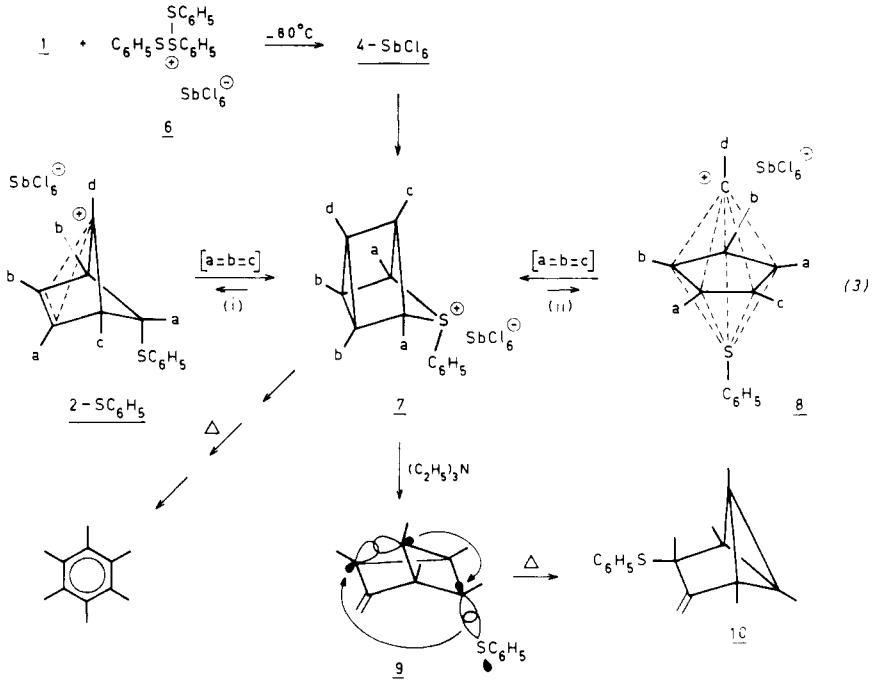


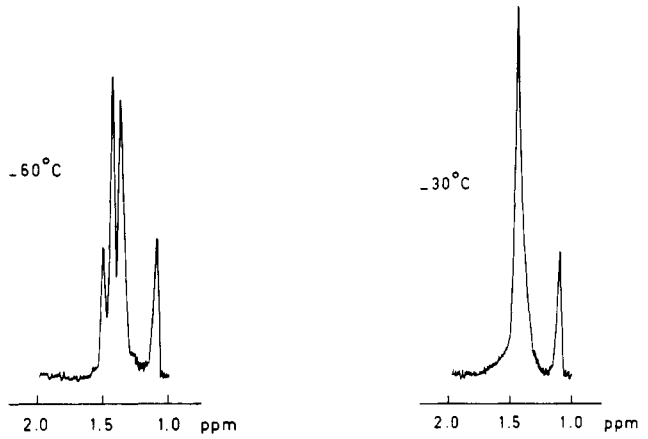


Figure 1. 60-MHz spectrum of (a) **7** at −60 °C; and (b) **8**/**2**-SC_6H_5 at −30 °C. Both samples in CH_2Cl_2 solution.

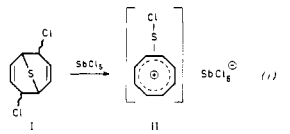
a simple β-elimination product of the sulfonium salt **7**.

The spectral behavior of **7**, as described above, is consistent with a rapid automerization of sulfonium salt **7** via cation **2**-SC_6H_5 or, indistinguishably, the highly symmetrical hypervalent sulfonium ion **8**. Either description leads to the observed degeneracy of five methyl groups (see i and ii in eq 3). The data now in hand are not sufficient to allow a decision between those two possibilities. The structure **8**, if it truly exists, can in formal sense be viewed as the pyramidal dication that we have previously described[1] to which a sixfold bonded thiolate ligand has been added opposite to the sixfold bonded carbon atom.[11,12]

As a final point we mention the quantitative room temperature rearrangement of **9** neat or in $CHCl_3$ or CH_2Cl_2 to **10** (eq 3).[13] This reaction can be an example of a $[2_s + 2_a]$ cycloaddition in the rearrangement of a cyclopropyl carbinyl sulfide; we are unaware of precedent for such a transformation.

