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Intramolecular Cyclopropanation of Glycals: Studies toward the Synthesis of Canadensolide, Sporothriolide, and Xylobovide

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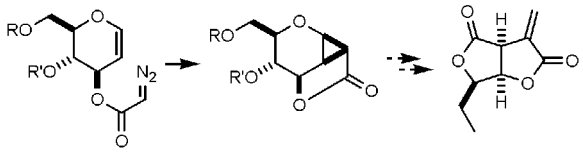
ABSTRACT



The first examples of copper-catalyzed intramolecular cyclopropanations of glycal-derived diazoacetates are reported. The new cyclopropanes are converted into advanced intermediates for the synthesis of bislactone natural products. Synthetic highlights include the selective monodeprotection of a di-*tert*-butylsilylene ether and a zinc-mediated ring opening cascade reaction.

Carbohydrates are an indispensable source of materials for asymmetric synthesis, supported by a history of well-documented functional group transformations.[1] One challenge in carbohydrate chemistry includes developing economical and stereoselective methods for the introduction of new carbon−carbon bonds bearing suitable functional handles.[2] Carbon-branched sugars[3] are found in numerous natural products and have been used as starting materials for indole alkaloid syntheses.[4] They commonly occur in the glycon portion of many antibiotics[5] and have been studied during the elucidation of biochemical pathways.[6] Additionally, naturally occurring macrolides often contain branched polyol sequences, a structural motif that portends an origin from a C-branched sugar.[7]

Glycals continue to attract attention as important substrates for the development of new synthetic methodologies.[8] Their cyclopropanation is a particularly attractive means for the efficient introduction of new carbon bonds onto the sugar backbone. Although the synthesis of cyclopropanated sugars was first described decades ago,[9] their importance continues

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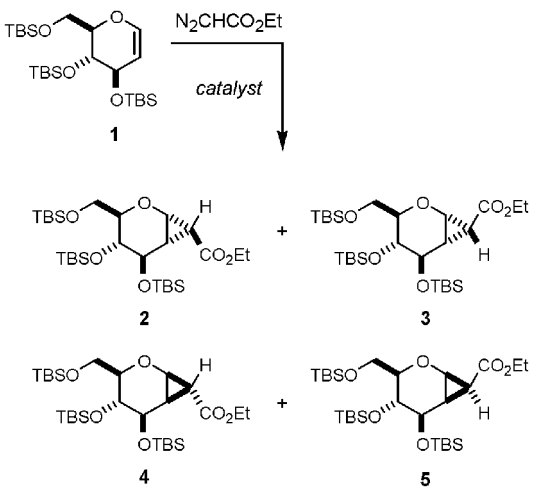
to prompt investigations that offer improved or alternative methods for their preparation.[10] The reactions of vinyl ethers with the Simmons−Smith[11,12] reagent or dihalocarbene[13] provide robust adducts that undergo ring opening reactions with Lewis acids,[12,13] by α alkoxide fragmentation[14] or platinum catalyzed hydration/isomerization.[15,16] The facial selectivity of the intermolecular cyclopropanation of glycal **1** with ethyl diazoacetate showed a pronounced dependency on the nature of the catalyst (Scheme 1).[17] These cyclopropanes possess vicinal functional groups that can in principle work synergistically in a "push−pull" relationship, an arrangement that engenders useful reactivity for further transformations when geminal electron-withdrawing groups are present.[18,19]

Scheme 1[a]

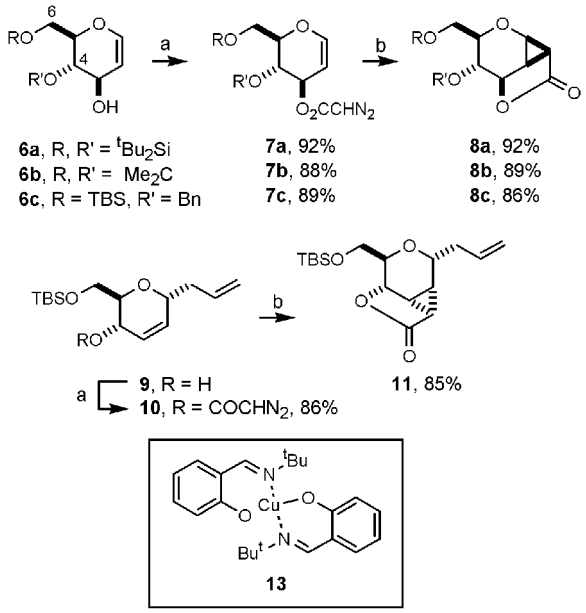


[a] Ratio of **2**:**3**:**4**:**5**: with cat. Cu^0 (ref 17a), 0:0:1:0; with cat. $Rh_2(OAc)_4$ (ref 17c), 31:0:1:0.

