An Improved Synthesis of Chiral α-(4-Bromobenzyl)alanine Ethyl Ester and Its Application to the Synthesis of LFA-1 Antagonist BIRT-377

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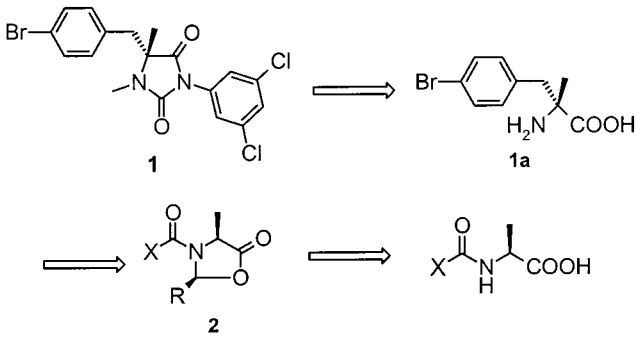
Introduction

Recently BIRT-377 (**1**) was identified as a potent inhibitor of the interaction between intercellular adhesion molecule-1 (ICAM-1) and lymphocyte function-associated antigen-1 (LFA-1), and thus it could play an important role in the treatment of a number of inflammatory and immune disorders.[1,2] To facilitate preclinical studies, a practical synthesis of **1** was needed. Because hydantoins can easily be prepared from amino acids, our initial target was the corresponding amino acid bearing a quaternary asymmetric center in the α position. A number of syntheses have been reported in the literature for this type of compounds.[3] We found the synthesis based on oxazolidinone chemistry to be very attractive for its simplicity. It takes advantage of the protocol called *Self-Regeneration of Stereocenters* devised and extensively studied by Seebach.[4] On the basis of this strategy, we envisioned the synthesis of **1** as shown in Scheme 1.

Scheme 1



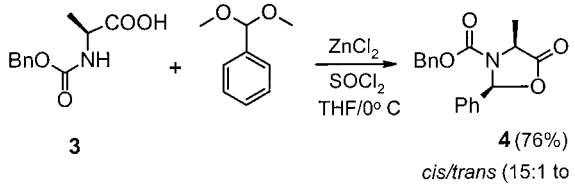
Thus, **1** can be synthesized from the amino acid **1a**, which, in turn, can be obtained from **2** by alkylation with 4-bromobenzyl bromide followed by hydrolysis. Acylated alanine can be used as the starting material to synthesize **2** either in cis or trans configuration.

A careful examination of the literature, describing several applications of Seebach's protocol, showed a very confusing trend regarding the stereoselectivity of the formation of the oxazolidinone template **2**. Using the same two-step approach, Seebach[5] reported cis as a major isomer (4:1, R = *t*-Bu, X = Ph), whereas Fadel[6] (7.5:1, R = X = Ph) and Mutter[7] (2.5:1, R = Ph, X = BnO) reported trans as the major product and Davies[8] obtained cis isomer (R = ferrocenyl, X = *t*-Bu) as the only product. Due to these inconsistencies and the fact that these procedures are carried out in two distinct steps, we decided to examine a one-step procedure developed first by Karady[9a] and later modified by Shrader[9b] and Jones,[10] each of whom reported cis as the major isomer. Unlike Karady, both Shrader and Jones condensed a carbamate-protected amino acid with an acetal in the presence of excess of BF_3 etherate to obtain the template **2** (R = Ph, X = BnO) in high yield. However, the drawback of this method is that it uses a corrosive acid at a very low temperature (−78 °C) in ether. Since we hoped to scale this reaction up to multikilogram scale, we needed to modify the reaction conditions in order to avoid the low temperature conditions, the hazardous ether solvent, and highly corrosive BF_3.

