A Highly Stereoselective Approach to the Synthesis of Functionalized Pyran Derivatives by Lewis Acid Assisted Ketal Reduction and Allylation

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Reduction of bicyclic ketal **1** gave functionalized pyran derivatives **7a** or **7b** in a highly stereoselective manner, depending upon the reduction conditions utilized. For example, treatment of ketal **1** with $TiCl_4/Et_3SiH$ produced exclusively diol **7b** with the 2,5-*syn* relationship in good yield. Alternatively, reduction of ketal **1** by DIBALH gave 2,5-*anti*-diol **7a** stereoselectively. Alane reductions of ketal **1** were highly stereoselective also; however, the *syn*/*anti* selectivity observed was strongly dependent on the ratio of reagents employed for in situ generation of the alane. Lewis acid catalyzed allylation of ketal **1** gave pyran **10** in a stereospecific alkylation reaction.

Introduction

The Lewis acid catalyzed reduction and alkylation of ketals affords ether derivatives.[1−6] This methodology has proven to be particularly effective for stereo- and enantioselective synthesis.[7−11] The utilization of this chemistry with bicyclic ketals for the stereo- and regioselective synthesis of cyclic ether derivatives has been investigated.[11−13] This approach is particularly well suited to the synthesis of polyether natural products incorporating pyran and furan functionalities with diverse structural complexity.[14−17]

We have previously reported a general approach to the synthesis of bicyclic ketals via oxidation of furfuryl alcohols and applied the methodology to several natural product syntheses including the (+)-pheromone of the male swift moth *Hepialus hecta L*[18] and tirandamycins A and B.[19,20]

It was noted that reductive ring opening of these bicyclic ketals (i.e., **1**) would yield highly functionalized ether derivatives that could then be employed in the syntheses of natural products.[21] For example, opening of bicyclic ketal **1** could yield either pyran **2** or oxepin **3**, depending on the regioselectivity of the bond cleavage (Scheme 1). In this paper, it is demonstrated that Lewis acid catalyzed reduction and allylation of bicyclic ketal systems occurs in a highly regio- and stereoselective manner to afford pyran derivatives.

Results and Discussion

Bicyclic ketal **1** was synthesized by initial oxidation of furfuryl alcohol **4** followed by a series of steps to generate key intermediates (Scheme 2).[22] Furfuryl alcohol **4** was oxidized with *m*-chloroperoxybenzoic acid, which resulted in a 10:1 mixture of anomeric pyranones, **5**. Cyclization of **5** under acidic conditions afforded bicyclic enone **6**. Reduction of enone **6** under Luche conditions[23] yielded bicyclic allylic alcohol **1**. As a result of the concave shape of bicyclic enone **6**, only the exo face is accessible to the reducing agent, and only the endo allylic alcohol **1** is observed.

The goal at the outset was to develop methodology such that reductive opening of ketal **1** would yield either *syn*- or *anti*-pyran derivatives, depending on the Lewis acid/reducing agent combination employed. Diisobutylaluminum hydride (DIBALH)[11,13,15,16] is an effective reducing agent for bicyclic ketal systems, affording predominantly the product resulting from reduction with retention of configuration. That is, the C,O-bond cleavage and subsequent C,H-bond formation occur with overall retention.

