Round Trip Radical Reactions from Acyclic Precursors to Tricyclo[5.3.1.$0^{2,6}$]undecanes. A New Cascade Radical Cyclization Approach to (±)-Isogymnomitrene and (±)-Gymnomitrene

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The synthesis and "round trip radical cyclization" of 11-iodo-2,7,11-trimethyldodec-6-en-5-one are described. The round trip cyclization is a sequence of 5-exo, 6-endo, and 5-exo cyclizations in which the last radical cyclization occurs at the same carbon atom as the initial radical generation. The key second (6-endo) cyclization produces two stereoisomers, one of which cyclizes efficiently to isogymnomitrene ketone, while the other cyclizes inefficiently to gymnomitrene ketone. Efforts to influence the kinetic or thermodynamic outcome of the second cyclization were not successful, and the results are contrasted with a related cyclization of Jung and Rayle where thermodynamic control was readily established.

Introduction

Cascade (tandem) radical reactions rank among the most powerful methods to construct polycyclic ring systems in one step from unsaturated acyclic precursors. Several of the strategies that have emerged are shown in Figure 1.[1] "Zipper" strategies start in the middle of the chain and work their way back and forth across toward the ends, while "macrocyclization/transannular cyclization"[2] strategies start at the ends and work toward the middle. A third, less common, class starts at one end of the chain and works its way back to the same end. We call this strategy a "round trip radical reaction". This is the only strategy among the three that readily incorporates the formation of non-vicinal carbon−carbon bonds.[3]

In 1991, Branchaud introduced the concept of a "round trip radical probe" and defined this as a "radical mediated skeletal isomerization that returns the radical to its initial site".[4] Branchaud's processes involved fragmentation and were therefore dissociative (Figure 2), although associative variants that use radical additions and cyclizations can be envisioned. We extend the concept of round trip radical reactions to include a second class of transformation defined as "a radical mediated skeletal isomerization in which an intermediate radical ultimately adds back to the initial site of radical generation". An early example of this type of round trip radical cyclization is shown in Figure 2.[5,6] Cyclization of **1** gives a mixture

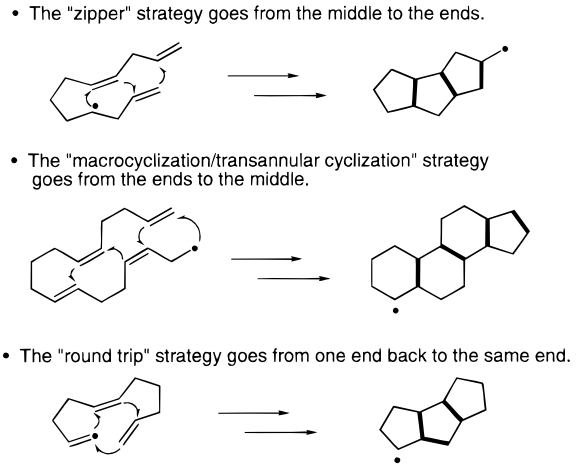

Figure 1. Cascade radical cyclization strategies from linear acyclic precursors (the formed bonds are highlighted in bold.)

of four stereoisomeric tricyclo[6.3.0.0]undecanes **2** along with some bicyclic products **3** in ratios that depend on the concentration of the reductant. The rapid assembly of the tricyclic ring **2** from a readily available precursor shows the power of the strategy, but the lack of stereocontrol in these simple examples is a major shortcoming. Classical "tandem radical cyclization" strategies to triquinanes avoid this problem by using one preformed ring to dictate stereoselection,[7] but at the cost of a more difficult precursor synthesis.

The cyclization of **1** to **2** in Figure 2 involves three sequential 5-exo cyclizations. The stereochemical mixture originates in the second cyclization, where four isomeric products are possible. We became interested in a modified round trip reaction wherein the second of the three cyclizations occurs in a 6-endo mode, as illustrated in Figure 3. This provides the bridged tricyclo[5.3.1.$0^{2,6}$]-

(1) (a) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (b) Curran, D. P. *Synlett* **1991**, 63. (c) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 779. (d) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195. (e) Malacria, M. *Chem. Rev.* **1996**, *96*, 289. (f) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339.

(2) (a) Porter, N. A.; Chang, V. H. T.; Magnin, D. R.; Wright, B. T. *J. Am. Chem. Soc.* **1988**, *110*, 3554. (b) Handa, S.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 843. (c) Hitchcock, S. A.; Houldsworth, S. J.; Pattenden, G.; Pryde, D. C.; Thomson, N. M.; Blake, A. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3181. (d) Jahn, U.; Curran, D. P. *Tetrahedron Lett.* **1995**, *36*, 8921.

(3) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177.

(4) (a) Branchaud, B. P.; Glenn, A. G.; Stiasny, H. C. *J. Org. Chem.* **1991**, *56*, 6656. (b) Branchaud, B. P.; Montague-Smith, M. P.; Kosman, D. J.; McLaren, F. R. *J. Am. Chem. Soc.* **1993**, *115*, 798.

(5) Curran, D. P.; Sun, S. N. *Aust. J. Chem.* **1995**, *48*, 261.

(6) Bogen, S.; Devin, P.; Fensterbank, L.; Journet, M.; Lacote, E.; Malacria, M. In *Recent Research Developments*; Pandalai, S. G., Ed.; Transworld: Trivandrum, India, 1997; Vol. 1, p 385.

(7) Curran, D. P. In *Advances in Free Radical Chemistry*; Tanner, D. D., Ed.; JAI: Greenwich, CT, 1990; Vol. 1, p 121.

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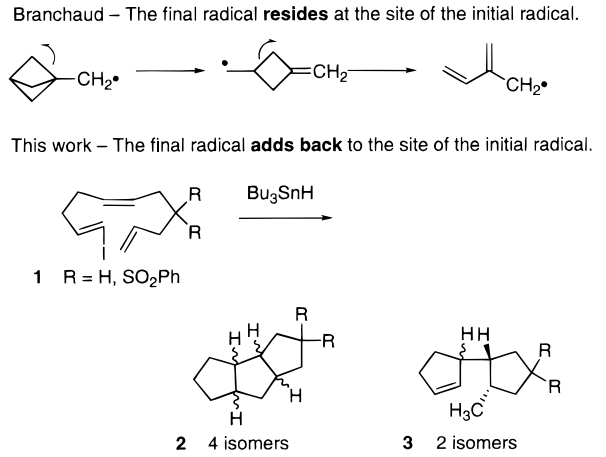


Figure 2. Types of "round trip" radical reactions.

