solid was recrystallized from isopropyl ether–*n*-pentane to give an off-white crystalline solid (2.73 g, 63.8%). An analytical sample was prepared by two additional crystallizations from isopropyl ether as white crystals, **21**: mp 126–128 °C; IR (Nujol) 3220, 1750, 1730, 1640 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.15 (s, 3, CH_3CO), 3.85 (s, 3, CH_3O), 5.15 (s, 2, CH_2), 6.9 (s, 1, C_4H), 8.4 (br, 1, NH, D_2O exchangeable). Anal. Calcd for $C_8H_{10}N_2O_5$: C, 44.86; H, 4.71; N, 13.08. Found: C, 44.53, 44.45; H, 4.69, 4.71; N, 13.51, 13.39.

Methyl [5-(Hydroxymethyl)-3-isoxazolyl]carbamate (22). A solution of crude **21** (4.0 g; 0.0187 mol) in MeOH (20 mL) and 4 N HCl (20 mL) was heated on a steam bath for 5 min, and the MeOH was evaporated. A white solid byproduct (AgCl) precipitated and was removed by filtration. The filtrate was evaporated to dryness to give an oil, which upon standing, slowly crystallized. The crude product was washed with Et_2O–*n*-pentane and then recrystallized from Et_2O, giving **22** (0.80 g, 24.9%) as tan crystals: mp 115–117 °C; IR (KBr) 3460, 3260, 3220, 1740, 1720, 1635 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.65 (s, 3, CH_3) 4.5 (d, 2, CH_2, J = 5.4 Hz), 5.6 (t, 1, OH, J = 5.4 Hz, D_2O exchangeable), 6.55 (s, 1, C_4H), 10.55 (s, 1, NH, D_2O exchangeable). Anal. Calcd for $C_6H_8N_2O_4$: C, 41.86; H, 4.68; N, 16.28. Found: C, 42.12; H, 4.41; N, 16.30.

5-[((Trimethylsilyl)oxy)methyl]-3-isoxazolamine (9b). A mixture of **21** (0.5 g, 2.3 mmol) in 50% aqueous ethanol (10 mL) and barium hydroxide (0.79 g, 4.6 mmol) was heated to reflux for 18 h (in subsequent experiments it was found that a 1-h reaction time was sufficient). After the mixture was cooled to room temperature, a few pieces of dry ice were added. The resulting barium carbonate was filtered, and the filtrate was evaporated to a residue, which was extracted with THF. The THF extract was treated with hexamethyldisilazane, and the mixture was heated to reflux for 1 h. The reaction mixture was evaporated to dryness and extracted with boiling *n*-pentane. The *n*-pentane solution was concentrated and cooled to give off-white platelet crystals (140 mg; 32.7%): mp 70–75 °C; IR (Nujol) 3400, 3300, 3200, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.15 (s, 9, Me_3Si), 4.1 (br, 2, NH_2), 4.6 (s, 2, CH_2), 5.8 (s, 1, C_4H). Anal. Calcd for $C_7H_{14}N_2O_2Si$: C, 45.13; H, 7.58; N, 15.04. Found: C, 44.95; H, 7.48; N, 15.43.

4-Hydroxy-*N*-[5-(hydroxymethyl)-3-isoxazolyl]-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (2). A mixture of **9b**[11] (559 mg; 3 mmol) and the benzothiazine ester 8[5] (807 mg; 3 mmol) in xylene (125 mL) was heated at reflux for 5 h in a Soxhlet apparatus, the thimble of which contained 20 g of Linde type 4A molecular sieves. The reaction mixture was evaporated to dryness, and the residue was dissolved in 75 mL of MeOH and 2 mL of 2 N HCl. The solution was concentrated with heating, and 2-propanol was added periodically maintaining a volume of ca. 35 mL. The solution was allowed to cool to give white crystals (465 mg, 44.1%): mp 240–244 °C dec; IR (KBr) 3450, 1630, 1610 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.85 (s, 3, NCH_3), 3–4 (br, OH, H_2O), 4.5 (s, 2, CH_2), 6.8 (s, 1, C_4H), 7.9 (m, 4, Ar), 11.5 (s, 1, NH); UV (MeOH) λ_{max} 323 (ϵ 12770), 239 (11650) nm; mass spectrum, *m/e* 351 (M^+), 173, 145, 117. Anal. Calcd for $C_{14}H_{13}N_3O_6S$: C, 47.87; H, 3.73; N, 11.96; S, 9.13. Found: C, 48.13; H, 3.90; N, 11.84; S, 9.32.

