A Concise, General Enantioselective Synthetic Route to 2(*R*)- and 2(*S*)-[1′(*S*)-Azido-2-phenylethyl]oxirane and Related Epoxides

Frank Bennett,* Viyyoor M. Girijavallabhan and Naginbhai Patel

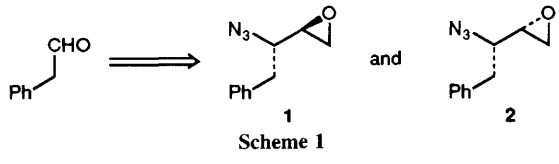
Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, New Jersey 07033, USA

The title oxiranes were constructed in >95% enantiomeric excess (e.e.) utilizing a Sharpless asymmetric epoxidation followed by regioselective azide displacement with $[Ti(OPr^i)_2(N_3)_2]$ as the key steps.

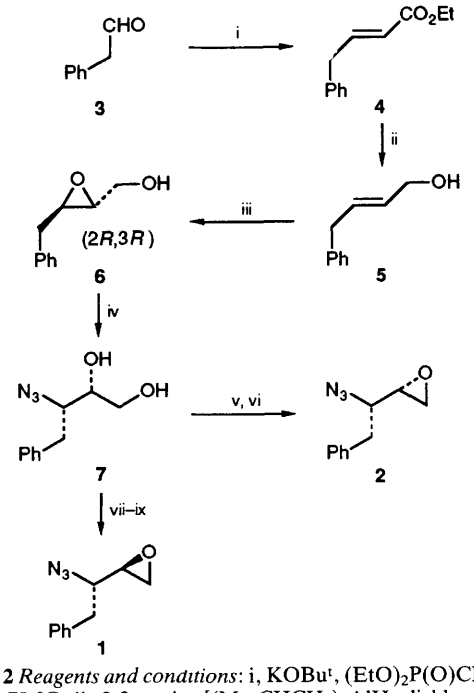
The syntheses of azidoalkyl[1] and protected aminoalkyl[2] epoxides have attracted considerable attention primarily due to their invaluable role in the construction of ethylene and ethylamine dipeptide isosteres. These subunits are subsequently incorporated into pseudopeptides that are potent inhibitors of aspartic proteases such as renin[3] and HIV-1 protease.[4]

Our interest in these epoxides arises from work related to the synthesis of HIV-protease inhibitors, requiring a variety of these compounds in a highly stereoselective and versatile manner. A recent report by Ghosh *et al.*[1] prompts us to submit our own results. In this paper we report the construction of these oxiranes from commercially available or readily accessible aldehydes. Thus, both 2(*R*)- and 2(*S*)-[1′(*S*)-azido-2-phenylethyl]oxiranes (**1** and **2**) are obtained from inexpensive phenylacetaldehyde **3** (Scheme 1) in six and seven steps, respectively. Our route employs a series of reliable reactions, potentially leading to all four possible diastereoisomers of the title compounds. This procedure can be performed routinely on a multigram scale, avoiding the commonly used but problematical protected α-amino aldehydes.

Phenylacetaldehyde **3** is converted to the (*E*)-α,β-unsaturated ester **4** with the potassium salt of triethylphosphonoacetate at −78 °C (Scheme 2) in moderate 59% yield. Diisobutylaluminum hydride reduction gave the allylic alcohol **5**, which was subjected to Katsuki–Sharpless asymmetric epoxidation conditions,[5] employing D-diethyl tartrate (DET) and titanium tetraisopropoxide to afford the (2*R*,3*R*)-benzyl epoxide **6** (80% overall yield from ester **4**). The e.e. was estimated to be >95% based on ^{19}F and ^1H NMR (400 MHz) analysis of a Mosher ester[6] derivative of the alcohol **6**.† Regioselective, nucleophilic azide opening of the epoxide **6** at



Scheme 1



Scheme 2 *Reagents and conditions*: i, $KOBu^t$, $(EtO)_2P(O)CH_2CO_2Et$, THF, −78 °C; ii, 2.2 equiv. $[(Me_2CHCH_2)_2AlH$, dichloromethane, −78 to 25 °C; iii, $Ti(OPr^i)_4$, Bu^tOOH, D-(−)-DET, dichloromethane, −23 °C; iv, $[Ti(OPr^i)_2(N_3)_2]$, benzene, 75 °C; v, MeC_6H_4-*p*-SO_2Cl, cat. DMAP py, 0 °C; vi, NaH, DMF, 0 °C; vii, C_6H_5COCl, py, −10 to 25 °C; viii, $MeSO_2Cl$, py, −10 to 25 °C, ix, NaOMe, THF, 25 °C

† An analogous reaction has been performed on the olefin **5** (obtained from a different method) using L- rather than D-DET to obtain the (2*S*,3*S*)-enantiomer of epoxide **6** with similar enantiomeric enrichment; see N. L. Lentz and N. P. Peet, *Tetrahedron Lett.*, 1990, **31**, 811.

the C-3 position to the azido diol **7** was achieved with $[Ti(OPr^i)_2(N_3)_2]$[7] in warm benzene (71% isolated yield after silica gel chromatography).

The azido diol **7** is the common, key intermediate from which both epoxides **1** and **2** are obtained in high yield in two and three step sequences, respectively (Scheme 2). Thus, the diol **7** is treated with tosyl chloride (1.1 equiv.) (tosyl = MeC_6H_4-*p*-SO_2] and a catalytic amount of 4-dimethylaminopyridine (DMAP) 5–10 mol% in pyridine (py) and the resulting intermediate primary tosylate is subsequently exposed to sodium hydride in dimethylformamide (DMF) to afford the oxirane **2** in *ca.* 70% overall yield. Alternatively, the diol **7** can be transformed to the isomeric oxirane **1** using a previously described three-step procedure.[1] Selective benzoylation of the primary hydroxy functionality, mesylation and treatment of the resulting ester–mesylate with sodium methoxide in tetrahydrofuran (THF) provides the oxirane **1** again in *ca.* 70% overall yield. Spectroscopic and analytical data obtained for both oxiranes **1** and **2** agree with previously reported results;[1] oxirane **1**: $([\alpha]_D^{25}$ + 18.5, *c* 0.76, $CHCl_3$); lit.: $([\alpha]_D^{23}$ + 20.1, *c* 1.29, $CHCl_3$); oxirane **2**: $([\alpha]_D^{20}$ + 14.3, *c* 1.3, $CHCl_3$); lit: $([\alpha]_D^{23}$ + 12.9, *c* 1.15, $CHCl_3$).

In summary, this synthetic strategy provides a more efficient alternate route to these azido alkyl oxiranes. By simply substituting phenylacetaldehyde **3** with a variety of aldehydes, the synthetic route outlined in Scheme 2 can allow access to substituted analogues not available by existing methodology. Application of these compounds in the synthesis of HIV-protease inhibitors is currently under investigation and will be reported elswhere.

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