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A practical synthesis of (*R*)- and (*S*)-3-amino-3,4-dihydro-1*H*-quinolin-2-one

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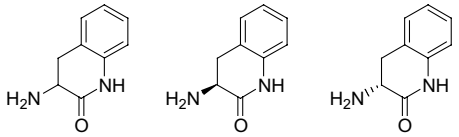
Abstract—Asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester with 2-nitrobenzyl bromide followed by reductive cyclization provides (*R*)- and (*S*)-3-amino-3,4-dihydro-1*H*-quinolin-2-one in high yield and high enantiomeric excess.

1. Introduction

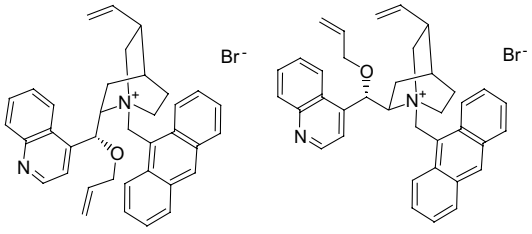
The building block 3-amino-3,4-dihydro-1*H*-quinolin-2-one **1** has been incorporated, usually in racemic form, into various compounds with interesting biological activity, such as antimicrobial agents,[1] angiotensin converting enzyme inhibitors,[2] tachikynin antagonists,[3] metalloprotease inhibitors,[4] or D2 receptor agonists.[5] More recently AstraZeneca[6] and Merck[7] scientists have shown that thienopyrrole or indole amides of (*R*)- and (*S*)-3-amino-3,4-dihydro-1*H*-quinolin-2-one are potent inhibitors of glycogen phosphorylase. The optically active parent compounds or suitably protected derivatives have until now been prepared by resolution or by the multistep transformation of phenylalanine. We herein report a practical synthesis of (*R*)- and (*S*)-3-amino-3,4-dihydro-1*H*-quinolin-2-one (***R***)-**1** and (***S***)-**1**, respectively, by a two-step process, via an asymmetric alkylation followed by a one-pot reduction/cyclization.



(±)-1 (*S*)-1 (*R*)-1

2. Results and discussion

The phase-transfer catalyzed asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester allows the preparation of α-amino acid derivatives with high enantioselectivity.[8] In this process, the tight association of the glycine ester anion with the chiral tetraalkylammonium salt (e.g., **2s** or **2r**) allows effective shielding of one of the faces of the enolate with alkylation predominantly from the more accessible side. This process thus appeared quite applicable to the synthesis of conformationally restricted phenylalanine analogues such as (***R***)- or (***S***)-**1**, wherein the glycine enolate could be reacted with an appropriately substituted benzyl halide and subsequently cyclized.



2s **2r**

The first step was accomplished by reacting *N*-(diphenylmethylene)glycine *tert*-butyl ester with 2-nitrobenzyl bromide in the presence of the cinchonidine-derived phase-transfer catalyst **2s**, to give the 2-nirophenylalanine derivative (***S***)-**3** in 92% yield and 92.5% enantiomeric excess (ee). The alkylation was followed by catalytic hydrogenation under acidic conditions, to

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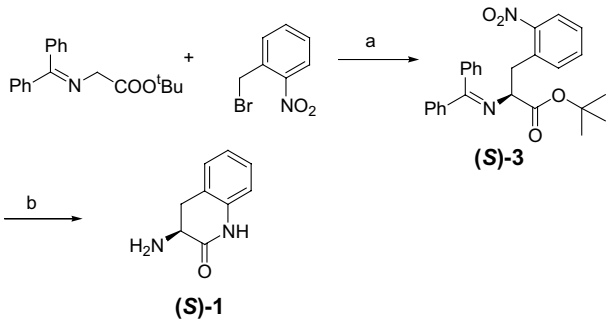
smoothly effect in one step the reduction of the nitro group, deprotection of the amine and carboxyl functions and cyclization (Scheme 1). (*S*)-**1** was obtained in 65% yield and 89% ee. A similar sequence was used for the (*R*)-enantiomer, using the quinine-derived catalyst **2r**, to provide the alkylated product (*R*)-**3** in 90% ee and the final product (*R*)-**1** in 88.5% ee.