Ethyl [(5-Methyl-3-isoxazolyl)amino]oxoacetate (24). A solution of 5-methyl-3-isoxazolamine (5.8 g; 0.051 mol) in CH_2Cl_2 (195 mL) and pyridine (8.1 g; 0.102 mol) was cooled to 5 °C and was treated slowly with ethyl oxalyl chloride (7.3 g; 0.0535 mol). The solution was stirred at 25 °C for 2 h and then at 40 °C for 15 min. The solvent was evaporated, and the residue was treated with 150 mL of water, stirred, and filtered. The residue was washed with Et_2O and dried to give **24** as a white solid (8.83 g; 87.3%): mp 130–134 °C; IR (KBr) 3211, 3080, 1747, 1718, 1626, 1546 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.28 (t, 3, CH_3), 2.40 (s, 3, CH_3), 4.25 (q, 2, CH_2), 6.58 (s, 1, C_4H), 11.75 (s, 1, NH). Anal. Calcd for $C_8H_{10}N_2O_4$: C, 48.49; H, 5.09; N, 14.14. Found: C, 48.37; H, 5.03; N, 14.17.

[(5-Methyl-3-isoxazolyl)amino]oxoacetic Acid (3). A mixture of **24** (7.23 g, 0.037 mol), EtOH (37 mL), water (37 mL), and 1 N NaOH (37 mL) was stirred at 25 °C for 40 min and then heated to 55 °C until a clear solution was obtained. The solution was filtered, diluted with absolute EtOH and allowed to crystallize. The white solid was filtered and dried to give 4.75 g (66.9%) of the sodium salt **25**: mp 275–280 °C dec; IR (KBr) 3354, 3184, 1701, 1649, 1557 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.4 (s, 3, CH_3), 6.6 (s, 1, C_4H). Anal. Calcd for $C_6H_5N_2O_4Na$: C, 37.51; H, 2.62; N, 14.58. Found: C, 37.39; H, 2.74; N, 14.73.

The mother liquor from the above crystallization was evaporated to dryness, and the residue was dissolved in water (38 mL) and acidified with 1 N HCl (38 mL) to give a white precipitate. The crude acid was recrystallized from aqueous HCl to give an analytical sample of **3** (220 mg): mp 215–219 °C dec; IR (KBr) 3288, 1763, 1718, 1700, 1619, 1549 cm^{-1}. Anal. Calcd for $C_6H_6N_2O_4$: C, 42.36; H, 3.56; N, 16.47. Found: C, 42.26; H, 3.60; N, 16.33.

Acknowledgment. We thank Dr. F. A. MacKellar and his associates for spectral data and for microanalyses. We also thank Drs. T. A. Pugsley and A. Boctor for performing the enzyme assay for the metabolites.

Registry No. **1**, 34552-84-6; **2**, 91933-53-8; **3**, 91933-54-9; **7**, 99356-54-4; **8**, 35511-15-0; **9a**, 99356-55-5; **9b**, 99356-56-6; **10a**, 1072-67-9; **10b**, 13223-74-0; **10c**, 99356-57-7; **11a**, 5819-40-9; **11b**, 99356-58-8; **13**, 75079-83-3; **14**, 3405-77-4; **15**, 95312-50-8; **16**, 99356-59-9; **17**, 95312-11-1; **18**(Br), 95312-12-2; **18**(Cl), 80173-68-8; **19**(Br), 95312-13-3; **19**(Cl), 95312-14-4; **20**(Br), 95312-15-5; **20**(Cl), 95312-16-6; **21**, 99356-60-2; **22**, 99356-61-3; **23**, 99356-62-4; **24**, 99356-63-5; **25**, 99356-64-6; $BrCH_2C{\equiv}CCH_2Br$, 2219-66-1.

Total Synthesis of Modhephene

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A new approach to the natural propellane modhephene is described. Critical to the success of this synthesis was a dianion-mediated cyclopentannulation procedure, a heteroatom-assisted stereoselective hydrogenation, a regioselective lactonization, and a dimethylation of a carbonyl.

Modhephene (**1**), isolated from the Rayless Goldenrod, has been the target of several innovative syntheses.[1] In a recent paper[2] we described the stero- and regiospecific synthesis of the Smith intermediate (**2**)[3], thus constituting

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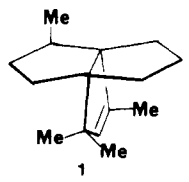

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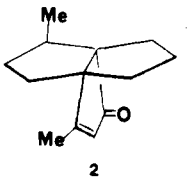


2

a *formal* synthesis of modhephene. We now report the details of this synthetic effort along with a new stereo- and regiospecific *total synthesis of modhephene.*

By retrosynthetic analysis, the key intermediate for both a formal and total synthesis of modhephene resided in **3**, potentially available from the diester (**4**) as shown in Scheme I. It appeared to us that depending on the direction of aldolization we could directly obtain **2** and/or **5**. The latter compound would serve as our entry into a new total synthesis of modhephene. Furthermore, there existed the possibility (described in a later section) that we could also obtain modhephene in a more unique, albeit less likely to succeed, route. In all of the potential synthetic schemes considered, the critical step involved preparation of intermediate **4**.

