New Approach to Bicyclo [5.3.0] Ring Systems

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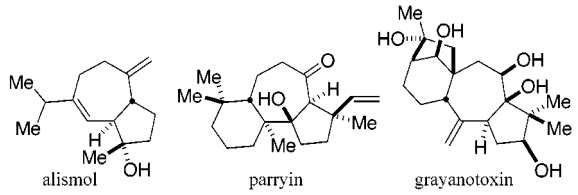
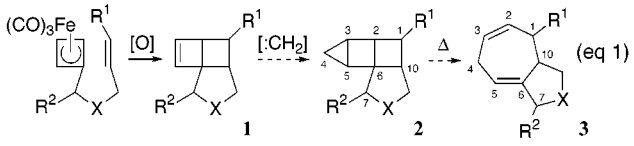
Received February 6, 2001
Revised Manuscript Received April 24, 2001

Natural product targets such as alismol, parryin, and grayanotoxin provide ample motivation for improved strategies toward [5.3.0] ring systems (5−7 ring systems).[1] Herein, we describe a new plan for generating this prevalent carbon framework. The approach relies on the cyclopropanation of highly functionalized cyclobutenes followed by selective fragmentation of the resulting strained adducts.[2]

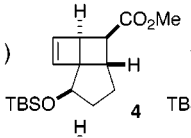
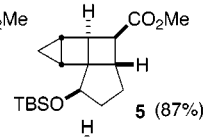
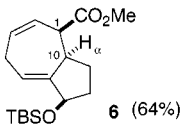
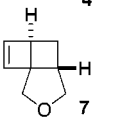
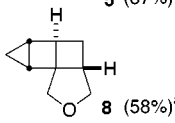
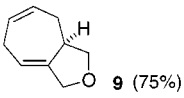
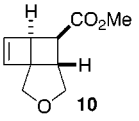
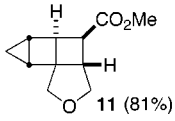
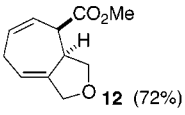
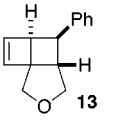
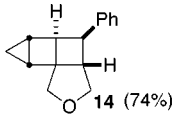
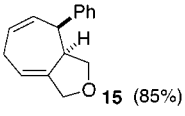
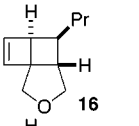
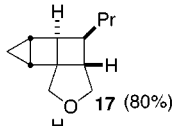
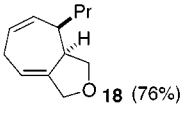
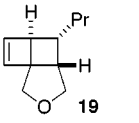
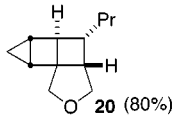


The strategy is illustrated in eq 1.[3] The desired 5−7 target is accessible in two steps from the readily available cyclobutene **1**.[4] The necessary methylene group, as well as additional strain, can be introduced through a cyclopropanation of the cyclobutene substrate **1**. Selective fragmentation of the resulting ring fusion bonds (i.e., C3−C5 and C2−C6) in adduct **2** can then afford the desired 5−7 skeleton **3**.



Of the cyclopropanation methods screened, a modified Simmons−Smith protocol provides the most reliable means of accessing substrate **2**.[5] Several cyclobutenes that have been cyclopropanated selectively are illustrated in Table 1.[6] Despite the presence of functional groups that could direct the stereochemistry of the cyclopropanation (e.g., methyl ester in substrates **4** and **10**),[7] the products obtained arise predominantly from approach of the carbenoid to the less hindered face of the cyclobutene (providing the *anti*-tricyclo[3.2.0.0^{4,2}] ring system).

Table 1. Cyclopropanation and Fragmentation

entry	cyclobutene	cyclopropane (yield)	thermolysis product (yield)
(1)	 **4**	 **5** (87%)	 **6** (64%)
(2)	 **7**	 **8** (58%)[a]	 **9** (75%)
(3)	 **10**	 **11** (81%)	 **12** (72%)
(4)	 **13**	 **14** (74%)	 **15** (85%)
(5)	 **16**	 **17** (80%)	 **18** (76%)
(6)	 **19**	 **20** (80%)	multiple products

[a] Low yield due to product volatility.

