Note Added in Proof. A recent single-crystal structure determination of the Ga(III) complex of racemized anguibactin shows a 1:1 metal to ligand stoichiometry, in which the O-hydroxy group, the nitrogen of the thiazoline ring, the hydroxamate (N–O) group, and the deprotonated nitrogen of the imidazole ring coordinate the metal ion. The crystal structure also confirms the chemical structure of anguibactin. (D. van der Helm, M. B. Hossain, M. A. F. Jalal and D. L. Eng-Wilmot, to be published.)

Registry No. 1, 117308-63-1; 2, 117308-64-2; 3, 117308-65-3; 13, 117369-56-9.

Supplementary Material Available: Listing of atomic parameters (Table S1), bond distances and angles (Table S2), hydrogen atom parameters (Table S3), anisotropic thermal parameters (Table S4) (7 pages); table of structure factors (6 pages). Ordering information is given on any current masthead page.

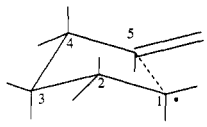
Stereochemical Control in Hex-5-enyl Radical Cyclizations: Axial vs Equatorial 2-(1-But-3-enyl)cyclohexyl Radicals

T. V. RajanBabu* and Tadamichi Fukunaga

Contribution No. 4745 from E. I. du Pont de Nemours & Company, Central Research & Development Department, Experimental Station, Wilmington, Delaware 19898.
Received May 5, 1988

Abstract: Free radical cyclization reactions of 4-substituted *cis*- and *trans*-2-(1-but-3-enyl)cyclohexyl radicals and the analogous 3,5-dioxacyclohexyl radicals were investigated. Within the framework of hex-5-enyl radical cyclization, 1,5-cis or 1,5-trans product predominates if the butenyl group occupies an equatorial or axial position of the cyclohexane chair form, respectively. The results are rationalized by the transition-state model *originally* proposed by Beckwith for acyclic hex-5-enyl radical cyclizations.

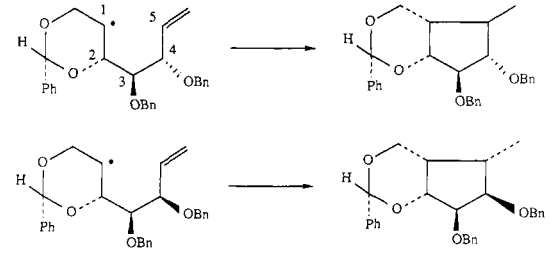
1,5-Ring closures of hex-5-enyl radicals followed by trapping of the resulting cyclopentylmethyl radicals have attracted considerable attention in both synthetic and physical organic chemistry.[1] Studies carried out by Beckwith and co-workers[2] with prototypical alkyl-substituted acyclic hexenyl radicals have provided general guidelines to predict the stereochemical outcome of the cyclization. It was proposed that the transition state resembles a cyclohexane chairlike conformation (**1**), in which



1

substituents preferentially occupy pseudoequatorial positions. Ring closures of cyclic radicals are not as predictable.[3] For example, 2-(1-but-3-enyl)cyclohexyl radicals generally cyclize to give predominantly 1,2-cis;1,5-cis products. (In this paper, atoms are numbered according to the hex-5-enyl radical numbering system to emphasize regio- and stereochemical relationships of the cyclizations, and other atoms such as those in the six-membered rings will be differentiated by primed numbers.) To account for the observed 1,2-cis;1,5-cis stereochemistry, Beckwith and co-workers[3b] concluded that the ring closure occurs through the cyclohexane conformer in which the butenyl substituent occupies an axial site, because in this conformation orbital overlap between the radical SOMO and the olefin π^* orbital was believed to be maximized. Irrespective of the mechanistic details, it is this 1,5-cis stereoselectivity that has found elegant uses in several natural product syntheses.[4] However, various other structural features also appear to influence the stereochemical outcome.

We have recently observed[5] that the stereochemistry of 2-butenyl-3,5-dioxacyclohexyl radical ring closure is critically influenced by the nature of the substituents at the 4-position. For example, as shown in eq 1 and 2, the glucose-derived hex-5-enyl radical cyclizes with unprecedented exclusive 1,5-trans selectivity (eq 1) whereas the corresponding radical in the manno series yields exclusively 1,5-cis product (eq 2). In these systems, the but-3-enyl



and phenyl groups are cis on the dioxane ring system and most likely occupy the equatorial sites. Therefore, the results indicate

(1) (a) Kochi, J. K. *Free Radicals*, Wiley: New York, 1973. (b) Julia, M. *Pure Appl. Chem.* **1974**, *40*, 553. (c) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. (d) Hart, D. J. *Science* **1984**, *223*, 883. (e) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: New York, 1986. (f) For a compilation of other relevant references, see: Park, S.-U.; Chung, S.-K.; Newcomb, M. *J. Am. Chem. Soc.* **1986**, *108*, 240. (g) For an exhaustive review of applications in synthesis, see: Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541.

(2) (a) Beckwith, A. L. J.; Blair, I.; Phillipou, G. *J. Am. Chem. Soc.* **1974**, *96*, 1613. (b) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 482. (c) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545.

