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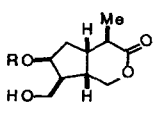
A β-Lactone-Based Route to Cyclopentanes via Intramolecular Allylsilane Additions. An Unexpected Friedel-Crafts Alkylation.

Cunxiang Zhao and Daniel Romo*

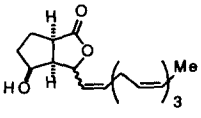
Department of Chemistry , Texas A&M University, College Station, TX 77843-3255

Abstract: Lewis acid promoted intramolecular additions of allylsilanes to β-lactones proceed smoothly to give variously substituted cyclopentanes. A proposed transition state assembly for this reaction guided our efforts to improve the stereoselectivity. A novel Friedel-Crafts alkylation of β-lactones is also described. © 1997 Elsevier Science Ltd.

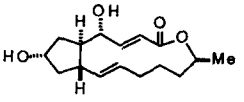
β-Lactones may be viewed as bipolar electrophiles since they can undergo either O-alkyl (oxygen-alkyl) or O-acyl bond cleavage depending on both the nucleophile and reaction conditions employed. For example, β-lactones undergo Lewis acid-promoted, nucleophilic addition via O-alkyl cleavage by pendant nucleophiles such as benzyl ethers to give tetrahydrofurans and tetrahydropyrans and by external nucleophiles to give unnatural amino acids.[1] On the other hand, reaction with aluminum amides or sodium alkoxides leads to O-acyl cleavage to deliver β-hydroxy amides or esters.[1a] As part of a program aimed at further exploiting the reactivity of β-lactones,[1b] we have explored the intramolecular addition of allylsilanes to these strained heterocycles (e.g. **2** → **1**). The resulting acetic acid cyclopentane products **1** resulting from O-alkyl ring cleavage are found in a variety of natural products such as the large iridoid class of which gibboside[2] is a representative member. In addition, these products can be readily converted to other cyclopentane ring systems such as those found in the bacillariolides and the brefeldins.[3] In comparison to related openings of epoxides[4] and aziridines,[5] these reactions uniquely provide cyclopentanes bearing an additional carbon and a carboxylic acid functionality. Our initial results in this area are described in this Letter.



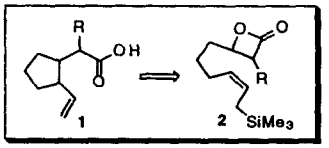
Gibboside
(R = D-glucopyranosyl)



Bacillariolides



Brefeldin A

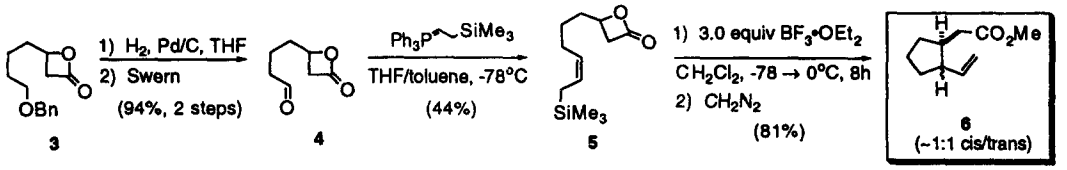


We first studied the intermolecular reaction of allylsilane and allyltributylstannane with a simple β-lactone. However, this gave only the β-hydroxy acid derived from hydrolysis of the β-lactone and polymeric materials presumably derived from Lewis acid catalyzed polymerization of the β-lactone.

