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Vinyllithium Cyclizations with Unactivated Alkenes as Internal Electrophiles: Stereoselective Formation of Substituted Methylenecyclopentanes†

A. Richard Chamberlin,* Steven H. Bloom, Laura A. Cervini, and Christopher H. Fotsch

Contribution from the Department of Chemistry, University of California, Irvine, California 92717. *Received January 7, 1988*

Abstract: Vinyllithium reagents derived from ketone [(2,4,6-triisopropylphenyl)sulfonyl]hydrazones undergo intramolecular addition to unactivated alkene groups, giving lithiated alkylidenecyclopentanes that can be trapped with electrophiles. The stereoselectivity of this cyclization has been studied for a variety of derivatives. In many cases there is a strong tendency for the formation of one of two possible product diastereomers, preferences that are explained in terms of a cyclic four-center transition state. In its present form, the reaction is limited to the formation of five-membered rings, but even so provides a useful complement to the more common cationic and radical cyclization methodologies.

Ring formation is a crucial element of synthetic methodology, and as a consequence a large number of strategies have been developed for cationic,[1] radical,[2] and stabilized anionic[3] cyclizations. On the other hand, related ring-forming reactions of highly reactive carbanions have received much less attention, although there are reports of synthetically useful cyclizations of organolithiums,[4] -magnesiums,[5] and -aluminums,[6] among others. In these systems, survival of the internal electrophile (terminator) during the generation of the nucleophile is a major consideration, i.e., the electrophilic site must tolerate the conditions necessary to form a highly reactive carbanion. Despite this potential difficulty, there are a variety of electrophiles, including alkyl halides,[4b,c,5c] carbonyl compounds,[4b,i,5a,7] Michael acceptors,[5e-g,j] epoxides,[4b,g,j] alkynes,[5b,e,h,8] and unactivated double bonds[4k,5i,9] that have been utilized as terminators for the formation of three- to six-membered rings by anionic cyclization.

Because of the unusual nature of the latter electrophile (simple alkenes are not generally thought of as sites of nucleophilic attack), there have been several mechanistic studies of intramolecular organometallic additions to simple alkenes. For example, the mechanism of organomagnesium cyclizations has been extensively investigated.[5j] The results indicate that the cyclization proceeds through a cyclic four-center transition state or a π-complex of the double bond and the metal. The mechanistic pathway of alkyllithium cyclizations has also been scrutinized, and specific attention has focused primarily on whether the cyclization of 5-hexenyllithium actually involves the organolithium itself or rather proceeds via a transient radical intermediate.[9] Studies that support the anionic pathway have been reported by Bailey[4m,o] and by Woolsey,[4n] but Ashby favors the radical mechanism.[10] The fact that alkyllithium cyclizations with 1,2-disubstituted alkenes as terminator rarely succeed (in direct contrast to "genuine" radical cyclizations)[11] mitigates against the transient radical proposal as the only possibility, but the operative mechanism may well be a function of the method of alkyllithium generation or the specific reaction conditions.

Despite these interesting mechanistic studies, organolithium cyclization as a synthetic tool has not been developed extensively, even though there are several important potential advantages over the corresponding radical cyclization. Most importantly, it should be possible to *functionalize* the initially formed cyclization product (an alkyllithium) by reaction with electrophiles, whereas it is not generally possible to trap the corresponding radical intermediate (usually a methylcyclopentane radical) before it abstracts hydrogen atom to give an unfunctionalized hydrocarbon.[12] Cyclizations of vinyllithiums, rather than alkyllithiums, would also incorporate additional functionality (an alkene) into the product and offer the possibility of constructing alkylidenecycloalkanes with control of alkene stereochemistry. In this paper we describe a number of examples that demonstrate the utility of such vinyllithium cyclizations for the stereoselective construction of five-membered ring carbocycles.

† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

Results and Discussion

At the outset of this project it was questionable whether the cyclization of a vinyllithium onto a simple alkene would succeed, despite the 5-hexenyllithium precedent cited above, because an energetically less favorable sp^2 to sp^3 carbanion transformation would be required in this case. Nonetheless, we have found that

(1) (a) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51. (b) Sutherland, J. K. *Chem. Soc. Rev.* **1980**, 265. (c) Van Tamelen, E. E. *Acc. Chem. Res.* **1975**, *8*, 152. (d) Speckamp, N. *Recl.: J. R. Neth. Chem. Soc.* **1981**, *100*, 345.

(2) (a) Julia, M. *Rec. Chem. Prog.* **1964**, *25*, 3. (b) Nonhebel, D. C.; Walton, J. C. *Free Radical Chemistry*; Cambridge University: Cambridge, 1974; Chapter 14.

(3) For example, intramolecular aldol, Diekman, and related enolate cyclizations.

(4) (a) Smith, M. J.; Wilson, S. E. *Tetrahedron Lett.* **1981**, *22*, 4615. (b) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982** *15*, 300. (c) Negishi, E.; Boardman, L. D.; Tour, J. M.; Sawada, H.; Rand, C. L. *J. Am. Chem. Soc.* **1983**, *105*, 6344. (d) Boardman, L. D.; Bagheri, V.; Sawada, H.; Negishi, E. *J. Am. Chem. Soc.* **1984**, *106*, 6105. (e) Cooke, M. P. *J. Org. Chem.* **1984**, *49*, 1144. (f) Piers, E.; Tse, H. *Tetrahedron Lett.* **1984**, *25*, 3155. (g) Cooke, M. P.; Houpis, I. N. *Ibid.* **1985**, *26*, 3643. (h) Shankaran, K.; Snieckus, V. *J. Org. Chem.* **1984**, *49*, 5022. (i) Trost, B. M.; Coppola, B. P. *J. Am. Chem. Soc.* **1982**, *104*, 6879. (j) Last, L. A.; Fretz, E. R.; Coates, R. M. *J. Org. Chem.* **1982**, *47*, 3211. (k) Drozd, U. N.; Ustynyuk, Yu. A.; Tseleva, M. A.; Dmitriev, L. B. *J. Gen. Chem. USSR (Engl. Transl.)* **1969**, *39*, 1951. (l) Dolzine, T. W.; Oliver, J. P. *J. Organomet. Chem.* **1974**, *78*, 165. (m) Bailey, W. F.; Patricia, J. J.; Delgobbo, V. C.; Jarret, R. M.; Okarma, P. J. *J. Org. Chem.* **1985**, *50*, 1999. (n) Ross, G. A.; Koppang, M. D.; Bartak, D. E.; Woolsey, N. F. *J. Am. Chem. Soc.* **1985**, *107*, 6742. (o) Bailey, W. F.; Nurmi, T. T.; Patricia, J. J.; Wang, W. *J. Am. Chem. Soc.* **1987**, *109*, 2442.

(5) (a) Crandall, J. K.; Magaha, H. S. *J. Org. Chem.* **1982**, *47*, 5368. (b) Fujikura, S.; Inoue, M.; Utimoto, K.; Nozaki, H. *Tetraheron Lett.* **1984**, *25*, 1999. (c) Okuda, Y.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Ibid.* **1984**, *25*, 2483. (d) Oppolzer, W.; Begley, T.; Ashcroft, A. *Ibid.* **1984**, *25*, 825. (e) Utimoto, K.; Imi, K.; Shiragami, H.; Fujikura, S.; Nozaki, H. *Ibid.* **1985**, *26*, 2101. (f) Cooke, M. P. *J. Org. Chem.* **1984**, *49*, 1144. (g) Andersen, N. H.; Duffy, P. E.; Denniston, A. D.; Grotjahn, D. B. *Tetrahedron Lett.* **1978**, 4315 and references therein. (h) Richey, H. G.; Rothman, A. M. *Ibid.* **1968**, 1457. (i) Richey, H. G.; Veale, H. S. *Ibid.* **1975**, 615. (j) Fuchs, P. L.; Braish, T. F. *Chem. Rev.* **1986**, *86*, 903. (k) For a review, see: Hill, E. A. *Organomet. Chem.* **1975**, *91*, 123.

(6) (a) Stefani, A. *Helv. Chem. Acta* **1974**, *57*, 1346. Ziegler, K. *Organometallic Chemistry*; Zeiss, H., Ed.; Reinhold: New York, 1960; p 234. Antonov, A. A.; Brodovskaya, C. F.; Nanetkin, N. S.; Smetanyuk, V. I. *Neftechkhimiya* **1975**, *15*, 264.

(7) Corey, E. J.; Kuwajima, I. *J. Am. Chem. Soc.* **1970**, *92*, 395.

(8) Crandall, J. K.; Battioni, P.; Wehlacz, J. T.; Bindra, R. *J. Am. Chem. Soc.* **1975**, *97*, 7171.

(9) For example, single-electron transfer from the anion to a trace of oxidant impurity, radical cyclization, and then electron transfer back to the resultant radical to give observed anionic cyclization product.

(10) (a) Ashby, E. C.; Pham, T. N., Park, B. *Tetrahedron Lett.* **1985**, *26*, 4691. (b) Ashby, E. C.; Pham, T. N. *J. Org. Chem.* **1987**, *52*, 1291.

(11) For reviews including radical cyclization, see: (a) Geise, B. *Radicals in Organic Synthesis*; Pergamon: New York, 1986. (b) Neumann, W. P. *Synthesis* **1987**, 665.

(12) For exceptions, see: ref 11a, pp 173-188.

