Tetrahedron Vol. 49, No 4, pp 755-770, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Tandem Transannular Radical Cyclizations. Total Syntheses of (±)-Modhephene and (±)-*Epi*-Modhephene

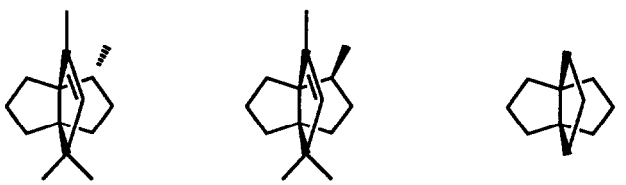
Dennis P. Curran*[1] and Wang Shen
Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA

(*Received in USA* 23 *July* 1992, *accepted* 12 *October* 1992)

Summary: Modhephene and *epi*-modhephene have been synthesized by a new tandem transannular radical cyclization strategy The key tandem cyclization is conducted by the Barton thiohydroxamate method with an exo(methylene)cyclooctane

Introduction: Modhephene (**1a**) is the parent of a small class of triquinane sesquiterpenes[2-4] that has stimulated the development of new methods to prepare [3.3 3]propellanes (Figure 1) [5-8] In our laboratory, modhephene has served as an inspiration for retrosynthetic planning based on radical reactions [9] We now report a total synthesis of (±)-modhephene that uses a tandem transannular radical cyclization as the key step to directly form the propellane ring from an exo(methylene)cyclooctane The synthesis features the use of the Barton thiohydroxamate method[10] for radical generation and trapping, which solves serious problems encountered in the preparation of traditional radical precursors

Figure 1



modhephene (**1a**) *epi*-modhephene (**1b**) [3 3 3]propellane

Modhephene began to interest us after we had completed tandem radical cyclization approaches to representative linear and angular triquinanes [11] Figures 2a and 2b summarize these closely related strategies in which two "outer" cyclopentane rings are formed about a "central" ring in the key tandem radical cyclization Figure 2c illustrates why this strategy cannot be directly extended to a propellane triquinane Simple tandem cyclizations like this form vicinal C–C bonds However, breaking vicinal bonds in propellane **2a** reveals an insurmountable synthetic problem, the first radical cyclization in the sequence must be 5-endo.

To circumvent this problem, we originally adopted a strategy that would retain a central cyclopentane ring precursor and conduct the two radical cyclizations individually rather than in tandem [8] This then frees the requirement that vicinal C–C bonds be formed We systematically dissected modhephene, and ultimately introduced new strategies and reactions to prepare both desmethylmodhephene and modhephene itself [9a] During the systematic dissection of modhephene, we realized that to design a viable tandem cyclization strategy to modhephene, we need only abandon the premise that the tandem cyclization start with a preformed cyclopentane ring. Figure 2d is a retrosynthetic dissection of the

propellane ring **2b** that leads to synthon **3**, and radical precursor **4** In contrast to the strategy in Figure 2c, both cyclizations in Figure 2d are 5-exo In this planned tandem cyclization, the first closure is a transannular cyclization across an exo(methylene)cyclooctane, while the second is a standard cyclization

Figure 2a

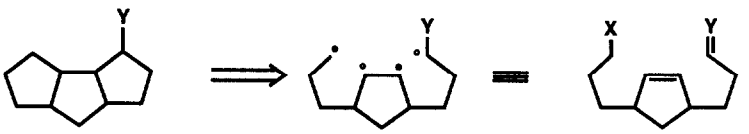


Figure 2b

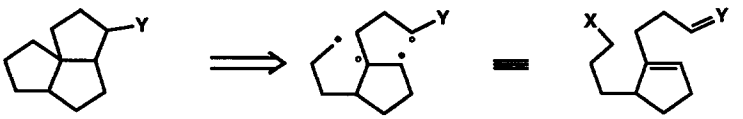
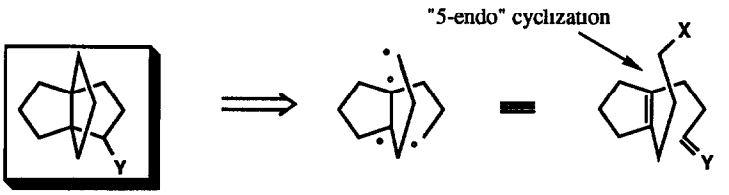
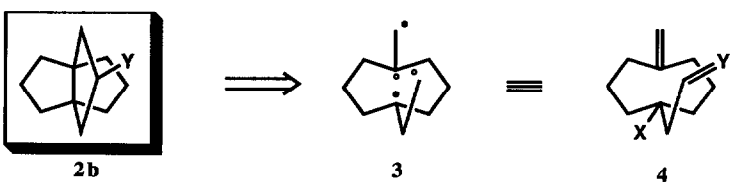


Figure 2c



2a

Figure 2d



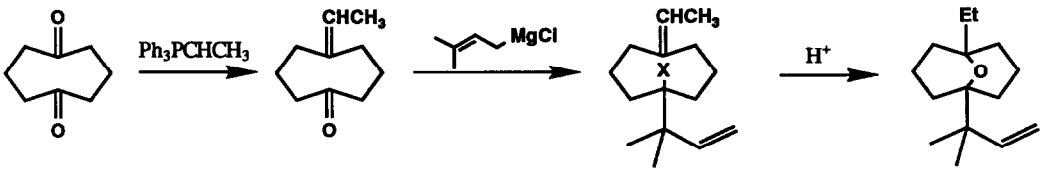
2b **3** **4**

Although quite a number of transannular radical cyclizations have been reported,[12] most are closures to double bonds inside the medium or large ring A few examples of transannular cyclizations to exomultiple bonds were reported either before[13a] or during our work [13b] Winkler and Sridar have reported tandem cyclizations in which transannular cyclizations follow 5-exo cyclizations,[14] and Porter and coworkers have reported sequences in which transannular cyclizations follow macrocyclizations [15] We are not aware of any sequence like that in Figure 2d, where the transannular cyclization leads off the sequence We embarked on our second synthesis of modhephene to test the viability and explore the features of the tandem transannular cyclization route outlined in Figure 2d

Model Studies: Given that the planned tandem cyclization was a significant departure from known reactions, we decided that a model study was in order We quickly ran into an unexpected difficulty—the introduction of an appropriate functional group to serve as a radical precursor The skeleton of the radical precursor was quickly assembled, as shown in Scheme 1 Mono-Wittig reaction of cyclooctane dione[16] proceeded with surprising efficiency to give **5** in 82% yield Addition of prenylmagnesium chloride[17] to **5** then provided the key alcohol **6** Despite our best efforts, alcohol **6** resisted all attempts at conversion to an appropriate radical precursor such as a halide or xanthate Alcohol **6** is very sensitive to acid, and readily closes to ether **7** under many mild conditions for conversion of alcohols to halides The use of more forcing Lewis acid conditions usually formed a multitude of products, probably derived from cationic processes

Tertiary neopentyl alcohol **7** is highly crowded, and all attempts at thioacylation under basic conditions resulted only in recovery of starting material. Though we managed to silylate **7**, we could not convert the silyl ether to a halide either

Scheme 1

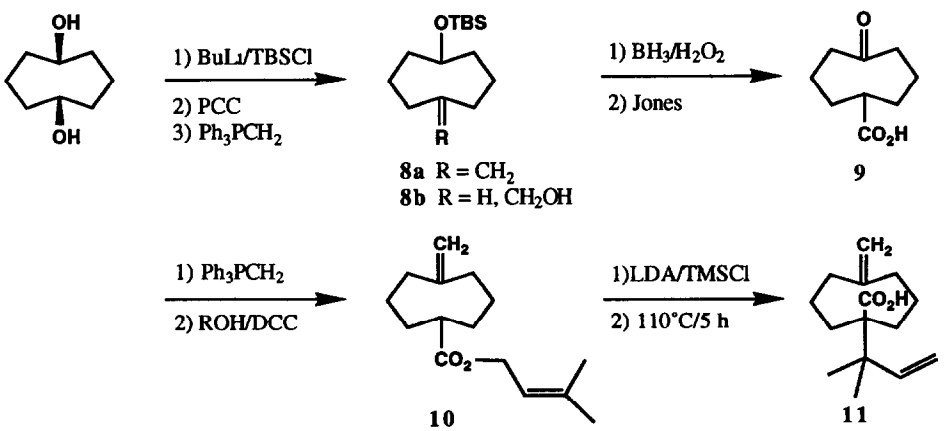


5 **6** X = OH, X = halide or xanthate **7**

To solve the problems inherent with crowded 3°-alcohol **7**, we changed our strategy to use the Barton thiohydroxamate method of radical generation [10] A key feature of this method is that the initial carbon-centered radical is generated by a decarboxylation Thus, a carboxylic acid, rather than a heteroatom, must stand at the site of radical generation Clearly this would solve the problems of ionic reactivity associated with **7** (ether formation, cationic rearrangements), and we did not expect any difficulty with steric crowding in precursor synthesis since Barton has already converted many 3°-acids to thiohydroxamates without event [10] Most importantly, the synthesis of the crowded skeleton of the precursor would still be easy thanks to the Claisen rearrangement

After trying several shorter routes to an appropriate acid precursor for the Claisen rearrangement, we settled on the longer, but very practical and high-yielding route outlined in Scheme 2 Monosilylation of cyclooctane diol, followed by PCC oxidation and Wittig reaction, provided alkene **8a** in 90% overall yield Hydroboration followed by direct Jones oxidation then gave keto acid **9** Wittig reaction and standard esterification[18] then provided isoprenyl ester **10**, which was purified by flash chromatography The conversion of **8a** to **10** was accomplished in 26% overall yield without purification of any intermediates Ireland Claisen rearrangement[19] of **10** then provided crude **11** in 99% yield Reflecting the crowded nature of the forming C–C bond, the intermediate ketene silyl acetal required heating at 110°C for 5 h to induce Claisen rearrangement (0-50°C is the typical temperature range for such reactions) [20]

