Radical Cation-Mediated Annulation. Stereoselective Construction of Bicyclo[5.3.0]decan-3-ones by Aerobic Oxidation of Cyclopropylamines

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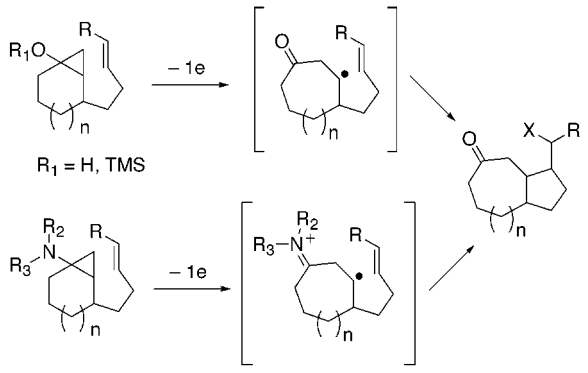
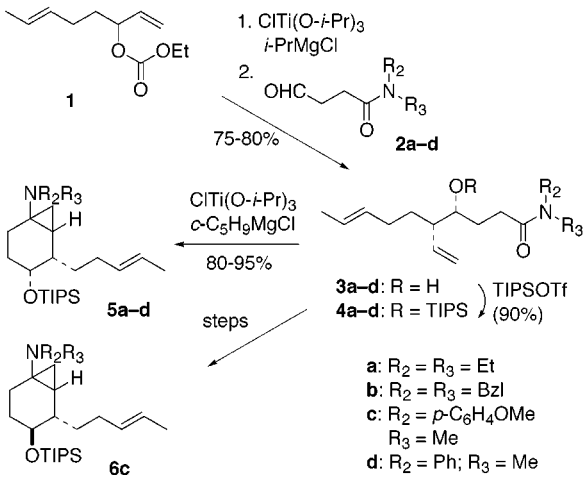
Medium-sized (seven- or eight-membered) carbocyclic rings which are typically embedded in polycyclic systems are found in an increasing number of bioactive natural products. The development of general methods for the construction of medium-sized carbocycles or their annulation onto existing carbocycles has thus become an active area of research.[1] One typical class belongs to hydroazulenic natural products which have prompted a spate of elegant syntheses. Despite many known approaches, conspicuous is the paucity of reliable methods for rapid assembly of functionalized hydroazulenes directly from acyclic substrates.[2] We envisioned the implementation of an intramolecular Kulinkovich cyclopropanation[3,4] of esters or amides and a tandem ring expansion−cyclization sequence of the resulting bicyclic heteroatom-substituted cyclopropanes for the stereocontrolled synthesis of bicyclo[5.3.0]decan-3-ones. The latter transformation was well-precedented by independent studies of the Booker-Milburn and Narasaka groups involving oxidative cleavage of bicyclic hydroxycyclopropanes and subsequent 5-exo cyclization of the resulting β-keto radicals to the pendant olefins (Scheme 1).[5,6] Herein we report analogous cyclization of bicyclic aminocyclopropanes.

The bicyclic aminocyclopropane functionality was chosen over the respective cyclopropanol substrate because of the possibility of tuning or modulating the oxidation potential of the former for facile generation of cyclopropylaminium radical intermediates under mild conditions. An additional advantage based on our earlier observation[7] that an intramolecular Kulinkovich cyclopropanation of carboxamides (especially those containing bulkier *N*-substituents) typically afforded higher yields than that of esters prompted us to investigate the aminium radical-based annulation approach.

Scheme 1



Scheme 2



Toward this end, starting materials were readily prepared by utilizing the addition of an in situ generated allyltitanium reagent to an aldehyde according to the method of Sato (Scheme 2).[8] Thus, slow addition of isopropylmagnesium chloride to a mixture of allylic carbonate **1** and chlorotitanium triisopropoxide in ether, followed by aldehydes **2a**−**d**, afforded the homoallyl alcohols **3a**−**d** in favor of the threo isomer in inseparable 8:1−10:1 mixtures (75−80%). TIPS ethers **4a**−**d** were obtained in 90% yield. Intramolecular cyclopropanation of **4a**−**d** was then achieved in excellent (80−95%) yield by the action of chlorotitanium triisopropoxide and cyclopentylmagnesium chloride to give the bicyclic cyclopropylamines **5a**−**d**.[4b,7,9] Also, the epimer **6c** was prepared by means of Mitsunobu inversion of the alcohol **3c** to examine the effect of a siloxy substituent on the efficiency and diastereoselectivity of the central cyclization (vide infra).

