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Total Synthesis of LFA-1 Antagonist BIRT-377 via Organocatalytic Asymmetric Construction of a Quaternary Stereocenter

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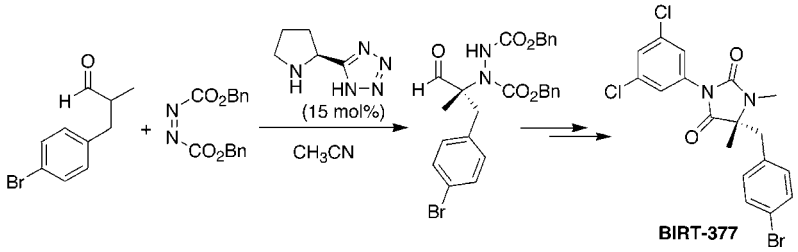
ABSTRACT



A catalytic route for enantioselective total synthesis of cell adhesion inhibitor BIRT-377 is described. The quaternary stereocenter was constructed through L-proline-derived, tetrazole-catalyzed direct asymmetric α-amination of 3-(4-bromophenyl)-2-methylpropanal with dibenzyl azodicarboxylate. In the course of these studies, a one-pot trifluoro acetylation/selective benzyloxycarbonyl deprotection method was developed.

BIRT-377 (**1**) is a potent inhibitor of the interaction between intercellular adhesion molecule-1 (ICAM-1) and lymphocyte function-associated antigen-1 (LFA-1). BIRT-377 has potential for treatment of a number of inflammatory and immune disorders. Reported syntheses of BIRT-377 are based on a chiral pool approach involving Seebach's self-regeneration of stereocenters strategy.[1] Asymmetric synthesis of quaternary amino acids, like BIRT-377, is a challenging task since these types of stereocenters cannot be made by catalytic asymmetric hydrogenation. Some of these unusual amino acids are components of enzyme inhibitors and their incorporation into peptides has been used to modulate secondary and tertiary structural conformations.[2] Existing methods for the synthesis of quaternary amino acids include auxiliary controlled Strecker syntheses[3] and diastereoselective alkylation of chiral enolates.[4] Recently, asymmetric phase transfer catalysis reactions[5] and other catalytic methods[6] have been reported. However development of a highly economical and broadly useful catalytic method for synthesis of quaternary amino acids is highly desirable.

(1) (a) Yee, N. K. *Org. Lett.* **2000**, *2*, 2781. (b) Kapadia, S. R.; Spero, D. M.; Eriksson, M. *J. Org. Chem.* **2001**, *66*, 1903. (c) Stehle, S.; Nummy, L.; Yee, N. *Tetrahedron: Asymmetry* **2001**, *12*, 101. (d) *Tetrahedron Lett.* **2001**, *42*, 3231. (e) Yee, N.; Nummy, L. J.; Frutos, R. P.; Song, J. J.; Napolitano, E.; Byrne, D. P.; Jones, P. J.; Farina, V. *Tetrahedron: Asymmetry* **2003**, *14*, 3495.

(2) (a) Shirlin, D.; Gerhart, F.; Hornsperger, J. M.; Harmon, M.; Wagner, I.; Jung, M. *J. Med. Chem.* **1988**, *31*, 30. (b) Karle, I.; Kaul, R.; Roa, R. B.; Raghothama, S.; Balaram, P. *J. Am. Chem. Soc.* **1997**, *119*, 12048.

(3) (a) Ma, D.; Tian, H.; Zou, G. *J. Org. Chem.* **1999**, *66*, 1903. (b) Davis, F. A.; Lee, S.; Zhang, H.; Fanelli, D. L.; *J. Org. Chem.* **2000**, *65*, 8704.

(4) (a) Lee, S.-H.; Lee, E. K. *Bull. Korean Chem. Soc.* **2001**, *22*, 551. (b) Vedezs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 2460. (c) Spino, C.; Gobdout, C. *J. Am. Chem. Soc.* **2003**, *125*, 12106.

