kinetic scheme of Figure 6 and good evidence for it. The intermediate **3** is so acidic (pK_a = ca. −19) that deprotonation, even in sulfuric acid, is diffusion controlled and is competitive with rotation about the C–N single bond. As a result, the lifetime of the intermediate is too short to permit H_E and H_Z to become equivalent. This means that, at least in part, the rate-limiting step for exchange of H_Z is a rotation, even though the rate constant for that process is $\geq 10^{11}$ s^{-1}.

How general is this conclusion? The result has been obtained only for aromatic amidines, since the coincidence of chemical shifts of H_E and H_Z of primary aliphatic amidinium ions in >70% H_2SO_4 has precluded measuring their individual exchange rates. By analogy to $RCONH_3^{+}$[1] it may be expected that aliphatic R groups would increase k_r, promote rotational equivalence, and make k_{ES} and k_{ZS} more nearly equal. However, the large, 6.4-fold greater reactivity of H_E in *N,N'*-dimethylacetamidinium ion (**2**, R = CH_3)[3] suggests that deprotonation and rotation are competitive in all protonated amidinium ions.

Note Added in Proof: We have confirmed this assignment for benzamidinium ion (**1**, R = C_6H_5) with the use of anionic lanthanide-shift reagents.[43]

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(43) Perrin, C. L., to be published.

Total Synthesis of (*R*)-Glycerol Acetonide and the Antiepileptic and Hypotensive Drug (−)-γ-Amino-β-hydroxybutyric Acid (GABOB): Use of Vitamin C as a Chiral Starting Material[1]

Michael E. Jung*[2] and Teresa J. Shaw

Contribution from the Department of Chemistry, University of California, Los Angeles, California 90024. *Received November 13, 1979*

Abstract: Ascorbic acid (Vitamin C) (**9**) is shown to be a useful, inexpensive chiral starting material for natural products synthesis. It is converted in high yield via two synthetic operations into (*R*)-glycerol acetonide (**7**), the more inaccessible enantiomer of glycerol acetonide. Since D-(*R*)-glyceraldehyde acetonide (**4**) and the corresponding alcohol **1** have been used in many total syntheses of a wide variety of compounds, the ready availability of the opposite enantiomers L-(*S*)-glyceraldehyde acetonide (**6**) and glycerol **7** should be of great value. As one indication of this potential synthetic utility, the hypotensive, antiepileptic compound (*R*)-(−)-γ-amino-β-hydroxybutyric acid (GABOB) (**8**) has been synthesized from ascorbic acid (**9**) via nine steps in 10% overall yield. As further evidence of the importance of these compounds in synthesis, several useful intermediates for the preparation of the highly active hypotensive agents, the aryloxypropanolamines (**5**), were prepared from Vitamin C.

Introduction

Recently great advances have been made in the total synthesis of optically active natural products from readily available chiral precursors. Especially useful as optically active starting materials have been the naturally occurring carbohydrate derivatives, particularly D-glucose.[3] Herein is reported the first use of a different inexpensive carbohydrate derivative, ascorbic acid, Vitamin C (**9**), as a chiral precursor and from it the total synthesis of the useful antiepileptic and hypotensive drug γ-amino-β-hydroxybutyric acid, GABOB (**8**). Also the utility of several intermediates, e.g., (*R*)-glycerol acetonide (**7**), for the synthesis of other interesting chiral drugs such as the aryloxypropanolamines (**5**) is described.

Background

(*S*)-Glycerol acetonide (**1**) and its derivatives have often been used as chiral intermediates for natural products synthesis.[4] The racemic form of **1** was first reported by Fischer in 1895[5] and has been prepared simply from glycerol many times.[6] For the synthesis of the optically active forms of glycerol acetonide, the naturally occurring, inexpensive polyhydroxy compound D-mannitol (**2**) was used. The bis(acetonide) of mannitol (**3**) was prepared in moderate yield and the resulting diol cleaved with lead tetraacetate to yield unstable (*R*)-glyceraldehyde acetonide (**4**).[7]

A number of biologically active compounds have been formed from **4**, including naturally occurring D-glyceraldehyde,[8] an amino acid,[9] prostaglandins,[10] and carbohydrates.[11] It has also been used to synthesize the unnatural enantiomer of the antibiotic pyridindolol.[12] However, due to its instability, (*R*)-glyceraldehyde acetonide (**4**) is usually reduced to (*S*)-glycerol acetonide (**1**) with hydrogen in the presence of a nickel catalyst.[13] This enantiomer

(1) Taken in part from the Ph.D. Thesis of T.J.S, UCLA, 1979.
(2) Camille and Henry Dreyfus Teacher-Scholar, 1978–1983. Fellow of the Alfred P. Sloan Foundation, 1979–1981.
(3) (a) Hanessian, S. *Acc. Chem. Res.* **1979**, *12*, 159 and references therein. (b) Anderson, R. C.; Fraser-Reid, B. *Tetrahedron Lett.* **1978**, 3233 and references therein.
(4) Two very recent examples include Kitahara's synthesis of Brefeldin A (Kitahara, T.; Mori, K.; Matsui, M. *Tetrahedron Lett.* **1979**, 3021) and Mori's synthesis of ipsdienol (Mori, K.; Takigawa, T.; Matsuo, T. *Tetrahedron* **1979**, *35*, 933).
(5) Fischer, E. *Chem. Ber.* **1895**, *28*, 1169.
(6) (a) Irvine, J.; MacDonald, J.; Soutar, C. *J. Chem. Soc.* **1915**, *107*, 337. (b) Böeseken, J.; Hermans, P. *Recl. Trav. Chim. Pays-Bas* **1923**, *42*, 1104. (c) Hibbert, H.; Morazain, J. *Can. J. Res.* **1930**, *2*, 35, 214. (d) Newman, M.; Renoll, M. "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol III, p 502. (e) AldoMacchi, R.; Crespi, F. *Rev. Argent. Grasas Aceites* **1967**, *9*, 29; *Chem. Abstr.* **1969**, *70*, 37088.
(7) (a) Fischer, H.; Baer, E. *Helv. Chim. Acta* **1934**, *17*, 622. (b) Baer, E.; Fischer, H. *J. Biol. Chem.* **1939**, *128*, 463.
(8) Baer, E. *J. Am. Chem. Soc.* **1939**, *61*, 2607.
(9) Fischer, H.; Feldman, B. *Helv. Chim. Acta* **1936**, *19*, 532.
(10) Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275.
(11) Fischer, H.; Baer, E. *Helv. Chim. Acta* **1936**, *19*, 519, 524.
(12) Wu, G.; Yamanaka, E.; Cook, J. *Heterocycles* **1978**, *9*, 175.

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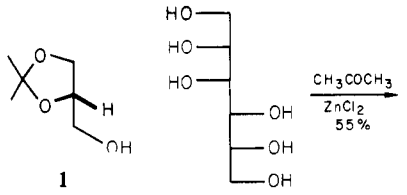

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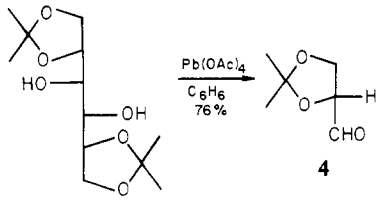
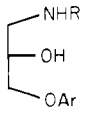


3 4

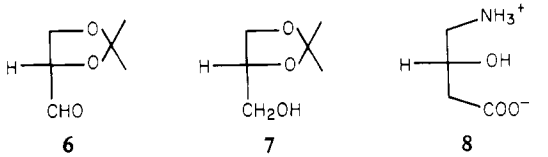
of glycerol acetonide has been transformed into a large variety of biologically important compounds including glycerides,[14] α-glycerophosphoric acid,[15] and other related compounds.[16] It has also been used for the chiral synthesis of (*S*)-propylene glycol,[17] (*R*)- and (*S*)-epichlorohydrins,[18] and (*R*)- and (*S*)-aryloxypropylene oxides.[19] Finally, (*S*)-glycerol acetonide (**1**) has been used recently in the synthesis of medicinally active unnatural products, including the hypotensive β-adrenergic blockers, aryloxypropanolamines of general structure **5**.[20]



5

Unfortunately, although both (*S*)-glycerol acetonide (**1**) and (*R*)-glyceraldehyde acetonide (**4**) are readily available, the enantiomeric compounds (*S*)-glyceraldehyde acetonide (**6**) and (*R*)-glycerol acetonide (**7**) are not. They have only been prepared a few times before, once by an analogous sequence[21] performed on the unnatural L-mannitol which must be made from L-mannose (and ultimately from L-arabinose[21] or L-inositol[22]). (*R*)-Glycerol acetonide (**7**) has also been prepared in two additional ways: from its enantiomer **1** by a six-step procedure in 7% overall yield[23] or from L-serine in four steps in good yield.[24] Thus both **6** and **7** are very inaccessible compounds.

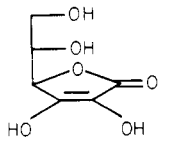
One of the many compounds for which (*R*)-glycerol acetonide (**7**) might serve as a simple starting material is (*R*)-γ-amino-β-hydroxybutyric acid, GABOB (**8**). Several years ago groups of Japanese and Italian workers reported the effectiveness of GABOB in the treatment of epileptic seizures[25] and hypertension[26] in



6 7 8

animals. Since that time, the drug has been extensively tested clinically in the treatment of human epilepsy.[27] All of the known syntheses of GABOB involve a final resolution of the (±)-amino acid into the biologically active (*R*)-(−)-enantiomer.[28] We envisioned that **7** would serve as an excellent chiral precursor of **8** since it possesses the same absolute configuration about the asymmetric carbon as does GABOB and has other functionality present for conversion into the necessary groups.