Scheme 2

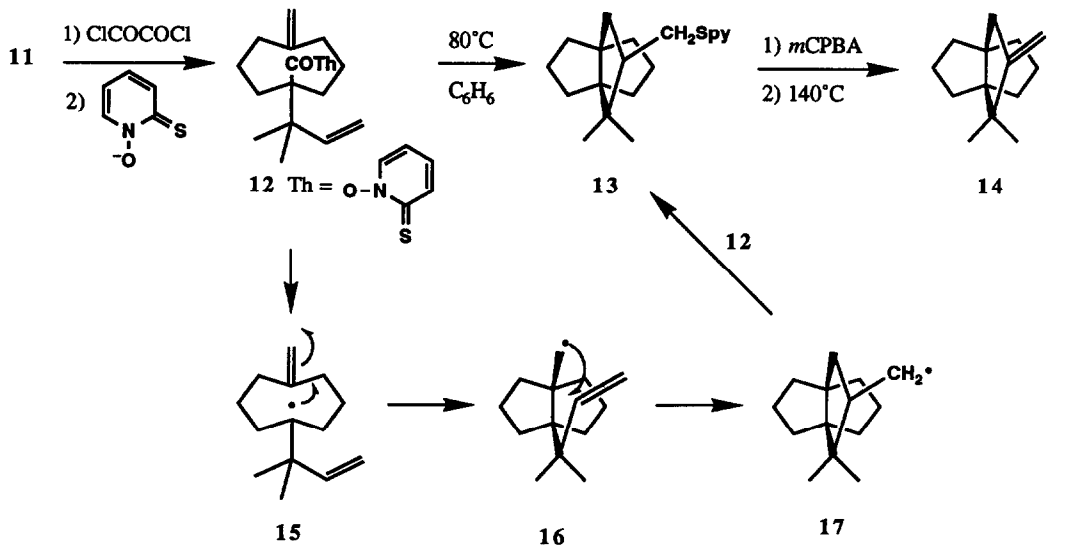


8a R = CH_2
8b R = H, CH_2OH

9 **10** **11**

Scheme 3 summarizes the results of the model tandem cyclization. Formation of the thiohydroxamate **12** followed standard procedures;[21] acid **11** was reacted with oxalyl chloride and the derived acid chloride was acylated in the dark at 25°C with the sodium salt of *N*-hydroxypyridinethione Thiohydroxamate **12** was isolated in 81% yield. On surveying several initiation methods, we found thermal conditions[22] to be much more effective than photochemical Heating of **12** at 80°C in benzene for 12 h provided a single major product **13**, which was isolated in 69% yield after flash chromatography A similar yield was obtained by heating **12** for 5 h at 105°C in toluene The product **13** was further characterized by standard oxidation and sulfoxide elimination[10,23] to give exocyclic alkene **14** in 67% yield The ^1H and ^{13}C NMR spectra of **14** support the structure assignment, and show that **14** has the expected plane of symmetry

Scheme 3



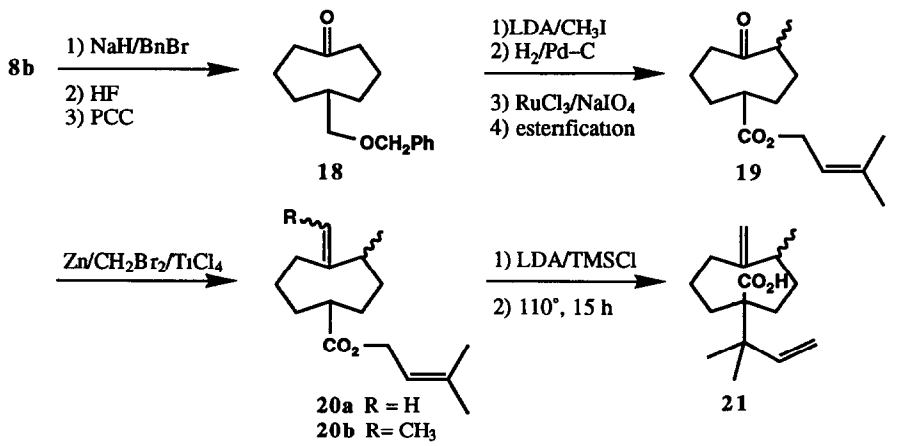
The lower part of Scheme 3 suggests the steps that are involved in the conversion of **12** to **13** [10] Radical **15** undergoes transannular cyclization to **16**, which in turn closes onto the pendant alkene to give **17** Addition of **17** to the starting thiohydroxamate transfers the chain providing product **13**, starting radical **15**, and CO_2 We saw no evidence in any reaction for premature trapping of either radical **15** or **16** by addition to the Barton ester We conclude that both radical cyclizations must be reasonably fast ($>10^5$ s^{-1}) [24] The transannular radical cyclization forms two new quaternary centers adjacent to an existing quaternary center with astonishing facility, especially when compared to the failed attempts at substitution or activation of alcohol **7** and the high temperature required for the Claisen rearrangement

A bonus of using the Barton method is that the final product is functionalized, and can be subjected to further transformations In the context of our modhephene synthesis, this means that we can continue to use a double bond as the second radical acceptor because the thiopyridyl group in the product provides the needed handle for the subsequent oxidative cleavage (see below) In our original reductive plan, we would have needed to change the second radical acceptor to provide the needed functionality

Synthesis of Modhephene: The synthesis of an appropriately functionalized tandem cyclization precursor for modhephene is outlined in Scheme 4. Timing of the various transformations was somewhat difficult, but we ultimately provided efficient solutions to all the problems Readily available alcohol **8b** (see Scheme 2)

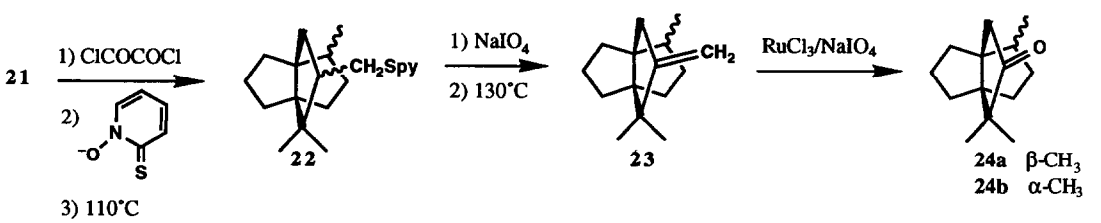
was benzylated, desilylated, and oxidized to provide ketone **18** in >95% overall yield Standard enolate methylation, followed by debenzylation and oxidation of the 1°-alcohol gave a keto acid (1/1 mixture of diastereomers[25]), which was directly esterified with prenyl alcohol to provide **19** After chromatography, **19** was isolated in 67% overall yield from **18** All attempts to prepare **20b** by olefination of **19** with two-carbon Wittig or Petersen reagents failed However, methylenation to give **20a** was smoothly accomplished by using the Lombardo/Nozaki reagent.[26] Ireland Claisen rearrangement of **20a** then provided crude acid **21** in high yield (>95%) as a 1/1 mixture of isomers. Since both isomers should give the same radical, the mixture is inconsequential Once again, forcing conditions (110°C, 15 h) were needed to induce the Claisen rearrangement to proceed at a reasonable rate

Scheme 4



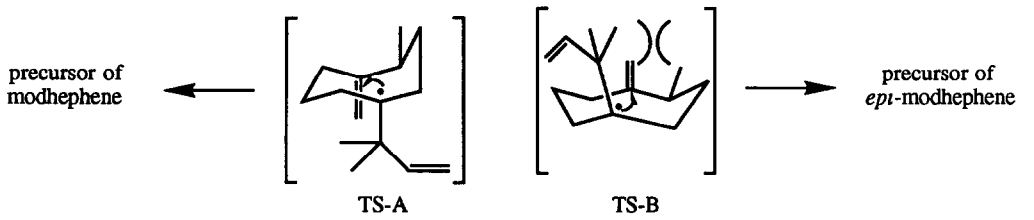
Scheme 5 summarizes the result of the key tandem cyclization Conversion of **21** to the thiohydroxamate and then heating for 8 h in toluene (110°C) provided a mixture of 4 diastereomers of **22** in 63% isolated yield At this stage, neither GC nor NMR was useful for accurately determining the isomer ratio Since two of the diastereomers are inconsequential for the synthesis, we forged ahead with oxidation of **22** and sulfoxide elimination to form **23** (71%), which was now clearly a 2.7/1 ratio of inseparable stereoisomers Oxidative cleavage of **23** with RuO_4 then provided ketone **24** (73%), again as an inseparable 2 7/1 mixture of stereoisomers By conversion to modhephene and *epi*-modhephene (see below), we ultimately determined that the major isomer **24a** has the desired stereochemistry foi modhephene while the minor isomer **24b** ultimately correlates to the known *epi*-modhephene [6]

Scheme 5



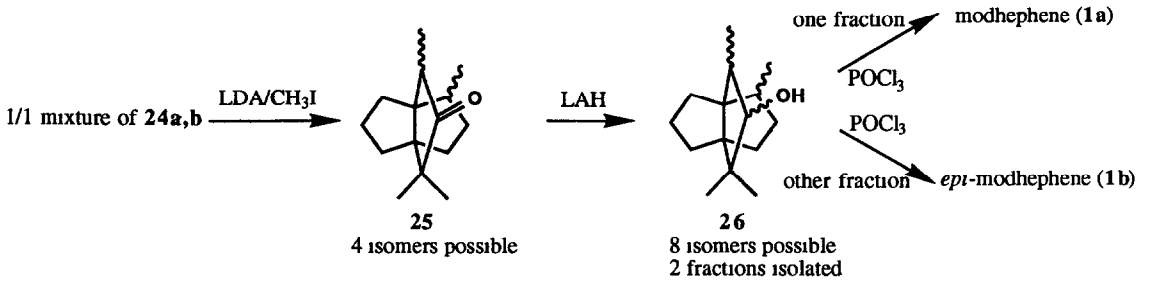
The steps in the tandem cyclization of **21** are analogous to those outlined in Scheme 2 Figure 3 provides stereochemical models[27] for the transannular cyclization In these models, the (exo)methylene group and the radical face each other to achieve the desired angle of attack (~109°) Closure through transition state-A (TS-A) ultimately produces the major product **24a** while closure through TS-B leads to the minor product **24b** An unfavorable interaction between the methyl group and the (exo)methylene group in TS-B may be responsible for the small difference in energy between A and B To test this idea, we wanted to replace the methylene group (=CH_2) with a Z-methylidene group (=$CHCH_3$) This would both shorten the synthesis and (perhaps) increase the selectivity in the radical cyclization because TS-B would now be strongly disfavored by A-strain. However, all attempts to olefinate ketone **19** by Wittig or Petersen methods failed.

