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Electrophilic Cyclizations of Vinylcyclopropanols to Tethered Aldehydes

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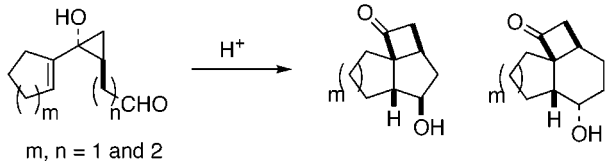
ABSTRACT



The intramolecular, stereoselective addition of 1-vinylcyclopropanols to tethered aldehydes has been achieved under mild conditions. Thus, sequential application of the titanium-mediated cyclopropanation of α,β-unsaturated esters and the electrophilic cyclization of the aldehyde-tethered cyclopropanol products provides the facile formation of carbocyclic rings.

Cyclopropanes have found frequent use in organic synthesis because of their high level of strain. Heteroatom-substituted cyclopropanes exhibit enhanced reactivity and also allow for convenient methods for regio- and stereocontrolled ring cleavage.[2,3] Attachment of an olefin functionality to heteroatom-substituted cyclopropanes generates several useful manifolds for ring opening, expansion, rearrangement, and cyclization reactions. For example, Trost and co-workers elegantly utilized the enhanced nucleophilicity of the trimethylsilyl ethers of 1-vinylcyclopropanols in cationic initiated cyclizations.[4] Herein we report the intramolecular, stereoselective addition of a 1-vinylcyclopropanol to a tethered aldehyde under mild conditions.

The requisite vinylcyclopropanols **4**−**8** were stereoselectively prepared in 53−77% yields by the Kulinkovich cyclopropanation of commercially available methyl 1-cyclopentene-1-carboxylate or methyl 1-cyclohexene-1-carboxylate with terminal olefins **1**−**3** (Scheme 1), followed by standard desilylation (89−93%).[5−7] The titanium-mediated cyclopropanation of α,β-unsaturated esters generally afforded lower yields than that of saturated esters. Nonetheless, this

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(2) For general reviews, see: (a) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (b) Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 899−970. (c) Piers, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 971−988. (d) Bronson, J. J.; Danheiser, R. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 999−1035.

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(7) An alternative preparation of 1-vinyl-1-cyclopropanols involves the condensation of diphenylsulfonium cyclopropylide with ketones and subsequent treatment of the resulting oxaspiropentanes with lithium diethylamide: (a) Trost, B. M.; Boddanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5311. (b) Boddanowicz, M. J.; Trost, B. M. *Org. Synth.* **1974**, *54*, 27.

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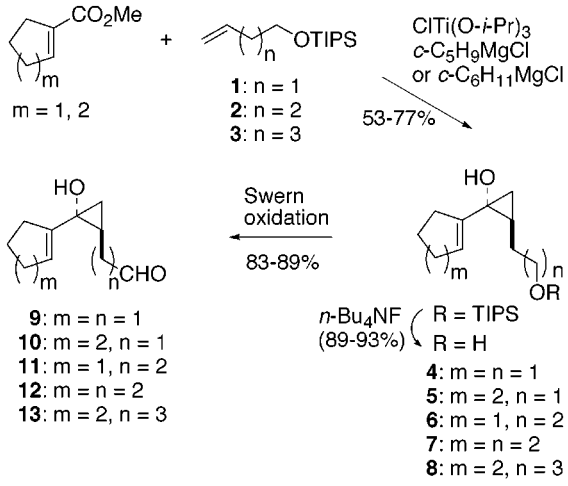
Scheme 1

