An appraisal of oxoketene cycloaddition methodology for the synthesis of 2,6-dideoxysugars and fluorinated 2,6-dideoxysugars†

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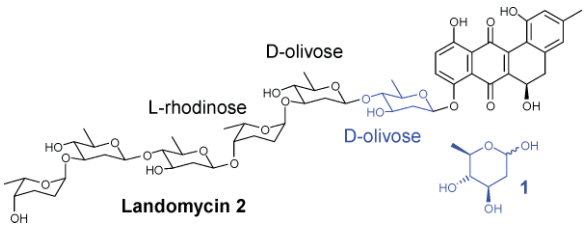
The cycloaddition reaction of acylketenes with vinyl ethers affords an extremely direct route to 2,6-dideoxysugars and their methyl ethers. The lithium enolate of commercial 2,6,6-trimethyldioxinone **3** was fluorinated in good yield to afford fluorinated dioxinone **8**. An illustrative range of fluorinated 2,6-dideoxysugar derivatives was prepared *via* the acetyl ketene–vinyl ether cycloadduct. Electronic structure calculations were carried out to investigate the effect of the fluorine atom on ease of formation and subsequent reaction of the (fluoroacetyl)ketene reactive intermediate. A single fluorine atom lowers the barrier to fragmentation by *ca.* 7.5 kJ mol^{-1}, consistent with experimental findings, but has almost no effect on the barrier to rate determining vinyl ether addition, or to oxoketene dimerisation.

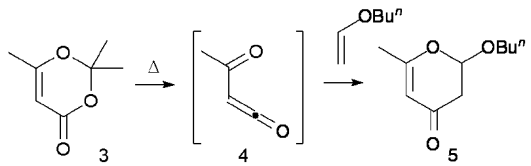
Introduction

2,6-Dideoxysugars are found in important natural products, including anthracycline antibiotics, aureolic acids and cardiac glycosides *inter alia.* D-Olivose (**1**), for example occurs several times in the complex antibiotic Landomycin **2**, a challenging target of some current synthetic interest.[1–3]



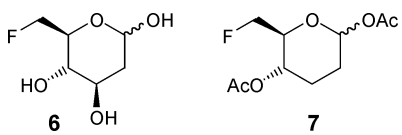
Deoxysugars have attracted the attention of many synthetic chemists and approaches to their syntheses have been well reviewed. For example, Coleman and Fraser[4] were able to synthesise an impressive range of racemic *n*-butyl glycosides of *arabino*-, *lyxo*-, *ribo*- and *xylo*-2,6-dideoxysugars, using the oxoketene cycloaddition as the first step (Scheme 1).

2,6,6-Trimethyldioxinone **3** extrudes acetone in hot toluene to afford oxoketene **4**; adding the dioxinone to a relatively dilute solution of an excess of vinyl ether minimizes side-reactions arising from oxoketene self-reaction and delivers a good yield of pyranone **5**. Conventional redox transformations were then carried out to introduce the vicinal hydroxyl groups. While



Scheme 1 The oxoketene route to 2,6-dideoxysugar precursors.

there have been extensive studies of syntheses of deoxysugars,[5,6] and fluorination reactions of hexoses,[7–9] fluorinated analogues of highly deoxygenated sugars are less common. O'Hagan and Nieschalk[10] prepared 6-fluoro-D-olivose **6** in 11 steps from D-glucose *via* isolation and activation of the 6-hydroxyl group followed by fluoride ion displacement and Thiem and co-workers[11] used an epoxide opening with TREAT·HF to synthesise protected 6-fluoro amicetose **7** from a D-gluconic acid salt, but we found no other focussed syntheses.[12,13]



A current project in our laboratory seeks concise routes to 6-deoxy-6-fluorosugars of various types with which we wish to explore structure–reactivity relationships in hydrolysis reactions; racemic sugars are quite adequate in the context of this work. If we could reproduce Coleman and Fraser's little-used methodology, then synthesise fluorinated dioxinone **8** by electrophilic fluorination of a metal enolate or synthetic equivalent, and deploy **8** successfully, we might benefit from the brevity of their approach and find a new route to a range of 2,6-dideoxy-6-fluorosugars of various types (Scheme 2).