Figure 3



Since ketones **24a,b** were known compounds,[7] we thought that the final steps of the synthesis of modhephene would move quickly Unfortunately, this was not to be In 1986, Mehta and Subrahmanyan had reported using the mixture of ketones **24a,b** in their synthesis of modhephene and *epi*-modhephene (Scheme 6) [7a] A full paper describing their work appeared as we were attempting to repeat it [7b] These workers reported that alkylation of a 1/1 mixture of **24a,b** with LHDMS/MeI provided an unspecified mixture of methylated ketones **25** (4 isomers possible) LAH reduction then provided an unspecified mixture of alcohols **26** (8 isomers possible) that could be separated into two fractions. Dehydration of one fraction with $POCl_3$ was reported to give pure modhephene (**1**, 36%), while the other fraction was dehydrated to give pure *epi*-modhephene (24%). Whether the more or less polar fraction gave modhephene was not stated Though experimental details were given for each step, little spectral data was provided, presumably because of the complication of having several isomers present Therefore, we were unable to confirm by spectral comparison the identity of our samples with Mehta's

Scheme 6



To confirm the structure and stereochemistry, we embarked on the completion of the synthesis following the reported experimental procedure (Scheme 6 and 7) Fortunately, the synthesis of **24a,b** was easy, and we had relatively large quantities in hand (~1 g) Alkylation of the **24a,b** (2 7/1) mixture with

LDA and methyl iodide produced a 60/40 mixture of the desired product **25** and recovered **24a,b** (still a 2 7/1) mixture Unreacted **24** and product **25** were separated from each other by flash chromatography, however, the isomers of **25** did not separate. From the ^{1}H NMR spectra and GC analysis of **25**, it appeared as if only three of the four possible isomers were present Though we did not attempt to assign stereochemistry, we suspect that the missing isomer could be the one in which the two 3°-methyl groups point at each other

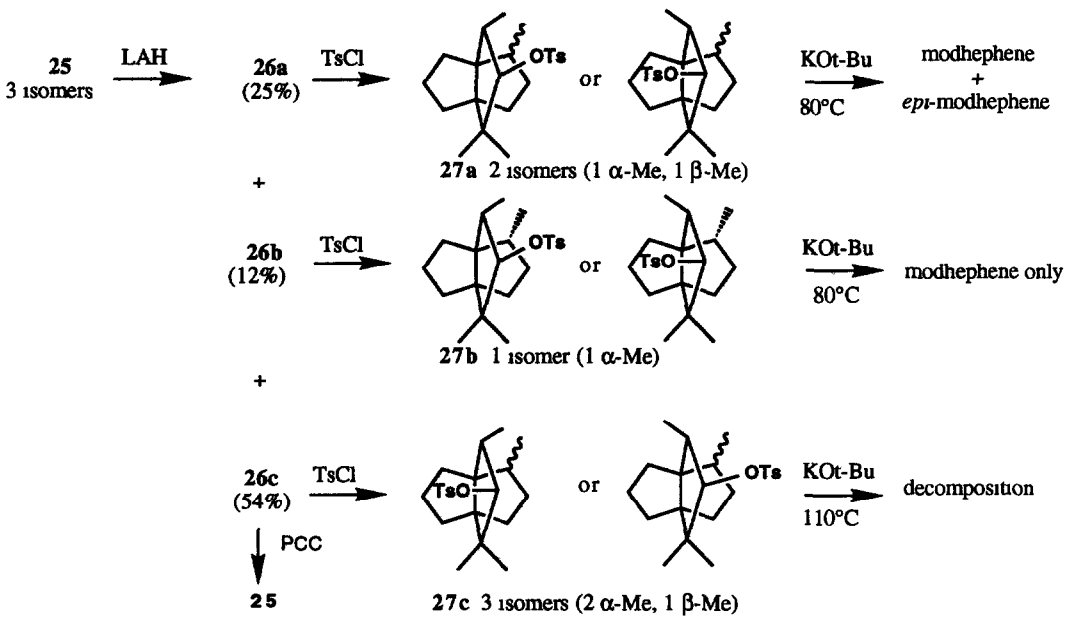
Reduction of **25** with LAH then provided a mixture of alcohols whose ratio we could not determine either by GC (due to dehydration) or by ^{1}H NMR (due to signal overlapping) In our hands, flash chromatography of this mixture provided not two fractions but three The first two fractions (**26a**, 28%, **26b**, 12%) were relatively non-polar, and the separation was narrow, the third fraction (**26c**, 54%) was considerably more polar than the other two We started by dehydrating fraction **26c** according to Mehta's procedure Starting alcohol **26c** rapidly disappeared (TLC) on reaction with $POCl_3$ (pyridine, DBU) at 25°C, but GC analysis showed no products in the region of the chromatogram where modhephene and *epi*-modhephene were expected Heating of this reaction at 80°C for 1 h then produced a very complex mixture containing five major products and a number of minor products We had authentic samples of modhephene and epi-modhephene on hand, and we determined by GC-coinjection and GC-MS that one of the major peaks was modhephene and one of the minor peaks was epi-modhephene According to the GC-MS data, all of the other major products and several of the minor products were isomers of modhephene We made similar observations when we subjected fraction **26c** to the Burgess reagent [28] These observations led us to suspect that phosphorylation or sulfenylation of the alcohol occurs at ambient temperature, but at the temperatures required for elimination, cationic rearrangements occur

Similar observations were made with fraction **26a** At ambient temperature, the starting material was consumed, but no low molecular weight products were evident At higher temperatures, a large number of products appeared in the GC chromatogram We did not attempt the reaction on the smallest fraction **26b**

We finally succeeded in the dehydration step by a sequence of tosylation and base-catalyzed elimination (Scheme 7) [29] As a bonus, we got some important stereochemical information at the stage of the tosylate Standard tosylation of fraction **26a** gave fraction **27a**. ^{1}H NMR analysis now clearly indicated that **27a** was a 1 8/1 mixture of two isomers Treatment of this mixture with potassium *t*-butoxide in DMSO at 85°C then cleanly produced an inseparable 1 8/1 mixture of *epi*-modhephene and modhephene in 66% overall yield Tosylation of fraction **26b** provided a single tosylate **27b**, which eliminated to provide pure modhephene in 58% overall yield Tosylation of fraction **26c** then provided **27c**, which was clearly a mixture of three isomeric tosylates, however, none of these tosylates eliminated on treatment with *t*-butoxide at 85°C When the temperature was raised to 105°C, decomposition occurred

The tosylation experiments provide useful information First, the LAH reduction of the three ketones **25** clearly provided all six possible alcohols two in fraction **26a**, one in **26b**, and three in **26c** Second, assuming that an anti orientation of the proton and the tosylate is favored for elimination, we can conclude from the failure of **27c** to eliminate that all three alcohols in fraction **26c** must have the vicinal hydroxy and methyl groups trans By default, fractions **26a** and **26b** must have these two groups cis This assignment seems consistent with the observed differences in polarity, the cis isomers (where the OH group is shielded by the methyl) are much less polar Further evidence for the stereochemical assignment came from ^{1}H NMR vicinal coupling constants of the protons adjacent to the Ts and Me groups The two isomers in **27a** and the lone isomer **27b** exhibited very small vicinal coupling constants (~3Hz), while all three isomers in **27c** exhibited large coupling constants (~11 Hz) MM2 calculations suggest that the cis isomers have proton/proton dihedral angles in the vicinity of 60° while the trans isomers have dihedral angles close to 180° Taken together, all the circumstantial evidence makes a good case for the cis/trans assignments

Scheme 7



We cannot reconcile our observations with those of Mehta and Subrahmanyam [7b] Their two fractions could correspond to our **26a** + **26b** (which are difficult to separate) and **26c**, however, both of their fractions should then have dehydrated to give mixtures of modhephene and *epi*-modhephene Perhaps they did separate **26a** and **26b** and missed entirely fraction **26c** (which is very much more polar than the other two) In this scenario, one of their fractions could have dehydrated to give pure modhephene, but the other should have given a mixture of modhephene and *epi*-modhephene However, we must emphasize that strict comparison of our results with Mehta and Subrahmanyam's cannot be made They started with a different mixture of isomers **24** than us, and we could not repeat the dehydration under conditions identical to theirs Clearly it is risky to compare eliminations conducted by different methods Finally, it is possible that different chromatographic conditions gave different separations results Nonetheless, our results indicate that significant polarity differences are present between cis/trans alcohol epimers, not between α/β methyl epimers

To improve the synthetic route, we reoxidized fraction **26c** back to ketone **25**, and then conducted the reduction of **25** with L-selectride [30] With this bulky reducing agent, only the cis alcohols formed, there was no spot corresponding to **26c** Unfortunately, attempted separation of these alcohols by flash chromatography on larger scale was not very successful, as we learned when tosylation/elimination of the first fraction gave 1/1 3 mixture of modhephene and *epi*-modhephene and the second fraction gave a 1 45/1 ratio of these products

Overall, the transformation of **25** to modhephene and *epi*-modhephene was rather efficient (8% yield of pure modhephene, 35% yield of a ~1 5/1 mixture of modhephene and *epi*-modhephene), and it could undoubtedly be improved by direct reduction of **25** with L-Selectride (which would eliminate the recycle of **26c**) The problem is that isolating pure modhephene requires either a very difficult separation at the alcohol stage (which would still yield only about half of the modhephene formed) or preparative GC The best solution to the problem is to conduct a stereoselective radical cyclization, but our efforts towards this goal were thwarted by unsuccessful olefinations (see Scheme 4)

In the end, the synthesis of modhephene and *epi*-modhephene takes 21 steps from commercially available *cis*-1,5-cyclooctane diol and proceeds in a respectable 6% overall yield. The key tandem transannular cyclization served very well to make the crowded propellane system, and it occurred with a modest stereoselectivity We think that it is highly likely that substrates giving higher selectivities could be designed and employed in related transannular cyclizations The Barton thiohydroxamate served well as a stable radical precursor, and it also facilitated both the introduction of the second radical acceptor (by Claisen rearrangement) and the degradation of the extra carbon atom after the cyclization By comparison, our earlier syntheses that used two individual radical cyclizations took 11 steps and proceeded in 16% overall yield The added length of the tandem route is due to the steps needed to prepare an appropriately functionalized cyclooctane like **19** from cyclooctane diol (11 steps) Only one C–C bond is formed during this part of the synthesis, though these steps are routine and high yielding

Experimental[31]

Ether and workup procedure The reaction mixture was diluted with ether, washed with water three times, followed by one wash with brine The organic layer was dried over anhydrous magnesium sulfate, and was then filtered The crude product after evaporation of the filtrate was either purified or used directly in the next step (as indicated)

Authentic Sample of 1-(1,1-Dimethyl-2-propen-1-yl)-5-ethyl-9-oxabicyclo[3.3.1]nonane (8) To the compound **7** (about 5 mg) in C_6D_6 (about 0 7 mL) in a NMR tube was added a catalytic amount of toluenesulfonic acid After 5 min, formation of **8** was complete ^{1}H NMR (C_6D_6) δ 6 19 (m, 1 H), 4 93 (m, 2 H), 1 79-1 10 (m, 14 H), 0 98 (s, 6 H), 0 89 (t, 3 H, J = 4 8 Hz), ^{13}C NMR δ 146 3, 110 8, 74 1, 70 9, 45 3, 40 6, 37 4, 32 8, 28 7, 21 1, 18 2, 7 2, HRMS calculated for $C_{15}H_{26}O$ (M), 222 1984, observed 222 1984

5-*t*-Butyldimethylsilyloxycyclooctan-1-ol To a solution of *cis*-1,5-cyclooctanediol (4 33 g, 30 0 mmol) in THF (150 mL) at 0°C was slowly added BuLi (20 9 mL, 1 44 M in hexane, 30 0 mmol) After the addition, the ice bath was removed, and the reaction mixture was stirred for 1 h The monoalkoxide was slowly added to a rapidly stirring solution of t-butyldimethylsilyl chloride (4 97 g, 33 0 mmol) in THF (50 mL) over 0 5 h via a cannula The reaction was continued for 10 min The crude product after the ether workup was purified by column chromatography (5/1 hexane/ethyl acetate) to give the product (7.21 g, 93%) ^{1}H NMR δ 3 80 (m, 2 H), 1 84 (m, 4 H), 1 66 (m, 6 H), 1 42 (m, 3 H), 0 88 (s, 9 H), 0 03 (s, 6 H), ^{13}C NMR δ 71 8, 71 4, 36 4, 36 1, 25 8, 19 8, 18 1, –4 82

