Tetrahedron Letters, Vol. 33, No 25, pp 3583-3586, 1992
Printed in Great Britain

0040-4039/92 $5.00 + 00
Pergamon Press Ltd

DIASTEREOSELECTIVE [4+2] CYCLOADDITIONS OF ACYL NITROSO COMPOUNDS

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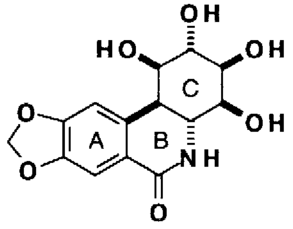
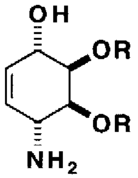
Abstract. A highly diastereoselective route to unsaturated amino alcohol derivatives has been developed that features the [4+2] cycloaddition of chiral acyl nitroso compounds to a variety of conjugated dienes; a useful oxidative method for generating acyl nitroso compounds from the corresponding hydroxamic acids under very mild conditions was also discovered.

As part of an effort directed toward the asymmetric synthesis of pancratistatin (**1**)[1,2] and related *Amaryllidaceae* alkaloids,[3] we had occasion to examine possible protocols for the enantioselective synthesis of aminocyclitols such as **2**. It occurred to us that one appealing entry to functionalized amino alcohols as **2** would involve the diastereoselective [4+2] cycloadditions of chiral nitroso dienophiles[4-6] with dienes (Scheme 1). Subsequent elaboration of the cycloadducts **7** by removal of the chiral auxiliary X_c and reductive cleavage of the nitrogen-oxygen bond would deliver unsaturated amino alcohols **8**. At the outset of our inquiry, there were reports of asymmetric Diels-Alder reactions of chiral α-chloro nitroso and acyl nitroso compounds.[6] However, the various methods appeared to suffer from one or more shortcomings, (1) only modest diastereoselectivities were observed in the cycloaddition; (2) a limited number of dienes were examined; and (3) both enantiomers of the chiral auxiliary were not equally accessible. Toward the goal of developing a more general approach to unsaturated, enantiomerically pure 1,4-amino alcohols, we examined the asymmetric Diels-Alder reactions of chiral nitroso carbamates **5** derived from the alcohol **3**, both antipodes of which are available from camphor by a simple and efficient sequence of reactions developed by Oppolzer.[7] During the course of these experiments, we also discovered a mild method for generating acyl nitroso intermediates. These studies are summarized herein.



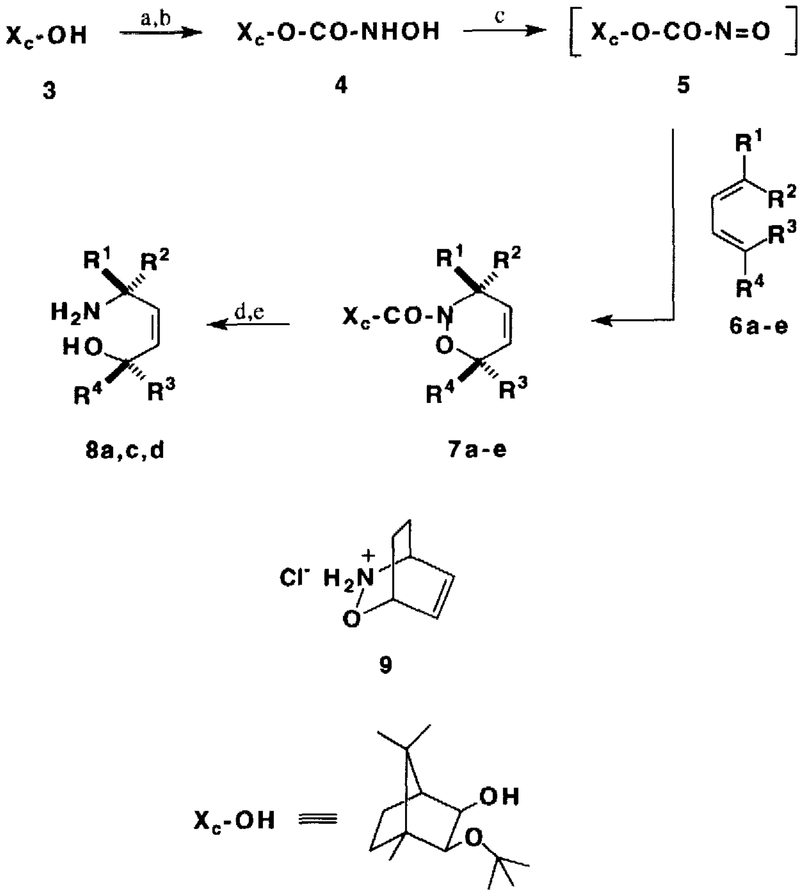
1



2

The alcohol **3**[7] was converted into the hydroxy carbamic acid **4** in 93% yield by reaction with triphosgene followed by hydroxylamine. Initial efforts directed toward the generation of **5** according to the classical procedure of oxidation with tetra-*n*-butylammonium periodate in CH_2Cl_2 at -20 °C were somewhat disappointing. Although excellent yields (80-90%) of cycloadducts of **5** with cyclohexadiene and cyclopentadiene were obtained, the