The preparation of **4**, achieved by the reaction sequence shown in Scheme II, was based on our recent studies of a dianion-mediated cyclopentannulation reaction protocol.[4] A second report of a very similar cyclopentannulation procedure has recently been published.[5]

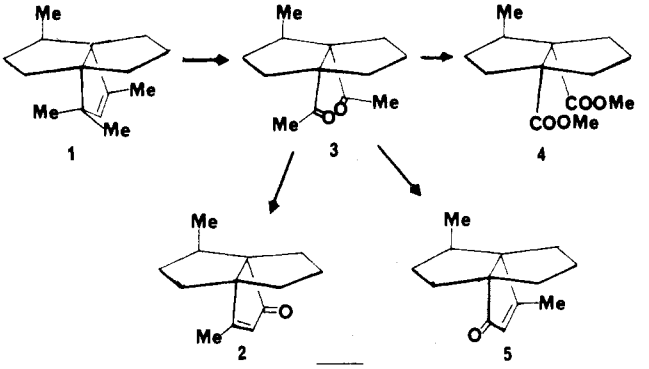
Consecutive dianion reactions provided the requisite cis-fused five-membered rings of **8**. The ensuing highly specific reduction of **9** to **4** was predicted from our own work on heteroatom influences on catalytic surfaces,[6] as well as from recent reports by others.[7] Such heteroatom-assisted specificity during hydrogenation resulted in the complete lack of a stereoisomer of **4** and provided the first critical step in the stereospecific synthesis of modhephene.

Initial plans for the cyclization of **4** to modhephene were based on the possibility of carrying out the sequence described by Scheme III. However, addition of 4 equiv of MeLi to **4** gave a 90% conversion to the enol ether (**16**) and a trace of the lactone (**14**). Use of 3 equiv of MeLi still gave **16** with about 5% **14**. Two equivalents of MeLi afforded almost pure **14**, and with only 1 equiv of MeLi, only starting material and **14** were obtained. This suggested the methylation cascade depicted in Scheme IV.

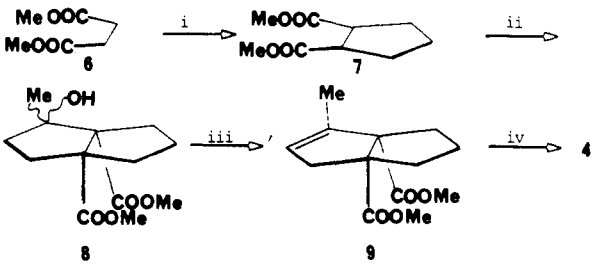
Origin of Regiospecific Lactone Formation. The second critical step of our modhephene synthesis was the unexpected, but greatly appreciated, regiospecific formation of lactone **14**. This lactonization involves an initial attack of the methyllithium on the carbomethoxy group of **4** distal to the C-2 methyl group. Why is there preferred attack here rather than on the proximal group? Examination of molecular models does not give an easy interpretation to the observation; however, since the observed specificity must be attributed to something more than luck, we searched for a rationale to the observations. Molecular mechanics analysis appears to offer some insight. The C-2 methyl breaks the symmetry of the bicyclo[3.3.0]octane skeleton and serves to discriminate between two possible reaction channels by sterically impeding nucleophilic attack on the proximal side of the ring system.

In Figure 1 we see why this happens. An empirical force field study[8] of **4** has been completed in which a large number of local minima on the multidimensional potential energy surface were located. The conformation with the C-2 methyl group in an "equatorial" conformation is the global minimum. The CO–C–C–CO torsion angle is 26°, the C-2 methyl group is parallel to the ester C=O π bond, and the distance between the methyl carbon and the carbonyl is a short 3.3 Å.

Scheme I. Proposed Retrosynthetic Analysis of Modhephene

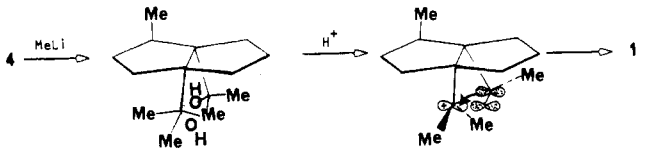


Scheme II. Synthesis of the Key Intermediate[a]

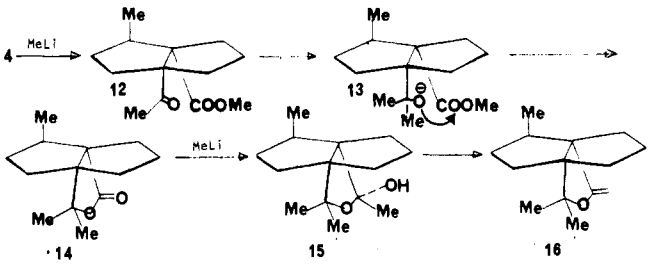


[a] (i), LDA, then $BrCH_2CH_2CH_2Br$; (ii) LDA, then $BrCH_2CH_2C(O)CH_3$; (iii) $POCl_3$; (iv) H_2/Pt.

