub>Cl<sub>2</sub> (2 × 25 mL). The organic phases were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give the triflate. The residual colorless oil, which was >95% pure, was used without further purification: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.02 (p, J = 7.7 Hz, 2 H), 2.67–2.78 (m, 4 H), 3.79 (s, 3 H).

To a suspension of PhSCu (6.0 g, 35 mmol) in THF (30 mL) at –30 °C under N<sub>2</sub> was added Me<sub>3</sub>SnLi (79.2 mL, 0.42 M, 33 mmol). Within 10 min, the solution became homogeneous (but for the slight excess of PhSCu). After 15 min, the above triflate in THF (50 mL) was added by cannula. After 1 h the mixture was poured into saturated NH<sub>4</sub>Cl (500 mL), and ether (100 mL) and petroleum ether (150 mL) were added.

This mixture was stirred for 20 min, the layers were separated, and the aqueous phase was washed with 1:1 ether/petroleum ether (2 × 40 mL). The organic portions were combined, filtered through a 10–15 fritted glass funnel bedded with sand, and then dried and purified by passage through a 3-cm bed of silica topped by a 3-cm bed of Na<sub>2</sub>SO<sub>4</sub>. The column was washed with ether (100 mL). The resulting pale yellow filtrate was concentrated and distilled (bulb-to-bulb, using Kugelrohr apparatus, 34–52 °C (0.35 mmHg)) to give 7.05 g (24.4 mmol, 76% yield overall) of pure stannane **24** as a colorless oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 0.17 (s, 9 H, <sup>3</sup>J<sub>Sn-H</sub> = 55.6 Hz), 1.92 (p, 2 H, J = 7.6 Hz), 2.62 (t, 4 H, J = 7.6 Hz), 3.72 (s, 3 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ –7.7, 25.2, 34.2, 41.9, 52.0, 144.2, 167.5; IR (neat) 2952, 2853, 1705, 1435, 1262, 1196, 766 cm<sup>–1</sup>.

**Methyl 1-(3-Bromobutyl)-2-(trimethylstannyl)cyclopent-2-ene-carboxylate (25).** To a solution of LDA (prepared from 47.2 mL of 1.54 M *n*-BuLi, 73 mmol, and 11.1 mL of diisopropylamine, 79 mmol) in THF (150 mL) and HMPA (20 mL) at –78 °C under N<sub>2</sub> was added the ester **24** (19.1 g, 66.0 mmol) in THF (50 mL) by cannula. After 20 min, 1,3-dibromobutane (11.9 mL, 100 mmol) was added neat, the cold bath was removed, and the mixture was stirred at room temperature for 1 h. The mixture was poured into 1:1 ether/petroleum ether (150 mL) and washed with water (200 mL), and the aqueous phase was backwashed with ether/petroleum ether (75 mL). The organic portions were combined, filtered through a 3-cm bed of silica topped with Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The oil was heated in vacuo (to 80 °C (0.5 mmHg)) with use of a Kugelrohr apparatus to remove residual impurities. The yellow residual oil (24.96 g, 58.9 mmol, 89% yield) was >98% pure (1:1 mixture of diastereomers) by GC analysis and was used without further purification: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 0.15 (two s, 9 H, <sup>3</sup>J<sub>Sn-H</sub> = 54 Hz), 1.45–1.53 (m, 0.5 H), 1.59–1.76 (m, 3.5 H), 1.68, 1.69 (two d, 3 H, J = 6.7 Hz), 1.93–2.00 (m, 0.5 H), 2.10–2.19 (m, 0.5 H), 2.35–2.44 (m, 2 H), 2.47–2.53 (m, 1 H), 3.65, 3.66 (two s, 3 H), 4.04–4.09 (m, 1 H), 5.97 (br s, 1 H, <sup>3</sup>J<sub>Sn-H</sub> = 41 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ –8.7, –8.5, 26.3, 26.4, 32.0, 33.9, 34.1, 34.4, 36.4, 36.5, 36.6, 51.5, 51.6, 51.9, 64.9, 143.4, 143.5, 143.7, 148.5, 176.6, 176.7; IR (neat) 2949, 2922, 2847, 1732, 1582, 1433, 1226, 770 cm<sup>–1</sup>; HRMS calcd for (C<sub>14</sub>H<sub>23</sub>BrO<sub>2</sub>Sn – CH<sub>3</sub>) 408.9825, found 408.9824.

