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Stereoselective synthesis of 5-[(1*S*)-*N*-Boc-amino-(2*S*)-(3-fluorophenyl)ethyl]-dihydrofuran-2-one

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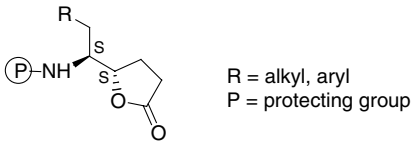
Abstract—A short, efficient, and highly diastereoselective synthesis of 5-[(1*S*)-*N*-Boc-amino-(2*S*)-(3-fluorophenyl)ethyl]-dihydrofuran-2-one (**1**) is described. Use of phthalic anhydride as thiolate scavenger effectively preserves the chiral integrity of the α-aminoketone **4** product obtained from the reaction of organozincate **3** with thioester **2**.

Compounds containing γ-hydroxy-δ-amino functional groups, such as lactone **1**, are key precursors to hydroxyethylene dipeptide isosteres, a class of compounds that have shown therapeutic potential as HIV and renin inhibitors.[1] Accordingly, in the past two decades, many reports have described the synthesis of these functionalized lactones.[2] We had a need to prepare multi-kilogram quantities of lactone **1a**. Commercially available α-amino acids and their derivatives are attractive starting materials as they are readily accessible in both enantiomeric forms, but direct conversion of these amino acids to lactones **1** has frequently been accomplished by utilizing racemization-prone α-amino aldehyde intermediates.[2f,j,3] We therefore proceeded to look at routes that avoided aldehyde intermediates.



1

Our first approach was inspired by Fukuyama and coworkers who described a novel ketone synthesis via addition of organozincates to thioester catalyzed by $PdCl_2(PPh_3)_2$,[4] $Pd(OH)_2$[5] and $Ni(acac)_2$.[6] These prompted us to explore the synthesis of α-aminoketone **4** by alkylation with organozinc homoenolate $BrZnCH_2CH_2COOEt$ (**3**) in THF[7] as shown in Scheme 1. Conversion of the γ-keto ester **4** to lactone **1a** was expected to be straightforward via an established stereoselective reduction with N-Selectride[8] followed by acid-catalyzed cyclization. Other hydride ($NaBH_4$,[9] $LiBH_4$,[10] L-Selectride[11]) reduction and catalytic hydrogenation of similar systems[2h,12] were known in the literature but with lower diastereoselectivity.

Thioester **2**, prepared from commercially available Boc-L-3-(fluorophenyl)alanine,[13] is a crystalline material and nearly odorless. Surprisingly, reaction of **2** with **3** (2.0 equiv) in the presence of $PdCl_2(PPh_3)_2$ (5 mol%) gave α-aminoketone **4** that was completely racemized.[14] We ascribed the loss of enantiopurity to the presence of catalytic amounts of ethoxide, which was generated by the displacement of the ethyl esters **3** or **4**[15] by thiolate anion. The presence of ethyl ester **5** (~15% by HPLC[16]) in the reaction mixture supported this hypothesis (Scheme 2).

To eliminate racemization in this reaction, we investigated the effect of added thiolate scavengers, which would minimize ethoxide generation. Phenyl acetate

