

Rapid syntheses of difluorinated polyols using a cleavable carbamate

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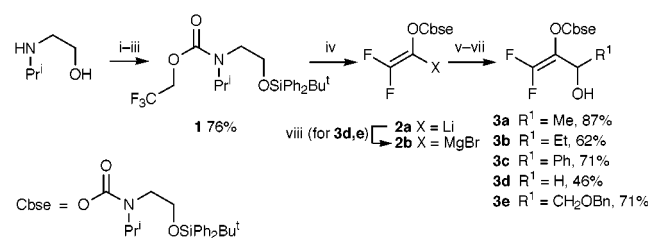
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Trifluoroethyl *N*-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-*N*-isopropylcarbamate undergoes smooth dehydrofluorination–metallation followed by BF₃·OEt₂ mediated addition to aldehydes to afford a range of allylic alcohols; aldol reaction with a second aldehyde, then reduction, affords products which can be deprotected to afford difluorinated polyols.

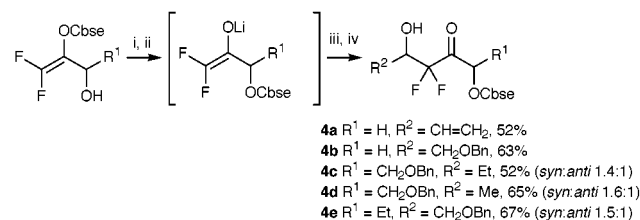
We have been developing metallated difluoro-enol carbamates¹ derived from trifluoroethanol as versatile building blocks² for the synthesis of selectively fluorinated polyfunctional molecules. To date, we have concentrated on *N,N*-diethylcarbamates which, while synthetically versatile^{3,4} and inexpensive to synthesise, are chemically robust. The latter property represents an apparent impediment to carbamate cleavage and hydroxy group unmasking so recently, we made use of the cleavable carbamate described by Derwing and Hoppe,⁵ synthesising **1** by a standard route (Scheme 1). Dehydrofluorination–metallation to **2a** proceeded smoothly under our published conditions⁶ and allylic alcohols **3a–c** were synthesised in moderate to good yield using BF₃·OEt₂ to attenuate the transacylation reaction.⁷ Acceptable yields of **3d** and **3e** (46 and 71% respectively) could only be secured by transmetallating **2a** to **2b** using MgBr·OEt₂ prepared freshly according to the method of Harwood *et al.*,⁸ and raising the reaction temperature to –30 °C before the addition of the Lewis acid and electrophile. Next, we explored the aldol chemistry and confirmed that our published conditions transferred smoothly; adducts **4a–e** were duly prepared (Scheme 2) in moderate to good yields by treatment of the allylic alcohols with BuLi at low temperature and allowing the enolate solution to warm to –10 °C before the addition of the

aldehyde electrophile. Stereoselectivities were low as expected but the *syn* and *anti* diastereoisomers could be separated by careful column chromatography.†

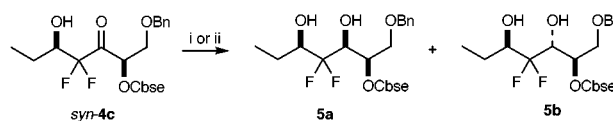
To make further progress in the direction of polyol targets, reduction of **4c** was attempted under the stereoselective conditions described by Kuroboshi and Ishihara,⁹ but very sluggish reactions ensued (Scheme 3). We had hoped that the reductions would proceed smoothly, and that the β-hydroxy group would provide control over the stereochemical course of the reduction, overriding any asymmetric induction exerted by the adjacent (α) stereogenic centre. Under the *syn*-selective conditions (DIBAL-H, ZnCl₂, TMEDA), both the yield of **5a** and **5b** (31% combined) and stereoselectivity (1.8:1 *syn*:*anti*)‡ were low from *syn*-**4c** and the conversion was poor (37% recovered **4c** after 6 h), a consequence presumably of the bulk of the carbamoyloxy group. The *anti*-selective Meerwein–Pondorf–Verley reduction [Al(OPrⁱ)₃, PhH] conditions were more successful affording a higher (66% combined) yield of **5a** and **5b**. However, whereas the published procedure achieves the reduction smoothly overnight at room temperature, we failed to observe any reaction until the mixture had stirred for 4 days. We then turned our attention to the less stereochemically complex **4b**; both stereoselective reductions failed completely, so to take compound through to the diol stage, we performed a simple NaBH₄ reduction and isolated a 2:1 mixture of *syn*- and *anti*-diols **6a** and **6b** in 78% yield (Scheme 4).§ Attempts to cleave the carbamate protection then ensued. We modified the published conditions and found that dilute HF in aqueous MeCN effected a satisfactory desilylation, allowing triols **7a** and **7b** to be isolated in 84% yield. Exposure to KOH (1 equiv.) in MeOH at room temperature allowed the isolation of **8a** and **8b** in a disappointing 20% yield. However, removing the MeOH *in vacuo* then taking the residue up in EtOAc followed by an extractive work up yielded separable triols **8a** and **8b** (78%),



