[3 + 3] Annulation Based on 6-*Endo-Trig* Radical Cyclization: Regioselectivity and Diastereoselectivity

Dale E. Ward,* Yuanzhu Gai, and Brian F. Kaller

Department of Chemistry, University of Saskatchewan, Saskatoon, Canada S7N 5C9

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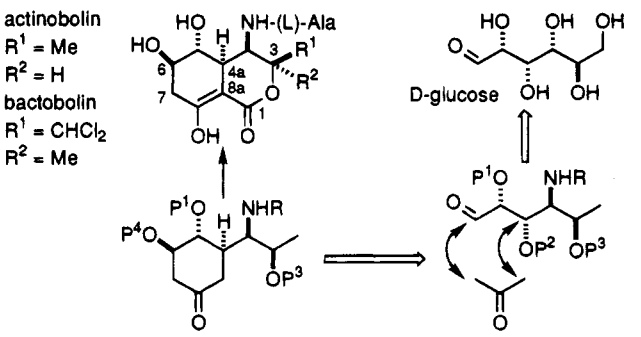
The development of a [3 + 3] annulation strategy based on sequential "two-electron" and "one-electron" allylation of β-substituted aldehydes and derivatives with the bifunctional isobutene conjunctive reagent **1** is described. The key step involves an unusual 6-*endo-trig* radical cyclization. Yields of 6-*endo* products are improved if the PhS group is oxidized to a $PhSO_2$ group prior to cyclization. The structural factors affecting the regioselectivity and stereoselectivity of the cyclization are examined. In general, the stereoselectivity of 6-*endo-trig* cyclization of 5-hexenyl radicals can be rationalized by conformational analysis of chairlike transition states and can be calculated effectively with an MM2 force field model. High 6-*endo* regioselectivity requires a strong driving force. Fragmentable allylic groups (R_3Sn, $PhSO_2$, and to a lesser extent PhS) are shown to be sufficiently activating to achieve 6-*endo* regioselectivity.

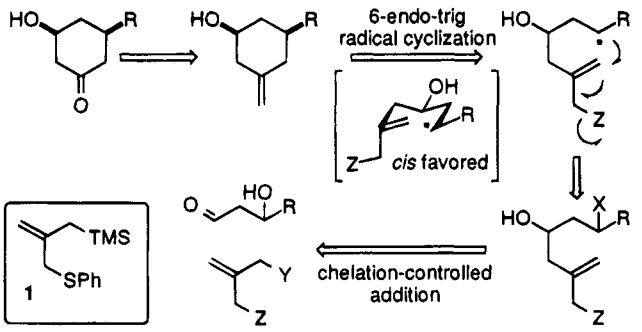
Carbocyclic annulations are extremely important processes in synthetic chemistry.[1] In particular, the development of methods for intramolecular carbon–carbon bond formation continues to attract considerable attention.[1] In connection with the synthesis of actinobolin[2] and bactobolin[3] from D-glucose, we had envisaged a [3 + 3] annulation process to construct the six-membered carbocyclic ring (see Scheme 1). Our synthesis plan required the coupling of a 3-hydroxy aldehyde with an acetone synthon to give a *cis*-5-alkyl-3-hydroxycyclohexanone by stereocontrolled formation of two carbon–carbon bonds. For application to actinobolin, the carbon–carbon bond formed by addition to the aldehyde carbonyl must occur with chelation-contolled stereoselectivity while that formed by substitution of the hydroxy group should occur with overall inversion of configuration.

The majority of methods for the construction of six-membered carbocycles involve [4 + 2] annulation (i.e. Diels–Alder and Robinson annulation).[1] There are relatively few [3 + 3] annulation methods available.[4] With few exceptions, the known methods for joining two C_3 components involve the double addition of a (d^1,d^3) reagent[5] to an (a^1,a^3) substrate.[5] We are unaware of any close analogies using a 3-hydroxy aldehyde (or derivative) as the (a^1,a^3) substrate with carbon–carbon bond formation by addition to the aldehyde carbonyl and nucleophilic substitution of a hydroxy derived leaving group. Although the formation of six-membered rings by intramolecular enolate alkylation on an epoxide or primary halide or tosylate is well precedented,[1] this reaction is difficult when the leaving group is not primary.[6] Our concern with the viability of the intramolecular nucleophilic

Scheme 1



Scheme 2



substitution reaction required for our actinobolin synthesis led us to develop a free radical based protocol for the formation this bond.[7] In this paper we present a full account of our development of a [3 + 3] annulation based on a regio- and stereoselective 6-*endo-trig* radical cyclization.[8]

Our [3 + 3] annulation strategy based on sequential "two-electron" and "one-electron" allylation of a β-substituted aldehyde is outlined in Scheme 2. The carbonyl group of the target cyclohexanone can be regarded as

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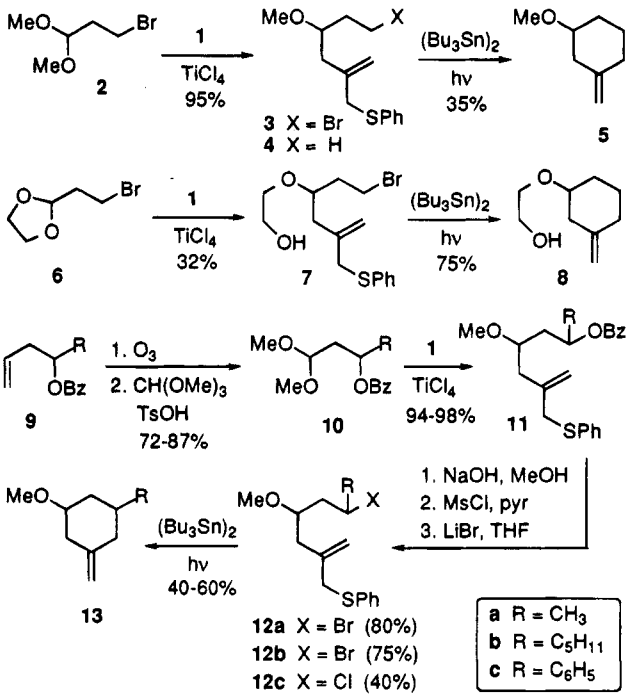
synthetically equivalent to an exocyclic methylene group. Retrosynthetic fragmentation of the allylic carbon–carbon bonds ultimately leads to a β-substituted aldehyde substrate and a bifunctional isobutene conjunctive reagent. The β-substituent would be derived from a hydroxyl group and be capable of conversion into a carbon-centered radical. The isobutenyl Y group would be chosen to promote a chelation-controlled addition to an aldehyde carbonyl. Suitable candidates for this group include R_3Si[9] and R_3Sn[10] as well as a variety of metals[11] such as Mg(II), Ti(IV), and Zn(II). The isobutenyl Z group would be selected to promote an S_H2' substitution reaction by a carbon-centered radical.[7] Suitable Z groups include R_3Sn,[12] RS,[13] RS(O),[14] and $RS(O)_2$.[14,15] Among the various possibilities, 3-(phenylthio)-2-[(trimethylsilyl)-methyl]propene (**1**)[16] was chosen as an initial candidate for the conjunctive reagent on the basis of its ready availability from simple starting materials.

