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Straightforward synthesis of enantiopure 2-aminomethyl and 2-hydroxymethyl pyrrolidines with complete stereocontrol

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Abstract—A practical synthesis of 2-aminomethyl- and 2-hydroxymethyl-3,4-dihydroxypyrrolidines via stereocontrolled addition of TMSCN and $LiCH_2OMOM$ to chiral 3,4 dihydro-2*H*-pyrroline *N*-oxides is reported.

Many naturally occurring polyhydroxylated pyrrolidines are interesting biologically active compounds showing a remarkable and selective inhibitory activity towards several glycosidase enzymes.[1] Unnatural stereoisomers and the corresponding amines behave as sugar mimics and also display a pattern of useful bioactivities.

Platinum complexes of bidentate amino pyrrolidines have also shown chemotherapeutic properties, which make them a potential alternative to the use of toxic cisplatin complexes in the cure of cancer.[2] Besides their possible biological properties, these compounds can find application as chiral ligands for metal-mediated enantioselective organic reactions.[3] In the last years, a great synthetic effort has spread out to assure easy and stereocontrolled routes to these molecules either employing starting materials from the chiral pool or by application of enantioselective strategies.[4]

The addition of organometallic reagents to five membered enantiopure cyclic nitrones has revealed a straightforward approach to substituted chiral pyrrolidines. Recent results have shown that nucleophilic additions of different reagents to nitrones **1**–**3** (Chart 1) proceed smoothly and with high stereoselectivity.[5,6]

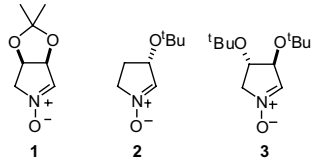

Chart 1.

The use of TMSCN was effective, affording as the only diastereoisomers the corresponding *trans*-hydroxy-amino-nitriles, which can be envisaged as direct precursors of 2-aminomethyl pyrrolidines.[5]

Several syntheses have been reported in recent years for 2-hydroxymethyl-3,4-dihydroxy pyrrolidines starting both from carbohydrate and from non-carbohydrate materials[7,8] while only few procedures are known for the synthesis of 2-aminomethyl-3,4-dihydroxy pyrrolidines.[2,8b,9]

In this communication, we report our preliminary results on the enantiospecific synthesis of 2-aminomethyl and 2-hydroxymethyl-3,4-dihydroxy pyrrolidines with both possible absolute configuration at the newly generated C-2 stereogenic centre, starting from enantiopure nitrone **1** (easily accessible from D-arabinose[10]).

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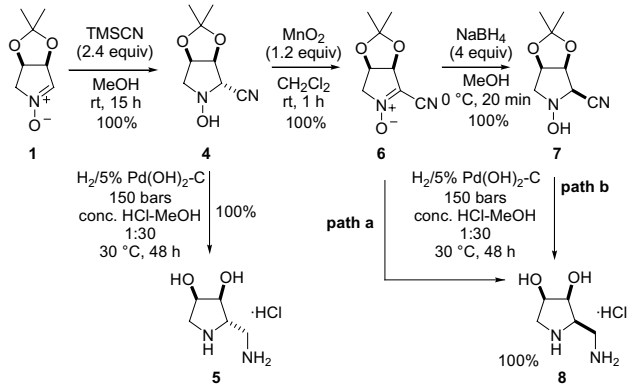


Scheme 1.

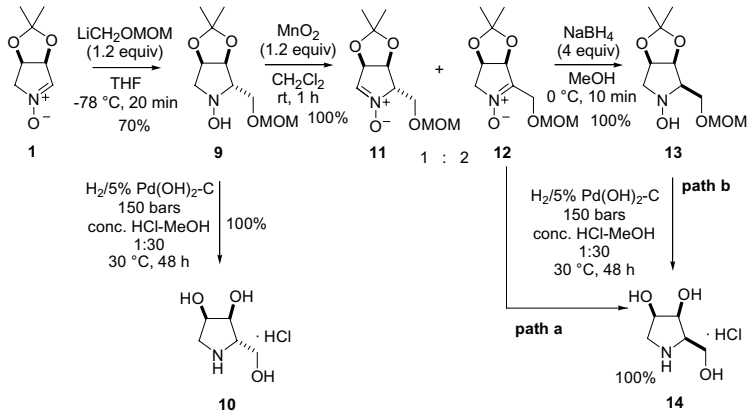
The addition of TMSCN to nitrone **1** in methanol afforded free hydroxylamine **4** as the only *trans* diastereoisomer as previously observed for racemic **4**.[5] The hydroxylamine **4** was exhaustively hydrogenated under high hydrogen pressure (150 bars) at 30 °C for 48 h in acidic conditions (Scheme 1). These two simple synthetic steps gave only one compound, which was assigned the structure of fully deprotected amine **5** as its hydrochloride salt on the basis of its spectroscopic data. Product **5** was thus obtained in quantitative yield.[11]

