A stereodivergent asymmetric approach to difluorinated aldonic acids‡

Christophe Audouard,a Igor Barsukov,b John Fawcett,a Gerry A. Griffith,a Jonathan M. Percy,a* Stéphane Pintat* and Clive A. Smithd

a Department of Chemistry, University of Leicester, University Road, Leicester, UK LE1 7RH. E-mail: jmp29@le.ac.uk; Fax: +44 116 252 3789; Tel: +44 116 252 2140
b Biological NMR Centre, University of Leicester, PO Box 138, University Road, Leicester, UK LE1 9HN
c Evotech OAI, 151 Milton Park, Abingdon, Oxon, UK OX14 4SD
d GlaxoSmithKline Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow, UK CM19 5AW

Received (in Cambridge, UK) 6th April 2004, Accepted 28th April 2004
First published as an Advance Article on the web 27th May 2004

A (bromodifluoromethyl)alkyne has been deployed in a stereoselective route to difluorinated aldonic acid analogues, in which a Sharpless asymmetric dihydroxylation reaction and diastereoisomer separation set the stage for phenyl group oxidation.†

Though there are hundreds of fluorinated sugars in the chemical literature, some of which have extremely useful properties, few have been made by the concise processing of readily-available fluorinated starting materials or building blocks. Fluorination approaches, in which an hydroxy group or ketone carbonyl is exposed selectively to a fluorinating agent such as DAST or DeoxoFluor are much more common. However, such methods lack the potential for stereodivergent synthesis; by this we mean that most syntheses start from an available sugar and deliver an unique product. Building block chemistry has the potential to generate families of related sugar analogues in high enantiomeric enrichment if suitable fluorinated materials can be transformed using the modern methods of asymmetric synthesis but aside from the asymmetric reductions of perfluoroalkylketones and related species, there are few useful methods.2

Recently, we described the first racemic syntheses of 4-deoxy-4,4-difluorosugars from 1-bromo-1,1-difluoropropene and a protected glycoaldehyde derivative.3 The target glycalsides appear to be of growing interest with recent publications by Liu4 and Mobashery. However, our syntheses were racemic, with no obvious potential for the control of absolute configuration. Retrosynthetic analysis (Scheme 1), exploiting the well-known synthetic equivalence of the phenyl group for a carboxyl function,6 detected glycolaldehyde derivative. The target glycalsides appear to be of growing interest with recent publications by Liu4 and Mobashery. However, our syntheses were racemic, with no obvious potential for the control of absolute configuration. Retrosynthetic analysis (Scheme 1), exploiting the well-known synthetic equivalence of the phenyl group for a carboxyl function,6 suggested that alkynyl diol 1 could be a strategic precursor to a family of 4-deoxy-4,4-difluorosugars. Key steps would include the addition of the alkyne to a glycoaldehyde, stereochemist selection to the E-alkene, Sharpless AD followed by diastereoisomer separation and oxidative cleavage of the phenyl group. Very few Sharpless AD reactions of fluorinated alkenes substrates have been reported.7 FMO influences upon the reaction are complex8 so the effect of the CF₂ centre was hard to predict, though we assume that the presence of a phenyl group will facilitate the oxidation, and that our substrates will follow the usual behaviour of β-substituted styrenes.

Kobayashi9 developed propargylation reactions (Scheme 2) with 2a–2c for a synthesis of the sugar portion of Gemcitabine.10 However, alkyne building blocks 2a–2c could only be synthesised in moderate yield. Hammond revisited this area profitably, developing an efficient synthesis of TIPS acetylene 2d,11 and showing that it reacts under zinc1b and indium11c mediated conditions and can be used to prepare a range of functionally complex molecules11d containing a CF₂ group. Alkyne 2a was prepared in modest yield by Wakselaman and co-workers12 from lithium phenylacetylide and dibromodifluoromethane; we found that pre-cooling the dibromodifluoromethane electrophile (to −78 °C) before addition to the lithioalkyne allowed 2a to be isolated in excellent (85%) yield after distillation on a 0.25 mole scale. Small scale (<5 mmole) additions of 2a to commercial glycoaldehyde proceeded smoothly under the Kobayashi conditions to afford 1, whereas the Hammond conditions delivered only diyne 4. On a 5 mmole scale, Kobayashi’s conditions resulted in the formation of 1 in poor yield. A 24 reaction screen revealed two effective sets of conditions based upon the common use of zinc metal. The highest yielding reactions occurred with either 5% Hg(OAc)₂/NaI/Zn in THF or 5% Hg(OCOCF₃)₂/Zn in DMF. The former regime delivered a reliable 68–70% yield of 1 at scales between 1 and 89 mmole. We were unable to obtain any product at all under aqueous conditions.