We then turned our attention to intramolecular variants of the reaction which we expected would favor the desired O-alkyl ring cleavage of the β-lactone. The β-lactone **5**[6] (>19:1 Z:E) bearing a pendant allylsilane was prepared in three steps from the known β-lactone **3**[7] using the trimethylsilyl Wittig reagent developed by Seyferth[8a] but using NaHMDS as base.[8b] Teatment of β-lactone **5** with BF_3•OEt_2, initially at -78°C followed

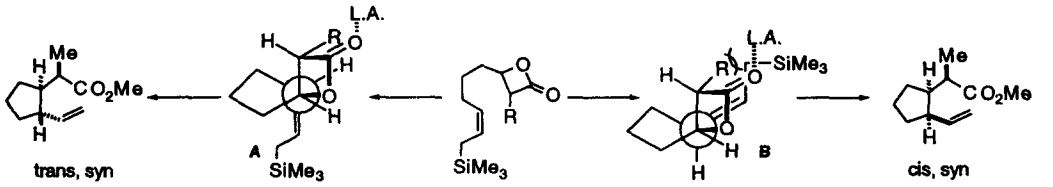
by warming to 0°C, gave two carboxylic acid products. These were directly methylated to give the methyl esters **6** as a ~1:1 ratio (GC analysis) of cis/trans isomers in 81% overall yield for the two steps.

Scheme 1



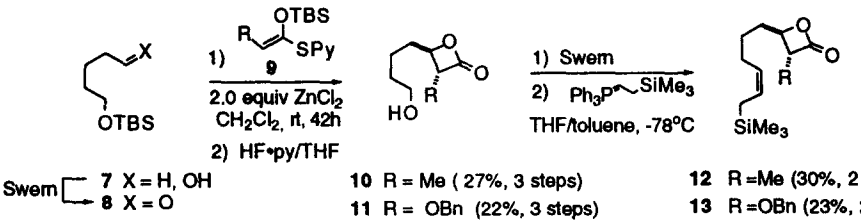
Plausible transition state arrangements for this cyclization leading to the trans and cis diastereomers are shown in Scheme 2. This reasonably explains the lack of selectivity observed in the reaction of β-lactone **5** (R=H) since there is little difference, considering steric or electronic effects, for the two transition states (**A**, **B**).

Scheme 2



Based on these proposed transition state arrangements, we reasoned that introduction of trans-α-substituents on the β-lactone would lead to improved diastereoselection in the cyclization favoring the trans, syn diastereomer as a result of non-bonded interactions between the α-substituent and the methylenetrimethylsilane moiety (Scheme 2, R≠H). Toward this end, the α-methyl-β-lactone **10** and the α-benzyloxy-β-lactone **11** were prepared using a tandem Mukaiyama aldol-lactonization[9] of aldehyde **8** derived from alcohol **7**.[10] Desilylation and oxidation followed by olefination of the β-lactone aldehydes gave the cyclization substrates **12** and **13**.

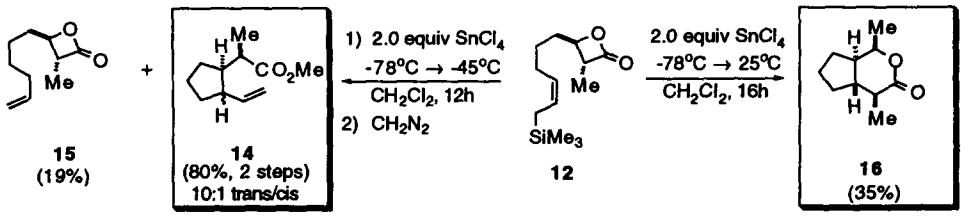
Scheme 3



As expected, cyclization of β-lactone **12** with $SnCl_4$ led to higher trans selectivity (10:1, trans/cis, 200 MHz ^1H NMR) providing the cyclopentane **14** in 80% overall yield after methylation (Scheme 4).[11] A minor product isolated in this reaction was the olefin **15** derived from desilylation and this by-product was formed in greater amounts when $BF_3•OEt_2$ was employed. Interestingly, if the reaction using $SnCl_4$ was allowed to warm to ambient temperature, the bis-cyclization product **16** could be isolated in moderate yield.[12] This product presumably arises from cyclization promoted by adventitious HCl present in the reaction mixture. The stereochemistry of the bis-cyclization product was assigned by a combination of coupling constant analysis and infrared spectroscopy which predicts the half-chair conformation for this bicyclic lactone.[13] The stereochemical outcome is also consistent with the expected reaction mechanism involving an S_N2-like reaction during O-alkyl bond cleavage of the β-lactone as previously observed for other intramolecular nucleophilic additions.[14] The