The search for an inexpensive chiral precursor of (*R*)-glycerol acetonide (**7**), and ultimately of GABOB (**8**), led to ascorbic acid, Vitamin C (**9**). This fairly inexpensive compound possesses the (*R*) configuration at C-5 (corresponding to the correct configuration at C-2 in **7** and at C-3 in **8**). Therefore, a study was initiated to prepare **7** and ultimately **8** and **9**.



9

Results and Discussion

Synthesis of (*R*)-Glycerol Acetonide (7). The saturated diol function of ascorbic acid (**9**) could be easily and cleanly protected as acetonide **10**. Although there were many procedures for this reaction,[29] the simplest method was to dissolve ascorbic acid in excess acetone containing a catalytic amount of acetyl chloride.[30] The acetonide crystallized directly from the reaction in yields of 80–85%.

Degradation of ascorbic acid acetonide (AAA) to desired compound **6** was attempted unsuccessfully by a variety of oxidative processes. For example, lead tetraacetate oxidation of **10** in a variety of solvents (benzene, glacial acetic acid, buffered acetic acid/potassium acetate, etc.) gave poor material recovery as did ozonolysis of AAA (**10**). The known dimethyl ether **11**[29d] could be prepared from **9** by either of two routes, namely, by methylation

(13) (a) See ref 7b. (b) Fischer, H.; Baer, E. *Chem. Rev.* **1941**, *29*, 287.
(14) (a) Baer, E.; Fischer, H. *J. Biol. Chem.* **1939**, *128*, 475. (b) Sowden, J.; Fischer, H. *J. Am. Chem. Soc.* **1941**, *63*, 3244. (c) Pfeiffer, F. R.; Miao, C.; Weisbach, J. *J. Org. Chem.* **1970**, *35*, 221.
(15) Baer, E.; Fischer, H. *J. Biol. Chem.* **1939**, *128*, 491.
(16) (a) Golding, B.; Ioannou, P. *Synthesis* **1977**, 423. (b) See ref 13b.
(17) Baer, E.; Fischer, H. *J. Am. Chem. Soc.* **1948**, *70*, 609.
(18) Baldwin, J. J.; Raab, A. W.; Mensler, K.; Arison, B. H.; McClure, D. E. *J. Org. Chem.* **1978**, *43*, 4876.
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(20) (a) Dukes, M.; Smith, L. *J. Med. Chem.* **1971**, *14*, 326. (b) Danilewicz, J.; Kemp, J. *Ibid.* **1973**, *16*, 168. (c) Weinstock, L; Mulvey, D.; Tull, R *J. Org. Chem.* **1976**, *41*, 3121. (d) Nelson, W.; Burke, T. *Ibid.* **1978**, *43*, 3641. (e) McClure, D. E.; Arison, B. H.; Baldwin, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 3666.
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(22) Angyal, S. J.; Hoskinson, R. "Methods in Carbohydrate Chemistry", Academic Press, New York, **1964**; Vol. II, p 87.
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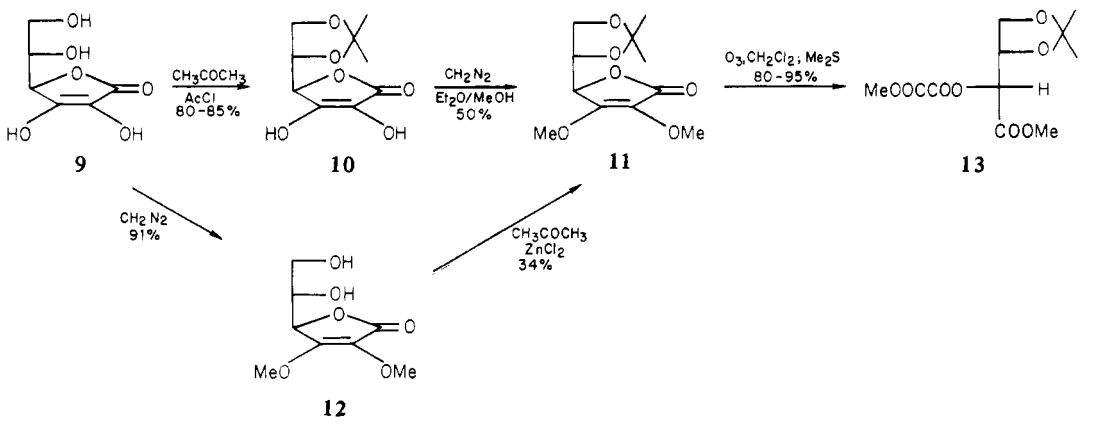
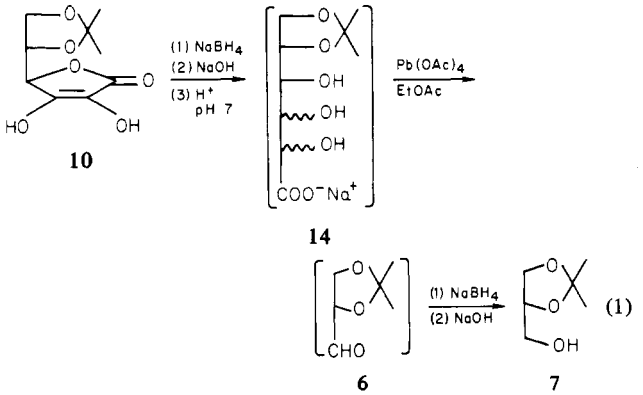
(25) (a) Ushikobo, K. *Nippon Seirigaku Zasshi* **1959**, *21*, 616; *Chem. Abstr.* **1960**, *54*, 9127*f*. (b) Yabhuchi, H. *Bitamin* **1958**, *14*, 131; *Chem. Abstr.* **1960**, *54*, 25321*g*. (c) Pinelli, P. *Farmaco, Ed. Sci.* **1970**, *25*, 187. (d) Koguchi, H. *J. Vitaminol.* **1962**, *8*, 1.
(26) (a) Tsujioka, T.; Masashi, F.; Tsuchiya, K. *Nippon Seirigaku Zasshi* **1960**, *22*, 63, 70; *Chem. Abstr.* **1960**, *54*, 14478*ef*. (b) Kimishima, K; Yoneda, H.; Otsubo, Z. *Yonago Igaku Zasshi* **1957**, *8*, 602; *Chem. Abstr.* **1959**, *53*, 1546*f*. (c) Yoshikawa, T. *Acta Med. Okayama* **1961**, *15*, 121; *Chem. Abstr.* **1962**, *56*, 1953*c*. (d) Kamei, K. *Toho Igakkai Zasshi* **1978**, *25*, 64; *Chem. Abstr.* **1978**, *89*, 140626.
(27) (a) DeMaio, D.; Madeddu, A.; Faggioli, L. *Acta Neurol.* **1961**, *16*, 366. (b) Buscaino, G. A.; Ferrari, E. *Ibid.* **1961**, *16*, 748. (c) Floris, V.; Morocutti, C.; Gaggini, N.; Napoleone-Capra, A. *Riv. Neurobiol.* **1961**, *7*, 824. (d) DeMaio, D.; Pasquariello, G. *Psychopharmacologia* **1963**, *5*, 84. (e) Hayashi, T.; Nagai, K. "Nervous Inhibition: Proceedings of the Second Friday Harbor Symposium"; Florey, E., Ed.; Pergamon Press: London, 1961; pp 389–394. See also: Hayashi, T. *Ibid.* pp 378–388.
(28) (a) Tomita, M. *Z. Phys. Chem., Abt. A* **1923**, *124*, 253. (b) Bergmann, M. *Ibid.* **1923**, *127*, 260. (c) Bergmann, M.; Brand, E. *Chem. Ber.* **1923**, *56*, 1280. (d) Tomita, M.; Sendju, Y. *Z. Phys. Chem., Abt. B* **1927**, *169*, 263. (e) Bergmann, M.; Lissitzin, M. *Chem. Ber.* **1930**, *63B*, 310. (f) Musashi, A.; Tomita, K. *Z. Phys. Chem. (Leipzig)* **1956**, *304*, 65. (g) Tomita, M.; Tomita, T.; Tomita, K. *Ibid.* **1959**, *316*, 121. (h) Lindstedt, S.; Lindstedt, G. *Ark. Kemi* **1964**, *22*, 93. (i) Kaneko, T.; Yoshida, R. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1153. (j) Tomita, K. Japanese Patent 772, 1958; *Chem. Abstr.* **1959**, *53*, 1172. (k) Gallardo, A. Spanish Patent 278 780, 1963; *Chem. Abstr.* **1964**, *60*, 2779. (l) Hayashi, T. French Patent 1 348 105, 1964; *Chem. Abstr.* **1964**, *60*, 11955. (m) Hebron, S. Spanish Patent 391 718, 1973; *Chem. Abstr.* **1974**, *80*, 47461. (n) D'Alo, F.; Masserini, A. *Farmaco, Ed. Sci.* **1964**, *19*, 30. (o) Balenovic, K.; Jambresic, I. *J. Org. Chem.* **1954**, *19*, 1589. (p) Pinza, M.; Pifferi, G. *J. Pharm. Sci.* **1978**, *67*, 120. (q) Sakai, S.; Miyaji, Y.; Furutani, H.; Kobata, M.; Hachisuka, T.; Nakayama, A.; Takada, S.; Hayashi, T. Japanese Patent 12 264, 1962; *Chem. Abstr.* **1963**, *59*, 9805.
(29) (a) Vargha, L. *Nature (London)* **1932**, *130*, 847. (b) Cutolo, E.; Larizza, A. *Gazz. Chim. Ital.* **1961**, *91*, 964. (c) Salomon, L. L. *Experientia* **1963**, *19*, 619. (d) Brimacombe, J.; Murray, A.; Haque, Z. *Carbohydr. Res.* **1975**, *45*, 45.
(30) Jackson, K.; Jones, J. *Can. J. Chem.* **1969**, *47*, 2498.