Support for the stereochemical assignment was obtained through NMR and X-ray crystallographic studies.[8]

With an effective cyclopropanation in hand, our attention was directed toward converting the cyclopropane adducts to the target 5−7 ring systems. Transition metal-catalyzed ring expansions proved unsuccessful;[9] however, in light of reported thermal fragmentations on related strained-ring systems,[3,10] the strained cycloadducts were subjected to thermolytic conditions.[11]

In general, heating the cycloadducts led to the desired 5−7 ring systems in 64−85% yields (Table 1). As expected from

(1) For representative approaches toward the bicyclo [5.3.0] ring system, see: (a) Snider, B. B.; Yang, K. *J. Org. Chem.* **1990**, *55*, 4392−4399. (b) Kim, D.; Shin, K. J.; Kim, I. Y.; Park, S. W. *Tetrahedron Lett.* **1994**, *35*, 7957−7960. (c) Lange, G. L.; Gottardo, C. *Tetrahedron Lett.* **1994**, *35*, 8513−8516. (d) Davies, H. M. L.; Doan, B. D. *Tetrahedron Lett.* **1996**, *37*, 3967−3969. (e) Wender, P. A.; Rice, K. D.; Schnute, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 7987−7988. (f) Wender, P. A.; Fuji, M.; Husfield, C. O.; Love, J. A. *Org. Lett.* **1999**, *1*, 137−139. (g) Lange, G. L.; Gottardo, C.; Merica, A. *J. Org. Chem.* **1999**, *64*, 6738−6744. (h) Trost, B. M.; Toste, F. D.; Shen, H. *J. Am. Chem. Soc.* **2000**, *121*, 2379−2380. (i) Carroll, G. L.; Allan, A. K.; Schwaebe, M. K.; Little, R. D. *Org. Lett.* **2000**, *2*, 2531−2534.

(2) For other cyclopropanation/fragmentation strategies, see: (a) Takaya, H.; Suzuki, T.; Kumagai, Y.; Yamakawa, M.; Noyori, R. *J. Org. Chem.* **1981**, *46*, 2846−2854. (b) Gassman, P. G.; Han, S.; Chyall, L. J. *Tetrahedron Lett.* **1998**, *39*, 5459−5462.

(3) For a related approach to 5−8−5 ring systems, see: Randall, M. L.; Lo, P. C.-K.; Bonitatebus, P. J., III; Snapper, M. L. *J. Am. Chem. Soc.* **1999**, *121*, 4534−4535.

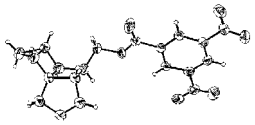
(4) (a) Tallarico, J. A.; Randall, M. L.; Snapper, M. L. *J. Am. Chem. Soc.* **1996**, *118*, 9196−9197. (b) Limanto, J.; Snapper, M. L. *J. Org. Chem.* **1998**, *63*, 6440−6441.

(5) (a) Nishimura, J.; Kawabata, N.; Furukawa, J. *Tetrahedron* **1969**, *25*, 2647−2659. (b) Zercher, C., University of New Hampshire, personal communication. To the best of our knowledge, previously reported Simmons−Smith cyclopropanations of cyclobutenes proceeded in yields of ≤17%. See ref 2a, as well as Gassman, P. G.; Mansfield, K. T. *J. Org. Chem.* **1967**, *32*, 915−920.

(6) Typical cyclopropanation procedure: In a reaction flask CH_2I_2 (10 equiv) was cooled to 0 °C followed by slow addition of diethylzinc (5 equiv) over 15 min. After stirring for 5 min at 0 °C, cyclobutene **1** in CH_2Cl_2 (2.1 M) was added. The reaction was allowed to warm to room temperature and continued to stir for 12 h. Upon complete consumption of cyclobutene, NH_4Cl(aq) was added and allowed to stir for 10 min. The mixture was then extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting clear oil was purified by silica gel chromatography.

(7) For examples of substrate-directed cyclopropanations, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370 and references therein.

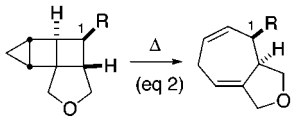
(8) ORTEP plot of 3,5-dinitrobenzoyl ester derived from compound **11**.



(9) For representative examples, see: (a) Gassman, P. G.; Atkins, T. J.; Lumb, J. T. *J. Am. Chem. Soc.* **1972**, *94*, 7757−7761. (b) Wiberg, K. B.; Bishop, K. C., III. *Tetrahedron Lett.* **1973**, 2727−2730. (c) Bishop, K. C., III. *Chem. Rev.* **1976**, *76*, 461−486.

