Efficient Synthesis of 2(*S*)-[1(*S*)-Azido-2-phenylethyl]oxirane

Sangwoo Park, Sangmi Lee, and Ho-Jung Kang*

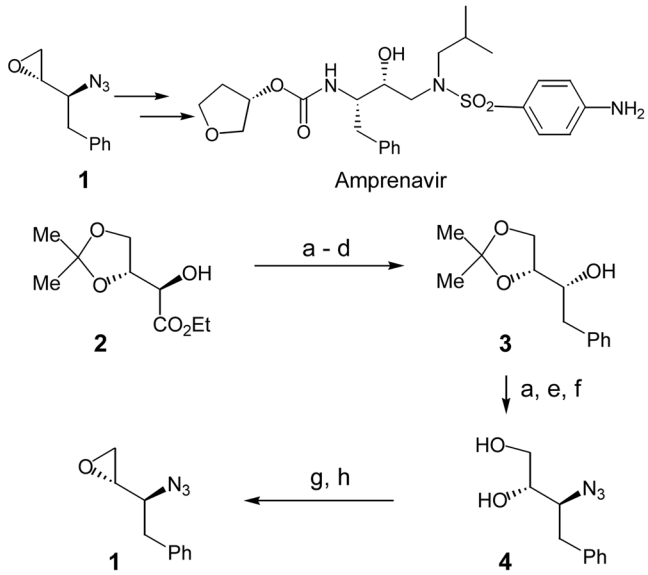
*Department of Chemistry, Kyunghee University, Seoul 130-701, Korea. *E-mail: hjkang@khu.ac.kr*
Received January 25, 2008

Key Words : Amprenavir, Aminoalkylepoxide, D-Isoascorbic acid, Antiviral agent

Various HIV protease inhibitors have been developed as promising chemotherapeutic agents for the treatment of AIDS.[1] The importance of hydroxyethylamine isosteres in the this field was well witnessed by antiviral agents such as saquinavir,[2a] amprenavir[2b] and nelfinavir.[2c] In connection of our studies on the development of an improved drug delivery system, we were interested in the synthesis of amprenavir and related compounds. Among many reports on the synthesis of this class of inhibitors,[3] we focused on the synthetic scheme that relies on the use of protected aminoalkyl epoxides.[4] On the way to the synthesis of crucial 2(*S*)-[1(*S*)-azido-2-phenylethyl]oxirane (**1**) according to the known procedure,[4b] we needed to devise a more efficient route to this key intermediate to avoid tedious experimental conditions. Here we wish to report a brief synthesis of oxirane **1** which is more efficient and suitable for preparation on a large scale.

In Scheme 1, our modified synthesis starts from acetonide **2** which was readily and cheaply available in large quantity from D-isoascorbic acid.[5] Mesylation and subsequent reduction with $NaBH_4$ converted acetonide **2** to a selectively mesylated diol. Sequential treatment of NaH with the mesylate and addition of PhMgBr to the resulting oxirane in the presence of CuI produced the known alcohol **3** in 80% overall yield. Next, alcohol **3** was mesylated and hydrolyzed to the diol which was then converted to the known diolazide **4** via azide displacement with CsN_3. This azidation was superior to the known Mitsunobu azidation of alcohol **3**. The resulting diolazide **4** was treated with 2-acetoxyisobutyryl chloride and NaOMe successively[6] to give the known key intermediate **1** in 60% overall yield from alcohol **3**.

In conclusion, 2(*S*)-[1(*S*)-azido-2-phenylethyl]oxirane (**1**) was efficiently synthesized from acetonide **2** as a starting material by 9 steps with two purification steps at alcohol **3** and oxirane **1** respectively in overall yield of 48%. This protocol avoids troublesome LAH reduction and Mitsunobu azidation[7] that were involved in the known method, providing an expedient route to the facile, practical and large production of the desired epoxide **1** and other related structural motives from the cheaper D-isoascorbic acid.



Scheme 1. reagents and conditions: (a) MsCl, Py; (b) $NaBH_4$, MeOH; (c) NaH, THF, −20 °C to rt; (d) PhMgBr, CuI, THF, −40 °C to 0 °C, 80% (overall 4 steps); (e) 1 N HCl, THF; (f) CsN_3, 18-Cr-6, PhH, reflux; (g) 2-acetoxyisobutyryl chloride, $CHCl_3$; (h) NaOMe, THF, 60% (overall 5 steps for a, e, f, g and h).

