and Dr. J. G. Dingwall for helpful comments regarding the manuscript.

Registry No. **1a**, 87282-40-4; **1b**, 85673-26-3; **1c**, 87282-41-5; **1d**, 87282-42-6; **1e**, 87282-43-7; **1f**, 87282-44-8; **1g**, 87282-45-9; **2e**, 87282-46-0; **3a**, 87282-47-1; **3b**, 85673-30-9; **3c**, 87282-48-2; **3e**, 87282-49-3; **4a**, 87282-50-6; **4b**, 87282-51-7; **4d**, 87282-52-8; **5a**, 87282-53-9; **5b**, 87282-54-0; **5c**, 87282-55-1; **5d**, 87282-56-2; **6f**, 87282-57-3; **6g**, 87282-58-4; **7f**, 87333-74-2; **7g**, 87333-75-3; cis-3-(3,5-dichlorophenyl)-5-methyl-3-azabicyclo[3.2.0]hepta-2,6-dione, 87282-59-5.

Intramolecular [8 + 2] Cycloadditions of Alkenylheptafulvenes

Ching-Yang Liu, Jiri Mareda, and K. N. Houk*

Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260

Frank R. Fronczek

Department of Chemistry, Louisiana State University
Baton Rouge, Louisiana 70803

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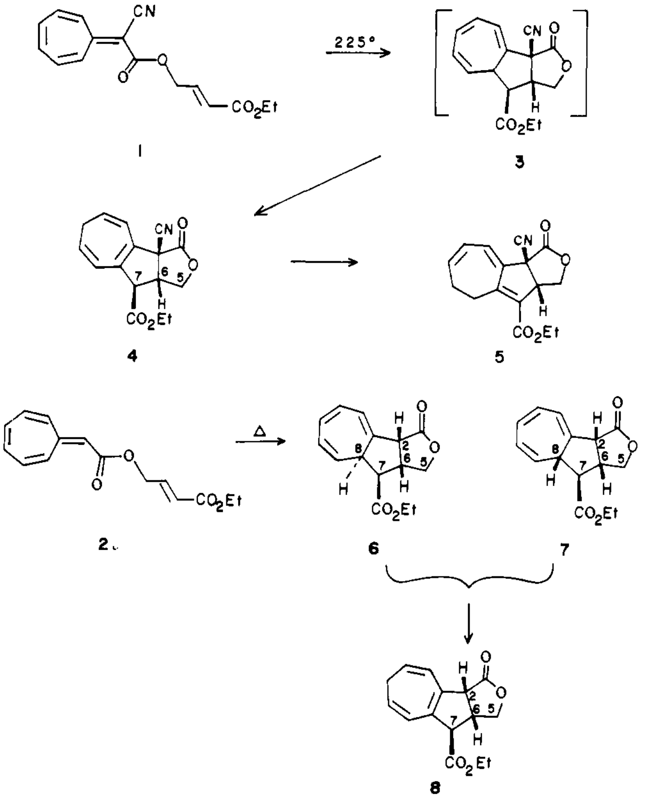
In the course of our investigations of intramolecular cycloadditions involving 10π electrons,[1] we have discovered the first examples of intramolecular [8 + 2] cycloadditions and have devised a computational method that successfully predicted the stereoselectivities of these reactions. This reaction is the prototype of a promising new technique for stereoselective hydroazulene synthesis, and the computational method should be of value of the prediction of stereoselectivities of intramolecular [4 + 2] cycloadditions[2] as well.

The intermolecular [8 + 2] cycloaddition was discovered by Doering and Wiley as a method to trap heptafulvene.[3] Subsequently, many substituted heptafulvenes have been synthesized[4,5] and have been found to undergo [8 + 2] cycloadditions with enamines or electron-deficient "tetraenophiles".[5]

The cyano-substituted compound **1** was prepared by condensation of 3-carbethoxyallyl cyanoacetate with 2 mol of tropylium fluoroborate.[4a] Thermolysis of the ditropyl compound gives cycloheptatriene and orange-red crystalline **1**, mp 106–107 °C, in 20% yield.[6] The synthesis of the heptafulvene **2**, possessing only one stabilizing substituent at C-8, involved reaction of α-tropylacetyl chloride with the 3-carbethoxyallyl alcohol. The resulting monotropyl ester was dehydrogenated with trityl fluoroborate followed by triethylamine[5] to give orange-red **2** (46%), a red oil that polymerizes slowly upon standing in solution and was used without further purification.