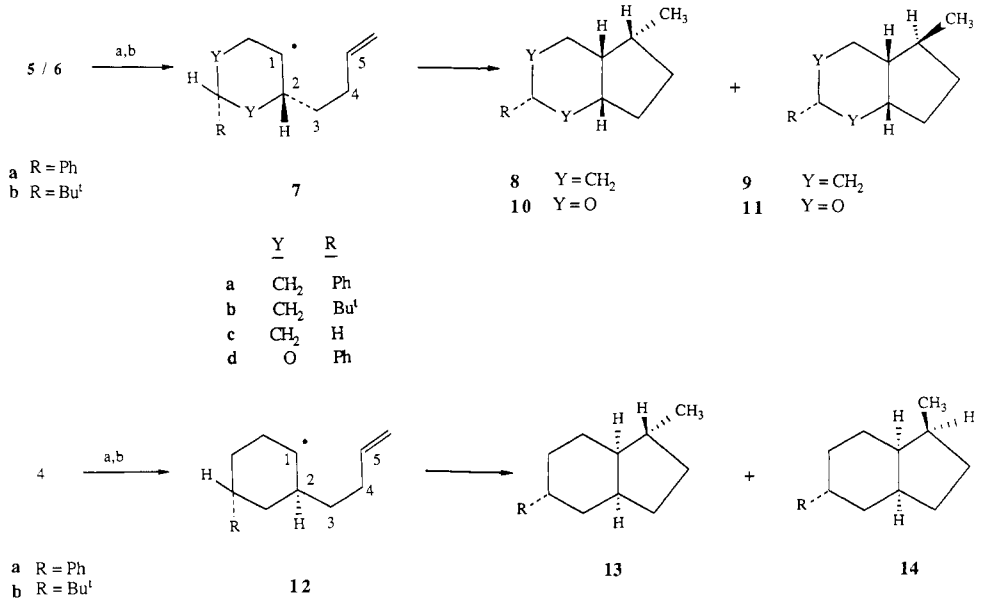
(3) (a) Wolff, S.; Agosta, W. C. *J. Chem. Res. (S)* **1981**, *78*. (b) Beckwith, A. L. J.; Phillipou, G.; Serelis, A. K. *Tetrahedron Lett.* **1981**, *22*, 2811. (c) For an exceptional case where the cis product formation is precluded by steric crowding, see: Leonard, W. R.; Livinghouse, T. *Tetrahedron Lett.* **1985**, *26*, 6431. For other exceptions, see ref 5.

(4) Some representative examples from various groups: (a) Burnett, D. A.; Choi, J.-K.; Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8201. (b) Stork, G. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon: Oxford, 1983. (c) Stork, G.; Sophia, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 6826. (d) Curran, D. P.; Chen, M. H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 1106. (e) Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3102. (f) Hutchinson, J. H.; Pattenden, G.; Myers, G. *Tetrahedron Lett.* **1987**, *28*, 1313. (g) Baldwin, J. E.; Li, C.-S. *J. Chem. Soc., Chem. Commun.* **1987**, 166. (h) Snider, B. B.; Mohan, R.; Kates, S. A. *Tetrahedron Lett.* **1987**, *28*, 841. (i) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116. (j) RajanBabu, T. V. *J. Org. Chem.* **1988**, *53*, 4522. (k) See also: *Selectivity and Synthetic Applications of Radical Reactions*; Tetrahedron: Symposia-in-Print No. 22; Giese, B., Ed.; Pergamon: Oxford, 1985; Vol. 41.

(5) (a) RajanBabu, T. V. *J. Am. Chem. Soc.* **1987**, *109*, 609. (b) RajanBabu, T. V. *Abstracts of Papers*, 193rd National Meeting of the American Chemical Society, Denver, CO; American Chemical Society: Washington, DC, 1987; ORGN 225. (c) RajanBabu, T. V.; Fukunaga, T.; Reddy, G. S. *J. Am. Chem. Soc.*, in press. (d) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.*, in press.

0002-7863/89/1511-0296$01.50/0

Scheme I[a]

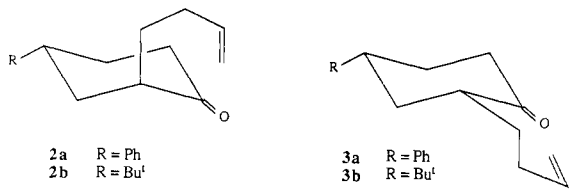


[a] a. Im_2CS. b. Bu_3SnH, AIBN.

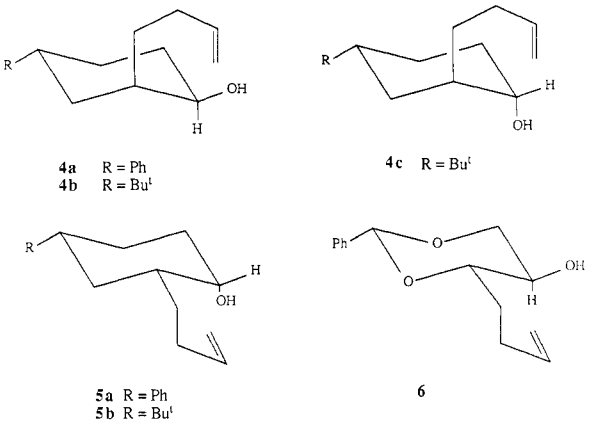
that an axially oriented but-3-enyl side chain may not be required either for the cyclization or for the 1,2-cis;1,5-cis stereoselectivity. In this paper we report on the ring closures of cyclohexyl and related cyclic radicals with a but-3-enyl side chain locked either in an axial or an equatorial position and show that the side-chain orientation does indeed influence the stereochemical outcomes of the cyclization. Also, we show that the results can be rationalized within the framework of the transition-state geometry *originally* proposed by Beckwith.