5-*t*-Butyldimethylsilyloxycyclooctan-1-one To the mixture of the above silyl ether (7 00 g, 27 1 mmol) and Florisil (10 g) in CH_2Cl_2 (150 mL) at 0°C was added pyridinium chlorochromate (5 84 g, 27 1 mmol) by portions over 10 min After completion of the addition, the cooling bath was removed, and the reaction was continued for 3 5 h at 25°C Anhydrous ether (300 mL) was added, and the mixture was filtered through a layer of Florisil Evaporation of the filtrate afforded the ketone (6 78 g, 98%) ^{1}H NMR δ 3 64 (m, 1 H), 2 55 (m, 2 H), 2 30 (m, 2 H), 2 02 (m, 2 H), 1 72 (m, 6 H), 0 86 (s, 9 H), 0 01 (s, 6 H), ^{13}C NMR δ 216 6, 70 7, 42 2, 36 9, 25 8, 22 2, 18 1, –4 85, IR (neat) 2932, 2857, 1701, 1464, 1254, 1100, 1071, 1003, 837, 776 cm^{-1}, HRMS calculated for $C_{13}H_{25}O_2Si$ (M – Me) 241 1624, observed 241 1624

5-Methylencyclooctan-1-yl *t*-Butyldimethylsilyl Ether (8a) To a suspension of methyltriphenylphosphonium bromide (7 81 g, 22 mmol) in THF (50 mL) was slowly added potassium *t*-butoxide (18 6 mL, 1 12 M in THF, 21 mmol) After 1 h, a solution of the above ketone (5 09 g, 19 8 mmol) in THF (10 mL) was added The crude product after ether workup was purified by column chromatography (20/1 hexane/ethyl acetate) to give **8a** (5 01 g, 99%) ^{1}H NMR δ 4 78 (s, 2 H), 3 96 (m, 1 H), 2 16 (m, 4 H), 1 84 (m, 2 H), 1 67 (m, 4 H), 1 50 (m, 2 H), 0 87 (s, 9 H), 0 01 (s, 6 H), ^{13}C NMR δ 151 1, 112 4, 71 4, 36 2, 35 8, 26 0, 24 3, 18 3, –4 83, IR (neat) 3073, 2928, 2855, 1645, 1472, 1252, 1067, 1034, 1003, 835, 774 cm^{-1}, HRMS calculated for $C_{12}H_{23}OSi$ (M – C_3H_7), 211 1518, observed 211 1518

(5-(*t*-Butyldimethylsilyloxy)-cyclooctanyl)methyl alcohol (8b) To a solution of **8a** (5 01 g, 19 6 mmol) in THF (30 mL) at 0°C was slowly added borane methyl sulfide complex (1 97 mL, 19 7 mmol) After completion of the addition, the cooling bath was removed, and the mixture stood at 25°C for 12 h The reaction mixture was then recooled to 0°C, and anhydrous ethanol was carefully added until no more gas was evolved NaOH (4 M in water, 10 mL) and H_2O_2 (30%, 10 mL) were added, the cooling bath was removed, and the mixture was refluxed 1 h Ether workup gave the crude product, which was purified by column chromatography with 5/1 hexane/ethyl acetate to afford an inseparable mixture of diastereomers **8b** (5 13 g, 96%, ratio of diastereomers, 1/1) ^{1}H NMR δ 3 87, 3 75 (2 m, 1

H), 3 36 (d, 2 H, J = 6 2 Hz), 1 93-1 48 (m, 12 H), 1 38 (m, 1 H), 1 17 (m, 2 H), 0 85 (s, 9 H), 0 02 (s, 6 H), ^{13}C NMR δ 72.3, 69 3, 39 9, 39 0, 36 1, 35 1, 30 4, 30.2, 26 0, 22.6, 21 3, 18 2, –4 7, IR (neat) 3343, 2930, 2857, 1472, 1447, 1360, 1254, 1061, 938, 835, 774, 666 cm^{-1}

5-Oxacyclooctane-1-carboxylic acid (crude) (9) To a solution of **8b** (1 00 g, 3 66 mmol) in acetone (5 mL) at 25°C was slowly added Jones reagent (1 M potassium dichromate in 50% aqeous sulfuric acid) until the red-orange color persisted (4 6 mL of Jones reagent used) After 20 min, the mixture was poured into a separatory funnel containing water (50 mL) and CH_2Cl_2 (20 mL) The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL each) The combined organic layers were dried over anhydrous magnesium sulfate, and then filtered Evaporation of the filtrate afforded the crude product **9**, which was used directly for the next step ^1H NMR of the crude **9** δ 2 60 (m, 2 H), 2 32 (m, 2 H), 2 25-1 96 (m, 5 H), 1 81 (m, 2 H), 1.65 (m, 2 H)

5-Methylenecyclooctane-1-carboxylic acid (crude) To a suspension of methyltriphenylphosphonium bromide (3 26 g, 9 15 mmol) in THF (15 mL) at 25°C was slowly added potassium *t*-butoxide (0 80 M in THF, 11 4 mL, 9 15 mmol) After 1 h, crude **9** in THF (5 mL) was added to the ylide, and the reaction was continued for 1 h Ether workup of the reaction afforded a mixture of the olefinated product and triphenylphosphine oxide This crude mixture at 25°C was used directly for the following step ^1H NMR of the crude product ^1H NMR δ 4 80 (s, 2 H), 2 72 (m, 1 H), 2 49-2 07 (4 H), 1 98-1 72 (m, 4 H), 1.72-1 43 (m, 2 H)

Prenyl 5-Methylenecyclooctane-1-carboxylate (10) To the crude alkene obtained above in CH_2Cl_2 (20 mL) at 25°C was added prenyl alcohol (3 15 g, 3 7 mmol), N,N'-dicyclohexylcarbodiimide (2 26 g, 11 0 mmol), and 4-dimethylaminopyridine (0.45 g, 3 66 mmol) After 12 h, aqueous hydrochloric acid (1 M, 20 mL) was added, and the mixture was stirred 4 h The crude product after filtration and ether workup was subjected to column chromatography (50/1 hexane/ethyl acetate) to afford pure **10** (223 mg, 26% overall yield from **8b**) ^1H NMR δ 5 32 (t, 1 H, J = 7 1 Hz), 4 80 (s, 2 H), 4 53 (d, 2 H, J = 7 1 Hz), 2 67 (m, 1 H), 2 29 (m, 2 H), 2 15 (m, 2 H), 1 91 (m, 4 H), 1 75 (s, 3 H), 1 70 (s, 3 H), 1 58 (m, 4 H)

1-(1,1-Dimethyl-2-propen-1-yl)-5-methylenecyclooctane-1-carboxylic acid (11) To a solution of diisopropylamine (366 mg, 3 62 mmol) in THF (15 mL) at 0°C was slowly added BuLi (1 44 M in hexane, 1 90 mL, 2 71 mmol) After 10 min, the reaction was cooled to –78°C, followed by addition of **10** (427 mg, 1 81 mmol) in THF (3 mL) Trimethylsilyl chloride (786 mg, 7 24 mmol) was added after 1 h, and the reaction was gradually brought to 25°C The THF was then distilled away under nitrogen atmosphere The reaction vessel was refilled with toluene (10 mL), and was refluxed at 110°C for 4 h Hydrochloric acid (1 M in water, 5 ml) was then added to quench the reaction The mixture was stirred 10 min, followed by ether workup The crude product **11** (428 mg, 100%) was clean (from NMR and GC), and was used for the next step without further purification ^1H NMR δ 5 95 (dd, 1 H, J = 10 8, 17 2 Hz), 4 97 (m, 2 H), 4.77 (s, 2 H), 2 26-2 02 (m, 6 H), 1 74 (m, 2 H), 1 58 (m, 4 H), 1 06 (s, 6 H), ^{13}C NMR δ 182 0, 149 8, 145 4, 114 6, 112 1, 55 9, 42 8, 37 4, 27 8, 24 4, 23 8, IR (neat) 3073 (very br), 1684, 1636, 1451, 1416, 1385, 1372, 1308, 1252, 1154, 1102, 1005, 912, 837, 733 cm^{-1}

1-(1,1-Dimethyl-2-propen-1-yl)-5-methenylcyclooctane-1-carboxyl chloride To a solution of **11** (95 2 mg, 0 40 mmol) in benzene (1 mL) at 25°C was added oxalyl chloride (0 5 mL) and DMF (1 drop) After 3 h, solvent and the excess oxalyl chloride were removed by rotary evaporation The crude product was used directly for the next step ^1H NMR δ 5 92 (dd, 1 H, J = 10 8, 17 3 Hz), 5 06 (d, 1 H, J = 10 7 Hz), 5 01 (d, 1 H, J = 17 3 Hz), 4 80 (s, 2 H), 2 29-2 03 (m, 6 H), 1 87-1 54 (m, 6 H), 1 13 (s, 6 H), IR (neat) 2934, 1773, 1734, 1636, 1472, 1456, 1387, 1157, 1092, 1011, 918, 781 cm^{-1}

2-Mercaptopyridin-1-yl 1-(1,1-Dimethyl-2-propen-1-yl)-5-metbhylene-cyclooctane-1-carboxylate (12) To a solution of the above acid chloride in methylene chloride (5 mL) was added 2-mercaptopyridine *N*-oxide sodium salt (72 1 mg, 48 3 mmol) and DMAP, (15 mg, 0 1 mmol) After 20 h, ether workup was conducted Purification of the crude product by column chromatography (10/1 hexane/ethyl acetate) afforded **12** (113 mg, 81% overall yield from **7**) ^1H NMR δ 7 68 (dd, 1 H, J = 1 8, 8 9 Hz), 7 42 (dd, 1 H, J = 1 2, 6 9 Hz), 7 15 (dt, 1 H, J = 1 5, 7 8 Hz), 6 57 (dt, 1 H, J = 1 8, 6 9 Hz), 6 15 (dd, 1 H, J = 10 7, 17 2 Hz), 5 06 (m, 2 H), 4 82 (s, 2 H), 2 35 (m, 4 H), 2 21-1 91 (m, 4 H), 1 81 (m, 4 H), 1 20 (s, 6 H)

2,2-Dimethyl-3-(2-pyridothiomethyl)tricyclo[3.3.3.$0^{1,5}$]undecane (13) A solution of **12** (90 0 mg, 0 29 mmol) in benzene (2 9 mL) in a sealed tube was heated at 100°C for 7 h After evaporation of solvent, the crude product was subjected to purification by column chromatography (5/1 hexane/ethyl acetate) to give **13** (55 0 mg, 69 % yield) ^1H NMR δ 8 41 (m, 1 H), 7 45 (m, 1 H), 7 16 (m, 1 H), 6 94 (m, 1 H), 3 31 (dd, 1 H, J = 3 3, 12 1 Hz), 2 90 (dd, 1 H, J = 10 4, 12 1 Hz), 1 92 (m, 4 H), 1 76-1 12 (m, 11 H), 0 99 (s, 3 H), 0 87 (s, 3 H), ^{13}C NMR δ 160 1, 149 4, 135 8, 122 0, 119 1, 67 7, 58 6, 47 7, 44 8, 44 2, 43 2, 41 5, 38 2, 35 8, 30 6, 27 6, 24 4, 24 2, 19 2, IR (neat) 3071, 3050, 2932, 2859, 1580, 1555, 1453, 1414, 1368, 1125, 756 cm^{-1}, HRMS calculated for $C_{19}H_{27}NS$ (M), 301 1864, observed 301 1864

(2,2-Dimethyltricyclo[3.3.3.0^{1,5}]undecan-3-yl)methyl 2-Pyridosulfoxide. To a solution of **13** (10 0 mg, 0 033 mmol) in CH_2Cl_2 (1 mL) at 0°C was slowly added *m*-chloroperoxybenzoic acid (12 0 mg, 50% purity, 0 035 mmol) After 1 h, ether workup gave the crude sulfoxide (mixture of isomers), which was used directly for next reaction ^{1}H NMR δ 8 77, 8 62 (2 d's, 1 H, J = 4.7 Hz), 8 02 (m, 2 H), 7 57, 7 36 (2 m, 1 H), 4 40, 3 20 (2 m, 1 H), 2 89, 2.75 (2 m, 1 H), 2 20 (m, 1 H), 2 35-0 94 (15 H), 0.90-0.74 (s's, 6 H).

