be 7.6×10^{12} s^{-1}. The straight line in Figure 2 is the linear relation expected from the classical reaction rate. In this calculation, we have assumed the continuous Boltzmann distribution for the translational kinetic energy of the transferred hydrogen atom.[2c] Although the agreement with the experimental points is satisfactory in the temperature range above 50 K, the slight disagreement at 4.2 K might be due to the failure of this assumption. However, the disagreement in the rate constant at 4.2 K is only a factor of 9.5. Since the classical reaction rate leads to a disagreement of a factor of 10^{764} at 4.2 K, the agreement within a factor of 10^1 is rather surprising. It should be mentioned that the rate constants (190-220 K) in DMG-d_2 reported by Lebedev et al.[5a] have been also fitted by our treatment as a result of the mass effect on tunneling.

Finally it is concluded that the tunneling process must be involved in the hydrogen atom transfer reactions. It is also suggested that the use of radical-pair conversion in single crystals is quite powerfull for the elucidation of the tunneling process in chemical reactions. One can study the reaction between two molecules which have well-defined relative orientation and dimension.

References and Notes

(1) For a review see E. F. Caldin, *Chem. Rev.*, **69**, 135 (1969).
(2) (a) E. D. Sprague and F. Williams, *J. Am. Chem. Soc.*, **93**, 787 (1971); (b) J. Wang and F. Williams, *ibid.*, **94**, 2930 (1972); (c) R. J. Le Roy, E. D. Sprague, and F. Williams, *J. Phys. Chem.*, **76**, 546 (1972); (d) G. Brunton, D. Griller, L. R. C. Barclay, and K. U. Ingold, *J. Am. Chem. Soc.*, **98**, 6803 (1976).
(3) A. F. Trotman-Dickenson, *Adv. Free-Radical Chem.*, **1**, 1 (1965).
(4) (a) Y. Kurita, *J. Chem. Phys.*, **41**, 3926 (1964); (b) Y. Kurita and M. Kashiwagi, *ibid.*, **44**, 1727 (1966).
(5) (a) O. Ye. Yakimchenko and Ya. S. Lebedev, *Int. J. Radiat. Phys. Chem.*, **3**, 17 (1971); (b) Ya. S. Lebedev, *Radiat. Effects*, **1**, 213 (1969).
(6) Since the half-life of the unstable radical pair is only 68 min at 77 K, the crystals were irradiated with a high dose rate (~1.4 Mrad/h) x-ray irradiator for 30 min at 77 K. Within a few minutes after irradiation, the crystals were transferred to a liquid helium Dewar.
(7) G. A. Russell in "Free Radicals", Vol. 1, J. K. Kochi, Ed., Wiley, New York, N.Y., 1973, p 275.
(8) H. S. Johnston and J. Heicklen, *J. Phys. Chem.*, **66**, 532 (1962).
(9) C. Eckart, *Phys. Rev.*, **35**, 1303 (1930).
(10) R. J. Le Roy, K. A. Quickert, and D. J. Le Roy, *Trans. Faraday Soc.*, **66**, 2997 (1970).

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Thermal Rearrangement of Dibromotetracyclo[5.1.0.0^{2,4}.0^{3,5}]octanes. Assessment of the Competitive Opening of Dibromocyclopropane and Bicyclo[1.1.0]butane Rings and a General Synthesis of *trans*-Bishomobenzenes

Sir:

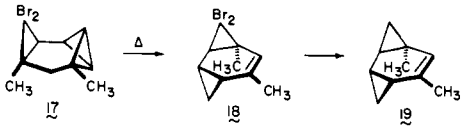
The ready availability of tricyclo[4.1.0.0^{2,7}]hept-3-enes[1] and their established high yield conversion to dibromotetracyclo[5.1.0.0^{2,4}.0^{3,5}]octanes (e.g., **1**)[1,2] prompted us to consider the latter as possible precursors to octavalenes (e.g., **3**), highly elusive[3] conjugated dienes of considerable theoretical interest.[3c,e] Christl had previously established that thermolysis of **6** in CCl_4 (80 °C, 15 h) proceeds exclusively with dibromocyclopropane ring opening to give **7**.[4] In striking contrast, the heating of **1** and related molecules has now been found to give neither functionalized tricyclo[5.1.0.0^{2,8}]octene derivatives (**2**), nor even dibromo-*trans*-tricyclo[4.2.0.0^{2,4}]oct-7-enes,[5] but to experience unprecedented bond reorganization not involving rupture of the halogenated three-membered ring. The mechanistically revealing mapping of the carbon atom translocations to be described require total fragmentation of the bicyclobutane moiety in **1** and subsequent construction of a new cyclopropane ring through unusual transannular hydrogen shifting. Given the ease of dehalogenation of **4** and its congeners, the overall scheme is seen to comprise a heretofore unavailable general synthetic entry to variously substituted *trans*-bishomobenzenes (e.g., **10, 13, 16,** and **19**).

Gentle heating of **8a** (CCl_4, 80 °C, 8 h) resulted in smooth isomerization to **9a**.[6] This finding shows that C_5 becomes the olefinic carbon atom proximal to the unsubstituted cyclopropane ring (consult numbering schemes on **1** and **4**). Comparable treatment of a mixture of **8b** and **11a** for 4 h gave the dibromides **9b** and **12a** and ultimately hydrocarbons **10a** and **13a.** Through examination of thermal rearrangement of **8c** and **11b,** we were able to establish further in the case of **9c** (and therefore also **10b**) that the deuterium atom was positioned exo on the cyclopropyl methylene carbon. These experiments served not only to uncover the ultimate fate of the two bridgehead carbons, but also to demonstrate that stereospecific hydrogen transfer to C_3 occurs during passage to the *trans*-bishomobenzene framework. The possibility of acid evolution during these reactions was considered; however, the use of epichlorohydrin-carbon tetrachloride (1:9) or pure tetramethylethylenediamine as solvents led to identical results. Because other methyl substitution schemes required higher temperatures (see below), it appears that a C_5 CH_3 group facilitates rearrangement. A further basis of comparison is provided by **1** which requires 8 h in refluxing chlorobenzene to achieve complete isomerization to **4.**

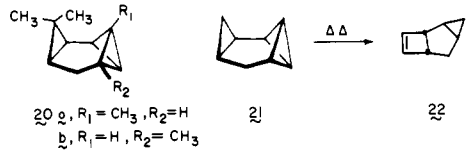
In light of the above findings, we were somewhat surprised to discover that heating of **14a** (60% syn; 40% anti) in refluxing chlorobenzene for 5 h produced a single dibromide (**15a**), characterization of which was achieved by dehalogenation to

give **16a.** It could be further demonstrated through thermolysis of **14b** (C_6H_5Cl, reflux, 12 h) that C_1 appears as that basal carbon of the halogenated ring distal from the double bond. Dehalogenation of **15b** as before led efficiently to **16b.** Accordingly, in the absence of a 5-methyl group, C_3 and C_4 of the dibromotetracyclooctane are capable of positional interchange in such a way that the bridgehead alkyl group ultimately appears at the allylic cyclopropyl site exclusively.

The information gained from **17** which isomerizes cleanly to **18** (C_6H_5Cl, reflux, 12 h) and ultimately provides **19** fixes C_7 and leaves only two sites to be labeled. However, if C_6 and C_2 maintain logical connectivities to their original neighboring atoms, they should be interposed between C_5 and C_7 and adjacent to C_1, respectively, as demonstrated in **4.**

