Asymmetric Synthesis of α- and β-Benzylhydroxy-γ-butyrolactones

Pedro Pinho,* Mikael Pelcman, Tatiana Agback, Bertil Samuelsson

Medivir AB, Box 1086, 141 22 Huddinge, Sweden
Fax +46(8)54683199; E-mail: pedro.pinho@medivir.se

Received 14 September 2009

Abstract: Herein we describe a new asymmetric synthesis of α-benzyl-α-hydroxy-γ-butyrolactone, a core building block of new HIV-1 protease inhibitors containing a tertiary alcohol in the transition-state mimic. Immediate access to β-benzyl-β-hydroxy-γ-butyrolactone is also possible from a common intermediate. Both lactones are useful building blocks in their own right.

Key words: lactones, asymmetric catalysis, epoxidations, oxidations, HIV

We have recently reported on new HIV-1 protease inhibitors containing a tertiary alcohol in the transition-state mimic **A** (Figure 1).[1] The central core of this type of inhibitor can be prepared by either epoxidation of **1** and subsequent ring opening[1a–1c] or by the opening of α-benzyl-α-hydroxy-γ-butyrolactone (**2**) with the appropriate amino alcohol.[1d] Unfortunately, both these methods require separation of diastereomers, which is not always possible and does not allow the use of non-chiral amino alcohols in P2 variations. A survey of the literature revealed only one asymmetric preparation of **2**,[2] and this approach gave low enantiomeric excesses of only 48 to 50%. Other aryl and alkyl substituents are rare in the literature.[3]

Therefore, in order to allow the study of further variations of the P2 unit and for practical purposes when preparing larger amounts of compound, an asymmetric synthesis of one of the core building blocks was designed (Scheme 1).

As in the racemic synthesis of **2**,[1d] simple condensation of γ-butyrolactone with benzaldehyde as reported elsewhere[4] yielded compound **3**. The lactone was then opened with a slight excess of NaOH and the acid was trapped as the corresponding 2-propyl ester. Alcohol **4** was protected with TBDMS under standard conditions and the ester was reduced to the allylic alcohol **5** with DIBAL-H.

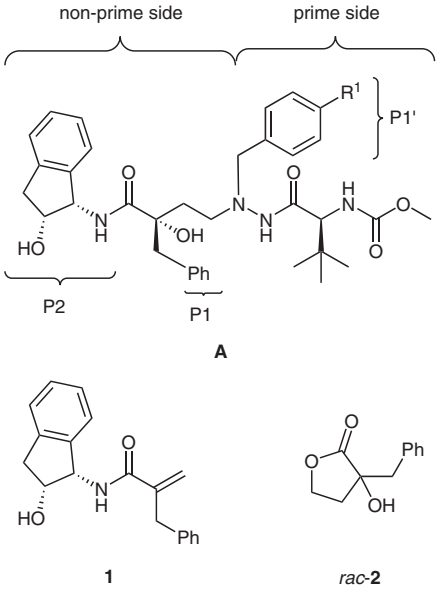
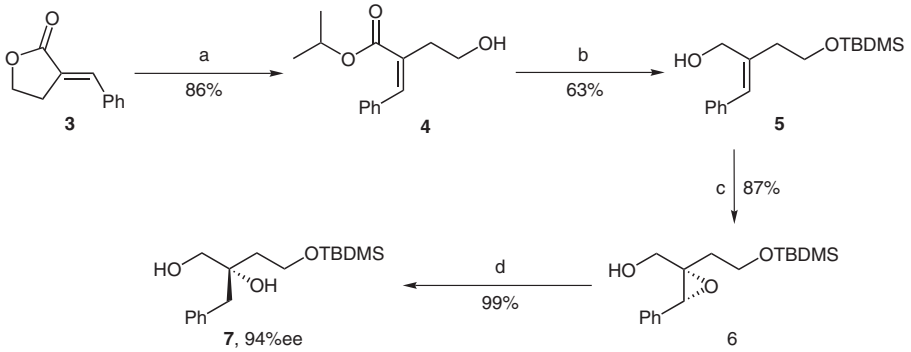