Sealed-tube thermolysis of the cyano compound **1** in toluene at 225 °C gave a light yellow crystalline product, **4**, mp 103–106 °C, in 65% yield. Adduct **4** must arise from a 1,5-sigmatropic hydrogen shift of the cycloheptatriene ring[5,7] of **3**. The adduct has characteristic γ-lactone and ester frequencies in the IR spectrum (1780, 1725 cm^{-1}), cycloheptatriene and ethyl resonances in the NMR spectrum, a doublet for H-7 at δ 3.72 (J_{67} = 1 Hz), and a complex ABX pattern at δ 3.95 and 4.77 assigned to the protons at C-5 and C-6. At higher temperatures, **5**, the product of further hydrogen shifts of **4**, was also formed,[6] along with trace amounts of two azulenes, whose structures were not further investigated.

Thermolysis of **2** in toluene at 145 °C gave **6** (mp 147–148 °C), **7**, and **8** (both oils) in 24% yield in a 7:1:1.6 ratio. At 180 °C, **6** and **8** are formed in a ratio of 2.8:1, along with traces of **7**.



The structures of **6–8** were assigned by analysis of 300- and 600-MHz NMR spectra in $CDCl_3$ and C_6D_6, double-resonance experiments, and use of Eu shift reagents. The couplings of 7.9 and 8.6 Hz between H-2 and H-6 in **6** and **7**, respectively, establish the cis fusion of the γ-lactone in both cases. Addition of Eu(tfc)$_3$ to $CDCl_3$ solutions causes the H-6 resonance of **6** to shift downfield 1.5 times faster than that of H-8. In **7**, both H-6 and H-8 resonances shift downfield to the same extent upon addition of the shift reagent. Therefore, H-6 and H-8 are trans in **6** and cis in **7**. The structure of **6** was completely established by single-crystal X-ray analysis.[8]

Four diastereomeric [8 + 2] adducts can be formed in these cycloadditions. We have modeled the four diasteromeric transition structures in the following manner. A transition state for the [8 + 2] reaction of heptafulvene with ethylene was approximated, using MNDO calculations[9] to locate the highest energy point on

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[1] Gupta, Y. N.; Doa, M. J.; Houk, K. N. *J. Am. Chem. Soc.*, **1982**, *104*, 7336.

[2] (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (b) Brieger, G.; Bennett, J. M. *Chem. Rev.* **1980**, *80*, 63. (c) Oppolzer, W. *Synthesis* **1978**, 793.

[3] Doering, W. v. E.; Wiley, D. W. *Tetrahedron* **1960**, *11*, 183.

[4] (a) Nozoe, T.; Mukai, T.; Osaka, S.; Shishido, N. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 1384. (b) Bertelli, D. J.; Golino, C.; Dreyer, D. L. *J. Am. Chem. Soc.* **1964**, *86*, 3329. Rapp, K. M.; Daub, J. *Tetrahedron Lett.* **1977**, 227. Reichardt, C.; Yun, K.-Y. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 65.

[5] Oda, M.; Kitahara, Y. *Chem. Commun.* **1969**, 352. Oda, M. Kitahara, Y. *Chem. Ind.* (*London*) **1969**, 920. Oda, M.; Kitahara, Y. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1920. Kuroda, S.; Funamizu, M.; Kitahara, Y. *Tetrahedron Lett.* **1975**, *24*, 1973. Kuroda, S.; Asao, T.; Funamizu, M.; Kurihara, H.; Kitahara, Y. *Ibid.* **1976**, 251. Oda, M.; Tani, H.; Kitahara, Y. *Chem. Commun.* **1969**, 739. Oda, M.; Kitahara, Y. *Ibid.* **1971**, 367. Yasunami, M.; Chen, A.; Noro, Y.; Takase, K. *Chem. Lett.* **1981**, 555. Yasunami, M.; Chen, A.; Yang, P. W.; Takase, K. *Ibid.* **1980**, 579. Yasunami, M.; Yang, P. W.; Kondo, Y.; Noro, Y.; Takase, K. *Ibid.* **1980**, 167. Rapp, M.; Daub, J. *Tetrahedron Lett.* **1976**, *24*, 2011. Hasenhundl, A. Rapp, K. M.; Daub, J. *Chem. Lett.* **1979**, 597. Baier, M.; Daub, J.; Hasenhundl, A.; Merz, A.; Rapp, K. M. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 198. Hafner, K.; Römer, M.; Fünten, W. a. d.; Komatsu, K.; Tanaka, S.; Okamoto, K. *Ann.* **1978**, 376.

[6] All new compounds gave elemental analysis or mass spectral accurate masses and spectral data in accord with the assigned structures.

[7] Conrow, K. *J. Am. Chem. Soc.* **1959**, *81*, 5461. Mironov, V. A.; Fedorovich, A. D.; Akhrem, A. A. *Russ. Chem. Rev.* **1981**, *50*, 666.