Results

Radical Precursors. Conformationally rigid cyclohexyl radical precursors were prepared from 4-phenyl- and 4-*tert*-butyl-substituted cyclohexanones according to well-established procedures. Imines derived from the ketones were first alkylated[6] with 4-bromobutene to obtain mixtures of *cis*- and *trans*-4-substituted-2-(1-but-3-enyl)cyclohexanones. The major products were readily identified by ^{13}C NMR to be the trans isomers, **2a** and **2b**, which exhibited well-known upfield steric-compression shifts of the ring carbon resonances, owing to the axial substitution[7] relative to the cis isomers, **3a** and **3b**. The cis and trans isomers were separated



by chromatography and reduced by L-Selectride (Aldrich) to the corresponding alcohols **4** and **5**. The relative stereochemistry of the OH group, although not relevant to the current study, was established by ^{13}C NMR.[7a] In agreement with the known stereoselectivity,[8] the major reduction product from ketone **2b** was the equatorial alcohol **4b**, which showed the carbinol carbon at δ 73.21 to be less shielded than that of the minor axial isomer **4c** at δ 69.78. The upfield shift of 3.43 ppm in the latter is consistent with the presence of an axial OH group. Similarly, axial alcohols **5a** and **5b**, derived from the minor ketone isomers **3a** and **3b**, showed the carbinol carbon signal at δ 67.73 and 67.88, respectively. For comparison, the equatorial carbinol **4a** exhibited the corresponding signal at δ 72.38.



The dioxane radical precursor **6** was prepared by a Wittig reaction of 2,3-dideoxy-4,6-*O*-(phenylmethylene)-D-glucopyranose with methylenetriphenylphosphorane.[5c]

Radical Cyclizations. The radicals were generated from the alcohols according to the Barton method.[9] Alcohols were first acylated with thiocarbonylbis(imidazole) and the resulting thiocarbonylimidazolides were refluxed in toluene in the presence of tributyltin hydride and azobisisobutyronitrile. Under these conditions the radicals readily cyclized; however, significant quantities of the starting alcohol (up to 50%) were often recovered after workup. Hydrocarbon products were isolated generally by column chromatography or distillation and were analyzed by a combination of gas chromatography, NMR spectroscopy, and high-resolution mass spectrometry.

The major ring closure products were cis-fused [4.3.0]bicyclononanes (1,2-cis selectivity) as in accord with results in the

(6) Fraser, R. R.; Banville, J.; Dhavan, K. L. *J. Am. Chem. Soc.* **1978**, *100*, 7999.

(7) (a) Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy: Methods and Applications*; Verlag Chemie: Weinheim, Federal Republic of Germany, 1987. (b) For assignments in a related system, see: Wanat, R. A.; Collum, D. B. *J. Am. Chem. Soc.* **1985**, *107*, 2078.

(8) Stereochemistry of Grignard additions to 2-methyl-4-*tert*-butylcyclohexanones follows a similar course. See: Finici, J.; Maujeau, A. *Bull. Soc. Chim. Fr.* **1971**, *219*. For a discussion of stereoselectivity in nucleophilic additions to carbonyl compounds, see: Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908 and references cited therein.

(9) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. For previous applications of Barton deoxygenation conditions for hexenyl radical cyclizations, see: Clive, D. L. J.; Beaulieu, P. L.; Set, L. *J. Org. Chem.* **1984**, *49*, 1314. See also ref 5. We have since found that the phenyl thionocarbonate procedure (Robins, M. J.; Wilson, J. S.; Hanske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059) is clearly superior in other related deoxygenative cyclization reactions.[5]

Table I. Cyclization of 2-(1-But-3-enyl)cyclohexyl Radicals

radicals	% yield[a]	1,5-cis:1,5-trans	note
7a	29	82:11	this work[b]
7b	37	80:13	this work
7c		74:21	ref 3b
7d	55	70:30	this work; ref 5c
12a	21	31:63	this work[c]
12b		22:60	this work[d]

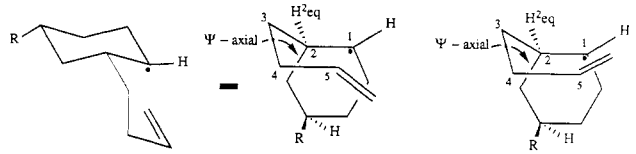
[a] Based on isolated pure isomers. GLPC shows that these are excellent reactions and that the only other contaminant in the products is the starting alcohol (see the Experimental Section). Isolation of pure products is complicated by the presence of Bu_3Sn residues and the volatility of the products. [b] 4% yield of another hydrocarbon with a methyl group. [c] 5% yield of another hydrocarbon with no methyl group. [d] 12% yield of another hydrocarbon with a methyl group.

literature.[3,4a-d,5,10] The cyclohexyl radicals **7a** and **7b**, derived from alcohols **5**, with an equatorial but-3-enyl group showed high selectivity toward 1,5-cis ring closure. As summarized in Table I, the ratios of 1,5-cis (**8**) to 1,5-trans products (**9**) from alcohol **5a** and **5b** were 82:11 and 80:13, respectively. For comparison, the 1,5-cis:1,5-trans ratio for the unsubstituted 2-butenylcyclohexyl radical **7c** is reported[3b] to be 74:21. The 1,5 selectivity of the dioxane radical **7d**, derived from **6**, was moderate; the 1,5-cis product (**10a**) predominated over the 1,5-trans isomer (**11a**) by 70:30. In contrast, radicals **12** (from **4**) with an axial but-3-enyl chain gave unexpected 1,5-trans product **13** as the major product. The 1,5-cis:1,5-trans ratios from **4a** and **4b** were 31:63 and 22:60, respectively (Scheme I).

