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Model Study for the Incorporation of the (*syn,anti*)-2-Amino-1,3-Diol Functionality in Carbocycles

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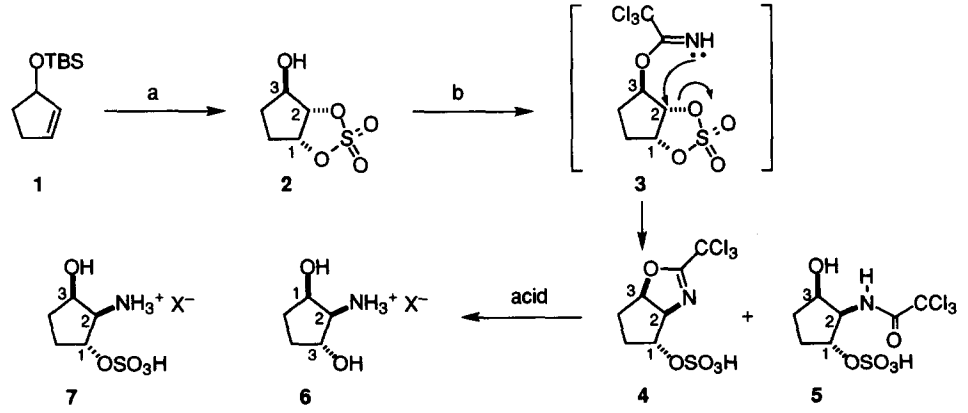
Abstract: (*syn,anti*)-2-Aminocyclopentan-1,3-diol was prepared by a one-pot trichloroacetimidate formation/ cyclic sulfate ring opening reaction followed by acid hydrolysis.

Keywords: amino diol; trichloroacetimidates; cyclic sulfate; intramolecular cyclization

For the synthesis of biologically active natural products, there is considerable interest in the fabrication of amino groups in polyfunctionalized carbocycles. Aminocyclitols such as allosamizoline,[1] trehalamine,[2] sannamine,[3] and hydroxyvalidamine[4] are representative examples which contain the (*syn,anti*)-2-amino-1,3-diol functional group array; these molecules constitute the aglycone portions of some biologically interesting pseudosaccharides. In conjuction with a project aimed at the synthesis of glucoallosamidin A pseudodisaccharide, we required a method for the stereo- and regio-selective incorporation of the 2-amino-1,3-diol functionality from cyclopent-2-en-1-ols.

The 2-amino-1,3-diol functional group assembly has previously been prepared by reaction of 2,3-epoxyalcohols with isocyanates to afford the corresponding oxazolidinones followed by subsequent ring opening.[5-9] Alternatively, Lewis acid-catalyzed cyclization of 2,3-epoxytrichloro-acetimidates has also been shown to be an excellent method for establishing this system.[6, 10-12] As an alternative, we undertook an investigation of the intramolecular ring opening of a cyclic sulfate by a tethered nitrogen nucleophile.

Scheme 1



Reagents and conditions: a. i) OsO_4, NMO, acetone/water (68%); ii) SO_2Cl_2, Et_3N, CH_2Cl_2, 0 °C (79%); iii) $(HF)_x$-pyridine, THF, 0 °C → rt (95%); b. i) DBU, CCl_3CN, THF, – 40 °C → rt; ii) method A. aq NH_4Cl workup (97%, **4** : **5** = *ca.* 2:1); method B. conc of solvent followed by silica gel chromatography (95% **4**).