[8] Crystal data of **6**: $C_{15}H_{16}O_4$, M_r 260.3 orthohombic, $P2_12_12_1$, a = 8.408 (2) Å, b = 10.246 (2) Å, c = 15.657 (4) Å, Z = 4, D_c = 1.282 g cm^{-3}. 614 observations with Mo Kα radiation were used and the structure was refined to an R index of 0.079. There is disorder in the location of the methyl group of the ethyl ester, which prevented further refinement. The fractional atomic corrdinates are available as supplementary material.

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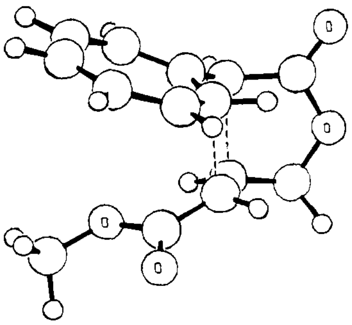
the pathway constrained to have synchronous formation of the two forming CC bonds.[10] The ester side chain was then substituted for the appropriate hydrogens in each of the four stereochemically distinct ways, and the geometry of the side chain was optimized by MNDO, keeping the heptafulvenyl and vinyl groups frozen in the geometries obtained from the model transition-state calculations. The relative energies of the terminal exo and endo ester moieties were calculated separately in the same manner. The preferred cis endo ester (cis-endo-E) transition structure, which leads to **6**, is shown below.



The relative energies of the four transition structures obtained by adding the contribution from the developing lactone side chain and the ester group are 0, +1.6, +28.9, and +37.3 kcal/mol for cis-endo-E, cis-exo-E, trans-endo-E, and trans-exo-E, respectively. Astonishingly, these calculations predict that **6** and **7** will be formed in a 7:1 ratio at 145 °C! While this perfect agreement must be considered accidental, the calculations provide at least qualitative clues to relative stabilities of isomeric transition structures. The difference in energy between cis and trans transition structures is calculated to be even larger than the difference in cis and trans fused products, because of severe angle strain required to connect the developing γ-lactone ring in a trans fashion to the [8 + 2] transition state. The cis-endo-E transition structure may be more stable than the cis-exo-E because of attractive secondary orbital interactions between the ester and tetraene orbitals. However, the MNDO calculations suggest that the CO_2CH_2 side chain can be substituted for exo hydrogens on the heptafulvene and ethylene (which gives the cis-endo-E transition state) with very little strain, while replacement of endo hydrogens with the CO_2CH_2 fragment (which gives the cis-exo-E transition state) introduces greater strain. The exo CH bonds are more nearly parallel than the endo, so the relatively small ring can be fused onto the transition state more easily in an exo fashion.

Synthetic applications of this reaction and the generality of this computational method will be described at a later date.

Acknowledgment. We are grateful to the National Science Foundation for research and equipment grants, the Swiss National Science Foundation for a Fellowship to J.M., and the National Institutes of Health (PROPHET and CMU NMR Facility).

Registry No. **1**, 87306-51-2; **2**, 87306-52-3; **4**, 87306-53-4; **5**, 87306-54-5; **6**, 87306-55-6; **7**, 87334-96-1; **8**, 87306-56-7.

Supplementary Material Available: ORTEP drawing and listing of fractional atomic coordinates of **6** (4 pages). Ordering information is given on any current masthead page.

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(9) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899, 4907.

(10) Although MNDO calculations predict an unsymmetrical reaction pathway and a diradical intermediate for the Diels–Alder reaction (Dewar M. S. S.; Olivella, S.; Rzepa, H. S. *J. Am. Chem. Soc.* **1978**, *100*, 5650), a C_s symmetry constraint gives a geometry very similar to the STO-3G transition structure (Townshend, R. E.; Ramunni, G.; Segal, G.; Hehre, W. J.; Salem, L. *J. Am. Chem. Soc.* **1976**, *98*, 2190). The procedure adopted here for the [8 + 2] reaction is expected to give a resonable transition structure, assuming that the reaction is concerted and approximately synchronous. For other intramolecular cycloadditions, we have had success in the use of ab initio transition-structure calculations on the parent system, followed by MM2 side chain and substituent calculations for stereochemical predictions (F. K. Brown and K. N. Houk, submitted for publication).

A Totally Synthetic Route to Lincosamine

Eric R. Larson and Samuel Danishefsky*

Department of Chemistry, Yale University
New Haven, Connecticut 06511

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The significant physiological properties of the higher monosaccharides as well as their varied substitution and chirality patterns[1] render them attractive targets for total synthesis. Aside from providing a response to the intrinsic chemical challenge, total synthesis could allow for the achievement of molecular modifications of a nature not readily accessible by the manipulative approach of partial synthesis. Such analogues could be helpful in the important matter of sorting the interplay of chemical structure and biological function. Thus far, however, these systems have been approached via known pentoses and hexoses[2] by resorting to chain extensions and multiple adjustments of functional groups.