The 1,5 stereochemistry of the ring-closure products was ascertained by examination of the ^{13}C NMR chemical shifts of the methyl group. It is well-known that, within a given series, the sterically more congested CH_3 groups always appear at a higher field.[7a,11,12] Thus, the major product from **5b** with the CH_3 signal at δ 17.50 was assigned the more congested endo-CH_3;1,5-cis structure **8b**, since the minor product showed the signal at δ 19.44, consistent with exo-CH_3;1,5-trans structure **9b**.[3,11,12] In the 4′-phenyl series, the minor exo-CH_3 product **9a** showed a signal at δ 19.51 very similar to that of **9b**, whereas the CH_3 group in the major isomer **8a** was somewhat less shielded (δ 18.85) than that in the corresponding *tert*-butyl analogue **8b**. The difference may be attributed to the 4′-substituents. Since both the methyl and substituent R groups lie in the concave side of the bicyclononane system, the difference in steric bulk between Ph group (A value = 2–3 kcal) and Bu^t group (A value = 5 kcal) may be reflected more significantly in this series. On the other hand, the products derived from radicals **12** with an axial butenyl chain would have the 4′-substituent on the convex exo face, and this substituent should have little effect on the CH_3 chemical shifts. Thus, in the minor products (**14a** and **14b**) these values are δ 15.54 and 15.56, consistent with endo-CH_3;1,5-cis structure, whereas the corresponding values for the major products **13a** and **13b** are δ 22.71 and 22.63, consistent also with exo-CH_3;1,5-trans structure.

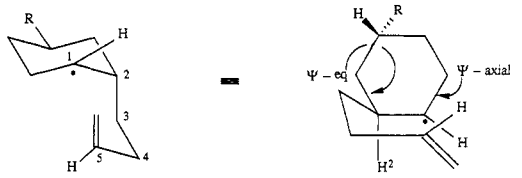
Discussion

As summarized in the table, radicals (**7a** and **7b**) with an equatorial but-3-enyl group preferentially cyclized to give 1,2-cis;1,5-cis products (**8a** and **8b**), and the selectivity of 1,5-cis ring closure over 1,5-trans ring closure was greater than 6:1. In contrast, radicals (**12a** and **12b**) with a but-3-enyl group in the axial orientation showed less pronounced selectivity but favored 1,5-trans cyclization products! These results are in stark contrast to the notion[3b] that the orbital overlap appropriate for the cyclization can develop only with an axial but-3-enyl group, leading predominantly to 1,5-cis products. The anchoring effect of the *tert*-butyl or the phenyl group in our system makes it possible to conclude with a reasonable assurance that 1,5-cis products arise from chairlike transition states,[2] depicted by **7**-chair, in which the



substituents are all in the most favorable equatorial positions of the cyclohexane ring. In this transition state the radical center in the cyclohexane ring system interacts from its axial face with the olefin π^* orbital. Results of this and other studies[5,10] on rigid systems indicate that the SOMO–LUMO overlap involving an equatorial but-3-enyl group is not as poor as it was alleged previously.

The 1,5-trans preference in the cyclization of **12a** and **12b** with an axial but-3-enyl group may be most reasonably rationalized by the chairlike transition state depicted by structure **12**-chair,



12-chair

which retains the butenyl group in the axial position.[13] However, the 1,5-trans selectivity in these cases is much lower than the cis selectivity observed with radicals **7a** and **7b**. Obviously, energetically more competitive transition states exist for the ring closures of **12a** and **12b** than for those of **7a** and **7b**, suggesting that the orbital overlap with an equatorial but-3-enyl group may be at least as efficient as that in the axial orientation. The minor ring-closure products (**9a**, **9b**, **14a**, and **14b**) may result from boatlike transition states[5] (for example, **7**-boat for the formation of **9**) as suggested by recent theoretical calculations,[14] which show that the energy difference between the chair- and boatlike transition states is small relative to the energy of activation for cyclization. We should note that a similar and perhaps more realistic transition-state model can be constructed based on the folded, envelope-like conformations of methylcyclopentane with the methyl group on one of the basal carbon atoms of the envelope. However, we find the cyclohexane model to be more useful, simply because at least at this time conformational preferences are better understood in the cyclohexane system than in methylcyclopentanes.

Curran[12] has suggested that minor products of radical cyclizations could arise also from a change in the conformation of cycloalkyl residues. The fact that less rigid and conformationally more flexible dioxane and unsubstituted cyclohexyl radicals (**7d** and **7c**) exhibit less pronounced 1,5-cis selectivity than **7a** and **7b** suggests that conformational flexibility diminishes the stereoselectivity.

Cyclization of 2-(1-but-3-enyl)cyclohexanones mediated by zinc in the presence of trimethylsilyl chloride may also be influenced by the same controlling factors. Corey[10b] reported that *cis*-2-(1-but-3-enyl)-4-*tert*-butylcyclohexanone (**3b**) gave mostly a cis-fused hydrindanol (**15**), in which the 1,5 stereochemistry is cis. The 1,5-cis:1,5-trans ratio was reported to be 66:7.[10b] We carried out the same reaction with the corresponding trans isomer **2b** under slightly modified conditions[15] and found that 1,5-trans

(10) (a) Pradhan, S. K.; Kolhe, J. N.; Mistry, J. S. *Tetrahedron Lett.* **1982**, *23*, 4481. (b) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821.