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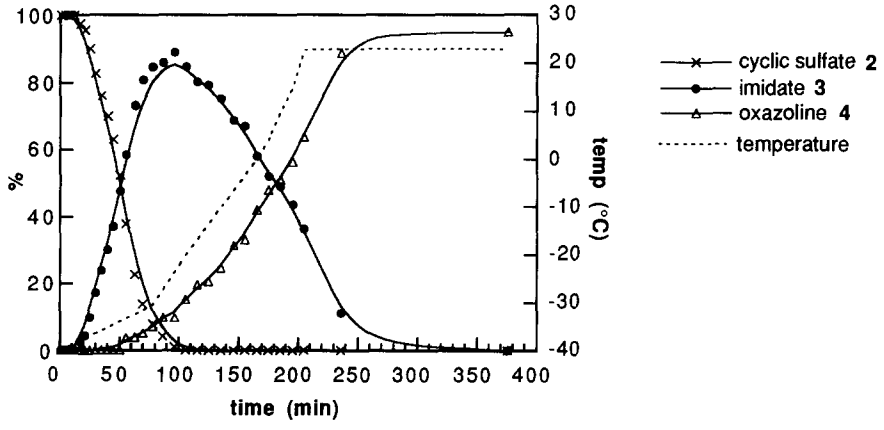
Cyclic sulfates, which are readily available from *vic*-diols by a one-step[13] or two-step procedure,[14] have been shown to react with a wide variety of nucleophiles[14, 15] and examples of intramolecular ring opening reaction are available.[16, 17]

As shown in Scheme 1, cyclic sulfate **2** was prepared from alkene **1** in 3 steps: stereoselective osmium-catalyzed dihydroxylation, cyclic sulfate formation with SO_2Cl_2/Et_3N, and deprotection of the *tert*-butyldimethylsilyl (TBS) group with HF/pyridine.[18] Treatment of cyclic sulfate **2** with excess CCl_3CN (50 eq.) in the presence of 2.3 eq. of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) at – 40 °C followed by subsequent warming to room temperature afforded a 97% yield of oxazoline **4** and the ring-opened product **5** in the ratio of *ca.* 2:1. This reaction was normally carried out in THF, however, CH_2Cl_2 was also shown to be effective. The reaction was monitored by variable temperature ^1H NMR spectroscopy and the percentage of starting material **2** (×), intermediate **3** (•), and product **4** (Δ) is illustrated in Figure 1. *O*-Alkylation of cyclic sulfate **2** occurred at *ca.* – 40 °C while the intramolecular ring opening of imidate **3** started at – 32 °C; however, the reaction rate for the *in situ* ring opening reaction was much slower compared to the initial step. The coupling constants $J_{1,2}$ in **2** and **3**, and $J_{2,3}$ in **4** are about 6 Hz which are characteristics of 1,2-*cis*-fused cyclopentane systems (Table 1).[19] It should be interesting to note that imidate **3** exhibited discrete N*H* proton at 9.52 ppm and the OSO_3H proton in **4** was found at 10.90 ppm in d_8-THF. From the above NMR experiment, the desired oxazoline **4** was found to be the major product (>90%) and the isolated ring-opened product **5** can be accounted for by the hydrolysis of **4** during aqueous workup. A modified workup procedure with the removal of solvent under reduced pressure (to *ca.* 1 mL) followed by flash column chromatography afforded the desired oxazoline **4** [–ve FABMS for $(M - H)^-$ at 322, 324] in 95% yield.

Figure 1 Percentage of compounds **2**, **3**, and **4** followed by VT ^1H NMR experiment.

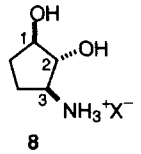


Acidic hydrolysis of oxazoline **4** with 5 M HCl/MeOH (1:4 v/v) at 40 °C for 24 hours gave the desired amino diol **6** (>95%, ESIMS for MH^+ at 118). The oxazoline ring in **4** was found to hydrolyze much faster than the sulfate moiety as sulfate **7** was detected as an intermediate during the hydrolysis. On the other hand, hydrolysis of **4** with AcOH (5 equivalents) in MeOH at 40 °C for 11 hours only resulted in a mixture of sulfates **5** and **7** in the ratio of 1:2.