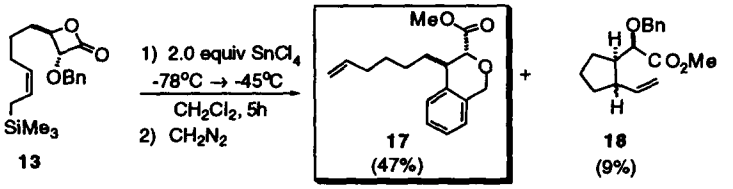
stereochemistry of the major diastereomeric cyclopentane **14** should also be trans since this compound could be converted to the bicyclic lactone **16** on warming the reaction mixture to ambient temperature.

Scheme 4



When the α-benzyloxy-β-lactone **13** was subjected to standard cyclization conditions, the expected cyclopentane product **18** was only obtained as a minor product while the major product was derived from a Friedel-Crafts alkylation (O-alkyl cleavage) leading to isochroman **17** (Scheme 5).[15] Butyrolactones are known to undergo intermolecular Friedel-Crafts alklylations[16] but to our knowledge this is the first example of a β-lactone participating in this reaction. The isochroman **17** was formed in 47% yield as a single diastereomer. Previous studies of intermolecular Friedel-Crafts alkylations with butyrolactones have shown that these reactions proceed with varying degrees of stereospecificity depending on the reaction conditions employed.[17] Although the stereochemistry of isochroman **17** has not been rigorously determined, we have tenatively assigned the trans configuration based on the expectation that the β-lactone **13** undergoes complete inversion during the Friedel-Crafts alkylation. However, we have not excluded the possibility of equilibration following ring formation.[18]

Scheme 5



In summary, we have demonstrated the ability of β-lactones to undergo O-alkyl ring cleavage by Lewis acid mediated, intramolecular nucleophilic addition of allylsilanes. A proposed transition state assembly for this reaction was proposed and guided the modification of a β-lactone substrate that provided higher diastereoselectivity. An unexpected intramolecular Friedel-Crafts alkylation of a β-lactone was also found in the course of these studies. Future studies will focus on improving the synthesis of the cyclization precursors and developing methods to obtain the cis-configured cyclopentanes.