Figure 1 HIV-1 protease inhibitors **A** and core building blocks

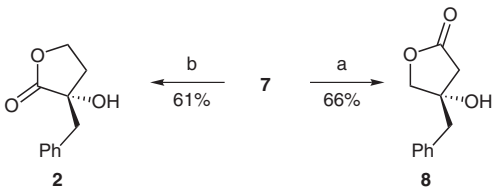


Scheme 1 *Reagents and conditions*: (a) i. NaOH (1.5 equiv), THF–H_2O (1:1), r.t., 1 h; ii. dry ice, r.t., 15 min; 2-iodopropane (1.5 equiv), DMSO, r.t., 20 h; (b) i. TBDMSCl (1.5 equiv), imidazole (2.5 equiv), DMF, 0 °C → r.t., 90 min; ii. DIBAL-H (3 equiv), Et_2O, –78 °C, 2 h; iii. sat. di-potassium tartrate, 90 min, r.t.; (c) Ti(*i*-PrO)$_4$ (8 mol%), (+)-DIPT (10 mol%), *t*-BuOOH (2 equiv), 4 Å MS, CH_2Cl_2, –20 °C, 5 h; (d) 10 wt% Pd/C (10 wt%), H_2 (1 atm), 20 h.

SYNLETT 2010, No. 1, pp 0131–0133
Advanced online publication: 30.11.2009
DOI: 10.1055/s-0029-1218529; Art ID: G30309ST

Chirality was then introduced using Sharpless asymmetric epoxidation.[5] Catalytic hydrogenation of the resulting epoxide **6** yielded diol **7**, which was treated with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenyl acetic acid to afford the corresponding Mosher ester.[6] The enantiomeric excess of the epoxidation step was then determined by integration of the ^{19}F NMR spectra and showed to be 94%. The process was then scaled up to produce 50 grams of the convenient precursor **7**.

Direct oxidation of **7** with Pt/C and oxygen[7] (Scheme 2) produced a lactone that was physically non-identical to racemic **2**. Careful NMR analysis revealed the presence of lactone **8**,[8] which was formed through loss of the silyl protection under the reaction conditions and oxidation of the less hindered alcohol; this conclusion was supported by observation of the intermediate triol by LC-MS analysis during the course of the reaction.



Scheme 2 *Reagents and conditions*: (a) i. 5 wt% Pt/C (40 wt%), air, $NaHCO_3$, H_2O, EtOAc, *i*-PrOH, 70 °C, 24–48 h; ii. 2 M H_2SO_4; (b) i. Et_3N (3 equiv), SO_3·pyridine complex (1.1 equiv), CH_2Cl_2–DMSO (3:1), 0 °C → r.t., 1 h; ii. $NaClO_2$ (2 equiv), $NaHCO_3$ (2.5 equiv), 2-methylbut-2-ene (1.1 equiv), *t*-BuOH–H_2O (3:1), r.t., 2 h; iii. concd HCl, MeOH–H_2O (4:1), r.t., 15 min.

Compound **7** was therefore stepwise oxidized, first to the aldehyde and then to the acid[9] to afford, after deprotection, the desired lactone. Compound **2** was then used for the synthesis of inhibitor **A**, which showed spectroscopic data similar to those observed previously, thereby confirming the absolute stereochemistry of the lactone produced by the process described here.

In conclusion, an asymmetric synthesis of both α- and β-benzylhydroxy-γ-butyrolactone has been developed. This has allowed us to further screen P2 variations on our family of HIV-1 protease inhibitors beyond chiral amino alcohols, as well as to produce larger amounts of selected compounds for extended biological studies.