(5) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013.

(6) (a) Trost, B. M.; Dogra, K.; *J. Am. Chem. Soc.* **2002**, *124*, 725. (b) Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3236. (c) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532. (d) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867. (e) Saaby, S.; Bella, M.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120. (f) Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3147.

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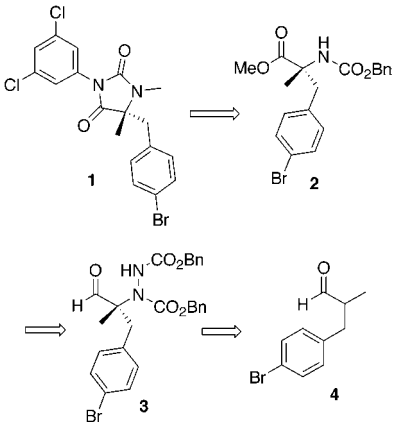
Recently, proline- and proline derivative-catalyzed asymmetric aldol,[7] Mannich,[8] Michael,[9] Diels−Alder,[10] amination,[11] oxidation,[12] chlorination,[13] Robinson annulation,[14] and multicomponent or assembly reactions[15] have been developed. Our laboratory recently reported the synthesis of all carbon quaternary stereogenic centers via organocatalytic Aldol-,[7g] Mannich-,[8i] and Michael-type[9g] strategies. Here we report a direct catalytic asymmetric amination reaction for synthesis of an aldehyde containing an amino-substituted quaternary carbon center and the elaboration of this aldehyde into BIRT-377.

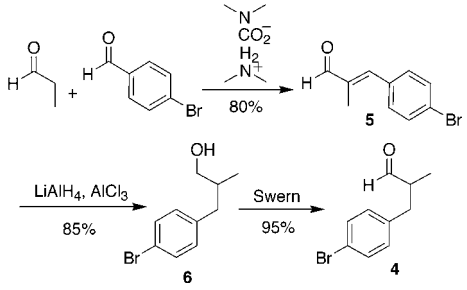
A retrosynthetic analysis of BIRT-377 leads to quaternary amino acid **2**, which we envisioned could be prepared by organocatalytic amination of aldehyde **4** (Scheme 1). We

Scheme 1. Retrosynthetic Analysis of BIRT-377



prepared the aldehyde **5** by condensation of propionaldehyde with 4-bromobenzaldehyde using dimethylammonium dimethyl carbamate[16] as a recoverable and reusable reaction medium and promoter (Scheme 2). Although selective

Scheme 2. Synthesis of 3-(4-Bromophenyl)-2-methylpropanal



double-bond reducing reagents are available,[17] we used $LiAlH_4$ reduction followed by oxidation as a more practical strategy. Accordingly, the unsaturated aldehyde was reduced with $LiAlH_4$ and oxidized using Swern conditions to afford aldehyde **4**.

We first evaluated the amination of aldehyde **4** with dibenzyl azodicarboxylate using a catalytic amount of L-proline (30 mol %) in CH_3CN at room temperature.[18] The reaction was complete in 5 days and provided the amino aldehyde in 90% yield with moderate enantioselectivity (44% ee). To improve enantioselectivity, we screened a number of catalysts and solvents. For example α-methyl-L-proline and (*S*)-4-(pyrrolidin-2-ylmethyl)morpholine with trifluoroacetic acid additive provided 69 and 57% ee, respectively. Tetrazole catalyst[19] (15 mol %) in CH_3CN gave the amination

(7) (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (c) Córdova, A.; Notz, W.; Barbas, C. F., III. *J. Org. Chem.* **2002**, *67*, 301. (d) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. (e) Bogevig, A.; Kumaragurubaran, N.; Jorgensen, K. A. *Chem. Commun.* **2002**, 620. (f) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D *J. Am. Chem. Soc.* **2003**, *125*, 5262. (g) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 2420. (h) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 1983. (i) Artikka, A.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2004**, *15*, 1831. (j) Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 3541. (k) Kofoed, J.; Nielsen, J.; Reymond, J.-L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2445. (l) Chandrasekhar, S.; Narsihmulu, Ch.; Reddy, N. R.; Sultana, S. S. *Chem. Commun.* **2004**, 2450. (m) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558.

