Synthetic Methods

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Dimerization of Lithiated Terminal Aziridines**

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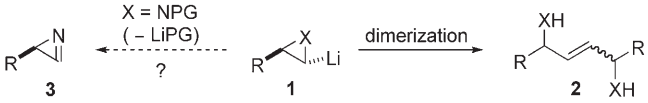
It has been known for a long time that lithiated epoxides **1** (Scheme 1, X = O) can display carbenoid-type reactivity, including dimerization.[1] Such dimerizations have been developed recently by our research group as a synthetic method for the preparation of symmetric 2-ene-1,4-diols **2** (X = O) from terminal epoxides.[2] Although a useful entry to this valuable class of compounds, this method unfortunately displayed only a 2:1 selectivity in favor of the *E* isomer of the newly formed alkene when using epoxides with primary (R = C_5H_{11}) or secondary (R = cyclohexyl) alkyl substituents (62% and 77% yield of 2-ene-1,4-diol olefin isomer mixtures, respectively).



Scheme 1. Possible reactions of lithiated epoxides or aziridines.

Following on from this, we considered the possibility that lithiated terminal aziridines **1** (X = NPG, PG = protecting group)[3] might undergo similar dimerization, thus leading to synthetically useful (protected) 2-ene-1,4-diamines **2** (X = NPG).[4] At the outset of our studies we were not aware of any examples of such dimerizations in the literature,[5] and it was not known whether the method would yield dimer compounds in useful efficiencies or whether other pathways such as formation of 2*H*-azirines **3**[6] (Scheme 1) would be favored. Although certain lithiated aziridines fused to 5- to 8-membered rings undergo carbenoid transformations,[7] formation of 2*H*-azirines in these cases would be significantly disfavored because of additional ring strain. There is little precedent for lithiated aziridines having carbenoid reactivity when the aziridine is not fused to a second ring.[7b]

One additional variable for aziridines (relative to epoxides) is the choice of the protecting/activating group at the aziridine nitrogen atom. In our initial studies we attempted to dimerize alkyl substituted terminal aziridines bearing the groups Boc (butyloxycarbonyl), tosyl, or Bus (*tert*-butylsulfonyl),[8] by using lithium 2,2,6,6-tetramethylpiperidide (LTMP) as the base.[3] Upon treatment with this base, the N-Boc- and N-tosyl-protected aziridines gave complex mixtures of products with no dimers observed, but the lithiated N-Bus-protected aziridine **1a** (X = NBus; R = C_5H_{11}) formed and underwent dimerization in 90% yield to give the protected 2-ene-1,4-diamine **2a** (X = NBus; R = C_5H_{11}) as a mixture of three discernible diastereoisomers.

There are only two possible isomers (alkene *E* and *Z* isomers) that could arise upon dimerization of an enantiopure terminal aziridine, and so this method seems better suited to enantiopure substrates. With this in mind, we examined the scope of the dimerization reaction with a range of enantiopure (99% *ee*) N-Bus-protected terminal aziridines[9] (Table 1).

The enantiopure aziridines (entries 1–5) all dimerized in high efficiency under the same straightforward reaction conditions (aziridine 0.32 mol dm^{-3} in THF/hexanes (2:3), 3 equiv LTMP, −78 °C to 0 °C, total reaction time 80 min; see Experimental Section).[10] Crucially, all these reactions proceeded with complete *E* selectivity for the alkene bond formed, with no traces of the *Z* alkene detectable in either the crude or purified products. The *E* geometry of the alkene was determined unambiguously in the case of **5b** (single-crystal X-ray structure, see Supporting Information), with the other products **5a** and **5c–e** assigned as *E* isomers by analogy. Other possible reaction pathways for the lithiated aziridines such as azirine formation, reaction with excess LTMP to give enamines/aldehydes,[11] or intramolecular cyclopropanation[12] (entry 4) did not feature significantly. Even when aziridine **4a** was added to LTMP in THF at RT with no cooling, dimer **5a**

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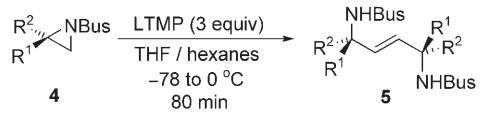
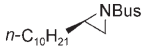
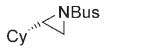
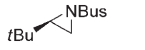
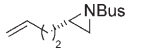
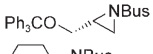
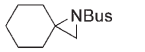
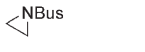
Table 1: Dimerization of lithiated N-Bus aziridines.



