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Enantioselective synthesis of β-amino-diacids

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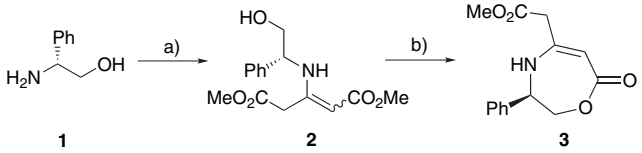
Abstract—An efficient route to orthogonally protected β-amino-diacids is described: chiral derivative **3** was shown to be a precursor of enantiopure substituted β-amino acids. The key step of the procedure is a diastereoselective reduction of β-enaminolactones **5** by $NaBH_3CN$ in CH_2Cl_2. A study concerning the regio- and diastereoselectivity of alkylation of β-enaminolactone **3** is also presented.

β-Amino acids have attracted much attention in recent years, whether as analogues of α-amino acids to increase the resistance of peptides to enzymatic degradation[1] or as building blocks for the synthesis of β-lactam antibiotics.[2] In addition, β-amino acids derivatives are crucial structural components of numerous biologically active natural products.[3] Although many methods for synthesizing enantiomerically pure β-amino acids have been reported, great effort continues to be devoted towards more efficient enantioselective methods.[4] There are many approaches for asymmetric synthesis of β-amino acids including homologation of α-amino acids,[5] enzymatic resolution,[6] addition of enolates to imines,[7] catalytic hydrogenations.[8] The most obvious strategy consists of chiral Lewis acid catalyzed conjugate addition of amines to α,β-unsaturated esters.[9] Another strategy is based on stereoselective alkylation en route to enantiopure β-amino acids using chiral auxiliaries.[10]

Herein, we report a novel synthetic strategy for the construction of orthogonally protected β-amino-diacids by using a new chiral auxiliary **3**. While β-amino-diacids and -diesters have a broad range of synthetic applications,[11] they have been used most extensively as precursors to β-lactams.[12]

The synthesis of compound **3** was realized in two steps (Scheme 1).



Scheme 1. Reagents and conditions: (a) acetonedicarboxylate, toluene, reflux 48 h 100%; (b) (i) NaH, THF, 1 h, (ii) NH_4Cl/H_2O, 83%.

The condensation of dimethyl acetonedicarboxylate with (*R*)-phenylglycinol **1** proceeds in toluene. This condensation to form the two *Z*- and *E*-diastereoisomers does not require the removal of water and, after two days in the refluxing solvent, β-enaminoester **2** was obtained in nearly quantitative yield by evaporation of the solvent. The next step involved the formation of the optically active heterocyclic compound via cyclization. The crude material was then dissolved in dry THF and the addition of NaH (1.1 equiv) at room temperature provided after 15 min, classical work-up and chromatography a good yield of the desired β-enaminolactone **3** (83% from starting (*R*)-phenylglycinol **1**) as a unique regioisomer.[13]

Next, we were interested by the regio- and stereoselectivity of alkylation of the β-enaminolactone **3**, a class of compounds which has been only scarcely explored to date.[14] The results are reported in Scheme 2.

Enolates **3′** derived from product **2** was generated by reaction with MeONa, which was liberated during the cyclization step at 0 °C in THF. The electrophiles (RX in conditions b and d) were added at 0 °C and the reaction mixtures were stirred for 1 h 30 min at this