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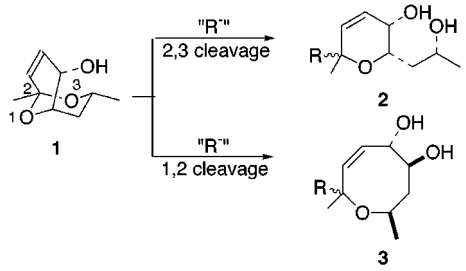
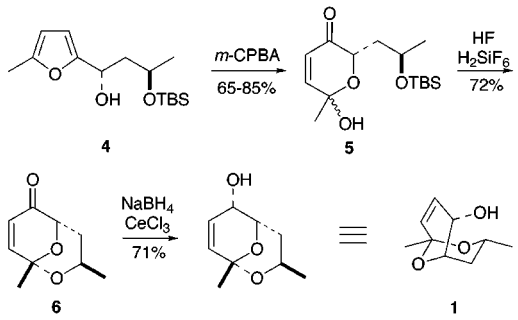
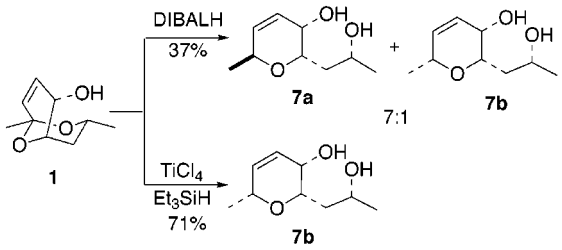
Scheme 1



Scheme 2



Scheme 3



As expected, reductive cleavage of ketal **1** with DIBALH resulted in a 7:1 ratio of diols **7a** and **7b** (Scheme 3). The relative stereochemistry of diols **7a** and **7b** was confirmed by NOE experiments of the respective diacetate derivatives (see discussion below). These experiments also confirmed that the regiochemistry of the ring opening process resulted in formation of only the pyran product. None of the oxepin product was observed (see discussion below).

It is proposed that in the DIBALH reduction under nonpolar conditions coordination of the aluminum reagent to the O3-ketal oxygen induced the formation of oxonium ion intermediate **8** (Scheme 4). Introduction of hydride from the same face occurred preferentially as a result of the rapid intramolecular capture of the oxonium ion by the hydride source.

Ketals can be reduced stereoselectively using titanium tetrachloride ($TiCl_4$) as the Lewis acid and triethylsilane (Et_3SiH) as the reducing agent.[11,13,15,16] In contrast to the DIBALH reaction, the product of an apparent S_N2 reduction is obtained. Indeed, when subjected to these reduction conditions, bicyclic ketal **1** yielded exclusively diol **7b** in good yield (Scheme 3). The excellent stereoselectivity of the reduction is attributed to coordination of titanium to the O3-ketal oxygen to give species **9**, followed by attack of the nucleophilic hydride in an S_N2-type fashion, resulting in an overall inversion of stereochemistry at the ketal center (Scheme 4).

The relative stereochemistry of pyrans **7a** and **7b** was confirmed by NOE experiments employing the diacetate derivatives. Particularly diagnostic was the lack of an NOE between the H2−H6 hydrogens of the *trans*-pyran derivative of **7a** and the strong NOE between these hydrogens in the product having the *syn*-relationship derived from pyran **7b** (see Figure 1).

The role of the free hydroxyl functionality of ketal **1** in controlling the stereoselectivity of the reduction process is believed to be minimal since attempts to make a derivative of this hydroxyl group (i.e., acetate, methyl ether, or silyl ether) were unsuccessful. Presumably the *endo*-alcohol is buried into the concave face of the ketal and cannot be accessed for derivatization. If the hydroxyl group is so hindered that it cannot be derivatized, it is unlikely that coordination with a bulky Lewis acid will occur.

The complete regioselectivity of the ketal cleavage to provide pyran derivatives rather than oxepins was anticipated. Modeling experiments suggested that coordination of the reagents to either of the ketal oxygens was equally energetic, suggesting that selective coordination was not responsible for controlling the regioselectivity of the cleavage. However, if one assumes that the transition state for the reduction had oxonium ion character (see **8** in Scheme 4), then the ring opening was expected to provide preferentially the pyran derivative since the corresponding oxepin oxonium ion intermediate had significantly higher energy (Figure 2).