Keywords: Thioester; Aminoketone; Organozincate.
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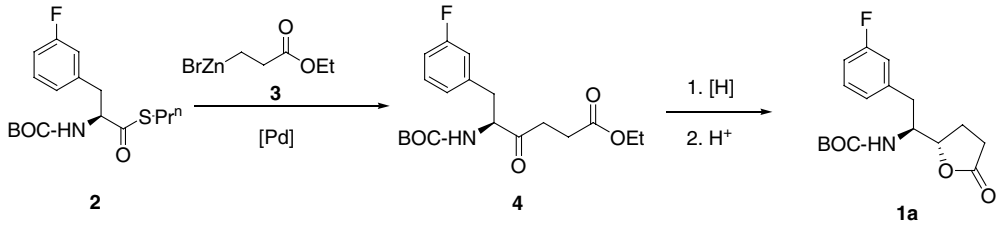
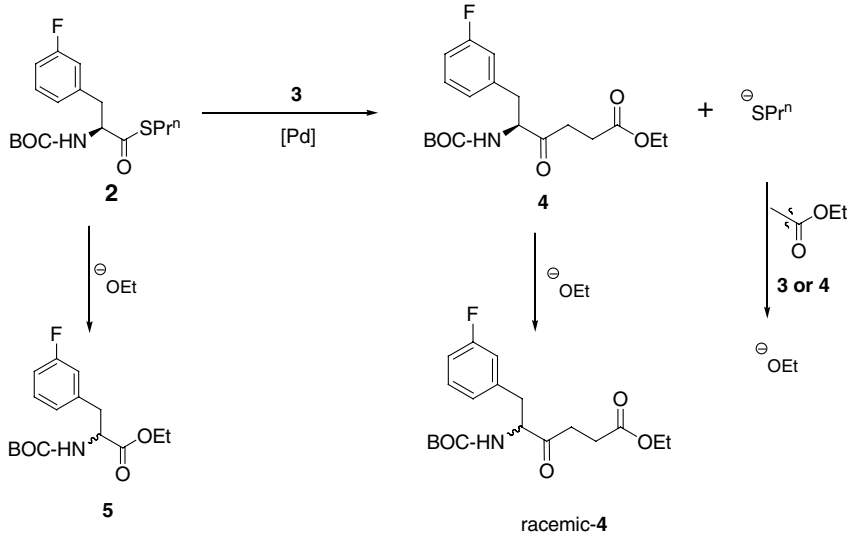
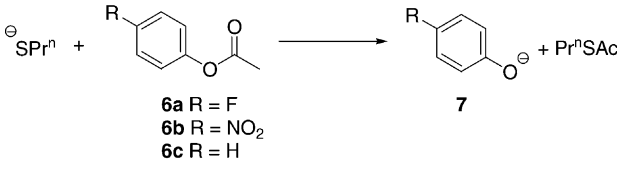


Scheme 1.

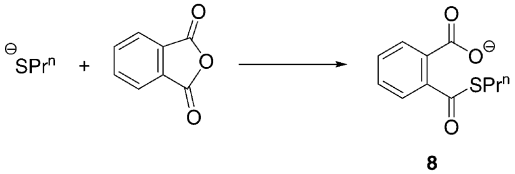


Scheme 2.

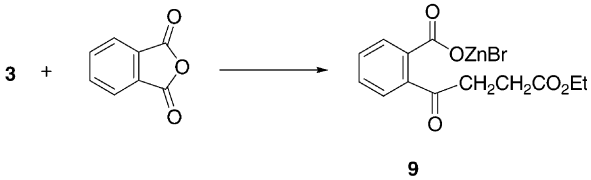
(**6a**), 4-fluorophenyl acetate (**6b**), and 4-nitrophenyl acetate (**6c**) were chosen for initial experiments (Eq. 1), as we reasoned that phenoxide anions generated (**7**, Eq. 1) were weak bases that would not cause epimerization of the α-aminoketone **4**. The use of **6a** or **6b** (3 equiv) reduced but did not eliminate formation of **5** (5% by HPLC), and racemic **4** was isolated. Use of **6c** (3 equiv) inhibited the formation of **5** completely and the α-aminoketone obtained was enantiomerically pure (>99% ee by HPLC chiral assay[17]). However, the odor from *n*-propylthioacetate generated in the reaction could not be adequately purged from the isolated product (Eq. 1). The use of phthalic anhydride, which was known to react slowly with PhZnCl at room temperature (3% conversion after 8 h),[18] resulted in formation of **4** without any racemization, and no **5** was detected. Byproducts **8** (Eq. 2), **9** (Eq. 3), and phthalic acid (from the hydrolysis of the unreacted phthalic anhydride[19]) were readily removed by an aqueous $NaHCO_3$ wash. $PdCl_2(PEt_3)_2$ was a good catalyst for the reaction, although extensive screening of palladium catalysts was not performed. The reaction required 6 equiv of **3** and 3 equiv of phthalic anhydride for complete conversion of **2** in 14 h at room temperature due to acceleration of the reaction of phthalic anhydride with the organozinc (Eq. 3).[20,21]



(1)



(2)



(3)

Conversion of α-aminoketone **4** to lactone **1a**[22] was straightforward (Scheme 1). In a one-pot process, stereoselective ketone reduction with N-Selectride[11a] at −78 °C was followed by acetic acid quench, and the crude reaction mixture was directly brought to reflux to afford lactone **1a**. The product obtained was of comparable quality with material obtained from other routes.[1f,3,8]

In summary, we have described a short and convenient synthesis of lactone **1a**. The use of phthalic anhydride as thiolate scavenger in the organozinc reaction effectively preserved the enantiopurity of α-aminoketone **4**. Furthermore, the addition of phthalic anhydride offered a convenient workup in removing the thiolate species, thus affording an attractive alternative for the preparation of **1a**.

