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Allylic fluorination via an unusual alkene *Z*/*E* isomerisation

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ABSTRACT

The isomerisation of readily available (*Z*)-4-(para-methoxybenzyloxy)-1-chloro-2-butene was achieved under mild conditions to afford the much less accessible E-diastereoisomer. This was an effective substrate in Sharpless asymmetric dihydroxylation (AD) reactions, delivering highly enantiomerically enriched fluorinated butene triol building blocks.

Allylic fluorination by nucleophilic displacement of a good leaving group by fluoride has proved to be a surprisingly difficult reaction to achieve generally and reliably.[1] S_N2 reactions at allylic centres are accelerated by the ability of the alkenyl group to lower the energy of the trigonal bipyramidal transition state, but when basic fluoride ion is the nucleophile, little advantage accrues and side reactions often compete effectively. Nucleophilic fluorinating agents such as DAST, or the Ichikawa reagent can be effective but S_N2' fluorination is a well-documented competing pathway.[2] Our work on the synthesis of 6-deoxy-6-fluorosugars[3] demanded a route to allylic fluoride building blocks **1** and **2** from which we intended to prepare the corresponding monoprotected fluorinated butene triols **3** or **4**, ideally in highly enantiomerically enriched form (Fig. 1).

The de novo approach to hexose synthesis was pioneered by Masamune and co-workers,[4] and it is worthwhile if an array of sugar analogues is sought, rather than a single compound. We therefore sought to develop direct routes to these species.

Monoprotected *Z*-but-2-ene diol is readily available from the diol via monoalkylation[5] (acceptable for benzylation to **5**), or by acetal formation[6] and reductive cleavage with DIBAl-H[7] (better for the formation of the mono PMB ether **7**) (Scheme 1).

We prepared both compounds **5** and **7** and chlorinated them; thionyl chloride in diethyl ether worked well for **6** but the in situ mesylation and displacement method[8] was superior for **8**. Fluorination was explored for **6** initially; treatment with 'anhydrous' TBAF (prepared by heating TBAF·$3H_2O$ at very low pressure below 40 °C for several hours)[9] in THF afforded small amounts of **9** with **5** and **10** dominating the reaction mixture (GC–MS) (Scheme 2). The TBAF·$3H_2O$ reagent was more effective, transforming **6** to **9** in moderate (26%) yield. Based on a solid–liquid phase transfer procedure (KF/TBAI) reported by Loupy and co-workers,[10] we reacted **6** with TBAI (2 equiv in THF at reflux) followed by the addition of neat TBAF·$3H_2O$; we were surprised to isolate *E*-fluoride **12** (the major component of a mixture of fluorides) with alcohol **11** (29%).[11] We isolated the products of the reaction with TBAI, identifying chlorides **6**, **13** and **14**, and followed the reaction by GC–MS.

These processes occurred for both benzyl and PMB ethers; Figure 2 shows the evolution of the reaction of **8** (3 equiv TBAI, THF, reflux) with time followed by GC–MS, affording products **15** and **16**.

No further change occurred up to 20 h, suggesting strongly that the reaction had reached equilibrium. Isomerisation to the more

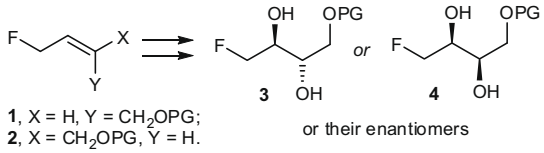
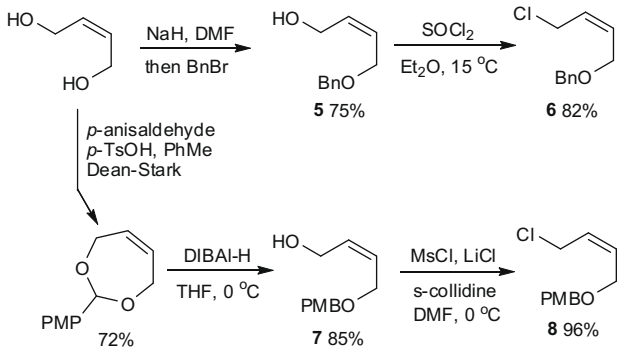


Figure 1.



Scheme 1. Preparation of *Z*-allylic chlorides.