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11. Representative procedure for the cyclization reaction as described for the synthesis of cyclopentane **14**: Allylsilane **12** (52 mg, 0.22 mmol, 1.0 equiv) in 1 mL of dry CH_2Cl_2 was cooled to -78°C under nitrogen. After addition of $SnCl_4$ (0.44 mL of 1.0 M in CH_2Cl_2, 0.44 mmol, 2.0 equiv) and stirring for 5.5 h at -78°C, the mixture was warmed to -45°C and stirred for an additional 6.5 h. The reaction was quenched with a few drops of pH 7 buffer and dried over Na_2SO_4. After concentration in vacuo the crude product was taken up in Et_2O and methylated with excess diazomethane. Concentration in vacuo and purification by flash chromatography (10% ethyl acetate/hexane) gave 7 mg (19%) of olefin **15** and 32 mg (80%) of the cyclopentane **14** as a colorless oil which displayed the following physical and spectral characteristics. An analytical sample was prepared by micro-distillation: R_f 0.64 (20% ethyl acetate/hexanes); ^1H NMR (200 MHz, $CDCl_3$) δ 5.71 (ddd, *J*= 8.3, 10.0, 17.1 Hz, 1H), 4.87-5.03 (m, 2H), 3.63 (s, 3H), 2.50 (app quintet, *J*= 7.0 Hz, 1H), 2.15-2.34 (m, 1H), 1.23-1.91 (m, 7H), 1.15 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.3, 143.1, 113.5, 51.2, 48.4, 47.9, 42.6, 33.6, 29.7, 24.0, 15.8; IR (neat) 3078, 2948, 2875, 1738 cm^{-1}; Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.63; H, 10.00.
12. Data for bicylic product **16**: R_f 0.21 (20% ethyl acetate/hexanes); ^1H NMR (200 MHz, $CDCl_3$) δ 1.21 (d, *J*=7.6 Hz, 3H), 1.34 (d, *J*=6.3 Hz, 3H), 1.10-2.02 (m, 4H), 2.92 (dq, *J*=6.0, 7.6 Hz, 1H), 4.15 (dq, *J*=6.3, 10.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.7, 83.2, 44.2, 42.3, 38.4, 26.8, 26.4, 23.2, 21.2, 13.2; IR (neat) 1726 cm^{-1}; EI HRMS Calcd for $C_{10}H_{16}O_2[M^+]$: 168.1150. Found 168.1138.
13. The stereochemical assignment for bicylic lactone **16** is based on its IR carbonyl absorption, calculated (Macromodel V4.0 MM2*: Mohamadi, G.; Richards, N.G.J.; Guida, W. C.; Liskamp, R.; Caufield, C. Chang, T.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.) versus observed coupling constants, and previous conformational /stereochemical studies of δ-lactones and the structurally related iridiolactones, see: a) Cheung, K. K.; Overton, K. H.; Sim, G. A. *J. Chem. Soc. Chem. Commun.* **1965**, 634-635. b) Sisido, K.; Inomata, K.; Kageyema, T.; Utimoto, K. *J. Org. Chem.* **1968**, *33*, 3149-3155.
14. For an intramolecular cleavage of a β-lactone by a pendant benzylether which proceeds with inversion of configuration, see: Mead, K. T.; Yang, H. *Tetrahedron Letters* **1989**, *30*, 6829-6832.
15. Spectral data for isochroman **17**: R_f 0.36 (20% ethyl acetate/hexanes); ^1H NMR (200 MHz, $CDCl_3$) δ 6.92-7.20 (m, 4H), 5.68-5.90 (m, 1H), 5.12 (d, *J*=15.1 Hz, 1H), 4.83 (d, *J*=15.1 Hz, 1H), 4.88-4.96 (m, 2H), 4.50 (d, *J*=3.0 Hz, 1H), 3.65 (s, 3H), 3.05-3.18 (m, *J*=3 Hz, 1H), 1.96-2.12 (m, 2H), 1.30-1.95 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.2, 138.7, 135.0, 133.0, 128.5, 126.4, 124.2, 114.4, 74.8, 64.9, 52.0, 39.7, 34.8, 33.6, 28.9, 26.4; IR (neat) 1747 cm^{-1}; FAB HRMS Calcd for $C_{17}H_{22}O_3$ [M+H]: 275.1647. Found 275.1628.
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18. Molecular modeling (Macromodel V4.0 MM2*) indicates that the boat and half-chair conformations of isochroman **17** are similar in energy and this may explain why our coupling constant analysis and nOe results are inconclusive. e.g. previously reported ^1H NMR data for 1,3,4-trisubstituted isochromans show the following trends for $J_{H3,\,H4}$: J_{cis}= 1.5-2 Hz and J_{trans}= 7-8.5 Hz (isochroman **17**, $J_{H3,\,H4}$ = 3.0 Hz), see: a) Giles, R. G. F.; Rickard, R. W.; Senanayake, B. S. *J. Chem. Soc. Perkin Trans. 1* **1996**, 2241-2248. b) Giles, R. G. F.; Green, I. R.; Knight, L. S.; Lee Son, V. R.; Yorke, S. C. *J. Chem. Soc. Perkin Trans. 1* **1994**, 865-873. c) Chorn, T. A.; Giles, R. G. F.; Green, I. R.; Mitchell, P. R. K. *J. Chem. Soc. Perkin Trans 1* **1983**, 1249-1254. d) Singh, R.; Singh, R. P. D. Srivastava, J. N. *J. Indian Chem. Soc.* **1991**, *68*, 276-280. (no coupling constants are reported for these 3,4-disubstituted isochromans)

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