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Towards stable analogues of inositol phosphates: stereoselective syntheses of (α,α-Difluoromethyl)phosphonic acid (DFMPA)-containing cyclohexanes

Afshan H. Butt,† B. M. Kariuki, Jonathan M. Percy‡* and Neil S. Spencer
School of Chemistry, University of Birmingham, Edgbaston, Birmingham, UK B15 2TT

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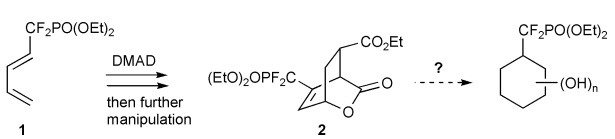
Diels–Alder and conjugate addition reactions were used to prepare precursors to a range of fully functionalised and deoxy inositol phosphate analogues.

Stereoselective syntheses of (α,α-difluoromethyl)phosphonic acid (DFMPA)-derivatised molecules that may act as hydrolytically stable analogues of naturally-occurring phosphate esters remain an important goal.[1] Recently, Yokomatsu and coworkers[2] described a strategy in which a DFMPA-butadiene was used to build a cyclohexane precursor to inositol phosphate analogues (Scheme 1), complementing our own earlier approach in which we incorporated the phosphate mimic within a dienophile.[3] Both approaches have their limitations; the former, based upon **1**, suffers from the relatively low reactivity of the diene, the rather limited range of dienophiles with which the key building block reacts, and that elaboration of **2** or related species to inositol phosphate analogues requires the stereoselective oxidative cleavage of two C–C bonds.

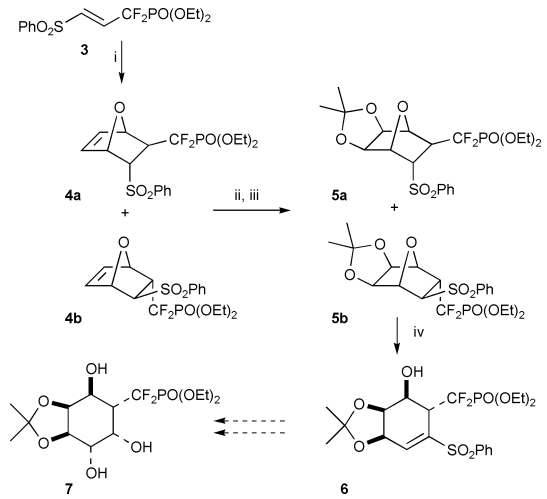
According to Yokomatsu, our Diels–Alder strategy 'met with only limited success due to the low *endo–exo* selectivity'. Undeniably, the reaction between furan and **3** afforded a disappointing outcome in the form of an almost equimolar mixture of *endo* and *exo* cycloadducts **4a** and **4b** in moderate yield (Scheme 2).[3a] Worse was to follow; dihydroxylation of the mixture of stereoisomers and protection as the acetonides **5a** and **5b** set the stage for ring opening. Treatment of the mixture with *n*-BuLi in THF at −78 °C returned the *endo*-isomer **5a** unchanged along with alcohol **6** in poor (12%) yield representing a further reduction in the potential of the route.§ The conjugate base of **5a** must undergo carbanion inversion to adopt the correct stereoelectronic relationship for ring opening to occur. Bulky groups must become eclipsed along this pathway and there appears to be a prohibitive steric barrier to carbanion inversion. We should point out though that the successful removal of the phenylsulfonyl group and dihydroxylation of the alkene delivers a fully functionalised inositol phosphate analogue **7** in which a key relationship is set between the (C-1)–CF_2 bond and the C-2, C-4 and C-6 hydroxy groups.[4]

In the quest for more stereoselective and efficient processes, we considered an alternative route *via* commercially-available 1-(trimethylsilyloxy)buta-1,3-diene, which reacted smoothly (Scheme 3) and completely stereoselectively with **3**. After hydrolysis, racemic *trans*,*trans*-alcohol **8** (in which the DFMPA and phenylsulfonyl groups occupy almost *pseudo*-axial positions in the crystal structure (and presumably in solution too, given the coupling constant of 0 Hz between the relevant protons) was obtained in good yield. Stereoselective dihydroxylation[5] and protection was followed by reductive elimination[6] to afford a mixture of alcohol **10** and alkene **11**. Acetylation of **9** to **12** followed by reductive elimination allowed the formation of **11** as the sole product in 69% yield. The alkene looks ideal for further manipulation—the topology and the presence of the DFMPA group would seem propitious for stereoselective dihydroxylation to deoxy analogue **13**.