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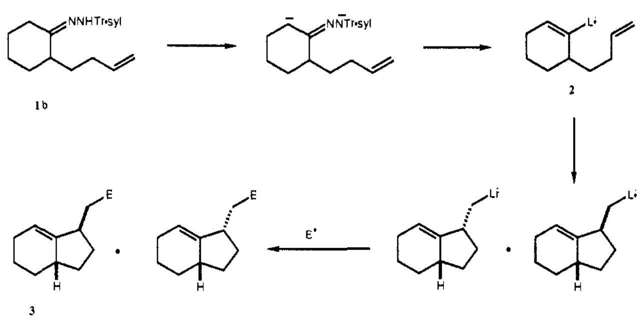
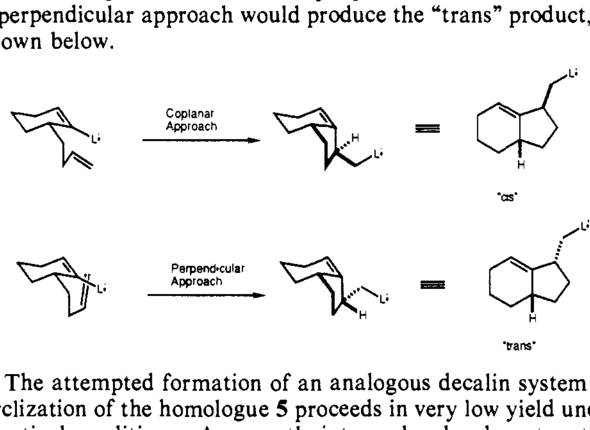
the cyclization does proceed smoothly at a reasonable rate.[13] For example, the vinyl anion **2**, prepared from the [(triisopropylphenyl)sulfonyl]hydrazone **1b** by treatment with *tert*-butyllithium (2.1 equiv in THF, $-78 \rightarrow 0$ °C),[14] cyclizes within approximately 10 min at 0 °C to the alkyllithium intermediate, which reacts with a variety of electrophiles to give the products **3a–e** (Table I). The unsaturated ketone starting materials for these studies were prepared by standard procedures and converted into the trisylhydrazone cyclization precursors by treatment with trisylhydrazine.[14]



Yields under these conditions were lower than expected because the alkyllithium intermediate was partially protonated prior to reaction with the electrophile. In order to assess this problem, the progress of the reaction was monitored by quenching a series of aliquots with D_2O, which clearly shows that the alkyllithium intermediate is protonated fairly rapidly ($t_{1/2}$ = 30 min), presumably by tetrahydrofuran (THF).[15] In an effort to increase the yield, the cyclization was attempted in a number of solvents other than THF. The rate of cyclization is approximately the same in 10% tetramethylethylenediamine (TMEDA)/hexane as that observed in THF, and the change in solvent increases the yield of trapped product substantially. For example, the yield of the alkyl bromide **3b** increases from 61% to 81%. Generally, then, the solvent of choice for these reactions is TMEDA/hexane,[14] although THF often is satisfactory for relatively rapid cyclizations.

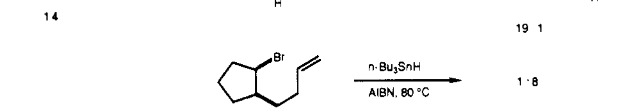
Initially the most surprising aspect of the cyclization of **2** was that a large excess of the "cis" diastereomer **3** was produced. Examination of the crude reaction mixture by ^{1}H NMR spectroscopy and by capillary GC showed the ratio of **3** to its diastereomer to be >50:1, despite the lack of any obvious reason for this selectivity. The stereochemistry of the major product was deduced as described previously.[13] The observed diastereoselectivity of this vinyllithium cyclization is consistent with a four-center transition state similar to one proposed by Oliver[41] and by Hill[5k] for the cyclizations of related 5-hexenyl organometallic compounds. A preferred coplanar approach of the C–Li bond to the double bond would give the observed major product, while in contrast, a perpendicular approach would produce the "trans" product, as shown below.



The attempted formation of an analogous decalin system by cyclization of the homologue **5** proceeds in very low yield under identical conditions. Apparently intramolecular deprotonation to form the allyllithium species is the predominate pathway, as indicated by deuterium quenching studies of the reaction. This 6-exo mode of cyclization also fails for the parent 2-lithio-1,7-octadiene, effectively limiting the use of the reaction to the formation of five-membered rings.

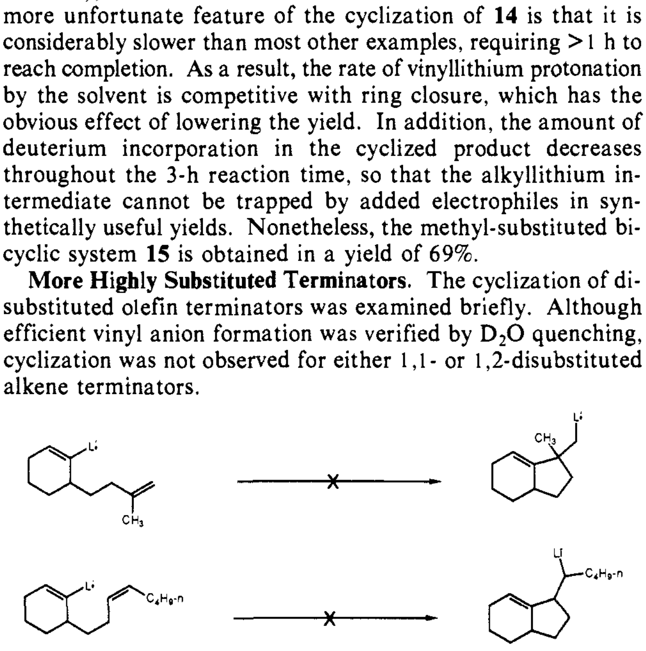
To test the effect of restricting conformations of the cyclizing tether, the trisylhydrazones **7b** and **10b** were prepared and converted into the vinyl anions **8** and **11**, respectively. The equatorially substituted vinyllithium **11** cyclizes only slightly faster than **8**, in which the side chain is axial: analysis of the ^{1}H NMR spectra of the H_2O-quenched crude reaction mixtures indicates that the cyclization of **11** was ca. 95% complete after 10 min at 0 °C in THF, while the cyclization of the **8** was 80% complete under exactly the same conditions. Thus the cyclization rate is relatively insensitive to whether the chain containing the nucleophile is axial or equatorial, a result that is consistent with the proposed cyclic four-center transition state, in which either an axial or an equatorial tether can assume the proposed conformation without undue strain.

Formation of the [3.3.0]Bicyclooctene System. The ability to annelate a five-membered ring onto an existing cyclopentene via a vinyllithium cyclization would provide a novel entry into the wide range of natural products containing fused cyclopentanes. To investigate this possibility, cyclization of the vinyllithium **14** was studied, a transformation that once again proves to be quite stereoselective, giving the "cis" diastereomer **15** as the major product in a ratio of 19:1. The stereochemistry of the major product was established by hydrogenation of the mixture and comparison with an authentic sample of known composition[16] prepared by radical cyclization. It is interesting to note that the cyclization of the radical generated from the secondary bromide shown produces the "trans" diastereomer as the major product, in direct contrast to the anionic cyclization/reduction sequence.



A small amount of six-membered ring formation also occurs in this case, as shown by comparison of the hydrogenated reaction mixture with an authentic mixture of cis and trans hydrindanes. Such cyclohexanes are usually formed in very small amounts (less than 5%); their formation will be discussed in a later section. A more unfortunate feature of the cyclization of **14** is that it is considerably slower than most other examples, requiring >1 h to reach completion. As a result, the rate of vinyllithium protonation by the solvent is competitive with ring closure, which has the obvious effect of lowering the yield. In addition, the amount of deuterium incorporation in the cyclized product decreases throughout the 3-h reaction time, so that the alkyllithium intermediate cannot be trapped by added electrophiles in synthetically useful yields. Nonetheless, the methyl-substituted bicyclic system **15** is obtained in a yield of 69%.

More Highly Substituted Terminators. The cyclization of disubstituted olefin terminators was examined briefly. Although efficient vinyl anion formation was verified by D_2O quenching, cyclization was not observed for either 1,1- or 1,2-disubstituted alkene terminators.



(13) Chamberlin, A. R.; Bloom, S. H. *Tetraheron Lett.* **1986**, *27*, 551.
(14) (a) Chamberlin, A. R.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147. (b) Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55.
(15) Jung, M. E.; Blum, R. B. *Tetrahedron Lett.* **1977**, 3791.
(16) Wolff, S.; Agosta, W. C. *J. Chem. Res., Synop.* **1981**, 78.