**Methyl trans-8-Methylbicyclo[3.3.0]oct-1-en-5-ylformate (26).** To a solution of bromide **25** (24.71 g, 58.3 mmol) and AIBN (500 mg, 3 mmol, 0.05 equiv) in refluxing benzene (120 mL) under N<sub>2</sub> was added Bu<sub>3</sub>SnH (4.7 mL, 17 mmol, 0.3 equiv) and AIBN (500 mg, 3 mmol) in benzene (20 mL) over 10 h, via a syringe pump. I<sub>2</sub> in ether was added until the solution turned brown. DBU (15 mL, 0.1 mol) and petroleum ether (100 mL) were immediately added, and after 5 min the resulting inhomogeneous yellow solution was filtered over a 3-cm column of silica and concentrated. Kugelrohr distillation (45–65 °C (0.5 mmHg)) gave 9.44 g (52.45 mmol, 90% yield) of pure bicyclic **26** as a colorless oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 1.08 (d, 3 H, J = 6.6 Hz), 1.35–1.45 (m, 2 H), 1.68–1.76 (m, 1 H), 2.14–2.26 (m, 2 H), 2.40–2.52 (m, 3 H), 2.70–2.80 (m, 1 H), 3.64 (s, 3 H), 5.38 (br s, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 17.8 (q), 31.4 (d), 33.7 (t), 35.5 (t), 36.2 (t), 38.7 (t), 51.8 (q), 65.0 (s), 120.2 (d), 157.7 (s), 177.1 (s); IR (neat) 2953, 1728, 1157, 770 cm<sup>–1</sup>; HRMS calcd for C<sub>11</sub>H<sub>16</sub>O<sub>2</sub> 180.1150, found 180.1150; LRMS 180, 121, 93, 79.

**trans-8-Methylbicyclo[3.3.0]oct-1-en-5-ylformic Acid (50).** To a solution of ester **26** (6.85 g, 38.0 mmol) in MeOH (100 mL) was added NaOH (4 g, 100 mmol) and H<sub>2</sub>O (10 mL). The mixture was refluxed for 3 h, cooled to room temperature, diluted with ether (50 mL), and extracted with 2 N NaOH (2 × 50 mL). The aqueous portions were combined, acidified to pH = 1 with ice-cold concentrated HCl, and washed with CH<sub>2</sub>Cl<sub>2</sub> (3 × 50 mL). The organic portions were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give 6.20 g (37.3 mmol, 98% yield) of acid **50** as a colorless oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 1.11 (d, 3 H, J = 6.7 Hz), 1.38–1.51 (m, 2 H), 1.72–1.80 (dt, 1 H, J = 12.7, 9 Hz), 2.20–2.30 (m, 2 H), 2.44–2.50 (br ddd, 1 H, J = 15, 9, 3 Hz), 5.54 (dd, 1 H, J = 12.6, 6.5 Hz), 2.52–2.60 (m, 1 H), 2.77–2.86 (m, 1 H), 5.43 (br s, 1 H); <sup>13</sup>C NMR (125 MHz) δ 17.8 (q), 31.5 (d), 33.5 (t), 35.6 (t), 36.3 (t), 38.6 (t), 64.8 (s), 120.7 (d), 157.5 (s), 183.4 (s); IR (neat) 3200–2300, 1694 cm<sup>–1</sup>; HRMS calcd for C<sub>10</sub>H<sub>14</sub>O<sub>2</sub> 166.0994, found 166.0994; LRMS 166, 121.

An aliquot was distilled (Kugelrohr, 85–90 °C (0.35 mmHg)) prior to analysis. Anal. Calcd for C<sub>10</sub>H<sub>14</sub>O<sub>2</sub>: C, 72.26; H, 8.49. Found: C, 71.95; H, 8.34.

