Table I. Percentage Rearrangement of Isotopic Label from C-2,3 to C-1,4–7 in the *exo*-Dehydro-2-norbornyl-*x*-*d* Acetate (I-*x*-*d*-OAc) from the Acetolysis of *exo*-Dehydro-2-norbornyl-2-*d* Brosylate (I-2-*d*-OBs) under Various Conditions

	% rearrangement		
	Present results		
Experimental conditions	Ms	Nmr[a]	Previous results
0.48 *M* I-2-*d*-OBs, 1.1 equiv of KOAc, 45°, 1 hr	35	33	38[b]
0.24 *M* I-2-*d*-OBs, 10 equiv of NaOAc, 24°, 11 hr	50	46	49.0; 47.5[c]
0.48 *M* I-2-*d*-OBs, 1.1 equiv of KOAc, 65°, 1 hr	43	43	
0.48 *M* I-2-*d*-OBs, 1.1 equiv of KOAc, 14°, 8 days	51	50	

[a] The nmr data gave the per cent rearrangement from C-2 to C-1,3–7. [b] From acetolysis of I-2,3-^{14}C-OBs, ref 2. The acetolysis of *endo*-dehydro-2-norbornyl-2-*d* brosylate at reflux temperature for 48 and 96 hr gave, respectively, 27 and 29% rearrangement, in substantial agreement with the 30% rearrangement reported in ref 2 for the acetolysis of *endo*-dehydro-2-norbornyl-2,3-$^{14}C_2$ brosylate at reflux temperature for 48 hr. [c] From acetolysis of I-3-*d*-OBs, ref 3.

scrambled brosylate. This conclusion has been confirmed in the present work. The H absorption at C-2 in the nmr spectra of the brosylate recovered after acetolysis of 0.48 *M* I-2-*d*-OBs in the presence of 10% excess KOAc at 25° for 30, 60, and 90 min, respectively, showed 10, 15, and 19% rearrangement of the D label from C-2 to C-1,3–7.

The temperature effects on the extents of rearrangement (Table I) may be rationalized by assuming that in the formation of the I-OAc product, competitive reactions involving two ion pairs could occur. At the

$$\begin{tikzcd}
 & \text{II}^{+}\text{OBs}^{-} \arrow[r] & \text{50\% rearrangement in I-OAc} \\
\text{I-OBs} \arrow[ur, shift left] \arrow[dr, shift left] & & \\
 & \text{III}^{+}\text{OBs}^{-} \arrow[ul, shift left] \arrow[r] & \text{0\% rearrangement in I-OAc}
\end{tikzcd}$$

lower temperatures of 14 or 24°, the I-OAc could arise only from an ion pair, the cationic part of which would be symmetrical such as II, giving rise to 50% rearrangement. At higher temperatures, formation of ion pair III$^+$OBs$^-$ became competitive, with the homoallylic cation III leading to isotopically unrearranged I-OAc. The net I-OAc product from both II and III would show less than 50% rearrangement. Concurrently, internal returns would produce isotopically scrambled I-OBs which could subsequently solvolyze and contribute to the overall scrambling. When the reaction was carried out at 65° instead of 45°, there could be more extensive equilibrations between I-OBs and II$^+$OBs$^-$ *via* internal returns; thus the overall rearrangement in the I-OAc was greater at 65° than at 45°. The present results could not eliminate the possibility that at 45 and 65°, interconversion between II$^+$OBs$^-$ and III$^+$OBs$^-$ might take place in conjunction with their competitive formation; such consecutive transformations between unsymmetrical and symmetrical ions have originally been suggested by Roberts.[2] The present data and the results of Cristols,[3] however, indicate that at 14 or 24°, the I-OAc product from the acetolysis of I-OBs arose essentially only from a symmetrical cationic intermediate; the formation of unsymmetrical ion III apparently was too slow to compete at these temperatures.