This methodology was extended to the use of allyltrimethylsilane as the nucleophile, replacing Et_3SiH. It has been demonstrated that allylsilanes react with ketal derivatives in a highly stereoselective manner.[24−26] As shown in Scheme 5, ketal **1** underwent cleavage in the presence of $TiCl_4$ and allyltrimethylsilane to afford pyran **10** in a stereospecific manner. Under these conditions, none of the eight-membered ring product (i.e., **3**) was observed. The relative stereochemistry of pyran **10** was established by homonuclear decoupling experiments and confirmed by X-ray analysis.

While the DIBALH reduction of bicyclic ketal **1** was highly stereoselective, the overall yield of the reaction was unsatisfactory and resulted in formation of overreduced products unless carefully controlled reaction conditions were employed. Accordingly, reductions utilizing other Lewis acid/nucleophile combinations were investigated. It was proposed that by altering the electronic characteristics of the groups bound to aluminum, it should be possible to affect both the Lewis acidity of the reagent and its potential to provide a hydride to the intermediate oxonium ion (see Scheme 4). In this vein, alane-type reagents were explored. Literature precedent for using alane as a ketal reducing agent involves the generation of the reagent in situ from alumnium chloride ($AlCl_3$) and lithium aluminum hydride ($LiAlH_4$) in diethyl ether.[11,13,14,27−30] Nonstoichiometric ratios of $AlCl_3$ and $LiAlH_4$ provide chloroalane reagents. A summary of the results obtained from reductive cleavage of ketal **1** with

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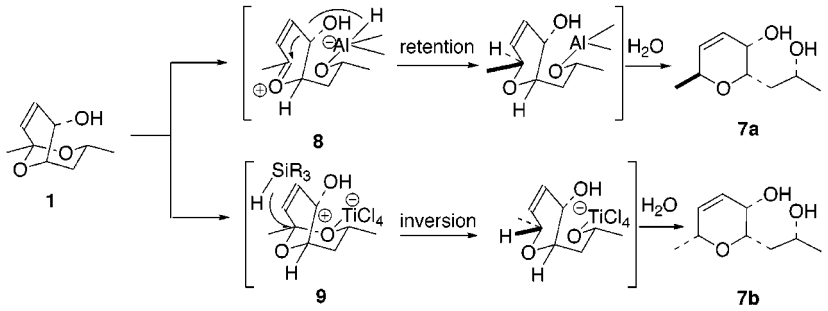
Scheme 4



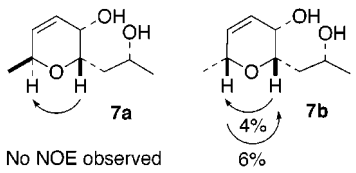


Figure 1. Stereochemistry of pyran products **7a** and **7b**.

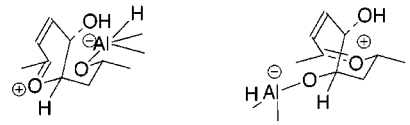


Figure 2. Oxonium ion intermediates.

Scheme 5

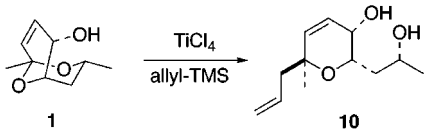


Table 1. $LiAlH_4$/ $AlCl_3$ Reductions of Bicyclic Ketal 1

entry	ratio $AlCl_3$:$LiAlH_4$	ratio[a] **7a**:**7b**	yield[b] (%)
1	3:1	1:14	44
2	2:1	1:8	41
3	1:1	1:2	57
4	1:2	6:1	33
5	1:3	4:1	35

[a] Ratios determined by 400 MHz ^{1}H NMR. [b] Combined isolated yield of both isomers.

$LiAlH_4$/$AlCl_3$ mixtures is provided in Table 1. The molar ratios of $AlCl_3$ to $LiAlH_4$ were varied in order to generate different reducing species, presumably $AlClH_2$ and $AlCl_2H$, having altered Lewis acid characteristics.

