ChemComm

The first isolation of an alkoxy-*N*,*N*-dialkylaminodifluorosulfane from the reaction of an alcohol and DAST: an efficient synthesis of (2*S*,3*R*,6*S*)-3-fluoro-2,6-diaminopimelic acid

Andrew Sutherland and John C. Vederas*

Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2.
E-mail: john.vederas@ualberta.ca

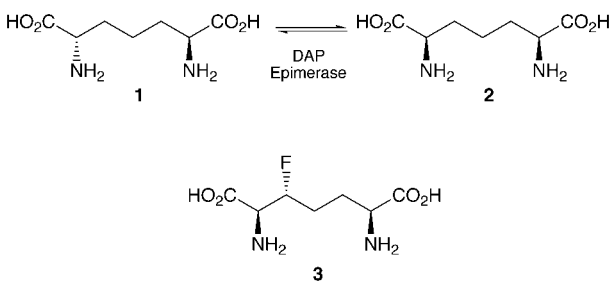
Received (in Corvallis, OR, USA) 15th June 1999, Accepted 14th July 1999

During improvement of the synthesis of (2*S*,3*R*,6*S*)-3-fluoro-2,6-diaminopimelic acid 3, a potent inhibitor of DAP epimerase, a stable alkoxy-*N*,*N*-dialkylaminodifluorosulfane 9 was isolated from the reaction of alcohol 6 with DAST

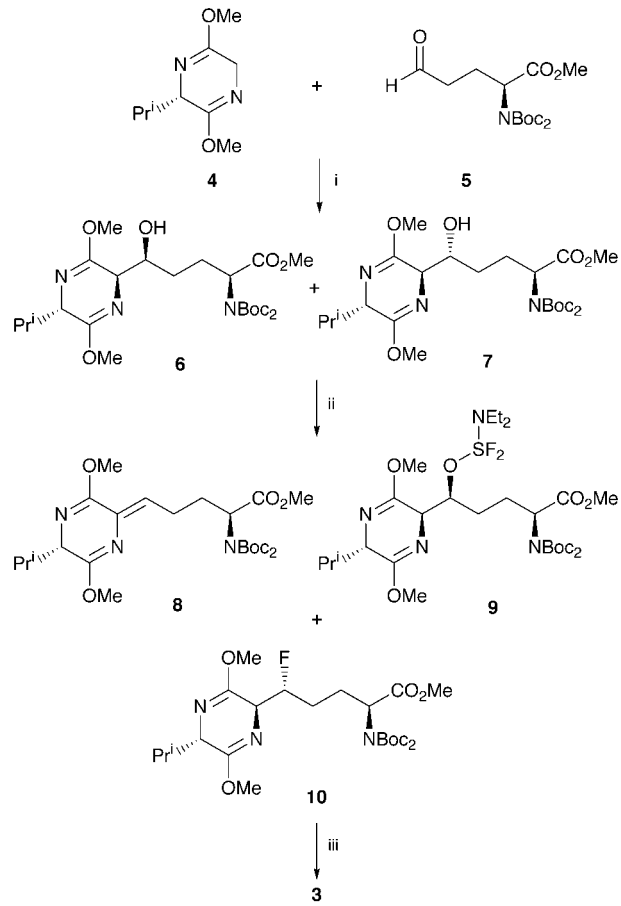
Emergence of multi-drug resistant bacteria has intensified efforts to develop new antibiotics that disrupt microbial cell wall synthesis.[1] Several studies have shown that inhibitors of the biosynthesis of diaminopimelic acid (DAP),[2] the key crosslinking amino acid in the peptidoglycan cell wall of Gram negative bacteria, possess antibiotic activity.[3] An important enzyme in this pathway, L,L-diaminopimelate epimerase, interconverts L,L-DAP **1** and *meso*-DAP **2** without the aid of any detectable metals or cofactors (Scheme 1). The mechanism has been suggested to be an unusual 'two-base' process that employs a thiolate as a general base and a thiol as a general acid.[4] We have previously shown that β-fluoro-DAP stereoisomers are potent inhibitors of DAP epimerase that can act as probes to help define substrate conformation in the enzyme active site.[5] Continued interest in the mechanism of this enzyme and recent crystallographic studies on an inactive form of this protein[4b] encouraged us to improve the synthesis[5] of pure β-fluoro-DAP isomers. We now report an efficient preparation of (2*S*,3*R*,6*S*)-3-fluoro-2,6-diaminopimelic acid **3** and the first isolation of an alkoxy-*N*,*N*-dialkylaminodifluorosulfane from the reaction of an alcohol with DAST.