Physical organic chemists' interests in oxoketene chemistry lie in the transition structures for cycloaddition reactions of these reactive intermediates. Unlike the familiar π-to-π face geometry encountered in the Diels–Alder reaction, the [4 + 2] cycloadditions of oxoketenes pass through almost planar transition states with pseudopericyclic orbital topologies.[14] Electronic structure

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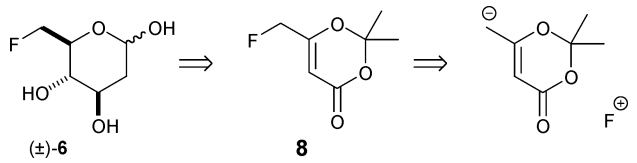
† Electronic supplementary information (ESI) available: Experimental details for all compounds not described in the main manuscript, characterisation spectra for **6**, **8**, **11**, **17**, **19**, **22**, **27**, **29**, **30a** and **30b**, **31**, **33**, **35**, **40**, **41** and **43**, Cartesian coordinates and energies for all ground state, product and transition structures. See DOI: 10.1039/b817672h



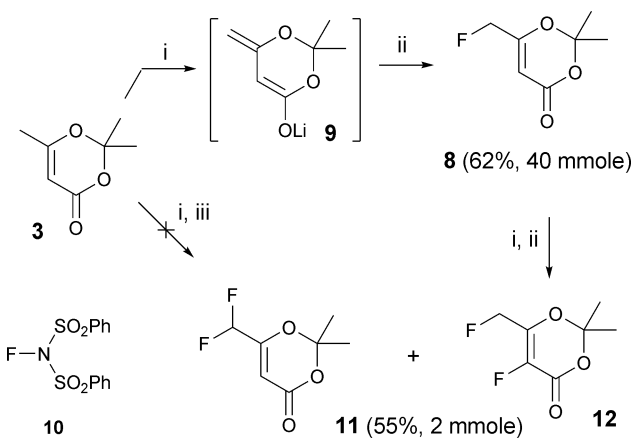
Scheme 2 Retrosynthetic analysis for racemic 6-fluoroolivose.

calculations have been used to investigate the cycloaddition between oxoketene and aldehydes (analogous to the fragmentation of **3** to **4**) but the reaction with vinyl ethers appears to be considerably less well explored. The identity of the rate determining step and the effects of polarizing substituents like fluorine atoms on the reaction and barrier energies were neither known[15] nor intuitively obvious, so we decided to carry out electronic structure calculations to learn more about the fragmentation and addition processes and complement the synthetic work.[16]

Results and discussion

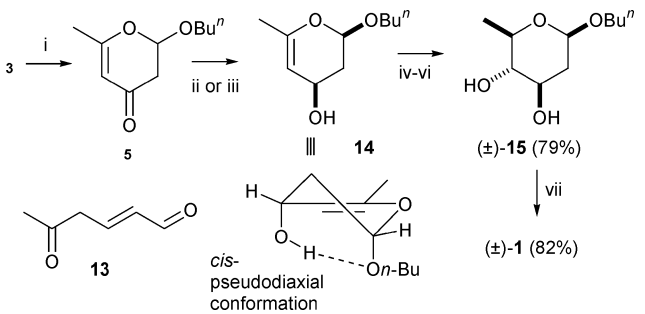
Synthetic studies

Enolate formation from **3** is known,[17] so we explored two fluorination approaches (Scheme 3). Enolate **9** was generated using LDA and trapped with *N*-fluorobenzenesulfonimide (NFSi, **10**).[18] The fluorination was achieved in close to 95% conversion and we were able to isolate gram quantities of **8** in reproducible 60–70% yield. The fluorinated dioxinone could be purified by column chromatography, though we were not able to obtain satisfactory microanalysis and we avoided distilling the product to maximize the throughput into the subsequent steps. We then attempted to prepare the difluorinated dioxinone **11** in one pot from **3** by treating it with an excess of LDA and NFSi but this failed to return difluorinated material. Deprotonation in the presence of manganese(II) chloride as reported by Matsumura *et al.* for a lactone substrate[19] also failed to return any of the desired product. Re-exposure of **8** to LDA then NFSi on a rather smaller (millimole) scale did afford difluorinated product **11** in 55% yield, along with traces of known **12**.[20]



Scheme 3 (i) LDA, THF, –78 °C; (ii) **10**; (iii) excess LDA, THF, –78 °C then **10**.

With **8** in hand, we evaluated the performance of the chemistry described by Coleman and Fraser from commercially-available **3** (Scheme 4). We noted that their method had not been used to prepare any free sugars (all their final products were *n*-butyl glycosides). Further, the published method for the oxoketene cycloaddition is carried out only on a millimole scale in the communication, and none of the transformations in the subsequent full paper use more than 10 millimole of starting material. This suggests that the initial reaction is severely scale limited and that perhaps products from multiple runs were pooled for the subsequent campaign.‡ We were able to carry out the reaction to afford a good (reproducibly over 70%) yield of pyranone **5** (R = *n*-Bu) at 0.112 M, instead of the published 0.028 M. The addition was carried out over 3 hours (rather than the two in the literature procedure) and the reflux after addition was extended to 21 hours. We could bring 112 mmole of dioxinone through in this way using only 1 L of toluene solvent. NMR scale experiments suggest that the concentration can be increased to 0.64 M without the formation of significant quantities of side products but we did not optimise a synthetic procedure at this higher concentration. We also found that Kugelrohr distillation of the crude product routinely returned material contaminated with γ-pyrone; column chromatography proved a much more reliable method, even for larger quantities of material, because the separation was very straightforward.