Scheme I

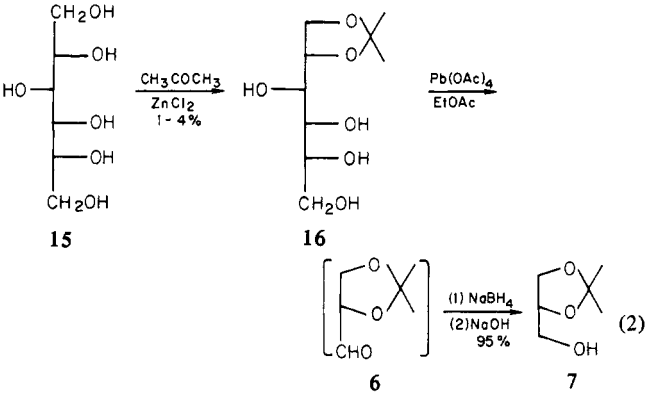


of the acetonide **10** or via the dimethyl ether of ascorbic acid (**12**).[31] Ozonlysis of **11** gave high yields of ester oxalate **13** but when further transformations of **13** proved difficult (due to isolation and solubility problems), this route was abandoned (Scheme I).

Several attempts to produce **7** from **10** by an initial reduction of the molecule followed by subsequent oxidation were also investigated. Both catalytic hydrogenation and lithium aluminum hydride reduction of **10** gave poor results. However, the following multistep one-pot procedure (i.e., no isolation of intermediates) proved highly successful. Treatment of **10** with 1 equiv of sodium borohydride presumably reduces the ene–diol functionality. Cleavage of the borate esters and the lactone with excess hydroxide followed by exact neutralization probably produces acetonide carboxylate **14**, although it could not be isolated from the inorganic materials and all attempts to form the free acid also hydrolyzed the ketal. The dry mixture of salts containing **14** was treated with 3.5 equiv of lead tetraacetate to cleave all of the glycol bonds and produce (*S*)-glyceraldehyde acetonide (**6**) in solution. The remainder of the molecule is cleaved to small volatile fragments which do not remain to form undesired byproducts. Although the glyceraldehyde acetonide could be isolated from this solution,[7b] due to its instability it was immediately reduced with excess sodium borohydride. Final workup with hydroxide then allows alcohol **7** to be isolated in 50–60% overall yield (eq 1). Thus in two synthetic operations ascorbic acid (**9**) is converted into (*S*)-glycerol acetonide (**7**) in 40–50% overall yield.



Other, less efficient methods for the preparation of **7** from inexpensive naturally occurring materials were also investigated. For example, D-glucitol (D-sorbitol) (**15**) was simply converted into D-glucitol 1,2-acetonide (**16**) in very poor yield.[32] Oxidation of **16** with lead tetraacetate in ethyl acetate produced desired aldehyde **6** which was not isolated but rather reduced directly to alcohol **7** in nearly quantitative yield (eq 2). However, due to the abyssmal yield of the acetonization step, this procedure is vastly inferior to the ascorbic acid route.



Synthesis of (*R*)-GABOB (8). (*R*)-Glycerol acetonide (**7**) was converted into known (*S*)-tosylate (**17**)[34] with tosyl chloride in triethylamine in 91% yield.[34] This tosylate (**17**) had previously been most readily prepared from (*S*)-glycerol acetonide (**1**) in five steps in ~10% overall yield.[35] The displacement of the tosylate in **17** with cyanide to produce butyronitrile **18**, although straightforward in principle, proved troublesome in practice. All of the initial attempts to displace tosylate with alkali metal cyanides in a variety of solvents (dimethylformamide, dimethyl sulfoxide, acetonitrile, and alcohols) resulted in recovered starting material or a very low mass recovery. It was eventually determined that the low recovery in dimethyl sulfoxide was due to acetonide hydrolysis and could be remedied by the addition of 10 equiv of sodium bicarbonate to ensure the basicity of the solution. Another problem, however, was still present. Under optimized conditions (2 h, 80 °C), 10–20% of the starting material remained. Longer reaction times merely increased the amount of decomposition, and the tosylate could not be separated from the product under a variety of chemical, physical, and chromatographic conditions. Substituting mesylate **19**[36] for tosylate **17** was not as satisfactory. The solution to this problem was provided by adding 5 equiv of sodium iodide as well as the 5 equiv of potassium cyanide to the reaction mixture. Presumably this serves to form the corresponding iodide in situ since shorter reaction times allow the isolation of some of iodide **20**. Although the yield of desired nitrile **18** was not increased, no starting material remained, thereby simplifying the isolation procedure. In this manner, tosylate **17**

(31) Herbert, R. W.; Hirst, E. L.; Percival, E. G. V.; Reynolds, R. J. W.; Smith, F. *J. Chem. Soc.* **1933**, 1270.

(32) Pressman, B. C.; Anderson, L.; Lardy, H. A. *J. Am. Chem. Soc.* **1950**, *72*, 2404.

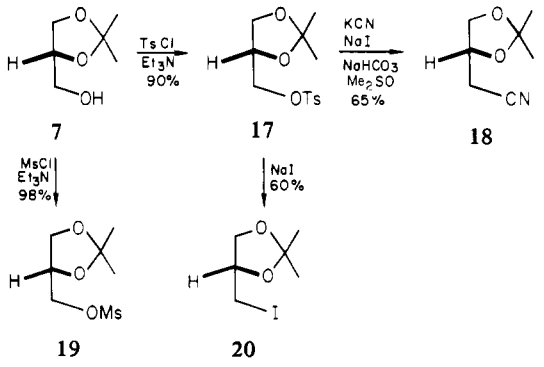
(33) Baer, E.; Fischer, H.; Rubin, M. *J. Biol. Chem.* **1947**, *170*, 337.

(34) From this point on, all reactions were first carried out on racemic material prepared from (*R,S*)-glycerol acetonide.[6] After conditions had been determined, the total synthesis of (*R*)-GABOB was then accomplished beginning with (*R*) enantiomer **7**.

(35) Nelson, W. L; Wennerstrom, J. E.; Sankar, S. R. *J. Org. Chem.* **1977**, *42*, 1006.

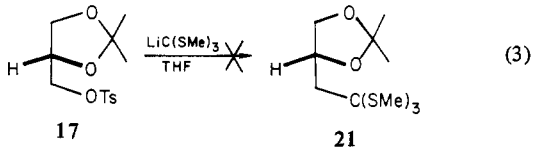
(36) For the formation of the (*R*)-mesylate see: Baer, E.; Newcombe, A. *Can. J. Chem.* **1951**, *29*, 805.

Scheme II



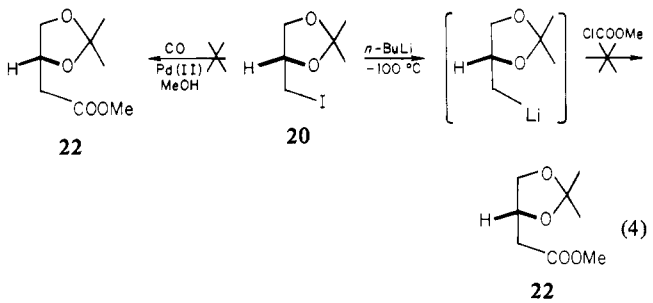
could be converted to desired nitrile **18**[37] in 65% yield (Scheme II).

In the course of the above work with cyanide, a number of other methods of adding one carbon to the system were tried. Treatment of tosylate **17** with the lithium anion of tris(thiomethyl)methane[38] provided none of desired addition product **21** and only starting materials were recovered (eq 3).



(3)

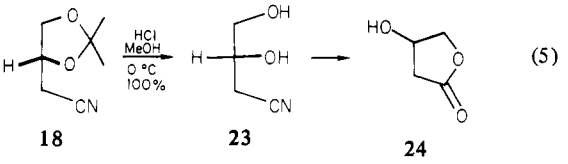
Iodide **20**[39] can be obtained from tosylate **17** by treatment with sodium iodide in acetone.[40] Treatment of the iodide with *n*-butyllithium at −100 °C to transmetallate followed by quenching with methyl chloroformate provided no methyl esters such as **22** but only fragmented olefinic products formed by β-elimination (eq 4).



(4)

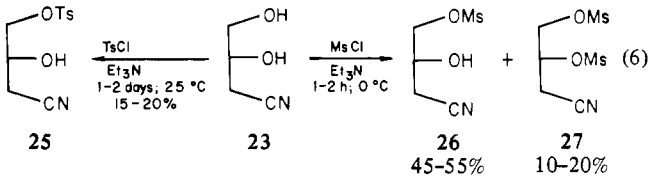
One other attempt to extend the molecule by one carbon was also attempted. It is known that various organic halides can be carboalkoxylated in the presence of a palladium catalyst under carbon monoxide.[41] However, treatment of iodide **20** with a catalytic amount of bis(triphenylphosphine)palladium chloride in a solution of methanol containing 1 equiv of diethylamine with carbon monoxide at 700 psi provided only unchanged starting material with none of desired ester **22**.