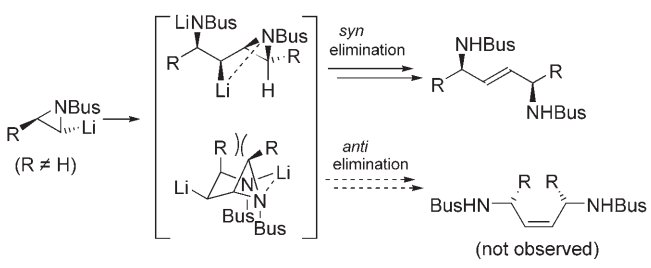
Entry	Aziridine **4**		Yield of dimer **5** [%]
1		(*R*)-**4a**	97
2		(*S*)-**4b**	97
3		(*R*)-**4c**	81
4		(*R*)-**4d**	88
5		(*R*)-**4e**	70
6		**4f**	86[a]
7		**4g**	41[b]

[a] Mixture of olefin isomers obtained (ratio 93:7). [b] Reaction quenched after 10 min at −78 °C and yielded a mixture of olefin isomers (ratio 57:43). Cy = cyclohexyl.

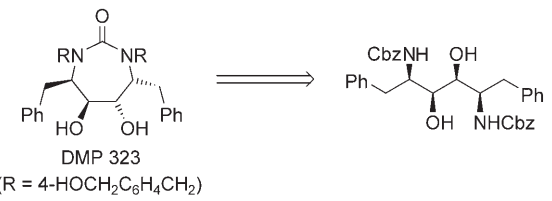
was isolated in 84 % yield and as a single alkene isomer after reaction for 30 minutes, thus demonstrating the inherent robustness and selectivity of the method. Enantiomeric aziridine (*S*)-**4a** also underwent dimerization in 97 % yield (entry 1), thus showing the methodology to be equally applicable to the preparation of either enantiomeric series of dimers **5**. The reaction was also efficient for an achiral 2,2-disubstituted aziridine **4f** and to a lesser extent with the nonsubstituted aziridine **4g** (entries 6 and 7, respectively). In both these latter cases heterochiral as well as homochiral dimerization pathways are possible, and the products were isolated as mixtures of *E* and *Z* isomers.

Formation of the *E* isomer from enantiopure substrates is consistent with an inital *trans*-lithiation of the aziridine at the terminal position,[3] followed by reaction of one lithiated aziridine as a nucleophile with a second acting as an electrophile, and finally *syn* elimination.[2] One possible reason for the superior alkene stereoselectivity seen with aziridines relative to their epoxide counterparts may be a further disfavoring of the *anti*-elimination pathway as a result of steric hindrance between the N-Bus groups (Scheme 2).

1,4-Diamine derivatives, especially cyclic ureas such as the parent DuPont Merck compound DMP 323 (Scheme 3), have



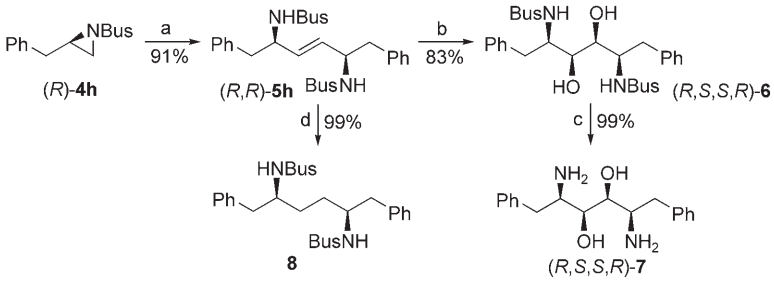
Scheme 2. Possible elimination pathways in dimer formation.



Scheme 3. DMP 323 and its derivation from a 1,4-diamine-2,3-diol unit.[13b]

received considerable attention in recent years as peptidomimetic HIV protease inhibitors.[13] A common structural feature of these inhibitors is a 1,4-diamine-2,3-diol unit with *R*,*S*,*S*,*R* configuration, often with flanking (1,4-) benzyl groups.