The original synthesis of β-fluoro-DAP involved an aldol reaction between a Schöllkopf bis-lactim ether[6] and a glutamate semialdehyde to afford an alcohol, which was fluorinated using diethylaminosulfur trifluoride (DAST).[5] However, the reactive nature of the oxazolidinone protecting group on the glutamate semialdehyde lowered yields and made extensive purification of the intermediates obligatory. A recent synthesis[7] of *N*,*N*-di-Boc glutamate semialdehyde **5**, a versatile intermediate,[8] suggested its application to the troublesome aldol condensation. Addition of **5** to the anion of (3*S*)-3,6-dihydro-2,5-dimethoxy-3-(1-methylethyl)pyrazine **4**[6] gave a 3:1 mixture of two inseparable diastereomeric alcohols **6** and **7** in 73% yield (Scheme 2).† Treatment of **6** and **7** with freshly distilled DAST permitted isolation of only the dehydrated compound **8**, which is presumably formed by base elimination of the activated intermediate **9**. By accident we found that this dehydration could be suppressed by using DAST contaminated with water. The presence of a trace amount of water causes the release of HF and results in the stabilisation of the activated intermediate, thereby allowing the preparation of the fluoro derivative **10** as a single diastereomer in 52% yield with only trace amounts of the dehydrated product **8** (7%). In some cases carbocation rearrangements accompanying the DAST preparation of alkyl fluorides have implied a mixed S_N1 and S_N2 mechanism,[9] but formation of **10** with complete inversion of stereochemistry from alcohol **6** indicates an S_N2 reaction. Surprisingly, the modified conditions permit the isolation of alkoxy-*N*,*N*-dialkylaminodifluorosulfane **9** as a single diastereomer in 12% yield.

Compound **9** is unexpectedly stable to column chromatography and amenable to characterisation,‡ although it does decompose after several weeks at room temperature. Alkoxy-



Scheme 1



Scheme 2 *Reagents and conditions*: i, BuLi, THF, −78 °C, 73%, **6**:**7** (3:1); ii, DAST, CH_2Cl_2, −78 °C, **8** (7%), **9** (12%), **10** (52%); iii, 6 M HCl, Δ, 71%.

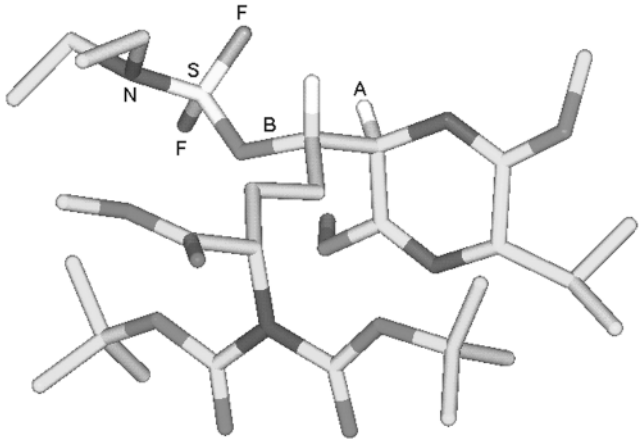


Fig. 1 A model of **9** representing a possible minimum energy conformation calculated using InsightII (MSI). Although elimination to give **8** can occur, in this geometry the orientation of hydrogen A and the cleaving bond B is disfavoured for a facile E2 process. An S_N2 reaction to cleave bond B is also sterically hindered. Only two adjacent hydrogens (white) are shown for clarity.

N,*N*-dialkylaminodifluorosulfanes are postulated as intermediates in the DAST fluorination of alcohols,[10] and the transient existence of these compounds has previously been inferred from ^{19}F NMR studies.[11] Although Markovskii *et al.* have reported the formation of analogous compounds having a perfluoroalkoxy group by reaction of polyfluoroalkyl trimethylsilyl ethers[12] with dialkylaminosulfur trifluorides, the fluoroalkyl groups obstruct elimination or substitution reactions. Preparation of **9** by reaction of an alcohol and DAST represents the first isolation of such a compound which in principle can readily undergo such decomposition. The unusual stability of **9** may be due to the steric crowding provided by nearby substituents (Fig. 1), including the two Boc groups, since DAST reactions with closely-related β-hydroxy-DAP derivatives bearing an *N*-Cbz substituted oxazolidinone[5] do not permit isolation of the corresponding intermediate.

Treatment of **9** with 1.0 equiv. of TBAF in an attempt to prepare **10** results in elimination to give **8**. Minor alcohol **7** could be recovered in quantitative yield as a single stereoisomer from the 'wet' DAST reaction of a mixture of **6** and **7**, thereby indicating that only alcohol **6** reacts to generate inverted fluoro derivative **10**. Molecular modeling of the two alcohols using InsightII (MSI) suggests that the alcohol functionality of **7** is more sterically crowded than **6**, which may account for the observed kinetic resolution. To complete the synthesis of (2*S*,3*R*,6*S*)-3-fluoro-2,6-diaminopimelic acid, the fluoro derivative **10** was hydrolysed with hydrochloric acid to give the desired β-fluoro-DAP **3** in 71% yield after cellulose chromatography. Further studies on synthesis of fluoro-DAP isomers and other DAP analogues[13] are in progress.

Financial support from the Natural Sciences and Engineering Research Council of Canada and the Alberta Heritage Foundation for Medical Research (Fellowship to A. S.) are gratefully acknowledged.

Notes and references

† Compound **4** is available from Merck Schuchardt (Hohenbrunn, Germany).