The results from these investigations reflect that varying the molar ratios of the two reactants forms different aluminum species that vary greatly in their reducing stereoselectivities. A higher ratio of $AlCl_3$ to $LiAlH_4$ (entries 1 and 2) results in predominant formation of the *syn*-diol **7b**, analogous to the $TiCl_4$/Et_3SiH reaction. This indicates that the species formed under these conditions, most likely $AlCl_2H$, is a strong enough Lewis acid that it acts similarly to $TiCl_4$, requiring an additional molecule of reducing agent to open the ring from the opposite face of the molecule. The complex generated may be relatively Lewis acidic and therefore is more likely to donate a hydride once coordinated to the ketal oxygen. Entry 3 shows that a 1:1 ratio of $AlCl_3$ to $LiAlH_4$ does not give appreciable selectivity. The reactions in which an excess of $LiAlH_4$ was used (entries 4 and 5) demonstrate the opposite selectivity. The *anti*-diol **7a** was the predominant species formed, which is similar to the results of the DIBALH reduction.

Conclusions

Reduction and allylation reactions of bicyclic ketal **1** occurred in a highly regio- and stereoselective fashion to afford functionalized pyran derivatives. Either the *syn*- or *anti*-pyran could be produced by the appropriate choice of reagent. Applications of this methodology to the synthesis of natural products are underway and will be reported in due course.

Experimental Section

General Methods. Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on a 200 or 400 MHz spectrometer in $CDCl_3$. Chemical shifts are reported in parts per million (δ) relative to the nondeuterated solvent peak. Coupling constants (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br s (broad singlet). Infrared spectra were recorded as solutions in CCl_4. Band positions are given in reciprocal centimeters (cm^{-1}), and relative intensities are listed as br (broad), s (strong), m (medium), or w (weak). Thin-layer chromatography (TLC) was performed with the compounds being identified in one or more of the following manners: UV (254 nm), iodine, or vanillin/sulfuric acid charring. Flash chromatography data is reported as (column diameter in mm, column height in cm, solvent). Melting points are uncorrected.

Et_2O was distilled from sodium/benzophenone ketyl, and methylene chloride (CH_2Cl_2) was distilled from calcium hydride. Glassware used in the reactions described below was dried for a minimum of 12 h in an oven at 120 °C. All reactions were run under an atmosphere of N_2 at room temperature unless otherwise noted. Cerium chloride heptahydrate ($CeCl_3 \cdot 7H_2O$), DIBALH (1.0 M solution in CH_2Cl_2), $TiCl_4$ (1.0 M solution in CH_2Cl_2), Et_3SiH, allyltrimethylsilane, and $LiAlH_4$ were purchased from Aldrich. Sodium borohydride ($NaBH_4$) was purchased from Fisher. $AlCl_3$ was purchased from J. T. Baker. Compounds **4**, **5**, and **6** were prepared as previously reported.[22] All reported compounds were >95% pure as determined by ^{1}H and ^{13}C NMR spectroscopy.

Bicyclic Allylic Alcohol 1. To a solution of 380 mg (2.3 mmol) of bicyclic enone **6** in 15 mL of MeOH was added 1.04 g (2.8 mmol) of $CeCl_3 \cdot 7H_2O$, followed by 105 mg (2.8 mmol) of $NaBH_4$. After 15 min, the reaction was quenched with 20 mL of saturated NaCl solution and 20 mL of H_2O. The layers were separated, and the aqueous phase was extracted with 3 × 30 mL of Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (20 mm, 20 cm, 2:3 Et_2O/hexane) gave 280 mg (71%) of bicyclic allylic alcohol **1** as a colorless oil. R_f = 0.35 (35% EtOAc/hexane); IR (CCl_4) 3625 (s), 3468 (br s), 3037 (s), 2975 (s), 2931 (s), 1544 (s) 1375 (s); ^{1}H NMR ($CDCl_3$) 1.11 (d, 3, J = 6.0), 1.35 (s, 3), 1.60 (ddd, 1, J = 6.4, 11.9, 13.7), 1.88 (dd, 1, 3.2, 13.7), 2.59 (br s, 1), 4.02−4.14 (m, 2), 4.54−4.57 (m, 1), 5.47 (dd, 1, J = 2.0, 9.9), 5.99 (d, 1, J = 9.9); ^{13}C