Further work on this remarkable chemical behavior of **1** with sulfenium ions is anticipated.

(11) In 1966 in a lecture at Princeton University Lautenschlager suggested that II could arise from I (eq i) on treatment with $SbCl_5$. There have been no further reports on this. See: Mueller, W. A. *Angew. Chem.* **1969**, *81*, 475.



(12) See also: (a) Ross, J. A.; Seiders, R. P.; Lemal, D. M., *J. Am. Chem. Soc.* **1976**, *98*, 4327. (b) Kwart, H.; George, T. J. *Ibid.* **1977**, *99*, 5215. (c) Vincent, J. A. J. M.; Schipper, P.; de Groot, Ae.; Buck, H. M. *Tetrahedron Lett.* **1975**, 1989. (d) Kwart, H.; King, K. G.; "d-Orbitals in the Chemistry of Silicon, Phosphorus and Sulfur"; Springer-Verlag: Heidelberg, 1977.

(13) Spectra for **10**: ^1H NMR ($CDCl_3$) δ 0.64 (s, 3 H), 0.92 (s, 3 H), 1.05 (s, 3 H), 1.20 (s, 3 H), 1.25 (s, 3 H), 4.69 (s, 1 H), 4.82 (s, 1 H), 7.1–7.5 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 2.8 (CH_3), 3.0 (CH_3), 6.0 (CH_3), 7.0 (CH_3), 23.9 (C), 24.2 (CH_3), 27.4 (C), 45.2 (C), 46.8 (C), 62.4 (C), 99.2 (sp^2 CH_2), 127.9 (aromatic C), 128.1 (aromatic CH, 2×), 128.9 (aromatic CH, 2×), 136.2 (aromatic CH), 164.4 (sp^2 C). Exact mass at *m/e* 270.143; calcd for $C_{18}H_{22}S$, *m/e* 270.144.

A Chiral Synthesis of L-Acosamine and L-Daunosamine via an Enantioselective Intramolecular [3 + 2] Cycloaddition

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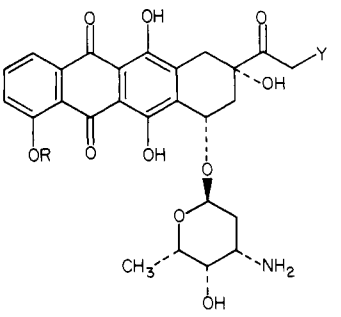
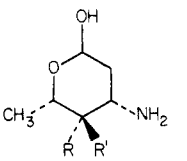
Received February 12, 1981

Anthracycline antibiotics adriamycin (**1a**), daunomycin (**1b**), and carminomycin (**1c**) are highly effective against a wide variety of tumors. The dose-limiting toxicity of these substances has



1a, R = CH_3; Y = OH
b, R = CH_3; Y = H
c, R = Y = H



2a, R = OH; R′ = H
b, R = H; R′ = OH

sparked intensive research in the areas of synthesis of modified

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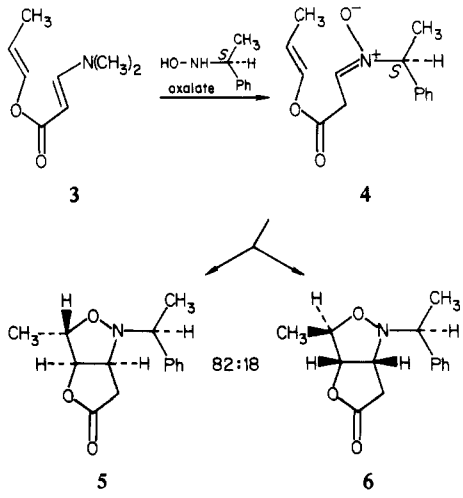
Scheme I

