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Electrophilic Capture by "Conjugated" Bis(bicyclo[1.1.0]butanes). Site Specificity of the Initiation Step and Thermodynamic Control of the Ensuing Electronic Reorganization

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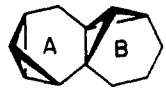
The intramolecular capture of cyclopropylcarbenes (or carbenoids) has emerged as one of the more important bicyclo[1.1.0]butane-forming reactions by virtue of its simplicity and selectivity.[2] Several years ago, we observed that twofold cyclopropylidene C–H insertion is an equally powerful synthetic technique that provides ready access to bis(bicyclo[1.1.0]butanes).[3] The elaboration of **1** and **2** in three convenient steps (Na, NH_3; KO-*t*-Bu, $CHBr_3$; CH_3Li, C_6H_6[4]) from tetralin and indan, respectively, is illustrative. We have been intrigued by the multiple sites offered by **1** and **2** to electrophilic reagents and now present



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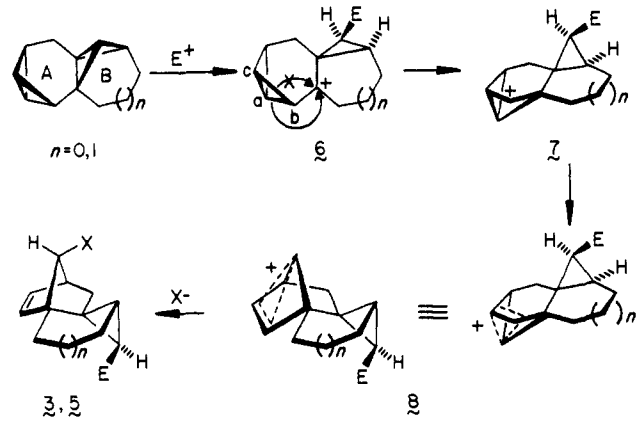
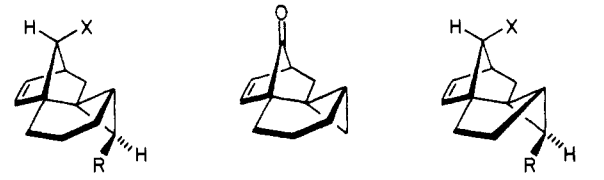
experimental evidence indicating that (a) only *one* of the *ten* available strained C–C σ bonds is cleaved by the attacking E^+ in remarkably regiospecific fashion; (b) this initiation step proceeds with retention of configuration at the reaction center; (c) the ensuing cascade of electronic rearrangements proceeds unidirectionally irrespective of the length of the polymethylene tether in ring B, presumably as a direct consequence of product stabilities; and (d) gradation in the nucleophilicity of the counter anion does in no case result in interception of the rearrangement prior to arrival at the 7-norbornenyl cation stage.

Addition of trifluoroacetic acid (8.2 equiv) to a chloroform solution of **1** at 20 °C resulted in rapid conversion to a single trifluoroacetate (86% isolated). Although the presence in this product of a trisubstituted cyclopropane ring, a pair of olefinic hydrogens, and a proton of the H–C–O type could be clearly inferred from the 300-MHz ^1H NMR spectrum, the remaining multiplets proved uninformative. Product identification as **3a** was achieved, however, by saponification (K_2CO_3, CH_3OH) to alcohol **3b** (mp 71–72 °C) whose three-dimensional structure was established by X-ray crystallographic analysis.[5]

Scheme I



The extendability of this unusual addition–rearrangement was investigated by next reacting **1** with acetic acid (8.2 equiv, $CHCl_3$, 20 °C) and with 70% perchloric acid (0.22 equiv, aqueous THF, 20 °C) to give **3c** (70%) and **3b** (77%), respectively. The corresponding conversion to **3d** (31%) was realized through the agency of anhydrous $AlCl_3$ (0.20 equiv) in ether under otherwise identical conditions. Improved access to chloride **3d** was achieved by displacement with retention of the hydroxyl group in **3b** using thionyl chloride in refluxing anhydrous ether.[6]



3a, X=OCOCF$_3$, R=H
b, X=OH, R=H
c, X=OCOCH$_3$, R=H
d, X=Cl, R=H
e, X=OCOCF$_3$, R=D
f, X=OH, R=D

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5a, X=OCOCF$_3$, R=H
b, X=OH, R=H
c, X=ODNB, R=H
d, X=Cl, R=H
e, X=OCOCF$_3$, R=D

From a reactivity standpoint, treatment with silver ion[7] was also of interest. In actuality, when **1** was exposed to silver nitrate in aqueous THF, qualitatively comparable conversion to **3b** was seen.[8] Swern oxidation of **3b** furnished **4** in 32% yield.

