## Rapid syntheses of difluorinated polyols using a cleavable carbamate

Andrew S. Balnaves,<sup>a</sup> Michael J. Palmer<sup>b</sup> and Jonathan M. Percy<sup>\*a</sup>

 <sup>a</sup> School of Chemistry, University of Birmingham, Edgbaston, Birmingham, UK B15 2TT. E-mail: jmpercy@chemistry.bham.ac.uk
<sup>b</sup> Pfizer Central Research, Sandwich, UK CT13 9NJ

Received (in Cambridge, UK) 6th September 1999, Accepted 28th September 1999

 $\label{eq:linear} Trifluoroethyl $N$-[2-(tert-butyldiphenylsilyloxy)ethyl]-N$-isopropylcarbamate undergoes smooth dehydrofluorina$  $tion-metallation followed by BF_3·OEt_2 mediated addition to$ aldehydes to afford a range of allylic alcohols; aldol reactionwith a second aldehyde, then reduction, affords productswhich can be deprotected to afford difluorinated polyols.

We have been developing metallated difluoro-enol carbamates1 derived from trifluoroethanol as versatile building blocks<sup>2</sup> for the synthesis of selectively fluorinated polyfunctional molecules. To date, we have concentrated on N,N-diethylcarbamates which, while synthetically versatile<sup>3,4</sup> 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,<sup>5</sup> synthesising 1 by a standard route (Scheme 1). Dehydrofluorination-metallation to 2a proceeded smoothly under our published conditions<sup>6</sup> and allylic alcohols 3a-c were synthesised in moderate to good yield using  $BF_3 \cdot OEt_2$  to attenuate the transacylation reaction.<sup>77</sup> Acceptable yields of 3d and 3e (46 and 71% respectively) could only be secured by transmetallating 2a to 2b using MgBr·OEt<sub>2</sub> 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



Scheme 1 Reagents and conditions: i, Bu<sup>i</sup>Ph<sub>2</sub>SiCl (1.1 equiv.), DMAP (0.5 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, reflux, 12 h; ii, diphosgene (0.5 equiv.), Et<sub>3</sub>N (1.5 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, then room temp., 16 h; iii, CF<sub>3</sub>CH<sub>2</sub>ONa, THF, reflux, 16 h; iv, LDA, THF (2.0 equiv.), -78 °C; v, R<sup>1</sup>CHO; vi, BF<sub>3</sub>•OEt<sub>2</sub>, then warm to 0 °C; vii, NH<sub>4</sub>Cl (aq.); viii, MgBr<sub>2</sub>•OEt<sub>2</sub>.



Scheme 2 Reagents and conditions: i, BuLi, THF, -78 °C; ii, warm to -10 °C; iii, R<sup>2</sup>CHO; iv, NH<sub>4</sub>Cl (aq.).

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

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  $\beta$ -hydroxy group would provide control over the stereochemical course of the reduction, overriding any asymmetric induction exerted by the adjacent ( $\alpha$ ) stereogenic centre. Under the syn-selective conditions (DIBAL-H, ZnCl<sub>2</sub>, TMEDA), both the yield of 5a and **5b** (31% combined) and stereoselectivity (1.8:1 syn: anti)<sup>±</sup> 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 NaBH<sub>4</sub> reduction and isolated a 2:1 mixture of syn- and antidiols 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 desilvlation, 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 3 Reagents and conditions: i, DIBAL-H, ZnCl<sub>2</sub>•TMEDA, THF, -78 °C; ii, Al(OPri)<sub>3</sub>, PhH, room temp., 4 days.



Scheme 4 Reagents and conditions: i, NaBH<sub>4</sub>, MeOH, 0  $^{\circ}$ 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.

The authors wish to thank the Engineering and Physical Sciences Research Council of Great Britain and Pfizer Central Research for a CASE Award (to A. S. B.).

## Notes and references

<sup>†</sup> Diastereoisomer ratios were assigned on the basis of <sup>19</sup>F NMR chemical shifts as described in ref. 6.

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

§ The two diastereoisomers have radically different <sup>19</sup>F NMR spectra; one isomer appears as a well-separated AB system split further by  ${}^{3}J_{H-F}$  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*<sub>2</sub> 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.
- 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 Lett.*, 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.

Communication 9/07174A