The resulting *trans* selectivity of the cyanide attack was not significantly influenced by the use of precomplexing agents such as Lewis acids in the addition step,[5] so the direct transformation of **1** into the epimeric cyano derivative **7** cannot be achieved. However, an inversion of configuration at C-2 might be operated through an oxidation–reduction sequence.[12] In fact, oxidation of **4** with MnO_2[6a] afforded exclusively and quantitatively the ketonitrone **6**, which was reduced directly and stereoselectively to the diastereomeric hydroxylamine **7** with sodium borohydride. The desired diamine **8** was then obtained by hydrogenation of **7** with concomitant deprotection (Scheme 1, path b). The same transformation of ketonitrone **6** to diamine **8** was also performed more straightforwardly in a one step process by direct hydrogenation (Scheme 1, path a). The relative all-*cis* stereochemistry of the substituents on the pyrrolidine ring of derivative **8** rests on its spectroscopic data, which differ from those of **5**.[11] It follows that both hydride reduction and hydrogenation of **6** are completely diastereoselective.

The same synthetic strategy has been used to synthesize chiral non-racemic 2-hydroxymethyl pyrrolidines **10** and **14** by using a different nucleophile. For this purpose, Li-CH_2OMOM was chosen as the synthetic equivalent of the hydroxymethyl anion.[13] This organolithium derivative, generated as previously reported,[13] reacted with nitrone **1** with the usual high *anti*-stereoselectivity to afford the hydroxylamine **9** (Scheme 2). This is, to our knowledge, the first example of the direct addition of an alkoxymethyllithium derivative to a cyclic nitrone.[14,15] The reduction of hydroxylamine **9** was performed by high pressure hydrogenation in acidic medium to give directly the fully deprotected polyhydroxy pyrrolidine **10** as its hydrochloride salt (Scheme 2), which gave spectroscopic and analytical data in agreement with those previously reported.[16]

Again, the synthesis of the C-2 epimeric pyrrolidine **14** was achieved by the oxidation–reduction process as described above. The oxidation of hydroxylamine **9**, although quantitative, was scarcely regioselective, affording a 2:1 mixture of the desired ketonitrone **12** and the aldonitrone **11**. After separation of the mixture, the desired pyrrolidine **14** could be obtained very efficiently both by the one step procedure (Scheme 2, path a) or by the two step procedure (Scheme 2, path b) through the intermediate hydroxylamine **13**. The complete stereoselectivity of the process was demonstrated by the comparison of the physical and spectroscopic properties of **14** with those described in the literature.[16]

The strategy outlined in this communication for the synthesis of compounds **10** and **14** compares well with those reported in the literature.[7] The main drawbacks of most of the synthetic approaches previously proposed for these compounds are their excessive length and the poor overall yields. Moreover, some of them require expensive starting materials or not commercial substrates,



Scheme 2.

which have to be prepared. The great advantages of our syntheses are: (i) the straightforward linear sequence to the targets (only two and three steps for **10** and **14**, respectively, obtained in 70% and 46% overall yield from nitrone **1**, which is in turn easily prepared in three simple steps from D-arabinose with a 43% overall yield [7f,10] or in four steps from D-isoascorbic acid with a 56% overall yield[10,17]); (ii) the access to both epimers with the same methodology operating a simple inversion of configuration at C-2 through an oxidation–reduction sequence; (iii) the generality of the method, since it is possible to access a vast range of polysubstituted cyclic enantiopure nitrones, such as **2** and **3** and, for example, it is possible to synthesize (*ent*)-**10** and (*ent*)-**14**, due to the fact that arabinose is available as both D and L enantiomers, equally inexpensive. Even more efficient are the syntheses of 2-aminomethylpyrrolidines, such as **5** and **8**, which benefit of all the above mentioned features plus take advantage of all essentially clean and quantitative reactions. It is worthy to note that intermediate compounds **4**, **6** and **7** are obtained analytically pure from crude reaction mixtures without need of separation or purification.

In summary, we have reported an alternative and practical synthesis of enantiopure 3,4-*cis*-dihydroxy-2-aminomethyl and 2-hydroxymethyl pyrrolidines starting from 3,4-*cis*-dihydroxy nitrone **1**, which can be readily obtained from D-arabinose. Further studies are currently underway in our laboratories to fully explore the synthetic potential of chiral α-alkoxy cyclic nitrones to verify the generality of the synthetic method and the possibility of generating new targets using orthogonal protections: the use of different substituted cyclic nitrones opens up the possibility of accessing a different series of targeted polyhydroxylated pyrrolidines.

