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Improved Schöllkopf construction of quaternary α-amino acids: efficient enantioselective synthesis of integrin LFA-1 antagonist BIRT-377

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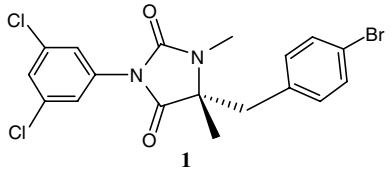
Abstract—The Schöllkopf methodology for the asymmetric synthesis of α-amino acids which was previously not applicable to the construction of α,α-dialkylated (quaternary) α-amino acids, has been rendered practical for this purpose and applied in a highly efficient enantioselective synthesis of integrin LFA-1 antagonist BIRT-377.

1. Introduction

The synthesis of α,α-dialkylated (quaternary) α-amino acids has recently received considerable attention since their incorporation in modified peptides, often improves both the biological activity and the pharmacological profile of the latter, due to the introduction of unusual conformational constraints which change their secondary or tertiary structure.[1] Furthermore, these peptides are rendered more stable metabolically due to the decreased rate of proteolysis.[2]

Along with recently developed catalytic enantioselective protocols,[3] alkylation of glycine or amino acid chiral enolate equivalents stands as one of the most convenient and general methodologies for the synthesis of enantiomerically pure α-amino acids, particularly, quaternary α-amino acids.[4] One of the most notable examples of the latter approach, is the bis-lactim ether methodology developed by Schöllkopf and co-workers.[5] Herein, we report an efficient enantioselective synthesis of the integrin LFA-1 antagonist BIRT-377 **1** (Fig. 1) which is essentially an *N*-aryl hydantoin derivative of such a quaternary α-amino acid by employing an improved Schöllkopf protocol, based on the use of *tert*-BuLi instead of *n*-BuLi[5] for the deprotonation of the substituted bis-lactim ether **2** (Scheme 1).



1

Figure 1. Structure of cell adhesion inhibitor BIRT-377.

Prior to the discovery of cell adhesion inhibitor BIRT-377,[6] potential therapeutics designed to block the binding of LFA-1 to ICAM-1 for the treatment of immunological disorders,[7] had been mostly mAb based,[8] mainly because of the problems inherent in identifying or designing small molecules that antagonize protein–protein interactions.[9] Specifically, blockade of integrin LFA-1 by monoclonal antibodies (mAbs) had shown efficacy in animal models of inflammation and autoimmune diseases such as arthritis, ischemia/reperfusion injury, and transplant rejection.[10] Therefore, an effective antagonist of LFA-1, such as BIRT-377, may prove useful for the treatment or prophylaxis of inflammatory diseases, autoimmune diseases including Crohn's disease,[6] tumor metastasis, allograft rejection, and reperfusion injury.[11]

2. Results and discussion

Despite a few recent reports describing catalytic enantioselective syntheses of BIRT-377,[3a,12] we envisioned that

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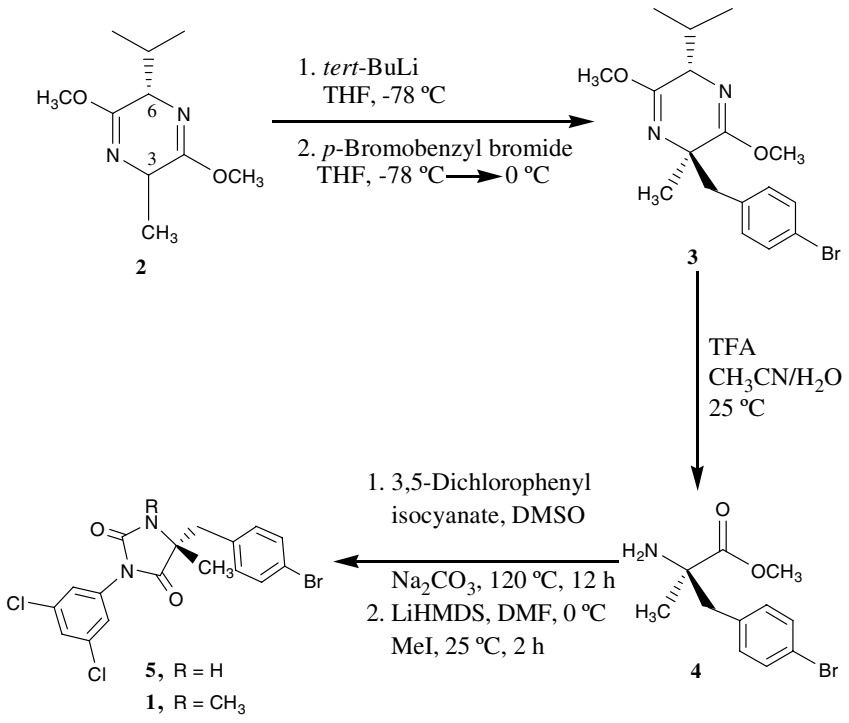

