Rational synthesis of all the four stereoisomers of 3-(*trans*-2-aminocyclopropyl)alanine

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All the four stereoisomers of 3-(*trans*-2-aminocyclopropyl)alanine – a key constituent of the potential antitumor agent belactosin A – were prepared by simple catalytic hydrogenation of (2*S*,1′*S*,2′*S*)-, (2*S*,1′*R*,2′*R*)-, (2*R*,1′*R*,2′*R*)-, and (2*R*,1′*S*,2′*S*)-3-(*trans*-2-nitrocyclopropyl)alanines in 95, 93, 91 and 92% yields, respectively.

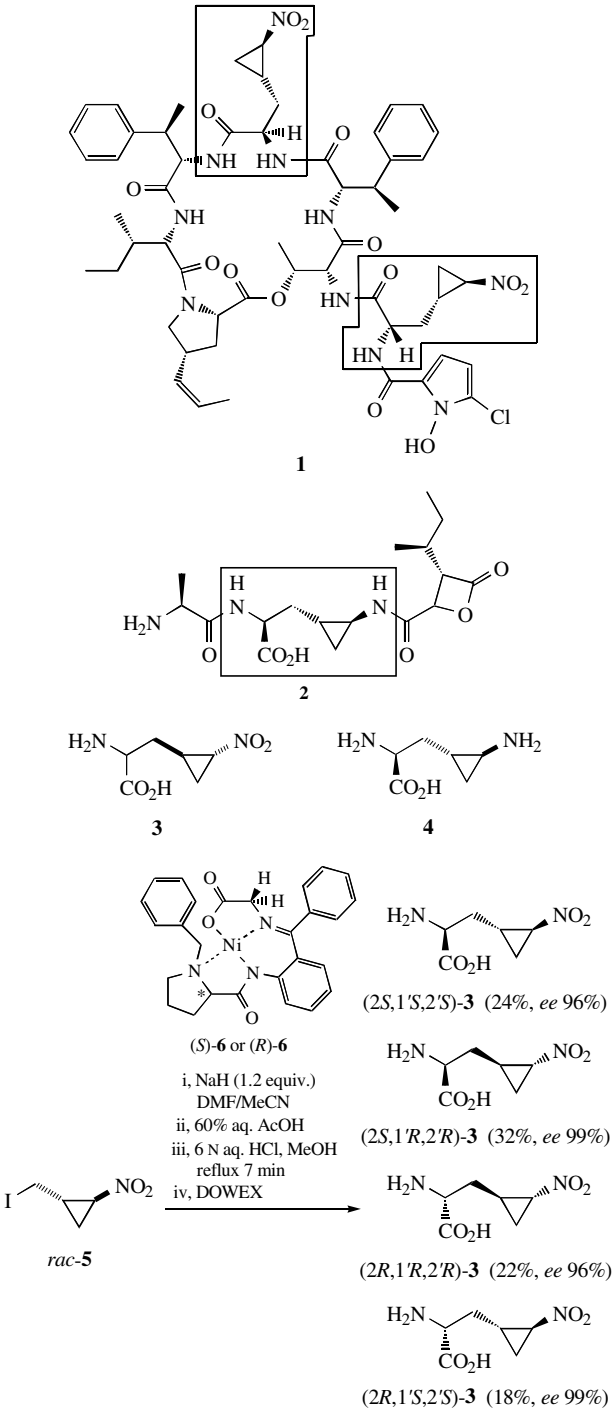
Most of the over two dozen known naturally occurring amino acids containing a cyclopropyl group, as well as most of the cyclopropyl analogues of natural amino acids, are responsible for interesting biological activities of compounds containing them as constituents.[1] Among such natural products, peptidolactone hormaomycin **1**, which influences the secondary metabolite production of certain bacteria,[2] and recently isolated belactosin A **2**, which is interesting as a potential antitumor agent and effects proteasome inhibition,[3] are especially intriguing as they contain previously unknown 3-(*trans*-2-nitrocyclopropyl)alanines [(NcP)ala] (2*S*,1′*R*,2′*R*)-**3** and (2*R*,1′*R*,2′*R*)-**3**, and 3-(*trans*-2-aminocyclopropyl)alanine [(AcP)ala] (2*S*,1′*R*,2′*S*)-**4** as key constituents (Scheme 1).