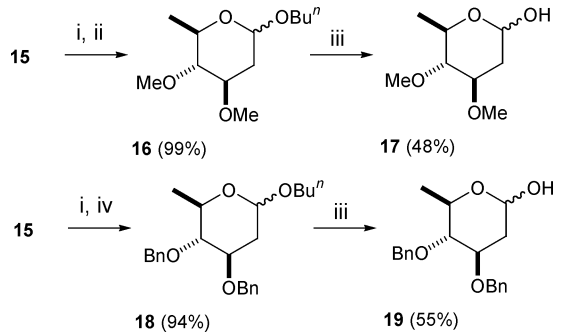
Scheme 4 *Reagents and conditions*: (i) *n*-butyl vinyl ether, PhMe, 110 °C; (ii) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, Et_2O; (iii) DIBAl-H, THF, –78 °C; (iv) $H_3B \cdot SMe_2$, THF; (v) Na_2BO_3; (vi) H_2O; (vii) 1 M HCl.

The selective 1,2-reduction of **5** (R = *n*-Bu) was reported with DIBAl-H, but we found this experiment very difficult to reproduce, isolating significant quantities of a side product believed to be 5-oxo-hex-2-enal **13** from significant peaks in the ^{1}H NMR spectrum. Luche reduction in methanol was more satisfactory (8.2 mmol scale, 61%)[21] but diethyl ether (23 mmol scale, 97%) was a better solvent.[22,23]

The hydroboration–oxidation was not optimized further but delivered diol **15** in good (79%) yield. In our hands, allylic alcohol **14** decomposes easily during attempted purification; however, we found that crude material could be used for the hydroboration–oxidation sequence. Coleman and Fraser were able to characterise **14** as the *cis* diastereoisomer, reporting $J_{1,2}$ values of 2.7 and 1.8 Hz for the anomeric proton. These small coupling constants are consistent only with a *cis*-pseudodiaxial conformation for **14**, stabilised presumably by the formation of an intramolecular hydrogen bond. The ^{1}H NMR spectra throughout these sequences were consistent with the presence of a single anomer.

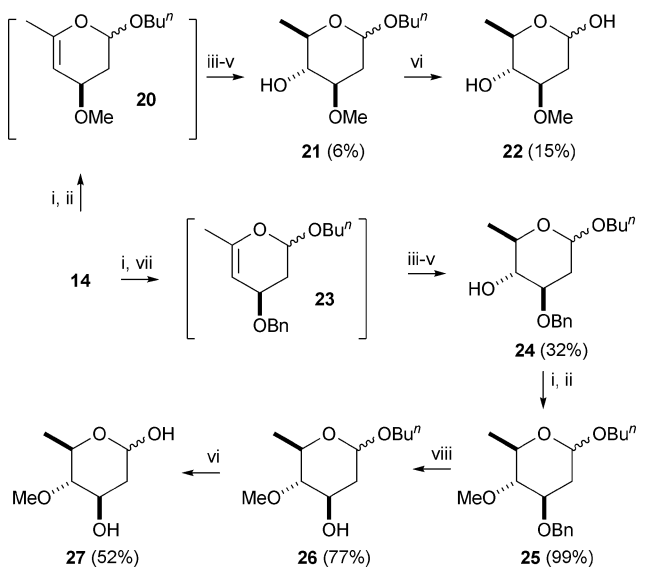
‡ None of the literature citations of the paper repeat or develop the synthetic chemistry.

A range of conditions (Amberlyst-15 in aqueous THF, HCl in THF, and formic acid) were explored for the hydrolysis, yielding either recovered butyl olivoside **15** or intractable gummy materials. We then attempted to follow the reaction in the NMR tube in DCl in D_2O. Starting material was recovered at 0.5 M DCl concentration, whereas 2 M acid delivered only decomposed products, but carrying out the reaction in 1 M acid allowed clean conversion of racemic olivose **1** in 82% yield as a mixture of anomers. The NMR data were identical to those reported by Roush and Brown for the D-sugars.[24] Methylated sugars appear in a number of natural products, and selective and random methylations have been used to explore aspects of protein:carbohydrate recognition.[25] We prepared dimethylated sugar **17** and dibenzylated **19** by standard methods (Scheme 5).