Table I. Cyclization of Olefinic Alkenyllithiums

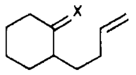
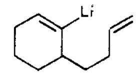
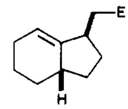
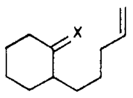
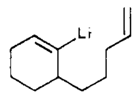
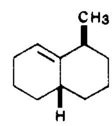
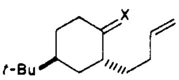
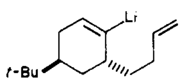
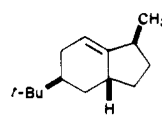
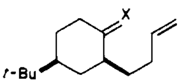
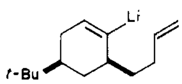
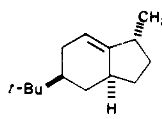
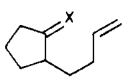
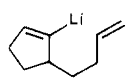
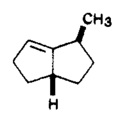
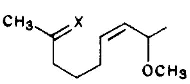
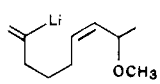
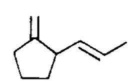
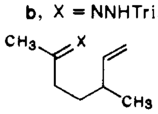
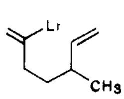
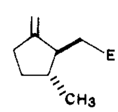
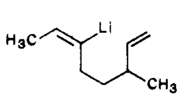
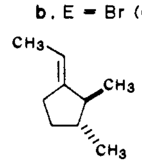
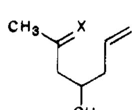
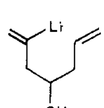
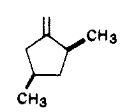
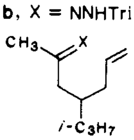
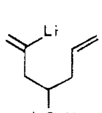
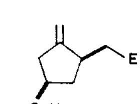
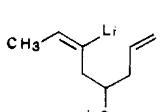
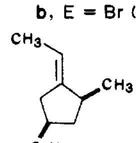
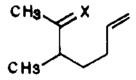
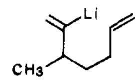
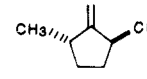
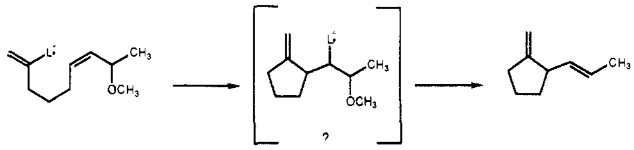
precursor	vinyllithium	electrophile	major product (yield, %)	diastereomer ratio
 **1a**, X = O **b**, X = NNHTris	 **2**	D_2O, $Br(CH_2)_2Br$, DMF, CO_2, ethylene oxide	 **3a**, E = D (87%) **b**, E = Br (81%) **c**, E = CHO (61%) **d**, E = CO_2H (50%) **e**, E = CH_2CH_2OH (49%)	>50:1
 **4a**, X = O **b**, X = NNHTris	 **5**	H_2O	 **6** (<20%)	—
 **7a**, X = O **b**, X = NNHTris	 **8**	H_2O	 **9**	≥10:1
 **10a**, X = O **b**, X = NNHTris	 **11**	H_2O	 **12**	≥10:1
 **13a**, X = O **b**, X = NNHTris	 **14**	H_2O	 **15** (69%)	19:1
 **16a**, X = O **b**, X = NNHTris	 **17**	H_2O	 **18** (60%)	—
 **19a**, X = O **b**, X = NNHTris	 **20a**	H_2O, $Br(CH_2)_2Br$	 **21a**, E = H(D) (70%) **b**, E = Br (61%)	10:1
	 **20b**		 **21c** (73%)	26:1
 **22a**, X = O **b**, X = NNHTris	 **23**	H_2O	 **24** (65%)	10:1
 **25a**, X = O **b**, X = NNHTris	 **26a**	H_2O, $Br(CH_2)_2Br$	 **27a**, E = H (93%) **b**, E = Br (80%)	>25:1
	 **26b**	H_2O	 **27c** (85%)	>25:1

Table I (Continued)

precursor	vinyllithium	electrophile	major product (yield, %)	diastereomer ratio
 **28a**, X = O; **b**, X = NNHTris	 **29**	H_2O	 **30** (70%)	5:1

In the former case, the methyl substituent increases steric interactions that disfavor the coplanar approach of the olefin and the C–Li bond of the vinyl anion. This result parallels the cyclization of a 5-methyl-5-hexenyl Grignard reagent, which has been reported to proceed approximately 1000 times slower than the unsubstituted case.[5i] In the latter reaction, cyclization requires the formation of a secondary carbanion, resulting in a substantially reduced driving force relative to the cyclizations that form primary organolithiums. Interestingly, however, it has been possible to obtain cyclized product for a 1,2-disubstituted terminator in which the initially formed alkyllithium product is substituted with a leaving group in a β-position. This cyclization succeeds where



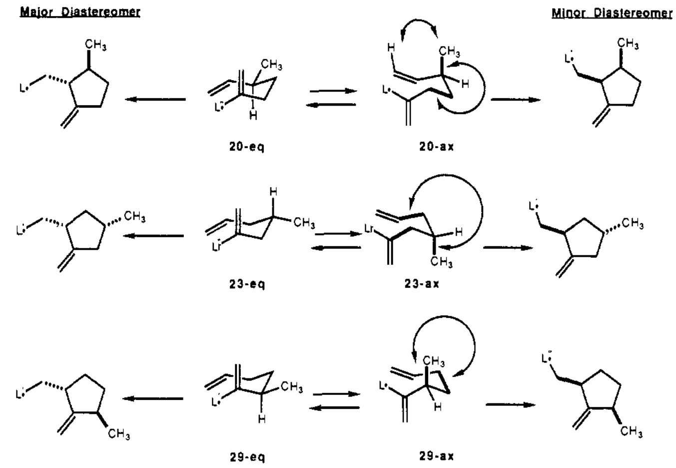
the other fails either because it is kinetically more favorable due to increased electrophilicity of the π-bond or because normally unfavorable thermodynamics are circumvented by rapid elimination of alkoxide.[17] The diastereoselectivity of this reaction is of no consequence in this case, but it currently is under study in related examples.

Formation of Substituted Methylenecyclopentanes. Results for the cyclization of a series of 3-, 4-, and 5-alkyl-substituted 2-lithio-1,6-heptadienes show that methylenecyclopentane formation is surprisingly stereoselective in several instances (Table I). Since these cyclizations are complete within 10 min at 0 °C, the resultant alkyllithiums can be trapped with H^+ and Br^+, as illustrated for **20a** and **26a**.

The stereochemistries of the 2,4- and 2,5-dimethylmethylenecyclopentane products were determined by capillary GC comparison of the reaction mixtures with authentic samples prepared by olefination of the commercially available ketones (equilibrium mixtures of cis and trans isomers). The stereochemistries of the 2,3-dimethyl products were determined by ozonolysis of the crude reaction mixtures and analysis of the resulting cyclopentanones. The chemical shifts of the C-3 methyl substituents of *cis*- and *trans*-2,3-dimethylcyclopentanone[18] easily distinguish between the diastereomeric products. In the case of **27**, ozonolysis gives a ratio of 96:4 by capillary GC. Exposure of the mixture to potassium *tert*-butoxide in methanol at 25 °C results in equilibration to an 80:20 mixture of cyclopentanones. Since the cis isomer of 2,4-disubstituted cyclopentanones is known to be more stable than the trans isomer,[18] the cis stereochemistry could assigned to the major cyclization product.

The observed selectivity of methylenecyclopentane formation can be rationalized once again by a coplanar four-center transition state,[6a] for which the conformations "eq" are favored over conformation "ax" because of the indicated torsional interactions. The predicted energy difference between the two conformations is in agreement with the observed ratios. Specifically, conformer **20**-ax suffers from two unfavorable interactions: first, a methyl group in the plane of the double bond, which is approximately 0.6 kcal higher in energy than the hydrogen in-plane conformer,[19] and

Scheme I



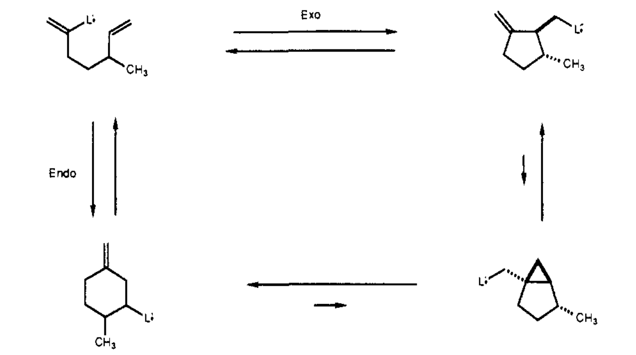
second, an additional gauche butane interaction which would increase the energy of this conformer by another 0.8 kcal. Therefore, conformation **20**-eq is favored over **20**-ax by approximately 1.4 kcal, which is consistent with the observed ratio of 10:1. Likewise, conformation **23**-eq is favored by 1.6 kcal (i.e. two gauche butane interactions), which would correspond to a ratio of 15:1 (somewhat higher than the observed ratio of 10:1).

In the last case, the analysis is not as straightforward. Although the conformer **29**-eq positions the C-3 methyl group in the plane of the double bond, which again would be expected to raise the energy by 0.6 kcal/mol, **29**-ax suffers from one additional gauche interaction *and* allylic strain between the methyl and lithium substituents. Apparently the methyl in-plane interaction and the allylic strain nullify one another, since **29**-eq is favored to the extent of single additional gauche interaction present in **29**-ax, consistent with a product ratio of 5:1.

