Notes

Straightforward Synthesis of Enantiomerically Pure (3*S*,4*R*)- and (3*R*,4*S*)-3,4-Isopropylidenedioxypyrroline 1-Oxide, Precursors of Functionalized *cis*-Dihydroxy Azaheterocycles, by a Novel "One-Pot" Procedure

Stefano Cicchi, Massimo Corsi, Alberto Brandi, and Andrea Goti*

Dipartimento di Chimica Organica "Ugo Schiff", Centro di Studio C.N.R. sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni (CSCEA), Università degli Studi di Firenze, via della Lastruccia 13, I-50019 Sesto Fiorentino, Firenze, Italy

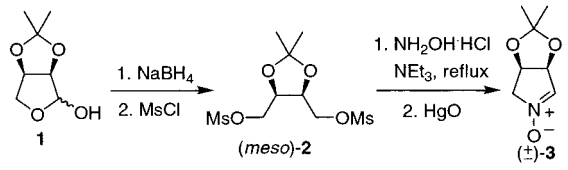
andrea.goti@unifi.it

Received May 15, 2001 (Revised Manuscript Received January 16, 2002)

Abstract: The enantiomerically pure nitrone **3**, a valuable precursor of mono- and bicyclic azaheterocycles, has been synthesized in 57% yield by a novel "one-pot" process starting from lactol **1**, in turn readily available from D-arabinose. The same process, consisting of reaction with a *O*-silyl-protected hydroxylamine followed by mesylation in pyridine, furnished *ent*-**3** in 55% yield when applied to L-arabinose.

Nitrones proved to be very useful tools in the construction of structurally complex molecules, usually allowing a high degree of diastereocontrol, particularly by means of the 1,3-dipolar cycloaddition to alkenes.[1] For example, five-membered cyclic nitrones, embodying a higher degree of complexity, are excellent building blocks for the synthesis of nitrogen heterocycles, pyrrolizidine and indolizidine alkaloids, and biologically active compounds.[1,2] Recent research has focused on the synthesis of optically active pyrroline *N*-oxides[2a,3] as precursors for such targets in enantiomerically pure form. In this context, we have reported the syntheses of optically active 3-hydroxy- and 3,4-*trans*-dihydroxypyrroline 1-oxides starting from malic and tartaric acids, respectively, which have been used in the synthesis of pyrrolizidine and indolizidine natural products and their analogues,[3a,b] interesting candidates as glycosidase inhibitors.[4]

Scheme 1



The same procedure is not amenable for the synthesis of the related *cis*-dihydroxy nitrone, e.g., **3** (Scheme 1), which was indeed produced as a racemate,[3a] due to the symmetry of its precursor **2**. The same nitrone **3** in racemic form has been prepared by Wightman and coworkers through oxidation of the corresponding pyrrolidine[3d] and then employed in the synthesis of racemic pyrrolizidine and indolizidine derivatives.

In this paper, we describe the facile and convenient synthesis of enantiopure (−)-(3*S*,4*R*)-**3**[5] by an unprecedented "one-pot" process that starts directly from lactol **1**,[6] easily accessible in turn from D-arabinose. Availability of its enantiomer L-arabinose, also inexpensive, secures equally easy and practical access to nitrone (+)-**3**.

To access enantiopure nitrone **3** from lactol **1**, we reasoned that the most direct method should transfer the stereochemical information at C-2 and C-3 of the erythrose derivative by retaining the desymmetry present at C-1 and C-4, which are already at the desired oxidation level as in nitrone **3**. The retrosynthetic analysis in Scheme 2 showed that transformation of the latent aldehyde of **1** into an oxime (in the event protected as in **5**) and of the ring oxygen into a suitable leaving group might well serve this purpose, since formation of nitrones by nucleophilic substitution from oximes (or better their conjugate anions) has been occasionally reported.[7]

While this work was in progress, Wightman and Closa have also reported the successful synthesis of enantiomerically pure nitrone **3** from the same lactol **1**, based

(1) (a) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984. (b) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1. (c) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; Feuer, H., Ed.; VCH Publishers: New York, 1988. (d) Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P. *Natural Products Synthesis Through Pericyclic Reactions*; Caserio, M. C., Ed.; ACS Monograph no. 180; American Chemical Society: Washington, 1983. (e) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Gazz. Chim. Ital.* **1989**, *119*, 253. (f) Frederickson, M. *Tetrahedron* **1997**, *53*, 403. (g) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.