After Lewis acid-catalyzed addition of **1** to an aldehyde substrate and generation of the appropriate radical, a regioselective (6-*endo-trig* vs 5-*exo-trig*) radical cyclization is required. With few exceptions, kinetically controlled cyclizations of 5-hexenyl radicals proceed with 5-*exo* regioselectivity.[7,17] Although the regioselectivity is modulated by substituent effects,[18] especially at the 5 position, few examples of regioselective 6-*endo* cyclization have been reported.[19] For example, while 5-hexenyl radical cyclizes with near 50:1 *exo* selectivity, cyclization of 5-methyl-5-hexenyl radical is slightly *endo* selective (1.5:1).[20] This reversal in regioselectivity is the result of steric inhibition of the 5-*exo* process rather than enhancement of 6-*endo* closure.[20] In our own case, we were hopeful

Scheme 3



that the presence of the phenylthio substituent would further enhance the regioselectivity in favor of the 6-*endo* product by increasing the rate of alkyl radical addition to the double bond in analogy to the effect of a trialkyltin group.[21] Additionally, the allylic sulfide allows the use of the fragmentation method (as opposed to the tin hydride method)[7d] and should increase the lifetimes of intermediate radicals, thereby facilitating the typically sluggish 6-*endo* cyclization.

To test this hypothesis, **1** was coupled with **2**[22] in the presence of $TiCl_4$ to give the adduct **3** in 95% yield (see Scheme 3). Treatment of **3** with Bu_3SnH (1.5 equiv) in refluxing benzene containing AIBN provided **5**[23] (30%) together with the reduced product **4** (17%). By contrast, irradiation of a benzene solution of **3** and $(Bu_3Sn)_2$ with a medium pressure Hg lamp gave the cyclized product **5** (35%) in the absence of **4**. We suspected that the low yield of **5** obtained was a result of its volatility.[23] Reaction of **1** and **6**[24] as above gave **7** in modest yield. Significantly, irradiation of **7** with a Hg lamp in the presence of $(Bu_3Sn)_2$ (method A) provided the 6-*endo-trig* cyclization product **8** in 75% yield.

Encouraged by these results, additional substrates **10** were prepared by ozonolysis of the allylic benzoates **9** followed by treatment with acidic $(MeO)_3CH$ (see Scheme 3). Reactions of **1** with **10a–c** and $TiCl_4$ proceeded smoothly to give the adducts **11a–c** (1.1–1.3:1 mixtures of diastereomers) in good yields. Hydrolysis of the benzoate groups in **11a–c** followed by mesylation and displacement with halide gave **12a–c**. The results of radical cyclizations of **12a–c** are presented in Table 1. In each case, the 6-*endo-trig* cyclization product **13** was produced in modest yield with low diastereoselectivity in favor of the *cis* product.[25]

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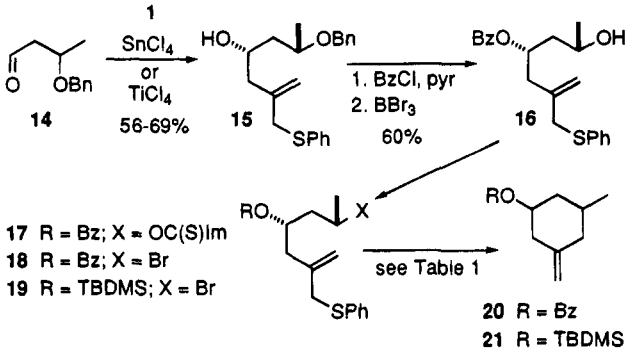
Table 1. 6-*Endo-Trig* Cyclization of Substituted 5-[(Phenylthio)methyl]-5-hexenyl Radicals

compd	cyclization method[a]	6-*endo* product	% yield[b]	*cis*:*trans*[c]
3	A	**5**	35	
7	A	**8**	79	
12a	A	**13a**	34	1.1:1
	B	**13a**	(50)	1.4:1
12b	A	**13b**	52 (63)	1.3:1
12c	A	**13c**	61 (65)	1.2:1
17	B	**20**	(17)	1.3:1
	C	**20**	(61)	1.3:1
18	A	**20**	25	1.5:1
	B	**20**	42 (65)	1.3:1
19	B	**21**	(48)	1.4:1
	C	**21**	(58)	1.4:1
24	B	**26**	39 (56)	5:1
28a	B	**29**	41 (45)	>10:1[d]

[a] Method A: $(Bu_3Sn)_2$, *hν* (Hg lamp), 10 °C. Method B: $(Me_3Sn)_2$, Ph_2CO, *hν* (Rayonet; 300 nm), 40 °C. Method C: $(Me_3SnOCPh_2)_2$, 80 °C. [b] Isolated yield (yield determined from ^1H NMR by integration relative to an internal standard). [c] Determined by ^1H NMR. [d] Only the *cis* isomer was detected.

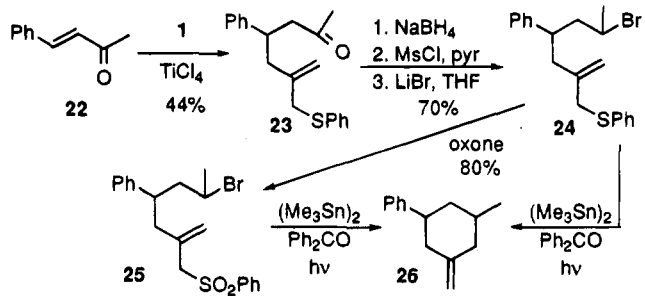
Scheme 4



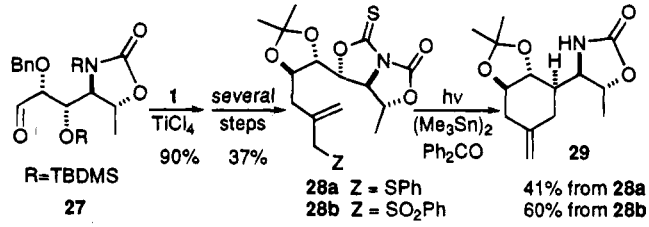
To evaluate the potential for chelation-controlled diastereoselectivity in addition of **1** to aldehydes, reaction with the β-alkoxy aldehyde **14**[26] was examined (see Scheme 4). In accord with literature precedent,[27] reaction of **1** with **14** in the presence of $TiCl_4$ or $SnCl_4$ gave the adduct **15** with good diastereoselectivity (>9:1 by ^1H NMR). The stereochemistry of the major isomer was assumed to be *anti* in analogy with similar examples.[27]