**4,6-Dimethyltricyclo[3.3.3.0]undec-3-en-2-one (37).** To a solution of the carboxylic acid **50** (332 mg, 2.00 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was added oxalyl chloride (0.5 mL, 6 mmol, 3 equiv). After 10 min, the solution was concentrated. To the residue dissolved in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) at –78 °C under N<sub>2</sub> was added 1-(2-bromo-2-propenyl)trimethylsilane (**35**) (0.519 mL, 3.0 mmol) and TiCl<sub>4</sub> (0.264 mL, 2.4 mmol). After 10 min, the cold mixture was poured directly into ether/petroleum ether (20 mL) and

(75) Smith (ref 10b) used a recycling procedure with Me<sub>2</sub>CuLi/BF<sub>3</sub> and commented that the successful use of MeCu/BF<sub>3</sub> reported by Dreiding (ref 10a) was not reproducible.

(76) None of the reactions in eq 15 were optimized.

water (20 mL). The aqueous phase was separated and backwashed with  $\text{CH}_2\text{Cl}_2$  (5 mL). The organic portions were combined, dried over silica/ $\text{Na}_2\text{SO}_4$ , concentrated, and heated in vacuo (35 °C (0.5 mmHg)) to give the bromoallyl ketone **36** as a pale yellow residual oil, which was unstable and was used immediately without further purification:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.10 (d, 3 H,  $J$  = 6.6 Hz), 1.25–1.44 (m, 2 H), 1.88 (dt, 1 H,  $J$  = 13.7, 9.5 Hz), 2.07–2.20 (m, 1 H), 2.26–2.46 (m, 4 H), 2.62–2.90 (m, 2 H), 3.65 (s, 2 H), 5.51 (br s, 1 H), 5.63 (br s, 1 H), 5.66 (br s);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  18.2, 31.1, 31.8, 34.8, 36.3, 36.8, 40.0, 49.1, 72.5, 121.1, 125.3, 132.4, 157.9, 206.6.

To this oil and AIBN (17 mg, 0.1 mmol) in refluxing benzene (30 mL) under  $\text{N}_2$  was added  $\text{Bu}_3\text{SnH}$  (0.915 mL, 3.40 mmol) and AIBN (17 mg, 0.1 mmol) in benzene (9 mL) over 7 h, via a syringe pump. The solution was cooled, diluted with ether (40 mL), treated with  $\text{I}_2$  (0.1 g) until the solution turned brown, and treated with DBU (0.9 mL, 6 mmol, 3 equiv) such that the solution turned inhomogeneous. The mixture was filtered over a 3-cm column of silica, which was rinsed with ether (25 mL). The filtrate was concentrated and the residue was purified by flash chromatography (17% EtOAc/Hex) to give pure propellane **37** (322 mg, 1.69 mmol, 85% overall yield from **50**) as a colorless oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  1.03 (d, 3 H,  $J$  = 6.7 Hz), 1.10–1.20 (m, 1 H), 1.27 (dt, 1 H,  $J$  = 5.9, 12.6 Hz), 1.40–1.52 (m, 4 H), 1.54–1.63 (m, 3 H), 1.66–1.80 (m, 2 H), 2.01 (s, 3 H), 5.61 (s, 1 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  15.2 (q), 15.7 (q), 25.2 (t), 27.9 (t), 32.0 (t), 36.1 (t), 36.4 (t), 39.9 (d), 67.8 (s), 68.7 (s), 128.8 (d), 181.7 (s), 213.8 (s); IR (neat) 2948, 2865, 1700, 1632  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{13}\text{H}_{18}\text{O}$  190.1258, found 190.1258; LRMS 190, 175, 162, 148, 133, 120, 105, 91. Anal. Calcd for  $\text{C}_{13}\text{H}_{18}\text{O}$ : C, 82.06; H, 9.53. Found: C, 81.90; H, 9.57.