(2) (a) Goti, A.; Cicchi, S.; Cordero, F. M.; Fedi, V.; Brandi, A. *Molecules* **1999**, *4*, 1. (b) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. (c) Ihara, M.; Takahashi, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2215. (d) DeShong, P.; Li, W.; Kennington, J. W., Jr.; Ammon, H. L.; Leginus, J. M. *J. Org. Chem.* **1991**, *56*, 1364.

(3) For leading references, see: (a) Goti, A.; Cicchi, S.; Cacciarini, M.; Cardona, F.; Fedi, V.; Brandi, A. *Eur. J. Org. Chem.* **2000**, 3633 and references therein. (b) Goti, A.; Cacciarini, M.; Cardona, F.; Cordero, F. M.; Brandi, A. *Org. Lett.* **2001**, *3*, 1367. (c) Giovannini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1995**, *60*, 5706. (d) McCaig, A. E.; Meldrum, K. P.; Wightman, R. H. *Tetrahedron* **1998**, *54*, 9429. (e) Murahashi, S.-I.; Imada, Y.; Ohtake, H. *J. Org. Chem.* **1994**, *59*, 6170. (f) Ishikawa, T.; Tajima, Y.; Fukui, M.; Saito, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1863.

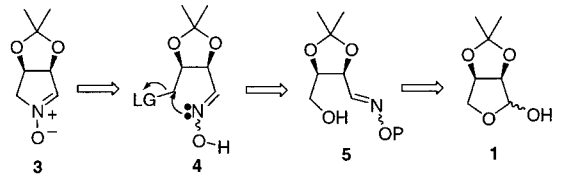
(4) (a) Stütz, A. E. *Iminosugars as glycosidase inhibitors: nojirimycin and beyond*; Wiley-VCH: Weinheim, 1999. (b) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-VCH: New York, 1987; Vol. 5, Chapter 1. (c) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319. (d) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199.

(5) For our previous efforts in this context, see: (a) Cicchi, S.; Nunes, J., Jr.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **1998**, 419. (b) Cardona, F.; Valenza, S.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **1999**, 1319. (c) Cicchi, S.; Cardona, F.; Brandi, A.; Corsi, M.; Goti, A. *Tetrahedron Lett.* **1999**, *40*, 1989. (d) Cicchi, S.; Corsi, M.; Goti, A. *J. Org. Chem.* **1999**, *64*, 7243.

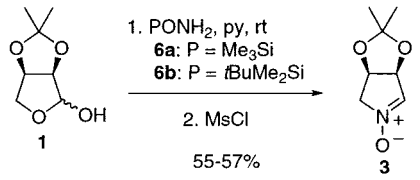
(6) For preliminary reports, see: (a) Angelini, A. Tesi di Laurea, Università di Firenze, 1997. (b) Corsi, M. Tesi di Laurea, Università di Firenze, 1999.

