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Stereoselective synthesis of pyrrolidinyl glycines from nitrones: complementarity of nucleophilic addition and 1,3-dipolar cycloaddition

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Abstract—Epimeric pyrrolidinyl glycines, a sort of conformationally constrained α,β-diaminoacids, were stereoselectively prepared using complementary approaches based on nitrone chemistry. Nucleophilic additions to pyrrolidinyl nitrones and 1,3-dipolar cycloadditions of L-serine derived nitrones to form the corresponding hydroxylamines and isoxazolidines, respectively, provided key intermediates for the synthesis of the target compounds. Whereas the nucleophilic addition route afforded the *syn* adduct, the 1,3-dipolar cycloaddition approach furnished the precursor for the preparation of the corresponding *anti* compound.

α,β-Diaminoacids **1** are interesting targets because of their utility as synthetic intermediates as well as their presence in several biologically active compounds.[1] In addition, much attention was focused during the last years on the preparation of conformationally constrained amino acids.[2] A recent surge of activity into the synthetic chemistry of hetaryl glycines, in particular, tetrahydrofuranyl derivatives is also indicative of the importance of this area.[3]

Pyrrolidinyl glycines **2** can be considered as conformationally restricted α,β-diamino acids whose preparation is still scarcely considered. To the best of our knowledge, such compounds have only been synthesized in particular cases. Compounds **3** have been used as synthetic intermediates for the preparation of bicyclic piperazine 2-carboxylic acids[4] that have been further utilized in asymmetric synthesis as either catalysts or building blocks.[5] Bicyclic pyrrolidinyl glycines **4** have also been employed as intermediates in the synthesis of models for the azinomycin[6] and ficellomycin[7] antibiotics (Fig. 1).

As a part of our continuing research program on the synthetic potential of nitrones, and in the preparation of non-proteinogenic aminoacids,[8] including α,β-diamino acids,[9] we now report on two new complementary routes leading to epimers at the β-stereogenic center of pyrrolidinyl glycines.

The synthetic approaches are based on nitrone chemistry and they make use of the two different and well-known reactivities of the nitrone functionality in 1,3-dipolar cycloadditions and nucleophilic additions.[10]

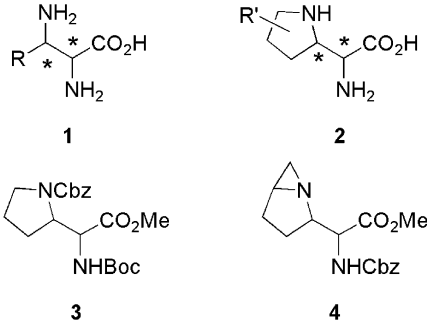

Figure 1.

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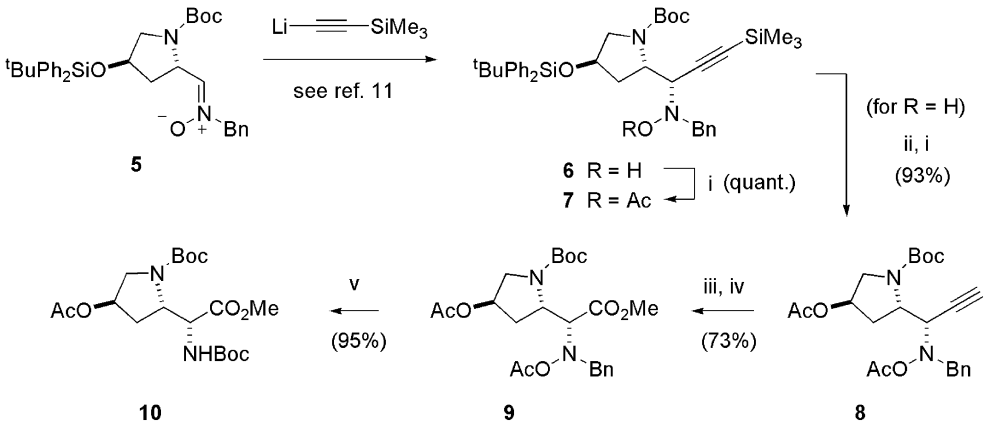