Scheme 1. Schöllkopf-type enantioselective synthesis of cell adhesion inhibitor BIRT-377.

the more established chiral auxiliary-based methodology might lead to an improved enantioselective route to BIRT-377.[13] Thus, deprotonation of chiral auxiliary **2** with *tert*-BuLi followed by alkylation of the resulting anion with *p*-bromobenzyl bromide, provided **3** in 85% yield and very high diastereoselectivity (≫95%, Scheme 1). Notably, the yield of this alkylation using *n*-BuLi as the base was only 60%.[14] This significant yield disparity is most likely due to the exclusively basic action of *tert*-BuLi toward the less hindered C-3 hydrogen as opposed to the C-6 one, as well as its negligible nucleophilicity toward the imino esters. Hydrolysis of **3** with TFA,[5b] and reaction of the derived α-amino ester **4** with 3,5-dichlorophenyl isocyanate, gave rise to hydantoin derivative **5** in 90% yield which was N-methylated to furnish the requisite LFA-1 antagonist BIRT-377 **1** (100% yield, Scheme 1).[15]

The asymmetric synthesis of BIRT-377 described herein is highly competitive with both previously reported chiral auxiliary-based syntheses,[16] and the more recent catalytic approaches.[3a,12,13]

The high efficiency of this method relies on both the ready availability of **2** (E. Merck),[17] and the two-step, one-pot conversion of **3** to **5** in >90% isolated yield.

3. Conclusion

We have shown that the Schöllkopf methodology can be conveniently employed for the enantioselective construction of quaternary α-amino acids in a practical manner,[4,5] and we have applied this protocol to the synthesis of quaternary α-amino ester **4** (Scheme 1),[18] which has been efficiently converted to the useful integrin LFA-1 antagonist BIRT-377.[6,7,10,11,16]

4. Experimental

4.1. General

All of the compounds, for which analytical and spectroscopic data are quoted, were homogenous by TLC. TLC analyses were performed using silica gel plates (E. Merck silica gel 60 F-254) and components were visualized by the following methods: ultraviolet light absorbance, and ninhydrin spray. Column chromatography was carried out on silica gel (E. Merck, 70–230 mesh), height 42 cm, diameter 2.3 cm. All the compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded on a 200 MHz Mercury Varian spectrometer. Electron spray mass spectroscopy (ESMS) was performed on a Surveyor MSQ instrument. Optical rotations were recorded on a Perkin–Elmer 349 Polarimeter ($\lambda = 589$ nm, 1 dm cell). HPLC was carried out using a Pharmacia LKB-HPLC consisting of a Waters 2487-dual λ Absorbance Detector and a 224B Pump.

4.2. (3*R*,6*S*)-3-(4-Bromobenzyl)-6-isopropyl-5-methoxy-3-methyl-3,6-dihydro-2-pyrazinyl methyl ether 3

To a solution of (6*S*)-6-isopropyl-5-methoxy-3-methyl-3,6-dihydro-2-pyrazinyl methyl ether (**2**, 0.30 g, 1.52 mmol) in dry THF (3 ml) under argon at −78 °C was added *tert*-BuLi (1.6 M, 0.95 ml, 1.52 mmol) dropwise. The resulting solution was stirred at −78 °C for 1 h and treated slowly with a solution of 4-bromobenzyl bromide (0.50 g,

2.00 mmol) in dry THF (4 ml). The reaction mixture was stirred at −78 °C for 10 h, allowed to slowly warm to ambient temperature, and was quenched with saturated NH_4Cl. The aqueous layer was extracted with Et_2O twice. The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified by column chromatography (silica gel, CH_2Cl_2) to afford **3** (0.47 g, 85%). $[\alpha]_D^{25} = -70.0$ (*c* 1, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$): δ 0.57 (d, 3H, $J = 6.6$), 0.93 (d, 3H, $J = 6.6$), 1.44 (s, 3H), 2.22–2.17 (m, 1H), 2.71, 3.05 (AB, 2H, $J_{AB} = 12.5$), 3.27 (d, 1H, $J = 3.7$), 3.65 (s, 6H), 6.87 (d, 2H, $J = 8.1$), 7.28 (d, 2H, $J = 8.1$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.8, 19.4, 28.8, 30.8, 46.8, 52.1, 52.3, 59.8, 60.7, 120.5, 130.9, 131.9, 136.8, 162.3, 164.0. MS (EI): 367.1 (M^+).