Recently, Armstrong and Scutt[4] reported an elegant multistep synthesis of an epimer of naturally occurring (AcP)ala **4** starting from commercially available, yet expensive, glycidol benzyl ether with a key step like the one in our previously published synthesis of 3,3-dideuterio-3-(*trans*-2-aminocyclopropyl)alanine 3,3-D_2-*rac*-**4**.[5] It is obvious that our recently developed asymmetric synthesis of all the four diastereomers of (NcP)ala **3** (Scheme 1),[6] which in terms of ease and productivity established a big leap forward in comparison with the previously reported multistep procedure,[7] also offered itself as a rational access to all the four stereoisomers of (AcP)ala **4** in multigramme quantities simply by chemoselective reduction of the nitro group in enantiomerically pure (NcP)ala **3**.

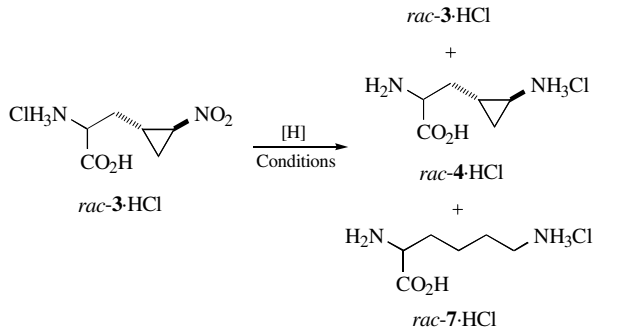
However, an attempted catalytic hydrogenation of the hydrochloride of racemic (NcP)ala *rac*-**3**·HCl in water, analogously to the preparation of 2-(*trans*-2-aminocyclopropyl)glycine,[7(b),(d)] furnished a non-separable mixture of starting *rac*-**3**·HCl, target *rac*-**4**·HCl and the hydrochloride of racemic lysine *rac*-**7**·HCl in different ratios (Scheme 2, Table 1). No improvement was observed upon either varying the solvent, the catalyst or the hydrogen pressure or by applying other reducing agents recommended for the chemoselective reduction of aliphatic nitro into amino derivatives,[8] such as ammonium formate under palladium catalysis or sodium borohydride under nickel catalysis (Table 1). Most probably, protonation of the amino group on the three-membered ring in the target molecule creates a kind of donor–acceptor-substituted cyclopropane,[9] which is particularly prone to undergo ring opening under hydrogenation conditions. However, catalytic hydrogenation of free *rac*-**3** under neutral

Table 1 Attempted chemoselective reduction of the nitro group in the hydrochloride of racemic 2-(*trans*-2-nitrocyclopropyl)alanine (*rac*-**3**·HCl) under various conditions at ambient temperature (see Scheme 2).

Entry	Reducing agent (catalyst)	Pressure of H_2/bar (Reaction time/h)	Solvent	Yield (%)		
				rac-**3**·HCl	*rac*-**4**·HCl	*rac*-**7**·HCl
1	H_2 (Pd/C)	1 (24)	H_2O	55	40	0
2	H_2 (Pd/C)	2 (60)	H_2O	0	60	35
3	H_2 (Pd/C)	2 (20)	H_2O	0	53	41
4	H_2 ($PdCl_2$)	1 (96)	MeOH	0	0	94
5	$NaBH_4$ ($NiCl_2·6H_2O$)	1 (20)	MeOH	15	0	80
6	HCO_2NH_4 (Pd/C)	1 (20)	MeOH	10	0	83



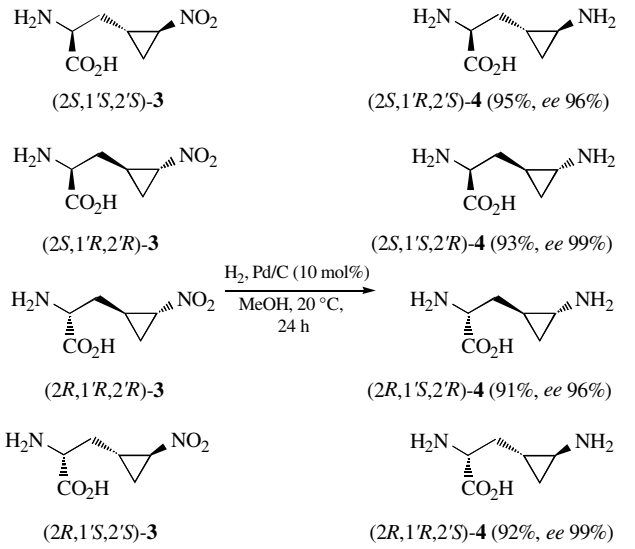
Scheme 1



Scheme 2

conditions in anhydrous methanol afforded the desired cyclopropyl-containing *rac*-**4** as the sole product.