Application of our [3 + 3] annulation strategy to actinobolin synthesis would demand that the intermediate carbon-centered radical be derived from a hydroxyl group. To test this scenario, **16** was prepared as a model substrate. Benzoylation of **15** followed by cleavage of the benzyl ether gave alcohol **16** which was converted into the thiocarbonylimidazolide **17**. Only unidentified products were obtained after irradiation of **17** in the presence of $(Bu_3Sn)_2$ under the conditions successfully employed for **12**. Cyclization of the corresponding bromide **18** was examined. A C_6D_6 solution of **18** containing $(Bu_3Sn)_2$ was irradiated as above, and the reaction was monitored periodically by ^1H NMR. The desired **20** was produced in low yield after 6 h. Because both substrate and product appeared to be sensitive to prolonged Hg lamp irradiation, alternative methods[28] for generating organotin radicals were investigated. Irradiation of a benzene solution of **18**, $(Me_3Sn)_2$, and benzophenone in a Rayonette reactor (300 nm) for 3 h gave **20** in good yield (method B). However, similar treatment of **17** gave the same product in only 17% yield. Finally, addition of **17** to a benzene solution of bis(trimethylstannyl)benzpinacol followed by heating at 80 °C for 16 h gave **20** in 61% yield (method C). Similar results were obtained with **19** (see Table 1).

Scheme 5



Scheme 6



In all cases examined, free radical cyclization proceeded with poor diastereoselectivity in favor of the *cis* product. These results could be rationalized by considering the four possible chairlike transition states for 6-*endo-trig* cyclization (see Scheme 2).[29] Thus, the diastereoselectivity should be controlled by the difference in energy between transition states with the smallest substituent (e.g. MeO in **12**) in a pseudoequatorial vs a pseudoaxial orientation. This difference should be considerably less than the *A* value for the MeO group (0.75 kcal/mol) due to the relatively long carbon–carbon bond in the transition state resulting in low selectivity. Replacement of the MeO group in **12** with an alkyl substituent should significantly improve the diastereoselectivity of the cyclization. Conjugate addition of **1** to **22** in the presence of $TiCl_4$ gave **23** (see Scheme 5). Reduction of the carbonyl group in **23** followed by conversion of resulting alcohol to a bromide provided **24**. Cyclization of **24** according to method B gave **25** as a 5:1 mixture of *cis*:*trans* diastereomers. With similar reasoning,[29] we predicted that the required diastereoselectivity for cyclization of **28** would be achieved by employing a cyclic protecting group for the C_5, C_6 diol (actinobolin numbering).

Our [3 + 3] annulation strategy had evolved to the point where its application to actinobolin synthesis was feasible. In the event, the method worked quite well and both carbon–carbon bonds were formed with excellent diastereoselectivity (see Scheme 6).[2] However, the yield obtained in the cyclization of **28a** was modest (41%) and could not be improved despite considerable experimentation. The reaction appeared to be very clean and, when

(25) The stereochemistry of the products was easily assigned by ^1H NMR on the basis of the $^3J_{HH}$ coupling constants observed for the C*H*OMe protons. This proton is axial in the *cis* products and equatorial in the *trans* products.

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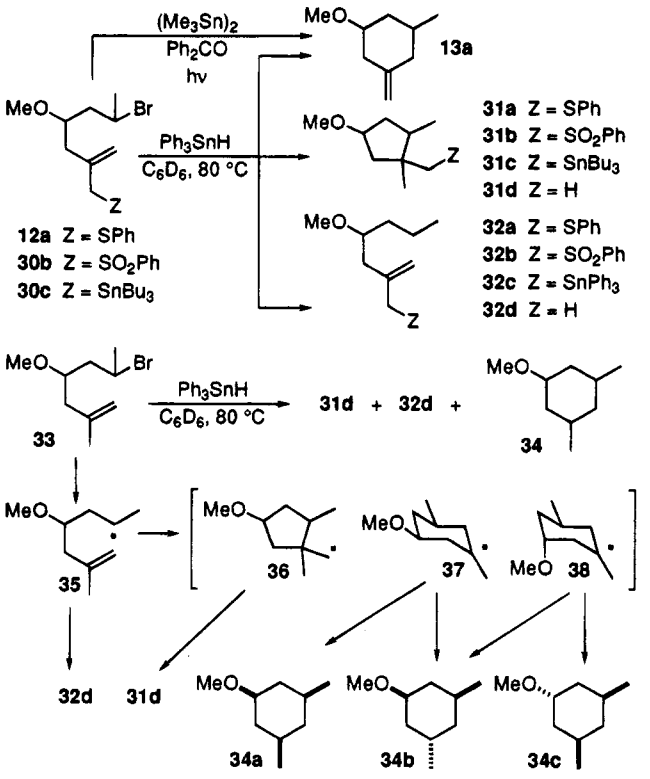
(29) For a discussion, see ref 2b.

Scheme 7



monitored by ^{1}H NMR, only signals attributable to the product were observed although integration of these signals against an internal standard indicated a maximum yield of 45% for **29**. Fractionation of the reaction mixture produced a large number of unidentified minor products along with **29**. To further investigate this process, the reaction of **12a** was reexamined.