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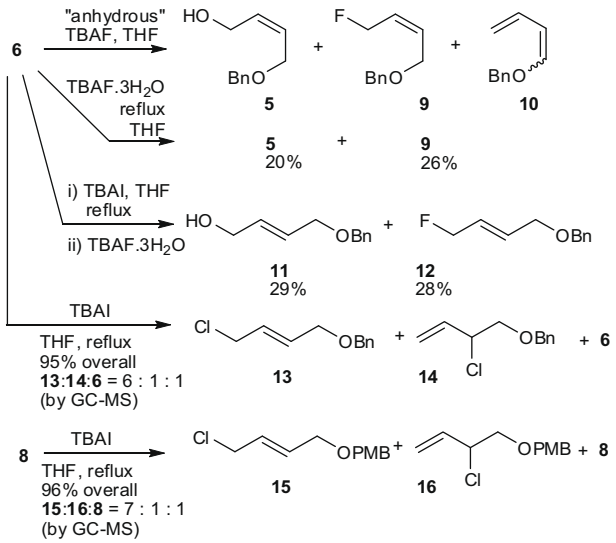


Scheme 2. Discovery of the *Z*/*E* isomerisation.

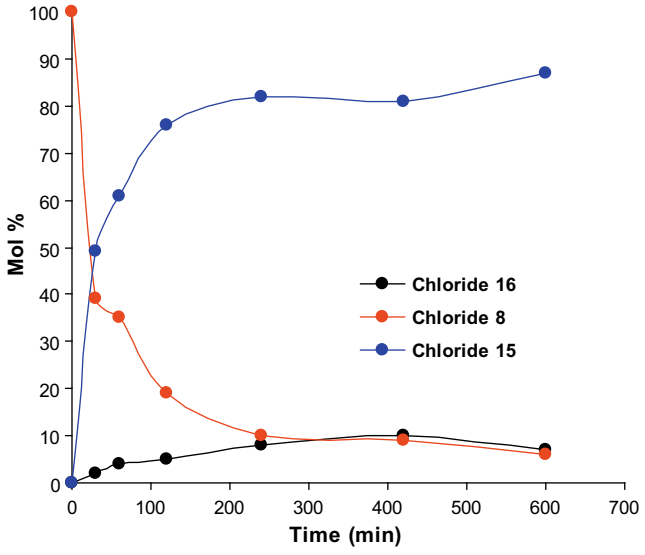
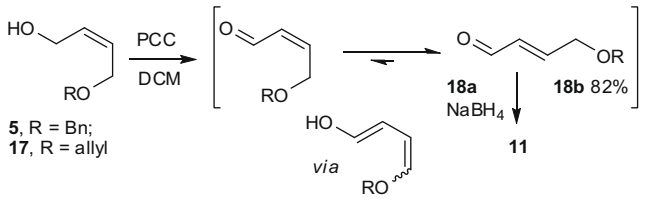


Figure 2. Following the course of *Z*-chloride isomerisation.

stable *E*-chloride **13** or **15** presumably involves sequential S_N2' displacements with iodide (the softest nucleophile present) and occurs via **14** or **16**. We have not found examples of alkene isomerisation by this type of mechanism; Danishefsky and Regan[12] prepared **11** via *E*-butenal **18a** by PCC oxidation of **5** (the recent PCC oxidation of ether **17** affords **18b** in excellent yield[13]); the isomerisation can proceed through acid-catalysed enolisation and reprotonation (Scheme 3). This would seem to be a very different process to the one we describe.

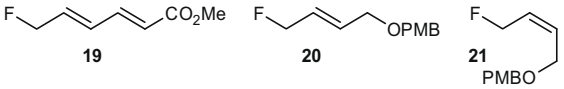
The persistence of **14** and **16** in these mixtures is interesting. To gain some insight, we determined the lowest energy conformations of **6**, **13** and **14** using the equilibrium conformer search algorithm within SPARTAN'06 v1.1.0 (MMFF94).[14] Geometries were optimised, with full frequency calculations (B3LYP/6-31G*), allowing free energies (gas phase, 298 K) to be determined relative to **13**; **6** (+6.75 kJ mol^{-1}) and **14** (+8.44 kJ mol^{-1}) are indeed less stable, but the free energy differences would suggest that **13** should be favoured more decisively at equilibrium. Of course, these are gas phase energies and it is possible that they may converge once solvent polarity is taken into account in the calculations. We also



Scheme 3. Preparation of **11** via PCC oxidation accompanied by an alkene isomerisation.

note that **14** is more hindered than **6** and may therefore react quite slowly once formed, so it would not be expected to be present in significant amounts at equilibrium.