Acknowledgment. Valuable comments from Professor N. C. Deno are greatly appreciated.

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[7] Holder of a Senior Research Fellowship of the National Research Council of Canada, 1969.

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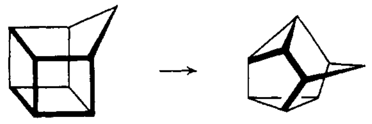
Silver Ion Catalyzed Rearrangements of Strained σ Bonds. Application to the Homocubyl and 1,1′-Bishomocubyl Systems

Sir:

The correlation of orbital symmetry conservation with the concertedness of many thermal and photochemical reactions has enjoyed outstanding recent success.[1] Despite these developments, surprisingly little is known about the capability of heavy metal ions to affect the molecular orbitals of reactants in a fashion which causes an otherwise forbidden bond reorganization to become allowed.[2] We now describe a remarkably facile skeletal isomerization of homocubane and 1,1′-bishomocubane derivatives which occurs uniquely in the presence of a heavy metal ion (*e.g.*, Ag$^+$).

When dilute $CDCl_3$ or acetone-d_6 solutions of homocubane (**1**), mp 104–105°,[3] are treated with catalytic amounts of silver fluoroborate, the hydrocarbon is converted quantitatively to pentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonane (**2**), mp 87–88°,[4] within 1 day at 25° (nmr analysis and isolation). In the absence of silver ion, **1** is stable to 240°.[3] Since the rearrangement of **1** to **2** is the formal result of a symmetry disallowed ${}_{\sigma}2_a + {}_{\sigma}2_a$ electrocyclic reaction, the indicated geometric changes (**3**) are expected to be associated with a high


1 2

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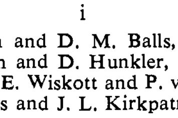
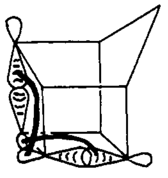
[1] R. B. Woodward and R. Hoffmann, *Angew. Chem.*, **81**, 797 (1969); *Angew. Chem. Intern. Ed. Engl.*, **8**, 781 (1969).

[2] (a) H. Hogeveen and H. C. Volger, *J. Amer. Chem. Soc.*, **89**, 2486 (1967); (b) W. Merk and R. Pettit, *ibid.*, **89**, 4788 (1967).

[3] W. G. Dauben and D. L. Whalen, *Tetrahedron Lett.*, 3743 (1966). In the present work, **1** was synthesized by photosensitized isomerization of i which was prepared by condensation of cyclobutadiene to cyclopentadiene [L. Watts, J. D. Fitzpatrick, and R. Pettit, *J. Amer. Chem. Soc.*, **88**, 623 (1966)].


i

[4] (a) P. K. Freeman and D. M. Balls, *J. Org. Chem.*, **32**, 2354 (1967); (b) H. Prinzbach and D. Hunkler, *Angew. Chem. Intern. Ed. Engl.*, **6**, 247 (1967); (c) E. Wiskott and P. v. R. Schleyer, *ibid.*, **6**, 694 (1967); (d) R. M. Coates and J. L. Kirkpatrick, *J. Amer. Chem. Soc.*, **90**, 4162 (1968).