Acknowledgements

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References and notes

1. (a) Nadin, A.; Owens, A. P.; Castro, J. L.; Harrison, T.; Shearman, M. S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 37; (b) Dias, L. C.; Diaz, G.; Ferreira, A. A.; Meira, P. R. R.; Ferreira, E. *Synthesis* **2003**, *4*, 603; (c) Benedetti, F.; Berti, F.; Norbedo, S. *J. Org. Chem.* **2002**, *67*, 8635; (d) Meek, T. D. *J. Enzym. Inhib.* **1992**, *6*, 65; (e) Lecki, B. J.; Grant, J.; Hallett, A.; Hughes, M.; Jones, D. M.; Szelke, M.; Tree, M. *Scot. Med. J.* **1984**, *29*, 125; (f) Kath, J.C.; Brown, M.F.; Poss, C.S. PCT Int. Apl. WO 9940061, 1999; *Chem. Abstr*. **1999**, *131*, 157767.
2. (a) Nadin, A.; Sanchez Lopez, J. M.; Neduvelil, J. G.; Thomas, S. R. *Tetrahedron* **2001**, *57*, 1861; (b) Brewer, M.; Rich, D. H. *Org. Lett.* **2001**, *3*, 945; (c) Benedetti, F.; Magnan, M.; Miertus, S.; Norbedo, S.; Parat, D.; Tossi, A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3027; (d) Kang, S. H.; Ryu, D. H. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2959; (2) Dondoni, A.; Perrone, D.; Semola, M. T. *J. Org. Chem.* **1995**, *60*, 7927; (f) Fray, A. H.; Kaye, R. L.; Kleiman, E. F. *J. Org. Chem.* **1986**, *51*, 4828; (g) Ghosh, A. K.; Shin, D.; Mathivanan, P. *Chem. Commun.* **1999**, *9*, 1025; (h) Lagu, B.; Liotta, D. C. *Tetrahedron Lett.* **1994**, *35*, 547; (i) Ghosh, A. K.; McKee, S. P.; Thompson, W. J. *J. Org. Chem.* **1991**, *56*, 6500; (j) DeCamp, A. E.; Kawaguchi, A. T.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1991**, *32*, 1867.
3. Jasys, V. J.; Urban, F. J. *Tetrahedron: Asymmetry* **2001**, *12*, 361.
4. (a) Tokuyama, H.; Yomoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189; (b) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Lin, S.-C.; Li, L.; Fukuyama, T. *J. Brazil. Chem. Soc.* **1998**, *9*, 381.
5. Mori, Y.; Seki, M. *J. Org. Chem.* **2003**, *68*, 1571.
6. Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2002**, *43*, 1039.
7. Commercially available from Rieke Metals, Inc. See also: Smith, R. D.; Simmons, H. E. *Org. Synth. Collect.* **1973**, *5*, 855.
8. (a) Urban, F. J.; Jasys, V. J. *Org. Process Res. Dev.* **2004**, *8*, 169; (b) Urban, F.; Jasys, V. J.; Li, Z. B.; Kath, J. C. PCT Int. Appl. WO 2003095440, 2003.
9. (a) Hanessian, S.; Claridge, S.; Johnstone, S. *J. Org. Chem.* **2002**, *67*, 4261; (b) Wuts, P. G. M.; Putt, S. R.; Ritter, A. R. *J. Org. Chem.* **1988**, *53*, 4503; (c) Hilborn, J. W.; Lu, Z.-H.; Jurgens, A. R.; Fang, Q. K.; Byers, P.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **2001**, *42*, 8919.
10. Radunz, H. E.; Eiermann, V.; Schneider, G.; Riethmueller, A. *Tetrahedron* **1991**, *47*, 1887.
11. (a) Estiarte, M. A.; Diez, A.; Rubiralta, M.; Jackson, R. F. W. *Tetrahedron* **2001**, *57*, 157; (b) Jackson, R. F. W.; Rettie, A. B.; Wood, A.; Wythes, M. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, *13*, 1719.