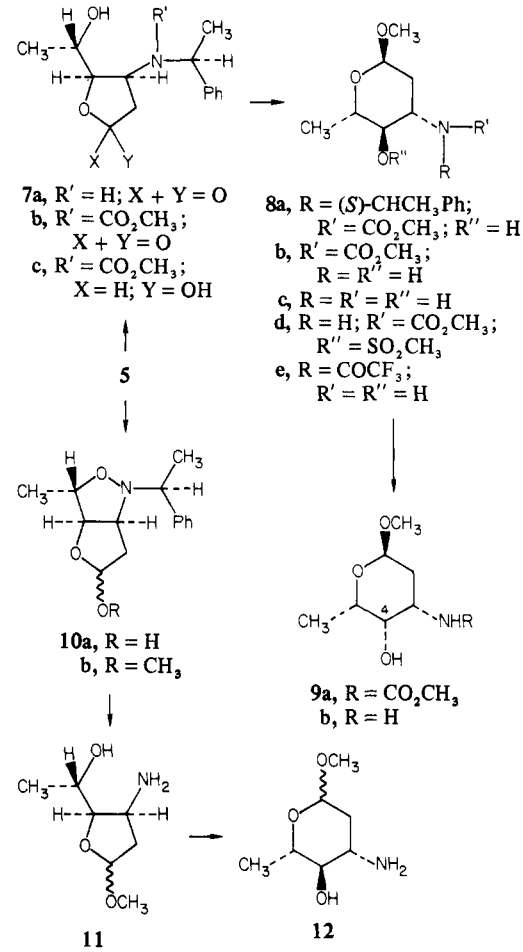


3 **4** **5** **6**

aglycones and sugar and improved methods for glycosidic bond formation. The replacement of the carbohydrate moiety, L-daunosamine (**2a**), for example, with its C4 epimer, L-acosamine (**2b**), has been reported to lower the cardiotoxicity of adriamycin.[1] We report here a new, chiral synthesis of both L-daunosamine and L-acosamine in which the key intermediate is prepared by an enantioselective [3 + 2] cycloaddition of a chiral nitrone.[2]

The pioneering work of LeBel has shown that the intramolecular cycloaddition of a nitrone to an olefin in which the participating functions are separated by a propylene chain produces the cis-fused 3-oxa-2-azabicyclo[3.3.0]octane.[3] We expected, therefore that if the same regio- and stereocontrols were operative in the case of enol ester **4**, cycloaddition would generate **5**. This cycloadduct would have three contiguous chiral centers of proper relative configuration, with each one bearing an appropriate heteroatom as in acosamine (**2b**). Furthermore, we expected that the desired absolute stereochemistry of these three chiral centers could be induced by a properly selected chiral substituent on the nitrogen.[4,5]

Scheme II



7a, R′ = H; X + Y = O
b, R′ = CO_2CH_3; X + Y = O
c, R′ = CO_2CH_3; X = H; Y = OH

8a, R = (*S*)-$CHCH_3Ph$; R′ = CO_2CH_3; R″ = H
b, R′ = CO_2CH_3; R = R″ = H
c, R = R′ = R″ = H
d, R = H; R′ = CO_2CH_3; R″ = SO_2CH_3
e, R = $COCF_3$; R′ = R″ = H

5

10a, R = H
b, R = CH_3

9a, R = CO_2CH_3
b, R = H

11 **12**

Nitrone **4** was prepared in the following manner. *trans*-Propenyl acetate was formylated by treatment with an excess of bis(dimethylamino)-*tert*-butoxymethane[7] to give the all-trans vinylogous urethane **3** (mp 48 °C) in 91% yield (Scheme I).[8] Heating this masked aldehyde with the oxalate salt of (*S*)-(−)-*N*-hydroxy-α-methylbenzenemethanamine[9] in refluxing xylene generated the nitrone **4** by extrusion of dimethylamine. Under the reaction conditions, nitrone **4** undergoes intramolecular cycloaddition to give in 68% yield an 82:18 mixture of diastereomers **5** and **6**.[10] The structure assignments of the cycloadducts were based on their respective NMR spectra and in particular on a ca. 1-ppm chemical shift difference between the methylene protons of the two products.[11] Inspection of Dreiding models indicated that the preferred

(1) The following reviews cover the progress of analogue synthesis and evaluation: Remers, W. A. "The Chemistry of Antitumor Antibiotics"; Wiley Interscience: New York, 1979: Vol. 1; Chapter 2. Henry, D. W. *Cancer Treat. Rep.* **1979**, *63*, 845. Arcamone, F. "Topics in Antibiotic Chemistry"; Wiley; New York, 1978; Vol. 2, pp 89–229. Brown, J. R. "Progress in Medicinal Chemistry"; Ellis, G. P., West, G. B., Eds.; Elsevier: New York, 1978; Vol. 15, pp 125–164. Henry, D. W. "Cancer Chemotherapy"; Sartorelli, A.C., Ed.; American Chemical Society: Washington, DC, 1976. Arcamone, F. *Lloydia* **1977**, *40*, 45.