Table 1 Selected ^{1}H NMR data for compounds **2–9, 11, 12.**

compound	H-1 (ppm)	H-2 (ppm)	H-3 (ppm)	$J_{1,2}$ (Hz)	$J_{2,3}$ (Hz)
2[a]	5.45 (t)[d]	4.93 (d)	4.25 (d)	5.6	0
3[a]	5.53 (t)	5.32 (d)	5.34 (s)	4.9	0
4[a]	4.65 (d)	4.97 (d)	5.38 (dd)	0	6.6
4[b]	4.83 (d)	4.96 (d)	5.49 (dd)	0	7.0
5[b]	4.93 (dt)	3.96 (dd)	4.31 (dt)	8.2	5.0
6[b] amine	4.15 (dt)	2.94 (dd)	4.05 (q)	5.4	7.2
6[c] HCl salt	4.13 (dt)	3.00 (m)	4.09 (q)	5.4	7.2
7[b]	4.9 (u)	3.50 (dd)	4.33 (dt)	6.8	5.2
8[c] HCl salt	3.81 (t)	3.74 (q)	3.15 (brq)	5.4	5.9
9[b]	4.84 (d)	3.65 (d)	3.57 (brs)	0	2.1
11[b]	4.76 (d)	4.30 (d)	5.00 (dd)	0	6.4
12[b]	4.94 (brd)	5.05 (dd)	5.20 (dd)	~1	6.8

[a] d_8-THF; [b] CD_3OD; [c] d_6-DMSO;
[d] multiplicity: br = broad; d = doublet; t = triplet; q = quartet; u = unresolved.



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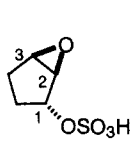
The regioselectivity of the intramolecular ring opening of cyclic sulfate **3** was determined based on a comparison of the hydrolyzed product **6** (hydrolysis from 1,2-oxazoline) with literature values of 3-amino-1,2-diol **8**[20] (hydrolysis from dihydrooxazine) (Table 1). The hydrochloride salt of amino diol **6** displayed a different ^{1}H NMR signature to that of **8**; in this way, the intramolecular cyclization was confirmed to result from a 1,2-cyclization.

Attempts to use a stoichiometric amount of trichloroacetonitrile (1.5 eq.) for this reaction resulted in isolation of epoxide **9** (26%) as a side-product. The intramolecular ring opening of cyclic sulfate **2**, analogous to the Payne rearrangement of the 2,3-epoxyalcohol,[21] now competes with the intermolecular addition to trichloroacetonitrile. Reaction of cyclic sulfate **2** with less reactive *N,N*-dimethylcyanamide (1.5 eq.) under the same conditions gave exclusively epoxide **9** instead of the corresponding dimethylaminooxazoline **10**.

Preliminary studies on the ring opening of cyclic sulfates by urethanes also proved to be satisfactory. Reaction of cyclic sulfate **2** with benzylisocyanate (1.5 eq.) or benzoylisocyanate (1.5 eq.) under similar reaction conditions gave oxazolidinones **11** [–ve FABMS for $(M - H)^-$ at 312] and **12** [–ve FABMS for $(M - H)^-$ at 326] in 89% and 76% respectively.



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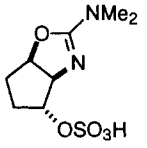

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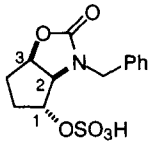

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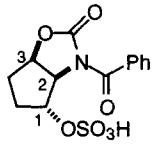

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In conclusion, we have demonstrated that the cyclic sulfate moiety, an epoxide surrogate, can be applied to the stereo- and regio-selective synthesis of (*syn,anti*)-2-amino-1,3-diols in cyclopentanes. The one pot trichloroacetimidate formation/cyclic sulfate ring opening reaction, in conjunction with the asymmetric dihydroxylation of alkenes, will complement the existing methods for the future preparation of 2-amino-1,3-diols.

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