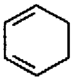
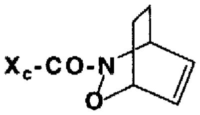
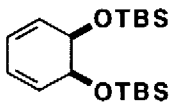
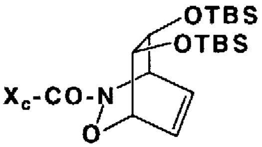
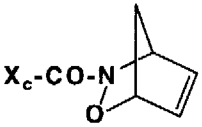
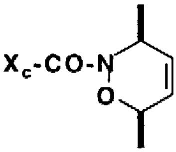
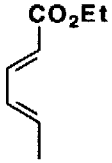
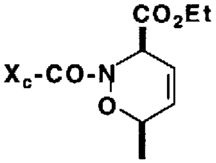
Scheme 1



(a) $Cl_3CC(=O)CCl_3$, quinoline, PhH, 5 °C. (b) $H_2NOH\,HCl$, aq. Na_2CO_3.
(c) $(COCl)_2$, CH_2Cl_2; DMSO; **6a-e**, Et_3N. (d) Na(Hg), aq. MeOH, NaH_2PO_4.
(e) NaOH, aq. EtOH; aq HCl.

diastereoselectivites were only 8-14:1 At lower temperatures oxidation of **4** proceeded only slowly, a problem we attributed to the heterogeneous nature of the reaction under these conditions. It occurred to us that oxidation of **4** at lower temperatures might ensue under homogeneous conditions using the Swern-Moffat protocol.[8] In the event, **4** was treated with oxalyl chloride and DMSO in CH_2Cl_2 at -78 °C, and the resulting complex was decomposed with triethylamine in the presence of cyclohexadiene to give the cycloadduct **7a** in 93% yield and 95% diastereomeric excess. The absolute sense of induction for this reaction was established by conversion of **7a** into the dextrorotatory bicyclic compound **9**{$[\alpha]_D^{22} = +24.4$, (c = 0.5, MeOH); lit.[6b] $[\alpha]_D^{20} = +24.0$, (c = 5.0, MeOH)}

Table 1. Diels-Alder Reactions of Chiral Acyl Nitroso Dienophiles with Dienes

Entry	Diene **6**	Major Product **7**[a]	Diastereomeric excess[b] (%)	Total Yield (%)
a			95	93
b			≥95	62
c			91	89
d			≥96	94
e			≥95	65

[a]Absolute stereochemical assignment based on correlation for **7a**. [b]Determined by HPLC and isolated yield.

by base induced hydrolysis; the chiral auxiliary could be recovered in 85-92% yield. As illustrated by the results summarized in Table 1, a variety of other dienes underwent [4+2] cycloaddition with **5** to give cycloadducts with similar diastereoselectivity and efficiency.[9] The conversion of the cycloadducts into unsaturated amino alcohols is exemplified by the transformation of **7a,c,d** into **8a,c,d**, respectively, by sequential reduction and hydrolysis.

Typical experimental procedure: To a stirred solution of oxalyl chloride (190 mg, 1.5 mmol) in CH_2Cl_2 (2 mL) at -78 °C was slowly added DMSO (234 mg, 3.0 mmol) in CH_2Cl_2 (1 mL) and then **4** (299 mg, 1 mmol); after 15 min, cyclohexadiene (120 mg, 1.5 mmol) was introduced. Triethylamine (604 mg, 6.0 mmol) in CH_2Cl_2 (3 mL) was then added using a syringe pump (1 h). After 3 h at -78 °C, the mixture was allowed to warm slowly to rt and stirred overnight. Addition of saturated NH_4Cl (5 mL) and extractive workup (ether, 3x15 mL) gave a mixture of **7a** and its diastereoisomer, which were separated by HPLC (hexane/EtOAc 8:1).

Acknowledgment. We thank the National Institutes of Health and the Robert A. Welch Foundation for their generous support of this research.

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8. This oxidation procedure was also effective for generating nitroso compounds from other hydroxamic acid analogues including BnOCONHOH, PhCONHOH, and $PhCH_2CONHOH$.
9. The structure assigned to each compound was in full accord with its spectral (^{1}H and ^{13}C NMR, IR and mass) characteristics. Yields cited are for compounds judged to be >95% pure by ^{1}H NMR. Analytical samples of all new compounds were obtained by distillation, recrystallization, preparative HPLC or flash chromatography and gave satisfactory combustion analysis (C, H) and/or identification by high resolution mass spectrometry.

(Received in USA 11 March 1992)