A tandem ring-opening-5-exo-cyclization sequence of **5a**,**b** was next investigated by use of photosensitized and chemical oxidations (Scheme 3).[10] Photosensitized oxidation of **5a** with 1,4-dicyanobenzene (DCB) (5 equiv) in a deaerated solution of 10:1 CH_3CN/MeOH containing 15 equiv of $Cu(OAc)_2$ afforded the annulation product **7** in 59% yield as an inseparable diastereomeric mixture (GC/MS). Photooxidation of **5b** under identical conditions also gave **7** in 60% yield, along with recovered starting material (23%). CAN oxidation of **5b** in CH_3CN containing sodium acetate

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(2) A powerful method has recently been developed by the Wender group by employing metal-catalyzed [5 + 2] cycloaddition of vinylcyclopropanes and alkynes or alkenes: (a) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720. (b) Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 1940. (c) Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc.* **1998**, *120*, 10976. (d) Wender, P. A.; Barzilay, C. M.; Dyckman, A. J. *J. Am. Chem. Soc.* **2001**, *123*, 179.

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(9) Chaplinski, V.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 413.

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Scheme 3

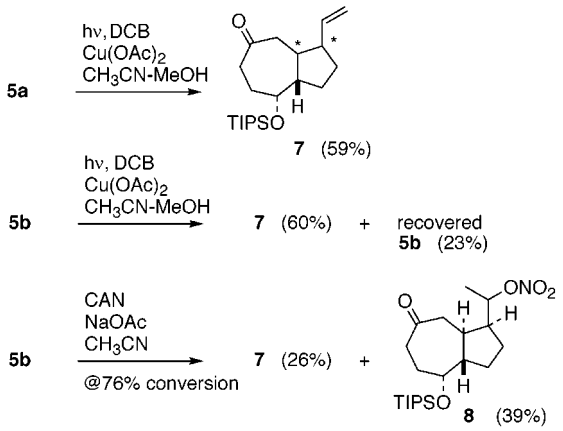
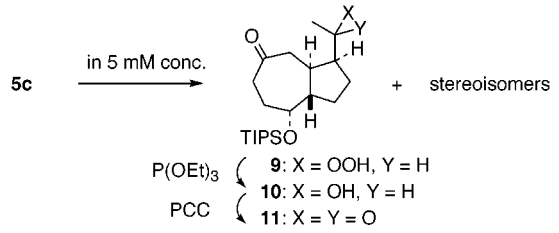


Table 1.



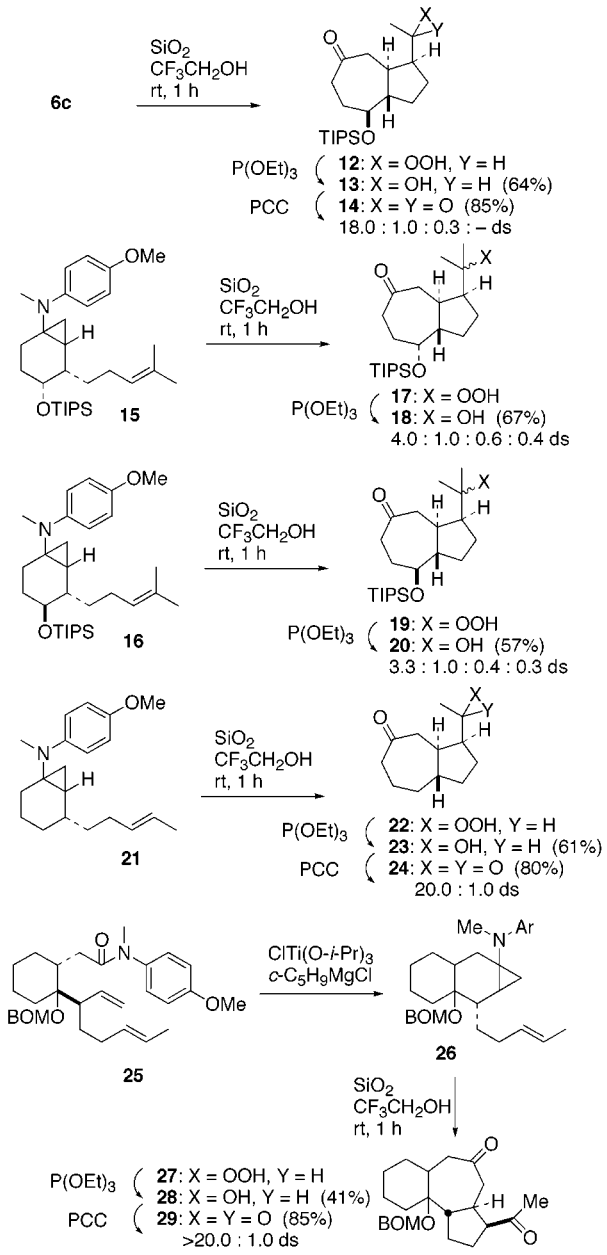
entry	reaction conditions[a]	yield[b]	selectivity[c]
1	MeCN, rt, 3 d	52%	4.5:1.0[d]
2	MeCN, SiO_2, rt, 1 d	65%	9.0:1.0:0.5
3	CF_3CH_2OH, rt, 2 h	58%	8.5:1.0:0.4
4	CF_3CH_2OH, SiO_2, rt, 1 h	68%	17.0:1.0:0.9
5	$(CF_3)_2CHOH$, SiO_2, rt, 0.5 h	75%	8.7:1.0:0.4
6	$(CF_3)_2CHOH$, rt, 0.5 h[a]	68%	9.0:1.0:0.3

