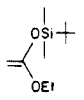
Table I

RM	reactn condtns	yield 4	amino acid 5[a]	% ee
	1.2$ZnCl_2$, THF, 25 °C, 1 h	71%	D-β-ethylaspartate	96.6
	1.2$ZnCl_2$, THF, 25 °C	54%	L-homophenylalanine	96.9
	2$ZnCl_2$, THF, 25 °C, 3 days	68%	L-norvaline, L-allylglycine[b]	98.3
MeZnCl	THF, 25 °C, 1 h	46%	L-alanine	96.8
$Me_2CuCNLi_2$	THF, −78 °C, 30 min	28%		
$Bu_2CuCNLi_2$	THF, −78 °C 30 min	48%	L-norleucine	99.5

[a] The conversions of 4 → 5 proceed in essentially quantitative yields in all cases. [b] The conversion of 4 → 5 is carried out with $Li/NH_3/EtOH$.

fluoromethyl)phenylacetyl chloride and examination of the crude mixture by ^{19}F and ^1H NMR and comparison to the authentic diastereomers prepared from the racemic amino acids. We have also found that for substrates containing unsaturated functionality, such as the allyl case, the conversion of 4 → 5 can be performed by a dissolving metal reduction ($Li/NH_3(l)/EtOH$) and thus precludes the saturation of the olefin (see Table I for allylglycine).

The substrate 3 is best suited for coupling with "neutral" carbon nucleophiles, such as the silyl enol ethers; the diminished yields for the more basic organometallic reagents is due to competing reduction of 3 → 2. Examination of the crude coupling reaction mixtures (3 → 4) provided no evidence for the formation of alternative diastereoisomers (4); the diastereoselectivity of the nucleophilic additions to 3 in the cases studied is, therefore, excellent.

A single-crystal X-ray analysis of 4 (R = $CH_2CH{=}CH_2$) has been performed[10] as shown in Figure 1. The structure clearly shows that the nucleophile has attacked 3 or putative iminium species from the least hindered face to furnish, from the D series (of 1) after hydrogenation, L-norvaline as expected. This trend is followed for most of the carbon nucleophiles examined thus far. The notable and curious exception, however, was found in the preparation of β-ethyl aspartate. From the D-series lactone, D-β-ethylaspartate is produced in >96% ee which indicates that the resulting lactone 4 (R = CH_2CO_2Et) must possess the all-syn configuration. The molecular structure of 4 (R = $CH_2CH{=}CH_2$), shown in Figure 1, shows that the tetrahydrooxazinone has adopted a twist-boat conformation that situates the phenyl ring at C-2 (X-ray numbering) in a pseudoaxial orientation. It is reasonable to assume that a reactive intermediate derived from 3 would also have a similar conformation, since that shown avoids A strain as well as 1,3-diaxial interactions that would be experienced in alternative conformations.

It must be concluded that the *tert*-butyldimethylsilyl enol ether of ethyl acetate is selectively coupling from the sterically more encumbered face or that epimerization of an initially formed anti isomer to the syn isomer occurs under the reaction conditions. Efforts are under way to elucidate the factors governing this anomalous, yet highly selective, coupling reaction.

In summary, a new and potentially highly versatile method[11,12] for the preparation of natural and unnatural α-amino acids in both the D and L configuration has been developed. The percent asymmetric synthesis (% ee) for the cases studied herein are uniformly high, and the entire sequence beginning with benzoin[7] proceeds with efficiency, requiring only a single chromatographic isolation at the stage of 4. Efforts to further expand the scope and utility of this methodology are presently under active investigation in these laboratories.

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for financial support of this work and an NIH Research Career Development Award (to R.M.W.). We also wish to express thanks to Professor Dave Evans for helpful discussions and communicating their results to us in a related system prior to publication.

Supplementary Material Available: Tables of atomic coordinates, bond lengths, bond angles, anisotropic thermal parameters, and hydrogen atom positions for the crystal structure of 4; ^1H NMR spectra of amino acids obtained without purification from the hydrogenation of 4, and listing of spectroscopic and analytical data for all new compounds (14 pages). Ordering information is given on any current masthead page.