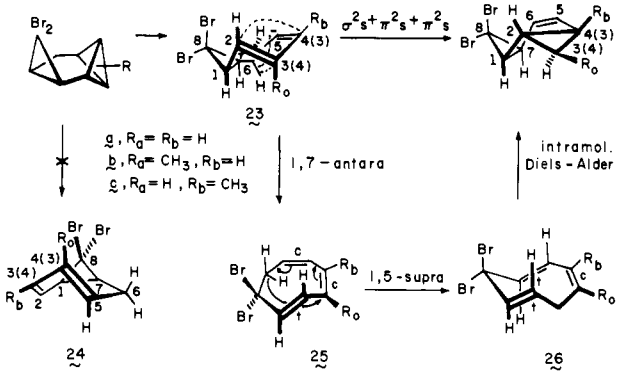


Under conditions comparable with those employed above, the tetracyclic hydrocarbons **20a, 20b,** and **21** showed no tendency to rearrange and could be recovered quantitatively. At somewhat more elevated temperatures (210 °C, toluene/tetramethylenediamine), **21** has previously been shown to give chiefly **22.**[5b] The pair of bromine atoms consequently not only reduce the temperature required for rearrangement but also exert a significant impact on its ultimate course.



The essentials of mechanistic thinking consistent with the experimental data (Scheme I) require no dependency on acid catalysis. In agreement with orbital symmetry constraints, the initial step is considered to involve $[_\sigma 2_s + {}_\sigma 2_a]$ fission of the bicyclobutane ring.[7] When the bridgehead positions (C_3 and C_4) are unsubstituted, there exist two idealized transition states for concerted fragmentation, but the one which gives rise to **23a** is far less sterically congested than that leading to **24a** and

Scheme I



should normally be favored. Although the presence of a bridgehead substituent triples the number of $[_\sigma 2_s + {}_\sigma 2_a]$ possibilities, models again clearly indicate that **23c** is the isomer uniquely devoid of nonbonded interaction. To the extent that these effects are reflected in the activation enthalpies for the various bicyclobutane openings, transient formation of **23c** should be favored and appears to be in the case of **14a** and **14b.** However, the presence of an added "wing" methyl group at C_5 as in **8** and **11** adds steric congestion at the $C_{4(3)}$-C_5 double bond in **23** which apparently is adequate to cause operation of the alternative fragmentation which places the bridgehead methyl at $C_{3(4)}$.

In cis,trans homotropilidenes such as **23,** simple geometric and conformational factors generate a number of stereoelectronic alignments of pivotal mechanistic significance. On the one hand, the pseudo-axial C_6 proton is so oriented that transannular shift to the suitably canted inner lobe of the $C_{3(4)}$ π orbital could result with concurrent bonding of C_2 to $C_{4(3)}$ and development of an interconnective π bond between C_5 and C_6 through full suprafacial utilization of all bonding components (Scheme I). Alternatively, H_6 could experience antarafacial 1,7 transfer to C_7 with formation of **25,** subsequent suprafacial 1,5-hydrogen migration within which delivers **26** whose intramolecular Diels-Alder cyclization also would furnish product. Although the first mechanistic option lacks precedent and the second passes through the strained intermediate **26** (note, however, that much energy is available in the original reactant), either scheme accounts for all the stereochemical facts, but other possibilities are not summarily dismissed.

The reactivity of **23** is seen to differ intrinsically from the usual conrotatory diene closure pathway followed by other endo,endo'-bridged bicyclo[1.1.0]butanes,[7b-d] but cyclobutene formation is necessarily dependent upon that conformational readjustment within the cis,trans homotropilidene intermediate which brings C_2 and C_5 into proximity. In **23,** the steric bulk of the syn-8-bromo substituent appears to deter this structural realignment sufficiently to allow operation of previously unobserved passage to *trans*-bishomobenzenes.