[a] Except for entry 6 (in 25 mM), the oxidative cyclization was performed in a 5 mM solution. [b] Purified (silica gel column) yield of **10** and stereoisomers. [c] Selectivity refers to ratios of **10** and diastereomers; determined by GC/MS except for entry 1. [d] Isolation ratio, where the minor fraction contained two isomers.

provided **7**[11] (20%) and the nitrate **8** (30%) (as a single isomer), in addition to recovered starting material (24%).

Next, the *p*-anisidine group was chosen for substituents R_2 (or R_3) to lower the amine oxidation potential.[12] Thus, **5c** was prepared in good yield, and cyclic voltammetry (CV) measurements[13] indicated that its oxidation potential was indeed significantly lower than that of **5b**. More importantly, **5c** was found to slowly undergo oxidative ring opening during silica gel column chromatography. Since molecular oxygen was the only oxidant present, we examined the use of silica gel and fluorocarbon solvents which are known to possess high solubility of oxygen (Table 1). Whereas cyclization took about 3 days in acetonitrile, it was accelerated by the use of silica gel (entries 1 and 2). A more dramatic solvent effect was observed in 2,2,2-trifluoroethanol, where the reaction was complete in 2 h (entries 3 and 4). The overall process became even faster in 1,1,1,3,3,3-hexafluoro-2-propanol (entries 5 and 6). The reaction rate was thus proportional to the increasing solubility of oxygen in solvents; in all solvents comparable yields and good diastereoselectivities were obtained. Particularly noteworthy is the excellent diastereoselectivity for **10** (as 1:1 epimers at the hydroxyl stereocenter,

Scheme 4



following reduction with triethyl phosphite),[14] the stereochemistry of which was assigned, as shown in Table 1 and Scheme 4, based on mechanistic considerations and also by analogy to the respective oxyradical-mediated cyclization.[5,6] The presence and stereochemistry of a siloxy substituent in the ring has an insignificant effect on the diastereoselectivity of the 5-hexenyl radical cyclization. The use of a trisubstituted olefin (e.g., **15** and **16**) as the radical acceptor results in lower diastereoselectivity, which may be considered as an outcome of the reactivity−selectivity principle. It should be emphasized that the use of the *p*-anisidine group for the *N*-substituent is central to facile aerobic oxidative ring opening of the aminocyclopropanes. For example, the *N*-phenyl derivative **5d** proved to be unreactive under identical reaction conditions.