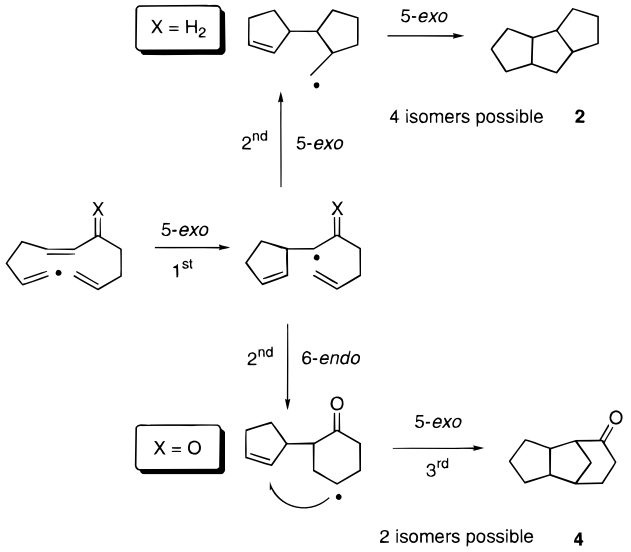
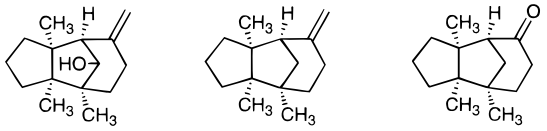


Figure 3. Variants of the round trip strategy.

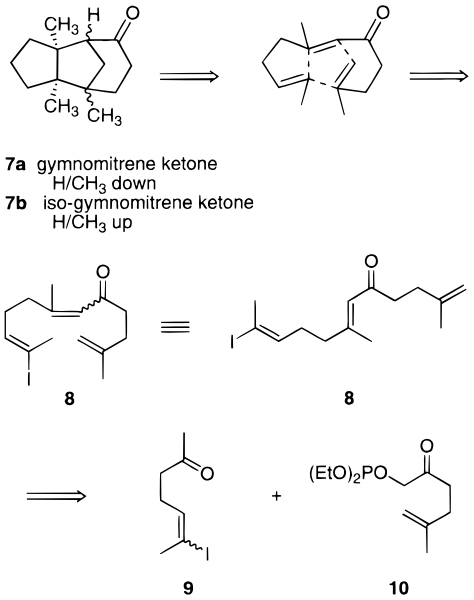
undecane ring system **4**. Literature precedent suggested that the addition of a ketone at the indicated position (X = O) would reorient the second cyclization from 5-exo toward 6-endo.[8,9] In addition, only two stereoisomers are generated in the second 6-endo cyclization, and accordingly, only two isomeric final products **4** are expected.

The ring system and the location of the ketone in **4** immediately suggest the application of this type of round trip strategy to the gymnomitrane class of diquinanes. Gymnomitrene **6a** and its relative gymnomitrol **5** were both isolated from the liverwort *Gymnomitrion obtusum* (Lindb.) pears by Connolly et al. in 1972 (eq 1).[10] The synthetic community quickly responded to these interesting structures with several syntheses of gymnomitrol **5** and two syntheses of gymnomitrene **6a**.[11,12] In most of the previous syntheses, the three rings were built up sequentially, necessitating several synthetic transformations. The immediate precursor of gymnomitrene **6a** in each synthesis was gymnomitrene ketone **7a**, which was later found by Connolly to be a natural product in its own right.[13]



(1)

We envisioned the synthesis of gymnomitrene ketone **7** from precursor **8** as shown in eq 2. This in turn can be dissected into two halves **9** and **10** to be assembled by a standard olefination reaction. Due to the stereoselection in the second cyclization, the sequence could produce gymnomitrene ketone **7a** and isogymnomitrene ketone **7b**, both of which are already known. We report herein the results of this study, which have resulted in a very short synthesis of isogymnomitrene (major product) and gymnomitrene (minor product). The key second cyclization occurs with a relatively low level of stereoselection, and largely unsuccessful efforts to influence this step either thermodynamically or kinetically will be discussed. Our lack of success in establishing thermal equilibrium will be contrasted with some recent related work of Jung and Rayle.[14]



(2)

Results and Discussion

Equation 3 shows the short, convergent route that we developed to the acyclic precursor **8**. Alkylation of the

(8) (a) Clive, D. L. J.; Cheshire, D. R. *J. Chem. Soc., Chem. Commun.* **1987**, 1520. (b) Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1987**, *28*, 2477. (c) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140. (d) Broeker, J. L.; Houk, K. N. *J. Org. Chem.* **1991**, *56*, 3651. (e) Snider, B. B.; Buckman, B. O. *J. Org. Chem.* **1992**, *57*, 4883.

(9) Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. In *Organic Reactions*; Wiley: New York, 1996; Vol. 48, p 301.

(10) (a) Connolly, J. D.; Harding, A. E.; Thornton, I. M. S. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2487. (b) Connolly, J. D.; Harding, A. E.; Thornton, I. M. S. *J. Chem. Soc., Chem. Commun.* **1972**, 1320.

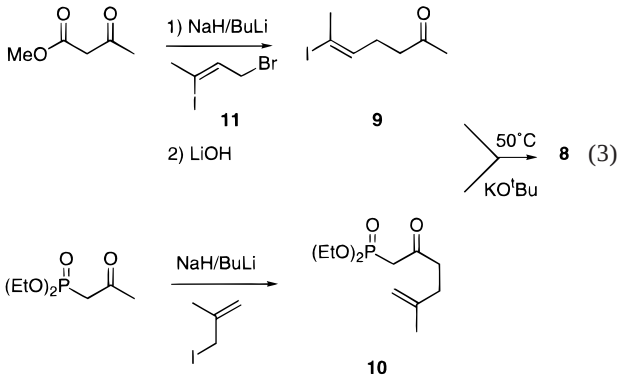
(11) (a) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671. (b) Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry—Synthesis and Reactions*; Verlag: Heidelberg, 1987.

(12) (a) Coates, R. M.; Shah, S. K.; Mason, R. W. *J. Am. Chem. Soc.* **1982**, *104*, 2198. (b) Buchi, G.; Chu, P.-S. *Tetrahedron* **1981**, *37*, 4509. (c) Paquette, L. A.; Han, Y.-K. *J. Am. Chem. Soc.* **1981**, *103*, 1831. (d) Welch, S. C.; Chayabunjonlerd, S.; Prakasa Rao, A. S. C. *J. Org. Chem.* **1980**, *45*, 4086. (e) Kodama, M.; Kurihara, T.; Sasaki, J.; Ito, S. *Can. J. Chem.* **1979**, *57*, 3343. (f) Imanishi, T.; Hirokawa, Y.; Yamashita, M.; Tanaka, T.; Miyashita, K.; Iwata, C. *Chem. Pharm. Bull.* **1993**, *41*, 31. (g) O'Neil, S. V.; Quickley, C. A.; Snider, B. B. *J. Org. Chem.* **1997**, *62*, 1970.

(13) Buchanon, M. S.; Connolly, J. D.; Kadir, A. A.; Rycroft, D. S. *Phytochem.* **1996**, *42*, 1641.