Products derived from scission of the dibromocyclopropane ring have not been detected, in agreement with the appreciably diminished strain relative to that localized in the bicyclobutane unit. How then is the chemical behavior of **6** explained? We believe the driving force underlying conversion of **6** to **27** to reside in the electronic structure of the benzvalene nucleus[8] which provides incipient stabilization to the associated transition state. For **1** and its congeners, experimental photoelectron spectral data have revealed a reversal in this ordering, with the Walsh-type bicyclobutane orbital now serving as the HOMO.[9]

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References and Notes

(1) R. T. Taylor and L. A. Paquette, *Tetrahedron Lett.*, 2741 (1976); L. A. Paquette and R. T. Taylor, *J. Am. Chem. Soc.*, in press.
(2) L. A. Paquette and R. T. Taylor, *Tetrahedron Lett.*, 2745 (1976).
(3) (a) P. J. Van Vuuren, R. J. Flatterick, J. Meinwald, and R. E. Hughes, *Chem. Commun.*, 883 (1970); *J. Am. Chem. Soc.*, **93,** 4394 (1971). (b) H. E. Zimmerman and L. R. Sousa, *J. Am. Chem. Soc.*, **94,** 834 (1972). (c) G. E. Gream, L. R. Smith, and J. Meinwald, *J. Org. Chem.*, **39,** 3461 (1974). (d) M. S. Baird and C. B. Reese, *Tetrahedron Lett.*, 2895 (1976). (e) R. Gleiter, P. Bischof, W. E. Volz, and L. A. Paquette, *J. Am. Chem. Soc.*, **99,** 8 (1977).
(4) (a) M. Christl and B. Brüntrup, *Angew. Chem., Int. Ed. Engl.*, **13,** 208 (1974); (b) M. Christl and G. Freitag, *ibid.*, **15,** 493 (1976).
(5) (a) R. T. Taylor and L. A. Paquette, *Angew. Chem., Int. Ed. Engl.*, **14,** 496 (1975); (b) M. Christl and M. Lechner, *ibid.*, **14,** 765 (1975).
(6) The thermal rearrangements were conducted at the 1–4-mmol level and the *isolated* yields ranged from 70 to 90% except in the case of the parent system (**1**) which afforded **4** in 40–50% yield. The efficiency of these conversions is not considered maximized. All of the dibromides and *trans*-bishomobenzenes exhibited ^1H and ^{13}C NMR spectra and accurate mass spectral *m/e* values fully compatible with the given assignments. Hydrocarbons **10a, 13a, 16a** and **16b** also gave satisfactory combustion data.
(7) (a) G. L. Closs and P. E. Pfeffer, *J. Am. Chem. Soc.*, **90,** 2452 (1968); (b) K. B. Wiberg and G. Szeimies, *ibid.*, **92,** 571 (1970); (c) L. A. Paquette S. E. Wilson, R. P. Henzel, and G. R. Allen, Jr., *ibid.*, **94,** 7761 (1972); (d) M. Christl, U. Heinemann, and W. Kristof, *ibid.*, **97,** 2299 (1975).
(8) P. Bischof, R. Gleiter, and E. Müller, *Tetrahedron*, **32,** 2769 (1976); P. J. Harman, J. E. Kent, T. H. Gan, J. B. Peel, and G. D. Willett, *J. Am. Chem.*

Soc., **99**, 943 (1977).
(9) P. Bischof, R. Gleiter, R. T. Taylor, A. R. Browne, and L. A. Paquette, unpublished work.
(10) The Ohio State University Dissertation Fellow, 1975–1976.

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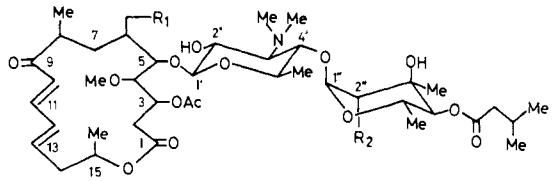
Synthesis of Carbomycin B. Introduction of the Amino Disaccharide onto the 16-Membered-Ring Aglycone

Sir:

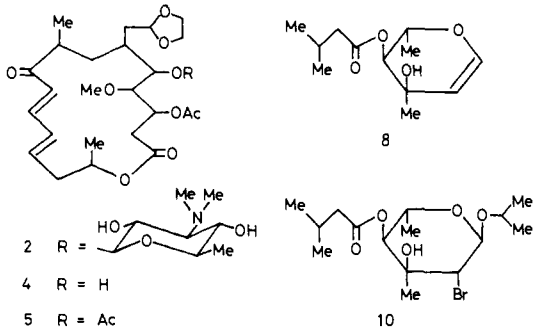
Sixteen-membered-ring macrolides[1] are an important class of antibiotics and most of their structures contain an amino disaccharide, namely 4-*O*-(α-L-mycarosyl)-D-mycaminose which seems to be indispensable for their antibacterial activities. It is apparent, therefore, that regio- and stereoselective introduction of this disaccharide onto the macrolide aglycone constitutes an essential part of the total synthesis of the macrolide antibiotics. We now wish to report a synthesis of carbomycin B,[2-4] a representative antibiotic of this class, by introduction of the amino disaccharide onto the 16-membered-ring aglycone of carbomycin B. This synthesis was achieved by using a new method[5] for the synthesis of 2-deoxy-α-glycosides, including diaxial opening of glycals with alcohols in the presence of a brominating agent.

Carbomycin B (**1**),[6] upon treatment with ethylene glycol and *p*-toluenesulfonic acid in acetonitrile (23 °C, 1 h), afforded



1 R_1 = ^{18}CHO R_2 = H
9 R_1 =  R_2 = Br
11 R_1 = CHO R_2 = Br

the ethylene acetal **2**[7] (84% yield), mp 102–106 °C (amorphous from acetone-hexane), $[\alpha]^{16}_D$ +13° (*c* 1.3, $CHCl_3$), and 2′-hydroxylethyl 4-*O*-isovalerylmycaroside (**3**,[7] 91% yield).



2 R =
4 R = H
5 R = Ac

8

10

Oxidation[8] of **2** with *m*-chloroperbenzoic acid (1.05 equiv, $CHCl_3$, 23 °C, 10 min) provided the *N*-oxide as a solid. The *N*-oxide, without purification, was treated with acetic anhydride (3 equiv, $CHCl_3$, reflux, 1 h) followed by treatment with sodium bicarbonate, affording the 16-membered-ring lactone **4**,[7] the aglycone part of carbomycin B (57% overall yield from **2**), mp 72–75 °C (amorphous from ether-hexane), $[\alpha]^{21}_D$ +10° (*c* 1.0, $CHCl_3$); the acetate **5**[7] (Ac_2O, pyridine, 45 °C, 14 h),[9] mp 220.5–221.5 °C (needles from chloroform-ether).

Condensation of **4** with 1-α-bromo-2,4-diacetylmycaminose hydrobromide[10] (5 equiv) in the presence of mercuric cyanide in nitromethane (20 °C, 10 h) gave the β-glycoside **6**[7] identical with the per-*O*-acetate (Ac_2O, pyridine, 23 °C, 1 h) of **2**, mp 103–110 °C (amorphous from ether-hexane), $[\alpha]^{20}_D$ −14° (*c* 1.0, $CHCl_3$), in 16% yield after column chromatography on silica gel.

Selective deacetylation of **6** by using its own basicity in methanol (23 °C, 14 h) quantitatively gave the product **2**[7] identical with the above-mentioned degradation product.