NMR ($CDCl_3$) 22.0, 26.5, 30.3, 63.9, 64.6, 70.4, 93.0, 128.6, 132.4; EI mass spectrum, *m*/*z* (relative intensity) 170 (M^+, 17), 108 (100), 100 (45), 95 (32), 72 (38); HRMS *m*/*z* (M^+ 170.0943, calcd for $C_9H_{16}O_3$ 170.0950).

***anti*-Diol 7a.** A solution of 111 mg (0.65 mmol) of bicyclic allylic alcohol **1** in 20 mL of CH_2Cl_2 was cooled to −78 °C. To this solution was added 3.9 mL (1.0 M solution in CH_2Cl_2, 3.9 mmol) of DIBALH. The solution was warmed to room temperature and stirred for 24 h. It was then quenched with 20 mL of saturated NaCl solution. The layers were separated, and the aqueous phase was extracted with 4 × 100 mL of EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (10 mm, 20 cm, 3:1 EtOAc/hexane) gave 42 mg (37%) of a 7:1 ratio of *anti*-diol **7a** to *syn*-diol **7b** as a clear oil. ***anti*-diol 7a**: R_f = 0.22 (EtOAc); IR (CCl_4) 3637 (w), 3531 (br m), 3106 (w), 2969 (s), 2931 (s). 2875 (s), 1562 (m); ^{1}H NMR ($CDCl_3$) 1.21 (d, 3, J = 6.4), 1.22 (d, 3, J = 6.8), 1.62 (ddd, 1, J = 4.5, 8.3, 14.7), 1.88 (ddd, 1, J = 2.8, 8.9, 14.7), 2.52 (br s, 2), 3.69 (dd, 1, J = 2.0, 5.2), 3.91−4.05 (m, 2), 4.30−4.38 (m, 1), 5.81 (dd, 1, J = 3.2, 10.0), 5.94 (ddd, 1, J = 2.0, 7.2, 10.0); ^{13}C NMR ($CDCl_3$) 18.0, 24.0, 39.2, 64.0, 65.0, 68.7, 69.1, 125.9, 134.0; EI mass spectrum, *m*/*z* (relative intensity) 172 (M^+, 0.1), 84 (100), 54 (26); HRMS *m*/*z* 172.1099 (M^+, calcd for $C_9H_{16}O_3$ 172.1092).

***syn*-Diol 7b.** A solution of 105 mg (0.62 mmol) of bicyclic allylic alcohol **1** in 20 mL of CH_2Cl_2 was cooled to −78 °C. To this solution was added 110 mL (0.67 mmol) of Et_3SiH, followed by 670 mL of $TiCl_4$ (1.0 M solution in CH_2Cl_2, 0.67 mmol). The reaction turned yellow and cloudy. After 30 min, the reaction was quenched with 20 mL of saturated NaCl solution, upon which the color of the solution turned bright pink. Upon warming to room temperature and exposure to the air, the reaction became colorless. The layers were separated, and the aqueous phase was extracted with 4 × 25 mL of EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (10 mm, 20 cm, 3:1 EtOAc/hexane) gave 61 mg (58%) of *syn*-diol **7b** as a clear oil. R_f = 0.24 (EtOAc); IR (CCl_4) 3631 (w), 3594 (m), 3450 (br s), 3037 (w), 2975 (s), 2931 (s), 2875 (m), 1375 (s); ^{1}H NMR ($CDCl_3$) 1.22 (d, 6, J = 6.8), 1.62 (ddd, 1, J = 4.5, 8.3, 14.7), 1.93 (ddd, 1, J = 2.8, 9.1, 14.7), 2.22 (br s, 2), 3.68−3.72 (m, 2), 3.99−4.11 (m, 1), 4.12−4.20 (m, 1), 5.78 (d, 1, J = 9.9), 5.96 (ddd, 1, J = 2.0, 4.8, 10.0); ^{13}C NMR ($CDCl_3$) 20.9, 24.1, 39.6, 64.4, 64.9, 71.4, 75.3, 126.6, 135.0; EI mass spectrum, *m*/*z* (relative intensity) 172 (M^+, 0.1), 84 (100), 54 (26); HRMS *m*/*z* 172.1099 (M^+, calcd for $C_9H_{16}O_3$ 172.1092).