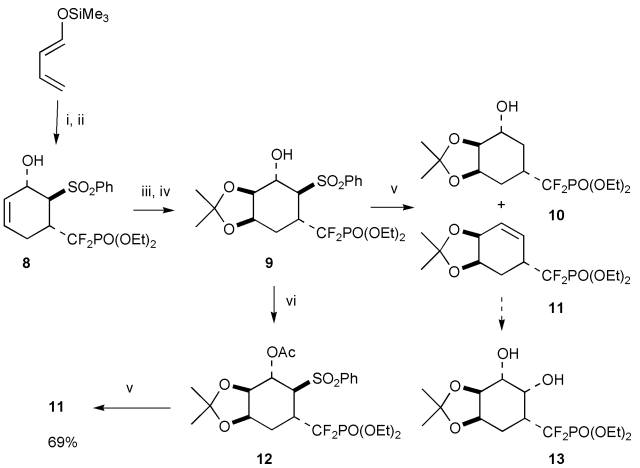
The Diels–Alder reaction can also be used to construct key precursors into which the DFMPA-group is introduced late in



Scheme 1



Scheme 2 Reagents and conditions: i, Furan, Ace tube, 80 °C, 18 h, 60%, (*endo*:*exo* 3:2); ii, OsO_4, *t*-BuOH, H_2O_2, rt, 48 h, 57%; iii, acetone, $CuSO_4$, TsOH, rt, 24 h, 62%; iv, n-BuLi, THF, −78 °C, 25 min then conc. HCl, **6** 12%, **5a** 48%.



Scheme 3 Reagents and conditions: i, **3**, Ace tube, 80 °C, 48 h; ii, HCl–EtOH, rt, 1 h, 77%; iii, OsO_4, NMO, *t*-BuOH–acetone–water, rt, 48 h, 69%; iv, acetone, $CuSO_4$, TsOH, rt, 24 h, 93%; v, 6% Na(Hg), Na_2HPO_4, MeOH, rt, 20 min, **9** 33%, **10** 33%; vi, Ac_2O, pyridine, DMAP, DCM, rt, 48 h, 87%.

† Current address: Evotech OAI, 151 Milton Park, Abingdon, Oxon, UK OX14 4SD.
‡ Current address: Department of Chemistry, University of Leicester, University Road, Leicester, UK LE1 7RH. E-mail jmp29@le.ac.uk

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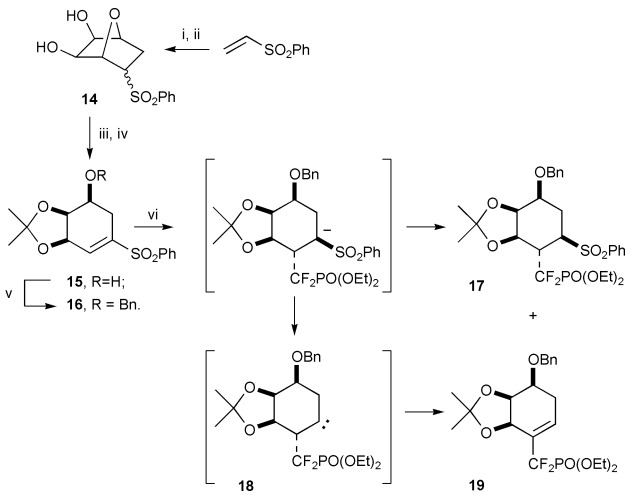
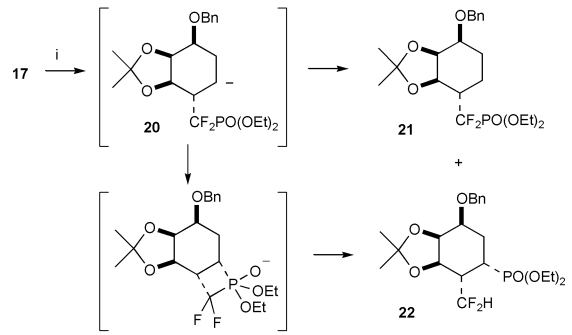
synthesis. Phenyl vinyl sulfone and furan undergo smooth cycloaddition to afford a mixture of adducts which afford **14** upon dihydroxylation (Scheme 4); protection and treatment with *n*-BuLi converges the diastereoisomers in **15**. Protection to **16** then cerium-mediated conjugate addition[7] from the least hindered face of the bicycle and quenching at low temperature delivers **17** in moderate (62%) yield stereoselectively (*trans* addition was observed in all previous cases and would be anticipated strongly here); however, when the reaction mixture was allowed to warm to rt before quenching, we also isolated a product which was revealed to be alkene **19** by 2D NMR (gradient HMBC). Presumably, this product arises from a 1,2-H shift in carbene **18**.