2,2-Dimethyl-3-methylenetricyclo[3.3.3.0^{1,5}]undecane (14) The solution of crude sulfoxide in C_6D_6 (1 mL) was heated at 140°C in a sealed tube for 17 h The reaction mixture was then diluted with pentane (20 mL), washed with water (2 x 5 mL) and brine (5 mL), and dried over anhydrous $MgSO_4$ The mixture was filtered, and the residue after evaporation purified by column chromatography with pentane to give **14** (4 2 mg, 67% overall yield from **13**): ^{1}H NMR δ 4 63 (q, 1 H, J = 1 4 Hz), 4 60 (q, 1 H, J = 1 5 Hz), 2 23 (t, 2 H, J = 1.4 Hz), 1 53 (m, 6 H), 1 22 (m, 6 H), 1 00 (s, 6 H), ^{13}C NMR δ 162 2, 102 2, 66 1, 57 8, 46 6, 42 2, 36 7, 29 8, 26 4, 24 7

5-(Benzyloxymethyl)-1-(*t*-butyldimethylsilyloxy)cyclooctane, and **5-(Benzyloxymethyl)cyclooctan-1-ol** To the suspension of sodium hydride (0 90 g, 37 5 mmol) in THF (50 mL) at 25°C was slowly added **8b** (6 80 g, 25 0 mmol) After 1 h, benzyl bromide (3 3 mL, 27 5 mmol) was added, and the reaction was stirred for 12 h Ether workup followed by column chromatography with hexane/ethyl acetate (40/1) afforded an inseparable mixture of diastereomers (1 3/1) mixed with a small amout of benzyl bromide ^{1}H NMR δ 7 33 (m, 5 H), 4 50, 4 49 (2 s's, 2 H), 3 88, 3 75 (2 m, 1 H), 3 22, 3 21 (2 d's, 2 H, J = 6 7 Hz), 1 92-1 11 (m, 13 H), 0 88 (s, 9 H), 0.03 (s, 6 H) The mixture was then dissolved in acetonitrile (5 mL), and was treated with aqueous hydrofluoric acid (50%, 5 mL) for 20 min Ether workup followed by purification by column chromatography (3/1 hexane/ethyl acetate) gave an inseparable mixture of diastereomers (1 3/1, 6 18 g, 100%). ^{1}H NMR δ 7 33 (m, 5 H), 4 49 (s, 2 H), 3 94, 3 78 (2 m, 1 H), 3 23 (d, 2 H, J = 6 6 Hz), 1 92-55 (m, 10 H), 1 45, (m, 2 H), 1 21 (m, 2 H), ^{13}C NMR δ 138 7, 128 4, 127 6, 127 5, 76 71, 76 69, 73 0, 72 0, 37 7, 36.4, 36 0, 34 6, 30 7, 30 5, 22.8, 21 3, IR (neat) 3378, 2921, 2851, 1470, 1453, 1362, 1098, 1028, 982, 735, 698 cm^{-1}

5-(Benzyloxymethyl)cyclooctan-1-one (18) To a suspension of PCC (25 3 g, 117 mmol) and Florisil (40 g) in methylene chloride (300 mL) at 0°C was slowly added the above alcohol (24 2 g, 98 mmol) After completion of addition, the reaction was refluxed for 1 5 h Anhydrous ether (700 mL) was then added, and the mixture was filtered through layers of silica gel and Florisil Evaporation of the filtrate afforded **18** (23 8 g, 99%) ^{1}H NMR δ 7.31 (m, 5 H), 4 45 (s, 2 H), 3 20 (d, 2 H, J = 6 2 Hz), 2 57 (m, 2 H), 2 29 (m, 2 H), 2 07 (m, 2 H), 1 76 (m, 2 H), 1 64 (m, 2 H), 1 45 (m, 1 H), 1 12 (m, 2 H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 209 5, 138 6, 129 6, 128 4, 127 5, 76 3, 72 8, 42 3, 36 7, 30 8, 25 1, IR (neat) 2928, 2855, 1700, 1451, 1335, 1273, 1204, 1177, 1098, 739, 714, 698 cm^{-1}, HRMS calculated for $C_{16}H_{22}O_2$ (M) 246 1620, observed 246 1620

5-(Benzyloxymethyl)-2-methylcyclooctan-1-one To a solution of diisopropyl amine (15 4 mL, 110 mmol) in THF (100 mL) at 25°C was added slowly butyllithium (10 0 M in hexane, 10 2 mL, 102 mmol) After 10 min, the solution was cooled to –78°C, and ketone **18** (24 7 g, 101 mmol) in THF (100 mL) was added to the reaction via a cannula After 1 h, methyl iodide (10 mL, 150 mmol) was rapidly added to the reaction by using a syringe with no needle attached to it After 1 h at –78°C, the reaction mixture was gradually warmed to 25°C Ether workup was followed by separation by column chromatography (15/1 hexane/ethyl acetate) to give an inseparable mixture of diastereomers (GC ratio 1/1) (22 0 g, 84% after recovery of **18**), along with **18** (1 75 g) ^{1}H NMR (all peaks overlapped) δ 7 31 (m, 5 H), 4 45 (s, 2 H), 3 18 (d, 2 H, J = 6 4 Hz), 2 67 (m, 1 H), 2 46 (m, 1 H), 2 18 (m, 1 H), 1 94 (m, 2 H), 1 76- 1 43 (m, 5 H), 1 27 (m, 2 H), 1 07 (d, 3 H, J = 6 9 Hz), ^{13}C NMR (mixture of diastereomers) δ 206 8, 138 6, 128 4, 127 5, 76 3, 72 8, 47 9, 37 8, 36 9, 30 9, 30 6, 29 7, 28 4, 16 7, IR (neat) 2926, 2855, 1698, 1455, 1364, 1333, 1271, 1192, 1096, 1028, 739, 698, HRMS calculated for $C_{17}H_{24}O_2$ (M) 260 1776, observed 260 1776

5-(Hydroxymethyl)-2-methylcyclooctan-1-one A flask containing a suspension of the above ketone (3 90 g, 15 0 mmol) and 10% palladium on carbon (0 50 g) in absolute ethanol (20 mL) was evacuated with a water aspirator, flushed with nitrogen four times, then with hydrogen five times Then, a balloon of hydrogen was attached to the top of the reaction vessel, and the reaction was stirred for 12 h Filtration of the reaction mixture through a layer of silica gel, followed by evaporation of solvent gave an inseparable mixture of diastereomers (2 54 g, 100%, GC ratio 1/1) ^{1}H NMR (peaks overlapped) δ 3 35 (m, 2 H), 2 72 (m, 1 H), 2 42 (m, 1 H), 2 17 (m, 1 H), 1 87 (m, 2 H), 1 65 (m, 4 H), 1 27 (m, 4 H), 1 08 (d, 3 H, J = 7 0 Hz), ^{13}C NMR (125 MHz, $CDCl_3$, mixture of diastereomers) δ 206 8, 206 1, 68 8, 48 3, 44 2, 42.6, 39 5, 38 9, 37.5, 33 8, 30 8, 30 6, 30 3, 29 3, 28 8, 27 9, 24 5, 18 7, 15 8, IR (neat) 3430, 2924, 1701, 1692, 1447, 1412, 1377, 1333, 1188, 1051, 839 cm^{-1}, HRMS calculated for $C_{10}H_{18}O_2$ (M) 170 1307, observed 170 1307

4-Methyl-5-oxocyclooctanyl-1-carboxylic Acid To a solution of ruthenium trichloride trihydrate (63 mg, 0 24 mmol) and sodium metaperiodate (7 34 g, 35 4 mmol) in a 1/1/1 5 carbon tetrachloride/acetonitrile/water solution (30

mL) at 0°C was slowly added the above alcohol (2 01 g, 11.8 mmol) After completion of the addition, the cooling bath was removed, and the reaction was stirred at 25°C for 30 min The reaction mixture was poured into a separatory funnel containing water (80 mL) and methylene chloride (40 mL), and the aquous layer was extracted with methylene chloride (4 x 40 mL). The combined organic extracts were dried over magnesium sulfate, and filtered Evaporation of the filtrate gave the crude acid, which was used directly for the following step For the mixture of diastereomers (ratio 1/1) ^{1}H NMR δ 9 78 (s, 1 H), 2.76 (m, 1 H), 2 61 (m, 2 H), 2 48 (m, 1 H), 2 33-1 49 (m, 8 H), 1 07 (d, 3 H, J = 6 8 Hz), IR (neat) 3185, 2940, 1703 (4 close peaks), 1451, 1414, 1277, 1181, 930, 857, 828 cm^{-1}

1-(4-Methylbut-2-enyl) 4-Methyl-5-oxocyclooctanyl-1-carboxylate (19) To a solution of the crude acid and triethylamine (4 9 mL, 35 4 mmol) in methylene chloride (40 mL) at –78°C was added dropwise methanesulfonyl chloride (2 70 g, 23.6 mmol) After 10 min, the reaction was moved to a dry ice-carbon tetrachloride bath (–20°C) for 1 h Isoprenyl alcohol (4 1 ml, 47 2 mmol) and DMAP (0.66 g, 5 9 mmol) were added, and the reaction was gradually warmed to 25°C over 12 h. Ether workup was followed by column chromatography purification (12/1 of hexane/ethyl acetate) to afford **19** (2.29 g, 77%) as an inseparable mixture of diastereomers (ratio 1/1) ^{1}H NMR δ 5 28 (t, 1 H, J = 7 2 Hz), 4.51 (d, 2 H, J = 7 2 Hz), 2 78 (m, 1 H), 2.63 (m, 1 H), 2.45, 2 29 (2 m's, 1 H), 2 24-1 56 (m, 9 H), 1 74 (s, 3 H), 1 68 (s, 3 H), 1 07 (d, 3 H), J = 6 7 Hz), ^{13}C NMR δ 208 1, 207 5, 176 5, 138 9, 118 6, 61.5, 47.8, 44 1, 42.5, 42 3, 41 8, 37 5, 33 2, 30.5, 29 9, 29.0, 28.0, 27 7, 25 8, 23 9, 18 5, 18 1, 15 9, IR (neat) 2934, 2863, 1730, 1701, 1447, 1379, 1331, 1248, 1219, 1169, 970 cm^{-1}