10.1021/jo0157573 CCC: $22.00
Published on Web 02/06/2002

Scheme 2



Scheme 3

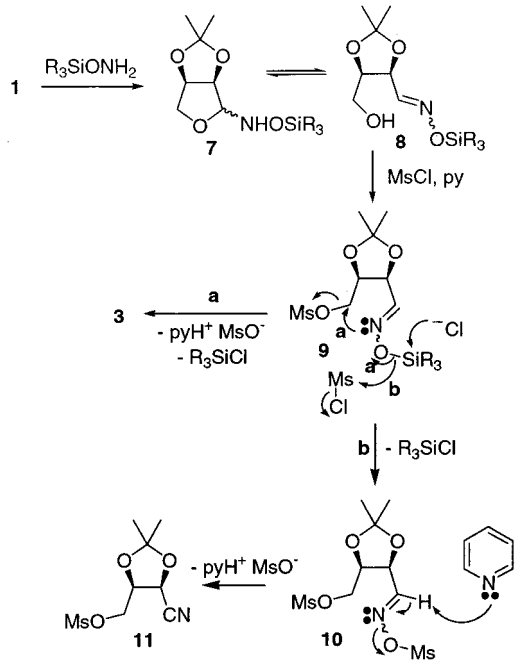


on a conceptually similar procedure. Their approach, however, consisted of a four-step process involving Wittig methylenation, mesylation, ozonization, and oxime formation and gave nitrone **3** with a 24% overall yield.[8]

The attempted direct tosylation or mesylation of lactol **1** afforded only complex mixtures of products. Consequently, we investigated exchanging the first two steps such that the oxime transformation was carried out first (to provide intermediate **5**) followed by the introduction of a leaving group. We chose to protect the oxime with a silylated group and anticipated that pyridine might work as a proper medium for both condensation with hydroxylamine and mesylation steps, yielding the process suitable to be performed in a "one-pot" fashion. Indeed, treatment of lactol **1** with an O-silylated hydroxylamine **6** in pyridine in the presence of molecular sieves, followed by addition of methanesulfonyl chloride directly furnished the desired nitrone **3** enantiomerically pure (Scheme 3). Presumably, this novel one-pot process may consist of the three individual steps outlined in Scheme 4, pathway a. The initially formed *N*-glycosyl hydroxylamine **7** undergoes O-mesylation through its acyclic tautomer **8** to afford the *O*-silyl oxime **9**. In situ chloride-mediated desilylation furnishes then the highly nucleophilic oximate anion, which displaces the leaving mesylate via an S_Ni reaction to give the desired nitrone **3** enantiomerically pure,[8] whose spectral data were identical with those reported for the racemic compound.[3a] The enantiomeric integrity of **3** was assessed by ^{1}H NMR spectra (see the Experimental Section) recorded in the presence of 5% of the chiral shift reagent Yb(hfc)$_3$[5c] and later confirmed by comparison with data reported in the literature: mp 110-111 °C; $[\alpha]^{20}_D$ −28.0 (*c* 0.46, CH_2Cl_2) [lit.[8] mp 110−112 °C; $[\alpha]_D$ = −26.5 (*c* 0.83, CH_2Cl_2)].

Evidence for formation of intermediate silyl oximes **8** in the first step of the process was collected by ^{1}H NMR experiments. However, the oximes underwent prompt desilylation and partial hydrolysis on attempted chromatographic purification. Monitoring of the first step of the process by recording ^{1}H NMR spectra on a reaction performed in pyridine-d_5 demonstrated that in this solvent the equilibrium is shifted toward tautomers **8**.

Scheme 4



Indeed, only the signals assigned to the two diastereomeric oximes (*E*)- and (*Z*)-**8** were evidenced in the spectra. The two diastereoisomers were present in solution in a ca. 2:1 *E*/*Z* ratio, on the basis of integration of the proton HC═N signals, which appear as doublets resonating at δ 7.93 and 7.21 ppm for the *E* and *Z* isomer, respectively. The progress of the reaction was monitored by recording the spectrum of the reaction mixture at 1 h intervals, which showed that the reaction occurs slowly, the lactol **3** being still present after 24 h.