10.1021/ja015640w CCC: $20.00
Published on Web 05/08/2001

Table 2. Influence of Substituent C1 on Thermal Fragmentation



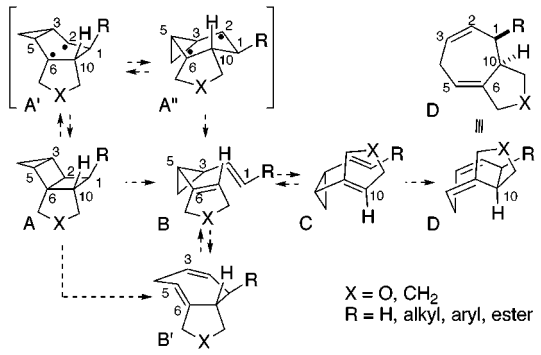
entry	R	temp.
(1)	-CO_2Me	240 °C
(2)	-Pr	180 °C
(3)	-Ph	150 °C
(4)	-C_6H_4*p*-NO_2	190 °C
(5)	-C_6H_4*o*-OMe	130 °C

studies on related systems, the rearrangement is more complex than simple cleavage of the two central carbon−carbon bonds.[10] For example, compared to starting materials, the products possess a configurational inversion at C10 (entries 1−5, Table 1).[12] Moreover, while the thermolysis of substrates with a β substituent at C1 proceed effectively, a mixture of products is obtained when the substrate possesses a C1 substituent in the α configuration (i.e., entry 6).[13]

In addition to the stereochemical issues, the *nature* of the C1 substituent also appears to influence the facility of the rearrangement. While fragmentation of the ester-substituted cycloadduct **11** (or **5**) requires 240 °C to proceed, rearrangement of the propyl-substituted substrate **17** is observed at 180 °C, and rearrangement of the phenyl-substituted cycloadduct **14** occurs at still lower temperatures (i.e., 150 °C). Table 2 summarizes the minimal thermolysis temperatures for a range of substrates differing at the C1 substituent. In general, C1 substituents that stabilize electron-deficient intermediates were found to facilitate the reaction. For example, the *p*-nitrophenyl substituted substrate isomerizes at 190 °C (entry 4), while the electron-rich *o*-methoxyphenyl substrate requires 130 °C for isomerization (entry 5). These stereochemical and kinetic observations support involvement of the bonds neighboring the C1 substituent in the fragmentation process.

A mechanistic rationale that accounts for the fragmentation is suggested in Scheme 1. Cyclopropane **B** is generated from the thermal fragmentation of cycloadduct **A** through either a concerted or stepwise process. After adopting the appropriate conformation, compound **C** can then rearrange to the observed cycloheptadienyl product **D**.[14] Similar to thermal fragmentations of bicyclo[2.2.0]-hexanes, a stepwise diradical cleavage of the tricyclo[3.2.0.$0^{4,2}$] ring system could begin with homolysis of the C2−C6 bond in compound **A**. The resulting diradical **A′** could then undergo relaxation from a boat conformation to a chair (→**A″**) followed by a symmetry-allowed second bond cleavage to generate intermediate **B** (or **B′**).[15] Unfavorable 1,3-interactions arising along this pathway can explain the mixtures observed for substrates possessing a C1 substituent in the α-configuration (i.e., entry 6, Table 1).[16] Moreover, analogous to electronic perturbations of the diradical resonance structure in the Cope rearrangement, the nature of the C1 substituent could influence energy barriers associated with the formation and chemistry of diradicals **A′** and **A″**.[17] This mechanistic possibility accounts for the significant rate enhancement observed with substrates possessing electron-rich substituents at C1 (Table 2). While an initial cleavage of the C3−C5 bond is also possible, the observed product stereochemistry, as well as the higher temperature required for fragmentation of bicyclo[2.1.0]pentanes, argues against this mechanistic pathway.[18]

Scheme 1. Stereochemical Rationale for Fragmentation



On the other hand, cyclopropane **B** could be formed through a concerted [$\sigma 2_S + \sigma 2_A$] fragmentation of the C3−C5/C2−C6 or C2−C6/C1−C10 bonds.[10e] The C3−C5/C2−C6 fragmentation generates the *cis*,*trans*-cycloheptadiene **B′**, which rearranges to cyclopropane **B**, while the latter pathway yields cyclopropane **B** directly. The observed inversion of stereochemistry at C10 in the products is consistent with either of these concerted pathways, as well as the diradical mechanism. Additional studies will be required to provide resolution of these mechanistic issues; nonetheless, the suggested pathways provide a useful and predictive model that accounts for the electronic and stereochemical outcome of the transformation.