Since ester **22** could not be directly obtained, nitrile **18** was used to continue the synthesis. Nonaqueous hydrolysis of the acetonide of **18** was accomplished in quantitative yield by treating with dry hydrogen chloride (1 equiv) in dry methanol at 0 °C to afford cyanodiol **23**.[42] Higher temperature, excess acid, and the presence of water all help to convert desired diol **23** into undesired lactone **24** (eq 5). Treatment of cyanodiol **23** with *p*-toluenesulfonyl



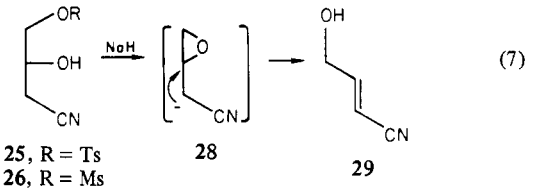
(5)

chloride at room temperature for an extended period provided only a low yield of desired monotosylate **25**. However, substitution of methanesulfonyl chloride caused a much faster reaction, and diol monomesylate **26** was produced in reasonable yield along with other products, one of which was tentatively assigned as dimesylate **27** (eq 6).



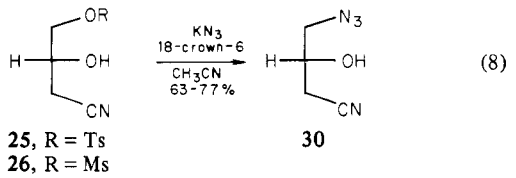
(6)

Theoretically, treatment of **25** or **26** with a kinetic base would provide epoxide **28** analogously to the formation of epoxides of this type in aryloxypropanolamine syntheses.[18-20] However, under the reaction conditions, **28** is opened to γ-hydroxycrotononitrile (**29**) (eq 7).[43] Therefore, an alternative method was necessary



(7)

to introduce the amino group. This was accomplished by treatment of **25** or **26** with potassium azide and a catalytic amount of 18-crown-6. Azide **30** was thereby produced cleanly and in good yield (eq 8). An alternative, unsuccessful method to produce **30** directly from diol **23** was also attempted. Primary alcohols have been converted directly to azides by treatment with hexamethylphosphorus triamide in carbon tetrachloride followed by the addition of sodium azide.[44] In this case, however, none of azide **30** could be obtained.



(8)

Hydrogenation of azide **30** in the presence of a palladium catalyst and a small amount of chloroform cleanly produced the amine hydrochloride **31**. Without purification, **31** was hydrolyzed with sulfuric acid to produce (*R*)-γ-amino-β-hydroxybutyric acid, GABOB (**8**) $[\alpha]_D = -7.1°$ in 93% overall yield. The physical data (IR, melting point) of the product **8** were in agreement with the published values.[28] The overall yield of (*R*)-GABOB from ascorbic acid (**9**) was about 10% for nine steps. Methylation of GABOB (**8**) under basic conditions produced (−)-carnitine (**32**) (Vitamin B_T)[28i] and thus this synthesis is also a formal total synthesis of natural carnitine (eq 9).

Synthesis of Aryloxypropanolamines (5). The intermediates in the synthesis of GABOB should also be quite useful for the

(37) The racemic material has been previously reported by: Petrov, K. A.; Nifant'ev, E.; Khorkhoyanu, L. *Zh. Obshch. Khim.* **1962**, *32*, 3720; *J. Gen. Chem. USSR (Engl. Transl.)* **1962**, *32*, 3647.

(38) Seebach, D. *Chem. Ber.* **1972**, *105*, 3280.

(39) Fischer, E.; Pfähler, E. *Chem. Ber.* **1920**, *53*, 1606.

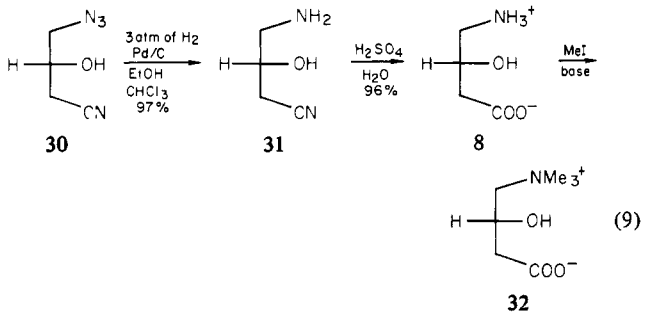
(40) (a) (DL)-material: Hessel, L; vanLohuizen, O.; Verkade, P. *Recl. Trav. Chim. Pays-Bas* **1954**, *73*, 842. (b) (S)-enantiomer: Baer, E.; Fischer, H. *J. Am. Chem. Soc.* **1948**, *70*, 609.

(41) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. *J. Org. Chem.* **1974**, *39*, 3318. (b) Stille, J.; Wong, P. *Ibid.* **1975**, *40*, 532. (c) Hidai, M.; Hikita, T.; Wada, Y.; Fujikura, Y.; Uchida, Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2075.

(42) The racemic diol was previously prepared from 3-chloro-1,2-propanediol by: (a) Rambaud, R.; Ducher, S. *C. R. Hebd. Seances Acad. Sci.* **1954**, *238*, 1231; (b) Rambaud, R.; Ducher, S.; Boudet, R. *Bull. Soc. Chim. Fr.* **1956**, 1419.

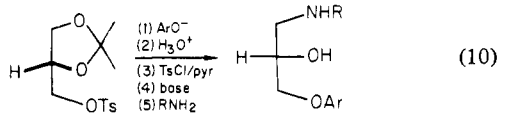
(43) (a) Culvenor, C.; Davies, W.; Haley, F. *J. Chem. Soc.* **1950**, 3123. (b) McClure, J. D. *J. Org. Chem.* **1967**, *32*, 3888.

(44) Castro, B.; Selve, C. *Bull. Soc. Chim. Fr.* **1971**, 2296.



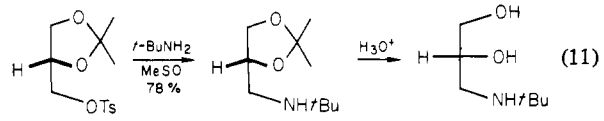
30 31 8 32 (9)

preparation of other chiral compounds of biological interest. For example, the (*R*) enantiomer of tosylate **17** has been converted into the inactive (*R*) enantiomer of the important hypotensive β-adrenergic blockers, aryloxypropanolamines (**5**).[20b,d] By an application of the exact reaction sequence (displacement with aryloxide, hydrolysis, monotosylation, epoxide formation, and opening with amine) to (*S*)-tosylate (**17**), one could produce the active (*S*)-aryloxypropanolamines (eq 10).[45]



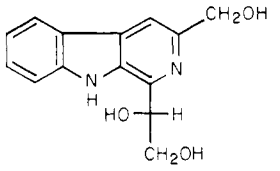
17 5 (10)

The inactive (*R*) enantiomers can also be prepared from the above intermediates. Treatment of tosylate **17** with *tert*-butylamine in Me_2SO produced corresponding amine **33** in 78% yield, which upon acidic hydrolysis furnished the (*R*)-aminodiol **34** (eq 11). The (*S*) enantiomer of **34** has been taken on to active



17 33 34 (11)

(*S*)-aryloxypropanolamines.[20c,e] Finally, as mentioned previously, (*R*)-glyceraldehyde acetonide (**4**) has used to prepare the unnatural enantiomer of the antibiotic pyridindolol **35**.[12] By using (*S*) enantiomer **6** as the starting material, one could prepare natural antibiotic **35** by the exact same procedure.[12]



35

Conclusion

Ascorbic acid (**9**) is a useful chiral precursor, permitting a rapid high-yielding preparation of the difficultly-accessible (*S*)-glyceraldehyde acetonide (**6**) and the derived (*R*)-glycerol acetonide (**7**). These compounds have been shown to be useful intermediates in the synthesis of chiral, biologically active materials such as (*R*)-GABOB (**8**), carnitine (**32**), and (*S*)-aryloxypropanolamines (**5**).

Experimental Section

General. Melting points were taken on a Büchi melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer Model 137B or 710B spectrophotometer as a thin liquid film, unless otherwise stated. Proton NMR spectra were measured on a Varion T-60 spectrometer in deuteriochloroform as solvent (unless otherwise specified) and are reported in parts per million downfield from internal tetramethylsilane. Mass spectra were recorded on an AEI MS-9 spectrometer. Optical rotations were obtained on a Perkin-Elmer 141 polarimeter. The following adsorbents were used: column chromatography, Merck silica gel 60 (70–230 mesh); thin-layer chromatography, Eastman 13181 silica gel chromatogram sheets; preparative layer chromatography, Merck silica gel PF-254. All solvents and reagents were used as obtained unless otherwise specified.