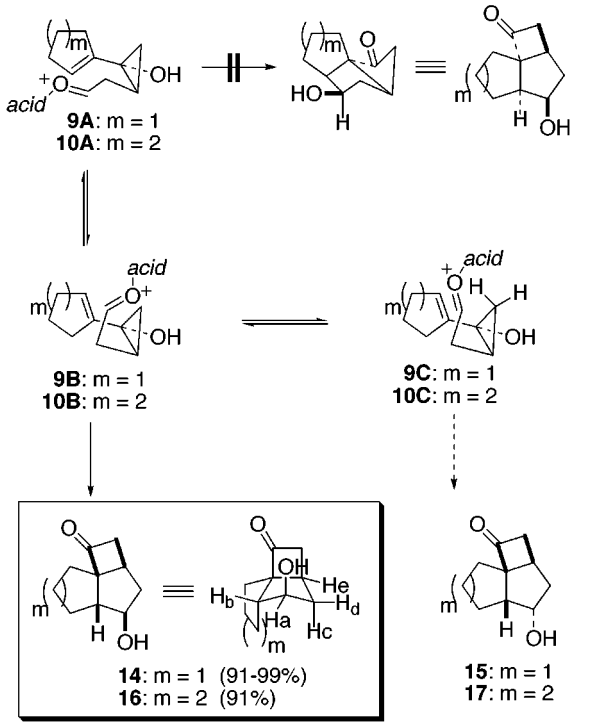


convenient procedure, which employed readily available starting materials and was also tolerant of a wide range of functional groups, more than offset the moderate to good yields of the vinylcyclopropanols observed.

Oxidation of the primary alcohols **4**−**8** was most conveniently achieved by Swern oxidation (1.5 equiv of oxalyl chloride and 2.5 equiv of DMSO in CH_2Cl_2, followed by 5.0 equiv of Et_3N) to afford the corresponding aldehydes **9**−**13** in good (83−89%) yields, along with small amounts of the methylthioether (protected at the tertiary hydroxy group) aldehydes.[8] When larger amounts of oxidants were employed, the yields of the latter protected aldehydes were increased at the expense of the former free aldehydes. Alternatively, the Nozaki [$RuCl_2(PPh_3)_3$] or Saigo−Mukaiyama procedures could also be utilized to circumvent the formation of the methylthio aldehydes.[9]

Treatment of the aldehyde **9** with a mild acid such as PPTS or silica gel at room temperature resulted in facile cyclization to give the tricyclic cyclobutanone **14** (IR 3440, 1763 cm^{-1}) as a single diastereomer in nearly quantitative yield (Scheme 2). The stereochemistry of the hydroxyl group was assigned by observation of the key diagnostic coupling constants, i.e., $J_{Ha-Hb} = J_{Ha-Hd} = J_{Hd-He} = 0$ Hz, which identified the respective dihedral angles to be approximately 0°.[10a,b] The stereochemical determination of **14** (as the TIPS ether) was facilitated by its rigid tricyclic skeleton and also supported by difference NOE measurements. Facile cyclization could undoubtedly be attributed to the known propensity of a

Scheme 2



cyclopropyl ring to stabilize an adjacent positive charge. Among four likely transition states for the cyclization, a Wagner-Meerwein type migration sequence, two of these [**9A** and its carbonyl rotamer (structure not shown)] could be easily discounted because of a prohibitively high activation barrier leading to a trans-fused cyclobutanone ring. With regard to the two alternative boatlike transition states (**9B** and **9C**), a priori, it would seem difficult to predict their relative energies. As depicted in Scheme 2, the cyclization was believed to proceed via **9B** leading to **14** in preference to **15** via **9C**. The cyclization of the homologous aldehyde **10** by the action of PPTS gave the tricyclic cyclobutanone **16** in 91% yield with a 15:1 (GC/MS) diastereoselectivity. The stereochemistry of the major product **16** was determined by similar observations of the distinctive ^3J values, as well as difference NOE measurements.[10c] The diastereoselective formation of **16** was presumed to proceed by a pathway (i.e., **10B**) identical to that leading from **9B** to **14**.