Usefully, the 300-MHz ^1H NMR spectra of **3a** and **3b** (in $CDCl_3$) cleanly distinguish the pair of cyclopropyl methylene hydrogens. For example, the endo proton in **3b** (δ 0.40) appears downfield of its exo counterpart (δ 0.27) and is seen to be equivalently coupled (J = 4.7 Hz) to its geminal and vicinal neighbors. In contrast, the dd pattern for H_{exo} (J = 4.7, 8.5 Hz) features a large spin interaction that is compatible with its cis relationship to the methine proton.

The stage was therefore set for the critical deuterium labeling experiments. Since treatment of **1** with CF_3COOD as before gave trifluoroacetate lacking the 0.40 signal, conversion to **3e** had obviously materialized. Isomerically pure **3f** was similarly obtained upon mixing **1** with $AgNO_3$ in a D_2O–THF solvent system.

Transformations involving **2** were conducted analogously and provided **5a** (58%) and **5d** (63%). As in the higher homologous series, trifluoroacetate **5a** exhibits well separated cyclopropyl methylene protons [δ 0.45 (dd, J = 4.9, 7.8 Hz) and 0.36 (dd, J = 4.9, 4.9 Hz)].[9] Following confirmation of the endo con-

(1) Undergraduate research scholar, 1984–1986.

(2) (a) Moore, W. R.; Ward, H. R.; Merritt, R. F. *J. Am. Chem. Soc.* **1961**, *83*, 2019. (b) Moore, W. R.; King, B. J. *J. Org. Chem.* **1971**, *36*, 1877, 1882. (c) Paquette, L. A.; Wilson, S. E.; Henzel, R. P.; Allen, G. R., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 7761. (d) Reinarz, R. B.; Fonken, G. J. *Tetrahedron Lett.* **1973**, 4013. (e) Paquette, L. A.; Zon, G. *J. Am. Chem. Soc.* **1974**, *96*, 203. (f) Paquette, L. A.; Zon, G.; Taylor, R. T. *J. Org. Chem.* **1974**, *36*, 2677. (g) Paquette, L. A.; Taylor, R. T. *J. Am. Chem. Soc.* **1977**, *99*, 5708.

(3) (a) Paquette, L. A.; Browne, A. R.; Chamot, E. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 546. (b) Paquette, L. A.; Browne, A. R.; Chamot, E.; Blount, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 643.

(4) Benzene has supplanted ether as the solvent originally employed for this step because it precludes formation of carbene insertion products into the reaction medium.

(5) The X-ray determinations were carried out jointly by Dr. Judith Gallucci (The Ohio State University) and Dr. Jan M. Troup and Dr. Paul N. Swepston of Molecular Structure Corporation (College Station, TX).

(6) Tanida, H.; Hata, Y. *J. Org. Chem.* **1965**, *30*, 977.

(7) Paquette, L. A. *Acc. Chem. Res.* **1971**, *4*, 280.

(8) Two isomeric polyolefinic hydrocarbons are produced concurrently (ca. 25% combined yield). For details of their structure, see ref 3b.

(9) The inversion in chemical shift of the methylene protons encountered as the larger ring is contracted from six- to five-membered has been previously noted and commented upon: Dauben, W. G.; Wipke, W. T. *J. Org. Chem.* **1967**, *32*, 2976.

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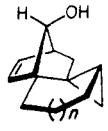
Table I. Calculated Gas-Phase Heats of Formation[a]

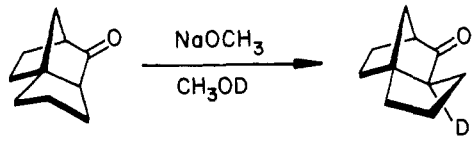
compd	$\Delta H_f°$ (25 °C) $n = 0$	$n = 1$
 3b, 5b	7.36	-3.44
 9	13.44	-0.51
 10	-15.40	-26.64
 11	-8.84	-24.83

[a] MMP2 (OCPE 395).

figuration of the three-membered ring in these products by X-ray crystallographic analysis of 3,5-dinitrobenzoate **5c**,[5] **2** was treated with CF_3COOD in $CHCl_3$ solution. In keeping with the trend, **5e** was produced exclusively within the limits of our spectral analysis. Thus, *full retention of configuration is operational within both series.*

The above results are best reconciled with a mechanism in which only the *central* and not the flanking bicyclobutane subunit experiences initial electrophile-induced cleavage to generate carbocation **6** (Scheme I). As detailed elsewhere,[10,11] two indistinguishable pathways can deliver the requisite stereospecificity. Although the direct[12a] and indirect[12b] routes also cannot be differentiated here, the evidence requires that product formation be triggered via **6**.