Scheme 5 *Reagents and conditions*: (i) NaH, THF, 0 °C; (ii) MeI; (iii) 1 M HCl; (iv) BnBr, Bu_4NI.

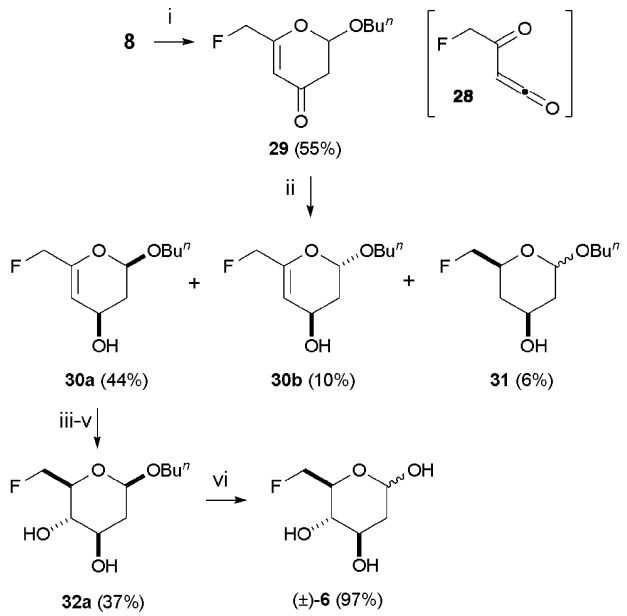
The sequence reveals the two hydroxyl groups of the sugar separately so we also prepared sugars **22** (racemic oleandrose) and **27**, methylated at the 3-OH and 4-OH groups respectively (Scheme 6).



Scheme 6 *Reagents and conditions*: (i) NaH, THF, 0 °C; (ii) MeI; (iii) $H_3B{\cdot}SMe_2$, THF; (iv) Na_2BO_3; (v) H_2O; (vi) 1 M HCl; (vii) BnBr, THF, DMF; (viii) H_2, Pd–C, EtOH.

The hydroboration–oxidation reaction is less effective when the C-3 hydroxyl group is alkylated; the yield of **21** was particularly disappointing.

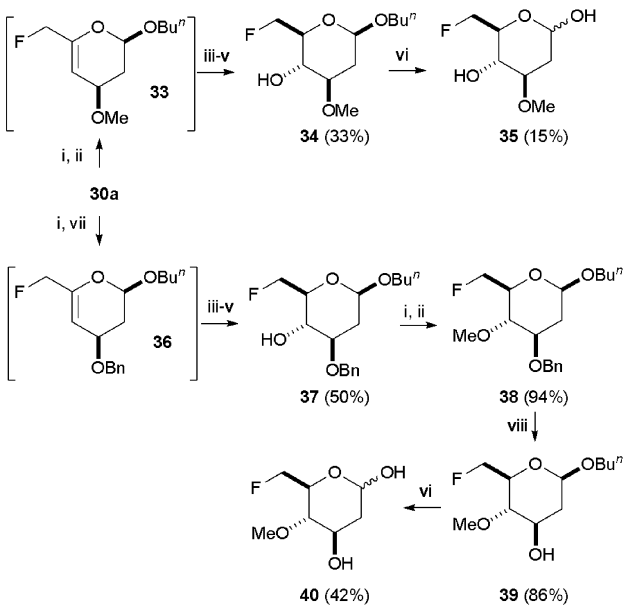
Our scale-up of the initial reaction in the sequence and the discovery of conditions for glycoside hydrolysis and free sugar isolation indicate that the chemistry is both reproducible and useful for the synthesis of racemic 2,6-dideoxysugars from dioxinone **3**. We then sought to use the knowledge gained in the reactions of the fluorinated dioxinone **8** (Scheme 7). Typically the cycloadditions were carried out on <2 mmole batches of the high value **8** at slightly higher dilution (0.09 M) delivering 55% of pyranone **29** in a typical case. The purified products were batched and taken on through the Luche reduction, which worked less well with this substrate, affording 54% of the dihydropyranols **30** (the *cis*- and *trans*-isomers were separable) which could be isolated, purified and stored, unlike non-fluorinated **14**, consistent with the fluorine atom inductive effect which opposes C–O cleavage and oxacarbenium ion formation. We also isolated some over-reduction product **31** (6%).