1-(4-Methylbut-2-enyl) 5-Methylene-4-methylcyclooctanyl-1-carboxylate (20a) [26] To a solution of **19** (20 1 g, 80 3 mmol) in methylene chloride (200 mL) was added Lombardo[26] reagent by portions until starting ketone **19** disappeared by TLC. The reaction mixture was poured into ether (800 mL) and 5% sodium bicarbonate (200 mL), and the aqueous layer was extracted with ether (2 x 100 mL) A long time was required for the separation of the two layers The combined organic extracts were washed with water (3 x 100 mL) and brine (100 mL), dried over magnesium sulfate, and filtered The residue after the evaporation of the filtrate was subjected to column chromatography with 50/1 hexane/ethyl acetate to give **20a** (15 1 g, 76%) as an inseparable mixture of diastereomers (ratio 1/1) ^{1}H NMR δ 5.31 (t, 1 H, J = 7 1 Hz), 4.84 (s, 1 H), 4 80, 4 75 (2 s's, 1 H), 4 52 (d, 2 H, J = 7 1 Hz), 2 75, 2 62 (2 m's, 1 H), 2 40-2 11 (m, 3 H), 2.05-1.84 (m, 4 H), 1 79-1 43 (m, 4 H), 1 75 (s, 3 H), 1 69 (s, 3 H), 1 07, 0 98 (2 d's, 3 H, J = 6.9 Hz), ^{13}C NMR (125 MHz, $CDCl_3$) δ 177 8, 177 5, 156 2, 155 4, 138 6, 128 3, 127 6, 118.9, 111 4, 110.3, 61 3, 42 9, 41.8, 41 6, 37.9, 35.8, 35 6, 31 5, 30.7, 30.3, 29 9, 28 6, 27 7, 25 8, 25 1, 23.9, 21.3, 18.1, IR (neat) 2926, 2861, 1730, 1690, 1635, 1447, 1379, 1277, 1227, 1157, 1048 cm^{-1}, HRMS calculated for $C_{16}H_{26}O_2$ (M) 250 1933, observed 250 1933

1-(1,1-Dimethyl-2-propen-1-yl)-5-methylene-4-methylcyclooctanyl-1-carboxylic Acid (21) To a solution of diisopropyl amine (1 22 mL, 8 7 mmol) in THF (20 mL) was added butyllithium (1 53 M in hexane, 5 20 mL, 8 0 mmol) at 25°C After 10 min, the solution was cooled to –78°C, followed by addition of **20a** (1 82 g, 7 3 mmol) in THF (10 mL) After 2 h, trimethylsilyl chloride (1.8 mL, 14 5 mmol) was added, and the reaction was gradually warmed to 25°C The THF was removed by distillation under nitrogen, and the reaction vessel was refilled with toluene (10 mL) The mixture was refuxed for 15 h, and was stirred with aqueous hydrofluoric acid (50%, 5 mL) for 10 min after cooling to 25°C. Ether workup afforded **21** (1 81 g, 100%) as an inseparable mixture of diastereomers (ratio 1/1) ^{1}H NMR δ 5 94 (m, 1 H), 5.97 (m, 2 H), 5 78 (m, 2 H), 2 41-1 23 (m, 11 H), 1 05 (s, 6 H), 1 02, 0 96 (2 d's, 3 H, J = 6 8 Hz), ^{13}C NMR δ 155 5, 152 9, 145 4, 145.3, 114 7, 112 5, 112 1, 55 8, 42 8, 42 7, 40 9, 34 8, 32 0, 30.7, 29 4, 28 2, 27.4, 25 9, 23 9, 23 6, 22 7, 21 3, 20.6, IR (neat) 3067, 2967, 1636, 1229, 1416, 1372, 1235, 1156, 912, 893, 787 cm^{-1}

1-(1,1-Dimethyl-2-propen-1-yl)-5-methenyl-4-methylcyclooctanyl-1-carboxyl Chloride To a solution of **21** (1 81 g, 7 23 mmol) in benzene (10 mL) at 0°C was added oxalyl chloride (3 mL) and DMF (one drop) The reaction was warmed to 25°C and stirred for 6 h Evaporation of solvent and excess oxalyl chloride afforded the crude acid chloride, which was used directly for the following step For the mixture (1/1) of diastereomers ^{1}H NMR δ 5 89 (dd, 1 H, J = 10 4, 17 0 Hz), 5.01 (m, 2 H), 4 78 (m, 2 H), 2 30 (m, 3 H), 2 03-1.12 (m, 8 H), 1 10 (s, 6 H), 1 02, 0 96 (2 d's, 3 H, J = 6.8 Hz), IR (neat) 2973, 1781, 1636, 1452, 1416, 1374, 1156, 1007, 918, 899, 858, 764 cm^{-1}

2-Mercaptopyridin-1-yl 1-(1,1-Dimethyl-2-propen-1-yl)-5-methylene-4-methylcyclooctanyl-1-carboxylate To crude acid chloride in methylene chloride (20 mL) was added anhydrous 2-mercaptopyridine *N*-oxide sodium salt (1 64 g, 10 9 mmol) and DMAP (0.45 g, 3 6 mmol). After 12 h, ether workup in the dark afforded the thiohydroxamate, which was used directly for the following step For the mixture of diastereomers (1/1) ^{1}H NMR δ 7 68 (t, 1 H, J = 7 6 Hz), 7 41 (t, 1 H, J = 7 3 Hz), 7 14 (t, 1 H, J = 7 5 Hz), 6.15 (m, 1 H), 5 06, (m, 2 H), 4 81 (m, 2 H), 2 49-1 52 (m, 11 H), 1 19 (s, 6 H), 1 08, 0 99 (2 d's, 3 H, J = 6 8 Hz), ^{13}C NMR δ 177 2, 177 0, 171 6, 171 3, 155 0, 153 4, 145 2, 145 0, 138 1, 137 9, 137 7, 114 2, 112 8, 112 4, 56 5, 44 0, 43 7, 42 6, 40 8, 34 8, 33 8, 31.3, 30 6, 30 0, 28.8, 27 8, 26 8, 25 8, 24 2, 23 9, 21 2, 20 6, IR (neat) 3063, 2969, 1777, 1734, 1634, 1607, 1522, 1442, 1406, 1371, 1281, 1124, 1013, 918, 741 cm^{-1}

3-(2-Pyridothiomethyl)-2,2,6-trimethyltricyclo[3.3.3.0^{1,5}]undecane (22). A solution of the above thiohydroxamate in benzene (50 mL) was heated at 80°C for 24 h. After evaporation of the solvent, the residue was subjected to column chromatography with 100/1 hexane/ethyl acetate to afford an inseparable mixture of diastereomers **22** (1 42 g, 62 % overall yield from **21a**) ^{1}H NMR (the mixture of isomers) δ 8 41 (d, 1 H, J = 4 7 Hz), 7 46 (dt, 1 H, J = 1 8, 7 9 Hz), 7 15 (d, 1 H, J = 8.2 Hz), 3 34 (m, 1 H), 2 91 (m, 1 H), 2 28-1 04 (m, 14 H), 1.00-0 89 (series of singlets and doublets, 9H), ^{13}C NMR δ 160 1, 149.5, 135 8, 122 1, 122 0, 119 1, 70 0, 69 8, 67.6, 67.3, 62 8, 62 2, 60 9, 51.8, 50.2, 47 9, 47 5, 46 7, 46.0, 45.3, 45.1, 44 9, 44 8, 44 6, 43.9, 42.8, 42.5, 41 5, 40 5, 38 4, 38 3, 38 0, 37.1, 36 61, 36 52, 36.46, 36.33, 36 07, 35 9, 35 1, 34 5, 33 6, 33 2, 31 9, 31 8, 31 4, 30 7, 30 6, 28 0, 27.5, 27 4, 25 0, 24 2, 24 1, 21 1, 19 9, 19 2, 18 9, 15 7, 14.7, 14 1 (56 of 60 expected peaks under 80 ppm observed), IR (neat) 2948, 2869, 1733, 1580, 1555, 1453, 1414, 1387, 1124, 756, 725 cm^{-1}, HRMS calculated for $C_{20}H_{29}NS$ (M) 315 2021, observed 315 2021

(2,2,6-Trimethyltricyclo[3.3.3.0^{1,5}]undecan-3-yl)methyl Pyridin-2-yl Sulfoxide To a solution **22** (1 98 g, 6 28 mmol) in methanol (20 mL) was added sodium metaperiodate (1.61 g, 7 54 mmol) dissolved in a minimum amount of water After 22 h at 25°C, ether workup afforded a crude mixture of sulfoxides, which was used directly for the following step. ^{1}H NMR δ 8.63 (d, 1 H, J = 4.8 Hz), 7 99 (m, 2 H), 7.39 (m, 1 H), 3 18, 2 89, 2 67 (3 m, 2 H), 2 60-0 92 (m, 14 H), 0 90-0 78 (overlapped singlets and doublets, 9 H)

3-Methenyl-2,2,6-trimethyltricyclo[3.3.3.0^{1,5}]undecane (23) The crude sulfoxide mixture in benzene (16 mL) in a sealed tube was heated at 110°C for 16 h, then 130°C for 6 h The reaction mixture was filtered through a layer of silica gel After careful evaporation of the filtrate at ≤ 20°C the residue was subjected to column chromatography with pentane to give two inseparable diastereomers **23** (0 935 g, 73%, GC ratio = 2 7/1) ^{1}H NMR (500 MHz, $CDCl_3$, many signals are overlapped) δ 4 64 (m, 2 H), 2 18 (d, 1 H, J = 19 1 Hz), 2 12 (d, 1 H, J = 19 1 Hz), 1 88 (m, 1 H), 1 73-1.08 (m, 11 H), 1 04, 1 02, 1 01, 0 99 (4 s's, 6 H, peaks too close to be well integrated for ratio caculation), 0 96, 0 92 (2 d's, 3 H, J = 6 7 Hz), ^{13}C NMR δ 162 4, 102 5, 66 0, 60 2, 46 3, 45 2, 45 0, 43 4, 40 6, 39.2, 38 0, 36 9, 36 1, 35 8, 34.4, 34 1, 32 9, 27 6, 25 8, 24 2, 23 9, 22 9, 14 9, 14 2 (24 peaks observed, 30 peaks expected), IR (neat) 3075, 2948, 2869, 1655, 1458, 1377, 1362, 1142, 884 cm^{-1}, HRMS (CIMS) calculated for $C_{14}H_{21}$ (M – Me) 189 1643, observed 189 1643

2,2,6-Trimethyltricyclo[3.3.3.0^{1,5}]undecan-3-one (24) To a solution of ruthenium trichloride trihydrate (33 mg, 0 13 mmol) and sodium metaperiodate (2 63 g, 12 70 mmol) in 1/1/1 5 actonitrile/carbon tetrachloride/water (21 mL) was added **23** (864 mg, 4 23 mmol) After 24 h, ether workup, followed by column chromatography (150 mL of pentane, then 200 mL of 10/1 pentane/ether) afforded **24** (470 2 mg, 71% after recovery of starting **23**), and **23** (215 mg, 2nd fraction, 25% recovery) For the mixture of diastereomers (2 7/1, ^{1}H NMR) ^{1}H NMR δ 2 50 (d, 1 H, J = 17 1 Hz, from minor diastereomer), 2 39 (d, 1 H, J = 17 1 Hz, from major diasteromer), 2.17 (d, 1 H, J = 17 1 Hz, from major diastereomer), 1 91 (d, 1 H, J = 17 1 Hz, from minor diastereomer, 1 99-1 06 (m, 11 H), 1 03-0 93 (series of singlets and doublets, 9 H), ^{13}C NMR δ 223 5, 223 1, 63 0, 62 4, 36 6, 56 4, 51 2, 50 6, 49 4, 46 9, 43 5, 42 6, 41 4, 38 2, 37.5, 35 7, 35 3, 35 2, 34 5, 33 3, 26 6, 24 5, 24 0, 23.3, 22 4, 21 9, 15 3, 15 4 IR (neat) 29 55, 28 70, 1736, 1460, 1416, 1381, 1364, 1262, 1142, 1113 cm^{-1}, HRMS calculated for $C_{14}H_{22}O$ (M) 206 1671, observed 206 1671.