Scheme III. Proposed Methodology for the Third Ring



Scheme IV. Reaction of the Diester with Methyllithium



(1) (a) Wrobel, J.; Takahashi, K.; Honkan, V.; Lannoye, G.; Cook, J. M.; Bertz, S. H. *J. Org. Chem.* **1983**, *48*, 139. (b) Wender, P. A.; Dreyer, G. B. *J. Am. Chem. Soc.* **1982**, *104*, 5805. (c) Karpf, M.; Dreiding, A. S. *Tetrahedron Lett.* **1980**, 4569. (d) Schostorez, H.; Paquette, L. A. *J. Am. Chem. Soc.* **1981**, *103*, 722. (e) Oppolzer, W.; Marazza, F. *Helv. Chim. Acta* **1981**, *64*, 1575. (f) Oppolzer, W.; Battig, K. *Ibid.* **1981**, *64*, 2489.

(2) Wilkening, D.; Mundy, B. P. *Tetrahedron Lett.* **1984**, 4619.

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(4) (a) Wilkening, D.; Mundy, B. P. *Synth. Commun.* **1984**, *13*, 227. (b) For other examinations of dianion methodology, the following references are appropriate: Bilyard, K. G.; Garrett, P. J. *Tetrahedron Lett.* **1981**, 1755 and earlier references from this group that are cited. Girard, C.; Bloch, R. *Tetrahedron Lett.* **1982**, 3683.

(5) Furuta, K.; Misumi, A.; Mori, A.; Ikeda, N.; Yamamoto, H. *Tetrahedron Lett.* **1984**, 669.

(6) (a) Mundy, B. P.; Glancy, S. B., unpublished observations. (b) Mundy, B. P.; Theodore, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 2005.

(7) (a) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072. (b) Crabtree, R. H.; Davis, M. W. *Organometallics* **1983**, *2*, 681.

(8) The empirical force field employed was MM2, using the original parameters: Allinger, N. L.; Yuh, Y. H. *QCPE* **1980**, *12*, 395.

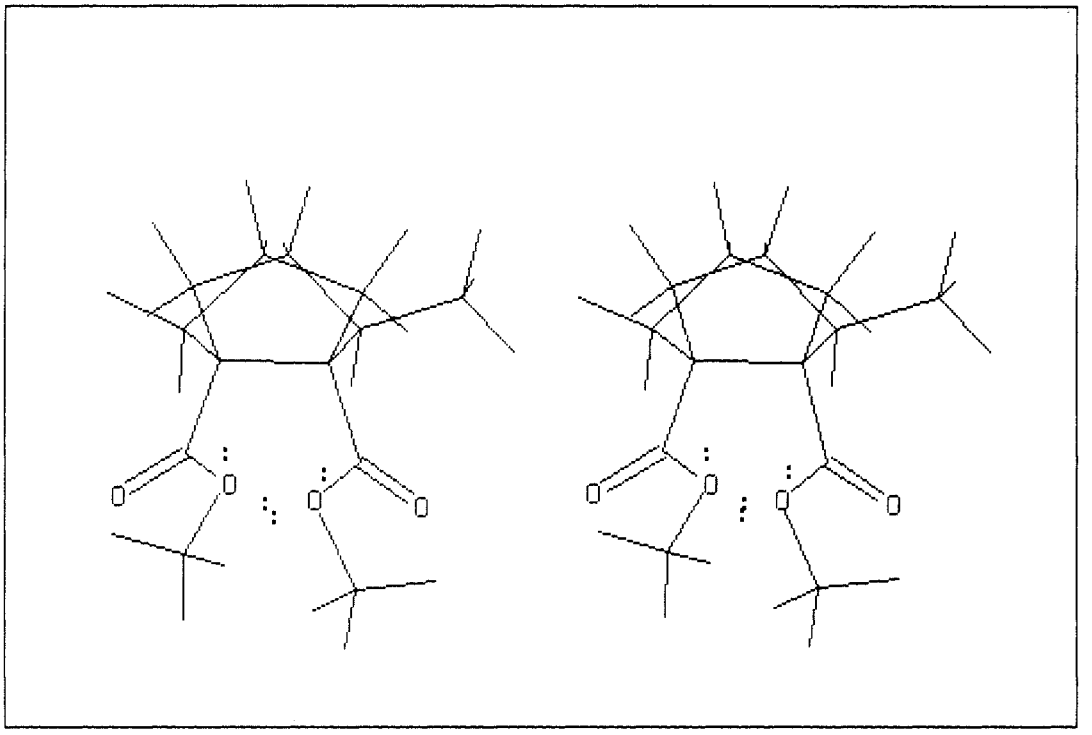


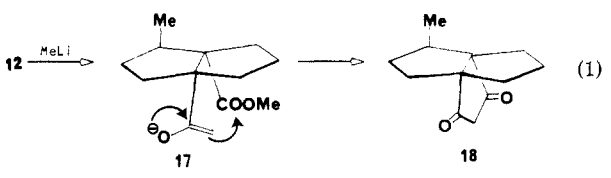
Figure 1. Stereoview of the lowest energy conformation of 4 as computed by molecular mechanics.

The two ester carbonyl groups are aligned in a dipole–dipole stabilizing orientation, with the carbonyl oxygen of the proximal ester below the C-2 methyl group. Rotation of both ester groups by 180° preserves the dipole–dipole stabilization and places the methoxy group below the C-2 methyl. This conformer is only about 0.2 kcal mol^{-1} less stable than the conformation shown in Figure 1 and is also heavily populated at ambient conditions.