**trans-3-Iodo-1-(trans-8-methylbicyclo[3.3.0]oct-1-en-5-yl)prop-2-en-1-one (52).** To a solution of (trimethylsilyl)acetylene (0.846 mL, 6.0 mmol) in THF (8 mL) at 0 °C under  $\text{N}_2$  was added BuLi (3.64 mL, 1.54 M, 5.6 mmol). After 2 min, this solution was added by cannula to  $\text{ZnCl}_2$  (870 mg, 6.4 mmol, dried by melting in vacuo) at 25 °C under  $\text{N}_2$ . After 20 min,  $\text{Pd}(\text{PPh}_3)_4$  (23 mg, 0.02 mmol) in THF (4 mL) was added by cannula, followed immediately by the acid chloride derived from **50** in THF (10 mL). The acid chloride was prepared by adding oxalyl chloride (1 mL, 11 mmol) to **50** (664 mg, 4.00 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (1 mL). Effervescence subsided within 5 min, and after 10 min the acid chloride [ $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.13 (d, 3 H,  $J$  = 6.6 Hz), 1.37–1.47 (m, 1 H), 1.50–1.63 (m, 1 H), 1.91 (dt, 1 H,  $J$  = 13.5, 9.1 Hz), 2.17–2.27 (m, 1 H), 2.35–2.44 (m, 1 H), 2.48–2.59 (m, 1 H), 1.60 (dd, 1 H,  $J$  = 13, 7 Hz), 2.83–2.96 (m, 1 H), 5.56 (br s, 1 H)] was concentrated. After 4 h at room temperature, the solution was diluted with ether/petroleum ether (20 mL), washed with water (20 mL), separated, dried over silica/ $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was diluted with DMF (10 mL) and treated with  $\text{KF}\cdot 2\text{H}_2\text{O}$  (564 mg, 6.0 mmol) at 25 °C. After 10 min, the solution was diluted with 1/1 ether/petroleum ether (25 mL), washed with water (3  $\times$  20 mL), dried over silica/ $\text{Na}_2\text{SO}_4$ , and concentrated to give the alkynone **51**, which turned brown upon standing and was therefore used directly without further purification:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  1.10 (d, 3 H,  $J$  = 6.7 Hz), 1.37–1.46 (m, 2 H), 1.86 (dt, 1 H,  $J$  = 13.3, 9.3 Hz), 2.10–2.20 (m, 1 H), 2.30–2.43 (m, 1 H), 2.39–2.46 (m, 1 H), 2.50–2.58 (m, 1 H), 2.59 (dd, 1 H,  $J$  = 13.3, 7 Hz), 2.83–2.92 (m, 1 H), 3.15 (s, 1 H), 5.51 (br s, 1 H).

To the crude ynone **51** in  $\text{CH}_2\text{Cl}_2$  (10 mL) at –78 °C under  $\text{N}_2$  was added neat TMSI (0.625 mL, 4.4 mmol). After 10 min, the solution was filtered directly over a 3-cm column of silica, which was washed with  $\text{CH}_2\text{Cl}_2$  (10 mL). To the filtrate was added *N,N*-diisopropylethylamine (1 mL, 6 mmol), and the mixture was refluxed for 4 h. The mixture was concentrated and purified by flash chromatography (3% EtOAc/Hex) to give iodoenone **52** (869 mg, 2.88 mmol, 72% overall yield from **50**) as a yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  1.12 (d, 3 H,  $J$  = 6.5 Hz), 1.33–1.44 (m, 2 H), 1.87–1.94 (m, 1 H), 2.02–2.11 (m, 1 H), 2.23–2.40 (m, 3 H), 2.60–2.70 (m, 1 H), 2.70–2.80 (m, 1 H), 5.51 (br s, 1 H), 7.35 (d, 1 H,  $J$  = 14.4 Hz), 7.84 (d, 1 H,  $J$  = 14.4 Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  18.0 (q), 31.1 (d), 31.6 (t), 34.7 (t), 36.3 (t), 36.6 (t), 70.4 (s), 99.1 (d), 121.1 (d), 140.4 (d), 157.1 (s), 198.3 (s); IR (neat) 2955, 2865, 1686, 1562, 945  $\text{cm}^{-1}$ ; HRMS calcd for ( $\text{C}_{12}\text{H}_{15}\text{OI}$  – I) 175.1123, found 175.1123; LRMS 274, 201, 175, 121.