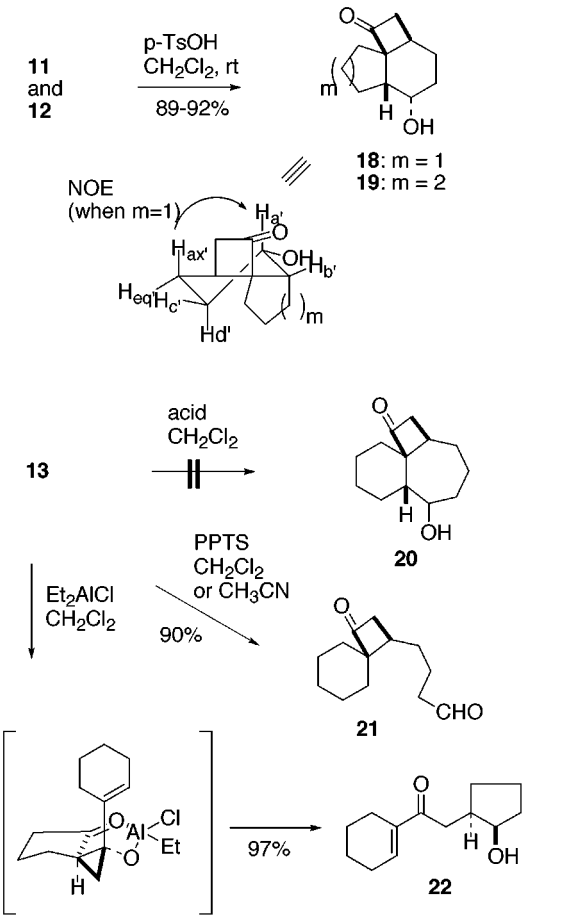
The efficiency and the stereochemistry of the cyclization reactions of the homologues **11** and **12** were next examined (Scheme 3). Both aldehydes readily underwent cyclization (with *p*-TsOH, rt) to afford **18** and **19** in 89% and 92% yield, respectively, as the sole products. Particularly noteworthy was the stereochemistry of the hydroxyl group of **18** and **19**, which was found to be opposite to that of **14** and **16**. The stereochemical assignment of **18** rested on an informative NOE to the proton $H_{a'}$ (δ 3.88 ppm) on irradiation of the axial proton $H_{ax'}$, along with evaluation of the *J* values.[11a] On the basis of similar coupling patterns exhibited by **18** and **19**, the α-stereochemistry was assigned to the hydroxyl group of **19** as well.[11b] Inspection of the molecular models indicated that the transition states leading to the unobserved

(8) Compare: Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc*. **1995**, *117*, 9919.

(9) (a) Tomioka, H.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett*. **1981**, *22*, 1605. (b) Narasaka, K.; Morikawa, A.; Saigo, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn*. **1977**, *50*, 2773. See also: (c) Meyers, A. I.; Comins, D. L.; Roland, D. M.; Henning, R.; Shimizu, K. *J. Am. Chem. Soc*. **1979**, *101*, 7104.

(10) Chemical shifts of selected protons. (a) For the TIPS ether of **14** (≡**23**): (360 MHz, $CDCl_3$) δ 4.35 (d, J = 4.5 Hz, H_a), 2.70 (t, J = 8.8 Hz, H_b), 2.46 (m, H_e), 2.18 (m, H_c), 1.95 (d, J = 14.1 Hz, H_d). (b) The individual proton and carbon chemical shifts of **23** were secured by COSY and HETCOR spectra. (c) For **16**: (360 MHz, $CDCl_3$) δ 4.11 (d, J = 4.2 Hz, H_a), 2.09 (dd, J = 6.0, 12.8 Hz, H_b), 2.57 (ddd, J = 3.3, 8.3, 9.5 Hz, H_e), 2.31 (ddd, J = 4.2, 8.3, 14.5 Hz, H_c), 1.83 (d, J = 14.5 Hz, H_d).

Scheme 3



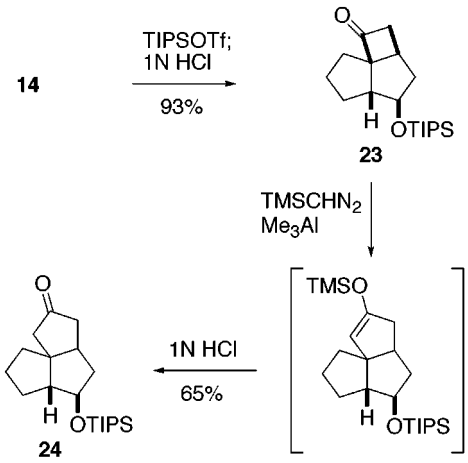
β-hydroxy isomers (i.e., analogous to **9B** and **10B**) suffered from severe nonbonded interactions between one of the hydrogen atoms of the cyclopropane ring and the carbonyl oxygen. Hence the divergence in the conformational preference between the five-membered and six-membered ring closure.