5,6-Isopropylidene-L-ascorbic Acid (10). L-Ascorbic acid (**9**) (Bronson Pharmaceuticals, 10 g, 0.055 mol) was weighed into a 125-mL Erlenmeyer flask. Acetone (40 mL, 0.55 mol) and acetyl chloride (1 mL, 0.015 mol) were added and a calcium sulfate drying tube was placed on the flask and the slurry stirred at room temperature 2–3 h. The flask was then stoppered and stored in the refrigerator (7 °C) for 4–8 h. The solid was then filtered off and washed with a small amount of cold acetone. After being dried for a short period of time, 9.63 g (81%) of ascorbic acid acetonide (**10**) was present. A small amount of residual acetic acid can cause hydrolysis if the product is left open to the atmosphere. Crude melting point = 195–200 °C. The product can be recrystallized from acetone/hexane; recrystallized mp 214–218 °C dec, lit.[30] mp 217–222 °C dec. NMR (acetone-d_6, Me_2SO-d_6): δ 3.9–4.65 (m, 6 H, C*H*O and O*H*), 1.35 (s, 6 H, CH_3). NMR ($CDCl_3$, Me_2SO-d_6): δ 6.15 (br s, 2 H, O*H*), 3.98–4.62 (m, 4 H, C*H*O), 1.35 (s, 6 H, CH_3). IR (KBr): 3300, 3000, 1720, 1630, 1300 (br), 1100 cm^{-1}.

2,3-Di-*O*-methyl-L-ascorbic Acid (12). Ascorbic acid (**9**) (1 g, 5.6 mmol) was dissolved in a solution of 10 mL of diethyl ether, 10 mL of methanol, and 10 mL of water. Diazomethane (prepared from *N*-methyl-*N*-nitrosourea) was added via pipet until a yellow color persisted. The solution was allowed to stand at 25 °C for 4 days. After removal of the solvent at reduced pressure, 30 mL of absolute ethanol was added to remove water by azeotropic distillation. This procedure was repeated several times to afford 1.04 g (91%) of oil. NMR: δ 4.67 (br s, 1 H, C*H*OCO), 4.14 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 2.67–3.80 (m, 5 H, C*H*O and O*H*). IR ($CHCl_3$): 3500, 3000, 1750, 1670, 1440, 1330, 1210, 1190, 1120, 1050 cm^{-1}.

2,3-Di-*O*-methyl-5,6-isopropylidene-L-ascorbic Acid (11) from 10. Acetonide **10** (1 g, 4.4 mmol) was dissolved in 20 mL of diethyl ether and 10 mL of methanol. Diazomethane (prepared from 5 g of *N*-methyl-*N*-nitrosourea and methanolic potassium hydroxide) in 100 mL of diethyl ether was added until a yellow color peristed. After the solution was allowed to stand at 25 °C overnight, it was dried over sodium sulfate, a small amount of acetic acid added and filtered, and the solvent evaporated with addition of carbon tetrachloride to help chase away any methanol or acetic acid present. Since the crude NMR and IR showed some loss of acetonide, 25 mL of acetone and 1 mL of acetyl chloride were added, and the solution was stirred at 25 °C for 15 h. After removal of the solvent, the residue was chhromatographed on 40 g of silica gel, eluting with chloroform to afford 793 mg (74%) of yellow crystals. After being washed with pentane and being filtered, 520 mg (48%) of yellow crystals were obtained; mp 83–87 °C. NMR: δ 3.93–4.53 (m, 4 H, C*H*O), 4.12 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 1.38 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3). IR ($CHCl_3$): 2970, 2950, 1750, 1670, 1450, 1320, 1215, 1135, 1115, 1050, 955, 850 cm^{-1}. Mass spectrum: *m/e* 244 (M^+).

Preparation of 11 from 12. A 30-mL sample of acetone was added to well-crushed zinc chloride (2 g, 15 mmol) and the slurry poured onto diol **12** (1 g, 4.9 mmol) and mixed well. After 21 h of stirring at 25 °C, the solution was neutralized with 30 mL of 10% aqueous potassium carbonate, 50 mL of diethyl ether was added, and the layers were separated. The aqueous layer was extracted with 2 × 50 mL of diethyl ether, and the organic layers were combined, washed with 2 × 25 mL of water, and dried over magnesium sulfate. Evaporation of the solvent gave 410 g (34%) of **12** as yellow crystals, mp 90–94 °C.

Methyl 3,4-Isopropylidene-2-(methyloxaloyl)-L-threonate (13). Acetonide **11** (500 mg, 2 mmol) dissolved in 200 mL of methylene chloride was ozonized by using a Welsbach ozone generator for 10 min. After the flask was flushed with nitrogen, dimethyl sulfide (25 μL, 3 mmol) was added at −78 °C followed by stirring at that temperature for 45 min and at 25 °C for 14 h. After the solution was washed with 4 × 50 mL of water and dried over magnesium sulfate, the solvent was evaporated to produce 560 mg (99%) of **13** as a yellow oil. NMR: δ 5.23 (d, 1 H, J = 6 Hz, $MeO_2CCHOCO$), 4.61 (br q, 1 H, J = 6 Hz, C*H*O), 3.5–4.17 (m, 2 H, CH_2O), 3.93 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 1.46 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3). IR ($CHCl_3$): 2960, 2920, 1770, 1750, 1440, 1370, 1315, 1200, 1160, 1070, 1010, 980, 845 cm^{-1}.

(*R*)-Glycerol Acetonide (7). Recrystallized ascorbic acid acetonide (**10**) (4.1 g, 19.0 mmol) was dissolved in absolute ethanol (350 mL) and was added over 1 h via an addition funnel with a calcium sulfate drying tube to a stirring solution of sodium borohydride (0.72 g, 19.0 mmol) in 50 mL of absolute ethanol. The slightly cloudy solution was then stirred an additional 4 h at room temperature, at which time it was made basic by addition of several pellets of sodium hydroxide followed by 50 mL of 1 N sodium hydroxide. The mixture stirred overnight at room temper-

(45) For reviews of the effectiveness of aryloxypropanolamines as antihypertensive agents, see: Evans, D. B.; Fox, R.; Hauck, F. P. *Annu. Rep. Med. Chem.* **1979**, *14*, 81 and earlier volumes.

ature was then exactly neutralized with concentrated hydrochloric acid, added dropwise with vigorous stirring. The solvents were removed in vacuo, adding absolute ethanol several times to azeotrope water, until a dry, powdery white solid is obtained. The white powder was scraped from the walls of the flask and mixed with 200 mL of ethyl acetate; a calcium sulfate drying tube was placed on the flask, and it was cooled to 0 °C. Lead tetraacetate (29.5 g, 0.66 mol, recrystallized from acetic acid) was added in one portion. The yellowish brown slurry stirred 1–1.5 h at 0 °C and then 1–2 hours at room temperature. After being recooled to 0 °C, it was suction filtered through a bed of Celite into a cooled receiver. The cold, yellow solution was then added over 30 min to a cooled solution of sodium borohydride (7.2 g, 0.19 mol) in 150 mL of absolute ethanol. The borohydride solution turns dark gray upon first addition of the ethyl acetate solution and may need occasional addition of ethanol to aid stirring and minimize foaming. After the addition was completed, the ice bath was removed and the gray solution stirred 2–2.5 h at room temperature. It was then made basic by adding several pellets of sodium hydroxide followed by 100 mL of 1 N sodium hydroxide. After the solution was stirred 30 min at room temperature, 100 mL of diethyl ether was added, the layers were separated, and the aqueous layer was extracted with 2 × 50 mL of diethyl ether. The combined organic phases were washed with 25 mL of brine, dried over anhydrous sodium sulfate, and evaporated under aspirator pressure at room temperature until about 50 mL remained. Diethyl ether (100 mL) was added, the aqueous phase was saturated with sodium chloride, and the layers were separated. The aqueous layer was extracted with 4 × 50 mL of diethyl ether. The combined ether layers were dried over anhydrous sodium sulfate and evaporated as above. Any residual water was then azeotroped by the addition of 25 mL of acetone and reevaporation. (*R*)-Glycerol acetonide (**7**) (1.32 g, 53%) was obtained as a clear liquid. The product can be purified by chromatography on 50 g of silica gel. Elution with 350 mL of methylene chloride removed impurities; the product was then eluted with 500 mL of 5% methanol/methylene chloride; 1.26 g obtained. NMR: δ 3.6–4.4 (m, 5 H, C*H*O), 2.95 (br s, 1 H, O*H*), 1.43 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3). IR: 3420, 2950, 1380, 1260, 1215, 1160, 1050 cm^{-1}.

A sample of 184 mg was distilled (24 °C (0.5 torr)) to yield 169 mg of clear liquid which was dissolved in 1.00 mL of methanol for the rotation at 24.8 °C. Rotation: $[\alpha]_D = -10.76°$ (lit. value[7b] = +10.7° for opposite enantiomer, $[\alpha]_D = -13.2°$ for neat sample[24]), $[\alpha]_{578} = -11.27°$, $[\alpha]_{546} = -12.99°$, and $[\alpha]_{436} = -23.59°$.

1,2-Isopropylidene-D-glucitol (16). Commercial D-glucitol (**15**) (D-sorbitol, Eastman, 100 g, 0.55 mol) was dried in a vacuum oven at 75 °C for 3 days to give the material a melting point of 93–94 °C. This material was added to a solution of zinc chloride (45 g, 0.33 mol) in 170 mL of acetone in a 500-mL round-bottomed flask and the mixture shaken at 25 °C for 4 h. Base (180 g of 50% aqueous potassium carbonate) was added and the mixture shaken for 15 min, after which time 25 mL of 60% aqueous potassium hydroxide was added and the mixture shaken another 15 min. After vacuum filtration, the solids were washed with 3 × 50 mL of acetone and the filtrates were evaporated with heating in vacuo to produce a thick syrup. Hot acetone (400 mL) was added, and as much of the syrup as possible was dissolved. The solution was filtered and the filtrate stored in the refrigerator for 36 h. The precipitated partly white solid was filtered off and recrystallized from absolute ethanol to give 1.71 g (1.4%) of **16**: mp 166–67 °C, lit.[32] mp 167.5–168 °C. NMR (acetone-d_6, DMSO-d_6): δ 3.37–4.60 (m, 12 H, C*H*O and O*H*), 1.46 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3). Mass spectrum: *m/e* 223 (M + 1), 207 (M^+ – 15).