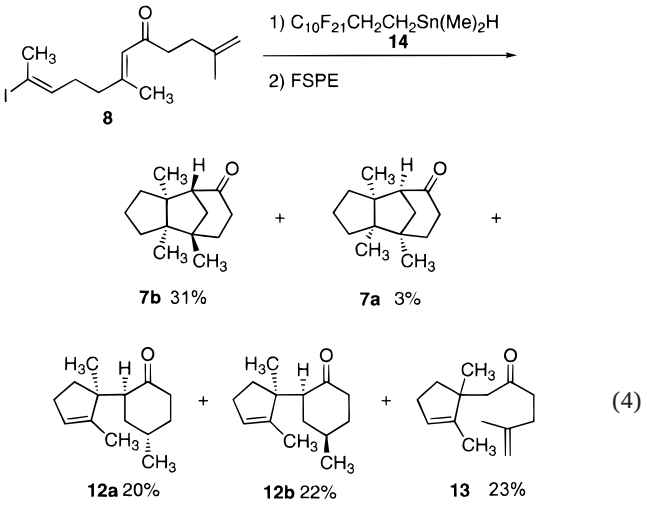
(14) Jung, M. E.; Rayle, H. L. *J. Org. Chem.* **1997**, *62*, 4601.

dianion of methyl acetoacetate with the known bromide **11**,[15] followed by decarboxymethylation with LiOH in aqueous THF and gentle heating, led to ketone **9** in good overall yield. Phosphonate **10** was prepared via the alkylation of the dianion of diethyl 2-oxopropylphosphonate[16] with methallyl iodide. The Horner−Wadsworth−Emmons coupling of the phosphonate **10** and ketone **9** required vigorous reaction conditions and furnished the radical cyclization precursor **8** in 72% yield with a 2.2/1 *E*/*Z* ratio with respect to the enone double bond. The subsequent cyclizations were performed with this mixture of isomers because it was expected that both isomers would yield the same radical intermediate after the initial cyclization of the cascade.



(3)

Initial experiments to cyclize **8** with either tributyltin hydride or triphenyltin hydride at moderate concentrations yielded mainly the product of monocyclization **13** and little of the desired tricyclic products **7** (eq 4). To



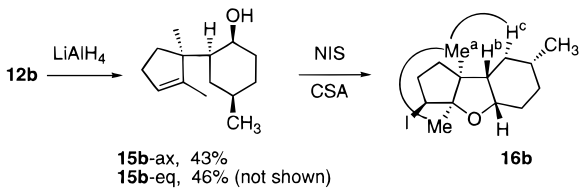
(4)

minimize the premature reduction of the intermediate radicals, we changed the hydride source to tris(trimethylsilyl)silane (TTMSH).[17] Reduction of **8** with TTMSH (0.005 M, AIBN) in refluxing benzene provided the two tricylic ketones **7a** and **7b** in 17% combined yield along with three other products (**12a**, **12b**, and **13**) resulting from incomplete cyclization. Chromatographic purification of these nonpolar (and somewhat volatile) products was very difficult due to contamination by nonpolar silicon-containing byproducts.

The isolation problem was solved by using fluorous tin hydride **14**, as shown in eq 4.[18] Reduction of **8** with **14** was conducted by the standard catalytic procedure ($NaCNBH_3$, *t*-BuOH), and the fluorous tin hydride (and any fluorous byproducts) were completely removed by fluorous solid-phase extraction (FSPE)[19] of the crude reaction mixture. Careful evaporation of the solvent provided a clean mixture of the aforementioned five products in 65% yield in the ratio indicated in eq 4. This mixture was then separated by HPLC for characterization. Monocycle **13** and bicycles **12a** and **12b** were isolated in good purities, while tricycles **7a** and **7b** were extremely difficult to separate even by HPLC. However, peak shaving did provide a pure sample of **7b** along with a sample enriched in **7a**.

With these pure samples in hand, the major tricycle was readily identified as isogymnomitrene ketone **7b** and the minor tricycle as gymnomitrene ketone **7a** by comparison of spectra to published data.[10,12] In addition, the structure of **7b** was confirmed by a crystal structure analysis (see Supporting Information). Both the pure sample of **7b** and the mixture enriched in **7a** were then olefinated to provide a pure sample of isogymnomitrene **6b** (from pure **7b**) and a mixture enriched in gymnomitrene (from the mixture). Our sample of gymnomitrene **6a** was identical to an authentic sample kindly provided by Prof. J. Connolly.

The structure of the monocycle **13** was readily apparent from its spectra, as was the general connectivity of the two bicycles **12a** and **12b**. There are four possible bicylic products of this reaction because in addition to the new stereocenter formed in the second cyclization there is an additional stereocenter formed in the tin hydride reduction. After considerable effort (spectroscopic studies, attempts to obtain crystalline derivatives), we were able to assign the configuration of these molecules with a reasonable level of confidence by the sequence of reactions shown in eq 5. The bicyclic product **12b** was reduced



(5)

with LAH to generate a 1.2:1 mixture of the axial and equatorial alcohols **15b** in 89% total yield. After chromatographic separation, the axial alcohol **15b**-ax was reacted with NIS to perform the iodo-etherification with the cyclopentene double bond forming **16b** quantitatively. NOESY analysis of this tricyclic ether showed cross-peaks between the two bridging methyl groups of the bicyclo[3.3.0]octane system and between methyl group a and one of the protons *c* of the methylene group of the six-membered ring. This, and the lack of a cross-peak between methyl group *a* and proton *b*, leads to the assignment of these groups being anti in the tricyclic ether **16b**. Bicycle **12a** was analyzed analogously (not

(15) Bromide **11** was formed by NBS/PPh_3 bromination of the alcohol synthesized according to: Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193.

(16) Grieco, P. A.; Pogonowski, C. S. *J. Am. Chem. Soc.* **1973**, *95*, 3071.

(17) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.

(18) Curran, D. P.; Hadida, S.; Kim, S.-Y.; Luo, Z. *J. Am. Chem. Soc.* **1999**, *121*, 6607.

(19) (a) Curran, D. P.; Hadida, S.; He, M. *J. Org. Chem.* **1997**, *62*, 6714. (b) Kainz, S.; Luo, Z.; Curran, D. P.; Leitner, W. *Synthesis* **1998**, 1425.