Scheme 7 *Reagents and conditions*: (i) *n*-butyl vinyl ether, PhMe, 110 °C; (ii) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, Et_2O; (iii) $H_3B{\cdot}SMe_2$, THF; (iv) Na_2BO_3; (v) H_2O; (vi) 1 M HCl.

The hydroboration–oxidation worked less well affording **32a** in 37% yield (only the major *cis*-isomer from the Luche reduction was taken forwards), though the final hydrolysis to (±)-**6** was successful (97%). Pyranol **30a** could be methylated almost quantitatively (99%) but this depressed the yield of the hydroboration–oxidation still further (to 33%) (Scheme 8). We also benzylated **30a**, then carried out the hydroboration–oxidation on the crude **36** to afford **37** in 50% over 2 steps. The new hydroxyl group could then be methylated in high yield (94%) and hydrogenolysis revealed the C-3 hydroxyl in good yield (86%).

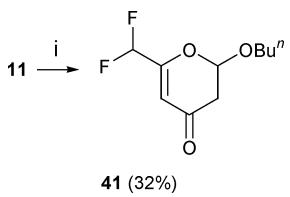
Cerium(III)-mediated addition of methyl Grignard reagent to **5** was also reported by Coleman and Fraser and used to enter the chromose B and olivomycose sugars. We were unable to reproduce these experiments with **5** or **29**, isolating only modest amounts of the starting pyranone (the only identifiable product from the reaction). The cycloaddition sequence was unsuccessful when ethyl vinyl sulfide was used in place of the vinyl ether, returning a



Scheme 8 *Reagents and conditions*: (i) NaH, THF, 0 °C; (ii) MeI; (iii) $H_3B{\cdot}SMe_2$, THF; (iv) Na_2BO_3; (v) H_2O; (vi) 1 M HCl; (vii) BnBr; (viii) H_2, Pd–C, EtOH.

dark and complex mixture of reaction products; we had hoped to prepare the (ethylthio)glycosides directly in this way.

Difluorinated dioxinone **11** could also be progressed through the cycloaddition though the yield of pyranone **41** was rather poor (32%, *ca.* 15% over two steps from **3**, Scheme 9). In view of the low yield, we did not progress this intermediate further and no attempt was made to optimise the reaction.



Scheme 9 *Reagents and conditions*: (i) *n*-butyl vinyl ether, PhMe, 110 °C.

Though the outcome with the difluorinated system was disappointing, the monofluorinated dioxinone **8** appears to be a useful intermediate for the preparation of selected (racemic) 2,6-dideoxy-6-fluorosugars.

Electronic structure calculations

Potential energy surface and choice of method. We wondered if electronic structure calculations would predict major changes in transition structures and energies as a fluorine atom was incorporated, and noted that whereas Birney and co-workers (*inter alia*) had studied the reactions of oxoketenes with nucleophiles like water, and with aldehydes,[26,27] thoroughly, the cycloaddition with vinyl ethers appeared to be unexplored, though a recent study by Cabaleiro–Lago *et al.* has characterized transition structures for the reaction between formyl ketene and ethylene.[28] Fig. 1 defines the general shape of the calculated potential energy surface and defines the free energy quantities for the reactions of **3** and **8** with methyl vinyl ether. Transition structures were obtained

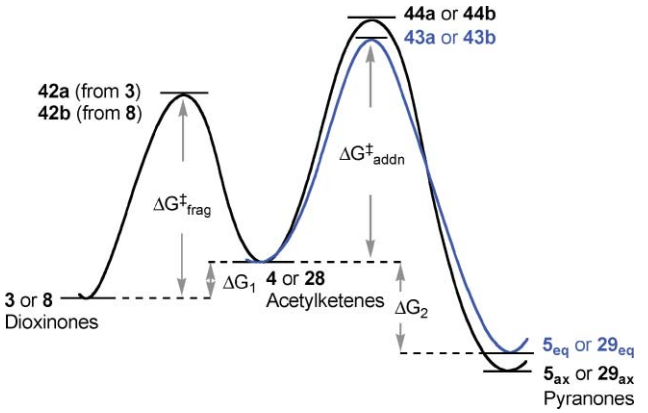


Fig. 1 Calculated potential energy surface for the reaction of **3** and **8** with methyl vinyl ether.

by fragmenting dioxinones and pyranones using the PM3 semi-empirical method (implemented in Spartan 06).[29,30]

The B3LYP functional[31,32] with the 6-31G(d) basis was then used to optimise reactant, intermediate, product and transition structures in the first instance. The overall reaction is exergonic and the initial endergonic fragmentation is driven by the escape of volatile acetone from the reaction. We reproduced the pseudopericyclic-type transition structures (**42**) for the extrusion of acetone described by Birney[26] and Kurth and co-workers.[33] However, we could only find one (very flat) transition structure related to the pseudoaxial pyranone products **5** or **29** (calculations were carried out on the *methyl* pyranosides whereas the synthetic chemistry uses the *n*-butyl congeners), for the vinyl ether addition; all attempts to find the transition structure corresponding to the pseudoequatorial products failed.