(*R*)-Glycerol Acetonide (7) from 16. A slurry of acetonide **16** (500 mg, 2.25 mmol) and 40 mL of ethyl acetate in a 125-mL Erlenmeyer flask was cooled to 0 °C and lead tetraacetate (3.2 g, 7.2 mmol) added. The flask was attached to a drying tube and the mixture stirred at 0 °C for 1 h and at 25 °C for 1 h. It was then recooled to 0 °C and filtered through Celite into a cooled receiver. This solution was then added slowly to a cooled (0 °C) solution of sodium borohydride (860 mg, 22.5 mmol) in 30 mL of ethanol in a 250-mL flask. After addition the mixture was stirred at 0 °C for 1 h and at 25 °C for 1 h. Six sodium hydroxide pellets were added and stirring was continued for 15 min, after which time 30 mL of 1 N sodium hydroxide solution was added and the mixture stirred for 45 min. The layers were separated, the aqueous layer was extracted with 2 × 25 mL of diethyl ether, and the organic layers were combined, dried, and evaporated in vacuo to produce 291 mg of **7**. NMR and IR spectra were the same as before. A sample of 99.2 mg was dissolved in 1.00 mL of methanol for the rotation at 25 °C. Rotation: $[\alpha]_D = -8.73°$.

(DL)-2,2-Dimethyl-4-(hydroxymethyl)-1,3-dioxolane *p*-Toluenesulfonate (17). (DL)-Glycerol acetonide[6] (12.3 mL, 0.10 mol) and dry triethylamine (20.8 mL, 0.15 mol, distilled from calcium hydride) were added to a 250-mL round-bottomed flask and dissolved in 100 mL of chloroform. A calcium sulfate drying tube was added, the solution cooled to 0 °C, and *p*-toluenesulfonyl chloride (21.0 g, 0.11 mol) added in several portions. The solution was then stirred 30 min at 0 °C and overnight at room temperature. The yellow chloroform solution was washed with 2 × 100 mL of ice water, 2 × 100 mL of saturated sodium bicarbonate, and 2 × 100 mL of brine and dried over anhydrous sodium sulfate. After evaporation of the solvent under reduced pressure, 27.55 g of orange oil was obtained which solidified upon sitting at room temperature. Filtration followed by washing with pentane provided 24.45 g (86%) of a waxy beige solid, mp 41–42 °C, lit.[46] mp 47 °C. Residual color can be removed by recrystallization from ethanol/water, but the crude material is satisfactory for succeeding reactions. NMR: δ 7.8 and 7.35 (A_2B_2, J = 8 Hz, 4 H, C*H*=C), 4.4–3.6 (m, 5 H, C*H*O), 2.45 (s, 3 H, ArCH_3), 1.34 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3). IR ($CHCl_3$): 3000, 2900, 1590, 1360, 1180, 1170 cm^{-1}. Mass spectrum: *m/e* 271 (M^+ – 15), 258, 200, 172, 155, 101, 91, 72, 65, 43.

(*S*)-(+)-2,2-Dimethyl-4-(hydroxymethyl)-1,3-dioxolane *p*-Toluenesulfonate (17). The same procedure as for the (DL) material was followed by using 0.63 g of (*R*)-glycerol acetonide (**7**) (4.77 mmol), 0.99 mL of triethylamine (7.16 mmol), and 1.00 g of *p*-toluenesulfonyl chloride (5.25 mmol). A light yellow oil (1.29 g, 95%) was obtained which does not crystallize. It can be purified by distillation at 125 °C (0.5 torr); 91% material distilled. The optical rotation was obtained on 0.170 g in 1.00 mL of absolute ethanol at 24.1 °C. $[\alpha]_D = +4.48°$ (lit. value[35] = +4.7° (c = 1.0, EtOH), also –4.6° (c = 13, opposite enantiomer[40b]), $[\alpha]_{578} = +4.62°$, $[\alpha]_{546} = +5.27°$, and $[\alpha]_{436} = +8.72°$.

(DL)-2,2-Dimethyl-4-(iodomethyl)-1,3-dioxolane (20). (DL)-Acetonide tosylate (**17**) (0.50 g, 1.75 mmol) and sodium iodide (5.25 g, 35 mmol) were dissolved in 25 mL of acetone in a 50-mL round-bottomed flask. A condenser and calcium sulfate drying tube were added, and the solution was heated to reflux for 22 h. After the solution was cooled, the sodium tosylate was filtered off and most of the acetone evaporated on the steam bath. Diethyl ether and water (25 mL each) were added and the layers separated. The aqueous layer was extracted with 2 × 10 mL of diethyl ether. The combined ether layers were washed with 25 mL of 1 N sodium thiosulfate and then 25 mL of brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to yield 0.253 g (60%) of a yellow liquid. The iodide can be purified, if necessary, by column chromatography on silica gel, eluting with chloroform (R_f = 0.50). NMR: δ 4.5–3.7 (m, 3 H, C*H*O), 3.4–3.1 (m, 2 H, CH_2I), 1.48 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3). IR: 3000, 2950, 2900, 1460, 1380, 1225, 1150, 1050, 840 cm^{-1}. Mass spectrum: *m/e* 227 (M^+ – 15), 212, 185, 171, 155, 101, 91, 75, 57, 43. High-resolution mass spectrum: *m/e* 226.9571 (M^+ – CH_3), calcd for $C_5H_8O_2I$, 226.9568.

(DL)-2,2-Dimethyl-4-(hydroxymethyl)-1,3-dioxolane Methanesulfonate (19). (DL)-Glycerol acetonide (1.23 mL, 0.01 mol) and dry triethylamine (2.08 mL, 0.015 mol, distilled from calcium hydride) were dissolved in 50 mL of dichloromethane in a 100-mL round-bottomed flask. The solution was cooled under nitrogen in an ice–salt bath and methanesulfonyl chloride (0.85 mL, 0.011 mol, distilled from P_2O_5 under aspirator pressure) was added over 5 min. After being stirred at 0 °C for 15 min, the solution was extracted with 2 × 25 mL of ice water, 25 mL of saturated sodium bicarbonate, and 25 mL of brine. It was then dried over anhydrous sodium sulfate and evaporated under reduced pressure to yield 2.06 g (98%) of a clear liquid which was used without further purification. NMR: δ 4.5–3.6 (m, 5 H, C*H*O), 3.07 (s, 3 H, SO_2CH_3), 1.45 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3). IR: 2920, 1340, 1210, 1165, 1040, 960 cm^{-1}. Mass spectrum: *m/e* 195 (M^+ – 15), 137, 135, 119, 114, 101, 96, 79, 72, 57, 43. High-resolution mass spectrum: *m/e* 195.0322 (M^+ – CH_3), calcd for $C_6H_{11}O_5S$, 195.0327.

(DL)-2,2-Dimethyl-4-(cyanomethyl)-1,3-dioxolane (18). (DL)-Acetonide tosylate (**17**) (5.0 g, 17.5 mmol), sodium bicarbonate (14.7 g, 0.175 mol), sodium iodide (13.1 g, 87.5 mmol), and dry potassium cyanide (5.7 g, 87.5 mmol) were weighed into a 250-mL round-bottomed flask. Dry dimethyl sulfoxide (75 mL, distilled from calcium hydride under reduced pressure) was added and a calcium sulfate drying tube placed on the flask. The slurry was heated at 80 °C with efficient stirring for 2 h. After being cooled to room temperature, the contents were poured into 700 mL of water and extracted with 4 × 150 mL of diethyl ether. The combined organic layers were then washed with 2 × 100 mL of brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The crude product (1.84 g) was then filtered through 60 g of silica gel with 750 mL of chloroform to yield 1.60 g of the desired product as a yellow-green liquid, bp 210 °C (decomposition begins about 180 °C). NMR: δ 4.6–3.7 (m, 3 H, C*H*O), 2.65 (d, J = 5 Hz, 2 H, CH_2CN), 1.48 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3). IR: 2950, 2820, 2210, 1360, 1210, 1175, 1150, 1070 cm^{-1}. Mass spectrum: *m/e* 126 (M^+ – 15), 101, 84, 82, 72, 66, 58, 43. High-resolution mass spectrum: *m/e* 126.0561 (M^+ – CH_3), calcd for $C_6H_8NO_2$, 126.0555.

(46) Freudenberg, K.; Hess, H. *Justus Liebigs Ann. Chem.* **1926**, *448*, 121.

(*R*)-2,2-Dimethyl-4-(cyanomethyl)-1,3-dioxolane (18). The same procedure as for the (DL) material was followed by using 1.69 g (5.9 mmol) of (*S*)-tosylate **17**, 4.96 g (0.059 mol) of sodium bicarbonate, 4.43 g (29.5 mmol) of sodium iodide, and 1.92 g (29.5 mmol) of potassium cyanide in 25 mL of dry dimethyl sulfoxide to yield 0.636 g of crude nitrile. After chromatography on 30 g of silica gel (750 mL of chloroform), 0.543 g (65%) of the desired product was obtained. Further purification can be achieved by distillation at 60 °C (1.0 torr) but is not necessary for the succeeding reaction. Rotation: $[\alpha]_D^{25} = -5.44°$ (*c* = 9.4, $CHCl_3$), $[\alpha]_{578} = -5.70°$, $[\alpha]_{546} = -6.56°$, $[\alpha]_{436} = -12.09°$.