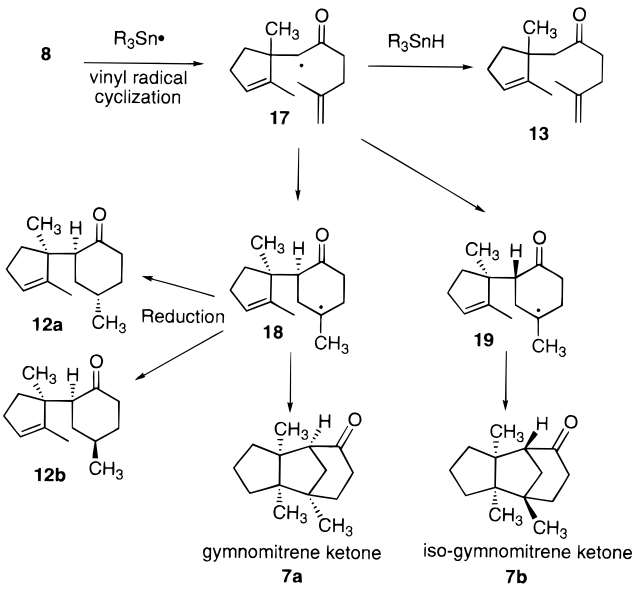


Figure 4. Pathways for product formation.

shown), and similar enhancements were seen for its tricyclic ether derivative (see the Supporting Information for COSY and NOESY spectra of both iodoetherification products). These experiments suggest that **12a** and **12b** have the same relative configuration for the carbons at the intra-ring bond and they differ only in the relative configuration of the methyl-bearing stereocenter.[20]

These results provide a partial, yet significant, picture of the mechanism of this reaction, as shown in Figure 4. Iodine abstraction from **8** provides a vinyl radical (not shown), which cyclizes efficiently to α-keto radical **17**. Even though a crowded bond is formed, this cyclization is efficient because vinyl radicals show good cyclization/reduction profiles[21] and because the ketone activates the first radical acceptor. As evidenced by the presence of significant amounts of monocyclized product **13**, the second cyclization (of **17**) is somewhat of a struggle. This is not surprising. It is known that α-keto radicals tend to give 6-endo products not because the 6-endo cyclization is accelerated by the substituent but because the 5-exo cyclization is decelerated.[8] Snider observed that a cyclization of a complex α-keto-radical was very poor at 80 °C, although the radical was coaxed into cyclizing at 150 °C in reasonable yield.[8e]

Despite some reluctance, the majority of radical **17** cyclizes under dilute tin hydride conditions to produce bicyclic radicals **18** and **19**. These are stereoisomers that arise from 6-endo cyclization. While we cannot completely rule out the formation of 5-exo cyclization products at this stage, the careful analysis of the mixture suggests that such products cannot be formed in more than trace amounts. Accordingly, the ketone had the intended effect of inducing 6-endo cyclization in stage 2 of the round trip sequence. The total yield of final products suggests that there is a slight preference for cyclization to radical **18** over **19** (roughly 3/2). The behavior of these two radicals is very different. No reduction products derived from radical **19** were isolated, so its cyclization to isogymnomitrene ketone **7b** must be considerably faster than the cyclization of **17**. In contrast, most of radical **18** is reduced to give the two stereoisomers **12a** and **12b**, thereby showing that its cyclization is slower than that of **17**. It is nonetheless fast enough to produce a small amount of gymnomitrene ketone **7a**.

Table 1. Reduction of 8: Effects of Temperature and Additives

entry	additive	init	*T* (°C)	**7a**,**b**	**12a**	**12b**	**13**
1	none	AIBN	80	41	30	22	7
2	none	Et_3B/O_2	rt	–	22	47	30
3	none	AIBN	105	48	40	12	
4	none	AIBN	130	40	41	15	4
5	$MgBr_2$	AIBN	80	26	41	29	4
6	$Zn(OTf)_2$	AIBN	80	29	39	32	
7	$Mg(ClO_4)_2$	AIBN	80	27	54	19	
8	$Yb(OTf)_2$	AIBN	80	20	50	25	5
9	Me_2AlCl	AIBN	80		dec		
10	$Sc(OTf)_3$	AIBN	80		dec		

That either one of these last two cyclizations is successful is remarkable because a bridged ring is formed and two adjacent quaternary carbons are generated in the process. That the cyclization of **19** leading to the iso series is more efficient than that leading to the natural series can be anticipated from prior results. Older MM2 calculations[22a] suggested that the isogymnomitrene ketone carbon skeleton is 6 kcal/mol more stable than the isomeric skeleton of gymnomitrene ketone. We have repeated these calculations with a modern software package[22b] on the complete molecules (isogymnomitrene ketone and gymnomitrene ketone) and found a 3.5 kcal/mol difference in favor of the iso series. Furthermore, in the original Coates synthesis of gymnomitrol,[12a] an intramolecular aldol reaction of a bicyclo[3.3.0]octanone to close the six-membered ring was successful in the iso series but not in the natural series. Taken together, these results suggest that there is an energy penalty that must be paid in cyclization transition states leading to the more strained natural isomer relative to the less strained nonnatural isomer.

These results show that the first cyclization occurs with good efficiency, while the second cyclization is reasonably efficient but occurs with very low 1,2-asymmetric induction. In the third cyclization, the major stereoisomer **18** is primed to form gymnomitrene ketone **7a**, but its cyclization is slow and reduction predominates. In contrast, the minor isomer **19** cyclizes efficiently to the iso skeleton **7b**. We conducted a series of experiments with TTMSH to learn if we could influence the outcome of these processes. Some of these experiments, which involved changing of concentration and temperature as well as addition of Lewis acids, are summarized in Table 1. These reactions were followed by GC, and Table 1 presents the raw peak ratios of the products normalized to 100%. Tricycles **7a** and **7b** were not separated under the analysis conditions, and Table 1 reports a combined amount for these. However, ^1H NMR spectra of each of the mixtures were recorded, and in every case **7b** was by far the major product (ratios **7b**/**7a**, about 10/1). Unless otherwise indicated, the reactions were fairly

(20) (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; VCH: Weinheim, 1996; p 283. (b) Damm, W.; Giese, B.; Hartung, J.; Hasskerl, T.; Houk, K. N.; Zipse, H. *J. Am. Chem. Soc.* **1992**, *114*, 4067.

(21) (a) Stork, G.; Mook, R. J. *Tetrahedron Lett.* **1986**, *27*, 4529. (b) Beckwith, A. L. J.; O'Shea, D. M. *Tetrahedron Lett.* **1986**, *27*, 4525.

(22) (a) Osawa, E.; Aigami, K.; Takaishi, N.; Inamoto, Y.; Fujikura, Y.; Majerski, Z.; von R. Schleyer, P.; Engler, E. M.; Farcasiu, M. *J. Am. Chem. Soc.* **1977**, *99*, 5361. (b) Calculations performed using Macromodel v5.5 (Monte Carlo, PM3 Basis Set) and Spartan v5.03 (6-31G* Basis Set).

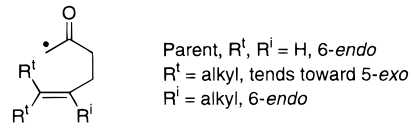


Figure 5. Trends in α-keto radical cyclizations.