(2) For syntheses of *d,l-* or *dl*-acosamine (3-amino-2,3,6-trideoxy-L-*arabino*-hexose), daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose) and derivatives, see: Richardson, A. C. *Carbohydr. Res.* **1967**, *4*, 422. Marsh, J. P.; Mosher, C. W.; Acton, E. M.; Goodman, L. *J. Chem. Soc., Chem. Commun.* **1967**, 973. Baer, H. H.; Capek, K. Cook, M. C. *Can. J. Chem.* **1969**, *47*, 89. Gupta, S. *Carbohydr. Res.* **1974**, *37*, 381. Wong, C.; Ho, T.-L.; Niemczura, W. P. *Can. J. Chem.* **1975**, *53*, 3144. Horton, D.; Weckerle, W. *Carbohydr. Res.* **1975**, *44*, 227. Arcamone, F.; Penco, S.; Vigevani, A.; Redaelli, S.; Franchi, G.; DiMarco, A.; Casazza, A.; Dasdia, T.; Formelli, F.; Necco, A.; Soranzo, C. *J. Med. Chem.* **1975**, *18*, 703. Lee, W. W.; Wu, H. Y.; Christensen, J. E.; Goodman, L.; Henry, D. W. *Ibid.* **1975**, *18*, 768. Arcamone, F.; Penco, S.; Vigevani, A. *Cancer Chemother. Rep.* **1975**, *6*, 123. Heyns, K.; Lim, M.; Park, J. *Tetrahedron Lett.* **1976**, 1477. Yamaguchi, T.; Kojima, M. *Carbohyrate Res.* **1977**, *59*, 343. Baer, H. H.; George, F. Z. *Can. J. Chem.* **1977**, *55*, 1100. Horton D.; Weckerle, W. F. U.S. Patent 4 024 333, 1977; *Chem. Abstr.* **1977**, *87*, 68584v. Horton, D.; Sorenson, R. J.; Weckerle, W. *Carbohydr. Res.* **1977**, *58*, 125. Whistler, R. L. U.S. Patent 4 181 795, 1978. Grethe, G.; Uskokovic, M. R.; Sereno, J. U.S. Patent 4 174 344, 1977; *Chem. Abstr.* **1980**, *92*, 94371w. Cheung, T.; Horton, D.; Sorenson, R. J.; Weckerle, W. *Carbohydr. Res.* **1978**, *63*, 77. Boivin, J.; Pais, M.; Monnert, C. *Ibid.* **1978**, *64*, 271. Dyong, I.; Wiemann, R. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 682. Dyong, I.; Bendlin, H. *Chem. Ber.* **1978**, *111*, 1677. Tanaka, S. *Japanese* Patent 79 14 913, 1979; *Chem. Abstr.* **1979**, *91*, 5437m. Fuchs, E.; Horton, D.; Weckerle, W.; Winter, B. *J. Antibiot., Ser. B.* **1979**, *32*, 223. Pelyvas, I.; Sztaricskai, F.; Bognar, R. *Carbohydr. Res.* **1979**, *76*, 257. Iwataki, I.; Nakamura, Y.; Takahashi, K.; Matsumoto, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2731. Grethe, G.; Uskokovič, M. R.; Sereno, J. U.S. Patent 4 228 080, **1980**. Fronza, G.; Fuganti, C.; Grasselli, P. *J. Chem. Soc. Chem. Commun.* **1980**, 442. Pelyvas, I.; Whistler, R. L. *Carbohydr. Res.* **1980**, *84*, C5. Boivin, J.; Pais, M.; Monnert, C. *Ibid.* **1980**, *79*, 193. Dyong, I.; Wiemann, R. *Chem. Ber.* **1980**, *113*, 2666. Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1981**, *46*, 227.