Cyclization of **12a** in C_6D_6 solution (sealed tube) according to method B was monitored by ^{1}H NMR. As with **28**, the reaction appeared to be quite clean, and after the disappearance of **12a** (20 h), the spectrum was dominated by the signals from **13a**. Integration of these signals against an internal standard indicated only a 50% yield for **13a**, and the presence of a large number of minor products (≤5% each) was suggested by the number of signals attributable to MeO groups. Because **13a** was shown to be stable under the reaction conditions and ejection of a phenylthio radical from a β-phenylthio alkyl radical is rapid ($k \approx 2 \times 10^8$ M^{-1} s^{-1}),[30] the low yield of product must be due to reactions of the radical **35** which are competitive with 6-*endo-trig* cyclization. Although products derived from a 5-*exo-trig* cyclization were not detected or isolated in any of the cyclization reactions conducted with the fragmentation method, we suspected that this process might be occurring after careful reexamination of our earlier work using the tin hydride method (see Scheme 7). A solution of **12a**, Ph_3SnH (1.5 equiv), and AIBN (0.15 equiv) in degassed C_6D_6 solution (sealed tube) was heated at 80 °C and monitored by ^{1}H NMR (method D). After 4 h, **12a** was consumed and ^{1}H NMR indicated the presence of a 1.5:1.1:1.3:1 mixture of **32a**, **32d**,[31] **13a** (*cis:trans* = 1.4:1), and **31a** (a 1.3:1 mixture of 2 diastereomers), respectively, which comprised >90% of the total products (the isolated yields were considerably lower). These results implied that the regioselectivity for 6-*endo* vs 5-*exo* cyclization was poor (i.e. 1.3:1) and offered an explanation for the modest yield of methylenecyclohexane products obtained previously. Although the ultimate fate of the radical resulting from 5-*exo* closure under fragmentation conditions is uncertain, ring opening of this radical is likely too slow to produce appreciable amounts of 6-*endo* product.[19c]

Spellmeyer and Houk[32] developed a transition state model for cyclization of carbon-centered radicals. This MM2-based method has been successfully applied to predict/rationalize the outcome of a variety of radical cyclizations.[33] Using this model, the energies for transition states for cyclization of the radicals **3**, **12a**, **24**, and **28a** were calculated. Because the steric effect of the PhS group was expected to be negligible, the calculations were performed with this group replaced by H.[34] Energies for all possible[32] chairlike and twist boatlike transition states for both *exo* and *endo* cyclization were calculated, and a Boltzman distribution of those transition states within 2.5 kcal/mol of the minimum was used to predict the product distribution. The results are presented in Table 2. In general, the 6-*endo* products (>90%) are predicted to result primarily from chairlike transition states and the 5-*exo* chairlike and twist boatlike transition states are similar in energy. The calculated and observed stereoselectivites are in reasonable agreement.[35] With the exception of **28a**, a significant amount of 5-*exo* products is predicted, and the 5-*exo* regioselectivity predicted for **7** and **12a** is not in accord with the isolated yield of 6-*endo* products obtained by the fragmentation method (method B). To determine if the discrepancy between the calculated and observed regioselectivities for cyclization was due to the electronic effect of the PhS group, the reaction of **33** was examined (Scheme 7). Cyclization of **33** according to method D gave a mixture of six products (^{1}H NMR). The identity of the products was determined by comparison with spectra from authentic samples prepared independently. In this way, the mixture was established as a 1.3:1.3:1 ratio of **31d**:**32d**:**34**, respectively, with **31d** as a 1.4:1 mixture of *cis*:*trans* diastereomers[36] and **34** as a 2.8:1.4:1 mixture of **34a**:**34b**:**34c**. The stereoselectivity for 6-*endo* cyclization

Table 2. Calculated and Observed Product Distributions for Radical Cyclization

	calculated			observed		
compd	*exo:endo*	*cis:trans* (*exo*)	*cis:trans* (*endo*)	*exo:endo*	*cis:trans* (*exo*)	*cis:trans* (*endo*)
3[a]	64:46			−:35[b]		
7[a]	(64:36)[c]			−:75[b]		
12a[d]	61:39	52:48	63:37	43:57	57:43[e]	58:42
12a[a]	62:38	53:47	66:34	−:50[b]		58:42
24[a]	42:58	50:50	89:11	−:56[b]		83:17
28a[a,f]	0:100		86:14	−:41[b]		>95:<5[g]
33[d]	61:39	52:48	63:37	57:43	58:42[e]	60:40[h]

[a] Calculated and observed at 40 °C (method B). [b] Products from *exo* cyclization were not detected. [c] Calculated with OMe replacing OC_2H_4OH. [d] Calculated and observed at 80 °C (method D). [e] Stereochemistry of the major product was not determined. [f] Calculated for NH. [g] Only the *cis* isomer was detected. [h] Estimated (see text).

Table 3. Effect of Fragmentable Group on Selectivity and Yield of 6-*Endo-Trig* Cyclization

	tin hydride method[a]			fragmentation method[b]	
compd	products (ratio)[c]	regioselectivity 6-*endo*:5-*exo*[c]	6-*endo* *cis*:*trans*[c]	6-*endo* % yield[d]	6-*endo* *cis*:*trans*[c]
12a	**13a**:**31a**:**32a**:**32d** (1.3:1:1.5:1.1)	1.2:1	1.4:1	34 (50)	1.4:1
30b	**13a**:**31b**:**32b**:**32c** (10:<2:3:1)	>5:1	1:1	(69)	1:1
30c	**13a**:**31c**:**32c** (1.5:<0.2:1)	>10:1	1.6:1	(89)	1.7:1
33	**31d**:**32d**:**34**	0.77:1	1.5:1[e]		
24				39 (56)	5:1
25				62 (76)	4.4:1
28a				41 (45)	>10:1[f]
28b				(63)	>10:1[e]

[a] Method D (Ph_3SnH, AIBN, 80 °C). [b] Method B [$(Me_3Sn)_2$, Ph_2CO, $h\nu$ (Rayonet; 300 nm), 40 °C]. [c] Determined by ^1H NMR. [d] Isolated yield (yield determined from ^1H NMR by integration relative to an internal standard). [e] Estimated (see text). [f] Only the *cis* isomer was detected.

of **33** (i.e. **37**:**38**) is estimated to be 1.5:1 by assuming that the diastereoselectivity for H atom abstraction of **37** is 9:1.[37] These results are in close agreement with the calculated product distribution (see Table 2).

Comparison of the 6-*endo*:5-*exo* regioselecivities for cyclizations of **12a** (1.3:1) and **33** (1:1.3) implies that the presence of the phenylthio group has a modest activating effect (i.e. × 1.5−2) for addition of a radical to the γ-carbon.[21] To examine the effect of other fragmentable groups, the cyclizations of **30b,c** were examined (Scheme 7). The results are presented in Table 3. Reaction of **30b** with Ph_3SnH according to method D (4 h) gave **13a** (as a 1:1 mixture of diastereomers) along with the reduced product (**32b**) and small amount of **32c** from S_H2' substitution of the $PhSO_2$ group with Ph_3Sn radical.[38] The presence of several minor products was suggested by ^1H NMR signals attributable to OMe groups. However, the maximum amount of 5-*exo* product (**31b**) present was judged to be <10% by comparison with the spectrum of an authentic sample of **31b** prepared from **31a**. The origin of the lower stereoselectivity for 6-*endo* cyclization of **30b** compared with **12a** (and **30c** and **33**) is unclear. Cyclization of **30b** by method B produced a higher yield of **13a** than similar reaction of **12a** consistent with enhanced 6-*endo* regioselectivity resulting from γ-carbon activation by the $PhSO_2$ group. These effects are further amplified in the cyclization of **30c**. In this case the reactions are very clean, and although an authentic sample of **31c** was not available, the 6-*endo* regioselectivity must be high as **13a** and **32c** account for ≥95% of the total products. An allylic Bu_3Sn is known[21] to increase the rate of addition of an alkyl radical to the γ-carbon by at least a factor of 10. The above results suggest that the PhS and $PhSO_2$ groups have a similar, albeit attenuated, effect. Cyclization of **25**, readily available by oxidation of **24**, improved the yield of **26** by a factor of ca. 1.4 (Scheme 5). A similar improvement in the yield of **29** was obtained by cyclization of **28b** (Scheme 6).[39]