(DL)-3,4-Dihydroxybutanenitrile (23). (DL)-Cyanoacetonide (**18**) (1.28 g, 9.08 mmol) was dissolved in 25 mL of dry methanol (distilled from sodium) in a 50-mL round-bottomed flask, a calcium sulfate drying tube added, and the solution cooled to 0 °C. A solution of dry HCl in methanol (5.1 mL, 1.87 M) was added with stirring and the solution then stored in the refrigerator (7 °C) for 20–24 h. After being recooled to 0 °C, it was made basic by bubbling in ammonia until blue to litmus paper and the methanol removed under reduced pressure. The residue was taken up in 10 mL of acetone, the solution filtered, and the ammonium chloride washed with another 10-mL portion of acetone. The acetone was then removed under reduced pressure to leave a quantitative yield (0.932 g) of crude diol **23** as a yellow oil which was used without further purification in the next reaction. NMR (acetone-d_6): δ 4.2 (br s, 2 H, O*H*), 3.95 (quintet, *J* = 5 Hz, 1 H, C*H*OH), 3.58 (d, *J* = 5 Hz, 2 H, CH_2OH), 2.65 (m, 2 H, CH_2CN). IR: 3300, 2950, 2900, 2270, 1420, 1100, 1050 cm^{-1}. Mass spectrum: *m/e* 101 (M^+), 71, 70, 61, 58, 55, 44. High-resolution mass spectrum: *m/e* 70.0289 ($M^+ - CH_2OH$), calcd for C_3H_4NO, 70.0293.

(*R*)-3,4-Dihydroxybutanenitrile (23). The acetonide was hydrolyzed by using the same procedure as for the (DL) material. (*R*)-Cyanoacetonide (**18**) (0.54 g, 3.83 mmol) and dry HCl in methanol (2.15 mL, 1.87 M) yielded 0.348 g (90%) of the desired diol as a yellow oil which was not purified further. Rotation (65 mg in 1.00 mL of absolute ethanol at 23.8 °C): $[\alpha]_D = +20.58°$, $[\alpha]_{578} = +21.42°$, $[\alpha]_{546} = +24.20°$.

(DL)-4-(Tosyloxy)-3-hydroxybutanenitrile (25). (DL)-3,4-Dihydroxybutanenitrile (**23**) (0.16 g, 1.59 mmol) was dissolved in 10 mL of ethyl acetate and dry triethylamine (0.22 mL, 1.59 mmol, distilled from calcium hydride) and recrystallized *p*-toluenesulfonyl chloride (0.303 g, 1.59 mmol) added to the solution. A drying tube was placed on the setup and the solution stirred at room temperature for 24 h. The precipitated triethylamine hydrochloride was filtered off and the solvent removed under reduced pressure to yield 0.488 g of brown oil which was purified by chromatography on 25 g of silica gel. Remaining *p*-toluenesulfonyl chloride (75 mg) was eluted with 500 mL of carbon tetrachloride. Elution with 350 mL of chloroform removed 85 mg of impurities. Another 350 mL of chloroform contained desired diol monotosylate **25** (64 mg, 16%). Further elution with 100 mL of acetone contained starting diol **23** (75 mg). The yield of the reaction based on consumed starting material was 30%. NMR: δ 7.82 and 7.40 (A_2B_2, *J* = 7 Hz, 4 H, C*H*=C), 4.15 (m, 3 H, C*H*O), 3.6 (br s, 1 H, O*H*), 2.60 (d, *J* = 5 Hz, 2 H, CH_2CN), 2.48 (s, 3 H, $ArCH_3$). IR: 3500, 2950, 2280, 1600, 1360, 1195, 1180, 1100, 1000 cm^{-1}. Mass spectrum: *m/e* 255 (M^+), 225, 191, 156, 155, 92, 91, 84, 65, 54. High-resolution mass spectrum: *m/e* 255.0578 (M^+), calcd for $C_{11}H_{13}NO_4S$, 255.0565.

(DL)-4-(Mesyloxy)-3-hydroxybutanenitrile (26). (DL)-3,4-Dihydroxybutanenitrile (**23**) (0.45 g, 4.5 mmol), dissolved in 25 mL of ethyl acetate, was cooled to 0 °C under a calcium sulfate drying tube. Dry triethylamine (0.92 mL, 6.7 mmol, distilled from calcium hydride) and methanesulfonyl chloride (0.35 mL, 4.5 mmol) were added, causing an immediate white precipitate. The mixture was stirred at 0 °C for 2 h, the triethylamine hydrochloride was filtered off, and the volatiles were removed under reduced pressure to yield 1.09 g of yellow oil. The crude mixture was purified by chromatography on 65 g of silica gel. Elution with 1000 mL of chloroform then 500 mL of 5% acetone/chloroform removed 233 mg of dimesylate **27** and other undesired products. Further elution with 900 mL of 5% acetone/chloroform produced 350 mg (44%) of desired monomesylate **26** and finally elution with 700 mL of 1:1 acetone/chloroform contained 75 mg of starting diol **23**. Based on the 3.76 mmol of starting material reacted, the yield was 52%. NMR ($CDCl_3$/acetone-d_6): δ 5.0 (br s, 1 H, O*H*), 4.35 (m, 3 H, C*H*O), 3.18 (s, 3 H, SO_2CH_3), 2.78 (br d, *J* = 6 Hz, 2 H, CH_2CN). IR: 3450, 3050, 2950, 2270, 1420, 1340, 1170, 1110, 1000, 970, 820, cm^{-1}. Mass spectrum: *m/e* 139, 134, 109, 81, 80, 79, 70, 65, 54, 42. High-resolution mass spectrum: *m/e* 139.0069 ($M^+ - CH_2CN$), calcd for $C_3H_7O_4S$, 139.0065.

(*R*)-4-(Mesyloxy)-3-hydroxybutanenitrile (26). Following the same procedure as for the (DL) material, (*R*)-3,4-dihydroxybutanenitrile (**23**) (0.23 g, 2.28 mmol) in 10 mL of ethyl acetate was reacted with triethylamine (0.47 mL, 3.42 mmol) and methanesulfonyl chloride (0.18 mL, 2.28 mmol) at 0 °C for 30 min to produce 0.56 g of crude yellow oil. The product was purified on 35 g of silica gel as before, yielding 209 mg (51%) of desired monomesylate **26** as well as a small amount of dimesylate **27** and diol **23**. Rotation (80 mg in 1.00 mL of absolute ethanol at 24.8 °C): $[\alpha]_D = +8.45°$, $[\alpha]_{578} = +8.78°$, $[\alpha]_{546} = +9.91°$, $[\alpha]_{436} = +16.00°$.

(DL)-4-Azido-3-hydroxybutanenitrile (30). Procedure A. 4-Tosyloxy-3-hydroxybutanenitrile (**25**) (0.30 g, 1.17 mmol) was dissolved in 10 mL of dry acetonitrile, potassium azide (0.96 g, 11.7 mmol) and 18-crown-6 (15 mg, 0.06 mmol) were added, and the mixture was heated to reflux under nitrogen for 6–9 h. After the solution was cooled, 50 mL of water was added and the aqueous solution extracted with 3 × 25 mL of ethyl acetate. The combined ethyl acetate washes were extracted with 10 mL of brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to yield 122 mg (83%) of the crude azide. Purification could be accomplished via column chromatography on 10 g of silica gel packed with chloroform. Elution in 8-mL fractions with 10% ethyl acetate/chloroform provided the product in the first 22 fractions as a yellow oil (93 mg, 63%).

Procedure B. 4-Mesyloxy-3-hydroxybutanenitrile (**26**) (0.225 g, 1.26 mmol) was dissolved in 20 mL acetonitrile, potassium azide (1.02 g, 12.6 mmol) and 18-crown-6 (25 mg, 0.10 mmol) were added, a calcium sulfate drying tube was placed on the setup, and the mixture was heated to reflux and left for 9 h. After the solution was cooled, 25 mL of water was added and the aqeuous solution was extracted with 3 × 25 mL of ethyl acetate. The combined ethyl acetate washes were dried over anhydrous sodium sulfate and evaporated under reduced pressure to yield 180 mg of liquid which was chromatographed on 10 g of silica gel with chloroform in 40-mL fractions. The product was eluted in fractions 4–6 to yield 100 mg (63%) of a light yellow oil. NMR: δ 4.20 (pentet, *J* = 5 Hz, 1 H, C*H*O), 3.60 (br s, 1 H, O*H*), 3.48 (d, *J* = 5 Hz, 2 H, CH_2N_3), 2.65 (d, *J* = 6 Hz, 2 H, CH_2CN). IR: 3400, 2920, 2270, 2120, 1440, 1410, 1280, 1090 cm^{-1}. Mass spectrum: *m/e* 126 (M^+), 70, 54, 44, 42, 41. High-resolution mass spectrum: *m/e* 126.0562 (M^+), calcd for $C_4H_6N_4O$, 126.0542.