(3) LeBel, N. A. *Trans. N.Y. Acad. Sci.* **1965**, *27*, 858 and references cited therein.

(4) For recent reviews on nitrone–olefin cycloaddition reactions, see: Black, D. S.; Crozier, R. F.; Davis, V. C. *Synthesis* **1975**, *205*. Padwa, A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 123. Oppolzer, W. *Ibid.* **1977**, *16*, 10.

(5) Chiral nitrones: Vasella, A. *Helv. Chim. Acta* **1977**, *60*, 1273. Panfil, I.; Belzecki, C. *J. Org. Chem.* **1979**, *44*, 1212 and references therein.

(6) The intermolecular cycloaddition of a nitrone and a heteroatom substituted olefin generally gives the product where the nitrone oxygen has added to the heteroatom end of the olefin.[4] Even in the only other reported intramolecular example that regiopreference was still 2:1. Oppolzer, W.; Keller, K. *Tetrahedron Lett.* **1970**, 1117.

(7) Bredereck, H.; Simchen, G.; Rebsdat, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffmann, H.; Grieschaber, P. *Chem. Ber.* **1968**, *101*, 41. For a review on the chemistry of formamide acetals, see: Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1974**, *35*, 1675.

(8) All new substances had satisfactory combustion analysis and ^1H NMR, IR, and mass spectral properties.

(9) Polonski, T.; Chimiak, A. *Tetrahedron Lett.* **1974**, 2453.

(10) The major isomer **5** was obtained pure directly in 35–40% yield simply by crystallization from the crude reaction mixture with ether. Silica gel chromatography (hexane/ethyl acetate 4:1) of the mother liquors produced the remainder of the major product **5** and all of the minor isomer **6**.

rotamer of the methylbenzyl group places the phenyl ring in a shielding position over the methylene protons in **5** but not in **6**. On this basis, structure **5** was assigned to the major isomer and **6** to the minor one. This assignment was confirmed by an X-ray crystallographic analysis of **5**. *To our knowledge, this represents the first example where the preference of the nitrone oxygen to add to the oxygen-bearing carbon of enol ethers or esters has been reversed.*[6]

Transformation of the chiral intermediate **5** to the amino sugars was carried out first by reduction of the N–O bond using zinc in aqueous acetic acid to give lactone **7a** [89%, mp 58–60 °C, $[\alpha]^{25}_D$ −17.11° (*c* 0.900, CH_3OH)] and followed by *N*-carbomethoxylation to **7b** [54%, mp 124.5 °C, $[\alpha]^{25}_D$ −82.10° (*c* 1.0378, $CHCl_3$)] with methyl chloroformate in aqueous tetrahydrofuran and sodium carbonate (Scheme II). Reduction with diisobutylaluminum hydride produced lactol **7c** which on stirring with Amberlite CG 120 resin (H^+ form) in methanol generated a 4:1 mixture of pyranose anomers (89% for the two steps). For simplification of the characterization of further intermediates, the major anomer **8a** [$[\alpha]^{25}_D$ −106.10° (*c* 0.9020, $CHCl_3$)] was isolated by chromatography. Debenzylation of **8a** to **8b** [75%, mp 143 °C, $[\alpha]^{25}_D$ −162.64° (*c* 0.7071, $CHCl_3$)] was accomplished with sodium in liquid ammonia. Basic hydrolysis then provided L-α-methyl acosaminide (**8c**) identical with authentic material by NMR and mass spectral properties as well as TLC characteristics and mixed melting point [$[\alpha]^{25}_D$ −140.4° (*c* 0.225, CH_3OH); lit.[2] −145.1° (*c* 0.61, CH_3OH)].[12] The hydrolysis of methyl acosaminide has been reported previously.[2]