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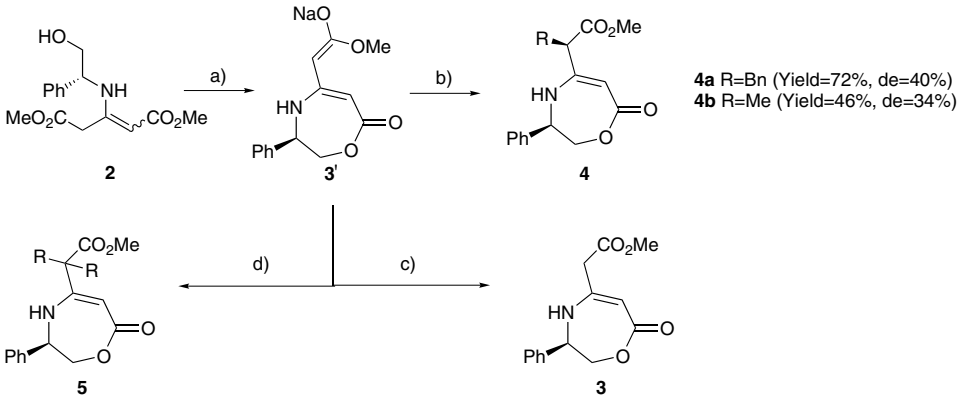
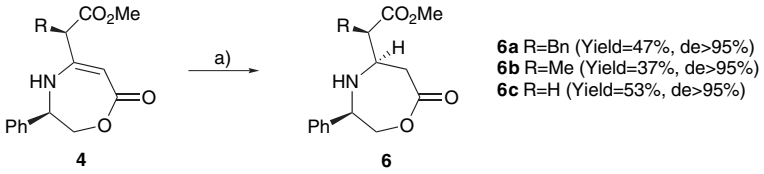


Scheme 2. Reagents and conditions: (a) NaH (1.1 equiv), THF, 0 °C, 15 min; (b) (i) RX (0.95 equiv), 1.5 h at 0 °C, (ii) aqueous NH_4Cl; (c) aqueous NH_4Cl; (d) (i) NaH (1.1 equiv), (ii) RX (2.2 equiv) 1.5 h at 0 °C, (iii) aqueous NH_4Cl.



Scheme 3. Reagents and conditions: (a) (i) AcOH (13 equiv), 0 °C, CH_2Cl_2, (ii) $NaBH_3CN$ (1.1 equiv), CH_2Cl_2 0 °C to rt, 1 h, (iii) aqueous NH_4Cl.

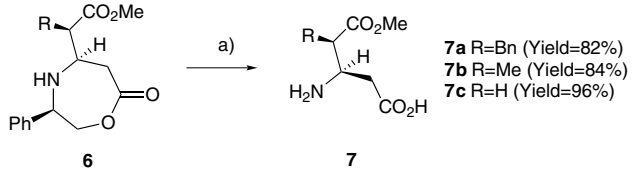
temperature and further hydrolyzed with a saturated aqueous ammonium chloride solution (conditions c correspond to those reported in Scheme 1 for the formation of compound **3**).

The results reported show that the electrophile (RX) attack the ambident enolate **3′** with total exo-regioselectivity (conditions b). In all cases, we observed the presence of the exo-dialkylated products **5** (**5a**: R = Bn, **5b**: R = Me). These products **5** were exclusively formed when 1.1 more equivalent of base and RX were used (conditions d). Unfortunately, the diastereoselectivity of alkylation was low (conditions b). The major diastereoisomer **4a** could be separated by crystallization from Et_2O.[15] The *R*-absolute configuration of the new created stereocenter in product **4a** was established by X-ray analysis.[16] Configuration of compound **4b** was deduced from the stereochemistry of product **4a**.

The reductions of compounds **4** were carried out with $NaBH_3CN$ (6 equiv) in dichloromethane with acetic acid (13 equiv) at 0 °C for 1 h to give the saturated aminolactones **6** (Scheme 3).[17]

In all experiments we observed, in the ^1H NMR spectrum of the crude material, compound **6** as almost pure.[18] Some loss of material during the extraction and chromatography processes could explain the yields, which were obtained as indicated in Scheme 3. The observed total diastereoselectivity corresponds to an attack of the reducing agent in an *anti* orientation with respect to the phenyl group.[19]

The generated β-aminolactones **6** were subjected to $Pd(OH)_2/C$-catalyzed hydrogenolysis to provide the corresponding β-enaminoesters **7** in enantiopure forms and in good yields (Scheme 4).[20]



Scheme 4. Reagents and conditions: (a) H_2, $Pd(OH)_2/C$ (0.5 equiv), MeOH, rt, two days.

In summary, we have developed a novel and diastereoselective method for the asymmetric synthesis of orthogonally protected β-amino-diacids in four steps starting from (*R*)-phenylglycinol **1**. Complete diastereocontrol in the reduction step allows easy access to β-aminolactones **6**. Heterocycles derived from β-enaminolactones **3** are currently used in the asymmetric synthesis of poly-substituted piperidines and quinolizidines.