Results and Discussion

With this goal in mind, we decided to screen commonly used Lewis acids. *n*-Butyl ether was chosen as the solvent because of its low flammability, and all the reactions were run at 0 °C. We looked at number of common Lewis acids derived from titanium, boron, aluminum, zinc, and ytterbium. Only $ZnCl_2$ and $ZnBr_2$ provided the oxazolidinone **4** in appreciable yield. Around this time, we came across a report by Micheel[11] describing the use of thionyl chloride to effect a similar cyclization. When we used 1 equiv of thionyl chloride in the presence of anhydrous $ZnCl_2$, we were delighted to find that the yield increased to 66% with a cis/trans ratio of 5.5:1. Changing the solvent to THF and some more fine-tuning of the reaction conditions gave **4** in 76% crude yield with a cis/trans ratio ranging from 15:1 to 25:1 (Scheme 2).

Scheme 2



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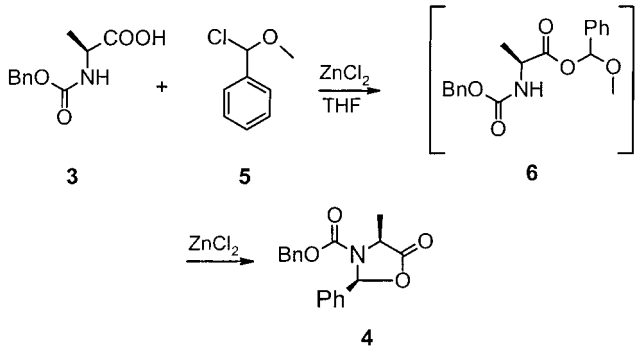
A preliminary study of this reaction indicated that both the $ZnCl_2$ and thionyl chloride are needed for the reaction to occur. Without at least an equivalent amount of each, the reaction remained incomplete. Oxalyl chloride can also be used in place of thionyl chloride. The reaction also occurs in other solvents such as ethyl acetate and acetonitrile. However, THF gives the highest *cis/trans* ratio. Scheme 2 shows the optimized reaction conditions.

At first, the use of thionyl chloride with the amino acid **3** led us to believe that the acid chloride could be the intermediate in this reaction. However, ^{1}H NMR experiments in d_8-THF showed a fast reaction, <20 min at room temperature, between $SOCl_2$ and benzaldehyde dimethyl acetal in the presence of $ZnCl_2$ to yield α-chloro ether **5**.[12] Furthermore, when $ZnCl_2$ is added to a mixture of Cbz-alanine, $SOCl_2$ and benzaldehyde dimethyl acetal, **5** is observed before the appearance of any **4** as determined by ^{1}H NMR. Thus, in the presence of $ZnCl_2$, **5** reacts with **3** to afford the cyclized product **4** (presumably through **6**) as shown in Scheme 3.

Scheme 3

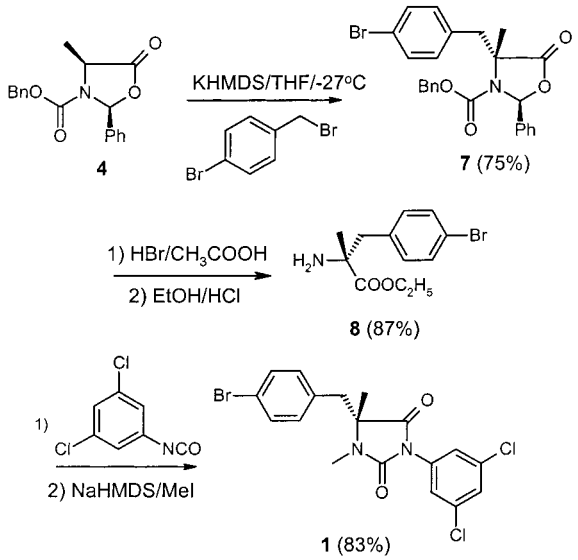


We also found that a 3:1 cis/trans mixture can be enriched to 8:1 simply by stirring it with $ZnCl_2$ in THF at room temperature for 20 h. This indicates that the cis isomer is the thermodynamic product. As shown in Scheme 2, the isolated product has a *cis/trans* ratio of 15:1 to 25:1, considerably higher than 8:1. Our preliminary results indicate that the improvement of the ratio may take place when the reaction mixture is quenched with water, through selective hydrolysis of the trans diastereomer.[13]

With the desired cis oxazolidinone **4** in hand, completion of the synthesis was carried out as shown in Scheme 4.