We decided to see if our new methodology could be applied in a concise synthesis of such a desirable structural motif, starting with the benzyl-substituted aziridine (*R*)-**4h** (Scheme 4). We found that treatment of aziridine **4h**[9] with LTMP gave the N-Bus-protected 2-ene-1,4-diamine **5h** in



Scheme 4. Applications of the dimerization methodology. Reagents and conditions: a) LTMP (3 equiv), THF/hexanes, −78 °C to 0 °C, 80 min; b) OsO_4 (2.5 mol %), NMO (1.4 equiv), THF/H_2O, RT, 2 days; c) F_3CSO_3H (0.1 N in CH_2Cl_2), anisole, 0 °C to RT, 16 h; d) H_2 (1 atm), Pd on C (5 mol %), EtOH, RT, 24 h.

91 % yield and with complete *E* selectivity. Importantly, potential side products arising from benzylic deprotonation rather than deprotonation at the aziridine were not observed to any significant extent.[14] Simple treatment of alkene **5h** with OsO_4/NMO (*N*-methylmorpholine-*N*-oxide) yielded the *R*,*S*,*S*,*R* diol **6** with high diastereoselectivity (ca. 7:1) over the *R*,*R*,*R*,*R* diol (83 % yield for **6**).[15] The *R*,*S*,*S*,*R* configuration of **6** (and also indirectly the *E* geometry of **5h** prior to *syn*-dihydroxylation) was confirmed by X-ray crystallographic analysis (see Supporting Information).

Removal of the N-Bus group[8a] of diol (*R*,*S*,*S*,*R*)-**6** gave the free diaminodiol (*R*,*S*,*S*,*R*)-**7** in 99 % yield; this is a core C_2-symmetric unit of a number of extremely potent HIV protease inhibitors. (*R*,*S*,*S*,*R*)-**7** has been prepared in a previous HIV protease inhibitor study[16] and has also found use as a ligand or ligand precursor in various enantioselective transformations.[17] The efficiency of deprotection to give the functionalized diaminodiol (*R*,*S*,*S*,*R*)-**7** is of particular note. Benzyl aziridine (*S*)-**4h** was also prepared and dimerized (94 % yield), thus demonstrating that the opposite enantiomeric series can also be accessed.[18] Finally, hydrogenation of

the alkene bond in the dimeric compound (*R*,*R*)-**5h** was also achieved under mild conditions (1 atm H_2, 5 mol% Pd on C, RT) to give the saturated analogue **8** in 99% yield. This result further highlights the utility of the dimerization methodology, and demonstrates efficient access to saturated protected enantiopure C_2-symmetric 1,4-diamines.

In summary, we have developed a dimerization pathway of terminal aziridines by lithiation to give N-protected 2-ene-1,4-diamines with complete *E*-olefin selectivity when starting with enantiopure substrates. The dimerization proved highly efficient for a range of alkyl-substituted and functionalized aziridines, by using the same straightforward reaction conditions in each case. The usefulness of the method was demonstrated by the efficient and selective synthesis of diaminodiol (*R*,*S*,*S*,*R*)-**7**, the core unit of a number of extremely potent HIV protease inhibitors.

Experimental Section

Representative procedure for dimerization of terminal aziridine **4**: *n*BuLi (1.6 M in hexanes, 1.88 mL, 3.0 mmol) was added dropwise to a solution of 2,2,6,6-tetramethylpiperidine (0.51 mL, 3.0 mmol) in THF (0.4 mL) at −78 °C. The mixture was warmed to 0 °C over 15 min, then cooled to −78 °C before dropwise addition of the aziridine **4** (1.0 mmol) in THF (0.8 mL). The mixture was stirred at −78 °C for 20 min, then at 0 °C for 1 h, before the addition of MeOH (0.8 mL), saturated aqueous NH_4Cl (8 mL), and Et_2O (16 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (16 mL). The combined organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue (SiO_2, petroleum ether/diethyl ether) gave the protected 2-ene-1,4-diamine **5**.

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[1] a) K. L. Dhawan, B. D. Gowland, T. Durst, *J. Org. Chem.* **1980**, *45*, 922–924; b) P. Lohse, H. Loner, P. Acklin, F. Sternfeld, A. Pfaltz, *Tetrahedron Lett.* **1991**, *32*, 615–618; c) for a review, see: D. M. Hodgson, C. D. Bray in *Aziridines and Epoxides in Organic Synthesis* (Ed.: A. K. Yudin), Wiley-VCH, Weinheim, **2006**, pp. 143–184.