(8) It was not possible to assign the relative configuration of the crude bromide due to slow conformational exchange on the ^1H NMR time scale.

(9) Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095.

(10) Data were collected on an Nicolet R3m X-ray diffractometer. All crystallographic computations were carried out using the SHELXTL program library (written by G. M. Sheldrick and supplied by Nicolet XRD for the Data General Eclipse S/140 computer in the crystallographic laboratory at Colorado State University). Lattice constants a = 29.325 (11) Å; b = 10.326 (1) Å; c = 25.316 (7) Å, β = 142.79 (1)°, monoclinic (C centered). R = 0.0711, R_w = 0.0637, GOF = 1.31.

(11) An example of racemic amino acid synthesis via electrophilic glycinates has recently appeared in addition to that mentioned in ref 6; see: O'Donnell, M. J.; Falmagne, J. B. *Tetrahedron Lett.* **1985**, *26*, 699.

(12) Various attempts at generating the enolate anions of 2 and 4 followed by electrophilic quenching resulted in decomposition only.

New Approach to Pyrrolo[1,2-*a*]indoles Using Azomethine Ylides‡

Albert Padwa*† and John R. Gasdaska

Department of Chemistry, Emory University
Atlanta, Georgia 30322

Received October 7, 1985

In this paper we describe an efficient method to form the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole nucleus which is based on 1,3-dipolar cycloaddition methodology. We expect that this method will prove amenable toward the synthesis of more complex mitosene derivatives.[1-5]

We have previously found that α-cyano silyl amines are useful and convenient synthons for azomethine ylides.[6] In the light of our earlier findings, we envisioned a convenient approach to the pyrrolo-indole nucleus to lie along the pathway (i.e., 1 → 3) illustrated in Scheme I. The development of this strategy was based on literature reports that (cyanomethyl)amines can function

‡ Dedicated to Rolf Huisgen on the occasion of his 65th birthday.

† Alexander von Humboldt Senior Scientist, 1985; University of Wurzburg.

(1) Rebek, J.; Shaber, S. H. *Heterocycles* **1981**, *16*, 1173.

(2) Rebek, J. R.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 1671.

(3) Kametani, T.; Kigawa, Y.; Nemoto, H.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1607.

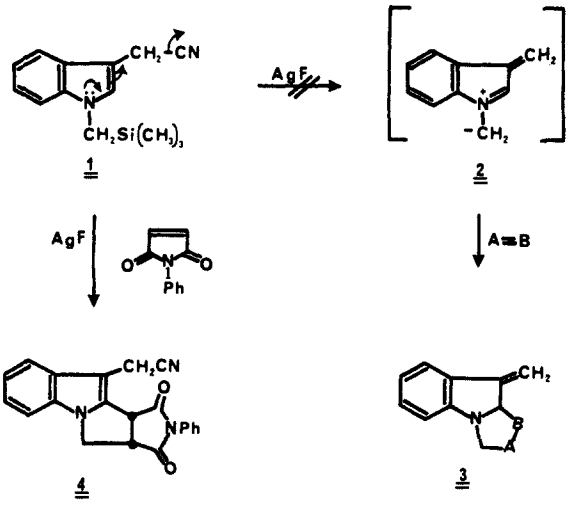
(4) Coates, R.; Hutchins, C. J. *J. Org. Chem.* **1979**, *44*, 4742.

(5) Okamoto, M.; Shunsaku, O. *Chem. Pharm. Bull.* **1980**, *28*, 1071.

(6) Padwa, A.; Chen, Y. Y. *Tetrahedron Lett.* **1983**, 3447. Padwa, A.; Chen. Y. Y.; Dent, W.; Nimmesgern, H. *J. Org. Chem.* **1985**, *50*, 4006.