2,2,4,6-Tetramethyltricyclo[3.3.3.0^{1,5}]undecan-3-one (25) (A) Alkylation of **24** To a solution of diisopropylamine in THF (8 mL) was added butyllithium (1 54 M in hexane, 1 6 mL, 2 4 mmol) After 10 min, the solution was cooled to –78°C, and **24** (412 mg, 2 0 mmol) in THF (2 mL) was slowly added to the reaction After 1 h at –78°C, the reaction mixture was placed in a ice-water bath for 30 min, and then it was recooled to –78°C Methyl iodide (0 25 mL, 4.0 mmol) was added quickly, and the reaction was gradually warmed to 25°C Ether workup, followed by column purification with 20/1 hexane/ether, afforded **25** (217 1 mg, 49% isolated yield, or 91% after recovery of **24**) as the first fraction, and then **24** (177 mg) The recovered **24** was remethylated with the same procedure Again, about 35% of **24** was recovered with 50% yield of **25** In both methylations, only three out of the four possible diasteromers of **25** were observed from GC and ^{13}C NMR.

(B) PCC oxidation of **26c**. To a solution of **26c** (51 6 mg, 0 23 mmol) in methylene chloride (2 mL), was added PCC (180 mg, 0 70 mmol) and Florisil (500 mg) After 2 h, anhydrous ether (8 mL) was added, and the mixture was filtered through a layer of silica gel Evaporation of the filtrate afforded **25** (50 7 mg, 100%)

All the spectral information is based on method A ^{1}H NMR δ 2 54-2 37 (m, 1 H), 2 08-1 91 (m, 1 H), 1 90-1 69 (m, 2 H), 1 65-1 40 (m, 4 H), 1 40-1 28 (m, 2 H), 1 28-1 11 (m, 2 H), 1 11-0 88 (series of singlets and doublets, 12 H), ^{13}C NMR δ 224 5, 223 0, 222 9, 62 0, 61 3, 60 3, 59 7, 59.4, 59 0, 49 6, 49 1, 48 9, 48 8, 43 8, 42 3, 39 7, 39 1, 38.2, 36 4, 35 9, 35.6, 34 5, 34 0, 32 9, 32 8, 32.4, 29.2, 28 1, 27 0, 25.8, 25 3, 25 1, 23 2, 21 3, 20 6, 15 4, 15 2, 15 0, 10 6, 9 7, 9 2, Low resolution GC-MS showed all three isomers have the identical molecular weight 220 15, HRMS calculated for $C_{15}H_{24}O$ (M) 220 1827, observed 220 1827

2,2,4,6-Tetramethyltricyclo[3.3.3.0^{1,5}]undecan-3-ol (26) (A) LAH reduction method [7b] To a solution of **25** (300 mg, 1 26 mmol) in ether (50 mL) was added lithium aluminum hydride (1 M in THF, 4 15 mL, 4 15 mmol)

After 10 h, ether workup and column purification with 10/1 hexane/ether afforded two fractions the first fraction contained **26a,b** (118 mg, 40%), the second fraction contained **26c** (165 mg, 54%) The first fraction was repurified by MPLC with 15/1 hexane/ether to give two fractions **26a** (76 0 mg, 26% from **25**), and then **26b** (34 0 mg, 12% from **25**)

(B) L-Selectride method To a solution of **25** (obtained from oxidation of **26c**, 50 7 mg, 0.23 mmol) in THF (5 mL), at 25°C was added L-Selectride (1 M in THF, 2 mL, 2 mmol). After 10 h, ether workup and column chromatography purification with 40/1 hexane/ether afforded two fractions (poor separation resulted from the column) the first fraction at 25°C is rich in **26a** (22 6 mg, 44%), and the second fraction is rich in **26b** (23.0 mg, 45%)

All the spectral data are based on LAH method **26a** (4-methyl and 3-hydroxyl are *cis*, 2 C8 epimers) ^{1}H NMR (500 MHz, $CDCl_3$) δ 3 53 (broad s, 1 H), 2 21 (m, 1 H, minor), 2 05-1 17 (m, 1 H, major), 1 13-0 88 (series of singlets and doublets, 12 H), ^{13}C NMR δ 89 74, 89 67, 67 0, 66 8, 65 3, 45 7, 45.5, 44.5, 39 8, 39 1, 37 8, 37 7, 37 0, 35 8, 35 7, 35 3, 33 7, 32 9, 27.3, 25 7, 25 3, 24 8, 20 9, 20 8, 15 4, 14 7, 11 0, 10 6, IR (neat) 3507, 2950, 2870, 1458, 1379, 1314, 1204, 1129, 1100, 1048, 974 cm^{-1}, HRMS calculated for $C_{15}H_{24}$ (M – H_2O) 204 1878, observed 204.1878

26b (4-methyl and 3-hydroxyl are *cis*, and correct C8 epimer for modhephene) ^{1}H NMR (500 MHz, $CDCl_3$) δ 3 71 (d, 1 H, J = 2 9 Hz), 2.08 (m, 2 H), 1 83 (m, 1 H), 1 71 (m, 2 H), 1 60 (m, 12 H), 1 47 (m, 2 H), 1 32 (m, 1 H), 1 21 (m, 2 H), 0.98 (s, 6 H), 0 97 (d, 3 H, J = 7 2 Hz), 0 93 (d, 2 H, J = 6 2 Hz), ^{13}C NMR δ 88 4, 67 7, 65 7, 49 8, 46 2, 45 5, 44 1, 39 5, 36 6, 35 8, 29 5, 28 0, 27.4, 20 4, 15 8, 11 2, IR (neat) 3507, 2950, 2874, 1462, 1381, 1198, 1153, 1098, 1048, 968 cm^{-1}, HRMS calculated for $C_{15}H_{26}O$ (M) 222.1984, observed 222 1984

26c (4-methyl and 3-hydroxyl are *trans*, with both C8 epimers, three isomers) ^{1}H NMR (500 MHz, $CDCl_3$) δ 3 29, 3 23, 3 16 (3 d's, 1 H, J = 10 8, 10 6, 11 1 Hz), 1 91 (m, 1 H), 1 76 (m, 1 H), 1 69-1 05 (m, 10 H), 1 03-0 83 (series of overlapping singlets and doublets, 12 H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 87 1, 84 3, 83 4, 65 2, 63 5, 61 5, 60 2, 49 4, 48 6, 46 3, 44 9, 43 7, 43 45, 43 38, 40 4, 39 8, 39 7, 38 7, 36 9, 36 7, 38 7, 36 9, 36 7, 35 8, 34 8, 34 7, 34 0, 32 6, 32.5, 31 8, 29 0, 27 3, 27 2, 24 0, 23 8, 23 6, 23 5, 22 7, 20 6, 18 0, 15 8, 15 5, 14 8, 13 9, 12 7, 12 1 IR (neat) 3349, 2952, 2870, 1462, 1454, 1379, 1312, 1123, 1065, 1040 cm^{-1}, HRMS calculated for $C_{15}H_{24}$ (M – H_2O) 204 1878, observed 204 1878

(*Cis*, 4-Methyl, 3-Hydroxy) 2,2,4,6-Tetramethyltricyclo[3.3.3.0^{1,5}]octan-3-yl Toluenesulfonate (27a) To a solution of **26a** (22.6 mg, 0 10 mmol) in THF (1 mL) at 0°C was added LDA (1 5 M solution in THF, 0 67 mL, 1 0 mmol). After 30 min, toluenesulfonyl chloride (191 mg, 1 0 mmol) was added, and the reaction was brought to 25°C over 30 min. Ether workup afforded crude **27a**, which was used for the following step without further purification ^{1}H NMR δ 7 85 (m, 2 H), 7.37 (m, 2 H), 4.61, 4 58 (2 d's, 1 H, J = 4 3 Hz, ratio = 1 3/1), 2 45 (s, 3 H), 2 37-1.21 (m, 12 H), 1 19-0 82 (series of series of singlets and doublets, 12 H)

Modhephene (1a) and *Epi*-modhephene (1b) To a solution of **27a** in anhydrous DMSO (2 mL) at 25°C was added potassium *t*-butoxide (170 mg, 1 5 mmol) After the reaction was heated at 90°C for 2 h, the reaction mixture was diluted with pentane (10 mL), and then poured into water (10 mL) The aqueous layer was extracted again with pentane (10 mL) The combined pentane extracts were washed with water (3 x 10 mL), brine (5 mL), and was then filtered through a layer of silica gel The residue after evaporation of the filtrate was subjected to purification by column chromatography with pentane to afford an inseparable mixture of modhephene (**1a**) and epimodhephene (**1b**) (10 1 mg, 49%, ^{1}H NMR ratio of **1a/1b** = 1/1 34) ^{1}H NMR of the mixture δ 4 95 (d, J = 1 4 Hz, vinyl proton from **1b**), 4 83 (d, J = 1 2 Hz, vinyl proton from **1**), 2 09-1 48 (m, 5 H), 1 61 (s, 3 H), 1 47-1 07 (m, 6 H), 0.984 (d, J = 9 8 Hz, methyl on C8 from **1a**), 0 980 (s, 6 H), 0 88 (d, J = 7 0 Hz, methyl on C8 from **1b**), ^{13}C NMR of **1b**, after modhephene peaks were substrated from the mixture) δ 138 4, 137 5, 75 1, 65 2, 45 8, 42 9, 38 7, 38 4, 35 4, 34 5, 27 8, 27 1, 26 7, 16 8, 15 1, IR (neat of the mixture) 2930, 2863, 1460, 1379, 1358, 845 cm^{-1}, The assignable peaks (protons from vinyl and methyl groups) of ^{1}H NMR are identical to those reported,[6b] and no ^{13}C spectrum has been reported previously