The overall yield of the process strongly depends on the experimental conditions used and particularly the solvent and hydroxylamine employed, the reaction times for each step, and the mode of addition of the sulfonyl chloride. After extensive efforts for optimization of these parameters, it was found that this process is remarkably reproducible, leading to >50% yield of nitrone **3** from lactol **1**, with the best yield of 57% being obtained on a 6 mmol scale (see the Experimental Section). Replacement of pyridine with CH_2Cl_2/NEt_3 or CH_2Cl_2/pyridine mixtures gave unsatisfactory results; therefore, the use of pyridine as a solvent for the reaction appears necessary. Strictly anhydrous conditions are essential to the success of the reaction, and 3 Å molecular sieves (pellets) turned out to be the most effective dehydration agent to drive the first step close to completion. The use of *O*-*tert*-butyldimethylsilylhydroxylamine (**6b**) is preferred to its trimethylsilyl analogue **6a** since the corresponding oxime **8** is less susceptible to the reaction conditions and the reaction yields are more reproducible. For practical reasons, the use of 1.2 equiv of **6b** and a reaction time of 16 h for the first step are recommended: use of a larger excess of hydroxylamine was detrimental, and longer reaction times did not improve the yield of the process. The use of leaving groups other than mesylate (acetate, triflate) caused only negligible formation of nitrone. Addition of excess fluoride ion (as CsF or TBAF) in the second step after formation of mesylate had no beneficial effect, indicating that desilylation occurs efficiently.

The rate of addition of methanesulfonyl chloride was particularly important in achieving a satisfactory product

(7) (a) Brandman, H. A.; Conley, R. T. *J. Org. Chem.* **1973**, *38*, 2236. (b) Shatzmiller, S.; Shalom, E. *Liebigs Ann. Chem.* **1983**, 897. (c) Stempel, A.; Douvan, I.; Sternbach, L. H. *J. Org. Chem.* **1968**, *33*, 2963. (d) Black, D. St. C.; Brown, R. F. C.; Dunstan, B. T.; Sternhill, S. *Tetrahedron Lett.* **1974**, 4283.

(8) Closa, M.; Wightman, R. H. *Synth. Commun.* **1998**, *28*, 3443.

yield. A regular addition rate over at least 40 min should be maintained (15 μL/min addition with a syringe pump on a 6 mmol scale). Indeed, when this rate was not carefully controlled, the yield of nitrone **3** dropped to less than 30%. This was ascribed to the formation of a side product, which was characterized as the mesylate nitrile **11**. A perusal of the literature furnished the proof of the structural assignment, since the same compound had been previously synthesized as a key intermediate in the synthesis of (+)-crotanecine.[9] We suggest that formation of **11** occurs through the mechanism reported in Scheme 4, pathway b, which explains its increasing amount when high local concentrations of MsCl arise. As a matter of fact, addition of a high excess of MsCl (12 equiv) in the synthetic sequence of Scheme 3 gave the nitrile **11** in an unoptimized 55% yield. On the other hand, the reported synthesis of **11** was obtained by permesylation in pyridine of the free oxime related to **8**.[9] However, when the above conditions were carefully controlled, formation of **11** as a side product was limited to ca. 5%. Other side products have been identified spectroscopically in the reaction mixture. Among them, desilylated isomeric oximes **8** and their mesylated products were the most abundant, albeit each one below a 5% amount. Their formation can be ascribed to chloride-mediated desilylation of **8** during addition of methanesulfonyl chloride, which is once again an evidence of a fast occurring desilylation step. Their formation can be furtherly decreased by a faster addition of methanesulfonyl chloride, but this, on the other hand, gave an increased amount of nitrile **11**. The obtained optimized >50% yield in nitrone after fine-tuning of the reaction conditions is remarkable in consideration of the delicate balance of these counteracting effects and of the several side reactions that may occur on the intermediates of the process.

The same "one-pot" process described in Scheme 3 furnished in 55% yield the expected nitrone *ent*-**3**, when carried out on the enantiomer of lactol **1**, similarly obtained from commercial and inexpensive L-arabinose.