Mechanistically, the overall transformation can best be explained by initial formation of the tertiary aminium radical **A** and

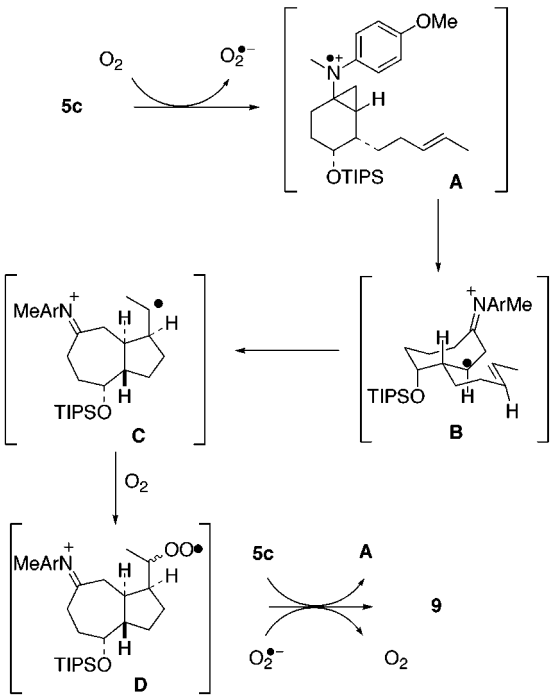
(11) The product **7** from CAN oxidation comprised four inseparable diastereomers in a 63:26:7:4 ratio (GC/MS).

(12) Aryl-substituted and strained cyclopropanes are known to undergo facile photosensitized ring opening via the corresponding radical cations: (a) Rao, V. R.; Hixson, S. S. *J. Am. Chem. Soc.* **1979**, *101*, 6458. (b) Dinnocenzo, J. P.; Simpson, T. R.; Zuilhof, H.; Todd, W. P.; Heinrich, T. *J. Am. Chem. Soc.* **1997**, *119*, 987 and references therein.

(13) Available in Supporting Information.

(14) (a) Inseparable (8:1−10:1) diastereomeric mixtures of the cyclopropylamines were subjected to the aminium radical cyclizations. Fortuitously, the major products (i.e., **10**, **13**, **18**, **23**, and **28**) were separated by column chromatography from a cluster of their remaining diastereomers. (b) The origin for the improved diastereoselectivity, compared to that of photochemical and chemical oxidation, is unclear at the present time.

Scheme 5



superoxide by one-electron oxidation with molecular oxygen (Scheme 5).[15] The ensuing ring cleavage of **A** generates the ring-expanded, β-immonium carbon radical **B**, which undergoes 5-hexenyl cyclization to afford **C**. Clearly, opening of the cyclopropane ring takes place faster than α-CH deprotonation, a well-documented alternate reaction pathway for tertiary aminium radicals.[16] Under our reaction conditions, the 5-exo closure of **B** is faster than its addition to oxygen, the rate of which was reported to be diffusion-controlled (i.e., $k > 10^9$ M^{-1} s^{-1}).[17] The stereochemistry of **C** involving the *trans*-fused ring junction and the *cis*-side chain is anticipated in terms of the chairlike conformation having the alkenyl side chain equatorial by adaptation of the Beckwith model and also in accord with literature precedents.[5,6,18] Subsequent trapping of **C** by oxygen then affords the peroxy radical **D** as a 1:1 epimeric mixture. Although the precise pathway for **D** → **9** is unknown, an electron transfer between **D** and **5c** could be involved as the chain propagation step leading to the corresponding hydroperoxide (hydrolysis of which affords **9**) and **A**.[15a] Alternatively, the hydroperoxide could be formed by an electron transfer with superoxide.[19]

In summary, we have developed a stereocontrolled synthesis of bicyclo[5.3.0]decan-3-ones, starting with readily available acyclic substrates, by employing an intramolecular Kulinkovich cyclopropanation of olefin-tethered amides, followed by a tandem ring expansion−cyclization sequence of the resulting bicyclic aminocyclopropanes by aerobic oxidation. Facile generation and applications of aminium radicals are particularly noteworthy and provide a useful entry to growing examples of radical cation chemistry in the carbon−carbon bond-forming reactions under mild conditions.[20]

Acknowledgment. This work is dedicated to Professors Thomas and Constance Harris on the occasion of their retirement. We thank the National Science Foundation (CHE98-13975) and the National Institutes of Health (GM35956) for generous financial support. We are also indebted to Drs. Jinhwa Lee and Jae Du Ha for preliminary experiments.

Supporting Information Available: CV measurements of **5b** and **5c**, typical experimental procedures, and characterization data of key intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Higher concentrations of oxygen would be detrimental by scavenging the radical **B** prior to 5-exo cyclization. The desired cyclization was anticipated to increase with increased lifetime of the 5-hexenyl radical **B**, as was the case with autoxidation reactions: Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1970**, *92*, 6609.

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