(11) For some representative structures, see: Whitesell, J. K.; Matthews, R. S. *J. Org. Chem.* **1977**, *42*, 3878. (b) Schneider, H.-J.; Nguyen-ba, N.; Thomas, F. *Tetrahedron* **1982**, *38*, 2327. (c) See also ref 12.

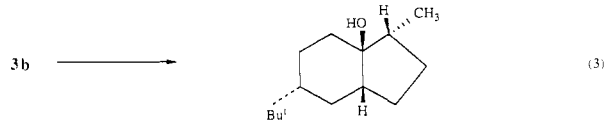
(12) Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943.

(13) For a related stereochemical rationale in a tandem radical cyclization, see: Kano, S.; Yuasa, Y.; Yokomatsu, T.; Asami, K.; Shibuya, S. *J. Chem. Soc., Chem. Commun.* **1986**, 1717.

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

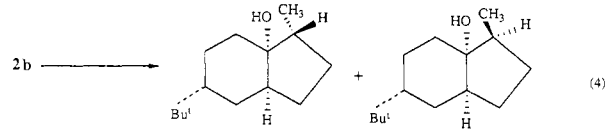
(15) Under the reported conditions[10b] silyl enol ethers of ketones and some uncyclized reduction products were detected in addition to the cyclization products as determined by high resolution GC–MS and ^1H NMR. We used activated Zn prepared according to the procedure of Rieke and Uhm (Rieke, R. D.; Uhm, S. J. *Synthesis* **1975**, 452).

ring closure is preferred over cis but only by 3:1. The results parallel closely those with the cyclohexyl radicals discussed above and can be readily accounted for within the framework of the transition states **7** and **12**.



(3)

15



(4)

16 **17**

Conclusion

In this study of cyclizations of conformationally rigid 2-(1-but-3-enyl)cyclohexyl radicals, we have conclusively shown that the stereochemical outcome of the reaction is critically influenced by the orientation of the butenyl side chain; an equatorial butenyl group leads predominantly to 1,5-cis cyclization products, whereas an axial butenyl group preferentially gives rise to 1,5-trans products. All of these stereochemical consequences can be satisfactorily accounted for by the cyclohexane chair-like transition states originally proposed by Beckwith and co-workers[2] for *acyclic* hex-5-enyl radical cyclizations. In related but conformationally less rigid systems, the transition states having an equatorial and an axial butenyl side chain may compete. Minor ring-closure products also may arise from less favorable boatlike transition states. Our results, however, are incompatible with the earlier proposal[3b] that an axially disposed butenyl side chain is favored for the cyclization and that it leads to 1,5-cis products.

Finally, the results reported here show that the proper alkylation protocols of cyclic ketones can be used to design free-radical ring annulation schemes and to control the stereochemistry of radical cyclization products. It is well-known that the axial product is formed in the alkylation of cyclohexanones under kinetic control and the more stable equatorial product is formed under thermodynamic control.[6] This together with the influence of a C-4 alkoxy substituent that we reported earlier[5] as another control element should make the hex-5-enyl radical cyclization an even more powerful reaction in the synthesis of complex cyclopentanoid natural products. Further applications in this area will be reported in due course.

Experimental Section

The NMR spectra were run in $CDCl_3$ solutions unless otherwise indicated. The proton and carbon assignments were made with the aid of decoupling, nuclear Overhauser, enhanced polarization transfer (INEPT), and carbon–proton correlation mapping experiments. Gas chromatography was done on Hewlett-Packard Instruments Model 5210A with column A (6 ft × 1/8 in. 3% SP2100 on Supelcoport 80/80 support) or Model 5890A with column B (25 m × 0.02 mm HP1 cross-linked methyl silicone, 0.33-μm film) with temperature programming.

The reactions were carried out in oven- or flame-dried glassware in an inert atmosphere (nitrogen or argon) wherever appropriate. Moisture- or air-sensitive reagents were weighed out inside a polyethylene glove bag under nitrogen. Column chromatography was performed according to the procedure described by Still.[16]

Preparation of 2b and 3b (*trans*- and *cis*-2-(1-But-3-enyl)-4-*tert*-butylcyclohexanone. These compounds were prepared by alkylation of *N*-(4-*tert*-butylcyclohexylidene)-2-butylamine with 4-bromobutene according to the procedure reported in the literature.[6] The isomers were separated on silica with 5–10% ethyl acetate/hexane as the solvent (**3b** has the higher R_f). The trans (**2b**) and cis (**3b**) alkylation products were obtained in a ratio of 9:1 and are readily identified by their respective ^{13}C NMR spectra.[7] **2b**: ^{13}C NMR δ 26.886 (3 C), 27.434, 30.619, 31.312, 31.385, 32.373, 38.422, 41.291 (*C*H), 48.474 (*C*H), 115.142, 137.724, 215.608. **3b**: ^{13}C NMR δ 27.646 (3 C), 28.356, 28.765, 31.290, 32.448, 35.058, 41.723, 47.137 (*C*H), 48.829 (*C*H), 114.587, 138.567, 213.29.