The synthesis of L-α-methyl daunosaminide (**9b**) was completed by inversion of the C4 hydroxyl group of a methyl acosaminide derivative.[13] The mesylate **8d** [69% from **8b**, mp 141 °C, $[\alpha]^{25}_D$ −109.50° (*c* 0.9717, $CHCl_3$)] was exposed to aqueous dimethylformamide (bath temperature 105 °C) to give the C4 α-hydroxy carbamate **9a** [50% unoptimized, mp 90 °C, $[\alpha]^{25}_D$ −166.71° (*c* 0.3983, $CHCl_3$)] which was then hydrolyzed with aqueous barium hydroxide to give L-α-methyl daunosaminide **9b** (46% unoptimized) which was identical with authentic material by NMR, TLC, and mixed melting point.[12] The hydrolysis to daunosamine has been carried out previously.[2]

An alternate, more direct route to L-methyl acosaminide from the initial cycloadduct **5** was also investigated. Reduction of **5** with diisobutylaluminum hydride in tetrahydrofuran (−78 °C) gave lactols **10a** as a 2:1 mixture which on treatment with Amberlite CG 120 (H^+ form) in methanol gave a 3:1 mixture of acetals **10b** (mp 105 °C, 80% for the two steps). Cleavage of both the N–O and *N*-benzyl bonds in **10b** was carried out by catalytic hydrogenation (50 psi, 5% Pd/C, CH_3OH) to give a mixture of furanose anomers **11** (94%)[14] which on exposure to Amberlite CG 120 (H^+ form) in methanol isomerized to the pyranose anomers **12** (90%). For the purpose of comparison, this mixture was converted to the *N*-trifluoroacetyl derivatives and separated by silica gel chromatography (hexane/ethyl acetate 2:1). The major anomer was found to be identical with an authentic sample of **8e** by NMR, TLC, and mixed melting point [$[\alpha]^{25}_D$ −122° (*c* 0.56, $CHCl_3$); lit.[2] −123° (*c* 0.5, $CHCl_3$)].[15,16] Since anomeric mixtures at this stage are of no consequence for the linking of the sugars to the anthracyclinones, the above is a highly efficient route to acosamine (**2b**).

We are presently examining intramolecular [3 + 2] cycloadditions of chiral nitrones related to **4** in order to gain some insight on the source and the generality of the observed enantioselectivity as well as to develop other applications for such chiral cycloadducts.

Acknowledgment. We express our gratitude to members of the Physical Chemistry Department of Hoffmann-La Roche Inc. for determinations of spectral and analytical data and Dr. J. Blount for the X-ray structure determination of **5**.

(11) **5**: NMR ($CDCl_3$, 100 MHz) δ 7.24 (s, 5 H), 4.52 (dd, *J* = 5, 8 Hz, 1 H), 4.02 (dq, *J* = 5, 7 Hz, 1 H) 3.69 (q, *J* = 7 Hz, 1 H, 3.44 (dt, *J* = 2, 8 Hz, 1 H), 1.98 (AB, J_{gem} = 18 Hz, J_{vic} = 8 Hz, 1 H), 1.69 (AB, J_{gem} = 18 Hz, J_{vic} = 2 Hz, 1 H), 1.52 (d, *J* = 7 Hz, 3 H), 1.37 (d, *J* = 7 Hz, 3 H); IR ($CHCl_3$) 1782 cm^{-1}; mp 138.5 °C; $[\alpha]^{25}_D$ +17.16 (*c* 0.6876, $CHCl_3$). **6**: NMR ($CDCl_3$, 100 MHz) δ 7.25 (s, 5 H), 4.56 (dd, *J* = 4, 7 Hz, 1 H), 3.99 (dq, *J* = 4, 7 Hz, 1 H), 3.85 (q, *J* = 7 Hz, 1 H), 3.52 (dt, *J* = 7,6 Hz, 1 H), 2.60 (d, *J* = 6 Hz, 2 H), 1.40 (d, *J* = 7 Hz, 3 H), 1.28 (d, *J* = 7 Hz, 3 H); IR ($CHCl_3$) 1785 cm^{-1}; mp 133 °C; $[\alpha]^{25}_D$ −54.34° (*c* 0.8303, $CHCl_3$).

(12) Authentic methyl 3-amino-2,3,6-trideoxy-α-L-*arabino*-hexopyranoside (**8c**) and methyl 3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranoside (**9b**) were prepared by Dr. G. Grethe.