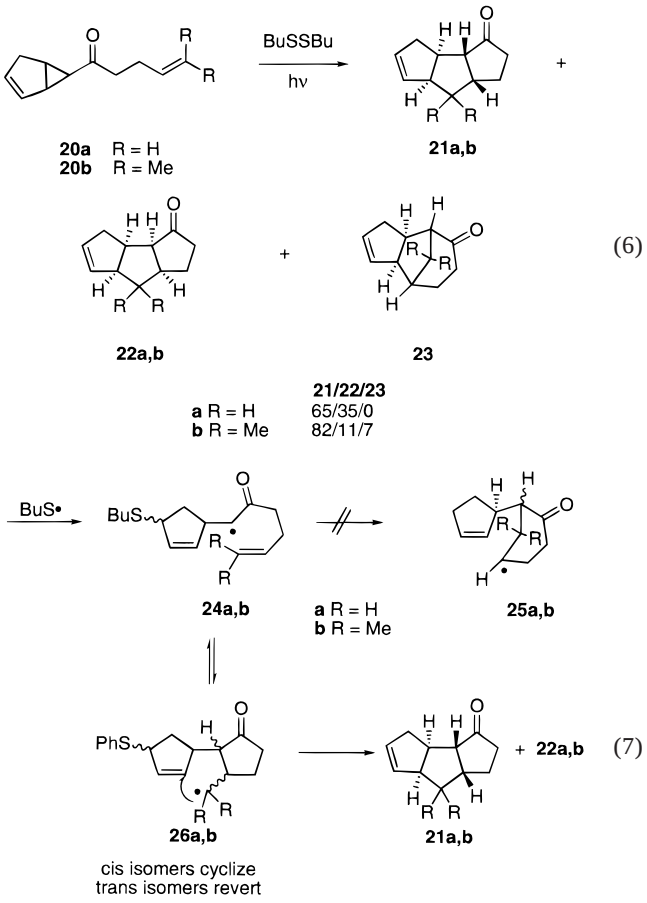
clean, and major new products were not evident. The effects of these changes were not very significant, so we ultimately decided not to further quantitate any of these results.

The standard experiment, shown in entry 1, provides a 41/30/22/7 ratio of tricycles **7a**, **7b**/bicycles **12a**/**12b**/ and monocycle **13**. The reduced amount of **13** relative to the fluorous tin hydride cyclization (eq 4) reflects the lower reducing ability of TTMSH. Conducting the reaction at room temperature resulted in a significant increase in the monocyclic product **13** (entry 2). Heating the reaction to 130 °C had relatively little effect in the product ratios (entries 3 and 4). An experiment was also conducted at 150 °C (data not shown), and while GC analysis suggested an increased amount of tricycles relative to bicycles, the reaction was not clean as evidenced by both GC and NMR analysis. Addition of several Lewis acids[23] may have helped to reduce the amount of monocyclic product **13**, but otherwise had only minor effect on product ratios (entries 5−8). Two Lewis acids (Me_2AlCl and $Sc(OTf)_3$) resulted in extensive decomposition (entries 9 and 10).

Our results are consistent with a number of other related cyclizations in the literature,[8] but contrast quite strongly with the observations of Jung and Rayle.[14] In general, α-keto radicals are thought to undergo relatively slow, irreversible cyclizations (Figure 5).[8] The parent undergoes exclusively 6-endo cyclization while substitution at the terminus (R^t) can promote competing 5-exo cyclization.[8c] Substitution at the internal alkene carbon (R^i), as present in round trip radical precursors **8**, is expected to further favor 6-endo cyclization. In this light, a reasonable interpretation of our results is that cyclization of **17** provides the 6-endo products under kinetic control, and reversibility is not important up to at least 130 °C.

In 1997, Jung and Rayle reported the cyclizations in eq 6.[14] Irradiation of **20a** with dibutyl disulfide at room temperature provided tricyclo[6.3.0.0]undecanes **21a** and **22a** in a slow reaction (1−6 weeks) but in good yield. The proposed sequence of events leading to **21a** is shown in eq 7. After addition of the thio radical and cyclopropane opening to **24**, the sequence intersects that shown in this paper in Figure 4 (compare **24** to **17**), although with different substituents. Similar treatment of the precursor **20b** bearing two methyl groups at the alkene terminus provided three products **21b**−**23b** in the indicated ratio (82/11/7).

These products are not consistent with kinetic expectations. On the basis of simple models, radical **24a** (eq 7) should undergo cyclization in a 6-endo mode to give **25**. And while radical **24b** might reasonably be expected to undergo cyclization in a 5-exo mode, it would not necessarily be expected to give only the two cis isomers (**21b**, **22b**) and no trans isomer. This led Jung and Rayle to



(6)

(7)

propose that the conversion of **24** to **26** was reversible,[14] and therefore, it is the subsequent reactions of the cyclized radicals that determine the products. Our prior work[5] shows (Figure 2) that radical cyclization to give cis-syn-cis and cis-anti-cis triquinanes are reasonably fast, while those to give trans-syn-cis and trans-anti-cis are slow, and this is nicely consistent with Jung and Rayle's work, assuming that the cyclizations of trans isomers of **26** are reversible. Nonetheless, the very divergent behavior of radicals **24a,b** and **17** is surprising. Radical **17** undergoes exclusive 6-endo cyclization, and it appears that this cyclization is irreversible. Radical **24** undergoes exclusive 5-exo cyclization, and this is reversible. Radical **24a** apparently never suffers 6-endo cyclization, because if it did, at least one of the possible isomers should cyclize very rapidly to the bridged tricyclo-[5.3.1.$0^{2,6}$]undecane, as shown by the rapid cyclization of **19** in the isogymnomitrene series.

In summary, the round trip radical cyclization approach provides highly substituted tricyclo[5.3.1.$0^{2,6}$]-undecanes **7a,b** in one step from the readily synthesized acyclic precursor **8**. However, the approach is limited by stereoselection in the second cyclization. Two isomers are generated, but only one of these cyclizes efficiently to the final tricycle. This results in a short and reasonably efficient route to iso-gymnomitrene. The synthesis of gynomitrene itself is also very short (5 steps), but not very efficient because it is the minor product of the round trip radical reaction. At this point, we believe that the key 6-endo cyclization is under kinetic control, and we have not yet been able to alter the kinetic stereoselection or to induce reversibility. The contrast between our irreversible system and the related, but reversible, system of Jung and Rayle[14] suggests that more study is

(23) (a) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2562. (b) Mero, C. L.; Porter, N. A. *J. Am. Chem. Soc.* **1999**, *121*, 5155.

needed on what factors control the reversibility in these types of systems.