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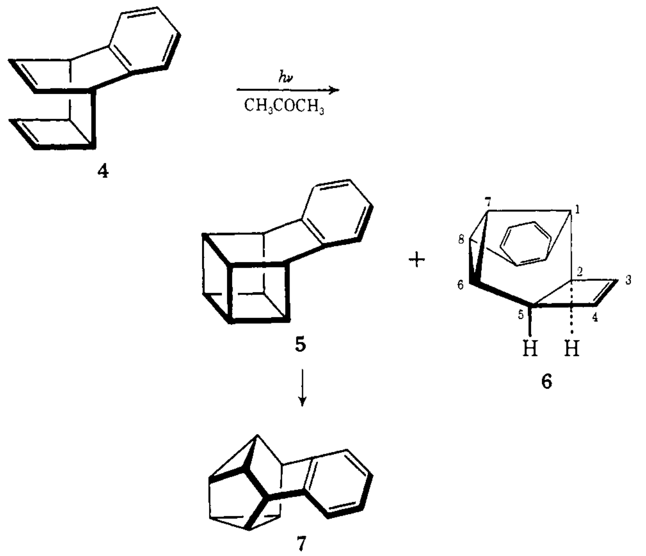
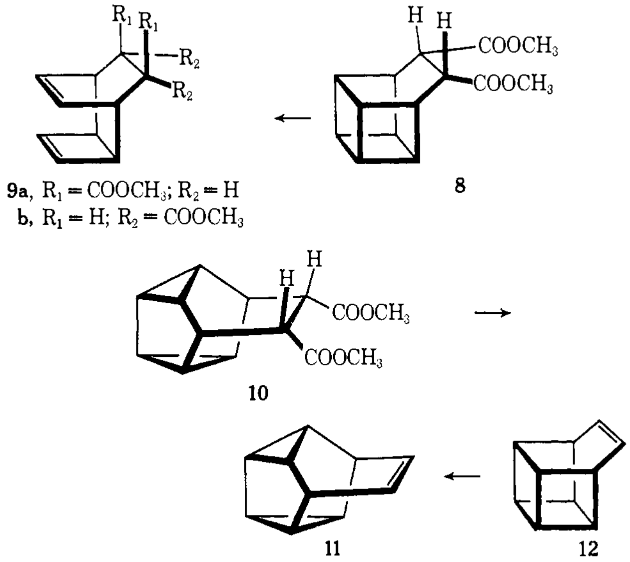
energy of activation. As a result, although **1** is estimated to be approximately 45 kcal/mol more strained than **2**,[5] the purely thermal conversion is inhibited by a sizable intervening energy barrier. In contrast, the readiness of the silver ion catalyzed process is presumably caused by complexation of the metal orbitals with the strained σ orbitals of **1** to produce new occupied molecular orbitals with symmetry properties compatible with an allowed isomerization.[6]

Such rearrangements appear entirely general. For example, benzobasketene (**5**),[7,8] prepared in 40% yield together with **6**[8,9] and an as yet unidentified hydrocarbon (6%) by acetone-sensitized photoisomerization of *anti*-7,8-benzotricyclo[4.2.2.0^{2,5}]deca-3,7,9-triene (**4**),[10,11] is stable at 350° in a flow system (N_2, 3 mm, contact time ~2 sec). However, exposure of dilute $CDCl_3$ solutions of **5** to $AgBF_4$ as above results in quantitative conversion to **7**, mp 105–106°[8] [$\delta_{TMS}^{CDCl_3}$ 7.05–7.35 (m, 4, aryl), 3.62 (m, 2, benzylic), 2.35 (m, 2, remote cyclopropyl), and 1.71 (m, 4, cyclopropyl)], within 1 hr at room temperature. Alternatively, the transformation can be achieved with equal efficiency, albeit somewhat less conveniently, by elution of **5** through a column of silica gel impregnated with silver nitrate.