The reaction sequence represents a new and rapid means of generating functionalized 5−7 ring systems. Highlighted in the approach is a tandem cyclopropanation/thermal fragmentation of functionalized cyclobutenes. Mechanistic studies, as well as applications toward the synthesis of more complex molecular targets, are presently underway.

Supporting Information Available: We are grateful to the NSF, ACS-PRF, and the NIH (SSS, Postdoctoral fellowship) for generous support of this research. Helpful discussions with Professor Larry T. Scott are also appreciated. M.L.S. also acknowledges the Alfred P. Sloan Foundation, the Camille and Henry Dreyfus Foundation, Glaxo-Wellcome, and DuPont for additional support.

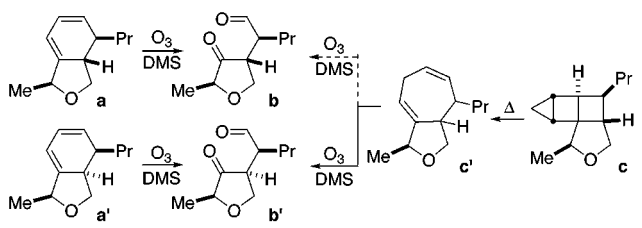
Supporting Information Available: Experimental procedures and data on new compounds are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA015640W

(10) (a) Criegee, R.; Rimmelin, A. *Chem. Ber.* **1957**, *90*, 414−417. (b) Tanida, H.; Teratake, S.; Hata, Y.; Watanabe, M. *Tetrahedron Lett.* **1969**, 5345−5347. (c) Paquette, L. A.; Leichter, L. M. *J. Am. Chem. Soc.* **1971**, *93*, 5128−5136. (d) Paquette, L. A.; Leichter, L. M. *J. Org. Chem.* **1973**, *39*, 461−467. (e) Roth, W. R.; Klärner, F.-G.; Grimme, W.; Köser, H. G.; Busch, R.; Muskulus, B.; Breuckmann, R.; Scholz, B. P.; Lennartz, H.-W. *Chem. Ber.* **1983**, *116*, 2717−2737.

(11) Typical thermolysis procedure: A degassed solution of cyclopropane and BHT (1.5 equiv) in benzene or pentane (c = 10 mM) was heated to 130−250 °C in a heavy-wall sealed tube. The reaction was monitored by GC. Upon consumption of starting material, the reaction mixture was concentrated in vacuo, and the product was purified by silica gel chromatography.

(12) Stereochemical inversion is presumed for entry 2. Stereochemical assignments of the thermolysis products were made through NMR and chemical correlation studies. For example, ozonolysis of dienes **a** and **a′** (of known stereochemistry; ref 4a) provided compounds **b** and **b′**. Oxidation of thermolysis product **c′** provided a compound that was identical to **b′**.



(13) See Table 1 entry 1 or eq 1 for compound numbering.

(14) For lead references of divinylcyclopropane rearrangements, see: (a) Davies, H. M. L. *Tetrahedron* **1993**, *49*, 5203−5223. (b) Hudlicky, T.; Fan, R.; Reed, J. W.; Gadamasetti, K. G. *Org. React.* **1992**, *41*, 1−129. (c) Piers, E. In *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, 971−998.

(15) (a) Wiberg, K. B.; Caringi, J. J.; Matturro, M. G. *J. Am. Chem. Soc.* **1990**, *112*, 5854−5861. (b) Goldstein, M. J.; Benzon, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 5119−5121. (c) Paquette, L. A.; Schwartz, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 3215−3217. (d) Roth, W. R.; Martin, M. *Tetrahedron Lett.* **1967**, 3865−3866.

(16) Schneider, M. P.; Rau, A. *J. Am. Chem. Soc.* **1979**, *101*, 4426−4427.

(17) For example, see: Hrovat, D. A.; Chen, J.; Houk, K. N.; Borden, W. T. *J. Am. Chem. Soc.* **2000**, *122*, 7456−7460 and references therein.

(18) Wiberg, K. B. *Adv. Alicycl. Chem.* **1968**, *2*, 185−254.