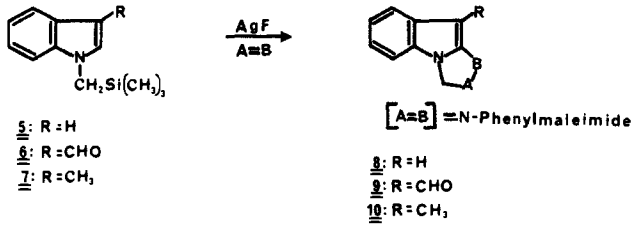
0002-7863/86/1508-1104$01.50/0

Scheme I



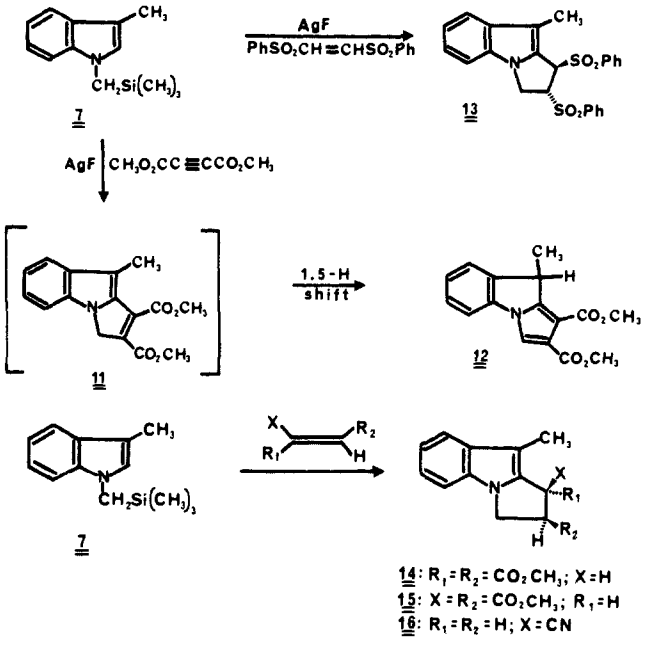
as convenient iminium precursors.[7] The propensity of silicon to transfer to a silylophile[8] when bound to an electronegative carbon strongly suggested that the treatment of indole **1** with silver fluoride would generate azomethine ylide **2**. Surprisingly, the reaction of **1** with silver fluoride in the presence of *N*-phenylmaleimide afforded cycloadduct **4** in 76% yield which still retained the nitrile functionality. The structure of cycloadduct **4** was assigned on the basis of its characteristic spectral data.[9] Unequivocal proof of this assignment derives from a single-crystal X-ray structure analysis.

It should be noted that the nitrile functionality is not necessary for the reaction to occur. We found that the cycloaddition proceeded with a number of related *N*-[(trimethylsilyl)methyl]-substituted indoles (**5–7**). The overall yield of the dihydropyrrolo-indole systems **8–10** ranged from 53% to 83%.



Since we were interested in the synthetic utility of this reaction, we undertook a systematic study of the cycloaddition with a number of related dipolarophiles. Heating a solution of **7** with dimethyl acetylenedicarboxylate at 80 °C produced pyrrole **12** in 75% yield: NMR (360 MHz, $CDCl_3$) δ 1.58 (d, 3H, J = 7.3 Hz), 3.86 (s, 3 H), 3.89 (s, 3 H), 4.24 (q, 1 H, J = 7.3 Hz), 7.2–7.45 (m, 4 H), 7.62 (s, 1 H). The conversion of **7** to **12** probably proceeds via the intermediacy of cycloadduct **11** which undergoes a subsequent hydrogen shift under the reaction conditions to give pyrrole **12**.

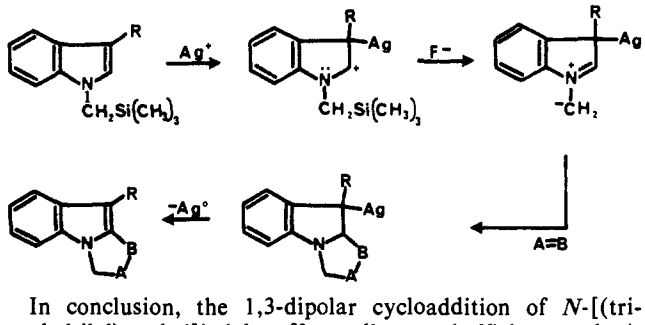
In order to ascertain the stereospecificity of the reaction, we studied the cycloaddition with cis- and trans-disubstituted dipolarophiles. Treatment of **7** with either (*Z*)- or (*E*)-1,2-bis(phenylsulfonyl)ethene in the presence of silver fluoride afforded cycloadduct **13** as the exclusive product. We found that the *Z*-substituted dipolarophile rearranged to the thermodynamically more stable *E* isomer before the cycloaddition had occurred. The reaction did proceed with complete stereospecificity with dimethyl fumarate and maleate, however, giving rise to cycloadducts **14** and **15**. We also examined the cycloaddition behavior of an