Experimental Section

1(*R*)-(2,2-Dimethyl-[1,3]dioxalan-4(*R*)-yl)-2-phenylethanol (3). Hydroxyester **2** (5.00 g, 24.4 mmol) was dissolved in pyridine (30 mL) and mesyl chloride (3.59 g, 31.36 mmol) was slowly added to it at 0 °C. After 30 min, the resulting mixture was warmed up to room temperature and stirred for 13 h before being quenched with saturated $NaHCO_3$ solution (50 mL). After extraction of the aqueous layer with CH_2Cl_2 (100 mL × 3), combined organic layers were washed with H_2O, dried over $MgSO_4$, and concentrated to give crude mesylate which was dissolved in MeOH (10 mL) and slowly added to a stirred solution of $NaBH_4$ (1.85 g, 48.8 mmol) in MeOH (20 mL) at 0 °C. The resulting mixture was warmed up to room temperaure and stirred for 2 h. Quenching the reaction mixture with saturated $NaHCO_3$ (30 mL) and following extraction with CH_2Cl_2 (150 mL × 3) produced crude alcohol after drying over $MgSO_4$, and solvent evaporation. To a stirred solution of NaH (60% dispersion, 1.78 g) in THF (20 mL) at −20 °C was slowly added crude alcohol in THF (10 mL) and the resulting mixture was stirred at room temperature for 20 min before it was quenched with saturated $NaHCO_3$ (5 mL). Usual work-up with CH_2Cl_2 gave crude epoxide which was used in the next step without further purification. A cold (−50 °C) solution of crude epoxide and CuI (0.37 g, 1.95 mmol) in THF (30 mL) was treated with PhMgBr (43 mL, 43 mmol, 1 M in THF)

and stirred at 0 °C for 3 h before being quenched with sturated $NaHCO_3$ (20 mL). Extraction with CH_2Cl_2, drying over $MgSO_4$, and solvent evaporation provided pure alcohol **3** (4.06 g, 80% for overall 4 steps) after chromatography on silica gel (elution with 50% EtOAc in hexane). $[\alpha]_D^{15}$ +7.67° (*c* 3.0, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.21 (m 5H), 4.05 (dt, *J* = 5.3, 6.6 Hz, 1H), 3.94 (dd, *J* = 6.6, 8.2 Hz, 1H) 3.77 (dq, *J* = 7.4, 5.3 Hz, 1H), 3.72 (dd, *J* = 6.6, 8.2 Hz, 1H), 2.86-2.73 (m, 2H), 2.28 (d, *J* = 5.3 Hz), 1.45 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 138.61, 129.80, 128.56, 126.54, 109.20, 78.37, 73.02, 66.01, 40.45, 26.67, 25.41; MS *m/z* $C_{13}H_{19}O_3$ $(M+H)^+$ calcd 223.13, obsd 223.36.

2(*S*)-[1(*S*)-Azido-2-phenylethyl]oxirane. To a stirred solution of alcohol **3** (4.02 g, 19.0 mmol) in pyridine (25 mL) at 0 °C was added mesyl chloride (3.05 g, 26.6 mmol) and the resulting solution was stirred at room temperature for 13 h. Quenching the reaction mixture with saturated $NaHCO_3$ (30 mL) and following extraction with CH_2Cl_2 (150 mL × 3) produced crude mesylate after drying over $MgSO_4$, and solvent evaporation. 1 M aqueous HCl (20 mL) was added to a solution of mesylate in THF (20 mL) and the mixture was stirred at room temperature for 4 h. Quenching with saturated $NaHCO_3$ and extraction with CH_2Cl_2 (200 mL × 3) produced diol after drying over $MgSO_4$, and solvent evaporation. A benzene (50 mL) solution of crude diol, CsN_3 (8.45 g, 48.5 mmol) and 18-crown-6 (2.14 g, 8.09 mmol) was refluxed for 15 h. The resulting mixture was cooled down and washed with H_2O (50 mL). the aqueous layer was extracted with EtOAc (100 mL × 3) and combined organic layers were dried over $MgSO_4$ and concentrated to give azide **4**. $[\alpha]_D^{15}$ +30.6 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.17 (m, 5H), 3.75-3.58 (m, 4H), 2.98 (dd, *J* = 4.0, 14.2 Hz, 1H), 2.73 (dd, *J* = 8.8, 14.2 Hz, 1H), 2.65 (s, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 137.21, 129.30, 128.67, 126.92, 72.98, 65.58, 63.16, 37.02; MS *m/z* $C_{10}H_{14}N_3O_2$ $(M+H)^+$ calcd 208.11, obsd 208.35.

A chloroform (20 mL) solution of azide **4** and 2-acetoxy-isobutyryl chloride (3.19 g, 19,4 mmol) was stirred at room temperature for 4 h and quenched with saturated $NaHCO_3$ (20 mL). Usual work-up with CH_2Cl_2 produced crude chloroacetate which was dissolved in THF (10 mL) and treated with NaOMe (3.50 g, 64.7 mmol). The resulting mixture was stirred at room temperature for 6 h, quenched with saturated $NaHCO_3$ (15 mL) and extracted with ether (100 mL × 3). Combined organic layers were dried over $MgSO_4$ and solvent was evaporated to give crude product which was purified by column chromatography on silica gel (elution with 25% EtOAc in hexane) to afford pure oxirane **1** (2.15 g, 60% for overall 5 steps). ^{1}H NMR spectrum was completely matched with the known literature value.[4b] $[\alpha]_D^{15}$ +14.3 (*c* 2.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.24 (m, 5H), 3.60 (dt, *J* = 8.7, 5.0 Hz, 1H), 3.07 (m, 1H), 3.00 (dd, *J* = 4.6, 14.0 Hz, 1H), 2.85-2.80 (m, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 136.53, 129.29, 128.51, 126.90, 63.50, 52.93, 45.05, 38.12; MS *m/z* $C_{10}H_{11}N_3NaO$ $(M+Na)^+$ calcd 212.08, obsd 212.34.