In conclusion, a [3 + 3] annulation strategy based on sequential "two-electron" and "one-electron" allylation of β-substituted aldehydes and derivatives with the bifunctional isobutene conjunctive reagent **1** has been developed. The key step involves an unusual 6-*endo-trig* radical cyclization. Yields of 6-*endo* products are improved if the PhS group is oxidized to a $PhSO_2$ group prior to cyclization. Excellent diastereoselectivity was achieved in application of this strategy to actinobolin synthesis. In general, the stereoselectivity of 6-*endo-trig* cyclization of 5-hexenyl radicals can be rationalized by conformational analysis of chairlike transition states and can be calculated effectively with Houk's transition state model. Understandably,[32] the same model cannot reproduce the regioselectivity when activating substituents are on the double bond. High 6-*endo* regioselectivity is observed with an acyl[19d,e] or 2-keto radical,[19a,b,c] by strong steric biasing,[19j] or by the presence of a Ph,[19h] $PhSO_2$,[19f,g] or other activating substituent on the double bond. Our results indicate that fragmentable allylic groups (R_3Sn, $PhSO_2$, and to a lesser extent PhS) are sufficiently activating to achieve 6-*endo* regioselectivity. Considering the above, bifunctional isobutene reagents with R_3Sn and R_3Si groups[40] or 2 R_3Sn groups[41] should prove effective in similar [3 + 3] annulations and related processes.

Experimental Section[42]

Transition State Calculations. The modified force field parameters[32] were implemented into the MM2 parameter set included in CAChe Worksystem (version 3.7 from CAChe Scientific Inc.). Both chairlike and twist boatlike transition states for 6-*endo* and 5-*exo* cyclization of 5-methyl-5-hexenyl radical were constructed and minimized (stretching, bending and torsional strain) with the Newton−Raphson block diagonal method to 0.001 kcal/mol convergence, thereby reproducing the

(30) Wagner, P. J.; Sedon, J. H.; Lindstrom, M. J. *J. Am. Chem. Soc.* **1978**, *100*, 2579.

(31) This product (**32d**), which was too volatile to isolate, is identical (^1H NMR) with the major product from reaction of **33** with Ph_3SnH and is consistent with the presence of the signal at δ 1.78 (3H, br s).

(32) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

(33) For recent applications see: (a) Meyers, A. G.; Condroski, K. R. *J. Am. Chem. Soc.* **1995**, *117*, 3057. (b) Takahashi, T.; Katouda, W.; Sakamoto, Y.; Tomida, S.; Yamada, H. *Tetrahedron Lett.* **1995**, *36*, 2273.

(34) The calculations were significantly simplified by this replacement (three fewer torsions). The similar *endo*:*exo* regioselectivities calculated for cyclization of 5-methyl- (53:47) and 5-ethyl-5-hexenyl radicals (58:42) indicated that the steric effect of replacing the PhS group by H would be small. Because only steric effects are included in this transition state model,[32] the electronic effect of the allylic PhS group on addition to the γ-carbon,[21] if any, would not be accounted for if this group were included.

(35) Stereoselectivity will be independent of any electronic effect of the PhS group if the effect is similar in all of the 6-*endo* chairlike tranisition states.

(36) We presume that the major isomer is *cis* although this was not rigorously established.

(37) Damm, W.; Giese, B.; Hartung, J.; Hasskerl, T.; Houk, K. N.; Hüter, O.; Zipse, H. *J. Am. Chem. Soc.* **1992**, *114*, 4067.

(38) Ueno, Y.; Aoki, S.; Okawara, M. *J. Am. Chem. Soc.* **1979**, *101*, 5414.

(39) Although a further improvement would presumably result from the corresponding R_3Sn derivative, insufficient material was available to prepare this substrate.

published results of Spellmeyer and Houk[32] for this system. Transition states for **3**, **12a**, **24**, and **28a** (with PhS changed to H)[34] were generated from those above by adding the appropriate substituents at the appropriate locations with all possible stereochemical permutations and minimizing. Additional minima were located by minimizing at least 10 conformations generated from driving the dihedral angles for each rotatable bond (i.e. C−C−O−Me in **3** and **12a**, C−Ph in **24**, and C−C−C−N in **28a**). A Boltzman distribution of those transition states within 2.5 kcal/mol of the minimum was used to predict the product distribution.

Method A. A Pyrex tube containing solution of the free radical precursor and $(Bu_3Sn)_2$ (1.0 equiv) in degassed, distilled C_6H_6 (3 mL/mmol of substrate) was placed in a Liebig condenser and irradiated using a 1200 W medium pressure mercury lamp. The reaction temperature was maintained at ca. 10 °C. After 6 h, the mixture was diluted with pentane, washed with 10% aqueous KF and with water, dried over Na_2SO_4, concentrated under reduced pressure, and fractionated. Similar reactions conducted in C_6D_6 in the presence of an internal standard (1,2-dimethoxybenzene) using a Rayonet photoreactor equipped with 300 nm lamps gave similar results, although reaction times were considerably longer.

Method B. A solution of the free radical precursor (0.01−0.10 mmol), $(Me_3Sn)_2$ (1 equiv),[43] Ph_2CO (1 equiv),[28] and an internal standard (anisole or 1,2-dimethoxybenzene, ca. 1 equiv) in C_6D_6 (0.4−1 mL) in a sealed 5 mm NMR tube was irradiated in a Rayonet photoreactor (300 nm). The reaction temperature was ca. 40 °C. The reaction was monitored by ^1H NMR, and when the precursor was consumed, the products were quantitated by integration relative to the internal standard. Larger scale reactions were conducted in C_6H_6 without an internal standard. For isolation of products, the mixture was diluted with pentane, washed with 10% aqueous KF and with water, dried over Na_2SO_4, concentrated under reduced pressure, and fractionated.