Experimental Procedures

6-Iodohept-5-en-2-one (9). NaH (95%, 0.62 g, 24.5 mmol) was added to dry THF (250 mL), and the mixture was cooled to 0 °C. Methyl acetoacetate (1.99 mL. 18.3 mmol) was added slowly with significant evolution of H_2 gas. After 30 min, BuLi (1.6 M, 11.4 mL, 18.3 mmol) was added slowly. The dark orange solution was cooled to −78 °C, and bromide **11** (4.56 g, 17.5 mmol) was added rapidly. The solution was warmed slowly to room temperature and allowed to stir for an additional 3 h. The reaction mixture was quenched by dropwise addition of H_2O and partitioned between Et_2O and H_2O. The aqueous layer was extracted into Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give a brown oil. The crude oil was purified by flash chromatography on silica gel eluting with hexanes/ethyl acetate (5:1) to give 2.30 g of the desired β-keto ester (45%): ^{1}H NMR (300 MHz, $CDCl_3$) 5.46 (tq, J = 1.2, 6.6 Hz, 1H), 3.74 (s, 3H), 3.47 (s, 2H), 2.65 (t, J = 7.2 Hz, 2H), 2.48 (s, 3H), 2.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 201.7, 167.5, 133.1, 102.6, 52.4, 48.9, 41.4, 33.5, 30.4; IR (cm^{-1}) 1754, 1722, 1645. The β-keto ester (2.21 g, 7.5 mmol) was dissolved in a 1:1 THF/H_2O mixture (40 mL). LiOH (0.62 g, 15.0 mmol) was added, and the solution was heated to 50 °C. After 24 h, the solution was cooled to room temperature and poured into H_2O (50 mL). The aqueous solution was extracted with Et_2O. The combined organic extracts were washed with H_2O and brine, dried over $MgSO_4$, and concentrated. The resulting yellow oil was purified by flash chromatography on silica gel eluting with hexanes/ethyl acetate (6:1) to yield 80% of the ketone **9** as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) 5.45 (tq, J = 1.5, 6.7 Hz, 1H), 2.53 (t, J = 7.3 Hz, 2H), 2.47 (s, 3H), 2.34 (q, J = 7.1 Hz, 2H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 215.6, 133.6, 102.3, 42.1, 33.6, 30.9, 29.9; IR (cm^{-1}) 3002, 2954, 1715, 1651; HRMS calcd for $C_7H_{11}IO$ 237.9855, found 237.9855.

(5-Methyl-2-oxohex-5-enyl)phosphonic Acid Diethyl Ester (10). Diethyl 2-oxopropylphosphonate (8.5 mL, 44 mmol) was added to dry THF (300 mL) and cooled to 0 °C. BuLi (1.6 M, 58.3 mL, 93 mmol) was added slowly. The dark orange solution was cooled to −78 °C, and methallyl iodide (8.89 g, 48 mmol) was added rapidly. The solution was warmed slowly to room temperature and allowed to stir for an additional 3 h. The reaction mixture was quenched by dropwise addition of H_2O and partitioned between Et_2O and H_2O. The aqueous layer was extracted into Et_2O. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated to give a yellow oil. The crude oil was purified by flash chromatography on silica gel eluting with hexanes/ethyl acetate (1:2) to give 7.92 g of the phosphonate **10** as a clear oil (73%): ^{1}H NMR (300 MHz, $CDCl_3$) 4.72 (d, J = 18.7 Hz, 2H), 4.17 (m, 4H), 3.13 (d, J = 22.7 Hz, 2H), 2.78 (t, J = 7.3 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 1.74 (s, 3H), 1.34 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 201.4, 144.0, 110.3, 62.5 (2C), 43.2, 42.1, 31.0, 22.6, 16.3 (2C); IR (cm^{-1}) 3076, 2977, 1717, 1648; HRMS calcd for $C_{11}H_{21}O_4P$ 248.1177, found 248.1177.

11-Iodo-2,7-dimethyl-dodeca-1,6,10-trien-5-one (8). KO^{t}Bu (1.68 g, 15.0 mmol) was added to dry toluene (200 mL), and the suspension was cooled to 0 °C. Phosphonate **10** (3.72 g, 15.0 mmol) was added dropwise, and the bright yellow solution was stirred for 1 h. Ketone **9** (1.42 g, 6.0 mmol) was added dropwise, and the solution was heated to 110 °C. After 23 h, the reaction mixture was cooled to room temperature, diluted with Et_2O, and poured into H_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The organic layers were combined and washed with brine, dried over $MgSO_4$, and concentrated by rotary evaporation to give a dark brown oil. The crude oil was purified by flash chromatography on silica gel eluting with hexanes/ethyl acetate (12:1) to give 1.43 g of a 2.2:1 mixture of the *E* and *Z* enone **8** (72%) as a light yellow oil along with 0.23 g of unreacted ketone **9** (16%):

8*E*: ^{1}H NMR (300 MHz, $CDCl_3$) 6.08 (s, 1H), 5.39 (tq, J = 1.5, 6.6 Hz, 1H), 4.69 (d, J = 17.9 Hz, 2H), 2.59 (t, J = 7.2 Hz, 2H), 2.49 (s, 3H), 2.37 (m, 6H), 2.15 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 200.5, 157.8, 145.2, 133.6, 123.4, 109.9, 104.4, 42.5, 39.4, 34.5, 33.5, 31.8, 22.7, 19.4; IR (cm^{-1}) 3077, 1713, 1689, 1648, 1619; HRMS calcd for $C_{14}H_{21}IO$ 332.0637, found 332.0628.

8*Z*: ^{1}H NMR (300 MHz, $CDCl_3$) 6.10 (s, 1H), 5.47 (tq, J = 1.5, 6.6 Hz, 1H), 4.69 (d, J = 19.7 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 2.56 (t, J = 7.1 Hz, 2H), 2.48 (s, 3H), 2.36 (m, 4H), 1.93 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 196.5, 157.8, 143.8, 134.6, 124.2, 109.9, 101.4, 42.4, 35.1, 33.4, 32.0, 31.7, 25.5, 22.7; IR (cm^{-1}) 3077, 1713, 1689, 1648, 1619; HRMS calcd for $C_{14}H_{21}IO$ 332.0637, found 332.0628.

Preparative Cyclization of 8 To Form 3a,8,8a-Trimethyloctahydro-4,8-methanoazulen-5-one (7b), 3a,8,8a-Trimethyloctahydro-4,8-methano-azulen-5-one (7a), 2-(1,2-Dimethylcyclopenta-2-enyl)-4-methylcyclohexanone (12a), 2-(1,2-Dimethylcyclopenta-2-enyl)-4-methylcyclohexanone (12b), and 1-(1,2-Dimethylcyclopenta-2-enyl)-5-methyl-hex-5-en-2-one (13). Enone **8** (0.07 g, 0.21 mmol) was dissolved in *tert*-butyl alcohol (40 mL). Sodium cyanoborohydride (0.020 g, 0.32 mmol) and AIBN (0.007 g, 0.042 mmol) were added, followed by tin hydride **14** (0.015 g, 0.021 mmol). The reaction mixture was heated to 80 °C and allowed to stir for 12 h. After being cooled to room temperature, the mixture was poured into H_2O and diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated. This residue was filtered through a small plug of fluorous reversed-phase silica gel rinsing with CH_3CN. The CH_3CN was removed by rotary evaporation, and the residue was purified by HPLC eluting with hexanes/ethyl acetate (97:3) to yield each of the title compounds.