Using the method of Karady and co-workers,[9a] addition of the 4-bromobenzyl bromide to the preformed enolate of **4** in THF at −27 °C gave a very low yield of the alkylated product. The low yield was attributed to the unstable nature of the enolate. However, the addition of the mixture of **4** and 4-bromobenzyl bromide in THF to the base at −27° C afforded the product **7** in 75% yield after flash column chromatography. The alkylation takes place at the face of the enolate opposite the phenyl ring and is completely stereoselective. Since the alkylated product was somewhat unstable to silica gel, the crude material was generally used in the next step.

Scheme 4



Hydrolysis of the crude alkylated template was accomplished by stirring with 30% HBr in acetic acid at room temperature for 20 h to give the amino acid hydrobromide. Amino ester **8** was obtained by stirring the hydrobromide salt in ethanol at 70 °C in the presence of HCl gas. Treatment of **8** with 3,5-dichlorophenyl isocyanate in the presence of sodium carbonate provided the hydantoin skeleton in high yield. Methylation with methyl iodide completed the synthesis of **1**.

In conclusion, we have demonstrated that the oxazolidinone **4** can be synthesized with very high cis selectivity. The key to this method is the use of $ZnCl_2$ as the Lewis acid in combination with thionyl chloride. Under this condition, cis isomer is obtained in >15:1 selectivity, which after crystallization from aqueous ethanol provided oxazolidinone **4** in >98% purity. Starting with pure cis isomer, **1** is obtained in >99% chemical and chiral purity[14] on a multigram scale. Thus, we accomplished a practical synthesis of BIRT-377.

Experimental Section

General Procedures. ^{1}H and ^{13}C spectra were measured at 400 MHz using TMS as standard. The commercial chemicals were used as received without further purification, and all solvents were dried by standard methods prior to use. Column chromatography was carried out on silica gel 60 (E. Merck, 230−400 mesh). All melting points are uncorrected.

(*S*,*S*)-4-Methyl-5-oxo-2-phenyl-oxazolidine-3-carboxylic Acid Benzyl Ester (4). Thionyl chloride (3.27 mL, 44.8 mmol) was added to a stirring solution of Cbz-L-alanine (10.00 g, 44.8 mmol) and benzaldehyde dimethyl acetal (6.73 mL, 44.8 mmol) in dry THF (75 mL) at 0 °C. After stirring for 5 min, anhydrous $ZnCl_2$ (6.11 g, 44.8 mmol) was added, and the reaction mixture was stirred at this temperature for 3 h. At this stage, 0.2 equiv each of $SOCl_2$ (0.65 mL, 9.0 mmol) and anhydrous $ZnCl_2$ (1.22 g, 9.0 mmol) were added, and the reaction mixture was stirred for an additional 1 h.

The reaction mixture was quenched by dropwise addition of water so that the reaction temperature did not exceed 10 °C. It was extracted with ether (200 mL). The ether extract was washed with water until almost neutral, with a saturated solution of $NaHCO_3$, and with water and finally dried over anhydrous Na_2SO_4. Evaporation of the solvent furnished light

(12) The formation of **5** is very slow, ca. 40% after 18 h, in the absence of $ZnCl_2$.

(13) HPLC monitoring of samples withdrawn from the reaction mixture during quench showed a gradual increase in the *cis:trans* ratio. More details will be provided in a forthcoming full paper.