**6-Methyltricyclo[3.3.3.0]undec-3-en-2-one (53).** To a solution of iodoenone **52** (310 mg, 1.03 mmol, 0.05 M), DPPE (16 mg, 0.04 mmol), and AIBN (9 mg, 0.05 mmol) in refluxing benzene (20 mL) was added  $\text{Bu}_3\text{SnH}$  (0.471 mL, 1.75 mmol) and AIBN (16 mg, 0.1 mmol) in benzene (5 mL) over 7 h, via a syringe pump. The solution was cooled, diluted with ether (20 mL), and treated with  $\text{I}_2$  until the color turned brown. Addition of petroleum ether (20 mL) and then DBU (0.6 mL, 4 mmol) caused the solution to become inhomogeneous. The solution was rinsed through a 3-cm column of silica, which was washed with 25 mL of ether. The filtrate was concentrated and purified by flash chroma-

tography (12% EtOAc/Hex) to give pure propellane **53** (159 mg, 0.90 mmol, 88% yield) as white needles:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  1.02 (d, 3 H,  $J$  = 6.8 Hz), 1.18–1.26 (m, 1 H), 1.36 (dt, 1 H,  $J$  = 5.8, 12.8 Hz), 1.46–1.54 (m, 3 H), 1.54–1.59 (m, 1 H), 1.59–1.68 (m, 2 H), 1.70–1.78 (m, 1 H), 1.79–1.85 (m, 1 H), 2.06 (dd, 1 H,  $J$  = 12.5, 5.9 Hz), 5.91 (d, 1 H,  $J$  = 5.5 Hz), 7.43 (d, 1 H,  $J$  = 5.5 Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  14.0 (q), 25.0 (t), 29.1 (t), 32.2 (t), 35.6 (t), 37.4 (t), 40.2 (d), 65.8 (s), 67.6 (s), 131.4 (d), 168.3 (d), 215.5 (s); IR (neat) 2951, 2866, 1705, 1600  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{12}\text{H}_{16}\text{O}$  176.1201, found 176.1201; LRMS 176, 161, 148, 134, 91. Anal. Calcd for  $\text{C}_{12}\text{H}_{16}\text{O}$ : C, 81.77; H, 9.15. Found: C, 81.60; H, 9.10.

The product **53** was identical in all respects with a sample of the same material generously supplied by Professor Amos Smith. We note, however, that the spectra for this molecule in the experimental section of Smith's paper are reversed with its methyl epimer (see ref 70).

**(±)-Modhephenone (1).** The enone **53** (103 mg, 0.58 mmol) was methylated and the resulting alcohol [major diastereomer:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  0.85–1.9 (m, 10 H), 0.95 (d, 3 H,  $J$  = 6.7 Hz), 1.32 (s, 3 H), 2.34 (ddm, 1 H,  $J$  = 12.5, 5 Hz), 4.92 (br s, 1 H), 5.42 (d, 1 H,  $J$  = 5.6 Hz), 5.67 (d, 1 H,  $J$  = 5.6 Hz)] was oxidized by Jones reagent following the procedure of Smith.<sup>10b</sup> The only modification was that the Jones oxidation was worked up after 15 min. Filtration over a 3-cm column of silica and rinsing with  $\text{CH}_2\text{Cl}_2$  (10 mL) followed by concentration gave 105 mg (0.55 mmol, 95% yield) of the enone **54**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.04 (d, 3 H,  $J$  = 6.6 Hz), 1.10–1.55 (m, 6 H), 1.58–1.69 (m, 2 H), 1.70–1.82 (m, 2 H), 1.93 (dd, 1 H,  $J$  = 12, 5 Hz), 2.01 (d, 3 H,  $J$  = 0.6 Hz), 5.64 (s, 1 H). The  $^1\text{H}$  NMR spectrum of product **54** is identical with that reported by Smith for the same compound.<sup>70</sup> As our material was >99% pure according to GC analysis, it was carried on without further purification.

The enone **54** was methylated by a modification of Smith's procedure.<sup>10b</sup> To a suspension of CuCN (269 mg, 3.0 mmol) in THF (6 mL) at 0 °C under  $\text{N}_2$  was added MeLi (5.66 mL, 1.06 M solution in ether). After 10 min, during which time the solution had become clear and homogeneous, the solution was cooled to –78 °C, and  $\text{BF}_3\cdot\text{OEt}_2$  (369  $\mu\text{L}$ , 3.0 mmol) was added. The enone **54** (105 mg, 0.55 mmol) in THF (5 mL) was then added via cannula. The solution was allowed to warm very slowly, to 0 °C over 3 h. The solution was filtered directly through a 3-cm column of silica, which was rinsed with 1:1 ether/petroleum ether (20 mL). Concentration gave 96 mg (0.47 mmol, 85% yield) of ketone **55**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  0.90–2.10 (m, 11 H), 0.95 (s, 3 H), 0.99 (d, 3 H,  $J$  = 6.6 Hz), 1.07 (s, 3 H), 1.97 (d, 1 H,  $J$  = 15.5 Hz), 2.66 (d, 1 H,  $J$  = 15.5 Hz). Spectra are identical with Smith's.<sup>70</sup> Our product was >90% pure according to GC and was carried on without further purification.