3a,8,8a-Trimethyloctahydro-4,8-methanoazulen-5-one (7a): 0.001 g, 2%, white paste; ^{1}H NMR (500 MHz, $CDCl_3$) 2.38 (m, 2H), 2.24 (d, J = 4.4 Hz, 1H), 2.10 (dt, J = 3.4, 12.5 Hz, 1H), 1.94 (m, 1H), 1.83 (m, 1H), 1.73 (m, 2H), 1.64 (m, 2H), 1.55 (m, 1H), 1.35 (m, 1H), 1.22 (m, 1H), 1.09 (s, 3H), 1.01 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 215.4, 62.4, 56.0, 54.4, 43.7, 41.9, 37.9, 37.1, 36.1, 33.7, 27.4, 26.6, 24.9, 23.6; IR (cm^{-1}) 1705; MS (*m*/*e*) 206 (10), 191 (10), 188 (20), 163 (10), 149 (5), 137 (20), 121 (20), 109 (50), 95 (100), 81 (50), 67 (40), 55 (50).

3a,8,8a-Trimethyloctahydro-4,8-methanoazulen-5-one (7b): 0.009 g, 20%, white paste; ^{1}H NMR (500 MHz, $CDCl_3$) 2.31 (dd, J = 9.0, 18.6 Hz, 1H), 2.26 (d, J = 5.2 Hz, 1H), 2.20 (dd, J = 9.0, 18.5 Hz, 1H), 2.05 (dt, J = 4.1, 12.7 Hz, 1H), 1.84 (qd, J = 3.7, 9.5 Hz, 1H), 1.67 (m, 1H), 1.59 (m, 2H), 1.51 (m, 2H), 1.45 (m, 1H), 1.35 (m, 1H), 1.26 (m, 1H), 0.96 (s, 3H), 0.92 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 214.1, 61.8, 52.7, 51.5, 45.3, 44.0, 42.1, 38.2, 36.1, 34.7, 23.5, 21.6, 20.6, 18.4; IR (cm^{-1}) 1705; HRMS calcd for $C_{14}H_{22}O$ 206.1671, found 206.1664.

2-(1,2-Dimethylcyclopenta-2-enyl)-4-methylcyclohexanone (12a): 0.005 g, 13%, clear oil; ^{1}H NMR (500 MHz, $CDCl_3$) 5.30 (s, 1H), 2.59 (dd, J = 5.5, 11.9 Hz, 1H), 2.48 (dt, J = 5.9, 12.7 Hz, 1H), 2.25 (m, 1H), 2.21 (dt, J = 4.9, 13.5 Hz, 1H), 2.08 (m, 2H), 1.98 (m, 1H), 1.88 (m, 2H), 1.77 (m, 1H), 1.67 (dt, J = 4.9, 12.1 Hz, 1H), 1.55 (m, 1H), 1.53 (s, 3H), 1.15 (d, J = 7.0 Hz, 3H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 213.5, 144.4, 125.2, 51.1, 50.5, 39.9, 35.7, 33.8, 32.9, 30.2, 27.4, 25.1, 18.3, 12.4; IR (cm^{-1}) 3041, 1707, 1658; MS (*m*/*e*) 206 (5), 107 (10), 95 (100), 94 (65), 79 (25), 67 (27), 55 (30).

2,2-(1,2-Dimethylcyclopenta-2-enyl)-4-methylcyclohexanone (12b): 0.006 g, 14%, clear oil; ^{1}H NMR (500 MHz, $CDCl_3$) 5.29 (s, 1H), 2.47 (dd, J = 4.9, 13.3 Hz, 1H), 2.38 (dt, J = 5.4, 13.8 Hz, 1H), 2.29 (m, 2H), 2.25 (m, 1H), 2.10 (m, 1H), 2.00 (m, 1H), 1.91 (m, 2H), 1.73 (m, 1H), 1.56 (s, 3H), 1.38 (dq, J = 3.8, 17.1 Hz, 1H), 1.16 (q, J = 13.0 Hz, 1H), 1.12 (s, 3H), 0.97 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 212.9, 144.4, 125.1, 55.6, 50.4, 43.2, 38.5, 36.5, 32.8, 32.6, 30.2, 24.8, 21.4, 12.5; IR (cm^{-1}) 3041, 1707, 1658; MS (*m*/*e*) 206 (5), 191 (3), 107 (10), 95 (100), 94 (40), 79 (20), 67 (20), 55 (25).

1-(1,2-Dimethylcyclopenta-2-enyl)-5-methylhex-5-en-2-one (13): 0.006 g, 14%, clear oil; ^{1}H NMR (300 MHz, $CDCl_3$) 5.30 (s, 1H), 4.68 (d, J = 17.3 Hz, 2H), 2.54 (td, J = 2.7, 8.5 Hz, 2H), 2.48 (q, J = 17.0 Hz, 2H), 2.25 (t, J = 7.8 Hz, 2H), 2.18 (m, 2H), 1.99 (m, 1H), 1.75 (m, 1H), 1.73 (s, 3H), 1.64 (q, J = 2.0 Hz, 3H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 210.5, 145.3, 144.8, 124.6, 110.1, 50.8, 47.3, 42.7, 37.2, 31.5, 29.4, 25.0, 22.8, 12.6; IR (cm^{-1}) 3076, 1709, 1649; MS (*m*/*e*) 206 (5), 95 (60), 94 (100).

2-(1,2-Dimethylcyclopenta-2-enyl)-4-methylcyclohexanone (15a). Bicycle **12a** (0.030 g, 0.14 mmol) was dissolved in dry THF and cooled to 0 °C. LAH (1 M in Et_2O, 0.14 mmol) was added, and the mixture was stirred for an additional 30 min. Dropwise addition of H_2O (0.008 mL) was followed by 10% NaOH (0.008 mL) and NH_4Cl (satd) (0.008 mL). The gray suspension was filtered by rinsing with Et_2O and concentrated by rotary evaporation to give a clear oil. The crude oil was purified by gravity chromatography on silica gel eluting with hexanes/ethyl acetate (9:1) to yield 0.015 g of the desired axial alcohol **15a**-ax (50%) and 0.005 g of the equatorial alcohol **15a**-eq (17%). Axial: ^{1}H NMR (300 MHz, $CDCl_3$) 5.32 (s, 1H), 4.20 (m, 1H), 2.18 (m, 3H), 1.84 (dq, J = 3.3, 14.5 Hz, 1H), 1.58 (s, 3H), 1.53−1.17 (m, 9H), 1.07 (s, 3H), 0.90 (d, J = 4.3 Hz, 3H); IR (cm^{-1}) 3417, 1649; MS (*m*/*e*) 190 (5), (M^+ − 18), 131 (10), 119 (5), 95 (100), 79 (10), 69 (20), 55 (15).