Herein we describe the first intramolecular cyclopropanation reactions of glucose-derived glycals and the selective mono-deprotection of a di-*tert*-butylsilylene ether.[20] The new cyclopropane **8a** was transformed by way of a zinc-mediated tandem ring opening reaction sequence into an advanced intermediate for the synthesis of the tetrahydro-furo[3,4-*b*]-furan-2,4-dione core found in several bislactone natural products.

The glycals **6a**,[21] **6b**,[22] and **6c**[23] and olefin **9**[24] were synthesized from D-glucose. The diazoesters shown in Scheme 2 were prepared by a modification of the method reported in the pioneering contribution by Corey and Myers on the intramolecular cyclopropanation of diazoacetates.[25] Treating a dichloromethane/*N*,*N*-dimethylformamide (DMF) solution of glyoxylic acid chloride *p*-toluenesulfonylhydrazone (**12**)[26] and the alcohol sequentially with *N*,*N*-dimethylaniline and triethylamine afforded the diazoacetates in greater than 85% yield. The addition of anhydrous DMF as cosolvent proved crucial for successful acylation, without which less than 5% of the desired diazoesters could be isolated. The cyclopropanations were achieved by the addition of the diazoester ester to a refluxing solution of 5 mol % bis(*N*-*tert*-butylsalicylaldiminato)copper(II) [$Cu(TBS)_2$]

Scheme 2[a]



[a] Conditions: (a) (i) *p*-$TolSO_2NHNCHCOCl$ (**12**), Me_2NPh, DCM/DMF; (ii) Et_3N; (b) 5 mol % **13**, PhMe, reflux.

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(**13**)[27] in either dichloromethane or toluene. Slow addition of the diazoester over 8−12 h was necessary to minimize formation of dimeric fumarates and maleates. The $Cu(TBS)_2$ precatalyst **13** performed admirably in the cyclopropanation reactions examined for this study, whereas other catalysts, including $Rh_2(OAc)_4$, gave lower yields.[28]

Scheme 2 shows that the intramolecular cyclopropanation of glycals is compatible with a variety of protecting groups at the C(4) and C(6) positions, including cyclic silylene or acetonide groups and acyclic benzyl and TBS groups. Each of the cyclopropanes shown in Scheme 2 was formed as an exclusive stereoisomer, as judged by TLC and inspection of the ^1H NMR spectra of the crude reaction mixtures. The stereochemistry of the cyclopropanation product **8a** was unambiguously established by X-ray crystallographic analysis of crystals (mp 199.5−201.0 °C), obtained from ethyl acetate/hexanes, Figure 1. As expected,[25] the cyclopropanation is not limited to electron-rich olefins, and reaction of **10** proceeded with equal efficiency. In addition to the high diastereoselectivity inherent to this intramolecular reaction, the products are formed with equal levels of selectivity regardless of the protecting groups that are employed at C(4) and C(6).

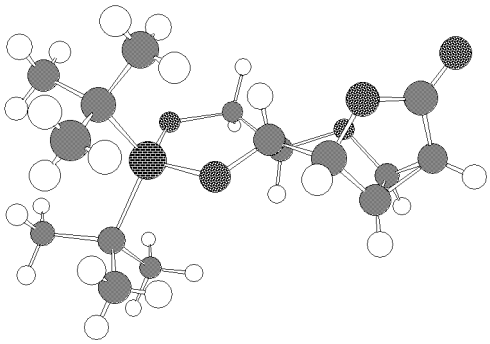

Figure 1. Chem3D representation of the X-ray structure of cyclopropane **8a**.

The phytotoxic natural product xylobovide **20**,[29] the fungicide canadensolide **22**,[30] and sporothriolide **23**,[31] an antibacterial, fungicidal, algicidal, and herbicidal agent, are closely related natural products that differ simply in the length of their side chain. These structures have received considerable attention as synthetic targets, with several reported total syntheses of canadensolide and one of sporothriolide appearing in the literature.[32,33] Inspection of xylobovide reveals that, excluding the exocyclic methylene,[34] all of the carbons with the correct stereochemistry necessary for its synthesis are present in cyclopropanes **8a**−**c**.