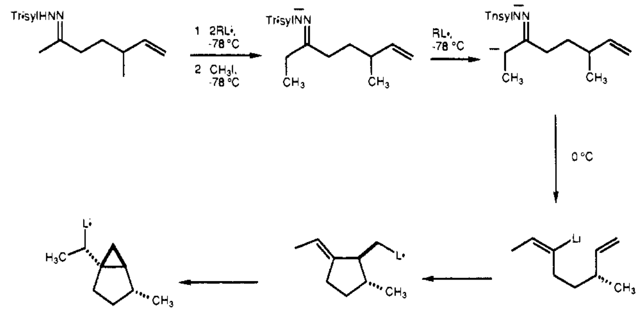
In the cyclizations described thus far, only trace amounts of the six-membered ring products are observed when the reaction is quenched within 10 min. However, when the cyclizations of **20a**, **23**, and **29** are allowed to proceed for longer times, the "normal" (i.e., lithiomethylcyclopentane) products **21**, **24**, and **30** slowly rearrange upon standing at 0 °C to give varying yields of the corresponding of methylenecyclo*hexanes*. Generally, this secondary reaction can be avoided by simply quenching with electrophile after 5–10 min at 0 °C; however, it was of interest to speculate on the mechanism of this rearrangement. The most obvious possibility is simple reversion of kinetically favored 5-exo[20] product to the starting vinyllithium, followed by 6-endo closure. Alternatively, the "normal" product could rearrange via a cyclopropyl derivative.[21]

The experiment shown below was designed to differentiate between these two pathways. The vinyllithium **20b** is easily generated stereoselectively via the dianion alkylation procedure shown.[22] If the rearrangement proceeds by the cyclopropane pathway, the rearrangement of **31** should be considerably slower because of the necessity of forming a secondary carbanion in the intermediate **32**; alternatively, reversible ring closure followed by

(17) For related examples, see: ref 4a and Crandall, J. K.; Batal, D. J. *J. Org. Chem.* **1988**, *53*, 1338.
(18) Stothers, J. B.; Tan, C. T. *Can. J. Chem.* **1974**, *52*, 308.
(19) For simple hydrocarbons such as 1-butene, there is a 0.6 kcal/mol preference for the H in-plane conformer vs methyl in-plane: Karabatsos, G. J.; Fenoglio, D. J. *Top. Stereochem.* **1970**, *5*, 167.
(20) Exo and endo are defined according to Baldwin's system; Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(21) For references to cyclopropylmethyl anions as intermediates in such processes, see: Maercker, A.; Guthlein, P.; Wittmayer, H. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 774.
(22) (a) Chamberlin, A. R.; Bond, F. T. *Synthesis* **1979**, 44. (b) Bond, F. T.; DiPietro, R. A. *J. Org. Chem.* **1981**, *46*, 1315.

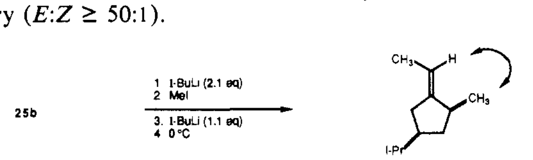


endocyclic ring closure should be essentially unaffected by this modification.



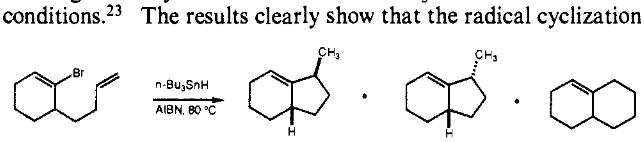
32 31 20b

The cyclization was monitored by GC analysis of aliquots quenched with aqueous sodium bicarbonate over 30 min. None of the six-membered ring product was observed, as determined by co-injection with an authentic sample of 4-methylethylenecyclohexane, clearly suggesting that the rearrangement proceeds via the cyclopropane pathway. Aside from providing mechanistic evidence, the combined process of alkylation/cyclization provides an efficient and stereoselective method of preparing alkylidenecyclopentanes. An additional example of this process is shown below. The stereochemistry of the exocyclic double bond was determined by difference NOE: irradiation of the vinyl proton of **27c** resulted in enhancement of the C-2 methyl protons, but no enhancement of the C-5 ring protons. Note that this one-flask procedure achieves not only stereoselective placement of the 1,3-alkyl appendages (cis:trans = 24:1) during cyclization, but also affords excellent control of the exocyclic double-bond geometry (E:Z ≥ 50:1).



27c

Comparison with Radical Cyclization. The radical cyclization analogous to the conversion of **2** into **3** was examined in order to compare stereoselectivities and to shed some light on the possibility that the observed vinyllithium cyclization might proceed through a transient radical intermediate. The cyclization precursor **33** was prepared by "premature" trapping of the vinyllithium **2** with dibromoethane; optimal yield (83%) was obtained in DME as solvent because the cyclization is somewhat slower in DME than in TMEDA/hexane. The vinyl radical was formed by treating the vinyl bromide **33** with n-Bu_3SnH under standard conditions.[23] The results clearly show that the radical cyclization



33 34 35 36

(23) Marinovic, N. N.; Ramanathan, H. *Tetrahedron Lett.* **1983**, *24*, 1871.

Table II. Trisylhydrazone Molecular Composition Data and Melting Points

ketone	trisyl-hydra-zone	formula	mp, °C	exact mass (M + 1) calcd	exact mass (M + 1) found[a]
1a	**1b**	$C_{25}H_{40}N_2O_2S$	118–119 °C	433.2888	433.2897
4a	**4b**	$C_{26}H_{42}N_2O_2S$	99–100 °C	447.3045	447.3032
7a	**7b**	$C_{29}H_{48}N_2O_2S$	116–117 °C	489.3514	489.3515
10a	**10b**	$C_{29}H_{48}N_2O_2S$	113–114 °C	489.3514	489.3515
13a	**13b**	$C_{24}H_{38}N_2O_2S$	130–132 °C	419.2732	419.2721
16a	**16b**	$C_{25}H_{42}N_2O_3S$	86–88 °C	451.2994	451.3003
19a	**19b**	$C_{23}H_{38}N_2O_2S$	81–83 °C	407.2732	407.2721
22a	**22b**	$C_{23}H_{38}N_2O_2S$	85–87 °C	407.2732	407.2720
25a	**25b**	$C_{25}H_{42}N_2O_2S$	87–89 °C	435.3045	435.3037
28a	**28b**	$C_{23}H_{38}N_2O_2S$	93–95 °C	407.2732	407.2744

[a] Chemical Ionization, direct inlet, CH_4 or NH_3, performed by the University of California, Riverside MS facility.

is less regio- and stereoselective than the corresponding anionic process. Nearly 50% of the product is **36**, and the ratio of the diastereomeric five-membered ring products is only 3:1 (**34**:**35**). In a related study, treatment of the bromide **33** with 4 equiv *tert*-butyllithium (0° C, THF, H_2O quench) gave a ratio of 24:1 (**34**:**35**). The loss in stereoselectivity (compared to >50:1 for the trisylhydrazone reaction) suggests the possibility of radical intermediates during the halogen–metal exchange, although other factors could also be responsible. This result does emphasize an advantage of utilizing trisylhydrazone-derived vinyl anions as the internal nucleophile in these cyclizations.

Conclusions

Vinyllithium reagents derived from ketone trisylhydrazones have been shown to undergo efficient anionic cyclization to give functionalized cyclopentanes. Specifically, vinyllithiums add to unactivated double bonds to give hydrindanes, [3.3.0]bicyclooctenes, and substituted methylenecyclopentanes in good yield. The resulting alkyllithium intermediates can be trapped efficiently with electrophiles in most cases. In addition, a general method of *stereoselective* alkylidenecyclopentane formation has been achieved by combining stereocontrolled 1,2-disubstituted vinyllithium formation with the cyclization process. In all cases the required vinyllithium regioisomers are readily available from unsaturated ketone trisylhydrazones. This cyclization method complements the corresponding radical procedure as a means of forming substituted cyclopentane derivatives because of the high stereoselectivity and regioselectivity of the process and because the initially formed cyclic products are easily functionalized by reaction with electrophiles.

Experimental Section

Flash chromatography[24] (FC) was carried out on silica gel (230–400 mesh) with the solvent mixtures indicated: (A) hexane/ether, 1/1; (B) hexane/ether, 4/1; (C) hexane/ether, 5/1; (D) hexane/ether, 10/1; (E) hexane; (F) pentane; or (G) ether.

Standard workup of reaction mixtures was conducted by using one of the following procedures. Standard workup A: The reaction mixture was diluted with several volumes of pentane, and saturated $NaHCO_3$ solution (1 equiv) was added, and the mixture was filtered through a plug of silica gel and then washed with a saturated $NaHCO_3$ solution and brine. The organic portions were dried (K_2CO_3), and concentrated. Standard workup B: The aqueous portion was extracted with ethyl acetate (3×), and the combined organic portions were washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. Standard workup C: The reaction mixture was poured into cold 1 M HCl. The organic portion was separated and washed successively with water, 1 M NaOH, and brine. The combined organic portions were dried (K_2CO_3) and concentrated.

Preparation of Trisylhydrazones. [(2,4,6-Triisopropylphenyl)sulfonyl]hydrazones (trisylhydrazones) were prepared according to the method reported by Bond,[14a] dried under vacuum at 25 °C for 12 h, and stored at −20 °C under Ar. Melting points and molecular composition data are summarized in Table II. Spectral data are included in the supplementary material.

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

Table III

	% yield (% *d*) for peak with t_R:		
time, min/temp, °C	4.99 min	5.07 min	5.45 min
0/−10	60 (90)	39 (90)	<1
0.1/0	80 (87)	20 (50)	<1
10/0	90 (77)	8 (0)	1
20/0	90 (61)	8 (0)	1
45/0	90 (33)	8 (0)	1

General Cyclization Procedure. Preparation of *rel*-(1*R*,3a*S*)-2,3,3a,4,5,6-Hexahydro-1-(deuteriomethyl)indene (3a). Trisylhydrazones were converted into the corresponding vinyllithiums according to published procedures,[14a] by using either THF or 10% TMEDA/hexane as specified individually below. For the preparation of **3a**, a solution of 0.432 g (1.00 mmol) of the trisylhydrazone **1b** in 5 mL of THF was cooled to −78 °C under argon, and 1.5 mL (2.10 mmol) of a 1.4 M solution of *sec*-butyllithium in cyclohexane was added dropwise. After 30 min the resultant red-orange solution was warmed to 0 °C with an ice bath, resulting in the vigorous evolution of nitrogen (vented through a bubbler) and a change of color to pale yellow. The reaction was quenched after 10 min by the dropwise addition of D_2O followed by standard workup A. Bulb-to-bulb distillation gave 0.119 g (87%) of **3a**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.02 (d, *J* = 7 Hz, 3 H), 1.45 (m, 2 H), 1.91 (m, 6 H), 2.21 (m, 1 H), 2.45 (m, 1 H), 5.38 (br s, 1 H); GC–MS, *m/e* 137 (12), 136 (20), 121 (100), 108 (12), 107 (17), 95 (36), 93 (37), 91 (21), 81 (12), 80 (14), 79 (60), 77 (19), 67 (19); HRMS, *m/e* calcd for $C_{10}H_{15}D_1$ (M^+) 137.1315, found 137.1302.