Not surprisingly, extension of the intramolecular cyclization procedure to the next homologue **13** failed to furnish the respective cycloheptanol product **20**. The cyclization of **13** gave different products depending on the type of acid. Treatment with a protic acid (PPTS or *p*-TsOH) resulted in a ring expansion to give the cyclobutanone **21** in 90% yield. Use of a Lewis acid such as Et_2AlCl at −78 °C or room temperature afforded the facile formation of cyclopentanol **22**, in 97% yield, presumably as a consequence of the involvement of an aluminum homoenolate.[3a] The stereochemistry of **22** was tentatively assigned, as depicted in Scheme 3, on the basis of mechanistic considerations.

It is useful to compare the electrophilic cyclization of 1-vinyl-1-cyclopropanols to aldehydes tethered to a distal position to that involving a proximal tether. Trost first developed an imaginative use of the vinylcyclopropanol "composite" functional group as an efficient terminator in electrophilic cyclizations to the proximal oxonium ions derived from acetals.[4,12] Particularly noteworthy was the convenient formation of six-, seven-, and eight-membered rings containing the spirocyclobutanones. Our complementary work utilizing a distal tether afforded the stereoselective formation of five- and six-membered rings bearing the fused cyclobutanones but was limited to the formation of five- and six-membered rings as a result of other competing pathways for longer tethers.

To illustrate the synthetic utility of the intramolecular electrophilic addition reactions of 1-vinyl-1-cyclopropanols, we developed a short, new route to the triquinane skeleton[13] by making use of cyclobutanone **14** (Scheme 4). Sequential

Scheme 4



treatment of **14** with triisopropylsilyl triflate and 1 N HCl gave **23** in 93% yield. Trimethylaluminum-mediated one-carbon ring enlargement of **23** by $TMSCHN_2$ took place smoothly according to the method of Yamamoto to afford a triquinane **24** in 65% yield.[14,15]

In summary, an electrophilic cyclization of vinylcyclopropanols to the tethered aldehydes has been developed to afford the tricyclic cyclobutanones, which contain useful functionalities for further elaboration. The present method nicely complements Trost's closely related cyclizations of vinylcyclopropanols to the oxonium ions derived from acetals that are tethered proximal to the olefinic group. Sequential application of the titanium-mediated cyclopropanation of α,β-

(11) Chemical shifts of selected protons, (a) For **18**: (360 MHz, $CDCl_3$) δ 3.88 (ddd, J = 3.2, 4.6, 7.2 Hz, H_a), 2.31 (m, H_b, where J_{Hb-Ha} = 4.6 Hz), 2.14 (m, H_{eq}), 1.60 (m, H_c), 1.59 (m, H_d), 1.37 (m, H_{ax}). (b)The analogous NOE interactions could not be measured, as the respective $H_{ax'}$ of **19** was not well resolved from a cluster of peaks: δ 3.94 (ddd, J = 3.7, 6.1, 7.0 Hz, $H_{a'}$, where $J_{Ha'-Hb'}$ = 6.1 Hz), 2.21 (m, $H_{eq'}$), 1.92 (ddd, J = 4.9, 6.1, 9.2 Hz, $H_{b'}$), 1.82 (m, $H_{c'}$), 1.65 (m, $H_{d'}$), 1.61 (m, $H_{ax'}$).

(12) For related "Prins-pinacol" reactions, see: (a) Overman, L. E.; Pennington, L. D. *Can. J. Chem.* **2000**, *78*, 732. (b) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352 and references therein.

(13) For recent reviews, see: (a) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671. (b) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1. See also: (c) Hanson, J. R. *Nat. Prod. Rep.* **1992**, *9*, 481.

(14) (a) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Synthesis* **1994**, 1283; *J. Org. Chem.* **1994**, *59*, 4725. See also: (b) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1980**, *21*, 4619.

(15) An alternative strategy could involve ring expansion of a vinylcyclobutanol intermediate; compare: Kocovsky, P.; Dunn, V.; Gogoll, A.; Langer, V. *J. Org. Chem.* **1999**, *64*, 101.

unsaturated esters and the electrophilic cyclization of the aldehyde-tethered cyclopropanol products should be of utility in the facile formation of carbocyclic rings.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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