In summary, the C-2 methyl group disrupts the bicyclo[3.3.0]octane symmetry of 4 and skews the conformation so that attack by a nucleophile encounters steric hinderance at the proximal carbomethoxy group. The less hindered distal ester is thus preferentially attacked, leading to the observed lactone.

It should be noted that at this point in our synthetic work that we did not known whether we had **14** or its regioisomer; however, subsequent conversion of **14** to the Smith intermediate (**5**) provided the proof for both the stereo- and regiochemistry of our sequences.

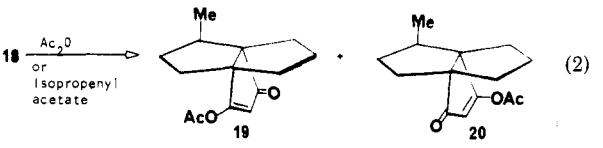
Formal Synthesis of Modhephene. Precedent for the conversion of dimethyl lactones to methylcyclopentenones exists,[9] so we focused our attention on how to improve the yields of **14**. Mass balance of the reaction mixture showed that although the product was quite pure from the reaction of **3** with MeLi, we were recovering only 60% of the material that we introduced (repeated extractions of the reaction mixture did not seem to improve this situation). We then acidified the reaction mixture and, following extraction, identified **18**, which had remained as the enolate salt in the basic aqueous phase after initial workup. The formation of **18** is rationalized by eq 1. This competing



(1)

reaction was responsible for the inability to obtain higher yields of **14**. We completed the formal synthesis of modhephene by the conversion **14** to **2** with $MeSO_3H$ and P_2O_5.[9] The product was identical with an authentic sample generously provided by Prof. A. B. Smith, III.

Total Synthesis of Modhephene. We next focused our attention on an alternative synthesis of modhephene that involved the conversion of **18** to **1**. This required the regioselective introduction of three methyl groups in the positions occupied by the two carbonyl groups. The most convenient way to achieve this conversion invokes the conjugate addition of dimethylcopperlithium to the corresponding enol acetate. Two questions immediately surfaced: (1) Could we specifically convert the 1,3-dione to the required enol acetate (**19**)? (2) Could we carry out the conjugate addition? Relative to the first question, we rationalized that the same factors controlling the regiochemistry of MeLi attack on **4** might also prevail for the chemistry of enol acetate formation (eq 2).



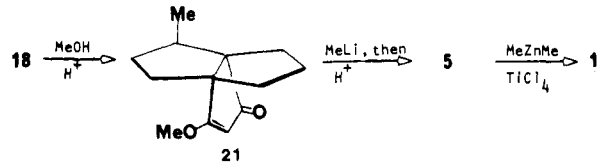
(2)

Treating **18** with acetic anhydride and a trace of amine produced a 1:1 mixture of **19** and **20**, as did the reaction catalyzed by HCl. Reaction of **18** with isopropenyl acetate also provided a 1:1 mixture. Although the two acetates could be separated by analytical GLC, we were unable to find a useful preparative chromatographic method.

Contrary to these findings, however, was the observation that refluxing **18** with MeOH and one drop of HCl provided **21** in about 98% purity. The regiochemistry of enol ether formation was known, ex post facto, by the conversion of **21** to modhephene. We cannot, at this time, rationalize the differences in formation of the enol ethers and the enol acetates. These conversions are summarized in Scheme V. Treatment of **21** with MeLi, followed by mild acid workup, yielded **5**. This was readily distinguished

(9) Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071.

Scheme V. The Total Synthesis of Modhephene



from the previously characterized isomer **2**. It should be recalled that the stereochemistry of the A-ring methyl group had been previously established in **4**, an intermediate used for both syntheses. Thus, *the only two possible enones were* **2** *and* **5**. We next had only to convert the carbonyl group to a *gem*-dimethyl functionality. A general procedure for this conversion has been previously reported by Reetz[10] and required a methyltitanium reagent.

The requisite dimethylzinc needed for the preparation of this reagent was synthesized from a Zn–Cu couple prepared by heating a mixture of cupric citrate and zinc powder with an open flame until gas evolution ceased.[11] This couple was then mixed with MeI, and after 24 h the Me_2Zn reagent was distilled in vacuo. Our product was shown, by NMR, to be contaminated with unreacted methyl iodide. However, since MeI would not interfere with our chemistry, we proceeded with the reagent without further attempts to purify it. Treatment of **5** with the reagent prepared from Me_2Zn and $TiCl_4$ resulted in a low yield of modhephene, accompanied by starting material as the only contaminant. The product mixture was purified by flash chromatography.