[2] D. M. Hodgson, C. D. Bray, N. D. Kindon, *Org. Lett.* **2005**, *7*, 2305–2308.

[3] The electrophile trapping of lithiated terminal aziridines has been developed recently, see: D. M. Hodgson, P. G. Humphreys, J. G. Ward, *Org. Lett.* **2005**, *7*, 1153–1156.

[4] For a review of the utility of diamine derivatives in asymmetric catalysis, see: F. Fache, E. Schulz, M. L. Tommasino, M. Lemaire, *Chem. Rev.* **2000**, *100*, 2159–2231; for the utility of 1,4-diamine derivatives as HIV protease inhibitors, see Ref. [13].

[5] Dimerization of a lithiated methylene aziridine to give a cyclopentene has been reported, see: H. Quast, C. A. W. Vélez, *Angew. Chem.* **1974**, *86*, 380–381; *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 342–343; dimerization of N-unprotected aziridines under Lewis acid catalysis to give aminoaziridines is known, see: A. Caiazzo, S. Dalili, A. K. Yudin, *Synlett* **2003**, 2198–2202.

[6] a) F. A. Davis, H. Liu, C.-H. Liang, G. V. Reddy, Y. Zhang, T. Fang, D. D. Titus, *J. Org. Chem.* **1999**, *64*, 8929–8935; b) V. K. Aggarwal, E. Alonso, M. Ferrara, S. E. Spey, *J. Org. Chem.* **2002**, *67*, 2335–2344; c) R. Luisi, V. Capriati, S. Florio, R. Ranaldo, *Tetrahedron Lett.* **2003**, *44*, 2677–2681; d) R. Luisi, V. Capriati, S. Florio, P. Di Cunto, B. Musio, *Tetrahedron* **2005**, *61*, 3251–3260.

[7] a) P. Müller, P. Nury, *Helv. Chim. Acta* **2004**, *87*, 227–239; b) D. M. Hodgson, B. Štefane, T. J. Miles, J. Witherington, *Chem. Commun.* **2004**, 2234–2235; c) C. M. Rosser, S. C. Coote, J. P. Kirby, P. O'Brien, D. Caine, *Org. Lett.* **2004**, *6*, 4817–4819.

[8] a) P. Sun, S. M. Weinreb, M. Shang, *J. Org. Chem.* **1997**, *62*, 8604–8608; b) A. V. Gontcharov, H. Liu, K. B. Sharpless, *Org. Lett.* **1999**, *1*, 783–786.

[9] Enantiopure aziridines were prepared in a straightforward manner and in excellent yield from the corresponding epoxides of opposite configuration (available commercially or according to: S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315) using the following sequence: a) *t*$BuSO_2NH_2$, $BnEt_3NCl$, K_2CO_3; b) $(MeSO_2)_2O$, 4-dimethylaminopyridine, pyridine; c) K_2CO_3 (see Ref. [3] and also: D. M. Hodgson, M. J. Fleming, S. J. Stanway, *Org. Lett.* **2005**, *7*, 3295–3298).

[10] In studies with substrate **4a**, the use of fewer equivalents of LTMP or extended reaction times at −78 °C led to incomplete reaction.

[11] D. M. Hodgson, C. D. Bray, N. D. Kindon, *J. Am. Chem. Soc.* **2004**, *126*, 6870–6781.

[12] a) D. M. Hodgson, Y. K. Chung, J.-M. Paris, *J. Am. Chem. Soc.* **2004**, *126*, 8664–8665; b) D. M. Hodgson, Y. K. Chung, J.-M. Paris, *Synthesis* **2005**, 2264–2266.