Cyclization of 2. Deuterium Incorporation Study. A solution of 2-lithio-3-(3-butenyl)cyclohexene (**2**) (1.00 mmol) in 5 mL of THF was prepared as described above and allowed to stir at 0 °C. Aliquots were periodically removed and quenched with D_2O, subjected to standard workup A, and analyzed by capillary GC (90 °C, 10 min, 10 °C/min, 200 °C) and by GC–MS. The results are summarized in Table III.

The first compound to elute was **3a**, identical with the sample prepared as described above.

The second compound to elute was uncyclized material corresponding to the protonation of **2**: ^{1}H NMR (250 MHz, $CDCl_3$, three-component mixture) δ 1.3–2.21 (m, 11 H), 4.9–5.1 (m, 2 H), 5.6–5.7 (m, 3 H); GC–MS, *m/e* 136 (28), 121 (86), 107 (28), 95 (46), 94 (100), 93 (50), 91 (43), 81 (43), 79 (93), 77 (36), 67 (50).

The third compound to elute exhibited a mass spectrum consistent with the minor trans isomer: GC–MS, *m/e* 137 (12), 136 (20), 121 (100), 108 (11), 107 (19), 95 (17), 94 (26), 93 (38), 91 (26), 81 (22), 79 (64), 77 (21), 67 (21).

***rel*-(1*R*,3a*S*)-2,3,3a,4,5,6-Hexahydro-1-(bromomethyl)indene (3b).** A solution of **2** (1.00 mmol) in 5 mL of 10% TMEDA/hexane was prepared according to the general procedure. The reaction was quenched by the addition of 0.376 g (2.00 mmol) of 1,2-dibromoethane after 10 min. After the mixture was stirred for 1 h, standard workup followed by FC (A) gave 0.348 g (81%) of **3b**: R_f 0.52 (hexane); IR 3050, 2950, 2870, 1640, 850, 780 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.9–1.5 (m, 3 H), 1.25–1.55 (m, 3 H), 1.7–1.85 (m, 1 H), 1.9–2.1 (m, 3 H), 2.22 (br s, 1 H), 2.86 (br s, 1 H), 3.29 (app t, *J* = 9.5 Hz, 1 H), 3.52 (dd, *J* = 4.6, 9.5 Hz, 1 H), 5.52 (br s, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 22.6, 25.6, 29.3, 30.7, 33.0, 40.0, 41.11, 45.6, 120.4, 145.9; HRMS, *m/e* calcd for $C_{10}H_{15}Br$ (M^+) 214.0357, found 214.0348.

***rel*-(1*R*,3a*S*)-2,3,3a,4,5,6-Hexahydro-1-(formylmethyl)indene (3c).** A solution of **2** (1.00 mmol) in 5 mL of THF was prepared according to the general procedure. After 20 min, 0.110 g (1.50 mmol) of DMF was added. The solution was allowed to stir at 0 °C for 1 h, poured into a cold solution of aqueous saturated $NaHCO_3$, and stirred for an additional hour. The aqueous layer was extracted with ether and washed with brine. The combined organic portions were dried (K_2CO_3) and concentrated. FC (D) gave 0.101 g (61%) of **3c**: R_f 0.52 (hexane/ether, 1:1); IR 2980, 2860, 2700, 1725 cm^{-1}; ^{1}H NMR (63 MHz, $CDCl_3$) δ 0.9–2.3 (m, 11 H), 2.47 (ddd, *J* = 16.3, 8.1, 2.2 Hz, 1 H), 2.60 (ddd, *J* = 16.3, 5.9, 2.2 Hz, 1 H), 2.90 (br s, 1 H), 5.45 (br s, 1 H), 9.78 (t, *J* = 2.2 Hz, 1 H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 22.4, 25.2, 28.9, 31.1, 33.1, 37.0, 40.7, 50.8, 118.7, 147.0, 202.6; HRMS, *m/e* calcd for $C_{11}H_{16}O$ (M^+) 164.1201, found 164.1163.

***rel*-(1*R*,3a*S*)-2,3,3a,4,5,6-Hexahydro-1-(carboxymethyl)indene (3d).** A solution of **2** (2.00 mmol) in 10 mL of THF was prepared according to the general procedure. The reaction was quenched after 20 min by the addition of excess gaseous CO_2. After being stirred for 1 h, the reaction mixture was poured into cold 1 M HCl. The solution was diluted with several volumes of pentane, and the pentane extracts were washed with brine. The organic portion was dried ($MgSO_4$) and concentrated. FC (D) gave 0.180 g (50%) of **3d**: R_f 0.22 (hexane/ether, 1:1); IR 2930, 2850, 2700–2500, 1710, 1450, 1410, 1290, 940, 850, 790 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.9–2.1 (m, 10 H), 2.19 (br s, 1 H), 2.34 (dd, *J* = 15.4, 8.8 Hz, 1 H), 2.53 (dd, *J* = 15.4, 6.2 Hz, 1 H), 2.85 (br s, 1 H), 5.52 (br s, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 22.4, 25.2, 28.9, 31.0, 33.0, 38.8, 40.6, 41.2, 118.6, 146.4, 178.8; HRMS, *m/e* calcd for $C_{11}H_{16}O_2$ (M^+) 180.1150, found 180.1155.

Table IV

	% yield (% *d*) for peak with t_R:		
time, min	11.58 min	12.05 min	16.98 min
15	94 (80)	6 (84)	<1
60	48 (64)	53 (53)	2 (0)
180	25 (0)	69 (6)	6 (0)

***rel*-(1*R*,3a*S*)-2,3,3a,4,5,6-Hexahydro-1-(3-hydroxypropyl)indene (3e).** A solution of **2** (2.00 mmol) in 10 mL of THF was prepared according to the general procedure. The reaction was quenched after 20 min by the addition of an excess of ethylene oxide. After being stirred for 1 h, the reaction mixture was poured into cold 1 M HCl. The solution was diluted with several volumes of ether, and the ether extracts were washed with brine. The organic portion was dried ($MgSO_4$) and concentrated. FC (D) gave 0.177 g (49%) of **3e**: R_f 0.43 (hexane/ether, 1:1); IR 3600–3200, 2930, 1640, 1450, 1410, 1290, 940, 850, 790 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.9–2.2 (m, 15 H), 2.65 (app br t, *J* = ~7 Hz, 1 H), 3.5 (m, 2 H), 5.52 (br s, 1 H); HRMS, *m/e* calcd for $C_{12}H_{20}O$ (M^+) 180.1514, found 180.1521.

***rel*-(1*S*,3a*R*,5*R*)-2,3,3a,4,5,6-Hexahydro-1-methyl-5-(2-methylpropyl)indene (9).** A solution of **8** (1.00 mmol) in 5 mL of THF was prepared according to the general procedure. Aliquots were quenched into D_2O and subjected to standard workup A. The aliquots were analyzed by ^{1}H NMR spectroscopy to determine the extent of cyclization by comparing the integrals of the alkene signals. **9**: ^{1}H NMR (250 MHz, $CDCl_3$, three-component mixture) δ 0.9 (s, 9 H), 1.0–1.4 (m, 6 H), 1.7–2.15 (m, 5 H), 2.28 (br s, 1 H), 2.45 (br s, 1 H), 5.4 (br s, 1 H); HRMS, *m/e* calcd for $C_{14}H_{23}D_1$ (M^+) 193.1941, found 193.1941.

***rel*-(1*R*,3a*S*,5*R*)-2,3,3a,4,5,6-Hexahydro-1-methyl-5-(2-methylpropyl)indene (12).** A solution of **11** (1.00 mmol) in 5 mL of THF was prepared according to the general procedure. Aliquots were quenched into D_2O and subjected to standard workup A. The aliquots were analyzed by ^{1}H NMR spectroscopy to determine the extent of cyclization by comparing the integrals of the alkene signals. **12**: ^{1}H NMR (250 MHz, $CDCl_3$, three-component mixture) δ 0.9 (s, 9 H), 1.0–1.4 (m, 6 H), 1.7–2.15 (m, 5 H), 2.28 (br s, 1 H), 2.45 (br s, 1 H); HRMS, *m/e* calcd for $C_{14}H_{23}D$ (M^+) 193.1941, found 193.1950.

***rel*-(1*S*,3a*R*)-1,2,3,3a,4,5-Hexahydro-1-methylpentalene (15).** A solution of **14** (0.50 mmol) in 5 mL of ether and 0.6 mL (2.0 mmol) of TMEDA was prepared according to the general procedure. The solution was allowed to warm to room temperature over several minutes. Aliquots were quenched into D_2O and subjected to the standard workup A. The aliquots were analyzed by capillary GC (40 °C, 1 min, 1 °C/min, 200 °C, 11.58, 12.05, and 16.98 min) and by GC–MS; the results are summarized in Table IV.

The first compound to elute was the uncyclized diene derived by protonation or deuteriation of **14**: GC–MS, *m/e* 122 (0.12), 81 (31), 80 (91), 79 (34), 68 (17), 67 (100).

The second compound to elute was **15**: GC–MS, *m/e* 123 (4), 122 (24), 107 (47), 94 (24), 93 (24), 81 (14), 80 (52), 79 (100); GC–HRMS, *m/e* calcd for C_9H_{14} (M^+) 122.1096, found 122.1080.

