

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

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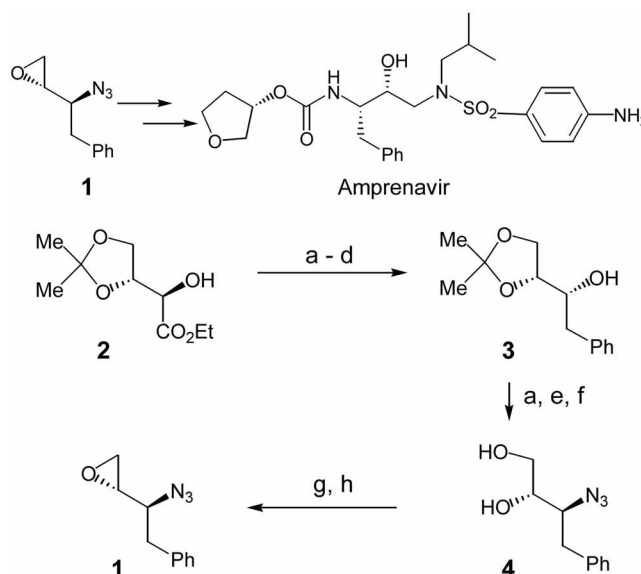
Various HIV protease inhibitors have been developed as promising chemotherapeutic agents for the treatment of AIDS.<sup>1</sup> The importance of hydroxyethylamine isosteres in the this field was well witnessed by antiviral agents such as saquinavir,<sup>2a</sup> amprenavir<sup>2b</sup> and nelfinavir.<sup>2c</sup> 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,<sup>3</sup> we focused on the synthetic scheme that relies on the use of protected aminoalkyl epoxides.<sup>4</sup> On the way to the synthesis of crucial 2(*S*)-[1(*S*)-azido-2-phenylethyl]oxirane (**1**) according to the known procedure,<sup>4b</sup> 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.<sup>5</sup> Mesylation and subsequent reduction with NaBH<sub>4</sub> 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<sub>3</sub>. 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<sup>6</sup> 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<sup>7</sup> 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.

### 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,



**Scheme 1.** reagents and conditions: (a) MsCl, Py; (b) NaBH<sub>4</sub>, 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<sub>3</sub>, 18-Cr-6, PhH, reflux; (g) 2-acetoxyisobutyryl chloride, CHCl<sub>3</sub>; (h) NaOMe, THF, 60% (overall 5 steps for a, e, f, g and h).

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<sub>3</sub> solution (50 mL). After extraction of the aqueous layer with CH<sub>2</sub>Cl<sub>2</sub> (100 mL × 3), combined organic layers were washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub>, and concentrated to give crude mesylate which was dissolved in MeOH (10 mL) and slowly added to a stirred solution of NaBH<sub>4</sub> (1.85 g, 48.8 mmol) in MeOH (20 mL) at 0 °C. The resulting mixture was warmed up to room temperature and stirred for 2 h. Quenching the reaction mixture with saturated NaHCO<sub>3</sub> (30 mL) and following extraction with CH<sub>2</sub>Cl<sub>2</sub> (150 mL × 3) produced crude alcohol after drying over MgSO<sub>4</sub>, 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<sub>3</sub> (5 mL). Usual work-up with CH<sub>2</sub>Cl<sub>2</sub> 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 saturated NaHCO<sub>3</sub> (20 mL). Extraction with CH<sub>2</sub>Cl<sub>2</sub>, drying over MgSO<sub>4</sub>, 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). [ $\alpha$ ]<sub>D</sub><sup>15</sup> +7.67° (c 3.0, EtOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  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<sub>13</sub>H<sub>19</sub>O<sub>3</sub> (M+H)<sup>+</sup> 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<sub>3</sub> (30 mL) and following extraction with CH<sub>2</sub>Cl<sub>2</sub> (150 mL  $\times$  3) produced crude mesylate after drying over MgSO<sub>4</sub>, 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<sub>3</sub> and extraction with CH<sub>2</sub>Cl<sub>2</sub> (200 mL  $\times$  3) produced diol after drying over MgSO<sub>4</sub>, and solvent evaporation. A benzene (50 mL) solution of crude diol, CsN<sub>3</sub> (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<sub>2</sub>O (50 mL), the aqueous layer was extracted with EtOAc (100 mL  $\times$  3) and combined organic layers were dried over MgSO<sub>4</sub> and concentrated to give azide **4**. [ $\alpha$ ]<sub>D</sub><sup>15</sup> +30.6 (c 2.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  137.21, 129.30, 128.67, 126.92, 72.98, 65.58, 63.16, 37.02; MS *m/z* C<sub>10</sub>H<sub>14</sub>N<sub>3</sub>O<sub>2</sub> (M+H)<sup>+</sup> calcd 208.11, obsd 208.35.

A chloroform (20 mL) solution of azide **4** and 2-acetoxyisobutyryl chloride (3.19 g, 19.4 mmol) was stirred at room temperature for 4 h and quenched with saturated NaHCO<sub>3</sub> (20 mL). Usual work-up with CH<sub>2</sub>Cl<sub>2</sub> 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<sub>3</sub> (15 mL) and extracted with ether (100 mL  $\times$  3). Combined organic layers were dried over MgSO<sub>4</sub> 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). <sup>1</sup>H NMR spectrum was completely matched with the known literature value.<sup>4b</sup> [ $\alpha$ ]<sub>D</sub><sup>15</sup> +14.3 (c 2.1, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$

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); <sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  136.53, 129.29, 128.51, 126.90, 63.50, 52.93, 45.05, 38.12; MS *m/z* C<sub>10</sub>H<sub>11</sub>N<sub>3</sub>NaO (M+Na)<sup>+</sup> calcd 212.08, obsd 212.34.

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- In our procedure, mesylate displacement by azide ion gave compound **4** in 80% yield, which was used directly in the next step without chromatography.