Under these conditions, (2*S*,1′*R*,2′*S*)-, (2*S*,1′*S*,2′*R*)-, (2*R*,1′*S*,2′*R*)-, and (2*R*,1′*R*,2′*S*)-3-(2-aminocyclopropyl)alanines **4** were obtained from corresponding (2*S*,1′*S*,2′*S*)-, (2*S*,1′*R*,2′*R*)-, (2*R*,1′*R*,2′*R*)-, and (2R,1′*S*,2′*S*)-3-(2-nitrocyclopropyl)alanines **3** in 95, 93, 91 and 92% yields, respectively (Scheme 3).†



Scheme 3

† *General procedure for hydrogenative transformation of the [(NcP)ala] diastereomers into the corresponding (aminocyclopropyl)alanines [(AcP)ala].* To a solution of enantiomerically pure amino acid **3** (348 mg, 2.0 mmol) in anhydrous MeOH (160 ml) was added Pd/C (Merck, 10% Pd, 0.2 mmol, 0.21 g). The mixture was vigorously stirred under H_2 (1 bar) at 20 °C for 24 h. The catalyst was filtered off, the filtrate was concentrated under reduced pressure to give desired (2*S*,1′*R*,2′*S*)-, (2*S*,1′*S*,2′*R*)-, (2*R*,1′*S*,2′*R*)-, and (2*R*,1′*R*,2′*S*)-3-(*trans*-2-aminocyclopropyl)alanines **4** in 95, 93, 91 and 92% yields, respectively, after recrystallization from Pr^iOH–H_2O.

(2*S*,1′*R*,2′*S*)-**4**: colourless solid, mp 148 °C (decomp.), $[\alpha]_D^{20}$ +29.3° (*c* 0.6, H_2O). ^1H NMR (250 MHz, D_2O) δ: 0.60 (ddd, 1H *J* 5.9, 6.3, 7.2 Hz), 0.77 (m, 1H), 0.97 (m, 1H), 1.68 (m, 1H), 1.81 (m, 1H), 2.28 (m, 1H), 3.66 (t, 1H, *J* 6.2, 6.2 Hz). ^{13}C NMR (62.9 MHz, D_2O) δ: 13.97 (CH_2), 17.07 (CH), 31.67 (CH), 36.51 (CH_2), 57.24 (CH), 179.66 (C). IR (ν/cm^{-1}): 3629, 3056, 2953, 1733, 1630, 1587.

(2*S*,1′*S*,2′*R*)-**4**: colourless solid, mp 150 °C, $[\alpha]_D^{20}$ –37.8° (*c* 0.4, H_2O). ^1H NMR (250 MHz, D_2O) δ: 0.60 (ddd, 1H, *J* 5.8, 6.5, 7.3 Hz), 0.76 (m, 1H), 0.92 (m, 1H), 1.71 (m, 1H), 1.80 (m, 1H), 2.23 (m, 1H), 3.63 (ddd, 1H, *J* 5.7, 5.7, 5.8 Hz). ^{13}C NMR (62.9 MHz, D_2O) δ: 14.19 (CH_2), 17.33 (CH), 31.88 (CH), 36.70 (CH_2), 57.82 (CH), 179.69 (C). IR (ν/cm^{-1}): 3359, 3072, 2927, 1617, 1406, 1322.

(2*R*,1′*S*,2′*R*)-**4**: colourless solid, mp 153 °C (decomp.), $[\alpha]_D^{20}$ –29.1° (*c* 0.4, H_2O). ^1H, ^{13}C NMR and IR spectra are virtually identical to those of (2*S*,1′*R*,2′*S*)-**4**.

(2*R*,1′*R*,2′*S*)-**4**: colourless solid, mp 148 °C (decomp.), $[\alpha]_D^{20}$ +37.7° (*c* 0.6, H_2O). ^1H, ^{13}C NMR and IR spectra are virtually identical to those of (2*S*,1′*S*,2′*R*)-**4**.

These achievements, which constitute an overall six-step enantioselective synthesis of (AcP)ala **4** from inexpensive achiral and racemic starting materials, not only facilitate the forthcoming total synthesis of belactosin A **2** but also approach to synthetic analogues of naturally occurring small peptides to modify their biological activity. For example, the (2*S*,1′*S*,2′*R*)-3-(*trans*-2-aminocyclopropyl)alanine [(2*S*,1′*S*,2′*R*)-**4**] has recently been incorporated instead of the corresponding (NcP)ala [(2*S*,1′*R*,2′*R*)-**3**] in the side chain of hormaomycin **1** in order to be able to test the potential biological activity of modified peptidolactones of the hormaomycin type.

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