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13. Spectral data for compound **3**: IR ν (cm^{-1}): 3293, 1743, 1715, 1655, 1610, 1560. ^1H NMR ($CDCl_3$, 250 MHz): 3.17 (s, 2H), 3.68 (s, 3H), 4.23 (d, 1H, $J = 12.75$ Hz), 4.44 (dd, 1H, $J = 6.75$ Hz, $J = 12.75$ Hz), 4.58 (s, 1H), 4.67 (d, 1H, $J = 6.75$ Hz), 6.05 (broad s, 1H), 7.28–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): 41.8, 52.8, 61.8, 70.2, 88.4, 126.8, 129.0, 129.5, 137.9, 148.4, 169.8, 170.2.
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15. Spectral data for compound **4a**: Mp: 202 °C. Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 67.34; H, 6.01; N, 3.87. $[\alpha]_D^{20}$ −38 (*c* 1, $CHCl_3$). IR ν (cm^{-1}): 3261–1736–1638–1580–1549. ^1H NMR ($CDCl_3$, 250 MHz): 3.05 (dd, 1H, $J = 7.5$ Hz, $J = 13.25$ Hz), 3.18 (dd, 1H, $J = 7.75$ Hz), 3.29 (t, 1H, $J = 7.75$ Hz), 3.68 (s, 3H), 4.20 (d, 1H, $J = 12.5$ Hz), 4.36 (dd, 1H, $J = 6.75$ Hz, $J = 12.5$ Hz), 4.69 (d, 1H, $J = 7$ Hz), 4.73 (s, 1H), 7.05–7.37 (m, 10H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): 39.8, 53.1, 55.2, 62.1, 70.3, 87.7, 126.9, 127.6, 129.1, 129.2, 129.8, 137.4, 138.0, 152.0, 170.1, 172.7.
16. Atomic coordinates, bond lengths and angles have been deposited at the Cambridge Crystallographical Data Center with the deposition number CCDC283799.
17. Reductions were realized on diastereomerically- and enantiomerically pure compounds **4a**,**c** and on a mixture of diastereoisomers of compound **4b**.
18. The stereochemistry of compounds **6a**,**c** was established by ^1H NMR spectroscopy (NOE experiments).
19. Spectral data for compound **6a**: Mp: 142 °C. $[\alpha]_D^{20}$ −45 (*c* 1.2, $CHCl_3$). IR ν (cm^{-1}): 3414–1717. ^1H NMR ($CDCl_3$, 250 MHz): 2.71–2.85 (m, 2H), 2.95–3.05 (m, 3H), 3.21 (dd, 1H, $J = 3.5$ Hz, $J = 9.75$ Hz), 3.60 (s, 3H), 4.01 (d, 1H, $J = 7.5$ Hz), 4.11 (d, 1H, $J = 12.5$ Hz), 4.25 (dd, 1H, $J = 7.5$ Hz, $J = 12.5$ Hz), 7.08–7.32 (m, 10H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): 34.8, 42.9, 52.3, 53.8, 54.3, 63.5, 75.4, 127.1, 127.2, 128.7, 129.0, 129.3, 129.4, 138.9, 140.2, 173.5, 174.1.
20. Spectral data for compound **7a**: Mp: 186 °C. $[\alpha]_D^{20}$ −35 (*c* 0.8, HCl (1 M)). IR ν (cm^{-1}): 3515–1716. Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: 60.96; H, 6.80; N, 5.34. ^1H NMR (CD_3OD, 250 MHz): 2.46 (dd, 1H, $J = 9$ Hz, $J = 17$ Hz), 2.63 (dd, 1H, $J = 4.5$ Hz, $J = 17$ Hz), 2.98–3.12 (m, 3H), 3.59 (s, 3H), 3.64 (dd, 1H, $J = 4.75$ Hz, $J = 9.25$ Hz), 7.18–7.32 (m, 5H). ^{13}C NMR (CD_3OD, 62.9 MHz): 36.4, 37.8, 51.1, 51.9, 52.9, 128.4, 130.1, 130.3, 139.1, 174.5, 176.