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Diastereoselective Synthesis of *cis*-1,2-Dialkenylcyclopropanols and Subsequent Oxy-Cope Rearrangement

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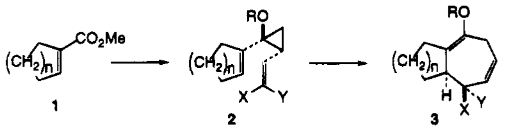
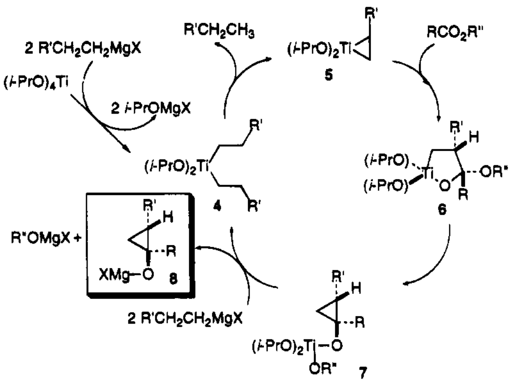
Development of a general synthetic method for the construction of seven-membered carbocycles or the annulation of a seven-membered ring onto an existing carbocycle has been an active area of research, in part due to a wide occurrence of hydroazulenic sesquiterpenes and related bicyclic natural products.[1] Among many elegant synthetic methods that have emerged, the Cope rearrangement of *cis*-divinylcyclopropanes proved to be of considerable synthetic utility.[2–5] Herein we report a diastereoselective synthesis of *cis*-1,2-dialkenylcyclopropanols (**2**: R = H and *tert*-butyldimethylsilyl) and subsequent oxy-Cope rearrangement (**2** → **3**) under relatively mild conditions.[6]

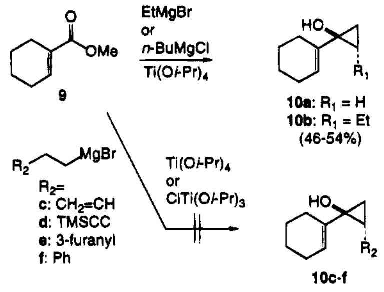


We envisioned that a convenient assembly of *cis*-1,2-dialkenylcyclopropanols could be developed by the Kulinkovich hydroxycyclopropanation, which involves treatment of a carboxylic ester with an excess (3 equiv) of Grignard reagent at −78 to 0 °C in the presence of Ti(O-*i*-Pr)$_4$ (1 equiv), affording 1-alkylcyclopropan-1-ols in good yields![7] In the case of 2-phenethylmagnesium bromide, Kulinkovich and co-workers documented the formation of the corresponding *cis*-1,2-disubstituted cyclopropanols.[7b] They also developed a catalytic process [2 equiv of Grignard reagent, 5–10 mol % Ti(O-*i*-Pr)$_4$, ether, 20 °C] and put forth an attractive reaction mechanism which involves the formal "double alkylation" of titanacyclopropane intermediate **5** (Scheme 1).[7cd,8–10] More recently, Corey reported an improved procedure for this hydroxycyclopropanation, along with the unequivocal determination of exceptionally high diastereoselectivity for *cis*-1,2-disubstituted cyclopropanols and an enantioselective version mediated by a chiral C_2-symmetric diol ligand.[11]

Scheme 1



Scheme 2



Our initial efforts were directed at the application of the Kulinkovich cyclopropanation to commercially available methyl 1-cyclohexene-1-carboxylate (**9**) (Scheme 2). Addition of EtMgBr or *n*-BuMgCl to **9** in the presence of Ti(O-*i*-Pr)$_4$ under catalytic conditions gave the expected cyclopropanols **10a** and **10b**, respectively (46–54%; unoptimized yield). However, none of the desired product was isolated from the use of $CH_2{=}CHCH_2CH_2MgBr$ under identical reaction conditions; a complex mixture of the unidentified products was found. No cyclopropanols were obtained from (2-(3′-furanyl)ethyl)magnesium bromide[12] or 2-phenethylmagnesium bromide.[13] If the reactions

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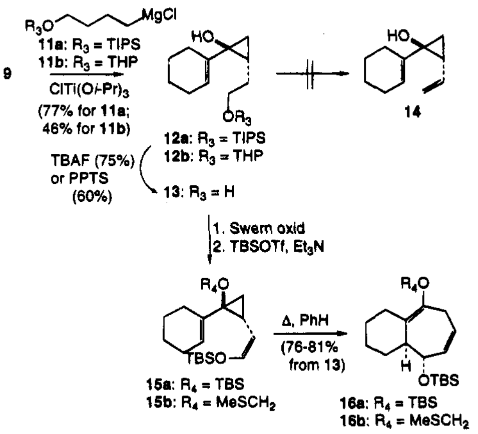
Scheme 3



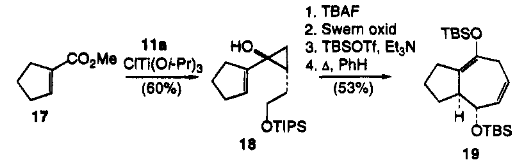
with these substrates had been successful, this procedure would have provided a one-step synthesis of the requisite substrates for the subsequent oxy-Cope rearrangement.