(*Cis*, 4-Methyl, 3-Hydroxy) 2,2,4,6-Tetramethyltricyclo[3.3.3.0^{1,5}]-undecan-3-yl Toluenesulfonate (27b) To a solution of **26b** (19 2 mg, 0 086 mmol) in THF (1 mL) at 0°C was added LDA (1 5 M solution in THF, 0 29 mL, 0 430 mmol) After 30 min, toluenesulfonyl chloride (95 mg, 0 50 mmol) was added, and the reaction was brought to 25°C over 30 min Ether workup afforded crude **26b**, which was used for the following step without further purification ^{1}H NMR δ 7 78 (d, 2 H, J = 8 2 Hz), 7 31 (d, 2 H, J = 8 2 Hz), 4 63 (d, 1 H, J = 5 52 Hz), 2 45 (s, 3 H), 2 17-1 02 (m, 12 H), 1 00-0 80 (series of singlets and doublets, 12 H)

Modhephene (1a) To a solution of **27b** in anhydrous DMSO (2 mL) at 25°C was added potassium *t*-butoxide (77 mg, 0 70 mmol) After the reaction was heated at 85°C for 2 h, the reaction mixture was diluted with pentane (10 mL), and poured into water (10 mL) The aqueous layer was extracted again with pentane (10 mL) The combined pentane extracts were washed with water (3 x 10 mL) and brine (5 mL), and then filtered through a layer of silica gel The residue after evaporation of the filtrate was subjected to purification by column chromatography with pentane to afford modhephene **1a** (10 2 mg, 58%) All data were identical to those of an authentic sample [8]

(*Trans*, 4-Methyl, 3-Hydroxy) 2,2,4,6-Tetramethyltricyclo[3.3.3.$0^{1,5}$]-undecan-3-yl Toluenesulfonate (27c) To a solution of **26c** (5.4 mg, 0 024 mmol) in THF (1 mL) at 0°C was added LDA (1 5 M solution in THF, 0 050 mL, 0.073 mmol) After 30 min, toluenesulfonyl chloride (14 mg, 0 073 mmol) was added, and the reaction was brought to 25°C over 30 min. Ether workup afforded crude **27c**, which was used for the following step without further purification ^{1}H NMR δ 7 78 (m, 2 H), 7 31 (m, 2 H), 4 36, 4 32, 4 27 (3 d's, 1 H, J = 10 4, 11 7, 11 2 Hz), 2 44 (s, 3 H), 1 99-1 07 (m, 12 H), 1 06-0 79 (series of singlets and doublets, 12 H)

Acknowledgement: We thank the National Institutes of Health for Funding of this work

REFERENCES AND NOTES

1 National Institutes of Health Research Career Development Awardee, 1987-92

2 Modhephene Zalkow, L H , Harris, R N , III; Van Derveer, D *J. Chem Soc , Chem. Commun* **1978**, 420 Jakupovic, J., Kuhnke, J , Schuster, A , Metwally, M A , Bohlmann, F *Phytochemistry*, **1986**, *25*, 1133 Bohlmann, F, Wallmeyer, M , Jakupovic, J , Gerke, T , King, R M , Robinson, H *Phytochemistry* **1985**, *24*, 505 Bohlman, F , Jakupovic, J , Ahmed, M , Schaster, A *Phytochemistry* **1983**, *22*, 1623 Bohlmann, F , Zdero, C *Phytochemistry* **1982**, *21*, 2537 Bohlmann, F , Adler, A , Jakupovic, J , King, R M , Robinson, H *Phytochemistry* **1982**, *21*, 1349 Bohlmann, F , Bapuji, M , King, R M , Robinson, H , *Phytochemistry* **1982**, *21*, 939

3 13-Acetoxymodhephene Bohlmann, F , Zdero, C , Bohlmann, R , King, R M , Robinson, H *Phytochemistry* **1980**, *19*, 579

4 Modhephene epoxide Bohlmann, F , Ahmed, M , Borthakur, N , Wallmeyer, M , Jakupovic, J , King, R M ; Robingson, H *Phytochemistry* **1982**, *21*, 167

5 Review· Paquette, L A , Doherty, A M "Polyquinane Chemistry", Springer-Verlag Berlin, 1987

6 Syntheses of modhephene (see also references 7 and 8) (a) Karpf, M , Dreiding, A S *Tetrahedron Lett* **1980**, *21*, 4569 Karpf, M , Dreiding, A S *Helv Chim Acta.* **1981**, *64*, 1123 (b) Smith, A B , III, Jerris, P J *J Am. Chem Soc* **1981**, *103*, 194 Smith, A B , III, Jerris, P. J *J Org Chem* **1982**, *47*, 1845 (c) Schostarez, H , Paquette, L A *J Am Chem Soc* **1981**, *103*, 722 Schostarez, H , Paquette, L A *Tetrahedron* **1981**, *37*, 4431 (d) Oppolzer, W , Marazza, F *Helv Chim Acta* **1981**, *64*, 1575 Oppolzer, W , Battig, K *Helv Chim Acta* **1981**, *64*, 2489 (e) Wender, P A , Dreyer, G B *J Am Chem Soc* **1982**, *104*, 5805 (f) Wrobel, J., Takahashi, K , Honkan, V , Lannoye, G , Cook, J M , Bertz, S H *J Org Chem* **1983**, *48*, 139 (g) Wilkening, D , Mundy, B P *Tetrahedron Lett* **1984**, *25*, 4619 Mundy, B P , Wilkening, D , Lipkowitz, K B *J Org Chem* **1985**, *50*, 5727 (h) Tobe, Y , Yamashita, S , Yamashita, T , Kakiuchi, K , Odaira, Y *J Chem Soc , Chem Commun.* **1984**, 1259 (i) Mash, E A , Math, S K , Flann, C J *Tetrahedron Lett* **1988**, *29*, 2147 Mash, E A , Math, S K , Flann, C J *Tetrahedron* **1989**, *45*, 4945 (j) Fitger, L , Kanschik, A , Majewski, M *Tetrahedron Lett* **1988**, *29*, 5525 (k) Synthesis of 13-acetoxy desmethyl modhephene Yamago, S , Nakamura, E *Tetrahedron* **1989**, *45*, 3081 (l) Kraus, G A , Shi, J *J Org Chem* **1990**, *55*, 5423 Kraus, G A , Shi, J *J Org Chem* **1991**, *56*, 4147 (m) Sha, C K , Jean, T S , Wang, D C *Tetrahedron Lett* **1990**, *31*, 3745

7 (a) Mehta, G , Subrahmanyam, D *J Chem Soc , Chem Commun* **1985**, 768 (b) Mehta, G , Subrahmanyam, D *J Chem Soc , Perkin Trans 1* **1991**, 395

8 Jasperse, C P , Curran, D P *J Am Chem Soc* **1990**, *112*, 5601

9 (a) Curran, D P *Synlett* **1991**, 63-72 (b) Jasperse, C P , Curran, D P , Fevig, T L *Chem Rev* **1991**, *91*, 1237

10 Recent reviews· (a) Barton, D H R *Tetrahedron* **1992**, *48*, 2529 (b) Barton, D H R *Aldrichimica Acta* **1990**, *23*, 1 (c) Crich, D , Quintero, L *Chem. Rev* **1989**, *89*, 1413

11 Reviews (a) Curran, D P *Advances in Free Radical Chemistry*, Tanner, D T , ed , JAI, Greenwich, **1990**, Vol 1, p 127 (b) Curran, D P *Comprehensive Organic Synthesis*, Trost, B M , Fleming, I , eds , Pergamon· Oxford, **1991**, Vol 4, p 779

12 Examples (a) Paquette, L A , Colapret, J A , Andrews, D R *J Org Chem* **1985**, *50*, 201 (b) Dowbenko, R , *Tetrahedron* **1964**, 20, 1843 (c) Friedman, L *J Am Chem Soc* **1964**, *86*, 1885

13 Transannular cyclizations to a carbonyl (a) Beckwith, A L J , Kazlauskas, R , Syner-Lyons, M R *J Org Chem* **1983**, *48*, 4718 (b) to an exo(methylene) group Beckwith, A L J , Bowry, V W , Schiesser, C H *Tetrahedron* **1991**, *47*, 121

14 (a) Winkler, J. D., Sridar, V. *J. Am Chem. Soc* **1986**, *108*, 1708 (b) Winkler, J D , Sridar, V *Tetrahedron Lett* **1988**, *29*, 6219.
15 Porter, N. A , Chang, V H.-T., Magnin, D R , Wright, B T *J Am Chem. Soc* **1988**, *110*, 3554
16 Kulkarni, S U ; Rao, C G , Patil, V D *Heterocycles* **1982**, *18*, 321
17 Oppolzer, W ; Schneider, P *Tetrahedron Lett* **1984**, *25*, 3305
18 Neises, B , Steglich, W *Org Synth.* **1984**, *63*, 183
19 Ireland, R E., Mueller, R H *J Am Chem. Soc.* **1972**, *94*, 5898
20 Wipf, P *Comprehensive Organic Synthesis*, Trost, B. M , Fleming, I , eds, Oxford **1991**, Vol 5, p 827
21 Barton, D H. R , Crich, D , Motherwell, W B *Tetrahedron* **1985**, *41*, 3901
22 Boivin, J , Crépon, E., Zard, S Z *Tetrahedron Lett* **1991**, *32*, 199
23 Trost, B M , Salzmann, T N , Hiroi, K. *J. Am. Chem Soc* **1976**, *98*, 4887
24 Newcomb, M , Kaplan, J. *Tetrahedron Lett.* **1987**, *28*, 1615
25 Though we did not pursue any approaches, asymmetric methylation would ultimately permit a synthesis of optically active modhephene
26 (a) Takai, K , Hotta, Y , Oshima, K.; Nozaki, H *Tetrahedron Lett* **1978**, 2417 (b) Lombardo, L *Org Syn* **1987**, *65*, 81 (c) Takai, K , Fujimura, O , Kataoka, Y , Utimoto, K *Tetrahedron Lett* **1989**, *30*, 211, and references therein
27 Leading references for controlling cyclic stereochemistry in radical reactions (a) Beckwith, A J J , Schiesser, C H *Tetrahedron* **1985**, *41*, 3925. (b) Spellmeyer, D C , Houk, K N *J Org Chem* **1987**, *52*, 959 (c) Rajanbabu, T. V *Acc Chem Res* **1991**, *24*, 139
28 Burgess, E M , Penton, H R , Jr , Taylor, E A *J Org Chem.* **1973**, *38*, 26
29 Salaun, J , Fadel, A *Org Syn* **1985**, *64*, 50
30 Brown, H C , Krishnamurthy, S *J. Am Chem. Soc* **1972**, *94*, 7159
31 ^{1}H NMR spectra were recorded at 300MHz in $CDCl_3$ unless otherwise indicated ^{13}C NMR spectra were recorded at 125MHz in $CDCl_3$ The purity of all key intermediates was assessed by ^{13}C NMR and GC analysis Where ^{13}C NMR data are listed, the compounds were sufficiently pure so that no extraneous resonances were observed All purified samples were analyzed by capillary GC Purities typically ranged from 96% to > 99% pure