Our recent asymmetric route to 6-deoxy-6-fluorosugars via hexadienoate **19** used two fluorination methods,[15] one a melt fluorination with KHF_2/TBAF·$3H_2O$ and the other the KF/$TBAHSO_4$ method of Hou and co-workers.[16]



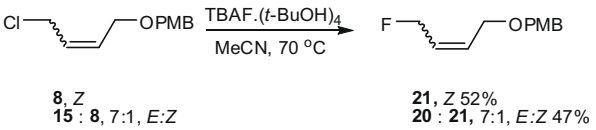
The *E*/*Z* mixture of **15** and **8** underwent melt fluorination with KHF_2/TBAF·$3H_2O$ quickly, but the reaction formed a significant number of side products. In contrast, the KF/$TBAHSO_4$ method gave a very clean product, but slowly, and required a large excess of reagent. The TBAF·(*t*-BuOH)$_4$ complex described recently by Kim et al.,[17] was the most effective of all the reagents tried (Scheme 4).

The knowledge gained was next applied in the 20 mmol scale synthesis of **20**. Sharpless asymmetric dihydroxylation (AD) reactions were now attempted with the usual commercial AD mixes [DHQ (for α) and DHDQ (for β) ligands]. As expected, *Z*-diastereoisomer **21** afforded **23a/23b** in good yield (90%) but in low (18%) ee (determined by chiral HPLC of the acetonides, Chiralcel OD-H column with 1:999 *i*-PrOH/hexane). The presence of *Z*-diastereoisomer in the isomerised *E*-material leads to a low dr (13:2 *syn*:*anti*) from the AD, though the ees (92% from AD-α, 84% from AD-β) are quite acceptable and consistent with the level of enantioenrichment obtained for related substrates.

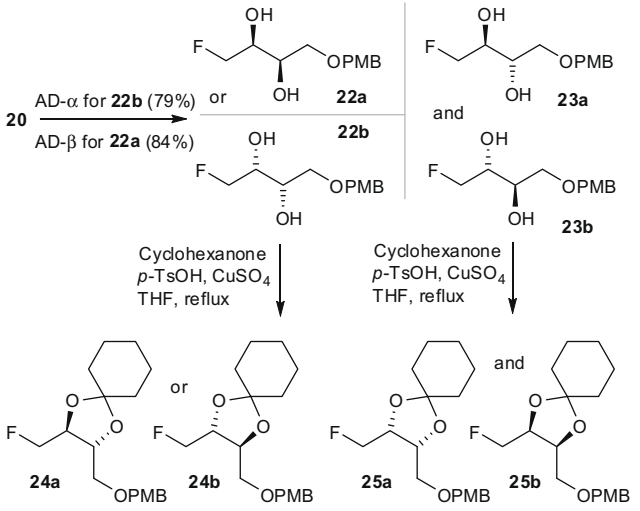
We found that cyclohexylidene acetal formation (Scheme 5) afforded a mixture from which **24a** (from AD-mix-α) and **24b** (from AD-mix-β) could be separated effectively (FCC, Buchi Sepacore with Biotage SNAP cartridge, 0–30% EtOAc in hexane). AD with the $(DHQD)_2AQN$ ligand[18] afforded no improvement in ee for **24a** or **24b**.

In conclusion, the *Z* to *E* isomerisation of allylic chlorides **6** and **8** affords a very convenient way of making mixtures enriched in the diastereoisomeric *E*-species. PMB ether **20** was an effective substrate in Sharpless AD reactions, delivering highly enantiomerically enriched fluorinated butene triol building blocks.

Procedure for isomerisation of **8***:* Chloride **8** (26.5 mmol, 6.00 g) was added to a solution of tetrabutylammonium iodide (52.9 mmol, 19.6 g) in dry tetrahydrofuran (70 mL). After 24 h at reflux, the mixture was diluted with diethyl ether (20 mL), filtered



Scheme 4. Fluorination of allyl chlorides with a new fluoride source.



Scheme 5. Sharpless AD and subsequent cyclohexylidene protection. Reagents and conditions: AD-mix-α: $K_2OsO_4{\cdot}2H_2O$ (1 mol %), $(DHQ)_2PHAL$ (5 mol %), $CH_3SO_2NH_2$ (1 equiv), $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv), *t*-BuOH/H_2O (1:1), 24 h, 0 °C; AD-mix-β: $K_2OsO_4{\cdot}2H_2O$ (1 mol %), $(DHQ)_2PHAL$ (5 mol %), $CH_3SO_2NH_2$ (1 equiv), $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv), *t*-BuOH/H_2O (1:1), 24 h, 0 °C; AQN AD-mix-β: $K_2OsO_4{\cdot}2H_2O$ (0.4 mol %), $(DHQD)_2AQN$ (1 mol %), $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv), *t*-BuOH/H_2O (1:1), 48 h, 0°C.