(13) For a similar inversion process, see: Marsh, J. P.; Mosher, C. W.; Acton, E. M.; Goodman, L. *J. Chem. Soc., Chem. Commun.* **1967**, 973.

(14) The major isomer crystallized from ether; mp 59–62 °C; $[\alpha]^{25}_D$ −120.82° (*c* 0.9982, CH_3OH).

(15) The minor isomer was converted to the major isomer by exposure to Amberlite CG 120 (H^+ form) in methanol.

(16) We are grateful to F. Arcamone for sending an authentic sample of methyl 2,3,6-trideoxy-3-trifluoroacetamido-α-L-*arabino*-hexopyranoside (**8e**).

Tetrakis(trifluoromethyl)semibullvalenes. Could Cope Degeneration Be Frozen Out?

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There are many reports concerning semibullvalene, an interesting "fluxional" cage compound.[1] Hoffmann et al.[2] and Dewar et al.[3] examined the effects of substituents theoretically and forecasted some substituents to favor one tautomer or lower the activation energy of the "fluxional" tautomerism. However, according to Hoffmann, the substituent effect of a trifluoromethyl group was not easily classified and remained to be worked out.[2] Therefore, we tried to synthesize trifluoromethylated semibullvalenes and have obtained two tetrakis(trifluoromethyl)-semibullvalenes from tetrakis(trifluoromethyl)cyclooctatetraene. Interestingly, one was nearly limited to one isomer, while the other was fluctuating very rapidly between two tautomers even at −90 °C or seemed to be frozen out in the transition state of the tautomerism.

As mentioned in the previous paper,[4] we synthesized 1,2,3,8-tetrakis(trifluoromethyl)cyclooctatetraene (**1**). Photolysis of **1** mainly gave [2 + 2] reaction products.[4,5] Therefore, we tried a [4a + 2a] intramolecular cycloaddition reaction of **1** to semibullvalene.[6] The thermolysis of the solution of **1** in pentane at 170–180 °C for 6 days gave three isomers, which were separated by preparative GLC.[7] One isomer was identified as 1,2,7,8-tetrakis(trifluoromethyl)bicyclo[4.2.0]octa-2,4,7-triene (**2**) by comparison of its spectral data with those of the authentic sample.[4] The other two isomers (**3** and **4**)[8] were found to be tetrakis(tri-

(1) (a) H. E. Zimmerman and G. L. Grunewald, *J. Am. Chem. Soc.*, **88**, 183 (1966); (b) L. T. Scott and M. Jones, Jr., *Chem. Rev.*, **72**, 181 (1972); (c) H. E. Zimmerman, R. W. Binkley, R. S. Givens, G. L. Grunewald, and M. A. Sherwin, *J. Am. Chem. Soc.*, **91**, 3316 (1969); (d) A. K. Cheng, F. A. L. Anet, J. Mioduski, and J. Meinwald, *ibid.*, **96**, 2887 (1974).

(2) R. Hoffmann and W. D. Stohrer, *J. Am. Chem. Soc.*, **93**, 6941 (1971).

(3) M. J. S. Dewar and D. H. Lo, *J. Am. Chem. Soc.*, **93**, 7201 (1971).

(4) Y. Kobayashi, A. Ando, K. Kawada and I. Kumadaki, *J. Chem. Soc., Chem. Commun.*, submitted for publication.

(5) Photolysis of the unsubstituted cyclooctatetraene to semibullvalene is well-known. See N. J. Turro, J.-M. Liu, H. E. Zimmerman, and R. E. Factor, *J. Org. Chem.*, **45**, 3511 (1980), and references therein.

(6) Concerning thermal isomerization of cyclooctatetraenes to semibullvalenes, see R. Criegee, and R. Askani, *Angew. Chem., Int. Ed. Engl.* **7**, 537 (1968); H. E. Zimmerman, and H. Iwamura, *J. Am. Chem. Soc.*, **92**, 2015 (1970). A theoretical aspect was given by H. Iwamura, *Tetrahedron Lett.*, 369 (1973).

(7) The preparative GLC Ohkura Gas Chromatograph (Model 701) (3 m × 3 mm in 10% SE 30 on 60/80 Uniport B, 60 °C). Order of elution is **4** (18%), **2** (trace), **1** (10%), and **3** (51%).

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