We then applied Møller–Plesset (MP2) methods,[34] which produced very similar transition structures for the fragmentation reaction that extrudes acetone. However, two distinct addition transition structures were now found, with the vinyl ether swinging out of the oxoketene plane. Fig. 2 shows an overlay of the B3LYP (blue) and MP2 (yellow) transition structures; the vertical displacements of the vinyl ether C-1 and C-2 carbons are substantial at 0.62 and 0.75 Å, respectively, away from the positions calculated by the DFT method.

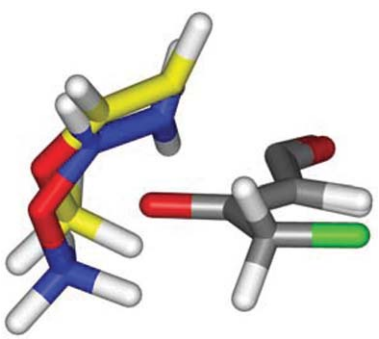


Fig. 2 Overlaid transition structures (for **43b**) from B3LYP/6-31G(d) (blue) and MP2/6-31G(d) (yellow) calculations for the reaction between **8** and methyl vinyl ether.

The differentiation of these pathways by the MP2 method suggests that while the correlated and DFT methods are

equally successful at describing the pseudopericyclic reaction with aldehydes,[27] the correlated method may provide a more informative picture of the reaction geometries with alkenes. The addition transition states deviate significantly from planarity at this level of theory, suggesting strongly that their character is more pericyclic; a more sophisticated treatment (for example the mapping of magnetic characteristics along the reaction coordinate) lies outside the scope of this manuscript.[35,36]

Fig. 3 shows the distinct transition structures obtained for the reaction of **8** with methyl vinyl ether.

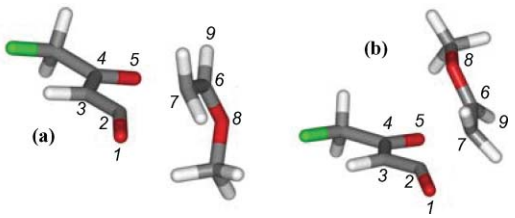


Fig. 3 (a) Pseudoequatorial transition structure **43b** (b) pseudoaxial transition structure **44b**.

Selected lengths, distances and angles are listed in Table 1. Of course, the pyranone products arising from these different transition structures undergo facile conformational exchange, but it is interesting to see the quite different topologies available to this reaction.

The use of the larger 6-311+G** basis has no effect on the order of energies or methyl/fluoromethyl difference, though the energies of the different pyranone conformers converge. However, these are gas phase calculations and we would expect the conformers to have different dipoles, and therefore to be subject to solvent effects. Consideration of the effect of fluorination upon anomer population lies outside the scope of this manuscript.

Calculated reaction and barrier energies. Table 2 lists the relative free energies obtained from the MP2 calculations. The calculated free energy barriers for the extrusion of acetone from **3** and **8** differed by 7.5 kJ mol^{-1} at 373 K (using the calculation with the larger basis). We would therefore expect the fluorinated compound to extrude acetone *ca.* 11 times faster under the synthetic conditions.

Both reactions were followed by withdrawing aliquots, which were concentrated under reduced pressure at room temperature and analysed by ^{1}H NMR (the approximate concentrations were obtained by integrating dioxinone and pyranone signals). We were able to estimate a rate constant similar to the one reported in the literature[15] (our value was 6×10^{-5} M^{-1} s^{-1} compared to 1×10^{-4} M^{-1} s^{-1}) for the fragmentation of **3**; the concentration–time profiles were consistent with the predicted order of reactivity, with **8** proving approximately 10 times more reactive (k = *ca.* 6×10^{-4} M^{-1} s^{-1} based on only four points) (Fig. 4).

Table 1 Selected lengths, distances and angles for transition structures[a] **43b** and **44b**

Length/distance (Å)	**43b**	**44b**
C-3–C-4	1.417	1.409
C-4–O-5	1.249	1.256
C-6–C-7	1.393	1.388
C-2···C-7	1.981	1.931
O-5···C-6	2.311	2.338
Angles (°)		
C-3–C-2–O-1	140.2	139.7
C-3–C-2–C-7	113.4	114.0
C-4–O-5–C-6	114.5	103.4
H-C–7-H	115.5	116.8

[a] Measured from the MP2/6-311+G** optimised transition structures.