Scheme 1. Reagents and conditions: (a) **2s**, $CsOH{\cdot}H_2O$, CH_2Cl_2, −30 °C, 92%; (b) H_2, Pd–C, methanol, 2 M HCl, 65%.

3. Conclusion

In conclusion, we have shown that (*R*)- and (*S*)-**1** can be obtained in an easy two-step sequence. This sequence proceeds in high yield and high enantiomeric excess, and can be easily adapted to large scale.

4. Experimental section

4.1. (*S*)-2-(Benzhydrylidene-amino)-3-(2-nitro-phenyl)-propionic acid *tert*-butyl ester (*S*)-3[9]

Diphenylmethylene glycine *tert*-butyl ester (10 g, 34 mmol), 2-nitrobenzyl bromide (10.5 g, 50 mmol) and the cinchonidine-derived catalyst **2s** (1.9 g, 3.4 mmol), were dissolved in dichloromethane at 0 °C. The solution was cooled to −30 °C and cesium hydroxide (8.53 g, 51 mmol) added. The mixture was stirred at −30 °C overnight, warmed to room temperature, diluted with ether, washed with water and brine, dried over sodium sulfate, and concentrated to dryness. The product was purified by flash-chromatography (hexanes/ethyl acetate, 9:1) and isolated as an oil (13.4 g, 92%). Enantiomeric excess [high pressure liquid chromatography on a Whelk-O-1 column (hexanes/isopropyl alcohol, 95:5)]: 92.5%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9 H), 3.39 (dd, $J = 9.3$, 13.3 Hz, 1H), 3.68 (dd, $J = 3.7$, 13.3 Hz, 1H), 4.30 (dd, $J = 3.7$, 9.4 Hz, 1H), 6.58 (d, $J = 6.6$ Hz, 2H), 7.23–7.45 (m, 10H), 7.55 (d, $J = 7.5$ Hz, 2H), 7.85 (dd, $J = 1.2$, 7.9 Hz, 1H); MS m/z 431 (MH^+).

4.2. (*S*)-3-Amino-3,4-dihydro-1H-quinolin-2-one hydrochloride (*S*)-1

10% Palladium on carbon (1.5 g) was added to a solution of (*S*)-**3** (13.4 g, 32 mmol) in 2 M hydrochloric acid (200 mL) and methanol (50 mL). The mixture was hydrogenated at 40 psi overnight. The solution was filtered over diatomaceous earth and concentrated to dryness. The solid was redissolved in methanol and precipitated with ether. Yield 4.3 g (65%). Enantiomeric excess [high pressure liquid chromatography on a Whelk-O-1 column (hexanes/isopropyl alcohol, 95:5)]: 89%. $[\alpha]_D^{20} = -112.74$ (*c* 10 mg/mL, CH_3OH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.07 (dd, $J = 15$, 15 Hz, 1H), 3.18 (dd, $J = 7$, 15 Hz, 1H), 4.19 (dd, $J = 7$, 15 Hz, 1H), 6.90 (d, $J = 8$ Hz, 1H), 6.97 (dt, $J = 1$, 7 Hz, 1H), 7.19 (t, $J = 8$ Hz, 1H), 7.26 (dd, $J = 8$, 20 Hz, 1H), 8.63 (br s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 29.7, 48.3, 116.2, 121.4, 123.5, 128.6, 129.0, 137.6, 166.9; MS m/z 163 (MH^+). Mp > 260 °C.

4.3. (*R*)-2-(Benzhydrylidene-amino)-3-(2-nitro-phenyl)-propionic acid *tert*-butyl ester (*R*)-3

Prepared by the same procedure as (*S*)-**3** using the cinchonine-derived catalyst **2r**. Enantiomeric excess [high pressure liquid chromatography on a Whelk-O-1 column (hexanes/isopropyl alcohol, 95:5)]: 90%.

4.4. (*R*)-3-Amino-3,4-dihydro-1H-quinolin-2-one hydrochloride (*R*)-1

Prepared by the same procedure as (*S*)-**1**. Enantiomeric excess [high pressure liquid chromatography on a Whelk-O-1 column (hexanes/isopropyl alcohol, 95:5)]: 88.5%. $[\alpha]_D^{20} = +121.9$ (*c* 10 mg/mL, CH_3OH). Mp > 260 °C.

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