A further interesting case is afforded by pentacyclic diester **8**, mp 80–82°.[3] When **8** is heated at 275° for 20 min, thermal retrogression to **9a** and **9b** is observed.[3] Clearly, no symmetry-allowed concerted rearrangement pathway is directly available to **8**. However, addition of $AgBF_4$ to $CDCl_3$ solutions of **8** at 25° results in very rapid (<3 min) conversion to **10**: mp 100–103°; $\delta_{TMS}^{CDCl_3}$ 3.68 (s, 6, $-OCH_3$), 3.14 (br, s, 2, α-carbonyl), 2.7 (m, 2, bridgehead), and 1.4–2.0 (m, 6, cyclopropyl). At this point, it is pertinent to introduce the fact that the claim by Furstoss and Lehn of the synthesis of basketene (**12**) is in error.[12] Although their synthetic approach paralleled closely that employed successfully by two other groups,[3,13] their samples of **8** were purified by column chromatography on silica gel–silver nitrate (10%). Under these conditions, rapid conversion to **10** was inadvertently achieved. Oxidative bisdecarboxylation of the diacid derived from **10** served to afford **11**, a new isomer in the $(CH)_{10}$ series of hydrocarbons: mp 61–62°; $\delta_{TMS}^{CCl_4}$ 6.33 (m, 2, vinyl), 3.15 (m, 2, allyl), 2.12 (m, 2, remote cyclopropyl), and 1.55 (m, 4, cyclopropyl). Further confirmation of this scheme is seen in the fact that basketene (**12**) is likewise converted to **11** (12% complete after 6 hr, $CDCl_3$ solution, 25°).[14]



The structures of **7** and **11** follow not only from their highly symmetrical nmr spectra and the analogous unequivocal formation of **2**, but also because all other symmetrical monounsaturated $(CH)_{10}$ isomers may be excluded. Thus, recourse to Lederberg's computer program[15] which lists all the possible $(CH)_{10}$ isomers

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(5) This estimate is based upon the assumption that the total strain energy should be approximately equal to the sum of the strain energies of the composite fused rings [K. B. Wiberg, *Advan. Alicyclic Chem.*, **2**, 185 (1968)]. In the present example, the rearrangement can be considered to entail the conversion of two bicyclo[2.2.0]hexane moieties ($E_s \approx 2 \times 53$ kcal/mol) to two bicyclo[3.1.0]hexane units ($E_s = 2 \times 31$ kcal/mol).

(6) For recent theoretical discussions of related topics, see: (a) F. D. Mango and J. H. Schachtschneider, *J. Amer. Chem. Soc.*, **89**, 2484 (1967); (b) D. R. Eaton, *ibid.*, **90**, 4272 (1968); (c) T. H. Whitesides, *ibid.*, **91**, 2395 (1969).

(7) Mp 58°; $\delta_{TMS}^{CDCl_3}$ 7.32 (s, 4, aryl), 4.17 (m, 2, benzylic), 3.46 (m, 2, remote cyclobutyl), and 3.00 (m, 4, cyclobutyl).

(8) Satisfactory elemental analyses were obtained for all new compounds.

(9) Colorless oil; $\delta_{TMS}^{CDCl_3}$ 7.06 (m, 4, aryl), 6.21 (d, J = 2.5 Hz, 1, vinyl), 5.96 (m, 1, vinyl), 3.55 (d, J = 5.0 Hz, 1, H_1), 3.10 (m, 1, H_2 or H_6), 2.99 (d, J = 2.5 Hz, 1, H_2 or H_6), 2.69 (m, 1, H_7), 2.35 (dd, J = 6.0 and 8.0 Hz, 1, H_8), and 1.97 (dd, J = 6.0 and 8.0 Hz, 1, H_8).

(10) L. A. Paquette and J. C. Stowell, submitted for publication. Complete details of this photoisomerization will be outlined in our full paper.

(11) The photoisomerization of 4 has been examined independently by L. Friedman and coworkers.

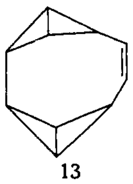
(12) R. Furstoss and J.-M. Lehn, *Bull. Soc. Chim. France*, 2497 (1966). This is particularly evident when one compares the published nmr spectrum of the French workers with that of authentic basketene.[13]

(13) S. Masamune, H. Cuts, and M. G. Hogben, *Tetrahedron Lett.*, 1017 (1966).

(14) Contrast the thermochemical behavior of basketene: H. H. Westberg, E. N. Cain, and S. Masamune, *J. Amer. Chem. Soc.*, **91**, 7512 (1969); E. LeGoff and S. Oka, *ibid.*, **91**, 5665 (1969).