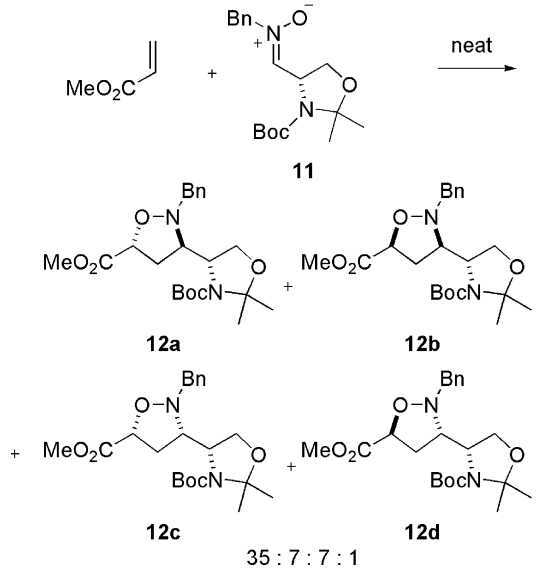
Scheme 1. Reagents and conditions: (i) Ac_2O, Py, rt; (ii) Bu_4NF, THF, rt; (iii) $RuCl_3$, $NaIO_4$, CH_3CN–CCl_4–H_2O (3:2:2), rt; (iv) CH_2N_2, Et_2O, rt; (v) H_2, 100 atm, $Pd(OH)_2$–C, Boc_2O, rt.

Our first approach started from the completely stereoselective addition of lithium trimethylsilyl acetylide to the pyrrolidinyl nitrone **5** (Scheme 1). Only one isomer could be detected in the reaction mixture and compound **6** ($[\alpha]_D$ +5 (*c* 0.21, $CHCl_3$)) was obtained in 93% chemical yield.[11] The stereochemical course of the reaction can be explained on the basis of our previously reported model for nucleophilic additions of Grignard reagents to pyrrolidinyl nitrones.[12] The absolute configuration of **6** was unambiguously assigned following our previously reported empirical rule based on NMR measurements.[13] After protection of the *N*-hydroxyamino group as an acetyl derivative, compound **7** (100%; $[\alpha]_D$ −27 (*c* 0.41, $CHCl_3$)) was obtained. Unfortunately, all attempts of oxidizing the ethynyl group to a carboxylic acid either with RuO_2 or $RuCl_3$ in the presence of an excess of sodium periodate as a reoxidant, failed; only decomposition products were recovered from the reaction mixtures. A similar behavior had already been observed in our laboratory.[14] Thus the silyl groups in **6** were cleaved with TBAF in THF and after acetylation of the resulting crude product, compound **8** (89%; $[\alpha]_D$ −37 (*c* 0.38, $CHCl_3$)) was obtained.

In this case, unmasking of the carboxyl moiety was carried out by oxidation of the triple bond with the system $RuCl_3$–$NaIO_4$ in good yield, thus demonstrating that the replacement of the *O*-silyl protecting group by the acetyl one and/or removal of the *C*-silyl group is crucial for the success of the oxidation. After esterification of the crude carboxylic acid with freshly prepared diazomethane, the *N*-(acetoxy) pyrrolidinyl glycine **9** (73%; $[\alpha]_D$ −39 (*c* 0.25, $CHCl_3$)) was obtained after purification by radial chromatography. Hydrogenation under pressure (100 atm) in the presence of the Pearlman's catalyst and Boc_2O afforded the protected pyrrolidinyl glycine **10** in 57.4% overall yield (six steps from nitrone **5**).[15]

Our second approach was based on the hitherto unknown 1,3-dipolar cycloaddition between the L-serine derived nitrone **11** and methyl acrylate (Scheme 2). The reaction was conducted without solvent at 90 °C in a sealed tube for 5 h. The NMR analysis of the crude mixture revealed the presence of four isomers in 35:7:7:1 ratio, which was further confirmed by HPLC (XTerra C18, 5 μm, MeOH–H_2O, 3:2). After separation of the adducts by OPLC (OPLC-50, 0.2 mm HTSorb™ 5 μm silica gel layer, hexane/EtOAc 8:2, 50 bar, 500 μL/min) the major adduct **12a** was obtained in 56% isolated yield.[16] The stereochemical assignment of **12a**–**d** was determined by careful NMR analysis utilizing homonuclear decoupling, multiple-difference NOE and 2D experiments including COSY, ROESY, and HMQC.

Moreover, the observed stereochemical induction is in agreement with previous observations for α-alkoxy and α-amino nitrones for which, in all cases, the diastereofacial induction showed to be *anti* with respect to the heteroatom in α position to the nitrone moiety.[17] Tentatively, we suggest that this stereochemical outcome is in agreement with the transition state model **A** illustrated in Figure 2 corresponding to an *endo* approach of the dipolarophile to the *Re* face of the nitrone.



Scheme 2. Cycloaddition between **11** and methyl acrylate.