(8) (a) Notz, W.; Sakthivel, K.; Bui, T.; Barbas, C, F., III. *Tetrahedron Lett.* **2001**, *42*, 199. (b) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (c) Córdova, A, Watanabe, S.-I.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866. (d) Chowdari. N. S.; Ramachary, D. B.; Barbas, C, F., III. *Synlett.* **2003**, 1906. (e) Notz, W.; Tanaka, F.; Watanabe, S.-I.; Chowdari, N. S.; Thayumanavan, R.; Barbas, C. F., III. *J. Org. Chem.* **2003**, *68*, 9624. (f) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. (g) Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558. (h) Zhuang, W.; Saaby, S.; Jorgensen, K. A. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 476. (i) Chowdari, N. S.; Suri, J. T.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2507.

(9) (a) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C, F., III. *Tetrahedron Lett.* **2001**, *42*, 4441. (b) Betancort, J. M.; Barbas, C, F., III. *Org. Lett.* **2001**, *3*, 3737. (c) Enders, D.; Seki, A. *Synlett* **2002**, 26. (d) Alexakis, A.; Andey, O. *Org. Lett.* **2002**, *4*, 3611. (e) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2002**, 1808. (f) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Tanaka, F.; Barbas, C, F., III. *Synthesis* **2004**, *9*, 1509. (g) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C, F., III. *Org. Lett.* **2004**, *6*, 2527.

(10) (a) Ramachary, D. B.; Chowdari. N. S.; Barbas, C, F., III. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 4233. (b) Ramachary, D. B.; Chowdari. N. S.; Barbas, C, F., III. *Synlett* **2003**, 1910. (c) Thayumanavan, R.; Ramachary, D. B.; Sakthivel, K.; Tanaka, F.; Barbas, C, F., III. *Tetrahedron Lett.* **2002**, *43*, 3817. (d) Ramachary, D. B.; Chowdari. N. S.; Barbas, C, F., III. *Tetrahedron Lett.* **2002**, *43*, 6743.

(11) (a) Bogevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W., Jorgensen, K. A. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1790. (b) Kumaragurubaran, N.; Juhl, K.; Zhuang, W., Bogevig, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254. (c) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656. (d) Vogt, H.; Vanderheiden, S.; Brase, S. *Chem. Commun.* **2003**, 2448. (e) Iwamura, H.; Mathew, S. P.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 11770.

(12) (a) Zhong, G. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 4247. (b) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed. Engl.* **2003**, *43*, 1112. (c) Omiyama, N.; Torii, H.; Saito, S.; Yamamoto, H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5374.

(13) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C.*J. Am. Chem. Soc.* **2004**, *126*, 4108.

(14) Bui, T, Barbas, C, F., III. *Tetrahedron Lett.* **2000**, *41*, 6951.

(15) (a) Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F., III. *Org. Lett.* **2003**, *5*, 1685. (b) Chowdari. N. S.; Ramachary, D. B.; Córdova, A.; Barbas, C, F., III. *Tetrahedron Lett.* **2002**, *43*, 9591. (c) Ramachary, D. B.; Barbas, C, F., III. *Chem. Eur. J.* **2004**, *10*, 5323.