Table 2 Relative free energies from MP2 calculations (gas phase)

		6-31G(d)[c]		6-311+G**[d]	
G_{rel}/kJ mol^{-1}		From **3**	From **8**	From **3**	From **8**
$\Delta G^{\ddagger}_{\ddagger frag}$[a]		118.4	108.5	110.0	102.5
	ax	135.3	132.3	125.1	120.9
$\Delta G^{\ddagger}_{\ddagger addition}$[b]	eq	131.7	129.3	120.9	117.2
ΔG_1		21.1	13.8	25.9	18.4
	ax	−65.1	−58.5	−63.1	−57.3
ΔG_2	eq	−60.1	−53.9	−61.1	−55.1

[a] Calculated from **3**. [b] Calculated from the free energies of **4** or **28**, and methyl vinyl ether. [c] At 373 K. [d] At 298 K.

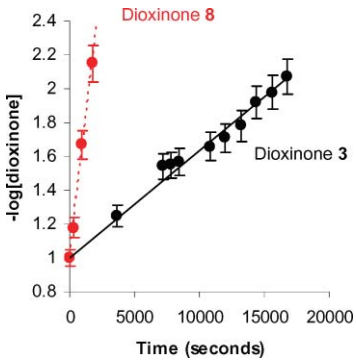


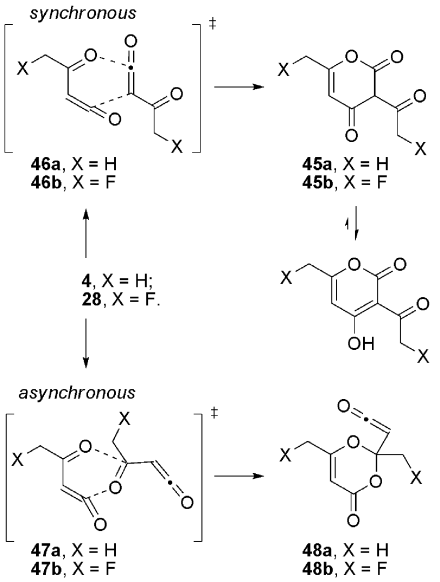
Fig. 4 Determination of approximate rate constants for dioxinone fragmentation.

The slow addition of the dioxinone to the vinyl ether suggests that the oxoketene is formed slowly and trapped rapidly; the literature rate constant and our own observations suggest that the converse is true with dioxinone consumption significantly ahead of pyranone formation.

Fluorination makes the fragmentation less unfavourable overall; at 373 K, K_{frag} is 1.1×10^{-3} for **3** ⇆ **4**, and 1.1×10^{-2} for **8** ⇆ **28**. Both fragmentations are driven by the escape of volatile acetone from the hot toluene; indeed, the major proportion of the four carbon oxoketene intermediate may be in the vapour phase above the reaction in each case, rather than present in solution in a significant concentration. The calculated effect of fluorination on the rate-determining addition of methyl vinyl ether is very small; we would therefore expect that the concentration of **8** would build up more quickly and to higher levels than that of **3**, given the more rapid fragmentation. This could lead to significantly higher levels of oxoketene dimerisation products, though the concentration of the reactive intermediate in the reaction solution may be low. We probed further to gain some insight into the size of the barriers to dimerisation.

Dimerisation pathways. Dehydroacetic acids **45** (the more favoured tautomer is shown in Scheme 10) are significant side

products of the pyranone syntheses, so we explored the dimerisations of **4** and **28**, finding synchronous transition structures **46** in which the ketene function crosses the plane of the heterodiene, and asynchronous transition structures **47** which lead to dioxinones **48** (Scheme 10, the structures are discussed more fully in the ESI)†.



Scheme 10 Dimerisation reactions available from the acetylketenes **4** and **28**.

The new dioxinone could react further through the pendant acetylketene, leading to complex mixtures of products; we did not pursue these possibilities. The calculated free energy barriers are listed in Table 3.

The dimerisation to **46** has a significantly (50 kJ mol^{-1}) lower barrier than the cycloaddition with the vinyl ether so it is important that the concentration of **4** does not build up in the reaction. The dimerisation barrier for fluorinated oxoketene **28** is only very slightly higher than that for the non-fluorinated species; this is most unlikely to compensate for the faster formation of the oxoketene in this case.