References and Notes

(1) (a) Ekegren, J. K.; Unge, T.; Safa, M. Z.; Wallberg, H.; Samuelsson, B.; Hallberg, A. *J. Med. Chem.* **2005**, *48*, 8098. (b) Ekegren, J. K.; Gising, J.; Wallberg, H.; Larhed, M.; Samuelsson, B.; Hallberg, A. *Org. Biomol. Chem.* **2006**, *4*, 3040. (c) Ekegren, J. K.; Ginman, N.; Johansson, Å.; Wallberg, H.; Larhed, M.; Samuelsson, B.; Unge, T.; Hallberg, A. *J. Med. Chem.* **2006**, *49*, 1828. (d) Ekegren, J. K.; Hallberg, A.; Wallberg, H.; Samuelsson, B.; Kannan, M. WO 2006/084688, **2006**. (e) Wu, X.; Öhrngren, P.; Ekegren, J. K.; Unge, J.; Unge, T.; Wallberg, H.; Samuelsson, B.; Hallberg, A.; Larhed, M. *J. Med. Chem.* **2008**, *51*, 1053.

(2) Curran, D. P.; Ku, S.-B. *J. Org. Chem.* **1994**, *59*, 6139.

(3) (a) For Me, using chiral auxiliary strategy, see: Davis, F. A.; Reddy, G. V.; Chen, B.-C.; Kumar, A.; Haque, M. S. *J. Org. Chem.* **1995**, *60*, 6148. (b) For Me, Et, *n*-Pr and *i*-Pr using a seven-step sequence from (–)-ephedrine, see: Pansare, S. V.; Jain, R. P.; Ravi, R. G. *Tetrahedron: Asymmetry* **1999**, *10*, 3103. (c) For Me, from (–)-malic acid, see: Ohba, M.; Izura, R.; Shimizu, E. *Tetrahedron Lett.* **2000**, *41*, 10251. (d) Ohba, M.; Izura, R.; Shimizu, E. *Chem. Pharm. Bull.* **2006**, *54*, 63. (e) Scherkenbeck, J.; Barth, M.; Thiel, U.; Metten, K.-H.; Heinemann, F.; Welzel, P. *Tetrahedron* **1988**, *44*, 6325. (f) Sugai, T.; Kakeya, H.; Ohta, H. *Tetrahedron* **1990**, *46*, 3463. (g) For Ph, see: Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 3195. (h) Eliel, E. L.; Bai, X.; Ohwa, M. *J. Chin. Chem. Soc.* **2000**, *47*, 63. (i) Frongia, A.; Girard, C.; Ollivier, J.; Piras, P. P.; Secci, F. *Synlett* **2008**, 2823.

(4) See, for example: Yato, M.; Homma, K.; Ishida, A. *Tetrahedron* **2001**, *57*, 5353.

(5) The procedure used was similar to that reported, see: Gao Y., Hanson R. M., Klunder J. M., Ko S. Y., Masamune H., Sharpless K. B.; *J. Am. Chem. Soc.*; **1987**, *109*: 5765; Note: Performing the reaction under non-anhydrous conditions leads to extended reaction times and lower enantioselectivity.

(6) Following the reported procedure a racemic sample of **7** was prepared through oxidation of **5** with *m*-CPBA. The Mosher ester of this sample was also prepared for comparison of the ^{19}F NMR spectra. See: Akhoon, K. M.; Myles, D. C. *J. Org. Chem.* **1997**, *62*, 6041.

(7) See for example: Bennani, Y. L.; Vanhessche, K. P. M.; Sharpless, K. B. *Tetrahedron: Asymmetry* **1994**, *5*, 1473.