The third compound to elute was identified as 2,3-butanocyclopentene by GC–HRMS: *m/e* calcd for C_9H_{14} (M^+) 122.1096, found 122.1080, and by hydrogenation for comparison with an authentic sample.

Hydrogenation of the Second Aliquot of the Cyclization of 14. The second aliquot from the cyclization of **14** was treated with Adams catalyst and hydrogen at 1 atm and analyzed by capillary GC (40 °C, 1 min °C/min, 200 °C), 11.8 min (65%), 13.2 min (25%), 13.9 min (4%), 14.7 min (1%), and 17.7 min (5%), and by GC–MS. The first compound to elute was identified as *exo*-2-methyl-*cis*-bicyclo[3.3.0]octene by co-injection with a known mixture:[16] GC–HRMS, *m/e* calcd for C_9H_{16} (M^+) 124.1252, found 124.1240. The second compound to elute was identified as *n*-butylcyclopentane by co-injection with an authentic sample. The third compound to elute was identified as *endo*-2-methyl-*cis*-bicyclo[3.3.0]octene by co-injection with a known mixture;[16] GC–HRMS, *m/e* calcd for C_9H_{16} (M^+) 124.1252, found 124.1240. The fourth and fifth peaks were identified as *cis*- and *trans*-hydrindane by co-injection with a known mixture (Fluka).

1-Methylene-2-(2(*E*)-propenyl)cyclopentane (18). A solution of 0.39 g (0.86 mmol) of **16b** in 3.9 mL of 10% TMEDA/hexanes was cooled to −78 °C under argon. To this was dropwise added 1.6 mL of *n*-BuLi (1.58 M solution in hexanes) over 5 min. The orange reaction mixture

Table V

solvent	time, min	% yield (% d) for peak with t_R: 3.65 min	4.47 min	4.88 min	5.77 min	5.93 min
DME	1	81	3	1	>1	>1
	20	45	3	30	3	1
	60	30	3	60	10	1
TMEDA/DME	0	84	3	1	>1	>1
	20	13	3	70	14	>1
	60	13	3	68	16	1
TMEDA/Et_2O	0	80	13	17	>1	>1
	20	15	14	59	11	4
	60	15	14	20	48	2
TMEDA/Hexane	30	1	5	70	8	7

was stirred 1 h at −78 °C and then was warmed to 0 °C for 3.5 h. The reaction was quenched with saturated bicarbonate solution and diluted with ether. The solution was then filtered through a plug of silica and washed with 1 M NaOH, water, and saturated brine solution. The yield of **18** was determined by GC (75 °C, 2.0 min, 10 °C, t_R 3.49 min) to be 60% (decane as an internal standard). An analytical sample was prepared by preparatory GC purification: ^1H NMR (500 MHz, $CDCl_3$) δ 5.48–5.43 (m, J(trans) = 15.1 Hz, 1 H), 5.33–5.28 (m, J(trans) = 15.2 Hz, 1 H), 4.89 (app s, 1 H), 4.76 (app s, 1 H), 2.91–2.89 (m, 1 H), 2.43–2.25 (m, 2 H), 1.93–1.86 (m, 1 H), 1.77–1.65 (m, 1 H), 1.69 (dd, J = 6.4, 1.5 Hz, 3 H), 1.60–1.50 (m, 1 H), 1.43–1.35 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.95, 133.73, 125.18, 105.66, 48.39, 34.13, 32.55, 24.42, 17.92; IR (neat) 3175, 3030, 2960, 2860, 1660, 1650, 1450, 960, 875 cm^{-1}; MS (EI, 70 eV), m/e 122 (25), 107 (34), 93 (29), 91 (28), 86 (29), 84 (58), 79 (100), 77 (27); HRMS (EI) calcd for C_9H_{14} 122.1095, found 122.1092.

***trans*-1,2-Dimethyl-3-methylenecyclopentane (21a).** A solution of 2-lithio-5-methyl-1,6-heptadiene (1.00 mmol) in 5 mL of solvent (indicated below) was prepared according to the general procedure. Aliquots were quenched into D_2O and subjected to standard workup A. The aliquots were analyzed by capillary GC (40 °C, isothermal, 3.65, 4.47, 4.88, 5.77, and 5.93 min) and by GC–MS; the results are summarized in Table V.

The first compound to elute was identified as 3-methyl-1,6-heptadiene: ^1H NMR (250 MHz, $CDCl_3$, five-component mixture, olefin region only) δ 4.9–5.1 (m, 4 H), 5.5–5.7 (m, 2 H); GC–MS (time 20 min), m/e 110 (2), 96 (24), 95 (28), 82 (39), 81 (40), 69 (56), 68 (100), 67 (58), 55 (69).

The second compound to elute was identified as 3-methyl-1,5-heptadiene: ^1H NMR (250 MHz, $CDCl_3$, five-component mixture, olefin region only) δ 5.35–5.5 (m, 2 H); GC–MS (time 20 min), m/e 110 (2), 96 (39), 95 (17), 82 (17), 81 (25), 68 (17), 56 (100).

The third compound to elute was identified as **21a**: ^1H NMR (250 MHz, $CDCl_3$, five-component mixture, olefin region only) δ 4.75 (br s, 1 H), 4.85 (br s, 1 H); GC–MS (time 20 min), m/e 111 (67), 110 (14), 96 (100), 95 (64), 82 (36), 81 (61), 70 (64), 69 (56), 68 (75), 67 (56), 55 (19), 54 (22), 53 (25); co-injection with an authentic sample.[25]

The fourth compound to elute was identified as 4-methylmethylenecyclohexane: ^1H NMR (250 MHz, $CDCl_3$ five-component mixture, olefin region only) δ 4.6 (br s, 2 H); GC–MS (time 20 min), m/e 111 (19), 110 (39), 96 (42), 95 (78), 82 (31), 81 (61), 70 (4), 69 (33), 68 (100), 67 (64), 55 (33), 54 (22), 53 (22); co-injection with an authentic sample.[25]

The fifth compound to elute was identified as the minor cis isomer *cis*-1,2-dimethyl-3-methylencyclopentane by coinjection with an authentic sample.[25]

***trans*-1-(Bromomethyl)-2-methyl-5-methylenecyclopentane (21b).** A solution of **20a** (1.00 mmol) in 5 mL of 10% TMEDA/hexane was prepared according to the general procedure. The reaction was quenched after 10 min by addition of 0.376 g (2.00 mmol) of 1,2-dibromoethane. After the reaction mixture was stirred for 1 h, standard workup (A) followed by FC (E) gave a three-component mixture: R_f 0.52 (E); IR 3050, 2950, 2870, 1640, 850, 780 cm^{-1}; GC (50 °C, 10 min, 15 °C/min, 200 °C, 7.87, 10,51, 10.95, and 11.82 min).

The first compound to elute (4%) was identified as 2-bromo-5-methyl-2,6-heptadiene: ^1H NMR (250 MHz, $CDCl_3$, three-component mixture) δ 1.03 (d, J = 6.8 Hz, 3 H), 2.05 (app t, J = 6.8 Hz, 2 H), 2.2 (s, 3 H), 2.42 (app t, J = 6.8 Hz, 1 H), 4.9–5.1 (m, 2 H), 5.6–5.9 (m, 2 H); GC–MS, m/e 190 (1), 188 (1), 135 (69), 133 (71), 109 (100).

The second component to elute (91%) was **21b**: ^1H NMR (250 MHz, $CDCl_3$, three-component mixture) δ 1.07 (d, J = 6.4 Hz, 3 H), 1.27 (m, 1 H), 1.8–2.1 (m, 2 H), 2.2 (m, 3 H), 3.94 (dd, J = 4.8, 1.7 Hz, 2 H), 4.94 (app dd, J = 4.5, 2.3 Hz, 1 H), 5.03 (app dd, J = 4.1, 2 Hz, 1 H); GC–MS, m/e 190 (14), 188 (14), 175 (6), 173 (6), 148 (8), 146 (8), 109 (100), 95 (3), 81 (36), 79 (36).

The third component to elute (4%) was identified as 3-bromo-4-methylmethylenecyclohexane: GC–MS, m/e 190 (8), 188 (8), 109 (100), 95 (42), 93 (33), 91 (22), 81 (33), 79 (33).

Ozonolysis of 21a. A solution of **21a** (0.220 g, 2.00 mmol) in 10 mL of hexane was ozonized according to the procedure of Pappas[26] to give 0.203 g (89%) of *trans*- and *cis*-2,3-methylcyclopentanone (92:8 by ^1H NMR). The IR, ^1H NMR, and ^{13}C NMR spectra were identical with those reported.[18]

1,2-Dimethyl-3-ethylidenecyclopentane (21c). Into a flame-dried flask was placed 0.406 g (1.00 mmol) of **19a** dissolved in 3 mL of DME and decane (0.010 mL) as internal standard. After cooling to −78 °C, *t*-BuLi (1.2 mL of a 1.7 M solution in pentane, 2.0 mmol) was added dropwise. The orange solution was stirred at −78 °C for 1 h. Methyl iodide (0.142 g, 1.00 mmol) was added dropwise, and the solution was stirred for 5 h at −78 °C. At the end of that time, the solution was faint yellow. TMEDA (0.30 mL, 2.0 mmol) and *t*-BuLi (1.00 mL of a 1.7 M solution in pentane, 1.7 mmol) were added successively. The dark red-orange solution was kept at −78 °C for 1.5 h, and then the temperature was raised to 0 °C. Three aliquots were quenched into aqueous saturated $NaHCO_3$ at the following times: 0, 15, and 30 min. Each aliquot was diluted with several volumes of pentane, and the organic portion was subjected to standard workup (A). The aliquots were analyzed by capillary GC (40 °C, isothermal, 7.89, 9.43, 11.91, and 12.69 min) by GCMS; the results are summarized in Table VI.