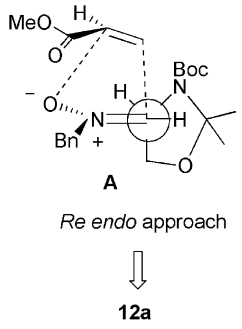
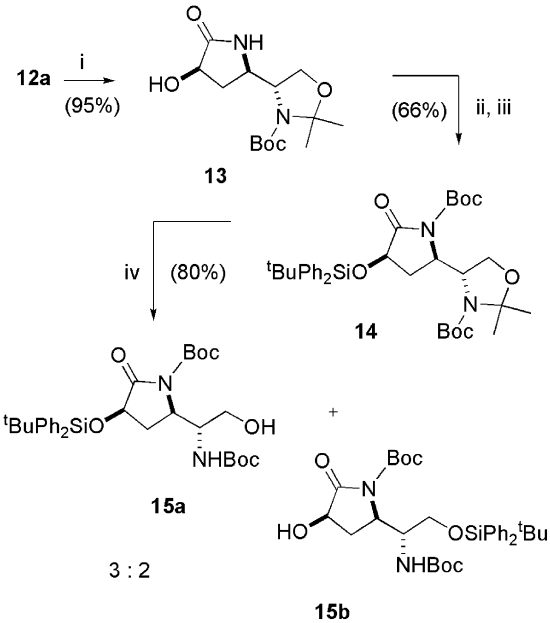


Figure 2. Proposed model for the 1,3-dipolar cycloaddition between **11** and methyl acrylate.

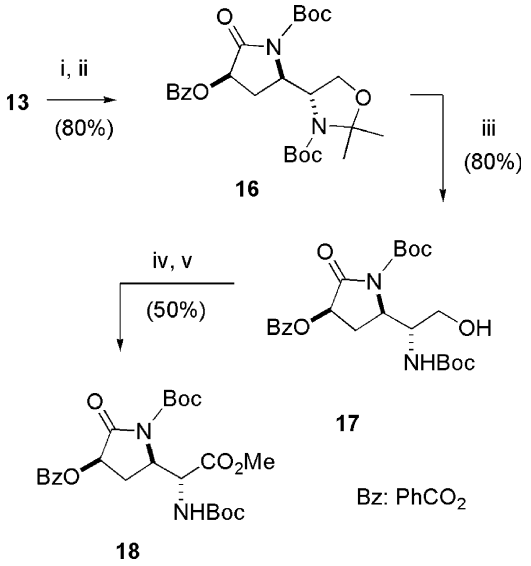
Catalytic hydrogenation of **12a** using Pearlman's catalyst provided pyrrolidinone **13** ($[\alpha]_D$ −33 (*c* 0.21, $CHCl_3$); mp 164–166 °C) in 95% yield (Scheme 3).

Compound **13** was treated with *tert*-butyldiphenyl silyl chloride and Boc_2O to afford the protected pyrrolidin-2-one **14** ($[\alpha]_D$ +34 (*c* 0.22, $CHCl_3$)). However, acidic hydrolysis of the oxazolidine moiety to liberate the primary hydroxyl group as a previous step for the oxidation reaction afforded a 3:2 mixture of the expected compound **15a** ($[\alpha]_D$ +25 (*c* 0.17, $CHCl_3$)) and **15b** ($[\alpha]_D$ −6 (*c* 0.30, $CHCl_3$)), the latter coming from an unexpected silyl migration.

In order to avoid the silyl migration, we then decided to change the protecting group of the hydroxyl group. After benzoylation and N-protection of **13**, compound **16** (80%, $[\alpha]_D$ +45 (*c* 0.25, $CHCl_3$)) was obtained as the immediate precursor of the target compound (Scheme 4). Treatment of **16** with catalytic *p*-TsOH in methanol gave rise to the free primary alcohol **17** (80%, $[\alpha]_D$ +20 (*c* 0.27, $CHCl_3$)) which was subsequently



Scheme 3. Reagents and conditions: (i) H_2, $Pd(OH)_2$–C, 100 atm, rt; (ii) $^tBuPh_2SiCl$, imidazole, DMF, 70 °C; (iii) Boc_2O, Et_3N, DMAP, CH_2Cl_2; (iv) *p*-TsOH, MeOH, 45 °C, 6 h.