unsymmetrically substituted dipolarophile so as to probe the regioselectivity of the reaction. When acrylonitrile was used as the dipolarophile, cycloadduct **16** was the exclusive product. Structure **16** was rigorously established by X-ray structure analysis.

The above cycloadditions show all the characteristics of a concerted reaction, including complete stereospecificity and regioselectivity and, therefore, are consistent with the intermediacy of an azomethine ylide.[10] Our inability to isolate a 1,3-cycloadduct when nonactivated olefins are used is perfectly consistent with the principles of frontier MO theory.[11] Azomethine ylides generally react only with electron-deficient dipolarophiles, since such a pair of addends possesses a narrow dipole HOMO–dipolarophile LUMO gap. The preferential formation of cycloadduct **16** is the result of the union of the larger azomethine ylide HO coefficient on the methylene carbon with that of the larger dipolarophile LU coefficient on the unsubstituted carbon.

Formation of the azomethine ylide intermediate can be rationalized by assuming that silver ion behaves as a very specific Lewis acid that attacks the indole ring to give a silver-bonded carbonium ion. This is followed by a rapid desilylation reaction to give the dipole. After the cycloaddition step, the resulting silver-bonded intermediate undergoes consecutive loss of silver and a hydrogen to give the observed product.[12] It should be pointed out that these reactions require a full equivalent of silver ion which ultimately results in the production of metallic silver.



In conclusion, the 1,3-dipolar cycloaddition of *N*-[(trimethylsilyl)methyl]indoles offers a direct and efficient synthesis of the pyrrolo[1,2-*a*]indole ring system and opens the way to various [1,2-*a*]-annelated indole quinones. It should be possible

(7) Overman, L. E.; Jacobsen, E. J. *Tetrahedron Lett.* **1982**, 2741.
(8) Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761.
(9) ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.92 (d, 1 H, J = 18.0 Hz), 4.10 (d, 1 H, J = 18.0 Hz), 4.34 (ddd, 1 H, J = 8.9, 8.3, and 2.1 Hz), 4.47 (dd, 1 H, J = 10.7 and 2.1 Hz), 4.69 (dd, 1 H, J = 10.7 and 8.9 Hz), 4.75 (d, 1 H, J = 8.3 Hz), 7.2–7.5 (m, 8 H), 7.66 (d, 1 H, J = 7.1 Hz); mp 138–139 °C.
(10) "1,3-Dipolar Cycloaddition Chemistry"; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 1, 2.
(11) Fleming, I. "Frontier Orbitals and Organic Chemical Reactions"; Wiley-Interscience: New York, 1976.
(12) The reduction of Ag(I) to the metallic state is somewhat reminiscent of results reported by: Koser, G. F.; Faircloth, J. J. *J. Org. Chem.* **1976**, *41*, 583.

to prepare analogues and derivatives of these compounds by altering the C_3 substituent and/or by using suitably substituted dipolarophiles. Further studies using (trimethylsilyl)methyl-substituted indoles and pyrroles in natural product synthesis are in progress and will be discussed in subsequent papers.

Acknowledgment. We gratefully acknowledge support of this work by the National Institutes of Health.

Supplementary Material Available: ^{1}H NMR and X-ray data for compounds **8-16** (7 pages). Ordering information is given on any current mastheat page.