These disappointing results prompted us to employ a 4-alkoxybutyl Grignard reagent. Indeed, both reagents **11a,b** gave the desired cyclopropanols **12a,b** in 77% and 46% yield (under stoichiometric conditions), respectively (Scheme 3). Removal of the protecting group provided alcohol **13** as a single isomer. Unfortunately, several attempts to convert **13** into olefin **14** were unsuccessful. This unexpected difficulty was circumvented by the formation of the silyl enol ether: 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) of alcohol **13**, followed by treatment with TBSOTf and triethylamine,[14] resulted in the exclusive formation of the (*Z*)-silyl enol ether **15a** ($J = 5.9$ Hz), along with a small amount of **15b**. When heated at reflux in benzene, the enol ethers underwent the oxy-Cope rearrangement to provide bicyclic cycloheptadiene **16a** in 72% overall yield from **13**, along with 4% of **16b**.[15] The stereochemical assignment of **16a** was initially made by consideration of the transition state for the Cope rearrangement of divinylcyclopropanes and was unequivocally confirmed by difference NOE spectroscopy of cyclopropane **20**, which was readily prepared from cyclopropanation of **16a** (vide infra).[16]

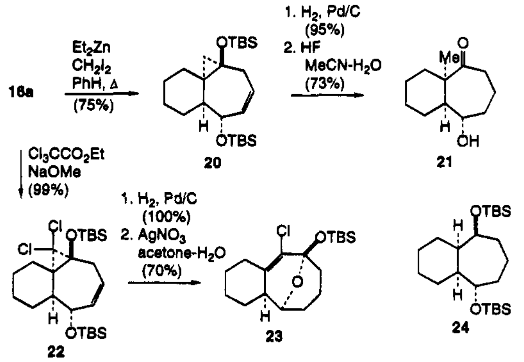
Oxidation of alcohol **13** could also be accomplished by the Saigo−Mukaiyama protocol[17] or TPAP.[18] As outlined above, the resulting aldehyde was then directly converted into cycloheptadiene **16a** in 69% and 57% overall yield (from **13**), respectively.

The identical synthetic sequence on methyl 1-cyclopentene-1-carboxylate (**17**)[19] afforded hydroazulene **19** in 53% overall yield by means of cyclopropanol **18** (Scheme 4).[20]

Scheme 4



Scheme 5



Having developed a convenient synthetic method for fused bicyclic systems **16a** and **19**, we briefly examined subsequent elaborations of the cycloheptadiene functionality. For example, Simmons−Smith cyclopropanation (CH_2I_2, Et_2Zn)[21] of **16a** gave cyclopropane **20** as a single diastereomer (75%) (Scheme 5). The stereochemical assignment was firmly established on the basis of the NOE difference experiment.[16] Hydrogenation (H_2, Pd/C) of the remaining double bond, followed by treatment with HF in aqueous acetonitrile, produced ketone **21** in 69% overall yield. Treatment of **16a** with dichlorocarbene[22] gave dichlorocyclopropane **22** in nearly quantitative yield. Hydrogenation (H_2, Pd/C), followed by treatment with silver nitrate in aqueous acetone, resulted in one-carbon ring expansion to afford ketal **23**, a bicyclo[6.4.0]dodecanone derivative, in 70% overall yield.[23] Also, hydrogenation (H_2, Pd/C) of **16a** took place readily to give the fully reduced product **24**.

In summary, tandem application on 1-cycloalkene-1-carboxylate of the Kulinkovich hydroxycyclopropanation and the oxy-Cope rearrangement provides a stereoselective synthesis of fused bicyclic compounds (such as bicyclo[5.4.0]undecanes or bicyclo-[6.4.0]dodecanes) bearing several sites for further structural elaboration. Further mechanistic and synthetic studies, as well as the development of enantioselective hydroxycyclopropanation,[20] will be reported in due course.

Acknowledgment. We are grateful to the National Institutes of Health (GM35956) for generous financial support. One of us (J.K.C.) also thanks the National Institutes of Health for a Research Career Development Award (GM00575). We thank Dr. Ken Belmore for the difference NOE measurement of **20**.

Supporting Information Available: Experimental details for the preparation of **12a** and its conversion to **16a** and the characterization data for new compounds (25 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(13) Most of the Grignard reagents in these unsuccessful reactions (including $TMSC{\equiv}CCH_2CH_2MgBr$) were isolated as the hydrocarbons generated from protonation, along with a small amount of the corresponding alcohols. Oxidation of the Ti−C bond with oxygen is known to occur readily: Nakamura, E.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1986**, *108*, 3745.

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(15) No purification is necessary for **13** → **16a,b**.

(16) Difference NOE data of **20** are included in the supporting information.

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(20) Corey's recent finding[11] suggests that the enantioselective cyclopropanation would be readily available by employing a chiral titanium reagent formed by ligand exchange of TADDOL.

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(23) Analogous results obtained for **19** will be published in a full paper.