The alkynyl group was reduced stereoselectively with Red-Al (72%), and protection of the racemic diol as the acetonide 6a was achieved smoothly (95%). Sharpless AD occurred slowly unless N-methane sulfonamide was present in the reaction. Pleasingly, the reactions reached completion after 3 days and were high yielding (83% for AD MIX – 91% for AD MIX –). No advantage was gained by constant pH adjustment.14

The two pairs of inseparable diastereomeric diols 6a and 6b were protected as the bis-acetonides (which were separated effectively by conventional flash column chromatography to afford 4 separate bis-acetonides 7a–7b (43, 41, 46 and 48% isolated yields in that order). The 1,3-anti (7a and 7b) and 1,3-syn (8a and 8b) diols have very different 19F NMR spectra as described by Ishihara,15 and we were able to obtain a crystal structure from 7b to confirm the assignment of relative configuration.‡‡ Samples of 7a and 7b were mixed and eluted through a Chiralcel OJ column; a good separation was obtained and the individual components were enantiomerically-enriched to a level of 95% from

Scheme 1 Retrosynthetic analysis and identification of pivotal intermediates

† Electronic supplementary information (ESI) available: preparation of 1 and 2a, NMR and electrospray for 14 (deuterium exchanged), chiral HPLC traces for 7a and 7b, optical rotations for 7a–7b. See http://www.rsc.org/suppdata/cc/b4/b405067c/ doi:10.1039/b405067c
AD-mix β and 99.5% from AD-mix α. Unfortunately, we were not able to separate 8a and 8b using any column available to us, though the similar measured rotations show clearly that these products are not racemic and that the ee’s are similar to those obtained for the separated isomers.

Oxidative cleavage of the phenyl ring has been reported in the presence of an acetonide protecting group.10 We attempted the oxidation, believing that the presence of the CF₂ centre would make acetal cleavage more difficult by suppressing the pre-equilibrium protonation at the beginning of the hydrolysis pathway. However, a complex mixture of products was obtained from which we identified desired product 9, along with 10 and 11. Given the measured pH of 2.9 at the start of the reaction, acetal hydrolysis is not surprising, so the literature observation is remarkable.

Methanolation of the bis-acetonide 7a and per-acetylation to 12[‡] set the stage for successful oxidative cleavage and catalytic K₂CO₃ in methanol delivered a product with the mass similar measured rotations show clearly that these products are able to separate the diastereoisomers can be treated in the same way and breaks new ground in the stereoselective synthesis of dihydroxyalanes of natural products.

We wish to thank the EPSRC (GR/K84882) and the Universities of Leicester and Birmingham and GSK (CASE studentship to SP) and the EPSRC (GR/R6835, fellowship to CA). We also wish to thank Mr M Lee for assistance with the chiral HPLC.

Notes and references

‡ Crystallographic data for 7b: C₁₇H₂₂F₂O₄, crystal size 0.36 × 0.21 × 0.14 mm, M = 328.15, orthorhombic, a = 9.7774(6), b = 11.6322(7), c = 14.7974(9) Å, α = 90, β = 90, γ = 90°, U = 1682.95(18) Å³, Z = 1502 K space group P2₁2₁2₁, Z = 4, μ(Mo-Kα) = 0.105 mm⁻¹, 11573 reflections measured, 2966 unique (Rint = 0.0260) which were used in all calculations. Final R indices (F² > 2σ(F)) R = 0.0298, wR = 0.0728; R indices (all data) R = 0.0315, wR = 0.0735.

¶ CCDIC 235709 and 235710. See http://www.rsc.org/suppdata/cc/b4/b405067c/ for crystallographic data in .cif or other electronic format.

¶ A crystal structure confirmed the stereochemistry was unchanged.

Crystallographic data for 12: C₁₇H₂₂F₂O₄, crystal size 0.36 × 0.19 × 0.06 mm, M = 416.37; monoclinic, a = 11.5206 (5), b = 5.7277 (7), c = 15.7922 (2) Å, α = 90, β = 107.1372 (2), γ = 90°, u = 995.82 (2) Å³, T = 150(2) K, space group P2₁2₁2₁, Z = 2, μ(Mo-Kα) = 0.120 mm⁻¹, 7929 reflections measured, 3466 unique (Rint = 0.0257) which were used in all calculations. Final R indices (F² > 2σ(F)) R = 0.0413, wR = 0.0877; R indices (all data) R = 0.0484, wR = 0.0910.

[‡] For data on 14. Semi solid, δp(D,OD, 500 MHz) 4.35–4.25 (2H, m, H-2, H-3), 4.10–4.01 (1H, m [app. δJ = 2.07 Hz]), 3.85 (1H, broad d, JH,F = 14.1), 3.68 (1H, dd, H-6, δJ = 14.1); δp(D,OD, 13C) 180.6 (C-1), 124.6 (t, 1F, JF-1 = 212.5, C-6, δJ = 72.5, δJ = 19.1, 14.4, C-3, δJ = 72.1 (dd, JF-1 = 33.6, 28.1, C-5), 62.8 (C-6), δF (D₂O, 282 MHz) = −121.7 (1F, dd, δJ=2.07, JF,F = 260.0, δH,F = 19.4), −123.3 (1F, dd, δF,F = 260.0, δH,F = 20.7); m/z (ES⁻) 215 (M−H, 100%).