2-(1,2-Dimethylcyclopenta-2-enyl)-4-methylcyclohexanol (15b). Bicycle **12b** (0.043 g, 0.21 mmol) was dissolved in dry THF and cooled to 0 °C. LAH (1 M in Et_2O, 0.21 mL, 0.21 mmol) was added, and the mixture was stirred for an additional 30 min. Dropwise addition of H_2O (0.008 mL) was followed by 10% NaOH (0.008 mL) and NH_4Cl (satd) (0.008 mL). The gray suspension was filtered rinsing with Et_2O and concentrated by rotary evaporation to give a clear oil. The crude oil was purified by gravity chromatography on silica gel eluting with hexanes/ethyl acetate (12:1) to yield 0.019 g of the desired axial alcohol **15b**-ax (43%) and 0.020 g of the equatorial alcohol **15b**-eq (46%). Axial: ^{1}H NMR (300 MHz, $CDCl_3$) 5.30 (s, 1H), 4.19 (m, 1H), 2.35 (m, 1H), 2.23 (m, 1H), 2.19 (m, 1H), 1.95−1.78 (m, 5H), 1.55 (m, 2H), 1.51 (s, 3H), 1.43 (m, 2H), 1.11 (m, 1H), 1.05 (s, 3H), 0.89 (d, J = 4.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 146.5, 124.5, 67.6, 51.3, 47.2, 39.9, 34.1, 30.2, 29.1, 27.3, 25.1, 24.5, 17.2, 12.7; IR (cm^{-1}) 3335, 1654; MS (*m*/*e*) 208 (2), 190 (5), 108 (5), 95 (100), 79 (10), 67 (15), 55 (15).

1-Iodo-3a,5,8a-trimethyldecahydro-8-oxacyclopenta[*a*]indene (16a). Alcohol **15a**-ax (0.005 g, 0.024 mmol) was dissolved in dry CH_2Cl_2 (1.5 mL). *N*-Iodosuccinimide (0.016 g, 0.072 mmol) was added, followed by camphorsulfonic acid (0.006 g, 0.024 mmol). After 2 h, the reaction mixture was diluted with Et_2O and poured into H_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The organic layers were combined, washed with $NaHCO_3$ (satd) and brine, dried over $MgSO_4$, and concentrated by rotary evaporation to give a red oil. Purification of the crude oil by flash chromatography on silica gel eluting with hexanes/ethyl acetate (20:1) gave 0.002 g of the desired iodide **16a** as a clear oil (25%): ^{1}H NMR (500 MHz, $CDCl_3$) 4.40 (t, J = 3.9 Hz, 1H), 4.03 (q, J = 2.1 Hz, 1H), 2.26 (m, 1H), 1.99 (m, 3H), 1.83 (m, 1H), 1.77 (m, 1H), 1.65 (m, 2H), 1.52 (s, 3H), 1.46 (m, 1H), 1.35 (m, 1H), 1.26 (m, 2H), 1.15 (s, 3H), 0.92 (d, J = 4.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 91.2, 74.2, 52.2, 44.9, 42.4, 41.9, 37.3, 29.8, 27.3, 26.7, 25.6, 22.8, 21.4, 16.6; IR (cm^{-1}) 2930, 2868; HRMS calcd for $C_{14}H_{23}IO$ 334.0794, found 3340778.

1-Iodo-3a,5,8a-trimethyldecahydro-8-oxacyclopenta[*a*]indene (16b). Alcohol **15b**-ax (0.016 g, 0.077 mmol) was dissolved in dry THF (1.5 mL). *N*-Iodosuccinimide (0.052 g, 0.230 mmol) was added, followed by camphorsulfonic acid (0.018 g, 0.077 mmol). After 2 h, the reaction mixture was diluted with Et_2O and poured into H_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The organic layers were combined, washed with $NaHCO_3$ (satd) and brine, dried over $MgSO_4$, and concentrated by rotary evaporation to give a red oil. Purification of the crude oil by gravity chromatography on silica gel eluting with hexane/ethyl acetate (20:1) gave 0.030 g of the desired iodide **16b** as a clear oil in quantitative yield: ^{1}H NMR (500 MHz, $CDCl_3$) 4.40 (t, J = 3.7 Hz, 1H), 4.02 (q, J = 1.3 Hz, 1H), 2.26 (m, 1H), 2.05−1.92 (m, 3H), 1.69 (dt, J = 3.3, 7.5 Hz, 1H), 1.63 (m, 1H), 1.54 (m, 1H), 1.52 (s, 3H), 1.49 (m, 1H), 1.41 (dq, J = 1.4, 7.7 Hz, 1H), 1.22 (m, 1H), 1.17 (s, 3H), 1.07 (qd, J = 2.3, 7.4 Hz, 1H), 0.90 (d, J = 3.9 Hz, 3H), 0.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 91.7, 73.5, 52.3, 50.4, 42.2, 41.9, 37.4, 33.9, 31.2, 29.0, 28.3, 27.4, 22.9, 21.4; IR (cm^{-1}) 2928, 2865; HRMS calcd for $C_{14}H_{23}IO$ 334.0794, found 334.0778.

Isogymnomitrene (6b). Tricycle **7b** (0.018 g, 0.09 mmol) was dissolved in dry THF (1 mL) and cooled to −40 °C. The Tebbe reagent (0.5 M in tol., 0.18 mL, 0.09 mmol) was added dropwise. After 1 h, the reaction mixture was diluted with dry THF (5 mL) and quenched by addition of 15% NaOH (0.07 mL). Additional stirring at room temperature for 2 h produced a gray precipitate that was removed by filtration, rinsing with Et_2O. The filtrate was concentrated and then resuspended in pentane, causing a reddish precipitate to form. This was removed by filtration, rinsing with pentane. Concentration of the filtrate gave a clear oil. Purification of the crude oil by flash chromatography on silica gel eluting with hexanes/ethyl acetate (9:1) gave 0.009 g of the desired olefin **6b** as a white paste (48%): ^{1}H NMR (300 MHz, $CDCl_3$) 4.56 (d, J = 2.0 Hz, 2H), 2.20 (dd, J = 6.0, 15.4 Hz, 2H), 1.92 (ddd, J = 3.2, 4.7, 11.7 Hz, 1H), 1.62−1.45 (m, 4H), 1.39 (m, 2H), 1.35−1.22 (m, 4H), 0.87 (s, 3H), 0.83 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 151.7, 107.1, 55.4, 52.6, 51.9, 46.1, 43.8, 42.3, 41.5, 37.0, 29.4, 23.9, 22.2, 20.8, 17.6; IR (cm^{-1}) 3067, 1645; HRMS calcd for $C_{15}H_{24}$ 204.1878, found 204.1892.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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