Experimental Section

Preparation of 2-Methyl-*cis*-1,5-dicarbomethoxybicyclo-[3.3.0]octan-2-ol (8). To 1 L of a THF solution of LDA (2.5 equiv) at −78 °C under N_2 was added 24.6 g (0.132 mol) of **7**.[4] After stirring for 30 min, 29 g (1.5 equiv) of 4-bromobutan-2-one was added. The reaction mixture was stirred for 3 h while slowly coming to room temperature. After this time the reaction was quenched with water, and most of the THF was removed by rotary evaporation. The residue was redissolved in dichloromethane, and this organic solution was rinsed with 5% HCl and brine and then dried over $MgSO_4$. Evaporation of solvent left 36 g of an orange syrup that was chromatographed on silica gel (5 cm × 45 cm; hexane–ethyl acetate, 9:1) to provide 6.1 g of **7**, 7.0 g of **8**, and 2.4 g of unidentified material. The **8** (28%, based on recovered starting material) was taken directly on to the next step.

Preparation of 2-Methyl-*cis*-1,5-dicarbomethoxybicyclo-[3.3.0]oct-1-ene (9). A solution of 5.25 g of **8** (20 mmol) and 75 mL of dry pyridine was placed under nitrogen and cooled to −5 °C. To this solution was carefully added, via syringe, 6.2 g (2.0 equiv) of $POCl_3$. The reaction mixture was allowed to stir overnight, after which time it was quenched by pouring into a beaker containing crushed ice and concentrated HCl. The product was extracted with dichloromethane, and after drying and evaporation of solvent, the residue was passed through a silica gel column (hexane–ethyl acetate, 6:4) to yield 1.94 g of **9** (57% yield) and 1.48 g of unreacted **8**.

9: MS (EI) M^+ 238, 206,178, 149, 119 (base), 91; ^1H NMR δ 4.80 (1 H, s), 3.71 (3 H, s), 3.69 (3 H, s), 2.52–2.40 (2 H, m), 2.08 (1 H, m), 1.90–1.50 (5 H, m), 1.44 (3 H, s); IR 2900, 1725, 1425, 1210, 1100, 1085, 1030, 800 cm^{-1}; HRMS for $C_{13}H_{18}O_4$, calcd 238.1205, found 238.1210.

Preparation of *anti*-6-Methyl-*cis*-1,5-dicarbomethoxybicyclo[3.3.0]octane (4). Hydrogenation of 1.85 g (7.7 mmol) of **9** over Pd/Al_2O_3 at 60 psi H_2 in MeOH was carried out overnight. After filtration of catalyst and removal of solvent, 1.87 g of a sweet-smelling material was obtained. There was no separation of **4** and **9** on packed GLC, so ^1H NMR was used to monitor the reaction. After 72 h no olefinic protons were visible. Sequential addition of Resolve-Al EuFOD indicated that the reduction had occurred stereospecifically from the carbomethoxy face, as evidenced by only one methyl doublet.

4: ^1H NMR δ 3.59 (6 H, s, 2.76 (1 H, ddd), 2.3–1.3 (10 H, m), 0.89 (3 H, d, J = 6.7 Hz); ^{13}C NMR δ 177.2 (s), 175.0 (s), 69.0 (s), 64.1 (s), 51.7 (q), 51.0 (q), 45.6 (d), 40.9 (t), 35.2 (t), 34.3 (t), 33.0 (t), 23.6 (t), 14.7 (q); IR 2900, 1725, 1450, 1430, 1240, 1190, 1135, 1010, 750 cm^{-1}; MS M^+ 240, 209, 208, 185, 180, 167, 153(base), 138, 121, 105, 93, 91, 79; HRMS for $C_{13}H_{20}O_4$, calcd 240.1362, found 240.1370.

Preparation of 2-Oxo-4,4,8-trimethyl-3-oxatricyclo-[3.3.3.0]decane (14). To a cooled solution of 25 mL of THF and 300 mg of **4**, under N_2, was added 2.1 mL of 1.3 M MeLi via syringe. After stirring overnight, the reaction was quenched with water and the volume reduced by rotary evaporation. The residue was taken up in dichloromethane, washed with brine, and dried over $MgSO_4$. Removal of solvent afforded 240 mg (80%) of the lactone (**14**).

14: ^1H NMR δ 5.08 (1 H, s), 2.05 (1 H, m), 1.83 (5 H, m), 1.52 (4 H, m), 1.35 (2h, m), 1.04 (3 H, d, J = 6.6 Hz); ^{13}C NMR δ 205.8, 203.9, 105.9, 68.7, 42.8, 35.2, 35.1, 34.6, 33.2, 27.3, 15.6; IR 2900, 1750, 1460, 1380 (d), 1340, 1260, 1100, 1025, 990, 910 cm^{-1}; MS M^+ 192, 164, 151, 135, 119, 107, 86 (base), 84, 47; HRMS for $C_{12}H_{16}O_2$, calcd 192.1128, found 192.1139.

Acidification of the aqueous phase with HCl, followed by ether extraction, yielded 130 mg of a golden-colored gum that crystallized upon standing. Flash chromatography (hexane–ethyl acetate, 1:1) gave 125 mg of **18** (95% recovery).