(14) Chiral purity: HPLC−Chiralpak AD, hexane:ethyl alcohol: diethylamine (95: 5: 0.5) Chemical purity: HPLC−Reverse phase C-18, 90% MeOH with 0.1% triethylamine.

yellow oil (21:1 cis by ^{1}H NMR) which solidified on stirring with hexane (75 mL). The product was filtered and dried under reduced pressure (9.12 g, 65%, 29:1 cis by ^{1}H NMR). The product was finally purified by crystallization from ethanol/water to give colorless needles, mp 52−53 °C (6.70 g, 48%, ≫50:1 cis by ^{1}H NMR). ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 3H), 4.47−4.52 (m, 1H), 5.14−5.21 (m, 2H), 6.65 (bs, 1H), 7.34−7.41 (m, 10 H). ^{13}C NMR ($CDCl_3$) δ 52.5, 68.4, 89.4, 126.6, 127.0, 128.5, 128.9, 129.0, 129.2, 129.3, 130.3, 135.8, 137.3 and 172.9. MS (CI) 312 (MH^+). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50 and N, 4.49. Found: C, 69.40; H, 5.52 and N, 4.40.

(*R*,*S*)-4-(4-Bromobenzyl)-4-methyl-5-oxo-2-phenyl-oxazolidine-3-carboxylic Acid Benzyl Ester (7). A solution of oxazolidinone **4** (51.62 g, 0.166 mol) and 4-bromobenzyl bromide (41.41 g, 0.166 mol) in dry THF (100 mL) was added to a stirring solution of potassium hexamethyldisilazane (0.38 M/toluene, 0.174 mol, 457 mL, 1.05 equiv) in dry THF (400 mL) at −30 °C at such a rate that the internal temperature remained between −27.5 °C and −26.5 °C. The addition was complete in 1.5 h. The reaction mixture was stirred at this temperature for 1 h followed by stirring at room temperature for 1 h. The reaction mixture was then poured into 1 L of ice cold saturated $NaHCO_3$ and extracted with ether (700 mL). The organic layer was separated and dried over anhydrous Na_2SO_4, and the solvent was evaporated to give crude **7** as yellow oil (80.0 g, 100%). Analytically pure sample was obtained by silica gel column chromatography using 10% ethyl acetate/hexane as the eluent to give colorless solid, mp. 59−60 °C. ^{1}H NMR ($CDCl_3$) two rotamers (∼3:1) δ 1.88 (s, 0.75H), 1.94 (s, 2.25H), 2.99−3.06 (m, 1H), 3.35 (d, 0.25H, J = 13.6 Hz), 3.71(d, 0.75H, J = 13.6 Hz), 4.89 (d, 0.75H, J = 13.6 Hz), 5.04−5.06 (m, 1H), 5.41−5.46 (m, 1.25H), 6.70 (m, 1H), 6.93−6.96 (m, 4H), 7.19−7.47 (m, 9H). ^{13}C NMR ($CDCl_3$) δ_23.9, 24.9, 40.2, 67.2, 68.1, 89.3, 89.5, 126.7, 128.2, 128.3, 128.5, 128.7, 128.9, 131.1, 131.3, 131.9 and 132.0. Anal. Calcd for $C_{25}H_{22}BrNO_4$: C, 62.51; H, 4.62 and N, 2.92. Found: C, 62.29; H, 4.70 and N, 2.77.

(*R*)-2-Amino-2-methyl-3-(4-bromophenyl)propionic Acid Ethyl Ester (8). HBr/acetic acid (30 wt %, 100 mL) was added over 20 min to a stirring solution of crude alkylated oxazolidinone **7** (80.0 g, from above) in glacial acetic acid (150 mL) at room temperature, and the reaction mixture was stirred for 20 h. Solvent was evaporated, and the residue was dissolved in water (600 mL). 2 N HBr (100 mL) was also added. It was extracted with ether (600 mL), which was discarded. The aqueous phase was evaporated to dryness to give the amino acid hydrobromide as an off-white solid (49.20 g, crude).

HCl gas was bubbled through a solution of the amino acid hydrobromide (49.20 g, from above) in ethyl alcohol (400 mL) at room temperature for 45 min. The reaction mixture was stirred at 70 °C (bath temp) for 24 h. To complete the reaction, additional HCl gas was bubbled through the reaction mixture (15 min) and stirred for an additional 10 h at 70 °C.