Reduction of 3b with L-Selectride (Preparation of *c*-2-(1-But-3-enyl)-*c*-4-*tert*-butylcyclohexanol (5b)). A solution of 0.368 g of **3b** in 5 mL of THF was treated with 2.12 mL of 1 M L-Selectride at −78 °C for 3 h and the reaction mixture was worked up by adding 1.5 mL of 10% sodium hydroxide, followed by the addition of 1.5 mL of 30% H_2O_2. The product was extracted into ether and purified by column chromatography. **5b**: IR (neat) 3390, 3080, 2940, 910 cm^{-1}; ^1H NMR δ 0.85 (s, 9 H), 0.90–2.15 (m, 13 H), 3.85 (s, br, 1 H), 4.95 (m, 2 H), 5.80 (m, 1 H); ^{13}C NMR δ 20.65, 27.38, 27.50 (3 C), 31.13, 32.18, 32.45, 33.81, 41.24, 47.83, 67.88, 114.29, 138.97; HRMS, *m/z* 210.2018 (M^+, calcd for $C_{14}H_{26}O$ 210.1962).

Reduction of 2b (Preparation of *c*-2-(1-But-3-enyl)-*t*-4-*tert*-butylcyclohexanol (4b) and *c*-4-*tert*-Butyl-*t*-2-(1-but-3-enyl)cyclohexanol (4c). Reduction of **2b** gave a mixture of two isomeric alcohols **4b** and **4c** in a ratio of 92:8. These isomers were separated by flash chromatography on silica gel with ethyl acetate/hexane as the solvent system. **4b**: IR (neat) 3410, 3080, 910 cm^{-1}; ^1H NMR δ 0.85, 0.95–2.30 (m, 13 H), 3.65–3.80 (m, 1 H), 4.90–5.10 (m, 2 H), 5.85 (m, 1 H); ^{13}C NMR δ 23.58, 25.69, 27.53 (3C), 28.38, 30.09, 31.99, 32.03, 39.38, 40.05, 73.21, 114.26, 139.15; HRMS, *m/z* 210.1942 (M^+, calcd for $C_{14}H_{26}O$ 210.1962). The minor isomer **4c** (8%) was characterized by the following ^{13}C NMR absorptions: δ 20.91, 24.66, 27.35, 27.70, 28.95, 30.33, 31.95, 40.29, 41.11, 69.78, 114.47, 139.00. The position of the *C*(OH)H (δ = 69.78) as compared to that of the major isomer, i.e. δ 73.21, is suggestive of an axial hydroxyl group.[7]

Cyclization of the Radical Derived from 5b. The thiocarbonylimidazolide prepared from **5b** was refluxed with 2 equiv of tributyltin hydride and trace amounts of azobisisobutyronitrile in toluene for 40 min. Additional half equivalents of tin hydride were then slowly added, and the refluxing was continued for 3 h. The products were isolated first by addition of 3 equiv of tetrabutylammonium fluoride followed by extraction into ether. The ether layer was repeatedly washed with saturated KF and was dried. The volatile hydrocarbons were sublimed into a trap held at dry ice temperature. The yield of sublimed products was 37%. The reaction is very clean and the GLPC yield is excellent. However, the isolated yield is relatively low because of the volatility of the products and problems associated with their separation from the tributyltin residues. Gas chromatography indicated the presence of one major and two minor components, all of which had the elemental composition $C_{14}H_{26}$ as determined by GC–HRMS (HRMS, *m/z* 179.1801, $M^+ - CH_3$, calcd for $C_{13}H_{23}$ 179.1800). ^1H NMR of the major (retention time 3.84 min, 80%) product (2α,4aβ,5α,7aβ)-5-methyl-2-*tert*-butylbicyclo[4.3.0]nonane (**8b**): ^1H NMR, inter alia, δ 0.94 (d, J = 7 Hz); ^{13}C NMR δ 17.50 (*C*H_3), 22.25 (*C*H_2), 23.85 (*C*H_2), 27.23 (3, *C*H_3), 30.10 (*C*H_2), 32.46 (*C*H_2), 32.77 (*C*), 33.01 (*C*H_2), 37.21 (*C*H), 39.78 (*C*H), 40.00 (*C*H), 44.57 (*C*H). The second major product (retention time 2.95 min, 13%) having a *C*H_3 signal at δ 19.44, was assigned the structure **9b** ((2α,4aβ,5β,7aβ)-5-methyl-2-*tert*-butylbicyclo[4.3.0]nonane) by analogy[3,10] to reported examples and relative downfield shift of this carbon as compared to that of the cis compound **8b**.[7,11]

Cyclization of the Radical Derived from 4b. This radical, upon cyclization, gave three hydrocarbons of exact mass (HRMS, *m/z* 194.2009, M^+, calcd for $C_{14}H_{26}$ 194.2034 for **13b**), corresponding to $C_{14}H_{26}$ in a ratio of 60:22:12 with retention time (column A, 140 °C for 4 min; 8 °C per min to 200 °C; 16 min at 200 °C) 3.05, 3.38, and 3.84, respectively. By analogy to the 4-phenyl system (vide infra, **13a** and **14a**), the two major compounds with *C*H_3 chemical shifts at δ 22.63 and 15.56, formed in a 3:1 ratio, were assigned structures **13b** ((2α,4aα,5α,7aα)-5-methyl-2-*tert*-butylbicyclo[4.3.0]nonane) and **14b** ((2α,4aα,5β,7aα)-5-methyl-2-*tert*-butylbicyclo[4.3.0]nonane), respectively.

***trans*- and *cis*-2-(1-But-3-enyl)-4-phenylcyclohexanone (2a and 3a).** These compounds were prepared by the alkylation of *N*-(4-phenylcyclohexylidene)-2-butylamine according to the procedure reported by Fraser et al.,[6] and the isomers were separated by careful chromatography on silica gel with 5–10% ethyl acetate/hexane as the solvent system.