18: ^1H NMR δ 7.60 (1 H, br), 2.20–1.30 (12 H, m), 1.08 (3 H, s); ^{13}C NMR δ 205.8, 203.9, 105.9, 68.7, 67.2, 42.8, 35.2, 35.1, 34.6, 33.2, 27.3, 15.6; MS M^+ 192, 164, 151, 119, 88, 86 (base), 84, 47; HRMS for $C_{12}H_{16}O_2$, calcd 192.1128, found 192.1139.

Preparation of 2-Methylene-4,4,8-trimethyl-3-oxatricyclo[3.3.3.0]decane (16). When 3 equiv of methyllithium was used in the above reaction with **4**, a nearly quantitative yield of **16** could be obtained: ^1H NMR δ 4.25 (1 H, s), 3.66 (1 H, s), 2.12 (2 H, dd), 1.90–1.60 (5 H, m), 1.29 (3 H, s), 1.00 (3 H, d, J = 6.5 Hz); ^{13}C NMR δ 165.7 (s, quaternary vinyl ether), 85.7 (s), 83.1 (t), 69.9 (s), 66.6 (s), 44.9 (d), 39.4 (t), 36.4 (t), 36.3 (t), 34.9 (t), 28.9 (t), 27.4 (q), 25.3 (q), 22.5 (t), 16.1 (q), 14.0 (q).

Preparation of 4,8-Dimethyltricyclo[3.3.3.0]undec-3-en-2-one (2). A flame-dried, three-necked flask fitted with a mechanical stirrer was placed under a nitrogen atmosphere. The flask was charged with 50 mL of 1:10 $P_2O_5/MeSO_3H$ solution and was heated to 85 °C before 280 mg of **14** was injected (using a minimal amount of $MeSO_3H$ as solvent). The solution immediately darkened, and after 24 h an additional gram of P_2O_5 was added. The reaction mixture was stirred for an additional 18–20 h.

The reaction was quenched by cautiously pouring the contents of the flask into a beaker containing 300 mL of saturated bicarbonate solution. The mixture was extracted three times with 100 mL of dichloromethane. The combined extracts were dried over $MgSO_4$ and were filtered through a short silica gel plug to give 120 mg of an amber-colored liquid. GLC (13% DEGS, 10 ft × $^1/_4$ in. 170 °C) indicated that we had obtained 22% of a product identical with an authentic sample of **2** provided by Prof. A. B. Smith, III: HRMS for $C_{13}H_{18}O$, calcd 190.1335, found 190.1346.

Preparation of the Enol Acetates 19 and 20. Method A. A 50-mL flame-dried flask was placed under a nitrogen atmosphere and was charged with 80 mg of **18** in mL isopropenyl acetate. The reaction was stirred and heated to 40 °C, at which temperature 1 drop of concentrated H_2SO_4 was injected. The reaction mixture darkened and was allowed to stirr for an additional 16 h. After this time, the excess isopropenyl acetate was removed by rotary evaporation and the reaction mixture was taken up in dichloromethane. The dichloromethane solution was washed with dilute bicarbonate and dried, and the excess solvent was removed by rotary evaporation to give 128 mg of an orange liquid. This was subjected to flash chromatography (silica gel; 8:2 hexane–ethyl acetate) to yield 74 mg (75%) of the vinyl acetate mixture. The isomers did not separate on packed GLC columns but were separable on a 30-m capillary column. A 1:1 mixture

(10) See: Reetz, M. T.; Westermann, J. *Synth. Commun.* **1981**, 647 and previous papers.

(11) Krug, R. C.; Tang, D. J. C. *J. Am. Chem. Soc.* **1954**, *76*, 2262.

of the two acetates was noted.

Method B. In a dry flask under nitrogen atmosphere were added 10 mg of **14**, 3 mL of acetic anhydride, and one drop of concentrated HCl. After the mixture was stirred at room temperature for 1 h, the excess acetic anhydride was removed by rotary evaporation and the residue was taken up in dichloromethane. The workup was the same as in method A, to give a quantitative yield of the two acetates (1:1): ^{1}H NMR (on mixture) δ 6.18 and 6.13 (1 H, s, vinyl proton), 2.29 and 2.28 (3 H, s, acetate methyl), 2.15–1.20 (11 H, m), 1.04 and 1.01 (3 H, d, J = 2.4 Hz, isomeric methyl groups); HRMS for $C_{14}H_{18}O_2$, calcd 234.1232, found for **19**, 234.1244, found for **20**, 234.1244.