(*R*)-4-Azido-3-hydroxybutanenitrile (30). (*R*)-4-Mesyloxy-3-hydroxybutanenitrile (**26**) (0.25 g, 1.4 mmol) was dissolved in dry acetonitrile (15 mL, distilled from calcium hydride) in a 25-mL round-bottomed flask. Potassium azide (1.13 g, 0.014 mol) and 18-crown-6 (25 mg, 0.095 mmol) were added, and the mixture was heated to reflux under nitrogen for 17 h. After the solution was cooled, 10 mL of water was added and the layers were separated. The aqueous solution was extracted with 3 × 25 mL of chloroform. The combined organic layers were washed with 10 mL of brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to yield 144 mg of yellow liquid. An additional 30 mg could be obtained by extracting the aqueous solution with 3 × 25 mL of ethyl acetate, drying with anhydrous magnesium sulfate and evaporating under reduced pressure. Purification was accomplished by chromatography on 20 g of silica gel with chloroform in 100-mL fractions. The product (136 mg, 77%) was obtained in fractions 3–6. Rotation (63 mg in 1.00 mL of absolute ethanol at 24.7 °C): $[\alpha]_D = -0.444°$, $[\alpha]_{578} = -0.508°$, $[\alpha]_{546} = -0.540°$.

(DL)-4-Amino-3-hydroxybutanenitrile Hydrochloride (31). Approximately 50 mg of 10% palladium on charcoal was placed in a 500-mL Parr bottle and was mixed with 25 mL of absolute ethanol. (DL)-4-Azido-3-hydroxybutanenitrile (**30**) (100 mg, 0.79 mmol) dissolved in 25 mL of absolute ethanol and 0.5 mL of chloroform were added and the mixture shaken under 45 psi hydrogen at room temperature for 1.5 h. The catalyst was filtered off through Celite and the solvent removed under reduced pressure to yield 115 mg (100%) of a light brown oil which was used without purification in the next reaction. NMR (D_2O, acetone-d_6): δ 4.6 (s, HOD), 4.1 (m, 1 H, C*H*O), 3.1 (m, 2 H, CH_2N), 2.75 (m, 2 H, CH_2CN). IR: 3400–2900, 2260, 1600, 1500, 1460, 1420, 1050 cm^{-1}.

(*R*)-4-Amino-3-hydroxybutanenitrile Hydrochloride (31). Following the same procedure as for the (DL) material, (*R*)-cyanoazide **30** (0.136 g, 1.08 mmol) yielded amine hydrochloride (**31**) (0.143 g, 97% yield) as a slightly oily beige solid, crude mp 87–95 °C. The material was not purified but was hydrolyzed directly to the amino acid. The rotation was not obtainable due to the yellow-brown coloration of the solution in 95% ethanol or water.

(DL)-4-Amino-3-hydroxybutanoic Acid (8). (DL)-Cyanoamine hydrochloride **31** (60 mg, 0.44 mmol) was dissolved in concentrated sulfuric acid (1.0 mL, 19 mmol) and heated on a steam bath for 5 min. It was then diluted with 10 mL of water and heated to reflux for 3 h. After being cooled, the solution was made basic with excess barium carbonate and heated on the steam bath for 1 h. It was then filtered with suction and exactly neutralized with several drops of 2% sulfuric acid. After evaporation under reduced pressure, 47 mg of yellow solid remained which showed no impurities by IR or NMR (70% combined yield for last two steps). Crystallization from ethanol/water provided 23 mg of a white solid: mp 214–215 °C, lit.[28a] mp 214 °C. NMR (D_2O, acetone-d_6): δ

4.6 (s, HOD), 4.1 (m, 1 H, CHO), 3.0 (m, 2 H, CH_2N), 2.32 (d, J = 6 Hz, 2 H, CH_2CO_2H). IR (KBr): 3450, 3100-2500, 2150, 1650, 1575-1250, 1100, 1050, 900 cm^{-1}. IR (lit.[28g] KBr): 3100, 2150, 1650, 1575, 1400, 1150, 1100, 1050 cm^{-1}.

(*R*)-4-Amino-3-hydroxybutanoic Acid (8). (*R*)-Cyanoamine hydrochloride (**31**) (143 mg, 1.05 mmol) was dissolved in concentrated suulfuric acid (1.0 mL, 19 mmol) and heated on the steam bath for 15 min. Water (10 mL) was added and the solution refluxed for 3 h. After being cooled, it was neutralized with lead carbonate and heated on the steam bath for 1 h. After filtration and evaporation under reduced pressure, 189 mg of a thick yellow oil remained. Dissolution in a small amount of water and dilution with absolute ethanol (about 30 mL) provided 120 mg of white crystals (96%); mp 202-205 °C, lit.[28d] mp 212 °C. Rotation: $[\alpha]^{25}_D$ = -7.09° (c = 3.5, H_2O) (lit.[28d] $[\alpha]_D$ = -3.4° or -21.06°), $[\alpha]_{578}$ = -7.49°, $[\alpha]_{546}$ = -8.49°.

(DL)-2,2-Dimethyl-4-((*tert*-butylamino)methyl)-1,3-dioxolane (33). (DL)-Acetonide tosylate (**17**) (100 mg, 0.35 mmol) was weighed into a 10-mL round-bottomed flask and dissolved in 3 mL of dimethyl sulfoxide. Dry *tert*-butylamine (1.0 mL, 9.45 mmol, distilled from calcium hydride) was added, a condenser and calcium sulfate drying tube were attached, and the solution was heated to 85 °C for 21 h. After being cooled, it was poured into 25 mL of diethyl ether, extracted with 3 × 10 mL of saturated sodium bicarbonate, and dried over anhydrous sodium sulfate. Evaporation of solvent under reduced pressure provided 51 mg (78%) of the desired amine **33**. NMR (acetone-d_6): δ 4.3-3.7 (m, 3 H, CHO), 2.8-2.5 (m, 3 H, CH_2N and NH), 1.35 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 1.10 (s, 9 H, *t*-Bu). IR ($CHCl_3$): 3550, 3400, 2950, 1350, 1250 cm^{-1}. Mass spectrum: m/e 187 (M^+), 172, 155, 129, 116, 114, 86, 84. High-resolution mass spectrum: m/e 187.1570 (M^+), calcd for $C_{10}H_{21}NO_2$, 187.1572.

(DL)-3-(*tert*-butylamino)-1,2-propanediol (34). (DL)-(*tert*-butylamino)acetonide (**33**) (50 mg, 0.27 mmol) was dissolved in 1 N hydrochloric acid (5 mL) and stirred at room temperature for 3 h. After the solution was cooled to 0 °C, sodium hydroxide (0.3 g, 7.5 mmol) was added and it was stirred until dissolved. Water (10 mL) was added, and the aqueous solution was extracted with 3 × 25 mL of dichloromethane. The combined extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure to yield 13 mg (33%) of a yellow oil. NMR: δ 3.7 (m, 3 H, CHO), 2.92 (d, J = 5 Hz, 2 H, CH_2N), 2.6 (br s, 3 H, OH and NH), 1.1 (s, 9 H, CH_3). IR ($CHCl_3$): 3400, 2980, 1370, 1350, 1045 cm^{-1}. Mass spectrum: m/e 132 (M^+ - 15), 114, 70, 57. High-resolution mass spectrum: m/e 132.1022 ($M^+ - CH_3$), calcd for $C_6H_{14}NO_2$, 132.1024.

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A Short New Azulene Synthesis

Lawrence T. Scott,* Mark A. Minton, and Mark A. Kirms

Contribution from the Department of Chemistry, University of Nevada, Reno, Nevada 89557.
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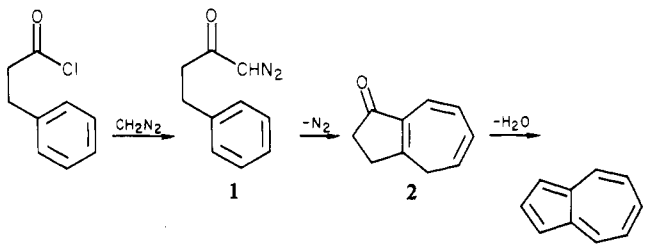
Abstract: A short new azulene synthesis, requiring no dehydrogenation step, has been developed (Scheme I). Intramolecular carbene addition creates the bicyclic ring system of azulene with a high degree of unsaturation and versatile functionality in a single step from a simple benzene derivative. The synthesis is particularly amenable to preparation of specific ^{13}C- and ^{2}H-labeled azulenes.

Azulene, the first and best known of all nonbenzenoid aromatic hydrocarbons, has played a major role in the advancement of our understanding of cyclic conjugation.[1] Since Plattner's original synthesis of this unusual, blue hydrocarbon in 1937,[2] a variety of new pathways to azulenes has been reported.[3] Prominent among these stands the remarkably simple and versatile Hafner-Ziegler synthesis[4] which avoids the low yield, dehydrogenation step typical of most other routes. Access to this class of compounds has resulted in the extensive exploration of azulene chemistry.[1]

One long-known reaction in this field, the thermal rearrangement of azulene to naphthalene,[5] continues to mystify mechanistic organic chemists.[6] We decided to study this unique interconversion of aromatic hydrocarbons by the use of ^{13}C labels. It soon became apparent, however, that none of the existing syntheses were suitable for preparation of the desired ^{13}C-azulenes. The Hafner-Ziegler method, for example, begins with cyclopentadiene anion and cannot be used to label specifically the five-membered ring positions. Consequently, we have developed the pathway outlined in Scheme I.[7]

Scheme I



This new azulene synthesis is short and simple. No dehydrogenation step is required. Furthermore, it can be easily adapted for the introduction of ^{13}C or ^{2}H at almost any position. We believe our new approach will prove useful in the rational preparation of many azulenes not previously accessible by existing methods.

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