12. (a) Sakurai, M.; Hata, T.; Yabe, Y. *Tetrahedron Lett.* **1993**, *34*, 5939; (b) Hoffman, R. V.; Kim, H. O. *Tetrahedron Lett.* **1992**, *33*, 3579; (c) Noyori, R.; Kitamura, M.; Ookuma, T.; Morisawa, Y.; Nishi, T. *Jpn. Kokai Tokkyo Koho*, JP 03002151, 1991; *Chem. Abstr*. **1991**, *114* 206574; (d) Nishi, T.; Kataoka, M.; Morisawa, Y. *Chem. Lett.* **1989**, *11*, 1993.
13. Preparation of thioester **2**. To a dry and nitrogen purged 1 L flask was added Boc-L-3-(fluorophenyl)alanine (purchased from Synthetech, 18 g, 63.5 mmol). Anhydrous methylene chloride (180 mL) was added, and the solution was subsequently cooled to −10 °C. Triethylamine (7.14 g, 69.9 mmol) was added over 10 min while keeping temperature below −10 °C. The mixture was stirred at −5 to −10 °C for 30 min, and isobutyl chloroformate (9.55 g, 69.9 mmol) was added via a drop funnel. After 30 min at −5 °C, *n*-propyl mercaptan (5.32 g, 69.9 mmol) was added over 10 min via addition funnel while keeping the temperature at −5 °C. The mixture was allowed to warm to 0 °C, and stirred for 30 min. HPLC assay of reaction aliquot showed complete conversion. Water (90 mL) was added, and layers were separated. The methylene chloride layer was washed once more with water, dried over $MgSO_4$, and concentrated. The residue was granulated in hexanes (50 mL). The mixture was filtered, and the filtrate was concentrated and filtered again to give a second crop. Both crops were of similar purity by HPLC assay; 21.3 g was obtained; as a crystalline solid (98.2% yield). HPLC: 99.7% pure by area (242 nm). Chiral assay not available due to lack of reference. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J = 7.46 Hz, 3H), 1.38 (s, 9H), 1.56–1.60 (m, 2H), 2.82 (t, J = 7.25 Hz, 2H), 2.95–3.13 (m, 2H), 4.54–4.62 (m, 1H), 4.94–4.99 (m, 1H), 6.83–7.25 (m, 4H); LC–MS: 364 $(M + Na)^+$, 242 $(M + H - Boc\ group)^+$.
14. Fukuyama and co-workers (Ref. 4a) reported reaction of *N*-CBZ-L-a-phenylalanine thiol ester with $IZn(CH_2)_3CO_2Et$ to give the corresponding ketone without appreciable racemization.
15. The thioester resulting from reaction of the thiolate with **4** was not detected. LC–MS analysis of the reaction mixture suggested it further reacted with **3**.
16. Achiral HPLC conditions: SB-CN column 4.6 × 150 mm; mobile phase: acetonitrile/buffer (0.6% NEt_3 and 0.2% H_3PO_4 in water): 45/54; flow rate: 2 mL/min, 210 nm.
17. Chiral HPLC conditions: ChiralPak column OD 4.6 × 250 mm; mobile phase: *n*-hexane/isopropanol/triethylamine: 1000/20/1; flow rate: 1.5 mL/min, 40 °C, 210 nm.
18. Tarbell, D. S.; Weaver, C. *J. Am. Chem. Soc.* **1940**, *62*, 2747.
19. Allowing at least 30 min of good stirring with the saturated bicarbonate solution for the phthalic anhydride hydrolysis before layer separation.
20. For examples of reactions of organozinc with mixed anhydrides in the presence of Pd catalyst: Jabri, N.;

Alexakis, J. F.; Normant, J. F. *Tetrahedron* **1986**, *42*, 1369.