(8) (a) For racemic **8** see: Plattner, P. A.; Heusser, H. *Helv. Chim. Acta* **1945**, *28*, 1044. (b) For Me through biotransformation, see: Holland, H. L.; Gu, J.-X. *Biotechnol. Lett.* **1998**, *20*, 1125. (c) For Me and Ph, see reference 3h; (d) Typical experimental procedure for the oxidation of **7** to **8**: A two-neck flask fitted with a reflux condenser was loaded with **7** (93 mg, 0.30 mmol) and EtOAc (4 mL). To the stirring solution was added $NaHCO_3$ (30 mg), H_2O (4 mL) and 2-PrOH (0.80 mL). Pt/C (5 wt%, 40 mg) was added and the mixture heated at 70 °C for 24 to 48 h while bubbling air through a gas dispersion tube. NOTES: 1) the reaction is considerably faster using oxygen, but the combination of O_2 and Pt(0) can easily cause fire and should be carefully controlled. 2) The transformation should be carefully monitored by LC-MS since, due to the four phase system, reaction times can vary. When complete, or nearly complete, the mixture was cooled to r.t. and the catalyst was filtered off. Organic solvents were removed by evaporation and MeOH (equal volume to that of H_2O) was added. The solution was acidified with 2 M H_2SO_4 and stirred for 30 min. The solution was diluted with EtOAc (20 mL) and poured into an extraction funnel. The organic phase was washed with H_2O (4 × 5 mL), dried over Na_2SO_4, filtered and concentrated. Flash chromatography on silica gel (EtOAc–hexane, 40%) yielded **8** (38 mg, 66%). $[\alpha]_D^{20}$ –49.9 (*c* 1.4, MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.40 (m, 5 H), 4.11–4.32 (m, 2 H, γ-CH_2), 2.97–3.02 (m, 2 H, β-Bn-CH_2), 2.44–2.73 (m, 2 H, α-CH_2), 2.27 (br s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3, 134.9, 129.8, 129.0, 127.6, 77.9, 76.8, 43.9, 41.9. The structure was confirmed through conventional gHMBC experiments. The 1D ^1H NMR spectrum shows three different sets of CH_2 protons. The first observed quartet at δ = 4.11–4.32 ppm was assigned to the γ-CH_2 due to the largest downfield chemical shift when compared to the others. Furthermore it also shows

a weak three-bond interaction with the carbonyl carbon in the gHMBC spectrum. The second set, a collapsed quartet at δ = 2.97–3.02 ppm, shows interaction with the aromatic carbons in the gHMBC spectrum, and was therefore assigned to the β-Bn-CH_2. Finally, the observed quartet at higher field, δ = 2.44–2.73 ppm was assigned to the α-CH_2, showing a strong two-bond interaction with the carbonyl carbon in the gHMBC spectrum. LC-MS (ESI^+): *m*/*z* = 193 [M + 1], 210 [M+NH_4^+].

(9) Typical experimental procedure for the oxidation of **7** to **2**: To a cold (0 °C) solution of **7** (2.12 g, 6.83 mmol) in CH_2Cl_2–DMSO (3:1, 20 mL) was added Et_3N (3 equiv) followed by SO_3·pyridine complex (1.1 equiv). The ice bath was removed and the reaction was allowed to stir at r.t. for 1 h. The solution was then poured into an extraction funnel, diluted with EtOAc (50 mL) and washed with brine (3 × 10 mL). The solvent was removed by evaporation and the crude aldehyde was dissolved in *t*-BuOH (25 mL). To the solution were added H_2O (5 mL), $NaHCO_3$ (2.5 equiv), 2-methyl-2-butene (1.1 equiv) and $NaClO_2$ (2.1 equiv). After stirring for 2 h the solvent was removed, the residue was taken into EtOAc (75 mL) and the pH was adjusted to 2 with 0.5 M $NaHSO_4$. Upon phase separation the solvent was removed and the crude acid was taken into MeOH (20 mL). H_2O (5 mL) was added and the stirring mixture was treated with concd HCl (6 mL). After 15 min the reaction was evaporated to dryness and the residue was purified by flash chromatography on silica gel (EtOAc–hexane, 40%) to yield **2** (800 mg, 61%). $[\alpha]_D^{20}$ –72.6 (*c* 1.5, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.36 (m, 5 H), 4.24–4.31 (m, 1 H), 3.73–3.81 (m, 1 H), 3.06 (s, 1 H), 2.89 (s, 1 H), 2.25–2.41 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.8, 134.2, 130.0, 128.7, 127.5, 73.3, 65.2, 43.5, 34.0; LC-MS (ESI^+): *m*/*z* = 193 [M + 1], 210 [M + NH_4^+].