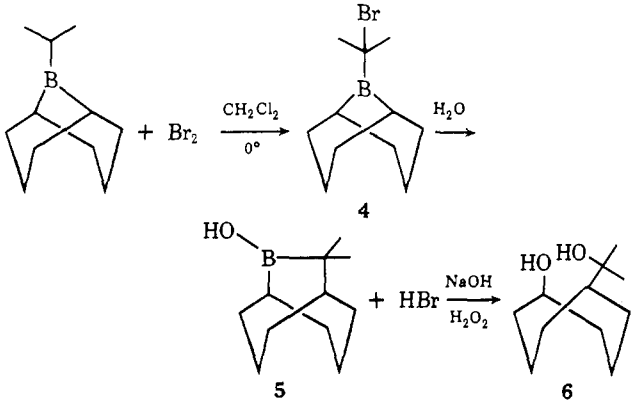
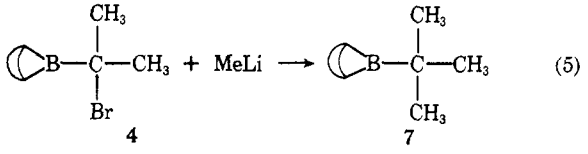
the isolation of 2-bromo-2-propyl-9-borabicyclo[3.3.1]-nonane (**4**) by removal of the solvent. This product decomposed on attempted distillation, even at very low pressures. However, the crude product could be utilized in various syntheses. Thus, treatment with water results in the migration of one of the bicyclooctyl bonds from boron to carbon to produce an interesting new bicycloorganoborane derivative (**5**), 9,9-dimethyl-10-hydroxy-10-borabicyclo[3.3.2]decane. The structure of **5** was confirmed by oxidation with hydrogen peroxide[5] to the diol, *cis*-5-(2-hydroxy-2-propyl)cyclooctanol[6] (**6**), mp 102.5–103°.



Alternatively, this synthesis can be achieved in essentially one operation by carrying out the bromination of **4** in the presence of water.[7]

Treatment of **4** with methyllithium in pentane at −78° results in an essentially quantitative formation (eq 5) of *B*-*t*-Bu-9-BBN (**7**). This product (**7**) was



(5)

identified by oxidation of *tert*-butyl alcohol and by glpc comparison with an authentic sample made from *B*-MeO-9-BBN and *tert*-butyllithium.[8] Clearly, these developments open the possibility for the synthesis of *B*-alkyl-9-BBN derivatives, such as **7**, not directly available by hydroboration.

(5) The oxidation was difficult and required forcing conditions, according to the procedure described in H. C. Brown, Y. Yamamoto, and C. F. Lane, *Synthesis*, 304 (1972).

(6) Physical data were all consistent with the assigned structure of the diol **6**.

(7) C. F. Lane and H. C. Brown, *J. Amer. Chem. Soc.*, **93**, 1025 (1971).

(8) We are indebted to G. W. Kramer for the authentic sample. The results of a detailed study of the reaction of *B*-MeO-9-BBN with organolithium reagents by G. W. Kramer will be published shortly.

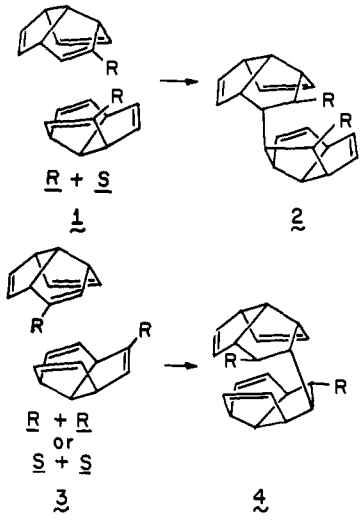
(9) Graduate research assistant on Grant No. GP-27742X from the National Science Foundation.