21. Preparation of α-aminoketone **4**. *Method 1*. To a dry and nitrogen purged 500 mL flask was charged **2** (10 mmol; 3.41 g), phthalic anhydride (3.00 equiv; 30.0 mmol; 4.48 g), and dichlorobis(triethylphosphine)palladium(II) (0.05 equiv; 0.499 mmol; 214 mg). Anhydrous THF (17 mL) was added, followed by addition 3-ethoxy-3-oxopropylzinc bromide (6.00 equiv; 60 mmol; 120 mL, 0.5 M solution in THF). After overnight stirring, the reaction was assayed by HPLC, and showed complete conversion. HCl (1 N, 34 mL) and ethyl acetate (50 mL) were added, and the mixture was stirred for 5 min before layer separation. The organic phase was stirred with saturated sodium bicarbonate solution for 30 min, followed by layer separation. The organic phase was washed once with brine solution, then dried over $MgSO_4$. The solution was concentrated under vacuum to give an oil. Upon standing overnight, the residue solidified. It was then triturated in isopropyl ether (7 mL) and filtered to give 2.46 g (67.0% yield) of the desired product. HPLC purity: 98.6% achiral; 99.8% chiral. NMR (400 MHz, $CDCl_3$) δ 1.24 (t, $J = 7.0$ Hz, 3H), 1.39 (s, 9H), 2.53–2.60 (m, 2H), 2.72–2.78 (m, 2H), 2.91 (dd, $J = 13.9$ and 7.0 Hz, 1H), 3.17 (dd, $J = 5.8$ and 13.9 Hz, 1H), 4.11 (q, $J = 7.0$ Hz), 4.52 (dd, $J = 7.0$ and 13.8 Hz), 5.08 (d, $J = 7.0$ Hz), 6.87–7.27 (m, 4H); MS: 390 $(M + Na)^+$, 268 $(M + H - \text{Boc group})^+$. *Method 2*. To a dry and nitrogen purged 50 mL flask was charged 0.5 M $ZnCl_2$ solution in THF (4 equiv, 8 mmol, 16 mL). [1-(Ethoxycyclopropyl)oxy]-trimethylsilane (8 equiv, 16 mmol, 2.81 g) was added via a syringe. The mixture was stirred at ambient temperature for 4 h, then stripped to an oil under vacuum at 25–30 °C. THF (10 mL) was added. This solution was transferred to another dry and nitrogen purged 25 mL flask that contained **2** (682 mg, 2.0 mmol), phthalic anhydride (3.00 equiv; 6.0 mmol; 897 mg), and dichlorobis-(triethylphosphine)palladium(II) (0.05 equiv; 0.1 mmol; 42.8 mg) in DMAc (3.4 mL). After overnight stirring at ambient temperature, the reaction was assayed by HPLC, and showed desired product, but the reaction was incomplete (28% starting material by HPLC area). The reaction was worked up as described in method 1. The final concentrated residue was chromatographed on silica gel eluting with 20% ethyl acetate/hexanes to give 285 mg of desired product (54% yield, 192 mg of **2** was recovered). Note: the product obtained should be treated once with DarCo-G60 to purge the residual palladium in order to obtain high diastereoselectivity in the N-Selectride reduction reaction.
22. Preparation of lactone **1a**. To a dry and nitrogen purged 100 mL flask was added α-aminoketone **4** (1.0 g, 2.72 mmol) and THF (10 mL). The resultant solution was cooled to −78 °C. N-Selectride (1.0 M, 3 mmol, 3 mL) in THF was added dropwise while keeping reaction below −72 °C over 30 min. After 10 min stirring at −78 °C, HPLC assay showed reaction completion. Acetic acid (0.62 mL) in THF (10 mL) was added dropwise. The reaction was allowed to warm to room temperature and subsequently heated at reflux for 10 min. After cooling to room temperature, ethyl acetate (10 mL) and 1 N HCl (10 mL) were added. The layers were separated, the organic layer was washed with saturated sodium bicarbonate and brine solutions. After drying over $MgSO_4$, the organic phase was concentrated to an oil in vacuo. The resulting residue was granulated in isopropylether (2 mL) for 10 min, then hexanes (2 mL) was added. The mixture was stirred at ambient temperature for 1 h, and filtered. This gave the desired product as a white solid (673 mg, 76.5%). HPLC purity: chiral 97.8% (enantiomer 1.1%, diastereomer 1.0%); achiral 98.0%. The material obtained co-eluted with an authentic sample in HPLC, and the spectroscopic data were identical to those reported.[8]