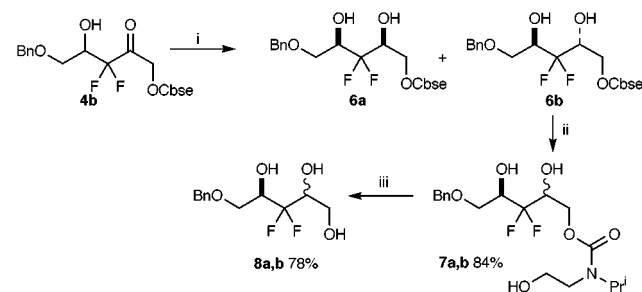
Scheme 1 Reagents and conditions: i, Bu^tPh₂SiCl (1.1 equiv.), DMAP (0.5 equiv.), CH₂Cl₂, reflux, 12 h; ii, diphosgene (0.5 equiv.), Et₃N (1.5 equiv.), CH₂Cl₂, 0 °C, then room temp., 16 h; iii, CF₃CH₂ONa, THF, reflux, 16 h; iv, LDA, THF (2.0 equiv.), –78 °C; v, R¹CHO; vi, BF₃·OEt₂, then warm to 0 °C; vii, NH₄Cl (aq.); viii, MgBr₂·OEt₂.



Scheme 2 Reagents and conditions: i, BuLi, THF, –78 °C; ii, warm to –10 °C; iii, R²CHO; iv, NH₄Cl (aq.).



Scheme 3 Reagents and conditions: i, DIBAL-H, ZnCl₂·TMEDA, THF, –78 °C; ii, Al(OPrⁱ)₃, PhH, room temp., 4 days.



Scheme 4 Reagents and conditions: i, NaBH₄, MeOH, 0 °C; ii, 48% HF (aq.)–MeCN (1:9), room temp.; iii, KOH (1.0 equiv.), MeOH, room temp.

proving that the Hoppe carbamate can be deployed successfully in our dehydrofluorination–metallation and aldol chemistry and that protecting group removal can be achieved under mild conditions. Clearly, there exists considerable scope for the improvement of functional group manipulation chemistry: studies describing our efforts to develop stereoselective reduction chemistry and optimise deprotection will be described elsewhere.

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Notes and references

† Diastereoisomer ratios were assigned on the basis of ^{19}F NMR chemical shifts as described in ref. 6.

‡ This assignment assumes the same sense of stereoselection as that described in ref. 9.

§ The two diastereoisomers have radically different ^{19}F NMR spectra; one isomer appears as a well-separated AB system split further by $^3J_{\text{H-F}}$ couplings whereas the other appears as a broad unresolved signal. We have tentatively assigned these spectra to the 1,3-*syn* and 1,3-*anti* diastereoisomers **6a** and **6b** respectively on the basis that the fluorine atoms in the former are decidedly heterotopic. In the latter, the *pseudo*- C_2 symmetry confers a degree of homotopicity upon the fluorine atoms, hence the appearance of the signal observed. Obviously, definitive proof of this assignment is being sought currently.

- 1 J. A. Howarth, W. M. Owton, J. M. Percy and M. H. Rock, *Tetrahedron*, 1995, **51**, 10289.
- 2 J. M. Percy, *Top. Curr. Chem.*, 1997, **193**, 131. For recent related chemistry of difluorinated enolates and enols, see I. Fleming, R. S. Roberts and S. C. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1215; T. Brigaud, P. Doussot and C. Portella, *J. Chem. Soc., Chem. Commun.*, 1994, 2117; T. Brigaud, O. Lefebvre, R. Plantierroyon and C. Portella, *Tetrahedron Lett.*, 1996, **37**, 6115; O. Lefebvre, T. Brigaud and C. Portella, *Tetrahedron*, 1998, **54**, 5939; Y. Kodama, H. Yamane, M. Okumura, M. Shiro and T. Taguchi, *Tetrahedron*, 1995, **51**, 12217; K. Uneyama, K. Maeda, T. Kato and T. Katagiri, *Tetrahedron Lett.*, 1998, **39**, 3741; O. Lefebvre, T. Brigaud and C. Portella, *Tetrahedron*, 1999, **55**, 7233.
- 3 M. Tsukazaki and V. Snieckus, *Tetrahedron Lett.*, 1993, **34**, 411.
- 4 J. Lee, M. Tsukazaki and V. Snieckus, *Tetrahedron Lett.*, 1993, **34**, 415.
- 5 C. Derwing and D. Hoppe, *Synthesis*, 1996, 149.
- 6 A. S. Balnaves, T. Gelbrich, M. B. Hursthouse, M. E. Light, M. J. Palmer and J. M. Percy, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2525.
- 7 The non-fluorinated system derived from acetaldehyde enolate proceeds from alkoxide to enolate unhindered by the presence of Lewis acids; see S. Sengupta and V. Snieckus, *J. Org. Chem.*, 1990, **55**, 5680.
- 8 L. M. Harwood, A. C. Manage, S. Robin, S. F. G. Hopes, D. J. Watkin and C. E. Williams, *Synlett*, 1993, 777.
- 9 M. Kuroboshi and T. Ishihara, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 1185.
- 10 M. Schlosser, T. Jenny and Y. Guggisberg, *Synlett*, 1990, 704.

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