Method C. A solution of $(Me_3Sn)_2$ (1.5 equiv), and Ph_2CO (1.5 equiv) in degassed C_6H_6 (1 mL/0.1 mmol) was irradiated at 10 °C with either a 1200 W medium pressure mercury lamp or a Rayonet photoreactor (300 nm).[28] After the benzophenone was completely consumed (IR: 1660 cm^{-1}), a solution of the free radical precursor (1.0 equiv) in degassed C_6H_6 (1 mL/mmol) was added and the mixture was heated at 80 °C in a sealed tube overnight. Similar reactions conducted in C_6D_6 in the presence of an internal standard were monitored and product yields measured by ^1H NMR. For isolation of products, the reaction mixture was processed as above.

Method D. A solution of free radical precursor (0.01−0.02 mmol), Ph_3SnH (1.5 equiv), and AIBN (0.2 equiv) in degassed C_6D_6 (0.4 mL) in a sealed NMR tube was heated at 80 °C. The reaction was monitored by ^1H NMR, and when the precursor was consumed, the product distribution was measured by integration of appropriate signals (typically OMe groups). Larger scale reactions were conducted in C_6H_6 and products isolated as above.

3-Methoxy-1-methylidenecyclohexane (5). Cyclization of **4** (47.0 mg, 0.15 mmol) according to method A gave the known **5**[23] (5.7 mg, 35%) after fractionation by PTLC (10% EtOAc in hexane).

3-(2-Hydroxyethoxy)-1-methylidenecyclohexane (8). Cyclization of **7** (22 mg, 0.064 mmol) according to method A gave **8** (8.0 mg, 79%) after fractionation by PTLC (25% EtOAc in hexane): IR (DRIFT) 3422, 3071, 2937, 1459, 1112, 1062 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.70 (1H, br s), 4.67 (1H, br s), 3.71 (2H, m), 3.57 (2H, m), 3.35 (1H, dddd, J = 4, 4, 13, 13 Hz), 2.54 (1H, dd, J = 4, 13 Hz), 2.18 (2H, m), 2.01 (3H, m), 1.79 (1H, m), 1.38 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3 (s), 109.4 (t), 78.1 (d), 69.1 (t), 62.0 (t), 41.0 (t), 34.4 (t), 31.7 (t), 24.0 (t); LRMS (CI, NH_3) m/z (relative intensity) 174 ($[M + 18]^+$, 17), 95 (100).

3-Methoxy-5-methyl-1-methylidenecyclohexane (13a). Cyclization of **12a** (42 mg, 0.13 mmol) according to method A and after FCC (10% EtOAc in hexane) gave crude **13a** (10 mg) as a 1.1:1 mixture of *cis*:*trans* isomers containing some tin byproducts. Further fractionation by PTLC (13% EtOAc in hexane) gave *cis* isomer (3 mg, 17%) and the *trans* isomer (3 mg, 17%). Cyclization of **12a** according to method B (20 h) in C_6D_6 indicated (NMR) the presence of a 1.4:1 mixture of *cis*:*trans* **13a** in 50% yield.[44] *cis*-**13a**: IR (DRIFT) 3068, 2924, 1463, 1262 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.69 (2H, m), 3.36 (3H, s), 3.13 (1H, t, t, J = 4.5, 11 Hz), 2.66 (1H, dddd, J = 1.5, 1.5, 4.5, 12.5 Hz), 2.20 (1H, dddd, J = 1.5, 1.5, 4.5, 13 Hz), 2.07 (1H, m), 1.84 (1H, ddd, J = 1.5, 11, 12.5 Hz), 1.60 (1H, ddd, J = 1.5, 12.5, 13 Hz), 1.43 (1H, m), 1.26 (1H, m), 0.97 (3H, d, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.0 (s), 109.2 (t), 79.5 (d), 55.7 (q), 43.0 (t), 40.7 (t), 40.4 (t), 31.4 (d), 22.1 (q); LRMS (EI), molecular ion not detected, m/z (relative intensity) 109 ($[M - 31]^+$, 34), 94 (30). *trans*-**13a**: IR (DRIFT) 3071, 2924, 1457 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.74 (1H, m), 4.69 (1H, m), 3.57 (1H, dddd, J = 3, 3, 4.5, 4.5 Hz), 3.31 (3H, s), 2.39 (1H, dd, J = 4.5, 13.5 Hz), 2.30 (1H, br dd, J = 3.5, 12.5 Hz), 2.18 (1H, br d, J = 13.5 Hz), 1.88 (2H, m), 1.71 (1H, br dd, J = 10, 12.5 Hz), 1.26 (1H, m), 0.91 (3H, d, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0 (s), 109.8 (t), 76.4 (d), 55.7 (q), 42.8 (t), 38.7 (t), 37.7 (t), 28.1 (d), 21.5 (q); LRMS (EI), molecular ion not detected, m/z (relative intensity) 109 ($[M - 31]^+$, 18), 95 (54), 80 (34).

3-Methoxy-5-pentyl-1-methylidenecyclohexane (13b). Cyclization of **12b** (20 mg, 0.052 mmol) according to method A and after PTLC (10% EtOAc in hexane) gave **13b** (4.8 mg, 52%) as a 1.3:1 mixture of *cis*:*trans* isomers. Cyclization of **12b** according to method A (Rayonet, 168 h) in C_6D_6 indicated (NMR) the presence of a 1.3:1 mixture of *cis*:*trans* **13b** in 63% yield. Pure samples of the individual diastereomers were available by MPC (50% hexane in CH_2Cl_2). *cis*-**13b**: IR (DRIFT) 3071, 2924, 1650, 1465, 1099, 858 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.70 (2H, br s), 3.37 (3H, s), 3.12 (1H, tt, J = 4.5, 11 Hz), 2.68 (1H, dddd, J = 1.5, 2, 4.5, 12.5 Hz), 2.27 (1H, br d, J = 13 Hz), 2.13 (1H, br d, J = 13 Hz), 1.85 (1H, br dd, J = 11, 12.5 Hz), 1.59 (1H, m), 1.29 (10H, m), 0.89 (3H, t, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.0 (s), 109.2 (t), 79.6 (d), 55.8 (q), 41.1 (t), 41.0 (t), 38.5 (t), 36.8 (d), 36.4 (t), 32.0 (t), 26.5 (t), 22.6 (t), 14.0 (q); LRMS (CI, NH_3) m/z (relative intensity) 214 ($[M + 18]^+$, 68), 197 ($[M + 1]^+$, 8), 182 (38), 165 (100), 141 (37). *trans*-**13b**: IR (DRIFT) 3070, 2925, 1649, 1459, 1097, 887 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.74 (1H, br s), 4.70 (1H, br s), 3.53 (1H, m), 3.31 (1H, s), 2.36 (2H, m), 2.21 (1H, br d, J = 13.5 Hz), 1.90 (1H, m), 1.72 (1H, m), 1.27 (10H, m), 0.90 (3H, t, J = 6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1 (s), 109.7 (t), 76.4 (d), 55.7 (q), 40.8 (t), 39.1 (t), 36.1 (t), 36.0 (d), 33.1 (t), 32.1 (t), 26.5 (t), 22.5 (t), 14.0 (q); LRMS (CI, NH_3) m/z (relative intensity) 214 ($[M + 18]^+$, 31), 165 (46), 151 (50), 141 (86).