At this crucial point, the systems respond by migrating bond a-b of the second bicyclobutane ring to the exclusion of bond b-c. Models of **6** suggest that this distinction is not stereoelectronically driven since both bonds appear to bisect the carbocationic center to a comparable degree. We note, however, that whereas the first option delivers **3** and **5**, the second would lead instead to **9**. MM2 calculations (Table I) of both isomeric systems denote the latter isomers to be significantly less thermodynamically stable. This ordering is comparable to that estimated for the less ornate hydrocarbons **10** and **11**[13,14] and in full agreement with the facile epimerization of ketone **12** to **13**.[15] It is, of course, this migratory event that determines the geometric orientation of the 7-norbornenyl cation in **8** relative to the cyclopropane ring. The presumption is that this facet of the rearrangement is thermodynamic in origin.



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The means with which **1** and **2** adapt to capture by uniparticulate electrophiles[16] has several implications[16,17] which await assessment at the experimental level.

Acknowledgment. Appreciation is expressed to the National Science Foundation for financial support and to Dr. M.-A. Poupart for his assistance with the MM2 calculations.

(10) Wiberg, K. B.; Szeimies, G. *J. Am. Chem. Soc.* **1976**, *92*, 571.
(11) (a) Zon, G.; Paquette, L. A. *J. Am. Chem. Soc.* **1974**, *96*, 215. (b) Paquette, L. A.; Zon, G. *Ibid.* **1974**, *96*, 224 and pertinent references cited in these papers.
(12) (a) Regiospecific edge bond cleavage. (b) Unidirectional SE2-like cleavage of the central bond followed by Wagner-Meerwein shift within the newly generated cyclobutyl cation. Protonolysis of the C-Ag bond is assumed to occur with retention where applicable.
(13) Engler, E. M.; Andose, J. D.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973**, *95*, 8005.
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Enantioselective Synthesis of β-Amino Esters through High-Pressure-Induced Addition of Amines to α,β-Ethylenic Esters

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β-Amino esters **3** are important intermediates in organic synthesis since they are direct precursors of β-lactam derivatives.[1]

Conceptionally, one of the simplest method for the construction of such compounds is through the conjugated addition of amines **2** to α,β-ethylenic esters **1**[2] (Scheme I). A major advantage of this route is the possibility of controlling the stereochemistry at the created asymmetric center (starred in formula **3**) by using an appropriate chiral starting material.

Such an approach was independently investigated by two groups in 1977;[3,4] however, the reported thermally activated addition gave only modest chemical yields and the corresponding diastereoisomeric excesses (de) were low (less than 20%).

In this paper we wish to report two significant modifications that confer an enhanced synthetic value to this reaction: viz., the use of high pressure as an activating agent to produce excellent chemical yields and the use of new chiral inductors (R^2 in **1**) to allow very high stereocontrol at the newly created asymmetric center.

While sluggish under thermal conditions,[3,4] the addition of primary amines[5] to alkyl crotonates is very efficient at room temperature under 5-15 kbar pressures[6] in methanol (Table I).

Our investigations were primarily made with crotonates derived from chiral alcohols since our initial work established that the addition of asymmetric amines to methyl crotonate provides low de (entries 1, 2).[7] As previously reported,[4] *l*-menthyl crotonate was found to give poor de (entry 3). We next examined 8-phenylmenthol (8-PhM) as the chiral inductor since this auxiliary,

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(2) Pfau, M. *Bull. Soc. Chim. Fr.* **1967**, 1117-1125 and references cited therein.
(3) Kinas, R.; Pankiewicz, K.; Stec, W. J.; Farmer, P. B.; Foster, A. B.; Jarman, M. *J. Org. Chem.* **1977**, *42*, 1650-1652.
(4) Furukawa, M.; Okawara, T.; Terawaki, Y. *Chem. Pharm. Bull. (Tokyo)* **1977**, *25*, 1319-1325.
(5) Because of their facile hydrogenolysis, α-substituted benzylamines were used as ammonia equivalents in this addition. Secondary amines (e.g., dibenzylamine) do not add to alkyl crotonates under high-pressure activation conditions.
(6) Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1-26.
(7) This in agreement with previously reported observations.[3,4]

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