Herbert C. Brown,* Norman R. DeLue[9]
Richard B. Wetherill Laboratory, Purdue University
West Lafayette, Indiana 47907
Received October 2, 1973

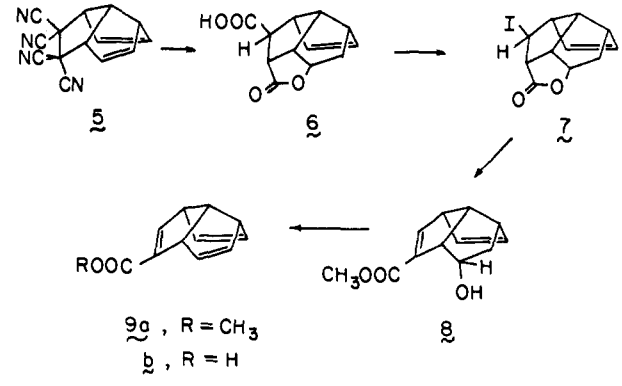
An Efficient Synthesis of (−)-Triquinacene-2-carboxylic Acid

Sir:

There is special interest in 2-substituted triquinacenes because of the possibility that appendage of an appropriate R group at C_2 could facilitate and direct endo,-endo coupling of the monomeric units in a manner which has not been realized with the parent hydrocarbon.[1] In this connection, there is seen to exist an intriguing relationship between the dissymmetry of such derivatized triquinacenes and the structural features of the corresponding "dimers." For the hypothetical reactions **1** → **2** and **3** → **4** where the coupling products



are drawn in their sterically encumbered conformations to facilitate visual analysis, it is evident that only when bonding between trienes of like configuration operates will a molecular array directly relatable to dodecahedrane result.[2] Because enantiomerically pure 2-substituted triquinacenes would be unable to produce **2**, the availability of such tricyclo[5.2.1.$0^{4,10}$]deca-2,5,8-trienes might permit efficient construction of the possible dodecahedrane precursor **4**. We report here the development of a convenient synthetic approach[3] to (−)-triquinacene-2-carboxylic acid (**9b**), a primary focal point for elaboration of this concept.



The tetranitrile **5**, readily available in 94% yield from cyclooctatetraeneiron tricarbonyl,[4] was hydrolyzed

(1) R. B. Woodward, T. Fukunaga, and R. C. Kelly, *J. Amer. Chem. Soc.*, **86**, 3162 (1964).

(2) Specifically, we note that 1,4-disubstituted dodecahedranes are of C_2 symmetry, requiring therefore precursor halves of the same configuration.

(3) Dr. Tadamichi Fukunaga, Central Research Department, E. I. du Pont de Nemours and Co. has kindly informed us that Professor R. B. Woodward and he have been aware of this interesting stereochemical aspect of optically active triquinacene derivatives and have also prepared optically active **9b** by suitable structural modification of triquinacene itself.

(4) (a) L. A. Paquette, S. V. Ley, M. J. Broadhurst, D. Truesdell, J. Fayos, and J. Clardy, *Tetrahedron Lett.*, 2943 (1973); (b) D. J. Ehntholt and R. C. Kerber, *J. Organometal. Chem.*, 38, 139 (1972).

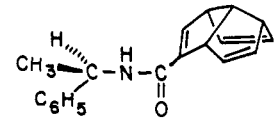
with concentrated hydrochloric acid at 130° (sealed tube, 11 hr) or, more simply, at the reflux temperature (28 hr) to afford the crystalline acid lactone **6**, mp 157.5–158°,[5] in 95 and 82% yields, respectively. Its pair of olefinic hydrogens appear in the nmr spectrum ($CDCl_3$) at δ 5.63 (br d, 1 H, J = 5.5 Hz) and 5.42 (br d, 1 H, J = 5.5 Hz), while the >C*H*O– proton is seen as a multiplet at 5.2–4.85 (the two >C*H*CO– are obscured by the other methine protons). Thus, the exo nature of the carboxyl group could not be unequivocally established spectroscopically but is rather inferred on thermodynamic grounds, our inability to achieve double lactonization, and the nonepimerizable nature of the derived (CH_2N_2) methyl ester. Treatment of **6** in carbon tetrachloride–benzene solution (1:1) under nitrogen with lead tetraacetate and iodine under conditions of concomitant irradiation from a 250-W tungsten lamp source[6] produced **7**, mp 153–154°,[5] in 56% yield.