Scheme 4 Reagents and conditions: i, Furan, ZnI_2, hydroquinone, Ace tube, 90 °C, 5 d, 85% (*endo*:*exo* 7:3); ii, OsO_4, NMO, *t*-BuOH–acetone–water, rt, 48 h, 69%, iii, acetone, $CuSO_4$, TsOH, rt, 48 h, 89% over 2 steps; iv, *n*-BuLi, THF, −78 °C, 0.5 h, 73%; v, NaH, BnBr, THF, 0 °C, 1 h, 67%; vi, $LiCF_2PO(OEt)_2$, $CeCl_3$, THF, −78 °C then quench (see text).

Reductive desulfonation of **17** to **21** was successful though we also isolated the intriguing product **22** in trace amounts (Scheme 5). We believe that this arises from intramolecular attack at phosphorus followed by C–C cleavage with protonation and assign the *cis*-stereochemistry to the C–CF_2 and C–P bonds accordingly.

Clearly considerable optimisation of a number synthetic steps is required but we would argue that *strategically*, these applications of the Diels–Alder reaction still represent powerful



Scheme 5 Reagents and conditions: i, 6% Na(Hg), Na_2HPO_4, MeOH, rt, 30 min, **21** 49%, (**22** trace).

and versatile approaches to analogues of inositol phosphates that bear the DFMPA-group.

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Notes and references

§ Selected data for **6**. R_f (60% ethyl acetate in light petroleum) 0.21; δ_H (300 MHz, CD_2Cl_2) 7.86–7.64 (3H, m), 7.54 (2H, t, ^3J 7.7), 7.27 (1H, br s), 4.74 (1H, d, ^3J 7.7), 4.66 (1H, br s), 4.55–4.47 (1H, m), 4.34–4.19 (4H, m), 3.91–3.73 (2H, m), 1.45 (3H, s), 1.40 (3H, s), 1.39 (3H, t, ^3J 6.8), 1.35 (3H, t, ^3J 6.9); δ_F (282 MHz, $CDCl_3$) −101.8 (ddd, ^2J 311.4, $^2J_{F\text{-}P}$ 99.2, $^3J_{F\text{-}H}$ 5.1), −111.1 (ddd, ^2J 311.4, $^2J_{F\text{-}P}$ 108.1, $^3J_{F\text{-}H}$ 33.1, $^4J_{F\text{-}H}$ 5.1); δ_P (121 MHz, $CDCl_3$) 5.1 (dd, $^2J_{F\text{-}P}$ 108.7, $^2J_{F\text{-}P}$ 99.2); [HRMS (ES, *M* + Na) Found: 519.1022. Calc. for $C_{20}H_{27}O_8F_2PSNa$ 519.1030]; *m*/*z* (ES) 519 (100%, *M* + Na).