Acknowledgements. The authors are grateful to Kyunghee University for its financial support (University Research Fund 20070595) for this work.

References

1. (a) Power, M. D.; Marx, P. A.; Bryant, M. L.; Gardner, M. B.; Barr, P. J.; Luciw, P. A. *Science* **1986**, *231*, 1567. (b) Kempf, D. J.; Marsh, K. C.; Denissen, J. F.; McDonald, E.; Vasavononda, S.; Flentge, C. A.; Green, B. G.; Fino, L.; Park, C. H.; Kong, X.-P.; Wideburg, N. E.; Saldivar, A.; Ruiz, L.; Kati, W. M.; Sham, H. L.; Robins, T.; Stewart, K. D.; Hsu, A.; Plattner, J. J.; Leonard, J.; Norbeck, D. *Pro. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 2484. (c) Flexner, C. *New Engl. J. Med.* **1998**, *338*, 1281.
2. (a) Roberts, N. A.; Martin, J. A.; Kinchington, D.; Broadhurst, A. V.; Craig, J. C.; Duncan, I. B.; Galphin, S. A.; Handa, B. K.; Krohn, A.; Lambert, R. W.; Merrett, J. H.; Mills, J. S.; Parkes, K. E. B.; Redshaw, S.; Ritchie, A. J.; Taylor, D. L.; Thomas, G. J.; Machin, P. J. *Science* **1990**, *248*, 358. (b) Kim, E. E.; Baker, C. T.; Dwyer, M. D.; Murcko, M. A.; Rao, B. G.; Tung, R. D.; Navia, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 1181. (c) Kaldor, S. W.; Kalish, V. J.; Davies, J. F.; Shetty, B. V.; Fritz, J. E.; Appelt, K.; Burgess, J. A.; Campanale, K. M.; Chirgadze, N. Y.; Clawson, D. K.; Dressman, B. A.; Hatch, S. D.; Khalil, D. A.; Kosa, M. S.; Tatlock, J. H. *J. Med. Chem* **1997**, *40*, 3979.
3. (a) Pearl, L. H.; Taylor, W. R. *Nature* **1987**, *329*, 351. (b) Huff, J. R. *J. Med. Chem.* **1991**, *34*, 2305. (c) Parkes, K. E. B.; Bushnell, D. J.; Cracjeff, P. H.; Dunsdon, S. J.; Freeman, A. C.; Gunn, M. P.; Popkins, R. A.; Lambert, R. W.; Thomas, G. J. *J. Org. Chem.* **1994**, *59*, 3656. (d) Beaulieu, P. L.; Wernic, D. *J. Org. Chem.* **1996**, *61*, 3635. (e) Rieger, D. L. *J. Org. Chem.* **1997**, *62*, 8546. (f) Corey, E. J.; Zhang, F.-Y. *Angew. Chem. Int. Ed.* **1999**, *38*, 1931. (g) Zook, S. E.; Busse, J. K.; Borer, B. C. *Tetrahedron Lett.* **2000**, *41*, 7017. (h) Tomasselli, A. G.; Heinrikson, R. L. *Biochim. Biophys. Acta* **2000**, 189. (i) Rocheblave, L.; Bihel, F.; Michelis, C.; Priem, G.; Courcambeck, J.; Bonnet, B.; Chermann, J.-C.; Kraus, J.-L. *J. Med. Chem.* **2002**, *45*, 3321. (j) Yanada, R.; Koh, Y.; Nishimori, N.; Matsumura, A.; Obika, S.; Mitsuya, H.; Fujii, N.; Takemoto, Y. *J. Org. Chem.* **2004**, *69*, 2417. (k) Honda, Y.; Katayama, S.; Kojima, M.; Suzuki, T.; Kishibata, N.; Izawa, K. *Org. Biomol. Chem.* **2004**, *2*, 2061.
4. (a) Luly, J. R.; Dellaria, J. F.; Plattener, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487. (b) Ghosh, A. K.; McKee, S. P.; Lee, H. Y.; Thompson, W. *J. Chem. Soc. Chem. Commun.* **1992**, 273. (c) Kim, B. M.; Bae, S. J.; So, S. M.; Yoo, H. T.; Chang, S. K.; Lee, J. H.; Kang, J. *Org. Lett.* **2001**, *3*, 2349.
5. Abushanab, E.; Vmishetti, P.; Leiby, R. W.; Singh, H. K.; Mikkilineni, A. B.; Wu, D. C.-J.; Saibaba, R.; Panzica, R. P. *J. Org. Chem.* **1988**, *53*, 2598.
6. Greenberg, S.; Moffat, G. J. *J. Am. Chem. Soc.* **1973**, *95*, 4016.
7. In our procedure, mesylate displacement by azide ion gave compound **4** in 80% yield, which was used directly in the next step without chromatography.