Mild hydrolysis and dehydroiodination of **7** was achieved concurrently by treatment with potassium carbonate in 1:1 tetrahydrofuran–water at 25° for 32 hr. Subsequent direct methylation of the resulting crystalline hydroxy acid (mp 152–153°)[5] with excess diazomethane gave 68% of the hydroxy ester **8**[5] as a clear oil showing infrared maxima at 3500 and 1720 cm^{-1}.

Introduction of the third double bond was effected by direct dehydration of **8** with ethyl(carboxysulfamoyl)-triethylammonium hydroxide inner salt[7] (dry THF, 25°, 60 min, N_2 atmosphere, 56% yield) or somewhat more conveniently by conversion of **8** to its mesylate (mp 105–106°)[5] and exposure of this derivative to a slurry of neutral alumina (activity I) in dichloromethane[8] (25°, 12 hr, 57% overall yield). The nmr spectrum ($CDCl_3$) of **9a** shows a downfield olefinic proton absorption at δ 6.64 (H_3), multiplets of area 4 at 5.95–5.5 and 4.1–3.7, and a three-proton singlet at 3.73. Saponification of **9a** (KOH, aqueous ethanol) proceeded quantitatively to give **9b**, mp 131–133°.[5,9]

In design, therefore, our synthesis proceeds formally by reorganization of the eight ring atoms in cyclooctatetraene with interposition of two carbon atoms (and the carboxyl substituent) from tetracyanoethylene. The susceptibility of **5** to acidic hydrolysis occurs with unusual facility for a 1,1,2,2-tetranitrile,[10] a finding of utmost significance to the scheme. Although loss of a double bond does occur during the conversion of **5** to **6**, the subsequent four-step elaboration of **9a** comprises a simple sequence for introduction of the second and third olefinic centers.

Resolution of **9b** was achieved by fractional crystallization of the (+)-(*R*)-α-phenethylamine[11] salts from methanol–water (4:1). The less soluble diastereomer exhibited $[\alpha]^{25}_{365}$ −97.8° (*c* 0.3, ethanol). Acidification of this salt afforded (−)-**9b**, mp 112–113°, $[\alpha]^{25}D$ −12.3°, $[\alpha]^{25}_{365}$ −339° (*c* 0.5, ethanol), which was shown to be enantiomerically pure (≥95%) by conversion to amide **10**[12] through stepwise treatment with oxalyl chloride[13] and (+)-(*R*)-α-phenethylamine in benzene containing pyridine (86% yield). Whereas the amides prepared from a partially resolved sample of **9b** ($[\alpha]^{25}_{365}$ +13°) exhibited a distinct pair of methyl doublets in the pmr spectrum (C_6D_6, $\Delta\nu$ = 2.7 Hz at 60 MHz; diastereomeric ratio *ca.* 55:45), pure **10** ($[\alpha]^{25}D$ −37.0°



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(*c* 0.7, ethanol)) showed only the upfield methyl doublet at δ 1.24.[14]

Enantiomerically homogeneous (−)-**9b** is characterized by a lone electronic absorption maximum at 224 nm (ε 6230) and a negative Cotton effect: $[\theta]_{278}$ 0, $[\theta]_{224}$ −79,800, $[\theta]_{210}$ 0, Γ/2 = 20 nm[15] (*c* 0.05, ethanol, 25°).[16]

(5) All new substances reported were shown to possess the correct molecular composition by combustion analysis (±0.3% of theory).