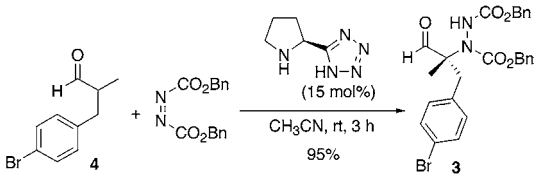
(16) Kreher, U. P.; Rosamilla, A. E.; Raston, C. L.; Scott, J. L.; Strauss, C. R.; *Org. Lett.* **2003**, *5*, 3107.

(17) (a) Saito, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 2928. (b) Keinan, E.; Greenspoon, N. *J. Am. Chem. Soc.* **1986**, *108*, 7314. (c) Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1989**, *30*, 5677.

(18) L-Proline was reported to be an excellent catalyst for amination of linear aldehydes (ref 11a,c) as well as α-aryl branched aldehydes, but failed to induce high ee's in cases involving α,α-dialkyl aldehydes (ref 11d).

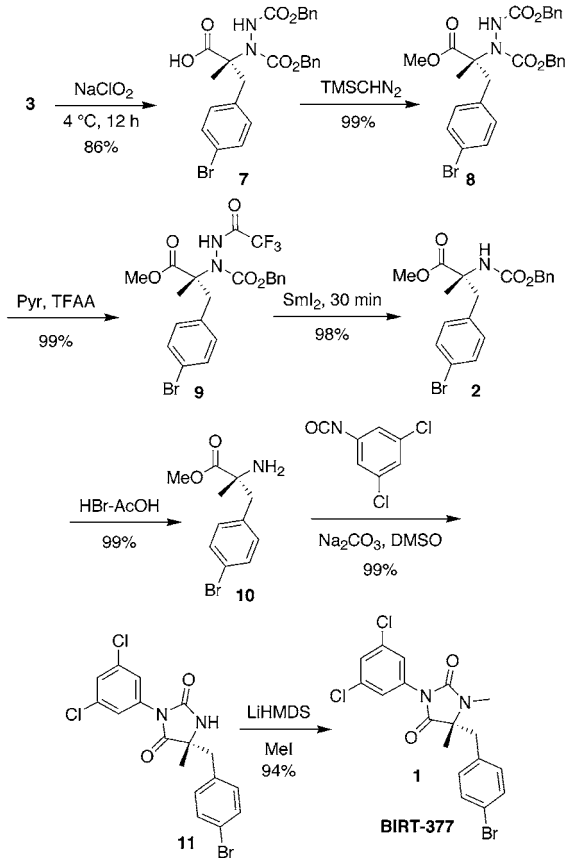
product (**3**) in 95% yield with 80% ee (Scheme 3). Upon recrystallization from ethyl acetate/hexane (3:7), the amino-aldehyde was obtained in >99% ee (71% yield).

Scheme 3. Organocatalytic Amination for the Synthesis of Quaternary Stereocenter



The amino aldehyde (**3**) was selectively oxidized with $NaClO_2$ at 4 °C to obtain the corresponding carboxylic acid (**7**) in 86% yield (Scheme 4). The carboxylic acid was treated

Scheme 4. Synthesis of BIRT-377

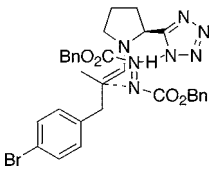


with (trimethylsilyl)diazomethane to afford the corresponding ester **8**. Next we attempted selective cleavage of the N−N bond in hydrazino ester **8** using SmI_2, which effectively cleaves trifluoroacetylated hydrazines,[20] but no product was obtained. We next tried trifluoroacetylation. Upon optimization we found that treatment of ester **8** with pyridine at 40 °C for 16 h followed by addition of trifluoroacetic anhydride (TFAA) gave the product **9** through selective removal of one of the carbamate groups. Although trifluoro acetic acid did not cleave any of the carbamate groups present in **8**, presumably the product formed after the trifluoroacetylation of product **8** underwent simultaneous carbamate cleavage. Selective N−N bond cleavage of **9** was readily achieved using SmI_2 and afforded the Cbz-protected quaternary amino acid methyl ester **2**. This one-pot trifluoroacetylation/selective benzyloxycarbonyl deprotection protocol should prove useful for the synthesis of a variety of Cbz-protected amino acids from precursors obtained through organocatalytic amination reactions.