The enone **55** was methylenated by Oppolzer's procedure.<sup>10d</sup> To methyl triphenylphosphonium bromide (1.43 g, 4.0 mmol) at room temperature under  $\text{N}_2$  was added potassium *tert*-butoxide (6.56 mL, 0.61 M solution in THF). The resulting solution was heated to 90 °C and added hot to the neat ketone **55** (96 mg, 0.47 mmol) under  $\text{N}_2$  via cannula. The resulting mixture was heated at 95–100 °C for 2.5 h and filtered directly through a 3-cm column of silica (which was rinsed with 25 mL of 1/1 ether/petroleum ether). Concentration gave 91 mg (0.44 mmol, 94% yield) of the desired alkene, which was >90% pure according to GC, and which was carried on without further purification.

The alkene (91 mg, 0.44 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (2.5 mL) and treated with *p*-TSA (30 mg) at room temperature. After 2.5 h, the mixture was filtered directly through silica, concentrated, and purified by flash chromatography (pentane) to give 50 mg (0.25 mmol, 56% yield, 43% overall yield from enone **52**) of (±)-modhephenone (**1**):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  0.85–1.81 (m, 11 H), 0.979 (s, 3 H), 0.985 (s, 3 H), 0.992 (d, 3 H,  $J$  = 6.8 Hz) 1.61 (d, 3 H,  $J$  = 1.2 Hz), 2.04 (dm, 1 H,  $J$  = 7.5 Hz), 4.83 (s, 1 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  13.75 (q), 15.6 (q), 26.3 (q), 27.2 (t), 29.3 (q), 29.9 (t), 34.3 (t), 35.8 (t), 38.7 (t), 43.9 (d), 45.9 (s), 66.1 (s), 73.1 (s), 135.4 (d), 140.9 (s); IR (neat) 3015, 2946, 2862, 1460, 1379, 843  $\text{cm}^{-1}$ ; HRMS calcd for  $\text{C}_{15}\text{H}_{24}$  204.1878, found 204.1878; LRMS 204, 189, 151, 147, 133, 119, 105, 91.

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**Registry No.** (±)-**1**, 76739-64-5; **4**, 3859-41-4; **5**, 14203-25-9; **6**, 127353-80-4; (±)-**7**, 127353-81-5; (±)-**8**, 127353-82-6; (±)-*cis*-**10**, 127353-88-2; (±)-*trans*-**10**, 127353-84-8; (±)-**11**, 127353-85-9; (±)-**15**, 127353-86-0; (±)-**15** alcohol, 127353-83-7; (±)-**16**, 127353-87-1; (±)-**19**, 127353-89-3; **24**, 93493-99-3; (±)-**25** (isomer 1), 127353-91-7; (±)-**25**



(isomer 2), 127354-08-9; (±)-26, 127353-92-8; (±)-27, 127353-93-9; (±)-28, 127353-94-0; (±)-29 (isomer 1), 127353-95-1; (±)-29 (isomer 2), 127354-09-0; (±)-30, 127353-96-2; (±)-31, 127353-97-3; (±)-32, 127353-98-4; 35, 81790-10-5; (±)-36, 127353-99-5; (±)-37, 127419-76-5; (±)-38 (isomer 1), 127354-00-1; (±)-38 (isomer 2), 127419-77-6; (±)-39, 127354-01-2; (±)-47, 127354-02-3; 48, 127354-03-4; 49, 127354-04-5; (±)-50, 127354-05-6; (±)-50 acid chloride, 127353-90-6; (±)-51, 127354-06-7; (±)-52, 127354-07-8; (±)-53, 76740-73-3; (±)-54, 76685-67-1; (±)-55, 76685-68-2;  $C_4H_7MgBr$ , 7103-09-5; (±)-Br-

$(CH_2)_2CHBrCH_3$ , 79390-67-3;  $TMSC\equiv CH$ , 1066-54-2; isobutyric anhydride, 97-72-3; methyl (±)-2-oxocyclopentanecarboxylate, 53229-93-9; methyl 2-[(trifluoromethylsulfonyl)oxy]-1-cyclopentanecarboxylate, 65832-21-5.