‡ *Selected data* for **9**: $[\alpha]_D^{26}$ −54.4 (*c* 0.2, $CHCl_3$); ν_{max}($CHCl_3$ cast)/cm^{-1} 2872 (CH), 1749, 1698 (C=O), 1459, 1436, 1382, 1367, 1240, 1146, 1123, 782 (SF); δ_H(300 MHz, $CDCl_3$) 0.64 [3H, d, *J* 6.6, C*H*$_3$(CH$_3$)CH], 1.02 [3H, d, *J* 6.6, CH$_3$(C*H*$_3$)CH], 1.13 [6H, t, *J* 7.8, N(CH$_2$C*H*$_3$)$_2$], 1.40–1.50 [19H, m, (CO$_2$Bu^t)$_2$ and OCHC*H*H], 1.69 (1H, m, NCHC*H*H), 1.90 (1H, m, NCHCH*H*), 2.26 [2H, m, (CH$_3$)$_2$C*H* and OCHCH*H*], 3.16 [4H, q, *J* 7.8, N(C*H*$_2$CH$_3$)$_2$], 3.64 (3H, s, OMe), 3.69 (6H, s, 2 × OMe), 3.89 (1H, t, *J* 3.5, (CH$_3$)$_2$CHC*H*], 4.21 (1H, t, *J* 3.5, NC*H*COMe), 4.28 (1H, ddd, *J* 8.3, 5.9, 2.6, NCHC*H*O), 4.81 [1H, dd, *J* 9.6, 6.1, C*H*N(CO$_2$Bu^t)$_2$]; δ_C(100 MHz, $CDCl_3$) 13.8 [N(CH$_2$*C*H$_3$)$_2$], 16.7 [(*C*H$_3$)CH$_3$CH], 19.0 [(CH$_3$)*C*H$_3$CH], 26.8 (OCH*C*H$_2$), 28.0 [OC(*C*H$_3$]$_3$), 29.0 (NCH*C*H$_2$), 31.2 [(CH$_3$)$_2$*C*H], 36.7 [N(*C*H$_2$CH$_3$)$_2$], 52.2, 52.3, 52.7 (O*C*H$_3$), 58.4 [(CH$_3$)$_2$CH*C*H], 59.4 (N*C*HCOMe), 60.7 [*C*HN(CO$_2$Bu^t)$_2$], 77.4 (NCH*C*HO), 83.1 [O*C*(CH$_3$)$_3$], 152.0, 160.5, 165.5, 171.0 (C=O); δ_F(376 MHz, $CDCl_3$) −123.02 (d, *J* 13.5, S*F*F), −123.07 (d, *J* 13.5, S*F*F) [Found (ES): [MH]$^+$, 671.3499. $C_{29}H_{52}N_4O_9SF_2$ requires [MH]$^+$, 671.3501].

1 T. D. H. Bugg and C. T. Walsh, *Nat. Prod. Rep*., 1992, **9**, 199.
2 R. J. Cox, *Nat. Prod. Rep*., 1996, **13**, 29; G. Scapin and J. S. Blanchard, *Adv. Enzymol. Relat. Areas Mol. Biol*., 1998, **72**, 279.
3 See for example: D. A. Berges, W. E. DeWolf Jr., G. L. Dunn, S. F. Grappel, D. J. Newman, J. J. Taggart and C. Gilvarg, *J. Med. Chem*., 1986, **29**, 89; J. G. Kelland, L. D. Arnold, M. M. Palcic, M. A. Pickard and J. C. Vederas, *J. Biol Chem*., 1986, **261**, 13 216; L. K. P. Lam, L. D. Arnold, T. H. Kalantar, J. G. Kelland, P. M. Lane-Bell, M. M. Palcic, M. A. Pickard and J. C. Vederas, *J. Biol Chem*., 1988, **263**, 11 814.
4 (*a*) C. W. Koo and J. S. Blanchard, *Biochemistry*, 1999, **38**, 4416; (b) M. Cirilli, R. Zheng, G. Scapin and J. S. Blanchard, *Biochemistry*, 1998, **37**, 16 452.
5 M. H. Gelb, Y. Lin, M. A. Pickard, Y. Song and J. C. Vederas, *J. Am. Chem. Soc*., 1990, **112**, 4932.
6 U. Groth and U. Schollkopf, *Synthesis*, 1983, 673.
7 J. M. Padron, G. Kokotos, T. Martin, T. Markidis, W. A. Gibbons and V. S. Martin, *Tetrahedron: Asymmetry*, 1998, **9**, 3381.
8 A. Sutherland, J. F. Caplan and J. C. Vederas, *Chem. Commun*., 1999, 555.
9 M. Hudlicky, *Org. React*., 1988, **35**, 513.
10 W. J. Middleton, *J. Org. Chem*., 1975, **40**, 574.
11 T. J. Tewson and M. J. Welch, *J. Org. Chem*., 1978, **43**, 1090.
12 L. N. Markovskii, L. S. Bobkova and V. E Pashinnik, *Zh. Org. Khim*., 1981, **17**, 1699 (English edition).
13 Y. Gao, P. Lane-Bell and J. C. Vederas, *J. Org. Chem*., 1998, **63**, 2133.

Communication 9/04821I