Reduction of the Ketones. Reduction of the purified ketones **2a** and **3a** with L-Selectride at −78 °C is highly stereoselective. Since these reduced products are more readily separated than the parent ketones, a mixture of the ketones was reduced, and the axial and equatorial butenyl compounds ***c*-2-(1-but-3-enyl)-*t*-4-phenylcyclohexanol (4a) and *c*-2-(1-but-3-enyl)-*c*-4-phenylcyclohexanol (5a)** were separated by column chromatography at this stage. These isomers are readily identified by their respective ^{13}C NMR spectra. **4a**: ^1H NMR δ 1.20–2.10 (m), 2.21 (m, 1 H), 2.71 (m, 1 H), 3.86 (m, 1 H), 5.00 (m, 2 H), 5.85 (m, 1 H), 7.10–7.40 (m, aromatic); ^{13}C NMR δ 24.373, 29.998, 31.705, 32.027, 34.798, 36.882, 39.339, 72.379, 114.551, 125.975, 126.871 (2C), 128.320

(16) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(2C), 138.929, 146.184. **5a**: ^{1}H NMR δ 1.20-1.90 (m), 1.97 (d, br, 1 H), 2.12 (q, br, 2 H), 2.55 (m, 1 H), 3.95 (s, br 1 H), 4.90-5.10 (m, 1 H), 5.75-5.90 (m, 1 H), 7.10-7.40 (m, aromatic); ^{13}C NMR δ 27.446, 31.012, 31.940, 33.664, 34.017, 41.087, 44.088, 67.725, 114.474, 125.888, 126.752 (2C), 128.259 (2C), 138.782, 147.177.

Cyclization of the Radical Derived from 5a. The cyclization was carried out as described above for **5b**. The products were isolated by column chromatography on silica gel with hexane as the solvent. The low recovery may be due to the volatility of the products. Analysis of the product mixture on column A (140 °C, 4 min; 8 °C per min to 200 °C; 200 °C, 16 min) revealed three volatile products. The isolated yield of the cyclic products was 29% and the starting alcohol recovered amounted to 47%. Major product (2α,4aβ,5α,7aβ)-5-methyl-2-phenylbicyclo[4.3.0]nonane (**8a**, retention time 10.14 min, 82%): ^{1}H NMR, inter alia, δ 1.05 (d, J = 7.5 Hz); ^{13}C NMR (assignments by INEPT experiment) δ 18.85 (*C*H$_3$), 23.61 (*C*H$_2$), 31.19 (*C*H$_2$), 31.76 (*C*H$_2$), 33.16 (*C*H$_2$), 36.63 (*C*H), 37.49 (*C*H$_2$), 39.37 (*C*H), 40.07 (*C*H), 41.71 (*C*H), 125.56, 126.72 (2C), 128.19, 148.10; HRMS 214.1755 (M$^+$, calcd for $C_{16}H_{22}$ 214.1721). Minor product (2α,4aβ,5β,7aβ)-5-methyl-2-phenylbicyclo[4.3.0]nonane (**9a**, retention time 9.53 min, 11%): ^{1}H NMR δ 0.96 (d, J = 7 Hz, *C*H$_3$); ^{13}C NMR δ 19.51 (*C*H$_3$); HRMS, m/z 214.1730 (M$^+$, calcd for $C_{16}H_{22}$ 214.1721). Another product (retention time 9.82 min, 4%) having a CH$_3$ signal at δ 17.84 has not been identified.

Cyclization of the Radical Derived from 4a. The cyclic products were obtained in 21% yield; the starting alcohol recovery was 50%. ^{13}C NMR of major (retention time 9.67 min, 63%) product ((2α,4aα,5α,7aα)-5-methyl-2-phenylbicyclo[4.3.0]nonane, **13a**): ^{1}H NMR, inter alia, δ 0.962 (d, J = 7 Hz); ^{13}C NMR δ 22.71 (*C*H$_3$), 27.97 (*C*H$_2$), 29.33 (*C*H$_2$), 31.87 (*C*H$_2$), 33.17 (*C*H$_2$), 35.21 (*C*H$_2$), 37.18 (*C*H), 38.65 (*C*H), 39.48 (*C*H), 46.18 (*C*H); HRMS, m/z 214.1713 (M$^+$, calcd for $C_{16}H_{22}$ 214.1721); minor (retention time 10.16 min, 31%) product ((2α,4aα,5β,7aα)-5-methyl-2-phenylbicyclo[4.3.0]nonane, **14a**): ^{1}H NMR, inter alia, δ 0.940 (d, J = 7 Hz); ^{13}C NMR δ 15.54 (*C*H$_3$), 22.57 (*C*H$_2$), 26.71 (*C*H$_2$), 30.53 (*C*H$_2$), 33.02 (*C*H$_2$), 35.76 (*C*H$_2$), 38.44 (*C*H), 38.70 (*C*H), 40.48 (*C*H), 43.14 (*C*H); HRMS, m/z 214.1731 (M$^+$, calcd for $C_{16}H_{22}$ 214.1721). Another hydrocarbon with no CH$_3$ group (5%) was not identified.