Preparation of 4-Methoxy-8-methyltricyclo[3.3.3.0]undec-3-en-2-one (21). A solution containing 20 mL of absolute MeOH and two drops of concentrated HCl was stirred under a nitrogen atmosphere while 570 mg of **18** was added in a minimum amount of methanol. This reaction mixture was stirred at reflux for 36 h, after which time the solvent was removed to leave about 600 mg of crude product. The crude product was subjected to flash chromatography (8:2, hexane–ethyl acetate) to give two fractions. The first fraction contained the desired **21** (379 mg) and the second fraction contained starting material (223 mg). On the basis of recovered starting material, this constituted a quantitative conversion. ^{1}H NMR δ 5.14 (1 H, s), 3.81 (3 H, s), 2.02 (1 H, m), 1.81 (4 H, m), 1.70–1.20 (10 H, m), 1.02 (3 H, d, J = 6.7 Hz); ^{13}C NMR δ 207.1 (s), 191.8 (s), 104.1 (d), 69.9 (s), 64.4 (s), 58.3 (q), 42.6 (d), 35.0 (t), 34.9 (t), 34.7 (t), 33.0 (t), 26.9 (t), 14.9 (q), *no* evidence in for any isomer; HRMS for $C_{13}H_{18}O_2$, calcd 206.1307, found 206.1320.

Preparation of 4,6-Dimethyltricyclo[3.3.3.0]undec-3-en-2-one (5). In a nitrogen-flushed flask were injected 20 mL of dry toluene and 370 mg of **21**. This was followed by 5 equiv of MeLi. After refluxing for 24 h the reaction was quenched with MeOH, rinsed with 5% HCl, and then dryed. Removal of solvent left 306 mg of a yellow oil. Flash chromatography (7:3 hexane–ethyl acetate) afforded two fractions. The second fraction was shown to be 79% **5**: ^{1}H NMR δ 5.81 (1 H, d, J = 2.6 Hz), 2.08 (3 H, d, J = 2.6 Hz), 2.00–1.20 (11 H, m), 0.97 (3 H, d, J = 6.9 Hz); HRMS for $C_{13}H_{18}O$, calcd 190.1355, found 190.1356.

Synthesis of Modhephene. A flame-dried flask was placed under an argon atmosphere and charged with 20 mL of freshly distilled dichloromethane. After the mixture was cooled to 0 °C, 1 equiv of $TiCl_4$ was added, followed by 2 equiv of dimethylzinc.[11] The presence of the Me_2Ti could be ascertained from the proton NMR spectrum, where the methyl resonance appears at −1.90 ppm (Me_2Zn has a methyl resonance at −1.90 ppm). After the mixture was cooled at 0 °C for 15 min, 239 mg of **5** was injected into the reaction vessel. The reaction mixture was protected from light and was allowed to stir overnight. *In the hood*, the reaction mixture was quenched by pouring the contents into a beaker and cautiously adding methanol and dry ice. When the evolution of gases had ceased, the reaction mixture was diluted with saturated ammonium carbonate and extracted with dichloromethane. Following drying and removal of solvents, there remained a liquid that was shown to consist of 200 mg of unreacted starting material and 20 mg of modhephene. We made no attempts to maximize yields or to recycle the starting material. The mass spectral fragmentation patterns of our synthetic material matched those for synthetic modhephene: HRMS for $C_{15}H_{24}$, calcd 204.1767, found 204.1822.

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The Oxyiodination of 5,8-Dimethoxy-1,4-dihydro-1,4-ethanonaphthalene

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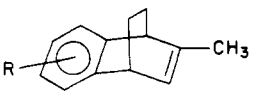
The Wagner–Meerwein rearrangements produced when iodine is added to 5,8-dimethoxy-1,4-dihydro-1,4-ethanonaphthalene (5,8-dimethoxybenzobicyclo[2.2.2]octadiene) in water, methanol, a water–methanol mixture, and acetic acid, respectively, have been studied. The amount of addition anti to the aryl ring increased directly with the electrophilic strength of the reagent. This result is consistent with the increasing importance of a homoconjugative stabilization of the transition state with weaker electrophiles. The results stand in contrast to earlier predictions based on MINDO/3 calculations.

Recently, Paquette et al.[1] have published an extensive experimental and theoretical study of electrophilic additions to a series of rigid olefins containing aryl groups located in such a fashion that π-electron interactions between the two systems might occur. The contrasting stereoselection offered by weak and strong electrophiles has been detailed. Of particular interest here are those additions in the benzobicyclo[2.2.2]octadiene systems I.[1b] Among the reactions studied were photooxidation, epoxidation, cyclopropanation, oxymercuration, and hydroboration. For each substrate and in each reaction it was found that electrophilic attack came preponderantly from the sterically more favored side of the double bond syn to the aromatic ring. In discussing these results, they produced a list of five potential contributing factors that might influence the course of these additions. Most obvious of these was the steric interference offered by the ethano



Ia, R = H
b, R = 5,8-$(OCH_3)_2$
c, R = 5,6,7,8-$(F)_4$

(1) (a) Paquette, L. A.; Hertel, L. W.; Gleiter, R.; Bohm, M. C.; Beno, M. A.; Christoph, G. C. *J. Am. Chem. Soc.* **1981**, *103*, 7106–7121. (b) Paquette, L. A.; Bellamy, F.; Wells, G. J.; Bohm, M. C.; Gleiter, R. *Ibid.* **1981**, *103*, 7122–7133. (c) Paquette, L. A., Klinger, F.; Hertel, L. W. *J. Org. Chem.* **1981**, *46*, 4403–4413.

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