In summary, the two nitrones (3*S*,4*R*)-*O*,*O*′-isopropylidenedioxypyrroline 1-oxide (**3**) and its (3*R*,4*S*)-configurated enantiomer (*ent*)-**3** are available from the two erythrose derivatives **1** and (*ent*)-**1**, which in turn are obtained from sugars of the chiral pool. In addition, lactol **1** can be also easily obtained starting from commercially available D-isoascorbic acid.[10] This one-pot procedure compares very well with the previously reported method,[8] furnishing nitrones **3** with a yield more than doubled and in a much more direct manner. The two nitrones **3** and *ent*-**3** are key precursors for structurally diversified azaheterocycles,[3] for example, for the synthesis of unnatural functionalized pyrrolizidinones related to the necine base (+)-crotanecine[9,11] and its congeners, according to well-established cycloaddition−ring-opening−ring-closing protocols.[2b,3a,12]

Further studies are currently underway in our laboratories in order to extend the synthetic utility of nitrones **3** and to investigate the generality of this novel one-pot process.

Experimental Section

General Methods and Materials. Lactols **1** and *ent*-**1** were synthesized from D- and L-arabinose, respectively, by protection as isopropylidene ketals[13] followed by glycol oxidative cleavage with $NaIO_4$,[14] according to the literature. For generalities and instruments, see ref 3a. ^{1}H and ^{13}C NMR spectra have been performed in $CDCl_3$ solutions at 200 and 50.3 MHz, respectively.

Synthesis of (3*S*,4*R*)-3,4-Isopropylidenedioxypyrroline 1-Oxide (3). Lactol **1** (960 mg, 6 mmol) and dry pyridine (6 mL) were added into a 50 mL round-bottom flask containing 3 Å activated molecular sieves (pellets, 5 g). Then, a solution of hydroxylamine **6b** (1.11 g, 7.2 mmol) in pyridine (6 mL) was added, and the mixture was reacted at rt for 16 h with magnetic stirring. The reaction mixture was cooled to 0 °C, and methanesulfonyl chloride (560 μL, 7.1 mmol) was added with a syringe pump at a rate of 15 μL/min during 40 min. The reaction was stirred for 2 h at 0 °C, warmed to rt, and stirred 4 h. The mixture was then added with CH_2Cl_2, filtered through Celite, and concentrated. The crude product was purified by flash column chromatography over silica gel, eluent CH_2Cl_2−AcOEt−MeOH 15:7:1, to give pure nitrone **3** (R_f 0.16; 540 mg, 3.44 mmol, 57%) as a white solid whose spectroscopic data were identical with those previously reported.[8,3a]

3: mp 110−111 °C; $[\alpha]^{20}_D$ −28.0 (*c* 0.46, CH_2Cl_2) [lit.[8] mp 110−112 °C; $[\alpha]_D$ = −26.5 (*c* 0.83, CH_2Cl_2)]; ^{1}H NMR δ 6.84 (q, J = 1.5 Hz, 1 H, H−C(2)), 5.26 (d, J = 6.2 Hz, 1 H, H−C(3)), 4.87 (ddd, J = 6.2, 5.1, 1.5 Hz, 1 H, H−C(4)), 4.20−3.90 (m, 2 H, H−C(5)), 1.41 (s, 3 H, Me), 1.33 (s, 3 H, Me). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.38; H, 7.19; N, 8.68.

Synthesis of (3*R*,4*S*)-3,4-Isopropylidenedioxypyrroline 1-Oxide (*ent*-3). Application of the same procedure as above to lactol *ent*-**1** (160 mg, 1 mmol) gave the nitrone *ent*-**3** (87 mg, 0.55 mmol, 55%) as a white solid, whose spectroscopic data were identical to those of its enantiomer.

***ent*-3:** mp 110−111 °C; $[\alpha]^{20}_D$ +27.7 (*c* 0.67, CH_2Cl_2). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.30; H, 6.86; N, 8.56.