When compound **2** was treated with 3,5-dichloroaniline in the presence of *n*BuLi, hydantoin **11** was obtained in 33% yield. Use of different bases such as NaOMe, NaH, or LDA did not provide any product. Better results were obtained when the Cbz group of **2** was removed with HBr/AcOH to give free amine **10**. The amine was treated with 3,5-dichlorophenyl isocyanate in the presence of Na_2CO_3 in dimethyl sulfoxide to obtain the hydantoin **11** in quantitative yield. *N*-methylation of hydantoin **11** was achieved using lithium bis(trimethylsilyl)amide to afford **1** in excellent yield (94%). The overall yield for the synthesis of BIRT-377 from aldehyde **4** in eight steps was 51%. The absolute stereochemistry of amino aldehyde was determined by comparison of optical rotation of **1** with the literature value.[21]

The synthesis of quaternary amino acids through organocatalytic amination reactions is challenging since the cis and trans enamines derived from α-branched aldehydes are energetically less distinct as compared to the cis and trans enamine intermediates in reactions involving linear aldehydes, and this leads to the low enantioselectivity observed for this class of amination reactions.[22] The higher reactivity and ee obtained with tetrazole catalyst relative to L-proline is ascribed to the lower pK_a and increased steric bulk of tetrazole relative to L-proline. Tetrazole and L- proline have pK_a's of ∼8 and ∼12, respectively, in DMSO. The hydrogen bonding interactions in the transition state of the reaction with the two catalysts are likely different and provide different levels of enantioselection. Based on the absolute configuration of the amino aldehyde and previous proline-catalyzed reactions,[7] we propose the transition state shown in Scheme 5. The approach of azodicarboxylate might be directed by interaction of the incoming nitrogen atom with the proton of the tetrazole of enamine intermediate.[11a,c]

Scheme 5. Transition State for Organocatalytic Amination of 3-(4-Bromophenyl)-2-methylpropanal



(19) Prepared according to literature procedure. See: Almquist, R. G.; Chao, W.-R.; White, C. J. *J. Med. Chem.* **1985**, *28*, 1067.
(20) Ding, H.; Friestad, G. K. *Org. Lett.* **2004**, *6*, 637.

In conclusion, we have developed the first catalytic asymmetric route to the total synthesis of BIRT-377. Quaternary amino aldehyde was constructed from readily available precursors using a small organic molecule catalyst. This method allows the synthesis of both enantiomers of BIRT-377. Analogues can be readily obtained by changing the α,α-disubstituted aldehyde and catalyst. Many of the steps reported here gave quantitative yields and did not require purification. Most of these reactions can be performed under operationally simple and safe conditions without the requirement for an inert atmosphere, dry solvents, or cooling equipment. This synthetic route should prove useful for high-throughput synthesis of BIRT-377 analogues. Full studies regarding scope of quaternary aminoaldehydes synthesis will be reported in due course.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) $[\alpha]^{25}_D = 131.6$ ($c = 1.0$, EtOH) [lit.[1e] $[\alpha]^{25}_D = 127.3$ ($c = 0.78$, EtOH)]; HPLC (Daicel Chirapak AD, hexane/EtOH/Et_2NH = 300:10:1, flow rate 1.0 mL/min, $\lambda = 254$ nm): $t_R = 15.62$ min, (+) **1** (BIRT-377); $t_R = 17.23$ min (−) **1**.

(22) The energy difference between cis and trans enamines of 3-(4-bromophenyl)-2-methyl propanal with L-proline is 0.266 kcal/mol, whereas propanal has a difference of 2.934 kcal/mol (based on MOPAC, PM3 calculations).