As part of our studies of the cyclocondensation of aldehydes with dienes,[3a,b] we have undertaken the total synthesis of several of the biologically active higher monosaccharides. Below are related a series of experiments that have resulted in a de novo stereospecific route to the aminooctose lincosamine (**2**). As its methyl thioglycoside ((methylthio)lincosaminide = MTL, **3**), lincosamine is the saccharide portion of the clinically important antibiotic lincomycin (**1**).[4] Numerous synthetic undertakings in the lincosamine series have been confined to chain extensions and modifications of D-galactose[5] with little in the way of stereocontrol of the side-chain functionality.

We hoped that methodology might be uncovered, wherein a *trans*-propenyl function, such as is found in structure **4**, could accommodate the installation of the *erythro* vicinal amino alcohol function at the appropriate carbons and in the proper stereochemical sense (relative to the pyranose chirality) required for lincosamine. Thus, a crucial element of the investigation was the study of the facial bias, if any, that would be exhibited by such a double bond toward attack by external reagents. *That such a bias has indeed been uncovered for several crucial reactions (vide infra) is a favorable augury for future prospects in this area.*

Our total synthesis starts with the cyclocondensation of crotonaldehyde[3b] with diene **5**[6] under the influence of $BF_3{\cdot}O(Et)_2$ ((i) CH_2Cl_2, −78 °C; (ii) TFA, room temperature). There is thus obtained a 67% yield of **6**.[7] Previous studies with a diene related to **5**[3a] and subsequent studies with **5**[8] itself have served to indicate

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[1] Representative examples. (a) Heptoses, purpurosamine: Umezawa, S. *Adv. Carbohydr. Chem. Biochem.* **1974**, *30*, 111. (b) Octoses, 3-deoxy-D-manno-2-octulosonic acid (KDO): Unger, F. M. *Ibid.* **1981**, *38*, 323. (c) Nonoses, acylneuraminic acids: Schauer, R. *Ibid.* **1982**, *40*, 132. (d) Decoses, sinefungin: Suhadolnik, R. J. "Nucleosides as Biological Probes"; Wiley: New York, 1979; p 19.

[2] For example: (a) Purpurosamine B: Honda, Y.; Suami, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2825. (b) KDO: Ref 1b. (c) *N*-Acetylneuraminic acid: Benzing-Nguyen, L.; Perry, M. B. *J. Org. Chem.* **1978**, *43*, 551. (d) Sinefungin: Lyga, J. W.; Secrist, J. A. III *Ibid.* **1983**, *48*, 1982.

[3] (a) Danishefsky, S.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358. (b) Danishefsky, S.; Kerwin, J. F.; *J. Org. Chem.* **1982**, *47*, 3183.

[4] Lincomycin is a copyrighted trademark of the Upjohn Co. Kalamazoo, MI. For an excellent review of the chemistry of lincomycin see: Magerlein, B. J. In "Structure–Activity Relationships Among the Semisynthetic Antibiotics"; Pearlamn, D., Ed.; Academic: New York, 1977; pp 601–650.

[5] Magerlein, B. J. *Tetrahedron Lett.* **1970**, 33. Saeki, H.; Ohki, E. *Chem. Pharm. Bull.* **1970**, *18*, 789. Howarth, G. B.; Szarek, W. A.; Jones, J. K. N. *J. Chem. Soc. C* **1970**, 2218. Hems, R.; Horton, D.; Nakadate, M. *Carbohydr. Res.* **1970**, *25*, 205. Atsumi, T.; Fukumaru, T.; Ogawa, T.; Matsui, M. *Agr. Biol. Chem.* **1973**, *37*, 2621. David, S. M.; Fischer, J. C. *Carbohydr. Res.* **1974**, *38*, 147. Woolard, G. R.; Rathbone, E. B.; Szarek, W. A.; Jones, J. K. N. *J. Chem. Soc., Perkin Trans. 1* **1976**, 950. Gateu-Olesker, A.; Sepulchre, A. M.; Vass, G.; Gero, S. D. *Tetrahedron* **1977**, *33*, 393. Hoppe, I.; Schöllkopf, U. *Liekigs Ann. Chem.* **1980**, 1474.

[6] Prepared from 1-[(trimethylsilyl)oxy]-4-methoxy-3-buten-2-one (ref 3a) via desilylation (MeOH, room temperature), benzoylation (PhCOCl, Et_3N, DMAP/CH_2Cl_2), and silylation (TMSOTf, Et_3N/Et_2O).

[7] All isolated compounds gave satisfactory IR, ^1H NMR (270 or 500 MHz), ^{13}C NMR (cmpd **6-14**), and elemental analyses (cmpd **8-13**) or exact masses (cmpd **6**, **7**, **14**, **15**).

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