To demonstrate the potential utility of this methodology in natural product synthesis, **8a** was converted into the advanced intermediate **19**, which, on the basis of literature precedent,[32g,h] will provide access to xylobovide **20**. The first synthetic task was the removal of the di-*tert*-buyl silylene ether. Complete desilylation with TBAF in THF afforded, as expected, the corresponding diol in 93% yield. However, the possibility of achieving a more interesting monodesilylation of the di-*tert*-buylsilylene ether was explored with this substrate. After some experimentation, it was discovered that treatment of **8a** with $BF_3{\cdot}Et_2O$ in toluene (room temperature to 85 °C, 30 min) in the presence an HF scavenger such as allyltrimethylsilane revealed exclusively the primary alcohol **14** in 95% yield.[35,36] Conversion of alcohol **14** to iodide **15** (ca. 90%, two steps) set the stage for a zinc-mediated reductive ring opening cascade.[37] Addition of iodide **15** to a room-temperature suspension of zinc−copper couple[38] in dry THF resulted in rapid reduction and cleavage of the pyran ether to zinc alkoxide **16**, which spontaneously underwent further ring opening to aldehyde **17**. Aldehyde **17** was converted without purification to the hemiacetal **18** by desilylation of the di-*tert*-butylfluorosilyl ether with HF·pyridine.[39] The di-*tert*-butylfluorosilyl ether protecting group utilized in this reaction sequence proved to be quite robust in the absence of fluoride ion and was labile only upon exposure for several hours to aqueous solutions at extremes of pH.

Reduction of olefin **18** with hydrogen over palladium on carbon provided hemiacetal **19** (96%), which maps[40] nicely onto an advanced intermediate in the Fraser−Reid total

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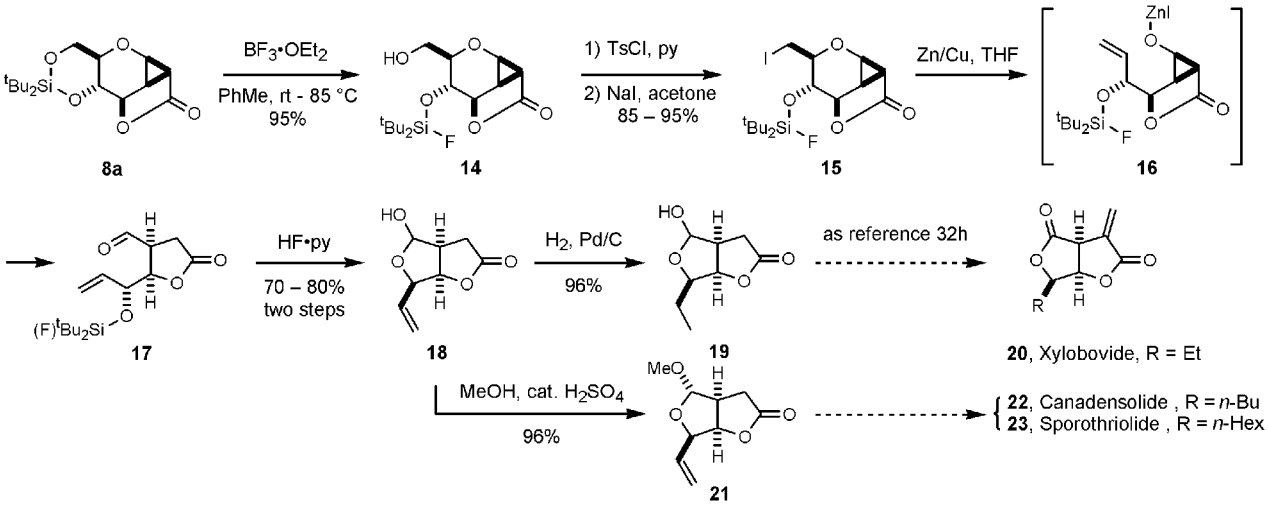
(40) Hemiacetal **19** differs from the canadensolide intermediate only in that it bears an ethyl side chain instead of a butyl.

Scheme 3



synthesis of canadensolide.[32g,h] Additionally, treatment of hemiacetal **18** with catalytic H_2SO_4 in refluxing methanol afforded acetal **21** in 96% yield. The acetal **21** presents a convenient divergence point for the synthesis of canadensolide **22**, sporothriolide **23**, and related structures by oxidative olefin cleavage and Wittig homologation (Scheme 3).

In conclusion, we have prepared advanced intermediates for the synthesis of bislactone natural products by the intramolecular cyclopropanation of glycals. Additionally, we have reported the first monodesilylation of a di-*tert*-buylsilylene ether.

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Supporting Information Available: X-ray structure data and CIF file for **8a** and detailed experimental procedures and characterization of all new compounds (**7**, **8**, **10**, **11**, **14**, **15**, **21**, **24**). This material is available free of charge via the Internet at http://pubs.acs.org.

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