(15) J. Lederberg, NASA report entitled "Dendral-64. A System for Computer Construction, Enumeration, and Notation of Organic Molecules as Tree Structures and Cyclic Graphs." The authors thank Professor R. Hoffmann for providing them with a copy of the computer-generated data.

in terms of polygonal[16a] and nonpolygonal graphs[16b] revealed that unknown hydrocarbons **12–15** were the only remaining feasible structural representations



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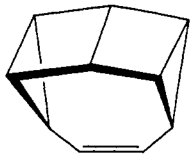

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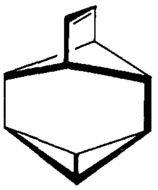

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(other than **11** and **12**). Of this group, **13** and **14** are incompatible with the nmr data, and **15** is discounted for mechanistic reasons.

Investigations of these and new types of metal ion induced isomerizations will continue to be made. Also, examination of the ground- and excited-state properties of **5**, **6**, **7**, and **11** is presently in progress.

Acknowledgment. We wish to thank Badische Anilin- und Soda-Fabrik for a generous gift of cyclooctatetraene required in the preparations of **1**, **4**, and **8**.

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(16) (a) Those molecules in which a continuous cycle of 10 atoms may be found; (b) those molecules which contain no continuous cycle of 10 atoms.

(17) National Institutes of Health Postdoctoral Fellow, 1969–1970.

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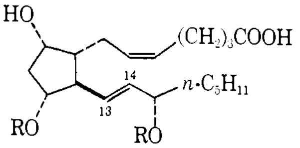
Total Synthesis of Prostaglandins F$_{1\alpha}$, E$_1$, F$_{2\alpha}$, and E$_2$ (Natural Forms) from a Common Synthetic Intermediate

Sir:

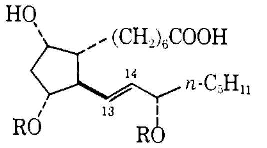
An effective stereocontrolled total synthesis of the naturally occurring hormones prostaglandins F$_{2\alpha}$ and E$_2$ has been reported recently from these laboratories.[1,2] These substances are produced from a common synthetic intermediate, the (dextrorotatory) 11,15-bistetrahydropyranyl ether of prostaglandin F$_{2\alpha}$ (**1**).[1] The intermediate **1** has now been employed successfully in the synthesis of the prostaglandins of the first series,[3] including the primary prostaglandins F$_{1\alpha}$ and E$_1$.

Hydrogenation of a solution of **1** ($[\alpha]^{24}\text{D}$ +13.3°, *c* 1.0 in chloroform) was carried out in methanol as solvent at −15 to −20° under 1 atm of hydrogen with 5% palladium-on-carbon (Engelhard Industries, Inc.) (amount, 0.25 times weight of substrate **1**) as catalyst using a thin layer chromatographic (tlc) analytical technique to follow the progress of reaction. The hydrogenation was interrupted as soon as tlc analysis[4] indicated that the only reaction components were the 11,15-bistetrahydropyranyl ether of prostaglandin F$_{1\alpha}$ (major product) (**2**) and its 13,14-dihydro derivative (in small amount).[5] The average time required for hydrogenation to this point was *ca.* 3 hr. The reaction product was isolated and subjected to hydrolysis in acetic acid–water–tetrahydrofuran (20:10:3) at 40° for 4 hr. Reisolation and chromatographic purification on silica gel (benzene–tetrahydrofuran–formic acid, 15:5:2, as eluent) afforded in 80% yield prostaglandin F$_{1\alpha}$ as a crystalline solid which was chromatographically homogeneous. Recrystallization from ethyl acetate–cyclohexane afforded fine colorless needles of prostaglandin F$_{1\alpha}$ (**3**), mp and mmp (with a sample of natural **3**) 101.5–102.5°, $[\alpha]^{24}\text{D}$ +24° (*c* 0.87, tetrahydrofuran). The infrared and nmr spectra and chromatographic behavior of synthetic and natural samples of prostaglandin F$_{1\alpha}$ were identical.