and concentrated in vacuo to obtain a crude mixture of inseparable allylic chlorides (*E*:*Z*:terminal = 7:1:1) in which *E*-allylic chloride **15** (5.73 g, 96%, 83% purity by GC–MS) was the major component as a brown and viscous oil; R_f (20% ethyl acetate in hexane) 0.62; ν_{max} (neat)/cm^{-1} 2954w (CH_2), 2837w (CH_2), 1612w (C=C), 1512s, 1245s, 1033s; δ_H (400 MHz, $CDCl_3$) 7.26 (2H, d, *J* 8.7, ArH), 6.88 (2H, d, *J* 8.7, ArH), 5.91–5.86 (2H, m, H-2, H-3), 4.45 (2H, s, CH_2Ar), 4.08–4.05 (2H, m, H-1), 4.02–4.00 (2H, m, H-4), 3.80 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 159.3, 131.4 (C-3), 130.1, 129.4, 128.3 (C-2), 113.8, 72.1 (CH_2Ar), 69.2 (C-4), 55.3 (OCH_3), 44.4 (C-1); [HRMS (EI, M^+) Found: 226.07611 Calcd For $C_{12}H_{15}O_2Cl$ 226.07606]; *m/z* (EI) 226 (4%, M^+), 191 (12), 161 (5), 136 (16, $[M-OPMB]^+$), 135 (14), 121 (100, PMB^+), 109 (10). Data for **8**: R_f (20% ethyl acetate in hexane) 0.62; ν_{max} (neat)/cm^{-1} 2935w (CH_2), 2837w (CH_2), 1611w, 1511s, 1245s, 1033s; δ_H (400 MHz, $CDCl_3$) 7.26 (2H, d, *J* 8.8, ArH), 6.88 (2H, d, *J* 8.8, ArH), 5.82–5.72 (2H, m, H-2, H-3), 4.44 (2H, s, CH_2Ar), 4.14–4.06 (4H, m, H-1, H-4), 3.80 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 159.3, 130.9 (C-3), 130.3, 129.5, 128.4 (C-2), 114.2, 72.1 (CH_2Ar), 64.8 (C-4), 55.6 (OCH_3), 39.6 (C-1); [HRMS (EI, M^+) Found: 226.07613 Calcd For $C_{12}H_{15}O_2Cl$ 226.07606]; *m/z* (EI) 226 (3%, M^+), 191 (10), 161 (5), 136 (13, $[M-OPMB]^+$), 121 (100, PMB^+), 109 (9).

Procedure for fluorination of 15 with TBAF·(t-BuOH)$_4$: TBAF·(*t*-BuOH)$_4$ (4.02 g, 2.1 equiv) was added to a solution (15 mL) of *E*-allyl chloride **15** (3.5 mmol, 798 mg, major component of a 7:1:1 mixture with **8** and **16**) in acetonitrile and the mixture was heated at 70 °C for 15 h. An immediate colour change from pale yellow to pale brown was observed. After cooling to room temperature, the mixture was diluted with diethyl ether (15 mL) and washed with water (2 × 15 mL) and brine (15 mL). The organic layer was then dried ($MgSO_4$), concentrated under vacuum and purified by flash chromatography (Buchi Sepacore, 25% diethyl ether in hexane) to afford **20** (major component of a 7:1:1 mixture) as a colourless oil (346 mg, 47%); R_f (20% ethyl acetate in hexane) 0.60; ν_{max} (neat)/cm^{-1} 2937w (CH_2), 2838w (CH_3), 1612w (C=C), 1512s, 1245s, 1033s (C–O); δ_H (300 MHz, $CDCl_3$) 7.25 (2H, d, *J* 8.8, ArH), 6.85 (2H, d, *J* 8.8, ArH), 5.96–5.84 (2H, m, H-2, H-3), 4.82 (2H, m, inc. app. d, $^2J_{F-H} \approx 46.8$, H-1), 4.43 (2H, s, OCH_2Ar), 4.04–3.97 (2H, m, H-4), 3.74 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 159.3, 131.5 (d, $^3J_{C-F}$ 11.6, C-3), 130.2, 129.4, 126.9 (d, $^2J_{C-F}$ 16.9, C-2), 113.8, 82.8 (d, $^1J_{F-C}$ 162.9, C-1), 72.1 (CH_2Ar), 69.3 (d, $^4J_{C-F}$ 1.5, C-4), 55.3 (OCH_3); δ_F (282 MHz, $CDCl_3$) (−212.7)–(−213.1) (m); {^{1}H}δ_F (282 MHz, $CDCl_3$)–212.85 (s); [HRMS (EI, M^+) Found: 210.10558. Calcd For $C_{12}H_{15}O_2F$ 210.10561]; *m/z* (EI) 210 (8%, M^+), 179 (6), 136 (30, $[M-OPMB]^+$), 135 (27), 122 (22), 121 (100, PMB^+), 77 (29).

Acknowledgements

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