Tandem Radical Cyclization Approach to Angular Triquinanes. A Short Synthesis of (±)-Silphiperfol-6-ene and (±)-9-Episilphiperfol-6-ene

Dennis P. Curran*[1] and Shen-Chun Kuo

Department of Chemistry, University of Pittsburgh Pittsburgh, Pennsylvania 15260

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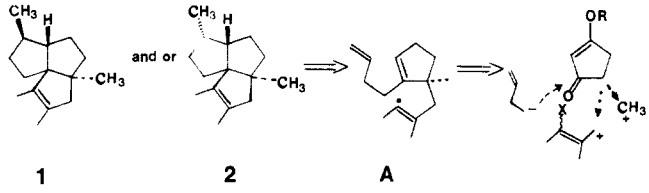
Largely through the effects of Bohlmann and co-workers, a variety of angular triquinanes have been isolated from natural sources over the past decade or so.[2] Synthetic strategies toward these compounds have most commonly employed sequential annulations to construct the interesting tricyclic ring system.[2] In principle, multiple cyclizations can present a more convergent approach to these compounds. We now outline a facile tandem radical cyclization approach to the representative angular triquinane silphiperfol-6-ene (**1**) and its C-9 epimer (**2**).

Silphiperfol-6-ene was isolated by Bohlmann and Jakupovic in 1980 from the roots of *Silphium perfoliatum*.[3] A recently reported synthesis by Paquette, et al. in 15 steps from (*R*)-(+)-pulegone served to determine the absolute stereochemistry of **1** and also confirm the initial spectroscopic structural assignment.[4]

We have recently demonstrated that a tandem radical cyclization strategy can provide a unified approach to the linear class of triquinane natural products.[5,6] In this approach, exemplified by the syntheses of hirsutene and $\Delta^{9(12)}$-capnellene, the two outer rings of the tricyclic system were simultaneously closed about a preformed central ring. Equation 1 depicts the adoption of a

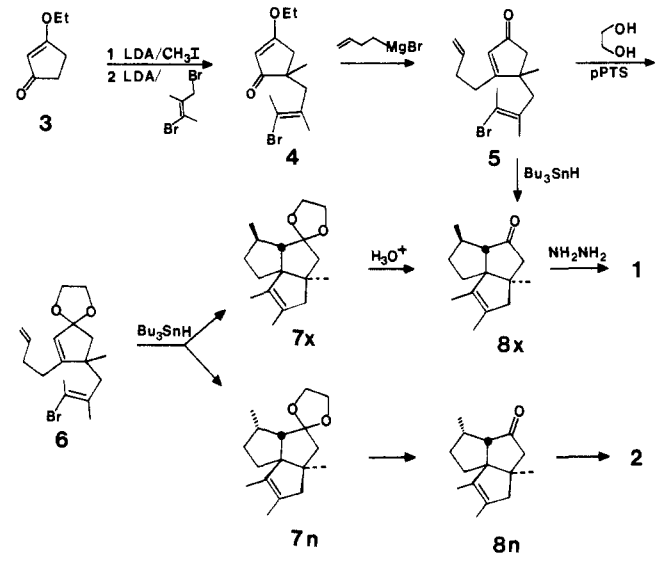


1 **2** **A**

(1)

related strategy for the synthesis of silphiperfolene. Note in particular that the cyclization precursor A should be readily available from an alkoxy cyclopentenone by routine transformations. Finally, note that the plan requires generation and cyclization of a vinyl radical.[7,8]

Scheme I



The synthesis is outlined in Scheme I. Cyclization precursor **5** is readily available in ~45% overall yield by sequential alkylation of 3-ethoxy-2-cyclopenten-1-one (**3**) with methyl iodide and (*E*)-2-methyl-1,3-dibromo-2-butene[8] to produce **4**, followed by standard Grignard addition of butenyl magnesium bromide and hydrolysis.[9] Direct tin hydride promoted tandem cyclization[5] of **5** gave a 66% isolated yield of a mixture of 2-oxosilphiperfol-6-ene (**8x**) and 9-epi-2-oxosilphiperfolene (**8n**). By no means unexpectedly,[10] the major product was the undesired epimer **8n** (ratio **8x**/**8n**:1/3). In addition, chromatographic separation of the **8x**/**8n** mixture was not readily accomplished. Standard Wolff-Kishner reduction[4] of the mixture provided a 1/3 mixture of silphiperfolene (**1**) and its C-9 epimer (**2**). While the stereochemical control (in the desired sense) at C9 is poor, it must be noted that the synthesis is exceptionally short and each of the five steps proceeds in good to excellent yield.[11]