**Supplementary Material Available:** General experimental details and the preparation and characterization of all the compounds that are not contained in the Experimental Section (11 pages). Ordering information is given on any current masthead page.

## Acylsilane Chemistry. Synthesis of Regio- and Stereoisomerically Defined Enol Silyl Ethers Using Acylsilanes<sup>1</sup>

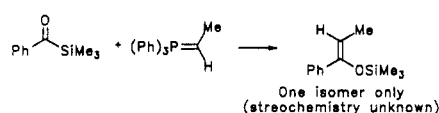
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**Abstract:** The preparation of enol silyl ethers using a carbonyl addition–Brook rearrangement–elimination sequence was studied. The key intermediate  $\alpha$ -silyl- $\beta$ -X-alkoxides could be prepared in several different ways, including the addition of organolithium or hydride reagents to  $\alpha$ -X-acylsilanes (path a, using RM with R = alkyl, aryl, vinyl, alkynyl, silyl, stannyl, phosphinyl, and cyano), the addition of  $\alpha$ -X-lithium reagents to acylsilanes (path b, X = phenylthio, phenylsulfonyl), or the addition of silyllithium reagents to  $\alpha$ -X-ketones (path c, X = phenylthio, alkoxy). All of the reactions gave complete regiocontrol of silyl enol ether formation, and many gave excellent (>99%) stereocontrol as well. The selectivity of the carbonyl addition, silyl rearrangement, and elimination was studied. For path a, when the R group of RM was a poor carbanion stabilizing group the elimination of the intermediate  $\alpha$ -silyl- $\beta$ -X-alkoxides was stereospecific, and there was a large difference in rate between erythro and threo (erythro > threo). When R was a carbanion stabilizing group, such as aryl or alkynyl, the elimination process became nonstereospecific in some cases, and only small differences between threo and erythro were observed. Path b was especially effective with  $\alpha$ -sulfonyl lithium reagents, and these reactions gave predominantly *E* enol silyl ethers (4/1 to 20/1). The addition of organolithium reagents to  $\beta$ -X-acylsilanes (the homologue of path a) was also briefly explored as a synthesis of siloxy-cyclopropanes.

Central to the utilization of the aldol condensation for the preparation of acyclic compounds with multiple asymmetric centers is the control of enolate geometry and regiochemistry. The preparation of stereoisomerically pure (or essentially pure) enol derivatives has relied on a variety of strategies.<sup>2,3</sup> Some are applicable to symmetric ketones or the thermodynamic enolate only. Many are not applicable to a broad range of enolate substitution patterns and geometries.

### Scheme I



For symmetric ketones, where regiochemical considerations are irrelevant, reasonable stereoselectivity can be achieved by enolization under kinetic control to give *E*-enolate<sup>2a,b</sup> or under thermodynamic control for *Z*-enolates.<sup>2c,d,e</sup> The selectivity can often be augmented by the use of sterically hindered bases<sup>2f,g</sup> or Lewis acids.<sup>2h</sup> Specially designed carbonyl substrates, in which a large, removable (and sometimes chiral) group on one side of the ketone ensures the regiochemistry of the deprotonation as well as the stereochemistry of the enolate and subsequent reactions have been widely explored.<sup>3</sup>

Alternatively, there are several techniques in which enol silyl ethers are prepared directly by processes that do not involve enolization of carbonyl compounds. Such methods are essential for systems in which the ketone lacks regiochemically controlling substituents. Conjugate addition to enones usually gives poor stereochemical control,<sup>4</sup> but selectivity can be quite high when substituents on the enone cause conformational homogeneity.<sup>5</sup> The enolates formed by treatment of the dibromomethyl lithium adducts of ketones and aldehydes with *n*-butyllithium show a significant stereochemical preference.<sup>6</sup> Acid-catalyzed rear-

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