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11. All compounds gave satisfactory elemental analyses. Selected data for **5**: yellowish solid; mp >150 °C (dec); $[\alpha]_D^{25}$ −19 (*c* 0.33, MeOH). ^{1}H NMR (400 MHz, D_2O) δ 3.32 (d, 1H, J = 12.8 Hz, H-5a), 3.35 (dd, 1H, J = 5.9,

13.5 Hz, H-1a′), 3.48 (dd, 1H, J = 7.3, 13.5 Hz, H-1b′), 3.60 (dd, 1H, J = 4.0, 12.8 Hz, H-5b), 3.75 (ddd, 1H, J = 5.9, 7.3, 9.2 Hz, H-2), 4.16 (dd, 1H, J = 4.0, 9.2 Hz, H-3), 4.30 (t, 1H, J = 4.0 Hz, H-4). ^{13}C NMR (100 MHz, D_2O) δ 40.3 (C-1′), 51.8 (C-5), 58.6 (C-2), 70.3 (C-4), 75.5 (C-3). Selected data for **8**: yellowish solid; mp >150 °C (dec); $[\alpha]_D^{25}$ −5 (c 0.38, MeOH). ^{1}H NMR (400 MHz, D_2O) δ 3.20 (dd, 1H, J = 6.1, 13.2 Hz, H-5a), 3.38 (dd, 1H, J = 6.8, 12.6 Hz, H-1a′), 3.42 (dd, 1H, J = 5.6, 13.2 Hz, H-5b), 3.53 (dd, 1H, J = 6.8, 12.6 Hz, H-1b′), 3.85 (q, 1H, J = 6.8 Hz, H-2), 4.40 (m, 2H, H-3+H-4). ^{13}C NMR (100 MHz, D_2O) δ 36.6 (C-1′), 48.2 (C-5), 57.2 (C-2), 69.8 (C-4), 70.0 (C-3).

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16. All compounds gave satisfactory elemental analyses. Selected data for **10**: white solid; mp 128–130 °C; $[\alpha]_D^{25}$ −52 (c 0.41, H_2O); [Lit.[7h] $[\alpha]_D^{25}$ −59.0 (c 0.59, H_2O); mp 126–131 °C]. ^{1}H NMR (400 MHz, D_2O) δ 3.36 (d, 1H, J = 12.8 Hz, H-5a), 3.50 (dd, 1H, J = 4.0, 12.8 Hz, H-5b), 3.63 (ddd, 1H, J = 3.5, 5.8, 8.3 Hz, H-2), 3.81 (dd, J = 5.8, 12.6 Hz; 1H, H-1a′), 3.97 (dd, 1H, J = 3.5, 12.6 Hz, H-1b′), 4.20 (dd, 1H, J = 4.0, 8.3 Hz, H-3), 4.38 (m, 1H, H-4). ^{13}C NMR (100 MHz, D_2O) δ 49.7 (C-5), 58.1 (C-1′), 61.9 (C-2), 69.5 (C-4), 71.2 (C-3). Selected data for **14**: white solid; mp 156–158 °C; $[\alpha]_D^{25}$ +20 (c 0.32, H_2O); [Lit.[7k] $[\alpha]_D^{25}$ +19.8 (c 0.45, H_2O); mp 159–161 °C]. ^{1}H NMR (400 MHz, D_2O) δ 3.11 (dd, 1H, J = 7.3, 12.1 Hz, H-5a), 3.42 (dd, 1H, J = 7.3, 12.1 Hz, H-5b), 3.63 (dt, 1H, J = 8.3, 4.0 Hz, H-2), 3.78 (dd, J = 8.3, 12.1 Hz; 1H, H-1a′), 3.88 (dd, 1H, J = 4.0, 12.1 Hz, H-1b′), 4.24 (t, 1H, J = 4.0 Hz, H-3), 4.38 (dt, 1H, J = 4.0, 7.3 Hz, H-4). ^{13}C NMR (100 MHz, D_2O) δ 47.1 (C-5), 57.7 (C-1′), 62.5 (C-2), 69.8 (C-3), 70.0 (C-4). The ^{1}H and ^{13}C NMR data of compounds **10** and **14** match those reported in the literature. The different assignment to protons at C-5 and C-1′, which are inverted, is based on bidimensional g-HMQC spectra, which unequivocally establish correlations of those protons with the connected carbon atoms.
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