3-Methoxy-5-phenyl-1-methylidenecyclohexane (13c). Cyclization of **12c** (98 mg, 0.28 mmol) according to method A and after FCC (20−50% EtOAc in hexane) gave **13c** (34 mg, 45%) as a 1.2:1 mixture of *cis*:*trans* isomers. Similar reaction of **12c** (39 mg, 0.11 mmol) in C_6D_6 using a Rayonet reactor (21 h) indicated (NMR) the presence of a 1.2:1 mixture of *cis*:*trans* **13c** in 65% yield. Fractionation of the reaction mixture by MPC (42% hexane in CH_2Cl_2) gave *cis*-**13c** (7.5 mg, 34%), *trans*-**13c** (6.7 mg, 27%), and **12c** (4 mg, 10%). *cis*-**13c**: IR (DRIFT) 3029, 2939, 2893, 1649, 1495, 1453, 1122 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (5H, m), 4.80 (1H, m), 3.40 (3H, s), 3.29 (1H, tt, J = 4.5, 11 Hz), 2.77 (1H, dddd, J = 2, 2, 4.5, 13 Hz), 2.58 (1H, tt, J = 3.5, 13 Hz), 2.44 (1H, dddd, J = 2, 2,

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(41) (a) Sano, H.; Okawara, M. Ueno, Y. *Synthesis* **1984**, *11*, 933. (b) Degl'Innocenti, A.; Dembech, P.; Mordini, A.; Ricci, A.; Seconi, G. *Synthesis* **1991**, 267. (c) Keck, G. E.; Palani, A. *Tetrahedron Lett.* **1993**, *34*, 3223.

(42) General procedures have been recently described.[2b] DRIFT refers to the technique of recording IR spectra on a fourier transform interferometer using a diffuse reflectance cell.

(43) Similar results were obtained with $(Bu_3Sn)_2$; cf. Hart, D. J.; Krishnamurthy, R.; Pook, L. M.; Seely, F. L. *Tetrahedron Lett.* **1993**, *34*, 7819.

(44) The products are difficult to isolate because of volatility. The discrepancy in stereoselectivity between method A and method B is due to measurement after workup in method A.

3.5, 13 Hz), 2.32 (1H, dddd, J = 2, 3.5, 4.5, 12.5 Hz), 2.13 (1H, ddd, J = 1, 13, 13 Hz), 2.00 (1H, ddd, J = 1, 11, 13 Hz), 1.64 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4 (s), 128.6 (d × 2), 126.8 (d × 2), 126.4 (d), 110.3 (t), 79.6 (d), 56.0 (q), 42.6 (d), 42.5 (t), 40.9 (t), 39.1 (t); LRMS (CI, NH_3) m/z (relative intensity) 220 ([M + 18]$^+$, 100), 203 ([M + 1]$^+$, 26), 171 (63). *trans*-**13c**: IR (DRIFT) 3064, 2927, 1452, 1098, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (5H, m), 4.84 (1H, d, J = 1.5 Hz), 4.80 (1H, d, J = 1.5 Hz), 3.71 (1H, tt, J = 3, 3 Hz), 3.36 (3H, s), 3.02 (1H, tt, J = 3.5, 12.5 Hz), 2.57 (2H, m), 2.22 (3H, m, H-2, 6, H4), 1.63 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7 (s), 132.5 (s), 128.5 (d × 2), 126.9 (d × 2), 126.2 (d), 110.5 (t), 76.2 (d), 55.9 (q), 42.4 (d), 39.1 (t), 38.3 (t), 36.5 (t); LRMS (CI, NH_3) m/z (relative intensity) 220 ([M + 18]$^+$, 82), 203 ([M + 1]$^+$, 26), 188 (28), 171 (100).

3-(Benzoyloxy)-5-methyl-1-methylidenecyclohexane (20). Cyclization of **18** (50 mg, 0.12 mmol) according to method A and after PTLC (10% EtOAc in hexane) gave **20** (6.9 mg, 25%) as a 1.5:1 mixture of *cis*:*trans* isomers. Cyclization of **18** according to method B (40 h) in C_6D_6 indicated (NMR) the presence of a 1.3:1 mixture of *cis*:*trans* **20** in 65% yield. The crude product from **18** (60 mg, 0.14 mmol) was fractionated by MPC (5% EtOAc in hexane) to give *cis*-**20** (7.3 mg, 23%) and *trans*-**20** (6.2 mg, 19%). Cyclization of **17** (12.5 mg, 0.027 mmol) according to method B (20 h) in C_6D_6 indicated (NMR) the presence of a 1.3:1 mixture of *cis*:*trans* **20** in 17% yield. Cyclization of **17** (12.5 mg, 0.027 mmol) according to method C (12 h) in C_6D_6 indicated (NMR) the presence of a 1.3:1 mixture of *cis*:*trans* **20** in 61% yield. *cis*-**20**: IR (DRIFT) 3072, 2952, 1717, 1451, 1274, 1106 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (2H, m), 7.56 (1H, m), 7.44 (2H, m), 4.95 (1H, tt, J = 4.5, 11 Hz), 4.79 (2H, m), 2.74 (1H, dddd, J = 1.5, 1.5, 4.5, 12.5 Hz), 2.30 (1H, m), 2.16 (2H, m), 1.64 (2H, m), 1.28 (1H, ddd, J = 11, 11, 12 Hz), 1.02 (3H, d, J = 6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9 (s), 144.6 (s), 132.8 (d), 130.8 (s), 129.5 (d × 2), 128.3 (d × 2), 110.5 (d), 73.4 (d), 42.6 (t), 402 (t), 40.0 (t), 31.4 (d), 21.9 (q); LRMS (CI, NH_3) m/z (relative intensity) 248 ([M + 18]$^+$, 35), 231 ([M + 1]$^+$, 100), 110 (53), 106 (55). *trans*-**20**: IR (DRIFT) 3071, 2951, 1715, 1451, 1272, 1115 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (2H, m), 7.56 (1H, m), 7.43 (2H, m), 5.34 (1H, tt, J = 3.5, 3.5 Hz), 4.79 (1H, br s), 4.72 (1H, br s, J = 1 Hz), 2.53 (1H, br dd, J = 3.5, 14 Hz), 2.37 (2H, m, H-6, H-2), 2.02 (2H, m), 1.79 (1H, dd, J = 11, 12 Hz), 1.44 (1H, ddd, J = 2.5, 11.5, 14.5 Hz), 0.98 (3H, d, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8 (s), 144.1 (s), 132.7 (d), 130.9 (s), 129.5 (d × 2), 128.2 (d × 2), 110.4 (t), 71.2 (d), 42.8 (t), 38.8 (t), 38.0 (t), 29.0 (d), 21.6 (q); LRMS (CI, NH_3) m/z (relative intensity) 248 ([M + 18]$^+$, 17), 231 ([M + 1]$^+$, 100), 110 (35), 106 (37).