Zn/TMSCl-Mediated Cyclization of 2b. Activated Zn was prepared according to the literature[15] from 2.73 g of anhydrous $ZnCl_2$ and to this were added 0.42 g (2 mM) of **2b** (97.5% pure) dissolved in 8 mL of freshly distilled THF, 1.53 mL (12 mM) of chlorotrimethylsilane, and 0.70 mL of distilled 2,6-lutidine. The mixture was refluxed for 18 h. Unreacted Zn was filtered off with the aid of Celite and 20 mL of saturated sodium bicarbonate and 50 mL of ether were added. The aqueous layer was separated and was repeatedly extracted. The organic layers was washed with brine, dried, and concentrated. Analysis on column B (100 °C, 5 min; 10 °C per min to 200 °C; 200 °C, 20 min) indicated complete absence of starting ketone. The three peaks at 15.75 min (23%), 16.03 min (65%), and 16.38 min (12%) were identified as a mixture of at least four silyl ether components: three of exact molecular composition $C_{17}H_{34}OSi$ (282.2379) and one of composition $C_{17}H_{32}OSi$ (280.2222) by GC-HRMS.

The mixture of silyl ethers was treated with tetrabutylammonium fluoride in THF, and the desilylated products were readily separated by column chromatography. The first fraction was identified as a mixture of **2b** and **3b** presumably formed by the desilylation of silylenol ethers of the ketone **2b**. The second component was identifed as the 1,5-trans cyclization product **16** and the third fraction as the 1,5-cis product **17**. The last fraction (17%) was readily identified as a ketone-reduction product **4b** by comparison of GC retention time and NMR spectra with those of an authentic sample. The yield of cyclization products under these conditions was about 20%. The ratio of 1,5-trans ((2α,4aα,5α,7aα)-2-*tert*-butyl-4a-hydroxy-5-methylbicyclo[4.3.0]nonane, **16**) to 1,5-cis ((2α,4aα,5β,7aα)-2-*tert*-butyl-4a-hydroxy-5-methylbicyclo[4.3.0]nonane, **17**) isomers was determined as 75:25 by the mass of the isolated compounds. More than 50% of the ketone was recovered as the silyl enol ethers. **16**: ^{1}H NMR δ 0.85 (s, 9 H), 0.93 (d, J = 7.50 Hz, 3 H), 1.10-2.10 (m, 14 H); ^{13}C NMR δ 16.692, 22.552, 25.123, 25.342, 27.516 (3C), 29.743, 32.300 (quaternary), 35.768, 41.387, 42.233, 42.288, 78.444; HRMS, m/z 210.1997 (M$^+$, calcd for $C_{14}H_{26}O$ 210.1984). **17**: ^{1}H NMR δ 0.85 (s, 9 H), 0.89 (d, J = 6.50 Hz, 3 H), 1.10-2.05 (m, 14 H); ^{13}C NMR δ 12.838, 22.080, 24.178, 25.283, 27.573 (3C), 28.277, 28.399, 32.188 (quaternary), 41.658, 45.151, 45.633, 77.911; HRMS, m/z 210.1997 (M$^+$, calcd for $C_{14}H_{26}O$ 210.1984).

Cyclization of 3b. For comparison of spectral data an authentic sample of (2α,4aβ,5α,7aβ)-2-*tert*-butyl-4a-hydroxy-5-methylbicyclo[4.3.0]-nonane (**15**) was prepared by cyclization of **3b** using activated Zn as described earlier.[10b,15] As in the case of **2b**, the product was invariably contaminated with the silyl enol ethers of the starting ketone. In our hands, the yield of the expected products was only about 46% based on the amount of unrecovered ketone. **15**: ^{1}H NMR δ 0.83 (s, 9 H), 0.98 (d, J = 6.5 Hz, 3 H), 1.15-2.10 (m); ^{13}C NMR δ 15.886 (*C*H$_3$), 21.311 (*C*H$_2$), 27.180 (3 C, *C*H$_3$), 30.250 (*C*H$_2$), 30.263 (*C*H$_2$), 30.298 (*C*), 32.251 (*C*H$_2$), 32.705 (*C*H$_2$), 43.444 (*C*H), 46.727 (*C*H), 48.840 (*C*H), 81.922 (*C*HOH).

Total Syntheses of (+)-Geissoschizine, (±)-Geissoschizine, and (±)-(*Z*)-Isositsirikine. Stereocontrolled Synthesis of Exocyclic Double Bonds by Stereospecific Iminium Ion-Vinylsilane Cyclizations

Larry E. Overman* and Albert J. Robichaud

Contribution from the Department of Chemistry, University of California, Irvine, California 92717. *Received July 5, 1988*

Abstract: (+)-Geissoschizine (**1**) was prepared in an efficient and stereocontrolled fashion in 11 steps and 7.5% overall yield from (*S*)-tryptophanamide (**20**). Key steps are the stereoselective 1,4-addition of cuprate **13a** to tetracyclic intermediate **8**, which establishes the C-3/C-15 stereorelationship of the product alkaloid, and cyclization of the (*E*)-vinylsilane iminium cation intermediate **4** (R^1 = H, R^2 = CH$_3$) to form the indoloquinolizidine ring system and elaborate the (*E*)-ethylidene side chain. The related cyclization of a (*Z*)-vinylsilane iminium ion intermediate (**4**, R^1 = CH$_3$, R^2 = H) is a key step in the stereocontrolled synthesis of the (19*Z*)-isositsirikines (**2**).

Geissoschizine (**1**), a pivotal early intermediate in the biosynthesis of polycyclic indole alkaloids of the *Corynantheine-Yohimbine*, *Strychnos*, *Aspidosperma*, and *Iboga* groups, was first isolated from hydrochloric acid cleavage of the dimeric indole

0002-7863/89/1511-0300$01.50/0