Table VI

time, min	% yield for peak with t_R: 7.8. min	9.43 min	11.91 min	12.69 min
0	0.2	53	42	1.5
15	1	15	66	1
30	1	17	73	2.8

Table VII

time, min	% yield for peak with t_R: 3.81 min	4.01 min	4.55 min	4.63 min
0.1	81	5	5	>1
10	6	13	72	7
20	5	22	64	6

The first compound to elute was identified as an isomer of 1,2-dimethyl-3-ethylidenecyclopentane: GC–MS, m/e 124 (27), 109 (97), 95 (30), 82 (58), 81 (27), 79 (11), 77 (10), 69 (53), 68 (39), 67 (100); GC–HRMS, m/e calcd for C_9H_{16} (M^+) 124.1252, found 124.1251.

The second compound to elute was identified as 6-methyl-2,7-octadiene: GC–MS, m/e 124 (0.5), 109 (9), 95 (33), 82 (12), 81 (19), 79 (3), 77 (2), 69 (4), 68 (100), 67 (58); HRMS, m/e calcd for C_9H_{16} (M^+) 124.1252, found 124.1256.

The third compound to elute was identified as an isomer of 1,2-dimethyl-3-ethylidenecyclopentane: GC–MS, m/e 124 (25), 109 (75), 95 (100), 82 (12), 81 (25), 79 (13), 77 (11), 69 (33), 68 (12), 67 (80); HRMS, m/e calcd for C_9H_{16} (M^+) 124.1252, found 124.1261.

The fourth compound to elute identified as an isomer of 1,2-dimethyl-3-ethylidenecyclopentane: GC–MS, m/e 124 (26), 109 (80), 95

(25) Adlercreutz, P.; Magnusson, G. *Acta Chem. Scand., Ser. B* **1980**, *B34*, 647 and references therein.

(26) Pappas, J. J.; Keaveney, W. P.; Gancher, E.; Berger, M. *Tetrahedron Lett.* **1966**, 4273.

Table VIII

time	% yield for peak with t_R: 7.69 min	7.83 min
0	96	4
10 min	90	10
1 h	83	17
36 h	80	20

(100), 82 (12), 81 (25), 79 (13), 77 (11), 69 (33), 68 (12), 67 (85); HRMS, *m/e* calcd for C_9H_{16} (M^+) 124.1252, found 124.1251.

***cis*-1,4-Dimethyl-2-methylenecyclopentane (24).** A solution of **23** (1.00 mmol) in 5 mL of 10% TMEDA/hexane was prepared according to the general procedure. Aliquots were quenched with H_2O and subjected to the standard workup A. The aliquots were analyzed by capillary GC (40 °C, isothermal, 3.81, 4.01, 4.55, and 4.63 min); the results are summarized in Table VII.

The first compound to elute was tentatively identified as 4-methyl-1,6-heptadiene on the basis of its conversion into **24**.

The second compound to elute was identified as 3-methylmethylenecyclohexane by co-injection with an authentic sample prepared by Wittig reaction of 3-methylcyclohexane.[25]

The third compound to elute was identified as **24** by co-injection with an authentic mixture of *cis*- and *trans*-1,4-dimethyl-2-methylenecyclopentane.[25]

The fourth compound to elute was identified as *trans*-1,4-dimethyl-2-methylenecyclopentane by co-injection with an authentic mixture of *cis*- and *trans*-1,4-dimethyl-2-methylenecyclopentane.[25]

***cis*-1-Methyl-3-(methylethyl)-5-methylenecyclopentane (27a).** A solution of **26a** (10.0 mmol) in 50 mL of 10% TMEDA/hexane was prepared according to the general procedure. The reaction was quenched by the addition of H_2O after 20 min at 0 °C. After the reaction mixture was stirred for 10 min, standard workup (A) followed by short-path distillation gave 0.972 g (70%) of **27a**: IR 3080, 2950, 2870, 1660, 1460, 1360 cm^{-1}; GC (40 °C, 1 min, 1 °C/min, 200 °C, 14.9 min); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.89 (d, J = 6.4 Hz, 3 H), 0.91 (d, J = 6.4 Hz, 3 H), 1.1 (d, J = 6.6 Hz, 3 H), 1.38 (septet, J = 6.4 Hz, 1 H), 1.48–1.65 (m, 1 H), 1.9–2.1 (m, 3 H), 2.3–2.5 (m, 1 H), 2.55 (dd, J = 16.4, 7.9 Hz, 1 H), 4.73 (br s, 1 H), 4.83 (br s, 1 H); HRMS, *m/e* calcd for $C_{10}H_{18}$ (M^+) 138.1409, found 138.1411.

***cis*-1-(Bromomethyl)-3-(methylethyl)-5-methylenecyclopentane (27b).** A solution of **26a** (0.5 mmol) in 5 mL of 10% TMEDA/hexane was prepared according to the general procedure. The reaction was quenched by the addition of 1,2-dibromoethane (0.376 g, 2.00 mmol) after 20 min. After being stirred for 1 h, standard workup (A) followed by FC (E) gave 0.066 g (61%) of **27b**: IR 3070, 2980, 1655, 1450, 1180, 770 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.92 (app t, J = 6.3 Hz, 6 H), 1.14 (app q, J = 11.6 Hz, 1 H), 1.43 (septet, J = 6.3 Hz, 1 H), 1.5–1.55 (m, 1 H), 2.02 (app t, J = 10 Hz, 1 H), 2.21 (app quintet, J = 6.9 Hz, 1 H), 2.58 (dd, J = 17.5, 6.9 Hz, 1 H), 2.75–2.95 (m, 1 H), 3.33 (app t, J = 9.3 Hz, 1 H, 3.65 (dd, J = 11.3, 4.2 Hz, 1 H) 4.82 (br s, 1 H), 4.97 (brs, 1 H); MS, *m/e* 218 (M^+, 2), 216 (2), 175 (8), 173 (8), 137 (36), 95 (60), 81 (100); HRMS, *m/e* calcd for $C_{10}H_{17}Br$ (M^+) 216.0514, found 216.0503.

Ozonolysis of 27a. A solution of 0.124 g (0.900 mmol) of 2-methyl-4-(1-methylethyl)methylenecyclopentane in 10 mL of hexane was ozonized according to the procedure of Pappas.[26] FC (D) gave 0.80 g (63%) of *cis*- and *trans*-2-methyl-4-(1-methylethyl)cyclopentanone (96:4) by GC analysis; GC (80 °C, 2 min, 2 °C/min, 200 °C, 7.69 and 7.83 min); R_f 0.62 (A); IR 2940, 2880, 1735, 1470, 1370, 1160, 1080 cm^{-1}.

The first compound to elute was *cis*-2-methyl-4-(1-methylethyl)-cyclopentanone: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.92 (app t, J = 6.9 Hz, 6 H), 1.07 (d, J = 6.8 Hz, 3 H), 1.48 (septet, J = 6.9 Hz, 1 H, 1.66–1.86 (m, 3 H), 1.15 (app sextet, J = 6.8 Hz, 1 H), 2.3–2.55 (m, 2 H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 13.8, 20.2, 21.0, 33.5, 36.9, 42.1, 42.8, 45.4, 220.2; MS, *m/e* 140 (M^+, 19), 97 (100), 83 (10), 70 (24), 69 (56), 56 (27), 55 (82); HRMS, *m/e* calcd for $C_9H_{16}O$ (M^+) 140.1201, found 140.1201.

Equilibration of 2-Methyl-4-(methylethyl)cyclopentanone. To a solution of 2-methyl-4-(methylethyl)cyclopentanone (4 mg, 0.002 mmol) in 1 mL of methanol was added potassium *tert*-butoxide (2 mg, 0.002 mmol). The equilibration was monitored by GC over 36 h, and the results are summarized in Table VIII.

(*E*)-*cis*-1-Ethylidene-2-methyl-4-(methylethyl)cyclopentane (27c). A solution of 0.868 (2.00 mmol) of **25b** was treated as was **20b**. FC (E) gave 0.259 g (85%) of **27c**: R_f 0.8 (hexane); IR 3070, 2970, 2940, 2880, 1670, 1440, 1360 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.94 (d, J = 6.6 Hz, 6 H, isopropyl methyl), 1.06 (d, J = 6.4 Hz, 3 H, C-2 methyl), 1.2–1.55 (m, 3 H, C-3, C-2, $CH(CH_3)_2$), 1.6 (d, J = 6.8 Hz, 3 H, allylic methyl), 1.83 (app br t, J = 14.8 Hz, 1 H, C-5), 1.98 (app dt, J = 18.1, 6 Hz, 1 H, C-3), 2.3–2.4 (m, 1 H, C-1), 2.53 (dd, J = 16.5, 7.4 Hz, 1 H, C-5), 5.1–5.25 (m, 1 H, vinyl). Irradiation of the vinyl proton resulted in enhancement of the C-2 methyl signal, but no enhancement was observed for the C-5 ring protons; MS, *m/e* 152 (M^+, 15), 137 (8), 109 (100), 98 (13), 97 (27), 96 (9), 95 (12), 83 (17), 82 (50), 81 (90), 79 (24), 69 (60), 68 (21), 67 (93), 65 (11), 57 (81), 56 (14), 55 (79); HRMS, *m/e* calcd for $C_{11}H_{20}$ (M^+) 152.1565, found 152.1560.