After evaporation of alcohol, the residue was dissolved in water (250 mL) and extracted with ether (300 mL). The ether extract was discarded. The aqueous phase was basified with solid $NaHCO_3$, and the product was extracted with CH_2Cl_2. It was dried over anhydrous Na_2SO_4 and concentrated to a light brown oil which solidified on standing. Amino ester **8** was finally purified by crystallization from light petroleum ether to give colorless crystals, mp 42−43 °C (31.5 g, 66% over three steps, chemical purity 95%, ee >99%), $[\alpha]^{25}_D$ = +5.12° (c = 1.0, EtOH), ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.0 Hz), 1.39 (s, 3H), 2.75 (d, 1H, J = 13.2 Hz), 3.09 (d, 1H, J = 13.2 Hz), 4.11−4.22 (m, 2H), 7.07 (d, 2H, J = 8.35 Hz) and 7.42 (d, 2H, J = 8.35 Hz). ^{13}C NMR ($CDCl_3$) δ 14.2, 26.6, 46.0, 58.4, 61.1, 120.9, 131.3, 131.7, 135.6 and 176.8. MS (CI) 286 (MH^+). Anal. Calcd for $C_{12}H_{16}BrNO_2$: C, 50.37; H, 5.64 and N, 4.89. Found: C 50.28; H, 5.51 and 4.83.

(*R*)-5-(4-Bromobenzyl)-3-(3,5-dichlorophenyl)-1,5-dimethylimidazolidine-2,4-dione (BIRT-377) (1). To a stirring solution the amino ester **8** (4.55 g, 16 mmol) in dry DMSO (25 mL) at room temperature was added 3,5-dichlorophenyl isocyanate (3.0 g, 16 mmol). After stirring for 1 h, sodium carbonate (3.40 g, 32.0 mmol) was added, and the reaction mixture was heated at 120° C for 1 h. The cooled reaction mixture was diluted with ethyl acetate, washed thoroughly with water, and dried over anhydrous Na_2SO_4. Evaporation of the solvent furnished the crude hydantoin (6.80 g, 98%), which was used as such in the next step.

To a solution of the crude hydantoin (6.80 g, from above) in dry DMF (20 mL) was added sodium hexamethyldisilazane (1M/THF, 16 mmol, 16 mL). After stirring the mixture for 15 min at room temperature, methyl iodide (1.20 mL, 19.20 mmol) was added and was stirred for 2 h. The reaction mixture was quenched with ice, diluted with water, and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated to give a crude material. It was purified using silica gel column and 20% ethyl acetate/hexane as eluent to give a colorless solid. It was finally purified by crystallization from ethyl acetate to give **1** as colorless crystals, mp 135−136 °C (5.87 g, 13.3 mmol, 83% over two steps, chemical purity: >99%, chiral purity: >99%). $[\alpha]^{25}_D$ = +134.3° (c = 1.0 EtOH) ^{1}H NMR ($CDCl_3$) δ 1.61 (s, 3H), 2.96 (d, 1H, J = 14 Hz), 3.06 (s, 3H), 3.08 (d, 1H, J = 14 Hz), 6.84 (d, 2H, J = 1.8 Hz), 6.94 (br d, 2H, J = 8.3), 7.28 (t, 1H, J = 1.8 Hz) and 7.42 (br d, 2H, J = 8.3 Hz). ^{13}C NMR ($CDCl_3$) δ 21.0, 25.2, 40.6, 65.6, 121.9, 124.4, 128.3, 131.0, 131.0, 132.8, 132.9, 135.0, 153.4 and 173.3. Anal. Calcd for $C_{18}H_{15}BrCl_2N_2O_2$: C, 48.89; H, 3.41 and N, 6.33. Found: C, 48.88; H, 3.06 and N, 6.28.

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