Selected data for **8**. R_f (ethyl acetate) 0.46; mp 82–83 °C; (Found: C, 48.0; H, 5.5%. $C_{17}H_{23}F_2O_6PS$ requires C, 48.1; H, 5.4%); δ_H (300 MHz, $CDCl_3$) 7.95 (2H, d, ^3J 8.5), 7.71–7.51 (3H, m), 5.90–5.80 (2H, m), 4.47 (1H, d, ^3J 7.0), 4.35–4.15 (4H, m, OCH_2CH_3), 3.92 (1H, s), 3.75 (1H, d, ^3J 7.0, O-*H*, exchanged with D_2O), 3.45–3.24 (1H, m), 2.59–2.42 (2H, m), 1.35 (6H, t, ^3J 7.0, OCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 137.6, 134.2, 129.5, 128.8, 127.3, 126.5, 120.6 (td, $^1J_{C\text{-}F}$ 264.5, $^1J_{C\text{-}P}$ 211.4), 65.5 (d, $^2J_{C\text{-}P}$ 6.2), 65.0 (d, $^2J_{C\text{-}P}$ 7.4), 64.7–64.5 (m)*, 60.6, 34.0 (td, $^2J_{C\text{-}F}$ 22.0, $^2J_{C\text{-}P}$ 17.0), 20.5–20.22 (m)*, 16.4 (d, $^3J_{C\text{-}P}$ 5.1), 16.3 (d, $^3J_{C\text{-}P}$ 5.7); δ_F (282 MHz, $CDCl_3$) −104.8 (ddd, ^2J 302.0, $^3J_{F\text{-}P}$ 102.1, $^3J_{F\text{-}H}$ 17.2), −111.2 (ddd, ^2J 302.0, $^2J_{F\text{-}P}$ 109.8, $^3J_{F\text{-}H}$ 19.9); δ_p (300 MHz, $CDCl_3$) 6.95 (ddd, $^2J_{P\text{-}F}$ 109.8, $^2J_{P\text{-}F}$ 102.1, $^3J_{P\text{-}H}$ 7.7); *m*/*z* (EI) 425 (15%, *M* + 1), 407 (70), 283 (75), 265 (100), 188 (85). *Multiplet signals arise from superimposed longer range C–F and C–P couplings. $C_{17}H_{23}F_2O_6PS$ crystal size 0.50 × 0.30 × 0.30 mm, *M* = 424.38, crystal system monoclinic, unit cell dimensions *a* = 9.9968(6), *b* = 16.8039(14), *c* = 12.5119(11) Å, β = 104.776(2)°, *U* = 2032.3(3) Å^3, *T* = 296(2) K, space group $P2_1/a$, Absorption coefficient μ(Mo-Kα) = 0.285 mm^{-1}, 11831 reflections collected, 3531 unique [*R*(int) = 0.0364], which were used in all calculations. Final *R* indices [$I > 2\sigma(I)$] *R*1 = 0.0715 *wR*2 = 0.1572; *R* indices (all data) *R*1 = 0.0756, *wR*2 = 0.1680. CCDC 178066. See http://www.rsc.org/suppdata/cc/b2/b200560n/ for crystallographic files in .cif or other electronic format.

Selected data for **11**. R_f (60% ethyl acetate in light petroleum) 0.51; δ_H (300 MHz, $CDCl_3$) 6.02 (1H, br d, ^3J 10.3), 5.83 (1H, br d, ^3J 10.3), 4.55–4.42 (2H, m), 4.35–4.20 (4H, m), 3.20–2.98 (1H, m), 2.35 (1H, dt, ^2J 14.7, ^3J 3.7), 2.00–1.88 (1H, m), 1.39–1.34 (12H, m); δ_C (75 MHz, $CDCl_3$) 129.5, 124.7 (td, $^3J_{C\text{-}F}$ 6.2, $^3J_{C\text{-}P}$ 3.4), 120.8 (td, $^1J_{C\text{-}F}$ 262.8, $^1J_{C\text{-}P}$ 212.5), 108.8, 71.6, 71.4, 64.8 (d, $^2J_{C\text{-}P}$ 6.8), 64.6 (d, $^2J_{C\text{-}P}$ 6.8), 36.6 (q, $^2J_{C\text{-}F=C\text{-}P}$ 20.4), 27.9, 26.7, 25.0–24.9 (m)*, 16.6, 16.5; δ_F (282 MHz, $CDCl_3$) −114.4 (dd, $^2J_{F\text{-}P}$ 108.1, $^3J_{F\text{-}H}$ 17.8); δ_P (121 MHz, $CDCl_3$) 6.73 (t, $^2J_{F\text{-}P}$ 108.3); [HRMS (ES, *M* + Na) Found: 363.1147. Calc. for $C_{14}H_{23}O_5F_2NaP$ 363.1149]; *m*/*z* (ES) 363 (100%, *M* + Na). *Multiplet signals arise from superimposed longer range C–F and C–P couplings.

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