Table IX

time, min	% yield for peak with t_R: 3.66 min	4.75 min	5.08 min	5.75 min
10	5	70	15	10
20	5	40	8	40

***trans*-1,3-Dimethyl-2-methylenecyclopentane (30).** A solution of **28b** (1.00 mmol) in 5 mL of 10% TMEDA/hexane was prepared according to the general procedure. Aliquots were quenched into D_2O and subjected to standard workup A. The aliquots were analyzed by capillary GC (40 °C, isothermal, 3.66, 4.75, 5.08, and 5.75 min); the results are summarized in Table IX.

The first compound to elute was identified as 3-methyl-1,6-heptadiene by co-injection with an authentic sample (see cyclization of **20a**) and by ^{1}H NMR comparison with the crude reaction mixture.

The second compound to elute was identified as **30** by co-injection with an authentic mixture of *cis*- and *trans*-2,5-dimethylmethylenecyclopentane[25] and by ^{1}H NMR comparison with the crude reaction mixture.

The third compound to elute was identified as *cis*-1,3-dimethyl-2-methylenecyclopentane by co-injection with an authentic mixture of *cis*- and *trans*-1,3-dimethyl-2-methylenecyclopentane[25] and by ^{1}H NMR comparison with the crude reaction mixture.

The fourth compound to elute was identified as 2-methylmethylenecyclohexane by co-injection with an authentic sample prepared from 2-methylcyclohexanone[25] and by ^{1}H NMR comparison with the crude reaction mixture.

2-Bromo-3-(3-butenyl)cyclohexene (33). A solution of **2** (2.00 mol) in 6 mL of DME was prepared according to general procedure B. The reaction was quenched after 1 min by the addition of 1.13 g (6.00 mmol) of 1,2-dibromoethane. After the reaction mixture was stirred for 1 h, standard workup (A) followed by FC (E) gave 0.358 g (83%) of 2-bromo-3-(3-butenyl)cyclohexene: R_f 0.62 (hexane); IR 3070, 2950, 2870, 1640, 1440, 1320, 980 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.3–2.25 (m, 10 H), 2.34 (m, 1 H), 4.9–5.15 (m, 2 H) 5.7–5.95 (m, 1 H), 6.09 (m, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 18.7, 27.8, 28.3, 31.0, 32.5, 41.9, 114.7, 128.7, 129.8, 138.4; HRMS, *m/e* calcd for $C_{10}H_{15}Br$ (M^+) 214.0357, found 214.0377.

Radical Cyclization of 2-Bromo-3-(3-butenyl)cyclohexene (33). A solution of 0.0215 g (0.100 mmol) of 2-bromo-3-(3-butenyl)cyclohexene in 3 mL of benzene was heated to reflux, and n-Bu_3SnH (1.1 mL of a 0.11 M solution in benzene containing AIBN 0.5 g/mL, 0.11 mmol) was added dropwise. After 18 h, the solution was cooled to room temperature, diluted with 20 mL of ether, washed several times with a 0.17 M KF solution, and dried (K_2CO_3). The solution was analyzed by capillary GC (90 °C, 10 min, 10 °C/min, 200 °C), 5.0 min (43%), 5.1 min (14%), 5.5 min (6%), and 6.2 min (51%), and by GC–MS.

The first compound to elute was **34**: GC–MS, *m/e* 136 (29), 121 (100), 107 (26), 94 (36), 93 (43), 91 (24), 79 (57), 77 (21), 67 (21).

The second compound to elute was the simple reduced diene: GC–MS, *m/e* 136 (29), 121 (86), 107 (30), 95 (46), 94 (100), 93 (43), 91 (40), 81 (43), 79 (93), 77 (36), 67 (50).

The third compound to elute was **35**: GC–MS, *m/e* 136 (26), 121 (100), 107 (26), 94 (26), 91 (29), 81 (22), 79 (64), 77 (21), 67 (21).

The fourth compound to elute was [4.4.0]bicyclodec-1-ene[27] **36**: GC–MS, *m/e* 136 (100), 107 (40), 105 (26), 94 (36), 78 (36). These assignments are also consistent with the ^{1}H NMR spectrum of the crude reaction mixture.

Reaction of 2-Bromo-3-(3-butenyl)cyclohexene with *t*-BuLi. A solution of 0.0215 g (0.100 mmol) of 2-bromo-3-(3-butenyl)cyclohexene in 3 ml of THF was cooled to 0 °C, and *tert*-butyllithium (0.68 mL of a 1.7 M solution in pentane, 0.40 mmol) was added dropwise. After being stirred for 20 min, the reaction was quenched by the addition of aqueous saturated $NaHCO_3$. The aqueous portion was extracted with pentane, the combined organic layers were dried (K_2CO_3), and the solution was analyzed by capillary GC (90 °C, 10 min, 10 °C/min, 200 °C), 5.0 min (17%), 5.1 min (82%), 5.5 min (0.7%). The three products were identified as **34**, the uncyclized diene, and **35**, respectively, by GC co-injection

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and ^{1}H NMR comparison with authentic material.

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Supplementary Material Available: Procedures and spectral data for the preparation of starting ketones, spectral data for the trisylhydrazones, and experimental details for proof of stereochemistry of the cyclization product from **2** are available (13 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-N^2-(Phenylsulfonyl)-CPI, (±)-CC-1065, (+)-CC-1065, *ent*-(−)-CC-1065, and the Precise, Functional Agents (±)-CPI-CDPI$_2$, (+)-CPI-CDPI$_2$, and (−)-CPI-CDPI$_2$ [(±)-(3b*R**,4a*S**)-, (+)-(3b*R*,4a*S*)-, and (−)-(3b*S*,4a*R*)-Deoxy-CC-1065][†]

Dale L. Boger*[,1a] and Robert S. Coleman[1b]

Contribution from the Department of Chemistry, Purdue University, West Lafayette, Indiana 47907. *Received February 11, 1988*

Abstract: Full details of the total synthesis of (±)-N^2-(phenylsulfonyl)-CPI (**3**), the spiro[2.5]octa-4,7-dien-6-one bearing left-hand segment of CC-1065, the coupling of the racemic and resolved immediate precursors (±)-(1*R**)-**33**, (−)-(1*S*)-**33**, and (+)-(1*R*)-**33** with synthetic PDE-I dimer (PDE-I$_2$, **39**), and incorporation into the total syntheses of (±)-CC-1065, natural (+)-CC-1065, and enantiomeric (−)-CC-1065 are described. The approach to the CC-1065 CPI left-hand segment is based on the regioselective, nucleophilic addition of 1-piperidino-1-propene to the selectively activated N^4-(phenylsulfonyl)-*p*-quinone diimide **11** for direct introduction of the CPI 3-methylpyrrole A ring and the subsequent implementation of a 5-*exo-dig* aryl radical–alkyne cyclization for indirect introduction of the CPI 3-(hydroxymethyl)pyrroline C ring (**23** → **24** → **25**). Adoption of the Winstein Ar-3′ spirocyclization provided the final introduction of the CPI spirocyclopropylquinone. Full details of additional incorporation of (±)-(1*R**)-**33**, (−)-(1*S*)-**33**, and (+)-(1*R*)-**33** into the total syntheses of (±)-, (+)-, and (−)-CPI-CDPI$_2$ [(±)-(3b*R**,4a*S**)-, (+)-(3b*R*,4a*S*)-, and (−)-(3b*S*,4a*R*)-deoxy-CC-1065] are described. CPI-CDPI$_2$ was anticipated and found to possess the precise structural and functional features that are responsible for the CC-1065 sequence-selective B-DNA minor groove association and the resulting expression of potent cytostatic activity. CC-1065, and the precise functional agent CPI-CDPI$_2$, constitute reactive alkylating agents *superimposed* on the CDPI trimer skeleton and derive their B-DNA associative properties through a common underlying mechanism: accessible hydrophobic binding-driven-bonding. It is predominantly hydrophobic interactions of the concave face of CC-1065 and its B-DNA minor-groove complementary shape (curvature and pitch) that permit (binding) the association with accessible AT-rich minor-groove regions and promote (bonding) the irreversible adenine N-3 covalent alkylation.

CC-1065 (**1**, NSC-298223), an antitumor–antibiotic isolated from cultures of *Streptomyces zelensis*,[2] has been shown to possess exceptionally potent in vitro cytotoxic activity,[3] broad-spectrum antimicrobial activity,[2] and potent in vivo antitumor activity.[4] The structure of CC-1065 was determined initially through a combination of spectroscopic and chemical degradation studies[5] and subsequently was confirmed in a single-crystal X-ray structure determination.[6] At the time of this initial structure determination, CC-1065 constituted the most potent antitumor–antibiotic identified to date, and consequently extensive investigations ensued to define the site and mechanism of the CC-1065 antitumor activity. CC-1065 has been shown to bind to double-stranded B-DNA within the minor groove in an initial high-affinity, nonintercalative manner and subsequently forms an irreversible covalent adduct.[6-9] The (+)-CC-1065 irreversible B-DNA minor groove covalent alkylation has been shown to proceed by acid-catalyzed, 3′-adenine N-3 alkylation of the electrophilic spiro[2.5]octa-4,7-dien-6-one unit present in the left-hand segment (CPI) of (+)-CC-1065[10] within two consensus sequences, 5′-d-(A/GNTTA)-3′ and 5′-d(AAAAA)-3′.[11-16] Consequently, the mechanism of CC-1065 antitumor activity has been proposed to be derived from (1) the inhibition of the normal unwinding and melting process required for DNA synthesis,[7,13] (2) the inhibition or alteration of replication and transcription enzyme action proximal or distal to its binding regions of DNA,[17] or (3) through the induction of unbalanced cell growth.[18]

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