4.3. Methyl (2*R*)-2-amino-3-(4-bromophenyl)-2-methylpropanoate 4

To a solution of compound **3** (0.30 g, 0.87 mmol) in acetonitrile–water 3:1 (4 ml), trifluoroacetic acid (0.5 ml) was added and the resulting solution was stirred at ambient temperature for 10 h. It was then evaporated to dryness and the residue diluted with ethyl acetate and water. The aqueous layer was neutralized with $NaHCO_3$ 5% solution and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH = 95/5) to afford **4** as solid (0.23 g, 97%). Mp: 40–42 °C. $[\alpha]_D^{25} = +16.7$ (*c* 1, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.69 (br s, 2H), 2.73, 3.02 (AB, 2H, $J_{AB} = 13.1$), 3.66 (s, 3H), 6.99 (d, 2H, $J = 8.1$), 7.37 (d, 2H, $J = 8.1$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.7, 46.4, 52.4, 58.9, 121.2, 131.6, 131.9, 135.8, 177.4. MS (EI): 273.9 (MH^+).

4.4. (5*R*)-5-(4-Bromobenzyl)-3-(3,5-dichlorophenyl)-5-methyl-1*H*-imidazole-2,4(3*H*,5*H*)-dione 5

A solution of α-amino ester **4** (72 mg, 0.265 mmol) and 3,5-dichlorophenyl isocyanate (50 mg, 0.321 mmol) in dry DMSO (0.5 ml) was stirred at ambient temperature for 1 h. Sodium carbonate (56 mg, 0.53 mmol) was then added and stirred at 120 °C for 12 h. The reaction mixture was brought to room temperature, diluted with ethyl acetate, and washed with water. The organic phase was dried over Na_2SO_4, concentrated and purified by column chromatography (silica gel, light petroleum ether/ethyl acetate = 60:30) to afford **5** (0. 10 g, 89%). $[\alpha]_D^{25} = +121.4$ (*c* 1, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$): δ 1.58 (s, 3H), 2.88, 3.13 (AB, 2H, $J_{AB} = 13.9$), 6.85 (br s, 1H), 6.98 (d, 2H, $J = 1.5$), 7.06 (d, 2H, $J = 8.8$), 7.33 (t, 1H, $J = 1.5$), 7.44 (d, 2H, $J = 8.8$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.6, 43.8, 62.9, 122.2, 124.8, 128.8, 131.9, 133.1, 135.4, 154.9, 177.4. MS (EI): 425.1 (M^+).

4.5. (5*R*)-5-(4-Bromobenzyl)-3-(3,5-dichlorophenyl)-1,5-dimethyl-1*H*-imidazole-2,4(3*H*,5*H*)-dione, BIRT-377 1

To a solution of hydantoin **5** (44 mg, 0.103 mmol) in DMF (0.5 ml) at 0 °C, lithium bis(trimethylsilyl)amide (0.119 mmol of 1 M in hexanes solution) followed by iodomethane (10 μl, 0.150 mmol) were added and stirred at ambient temperature for 2 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, concentrated, and purified by column chromatography (silica gel, light petroleum ether/ethyl acetate = 60:30) to afford **1** as solid (45 mg, quantitative). Mp: 135–136 °C $[\alpha]_D^{25} = +127.1$ (*c* 1, EtOH). ^1H NMR (200 MHz, $CDCl_3$): δ 1.61 (s, 3H), 2.89, 3.12 (AB, 2H, $J_{AB} = 13.9$), 3.06 (s, 3H), 6.83 (d, 2H, $J = 1.5$), 6.94 (d, 2H, $J = 8.8$), 7.28 (t, 1H, $J = 1.5$), 7.44 (d, 2H, $J = 8.8$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.3, 25.6 40.9, 65.9, 122.2, 124.8, 128.6, 131.3, 132.1, 133.0, 135.3, 153.7, 173.6. MS (EI): 442.9 (MH^+). HPLC (Daicel Chiralcel OD, hexane/isopropanol/Et_2NH = 90:9.9:0.1, flow rate 0.8 ml/min, $\lambda = 254$ nm): t_R = 17.30 min (−), (BIRT-377, *ent*-**3**), $t_R = 20.40$ min (+), (BIRT-377, **1**).

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