The glycal **8**,[7] $[\alpha]^{26}_D$ −148° (*c* 2.4, $CHCl_3$), was prepared by hydrolysis of the glycoside **3** (0.5 N hydrochloric acid, in aqueous dioxane, 40 °C, 4 h) to give 4-*O*-isovalerylmycarose **7**,[7] mp 74–75 °C (EtOAc-hexane), followed by treatment of **7** with *p*-toluenesulfonyl chloride (1.4 equiv) and triethylamine (2.8 equiv) in acetonitrile (23 °C, 5 h), in 51% overall yield. Reaction[5] of **8** with 1 equiv of the acetal **2** and 1 equiv of 1,3-dibromo-5,5-dimethylhydantoin in a mixture of acetonitrile and benzene (from −20 to 23 °C, 4 h) afforded, after column chromatography on silica gel (benzene-EtOAc followed by EtOAc-acetone-EtOH), a single condensed product and unreacted starting material **2** (recovered in 65% yield). Recrystallization (ether-hexane) of the product afforded needles of pure **9**[7] (11% yield,[11] mp 194–196 °C, $[\alpha]^{16}_D$ −18° (*c* 1.2, $CHCl_3$). The chemical shifts and coupling constants of H-1″ and H-2″ in the ^{1}H NMR were practically the same as those of the 2-bromo-α-L-altropyranoside **10**[12] and the signal due to C-4′ in the ^{13}C NMR was deshielded about 4.5 ppm in comparison with that of **2**, supporting that **9** possesses an α-glycosidic linkage at C-4′ with diaxially opening of the olefin group of **8**.[5]

Although the glycosidic linkage of 2-deoxyglycosides is generally cleaved under acidic conditions, the presence of a bromine atom at C-2 induces the glycoside to resist even drastic acid hydrolysis. Thus, deprotection of **9** with 90% trifluoroacetic acid (5 °C, 15 min) gave rosettes of 2″-bromocarbomycin B (**11**)[7] in nearly quantitative yield, mp 172–174 °C (ether-hexane), $[\alpha]^{21}_D$ −20° (*c* 1.0, $CHCl_3$), λ_{max}^{MeOH} 279 nm (ε 23 000), without cleavage of the α-glycosidic linkage.

Debromination[5] of **11** by using tri-*n*-butyltin hydride (1.2 equiv) in benzene (60 °C, 1 h under argon) with α,α′-azobisisobutyronitrile as catalyst completed the synthesis, giving carbomycin B (**1**)[13] (90% yield) identical with that obtained from natural sources by IR ($CHCl_3$), UV (MeOH), ^{1}H NMR and mass spectra, and antimicrobial activity.

The utility of the masked macrolide aglycone **4** for regioselective glycosylation is thus demonstrated.

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References and Notes

(1) S. Ōmura and A. Nakagawa, *J. Antibiot.*, **28**, 401 (1975), and references cited therein.
(2) (a) F. A. Hochstein and K. Murai, *J. Am. Chem. Soc.*, **76**, 5080 (1954); (b) L. A. Freiberg, R. S. Egan, and W. H. Washburn, *J. Org. Chem.*, **39**, 2474 (1974).
(3) R. B. Woodward, *Angew. Chem.*, **69**, 50 (1957); R. B. Woodward, L. S. Weiler, and P. C. Dutta, *J. Am. Chem. Soc.*, **87**, 4662 (1965).
(4) M. Kuehne and B. W. Benson, *J. Am. Chem. Soc.*, **87**, 4660 (1965).
(5) K. Tatsuta, K. Fujimoto, M. Kinoshita, and S. Umezawa, *Carbohydr. Res.*, **54**, 85 (1977). For another approach to the synthesis of 2-deoxy disaccharides, see R. U. Lemieux and A. R. Morgan, *Can. J. Chem.*, **43**, 2190 (1965).
(6) Prepared from josamycin[1] (leucomycin A_3, the C-9 hydroxyl derivative of **1**) by oxidation with sulfur trioxide–pyridine complex and triethylamine in Me_2SO in 86% yield, mp 193–195 °C (prisms from acetone–hexane), $[\alpha]^{21}_D$ −36° (*c* 1.0, $CHCl_3$), λ_{max}^{MeOH} 279 nm (ε 23 000),[2b] although in 30% yield by oxidation with MnO_2.[1]
(7) All compounds gave satisfactory combustion analyses, IR, UV, NMR, and mass spectra consistent with the reported structures. ^{1}H and ^{13}C NMR (δ, parts per million from TMS) were in $CDCl_3$ solution and the latter was analyzed in comparison with data of 16-membered macrolide antibiotics