[13] a) P. Y. S. Lam, P. K. Jadhav, C. J. Eyermann, C. N. Hodge, Y. Ru, L. T. Bacheler, J. L. Meek, M. J. Otto, M. M. Rayner, Y. N. Wong, C.-H. Chang, P. C. Weber, D. A. Jackson, T. R. Sharpe, S. Erickson-Viitanen, *Science* **1994**, *263*, 380–384; b) M. E. Pierce, G. D. Harris, Q. Islam, L. A. Radesca, L. Storace, R. E. Waltermire, E. Wat, P. K. Jadhav, G. C. Emmet, *J. Org. Chem.* **1996**, *61*, 444–450; c) D. A. Nugiel, K. Jacobs, T. Worley, M. Patel, R. F. Kaltenbach III, D. T. Meyer, P. K. Jadhav, G. V. De Lucca, T. E. Smyser, R. M. Klabe, L. T. Bacheler, M. M. Rayner, S. P. Seitz, *J. Med. Chem.* **1996**, *39*, 2156–2169; d) P. Y. S. Lam, Y. Ru, P. K. Jadhav, P. E. Aldrich, G. V. DeLucca, C. J. Eyermann, C.-H. Chang, G. Emmett, E. R. Holler, W. F. Daneker, L. Li, P. N. Confalone, R. J. McHugh, Q. Han, R. Li, J. A. Markwalder, S. P. Seitz, T. R. Sharpe, L. T. Bacheler, M. M. Rayner, R. M. Klabe, L. Shum, D. L. Winslow, D. M. Kornhauser, D. A. Jackson, S. Erickson-Viitanen, C. N. Hodge, *J. Med. Chem.* **1996**, *39*, 3514–3525; e) A. M. Davis, S. J. Teague, G. J. Kleywegt, *Angew. Chem.* **2003**, *115*, 2822–2841; *Angew. Chem. Int. Ed.* **2003**, *42*, 2718–2736; f) W. A. Loughlin, J. D. A. Tyndall, M. P. Glenn, D. P. Fairlie, *Chem. Rev.* **2004**, *104*, 6085–6117.

[14] Conversely, when 2,3-epoxypropylbenzene was subjected to dimerization conditions (see Experimental Section) the major product was cinnamyl alcohol (arising from benzylic deprotonation and eliminative rearrangement), and no significant 2-ene-1,4-diol was observed.

[15] Similar dihydroxylation of the analogous N-Boc-protected 2-ene-1,4-diamine displayed poor diastereoselectivity (2:3) and favored the opposite (less desirable for HIV protease inhibition) diastereoisomer to that seen in our case, see: a) A. V. R. Rao, M. K. Gurjar, S. Pal, R. J. Pariza, M. S. Chorghade, *Tetrahedron Lett.* **1995**, *36*, 2505–2508; b) M. K. Gurjar, S. Pal, A. V. R. Rao, R. J. Pariza, M. S. Chorghade, *Tetrahedron* **1997**, *53*, 4769–4778.

[16] A. Dondoni, D. Perrone, M. Rinaldi, *J. Org. Chem.* **1998**, *63*, 9252–9264.

[17] a) A. Zhang, Y. Feng, B. Jiang, *Tetrahedron: Asymmetry* **2000**, *11*, 3123–3130; b) J. Zhao, X. Bao, X. Liu, B. Wan, X. Han, C.

Yang, J. Hang, B. Jiang, *Tetrahedron: Asymmetry* **2000**, *11*, 3351 – 3359; c) B. Jiang, Y. Feng, J.-F. Hang, *Tetrahedron: Asymmetry* **2001**, *12*, 2323 – 2329.

[18] Derivatization of (*S*,*R*,*R*,*S*)-**7** has been used to produce arrays of HIV protease inhibitors for biological evaluation and has yielded a number of highly active compounds, see: a) D. J. Kempf, L. Codacovi, X. C. Wang, W. E. Kohlbrenner, N. E. Wideburg, A. Saldivar, S. Vasavanonda, K. C. Marsh, P. Bryant, H. L. Sham, B. E. Green, D. A. Betebenner, J. Erickson, D. W. Norbeck, *J. Med. Chem.* **1993**, *36*, 320 – 330; b) K.-H. Budt, A. Peyman, J. Hansen, J. Knolle, C. Meichsner, A. Paessens, D. Ruppert, B. Stowasser, *Bioorg. Med. Chem.* **1995**, *3*, 559 – 571; c) S. F. Martin, G. O. Dorsey, T. Gane, M. C. Hillier, H. Kessler, M. Baur, B. Mathä, *J. Med. Chem.* **1998**, *41*, 1581 – 1597.