Scheme 4. Reagents and conditions: (i) PhCOCl, Py, CH_2Cl_2, 0 °C; (ii) Boc_2O, Et_3N, DMAP, CH_2Cl_2; (iii) *p*-TsOH, MeOH, 45 °C, 6 h; (iv) TEMPO, [bis(acetoxy)iodo]benzene, MeCN–H_2O; (v) CH_2N_2, Et_2O, rt.

oxidized with the system TEMPO-BAIB[18] to afford the crude carboxylic acid. This compound was isolated and fully characterized[19] as the corresponding methyl ester **18** which was obtained by treatment of the acid with an ethereal solution of freshly prepared diazomethane. Compound **18** was obtained in 17% overall yield (seven steps from nitrone **11**).

We also attempted the reduction of the lactam moiety in compound **18** to obtain the corresponding saturated pyrrolidine, following the Garcia-Ruano's procedure.[20] Unfortunately, the reduction failed and only the starting compound was obtained.[21]

In conclusion, two complementary routes leading to *syn*- and *anti*-pyrrolidinyl glycines via a nucleophilic addition to nitrone **5** and a cycloaddition reaction of **11** with methyl acrylate, respectively, have been achieved. In the first approach, an ethynyl group has been used as a synthetic equivalent of the carboxyl unit. For the second approach, the synthetic equivalence between the oxazolidine ring and the glycine unit has been utilized. Unusual conformationally constrained α,β-diamino-acids containing both a saturated ring of pyrrolidine and a pyrrolidin-2-one ring have been successfully prepared in this work. The preparation of other pyrrolidinyl glycines of interest through these methods, as well as chemical modifications of the prepared compounds are now underway in our laboratories.

Acknowledgements

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15. Data for **10**: oil, $[\alpha]_D$ −54 (*c* 0.11, $CHCl_3$). ^1H NMR (400 MHz, 100 °C, DMSO-d_6): δ 1.42 (s, 9H), 1.44 (s, 9H), 1.96 (s, 3H), 2.10–2.30 (m, 2H), 3.06 (dd, $J = 3.8$, 12.0 Hz, 1H), 3.15 (dd, $J = 3.5$, 12.0 Hz, 1H), 3.59 (s, 3H), 4.10 (m, 1H), 4.70 (d, $J = 8.1$ Hz, 1H), 6.10 (br s, 1H). Anal. Calcd for $C_{21}H_{36}N_2O_6$ C, 61.14; H, 8.80; N, 6.79. Found: C, 61.37; H, 8.61; N, 6.55.
16. Data for **12a**: white solid; mp 63–66 °C. $[\alpha]_D$ −54 (*c* 0.11, $CHCl_3$); ^1H NMR (400 MHz, 70 °C, DMSO-d_6): δ 1.44 (s, 3H), 1.45 (s, 12H), 2.56 (ddd, $J = 2.4$, 8.3, 12.8 Hz, 1H), 2.63 (ddd, $J = 7.5$, 8.1, 12.8 Hz, 1H), 3.45 (ddd, $J = 2.4$, 7.4, 7.5 Hz, 1H), 3.72 (s, 3H), 3.80–3.83 (m, 4H), 4.07 (d, $J = 13.6$ Hz, 1H), 4.60 (dd, $J = 8.1$, 8.3 Hz, 1H), 7.26–7.30 (m, 5H). Anal. Calcd for $C_{22}H_{32}N_2O_6$ C, 62.84; H, 7.67; N, 6.66. Found: C, 62.71; H, 7.53; N, 6.70.
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19. Data for **18**: oil, $[\alpha]_D$ −2 (*c* 0.13, $CHCl_3$). ^1H NMR (400 MHz, 70 °C, DMSO-d_6): δ 1.39 (s, 9H), 1.50 (s, 9H), 2.04 (ddd, $J = 6.3$, 6.7, 13.7 Hz, 1H), 2.52–2.54 (m, 1H), 3.70 (s, 3H), 4.54–4.56 (m, 1H), 5.03 (dd, $J = 3.5$, 9.1 Hz, 1H), 5.56 (dd, $J = 6.7$, 9.8 Hz, 1H), 7.01 (d, $J = 9.1$ Hz, 1H), 7.50–7.54 (m, 2H), 7.67–7.70 (m, 1H), 8.02–8.05 (m, 2H). Anal. Calcd for $C_{24}H_{32}N_2O_9$ C, 58.53; H, 6.55; N, 5.69. Found: C, 58.49; H, 6.60; N, 5.76.
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21. Quite probably the reaction conditions are too mild for performing the reaction, and other conditions could lack of chemoselectivity with the different ester functionalities present in the molecule. This reduction step should be attempted at a earlier stage (i.e., with compound **13**) in order to have some guarantee of success. We are currently studying this possibility and it will be reported in due course.