In order to disfavor formation of the 9-endo isomer **8n**, a substituent was introduced on the "endo" face of the forming tricyclic system by the simple process of ketalization of **5** with ethylene glycol. Ketal **6** was isolated in nearly quantitative yield in a good state of purity. Due to its hydrolytic sensitivity, crude **6** was directly subjected to tandem cyclization to produce a mixture of **7x**/**7n** in 65% yield. In the absence of the carbonyl group to activate the initial cyclization, the use of a vinyl (rather than alkyl)

(1) Sloan Foundation Fellow, 1985-1987. Dreyfus Teacher-Scholar, 1986-1991. Eli Lilly Grantee, 1985-1987. Merck Young Faculty Development Grantee, 1986.

(2) For comprehensive reviews, see: Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1; **1979**, *79*, 41.

(3) Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1980**, *19*, 259. For structurally related natural products, see: Bohlmann, F.; Suding, H.; Cuatrecasas, J.; Robinson, H.; King, R. M. *Ibid.* **1980**, *19*, 2399. Bohlmann, F.; Wallmeyer, M.; Jakupovic, J.; Ziesche, J. *Ibid.* **1983**, *22*, 1645.

(4) Paquette, L. A.; Roberts, R. A.; Drtina, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 6690. Following the acceptance of this manuscript, a second synthesis has appeared: Wender, P. A., Singh, S. K. *Tetrahedron Lett.* **1985**, *26*, 5987.

(5) (a) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448. (b) Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943. (c) Curran, D. P.; Chen, M.-H. *Tetrahedron Lett.* **1985**, *26*, 4991.

(6) For a recent review of "Free-Radical Carbon-Carbon Bond Formation in Organic Synthesis", see: Hart, D. J. *Science* (*Washington*, D.C.) **1984**, *223*, 883.

(7) Over the past several years, Stork has elegantly developed and exploited the chemistry of vinyl radicals, see: (a) Stork, G. In "Current Trends in Organic Synthesis"; Nozaki, H., Ed.; Permagon Press: New York, 1982; pp 359-370. (b) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741. (c) Stork, G.; Mook, R., Jr. *Ibid.* **1983**, *105*, 3720. (d) Stork, G.; Baine, N. H. *Ibid.* **1982**, *104*, 2321. (e) Baine, N. H. Ph.D. Thesis, Columbia University, 1981. (f) For addition of vinyl radicals to enones, see: Marinovic, N. N.; Ramanathan, H. *Tetrahedron Lett.* **1983**, *24*, 1871.

(8) The stereochemistry of the vinyl bromide is inconsequential for the radical cyclization (see ref 7d,e). The *E* olefin was chosen simply for ease of preparation from β-bromoangelic acid (Buckles, R. E.; Mock, G. V. *J. Org. Chem.* **1950**, *15*, 680) by reduction (LAH, Et_2O) and bromination (HBr gas, CH_2Cl_2).

(9) Quesada, M. L.; Schlessinger, R. H.; Parsons, W. H. *J. Org. Chem.* **1978**, *43*, 3968. Koreeda, M.; Chen, Y. P. L. *Tetrahedron Lett.* **1981**, *22*, 15. Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.

(10) The formation of the less stable "endo" product in related bicyclo[3.3.0]octane systems is quite general: Hart, D.J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8209. Keck, G. E.; Enholm, E. J. *Tetrahedron Lett.* **1985**, *26*, 3311. Wolff, S.; Agosta, W. C. *J. Chem. Res. Synop.* **1981**, 79. For a mechanistic rationale and supporting calculations, see ref 5b and: Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373; *Tetrahedron* **1985**, *41*, 3925. Spellmeyer, D.; Houk, K. N., in press.

(11) (±)-Silphinene, a related triquinane, has been synthesized in only three steps! Wender, P. A.; Ternansky, R. J. *Tetrahedron Lett.* **1985**, *26*, 2625.

0002-7863/86/1508-1106$01.50/0