NMR Studies with Chiral Shift Reagent. The studies for the assessment of ee of the above synthesized **3** and *ent*-**3** have been carried out via ^{1}H NMR in the presence of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-l-camphorate]ytterbium(III) [Yb(hfc)$_3$]. Applicability of the method has been preliminarly evaluated by ascertaining signal separation on a sample of *rac*-**3** synthesized according to ref 3a. Best results have been obtained by adding 5−7 mol % of Yb(hfc)$_3$ to **3**. For example, addition of 2.3 mg of Yb(hfc)$_3$ (5%) to an NMR tube containing 6 mg of *rac*-**3** in $CDCl_3$ (0.7 mL) caused a splitting of the two methyl signals (at δ 1.41 and 1.33 ppm in the spectrum without shift reagent), allowing integration of the signals of the two enantiomers. The methyl originally resonating at δ 1.41 ppm was shifted of about 0.3−0.4 ppm and split into two broadened signals at δ 1.81 and 1.73 ppm, respectively, while the other methyl signal at δ 1.33 ppm experienced a lower shift and broadening effect, but was equally efficiently splitted into two signals resonating at δ 1.56 and 1.50 ppm. All the other signals in the spectrum were much more shifted and broadened. Application of the method to samples of **3** and *ent*-**3** allowed assignment of the two more shifted signals at δ 1.81 and 1.56 ppm to **3** and the more shielded signals at δ 1.73 and 1.50 ppm to *ent*-**3**. No signal assigned to the enantiomer was evidenced in the spectrum of **3** nor in that of *ent*-**3** in the presence of the chiral shift reagent. Accuracy of this method was based on integration of the most shielded methyl signal and was evaluated as >95%.

Synthesis of (2*S*,3*R*)-2,3-*O*-Isopropylidene-4-*O*-methanesulfonylerythrononitrile (11). Lactol **1** (160 mg, 1 mmol) and dry pyridine (1 mL) were added into a 10 mL round-bottom flask containing 3 Å activated molecular sieves (pellets, 1 g). Then, a solution of hydroxylamine **6a** (126 mg, 1.2 mmol) in pyridine (1 mL) was added, and the mixture was reacted at rt for 16 h with

(9) Buchanan, J. G.; Jigajinni, V. B.; Singh, G.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2377.
(10) Cohen, N.; Banner, B. L.; Laurenzano, A. J.; Carozza, L. *Org. Synth.* **1985**, *63*, 127.
(11) Denmark, S. E.; Thorarensen, A. *J. Am. Chem. Soc.* **1997**, *119*, 125.
(12) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137.
(13) Kiso, M.; Hasegawa, A. *Carbohydr. Res.* **1976**, *52*, 95.
(14) Thompson, D. K.; Hubert, C. N.; Wightman, R. H. *Tetrahedron* **1993**, *49*, 3827.

magnetic stirring. The reaction mixture was cooled to 0 °C, and methanesulfonyl chloride (930 μL, 12 mmol) was added with a syringe all at once. The reaction was stirred for 2 h at 0 °C, warmed to rt, and stirred 4 h. The mixture was then added with CH_2Cl_2, filtered through Celite, and concentrated. The crude product was purified by flash column chromatography over silica gel, eluent CH_2Cl_2−petroleum ether 10:1, to give the pure nitrile **11** (R_f 0.18; 130 mg, 0.55 mmol, 55%) as an oil, whose spectroscopic data were identical with those previously reported.[9]

11: $[\alpha]^{20}_D$ −50.0 (*c* 0.20, $CHCl_3$) [lit. $[\alpha]_D$ -50.4 (*c* 1.07, $CHCl_3$)].[9] Anal. Calcd for $C_8H_{13}NSO_5$: C, 40.84; H, 5.57; N, 5.95. Found: C, 41.20; H, 5.74; N, 6.00.

Acknowledgment. We thank MURST (Ministero dell'Università e della Ricerca Scientifica e Tecnologica), Italy, for financial support (Cofin 2000) and Dr. Arianna Angelini for early experiments.

JO0157573