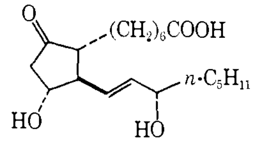
Oxidation of a sample of **2** obtained as described above with Jones chromic acid reagent[1] at −10° for 5 min and subsequent work-up and hydrolysis in acetic acid–water–tetrahydrofuran (20:10:3) at 39° for 7 hr afforded a product which was chromatographed on acid-washed silica gel using acetone–ethyl acetate–cyclohexane (1:2:2) as eluent and recrystallized from ethyl acetate–cyclohexane to give prostaglandin E$_1$ (**4**) (63.5% from **1**), mp and mmp 113.5–114.0°, $[\alpha]^{26}\text{D}$ −61.1° (*c* 0.256, tetrahydrofuran).[6] The spectra and chromatographic properties of synthetic and natural samples of prostaglandin E$_1$ were identical.



1, R = tetrahydropyranyl



2, R = tetrahydropyranyl
3, R = H



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The reduction method described above has also been applied to the synthesis of tritium-labeled prostaglandins of high specific activity, including prostaglandin F$_{1\alpha}$ (from **1**) and prostaglandin E$_1$ (from the corresponding 11,15-bistetrahydropyranyl ether). The labeled prostaglandins, obtained using carrier-free tritium gas with isopropyl alcohol as the solvent for hydrogenation, are now commercially available (New England Nuclear Co.).

This work completes a second total synthesis of the E$_1$ and F$_{1\alpha}$ prostaglandins in natural optically active

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(1) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Amer. Chem. Soc.*, **92**, 397 (1970).

(2) See also E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *ibid.*, **91**, 5675 (1969).

(3) See S. Bergström, *Science*, 157, 382 (1967).

(4) Aliquots of the reaction mixture were subjected to hydrolysis in 1:1 methanol–0.1 *N* hydrochloric acid at 75° for 2 min to remove the tetrahydropyranyl groups and analyzed by tlc using silver nitrate impregnated silica gel plates with the ethyl acetate–acetic acid–methanol–2,2,4-trimethylpentane–water (110:30:35:10:100) system as eluent [see K. Gréen and B. Samuelsson, *J. Lipid Res.*, **5**, 117 (1964)]. For this tlc system the R_f values for prostaglandin F$_{2\alpha}$, prostaglandin F$_{1\alpha}$, 13,14-dihydroprostaglandin F$_{2\alpha}$, and 13,14-dihydroprostaglandin F$_{1\alpha}$ were found to be 0.47, 0.64, 0.57, and 0.74, respectively.

(5) If the hydrogenation is stopped immediately after consumption of the starting material, the reaction mixture is found to contain in addition to the major component **2** small amounts of the bistetrahydropyranyl ethers of 13,14-dihydroprostaglandin F$_{2\alpha}$ and 13,14-dihydroprostaglandin F$_{1\alpha}$. Because 13,14-dihydroprostaglandin F$_{2\alpha}$ is much less readily separated by chromatography from prostaglandin F$_{1\alpha}$ than is 13,14-dihydroprostaglandin F$_{1\alpha}$, it is advantageous to carry out hydrogenation until 13,14-dihydroprostaglandin F$_{2\alpha}$ has been saturated. Chromatographic separation of the various bistetrahydropyranyl ethers is quite difficult, and for this reason the THP protecting group is removed for analysis or purification on a preparative scale.

(6) Reported previously for prostaglandin E$_1$, $[\alpha]^{25}\text{D}$ −61.6°; see E. J. Corey, I. Vlattas, and K. Harding, *J. Amer. Chem. Soc.*, 91, 535 (1969).