(6) D. H. R. Barton, H. P. Faro, E. P. Serebryakov, and N. F. Woolsey, *J. Chem. Soc.*, 2438 (1965); T. Sakan and K. Abe, *Tetrahedron Lett.*, 2471 (1968); U. Scheidegger, J. E. Baldwin, and J. D. Roberts, *J. Amer. Chem. Soc.*, 89, 894 (1967); for a review, consult R. A. Sheldon and J. K. Kochi, *Org. React.*, 19, 279 (1972).

(7) E. M. Burgess, H. R. Penton, Jr., and E. A. Taylor, *J. Amer. Chem. Soc.*, 92, 5224 (1970); *J. Org. Chem.*, 38, 26 (1973).

(8) C. Mercier, P. Soucy, W. Rosen, and P. Deslongchamps, *Syn. Commun.*, 3, 161 (1973); G. H. Posner, R. J. Johnson, and M. J. Whalen, *J. Chem. Soc., Chem. Commun.*, 281 (1972).

(9) Identical in all respects to a sample provided by Dr. Fukunaga.[3]

(10) W. J. Middleton, R. E. Heckert, E. L. Little, and C. G. Krespan, *J. Amer. Chem. Soc.*, 80, 2783 (1958); H. E. Simmons, private communication.

(11) W. Leithe, *Chem. Ber.*, 64, 2827 (1931); G. Fodor and G. Csepreghy, *Tetrahedron Lett.*, No. 7, 16 (1959); E. Benedetti, P. Corradini, and C. Pedone, *J. Organometal. Chem.*, 18, 203 (1969).

(12) In the absence of absolute configuration data, the diastereomeric identity of 10 remains, of course, an unresolved issue.

(13) Ch. R. Engel and G. Just, *Can. J. Chem.*, 33, 1515 (1955); F. Reber, A. Lardon, and T. Reichstein, *Helv. Chim. Acta*, 37, 45 (1954).

(14) Attempts to establish the enantiomeric composition of (−)-**9b** by conversion (CH_2N_2) to ester **9a** and application of the chiral shift reagent tris(3-trifluoromethylhydroxymethylene)-*d*-camphoratoeuropium(III) [H. L. Goering, J. N. Eikenberry, and G. S. Koermer, *J. Amer. Chem. Soc.*, 93, 5913 (1971)] did not result in "resonance doubling" (100 MHz) of the signals due either to the methyl group or the downfield shifted olefinic proton H_3.

(15) C. Djerassi and E. Bunnenberg, *Proc. Chem. Soc., London*, 299 (1963).

(16) This work was assisted financially by grants from the National Science Foundation and Eli Lilly and Co.

(17) National Institutes of Health Postdoctoral Fellow, 1972–1974.

Leo A. Paquette,* Steven V. Ley, William B. Farnham[17]
Department of Chemistry, The Ohio State University
Columbus, Ohio 43210
Received September 12, 1973

Cyclophosphamide. Complete Inhibition of Murine Leukemia L1210 *in Vivo* by a Fenton Oxidation Product

Sir:

Cyclophosphamide,[1] an effective agent against many animal and human tumors, is oxidized *in vivo* by the mixed function oxidase of liver microsomes to produce a cytotoxic form of the drug.[2,3] A recent communication[4] prompts us to report our results on the chemical synthesis of a stable, crystalline, oxidation product of cyclophosphamide that is cytotoxic *in vitro*, is able to

(1) H. Arnold, F. Bourseaux, and N. Brock, *Arzneim.-Forsch.*, 11, 143 (1961).

(2) D. L. Hill, W. R. Laster, Jr., and R. F. Struck, *Cancer Res.*, 32, 658 (1972), and references cited therein.

(3) R. F. Struck and D. L. Hill, *Proc. Amer. Ass. Cancer Res.*, 13, 50 (1972).

(4) A. Takamizawa, S. Matsumoto, T. Iwata, K. Katagiri, Y. Tochino, and K. Yamaguchi, *J. Amer. Chem. Soc.*, 95, 985 (1973).