Allyl Diol 10. A solution of 58 mg (0.34 mmol) of bicyclic allylic alcohol **1** in 25 mL of CH_2Cl_2 was cooled to −78 °C. To this solution was added 60 μL (0.38 mmol) of allyltrimethylsilane, followed by 370 μL (1.0 M solution in CH_2Cl_2, 0.37 mmol) of $TiCl_4$. After 10 min, the reaction was quenched with 20 mL of saturated NaCl solution. The layers were separated, and the aqueous phase was extracted with 4 × 25 mL of EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (10 mm, 20 cm, 3:1 EtOAc/hexane) gave 23 mg (32%) of allylated diol **10** as a white solid. The solid was recrystallized with hexane/EtOAc to give platelike crystals: mp 119−120 °C; TLC R_f = 0.36 (EtOAc); IR (CCl_4) 3626 (w), 3590 (m), 2975 (m), 2925 (m), 1546 (s); ^{1}H NMR ($CDCl_3$) 1.21 (s, 3), 1.22 (d, 3, J = 6.3), 1.57 (ddd, 1, J = 4.0, 9.7, 14.7), 1.90 (ddd, 1, J = 2.4, 9.7, 14.7), 2.23 (dd, 1, J = 8.0, 14.3), 2.45 (dd, 1, J = 6.8, 14.3), 3.65 (dd, 1, J = 1.6, 5.6), 3.98 (ddd, 1, J = 1.6, 3.6, 9.1), 4.02−4.10 (m, 1), 5.06−5.10 (m, 2), 5.78 (d, 1, J = 10.3), 5.77−5.88 (m, 1), 5.97 (dd,1, J = 5.6, 9.9); ^{13}C NMR ($CDCl_3$) 24.1, 26.7, 39.9, 41.1, 64.2, 64.7, 69.3, 74.8, 118.1, 125.4, 133.7, 137.6; FAB mass spectrum, *m*/*z* (relative intensity) 235 $(M + Na)^+$, 213 $((M + H)^+$, 31), 195 (61), 171 (73), 154 (45), 95 (100); HRMS *m*/*z* 213.1489 $((M + H)^+$, calcd for $C_{12}H_{21}O_3$ 213.1491).

General Procedure for $LiAlH_4/AlCl_3$ Reductions. A solution of 80 mg (0.51 mmol) of bicyclic allylic alcohol **1** in 10 mL of Et_2O was cooled to 0 °C. Separately, 1.8 mL of $AlCl_3$ (0.285 M solution in Et_2O, 0.51 mmol) was added to a solution of 520 μL of $LiAlH_4$ (1.0 M solution in Et_2O, 0.52 mmol) in 5 mL of Et_2O. A white precipitate formed. The supernatant was added by syringe to the allylic alcohol solution at 0 °C. The solution was warmed to room temperature and stirred for 12 h. The reaction was quenched with 5 mL of saturated NaCl solution. The layers were separated, and the aqueous phase was extracted with 4 × 100 mL of EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (10 mm, 20 cm, 3:1 EtOAc/hexane) gave 50 mg (57%) of a ratio of 1:2 mixture of diols **7a**:**7b** as a clear oil.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **1**, **7a**, **7b**, and **10** and X-ray crystallograpic data for diol **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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