3-[(*tert*-Butyldimethylsilyl)oxy]-5-methyl-1-methylidenecyclohexane (21). Cyclization of **19** (10.1 mg, 0.023 mmol) according to method B (23 h) in C_6D_6 indicated (NMR) the presence of a 1.4:1 mixture of *cis*:*trans* **21** in 48% yield. Cyclization of **19** (10.1 mg, 0.023 mmol) according to method C (14 h) in C_6D_6 indicated (NMR) the presence of a 1.3:1 mixture of *cis*:*trans* **20** in 58% yield. The crude products from the above reactions were combined and fractionated by PTLC (5% EtOAc in hexane) to provide pure samples of *cis*-**21** and *trans*-**21**. *cis*-**21**: IR (DRIFT) 3065, 2928, 1255, 1095, 1060, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.66 (2H, m), 3.53 (1H, tt, J = 4.5, 11 Hz), 2.44 (1H, dddd, J = 1.5, 1.5, 4.5, 12.5 Hz), 2.17 (1H, dddd, J = 1.5, 1.5, 3.5, 12.5 Hz), 1.94 (1H, ddd, J = 1, 11, 12.5 Hz), 1.87 (1H, m), 1.56 (1H, ddd, J = 1, 11.5, 12.5 Hz), 1.42 (1H, m), 1.08 (1H, ddd, J = 11, 12, 12 Hz), 0.95 (3H, d, J = 6.5 Hz), 0.88 (9H, s), 0.06 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6 (s), 108.8 (t), 71.6 (d), 44.7 (t), 44.5 (t), 42.8 (t), 31.5 (d), 25.8 (q), 22.1 (q), 18.1 (s), −4.6 (q); LRMS (CI, NH_3) m/z (relative intensity) 241 ([M + 1]$^+$, 88), 184 (31), 110 (98), 70 (100). *trans*-**21**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.69 (1H, m), 4.63 (1H, m), 4.02 (1H, dddd, J = 3, 3, 5, 5 Hz), 2.26 (1H, dd, J = 4, 13.5 Hz), 2.21 (1H, dd, J = 3, 13 Hz), 2.13 (1H, dd, J = 5, 13 Hz), 1.99 (1H, m), 1.67 (2H, m), 1.31 (1H, ddd, J = 3, 9.5, 13.5 Hz), 0.87 (3H, d, J = 6 Hz), 0.86 (9H, s), 0.02 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4 (s), 109.5 (t), 68.0 (d), 43.1 (t), 42.7 (t), 41.9 (t), 28.0 (d), 25.8 (q), 21.2 (q), 18.1 (s), −4.8 (q); LRMS (CI, NH_3) m/z (relative intensity) 241 ([M + 1]$^+$, 47), 153 (11), 109 (100).

3-Methyl-5-phenyl-1-methylidenecyclohexane (26). Cyclization of **24** according to method B (20 h) in C_6D_6 indicated (NMR) the presence of a 5:1 mixture of *cis*:*trans* **26** in 56% yield. The crude product from **24** (96 mg, 0.25 mmol) was fractionated by MPC (hexane) to give **26** (18 mg, 39%) as a 5:1 mixture of *cis*:*trans* isomers. Cyclization of **25** (30 mg, 0.073 mmol) according to method B (13 h) in C_6D_6 (1 mL) indicated (NMR) the presence of a 4.4:1 mixture of *cis*:*trans* **26** in 76% yield. Fractionation by MPC (hexane) gave **26** (8.4 mg, 62%) as a 4.4:1 mixture of *cis*:*trans* isomers: IR (DRIFT) 3066, 3026, 2924, 1649, 1493, 1453, 884 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (*cis* isomer) 7.26 (5H, m), 4.71 (2H, m), 2.64 (1H, tt, J = 3.5, 12.5 Hz), 2.48 (1H, dddd, J = 1.5, 1.5, 3.5, 13 Hz), 2.36 (1H, br d, J = 12.5 Hz), 2.14 (1H, ddd, J = 1, 12.5, 13 Hz), 1.92 (1H, dddd, J = 1.5, 3, 5, 13 Hz), 1.74 (1H, ddd, J = 1, 12.5, 12.5 Hz), 1.66 (1H, m), 1.28 (1H, ddd, J = 12.5, 12.5, 13 Hz), 1.01 (3H, d, J = 6 Hz), (*trans* isomer, partial data) 4.80 (1H, br s), 4.71 (1H, br s), 2.93 (1H, tt, J = 4, 10.5 Hz), 1.01 (3H, d, J = 6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (*cis* isomer) 148.8 (s), 146.6 (s), 128.4 (d × 2), 126.7 (d × 2), 126.0 (d), 107.6 (t), 45.3 (d), 43.3 (t), 42.7 (t), 42.3 (t), 34.3 (d), 22.5 (q), (*trans* isomer) 146.2 (s), 128.2 (d × 2), 127.0 (d × 2), 125.9 (d), 109.5 (t), 42.0 (d), 41.2 (t), 39.8 (t), 39.4 (t), 28.9 (d), 18.8 (q); LRMS (EI) m/z (relative intensity) 186 ([M]$^+$, 16), 130 (84), 91 (100).

Compound 29. Cyclization of **28a** to **29** was previously described.[2b] Cyclization of **28b** (2.0 mg, 0.0043 mmol) according to method B (43 h) in C_6D_6 (0.4 mL) indicated (NMR) the presence of **29** in 61% yield.

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Supporting Information Available: Experimental procedures and spectral data for the preparation of **3**, **7**, **9**–**12**, **15**–**19**, **23**–**25**, **28b**, and **30**–**34**, and ^{13}C NMR spectra for **8**, **13a**–**c**, **20**, **21**, and **26** (36 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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