Conclusions

The oxoketene sequences described by Coleman and Fraser can be repeated, scaled up and carried out under relatively concentrated conditions to prepare racemic olivose, oleandrose and related free sugars. Electrophilic fluorination of a commercial and inexpensive dioxinone affords a fluorinated analogue which can be taken through a similar sequence successfully, though in lower yield. The difluorinated dioxinone was also prepared and elaborated, though less successfully. The dioxinones may be useful intermediates in a number of roles other than those described here.

Electronic structure calculations predict that while a single fluorine atom has a minimal effect on the pseudopericyclic addition with methyl vinyl ether, it facilitates oxoketene formation, indicating that the reactive intermediate may reach a higher concentration when the fluorine atom is present. This fails to translate into an increase in yield of fluorinated pyranones **29**.

Table 3 Relative free energies from MP2 calculations[a]

Relative free energy/kJ mol^{-1}	**4** → **46a** → **45a**	**28** → **46b** → **45b**
$\Delta G‡$	+81.9	+84.7
$\Delta G°$	−69.0	−42.4
	4 → **47a** → **48a**	**28** → **47b** → **48b**
$\Delta G‡$	+104.5	+105.7
$\Delta G°$	+6.1	−17.8

[a] MP2/6-31G(d) at 373 K relative to 2 x G(acetylketene).

Experimental

General experimental procedures, and details of spectrometers and computational hardware and software are described in the ESI†. Coupling constants are reported in Hz.

2-(*n*-Butoxy)-6-methyl-2,3-dihydro-4*H*-pyran-4-one 5

Cycloaddition procedure. A solution of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **3** (4.0 g, 28.1 mmol) in dry toluene (50 mL) was added *via* syringe pump over 5 hours to a refluxing solution of butyl vinyl ether (18 mL, 141.0 mmol) in dry toluene (200 mL). The orange solution was stirred overnight at reflux. The solution was concentrated *in vacuo* to give a dark orange oil, which was purified by flash chromatography on silica gel to afford 2-(1-butoxy)-6-methyl-2,3-dihydro-4*H*-pyran-4-one **5** as a light orange oil (3.16 g, 61%,); R_f (20% ethyl acetate in light petroleum) 0.30; ν_{max} (film)/cm^{-1}: 2958 s, 1675 s, 1623 s, 1394 s, 1332 s, 976 s, 831 m; δ_H ($CDCl_3$, 300 MHz) 5.27 (1H, dd, *J* 5.5, 3.9), 5.24 (1H, s), 3.73 (1H, dt, ^2J 9.4 *J* 6.6), 3.52 (1H, dt, ^2J 9.4 *J* 6.3), 2.57 (1H, part of an ABX system, ^2J 16.7 *J* 3.9), 2.45 (1H, part of an ABX system, ^2J 16.7 *J* 5.5), 1.90 (3H, s), 1.52–1.42 (2H, m), 1.32–1.20 (2H, m), 0.81 (3H, t, *J* 7.5); δ_C ($CDCl_3$, 75 MHz) 190.9, 170.4, 105.1, 101.4, 69.3, 41.5, 31.4, 20.9, 19.0, 13.6; HRMS (EI$^+$, M$^+$) Found: 184.10996, Calc. for $C_{10}H_{16}O_3$ 184.10995; *m/z* (EI): 184 (M$^+$, 29%), 169 (3), 108 (100). The data were in agreement with those reported by Coleman and Fraser.[4]

2,2-Dimethyl-6-(fluoromethyl)-4*H*-1,3-dioxin-4-one 8

Fluorination procedure. Freshly distilled 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **3** (5.63 g, 39.6 mmol) was added to a freshly prepared solution of LDA (60 mmol) in THF (200 mL) at −78 °C. The yellow solution was stirred for 30 minutes at this temperature. A solution of NFSi (25.0 g, 79.3 mmol) in THF (100 mL) was added slowly over one hour. The mixture darkened from light yellow to orange and was stirred at −78 °C over 2 hours. The reaction was quenched by the addition of ammonium chloride (100 mL of a saturated aqueous solution). The mixture was then extracted in diethyl ether (3 × 150 mL), and the combined organic extracts were washed with brine (300 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The crude mixture was taken up with diethyl ether (50 mL) and filtered through Celite and concentrated again. This procedure was repeated until no further white precipitate appeared. The solution was concentrated and the crude product was purified by flash chromatography on silica gel to afford 2,2-dimethyl-6-(fluoromethyl)-4*H*-1,3-dioxin-4-one **8** as a yellow oil (4.41 g, 62%); R_f (20% ethyl acetate in light petroleum) 0.32; ν_{max} (film)/cm^{-1}: 3000 w, 2947 w, 1730 s, 1649 m, 1393 m, 1378 m, 1272 m, 1201 m, 1003 m, 809 m; δ_H ($CDCl_3$, 300 MHz) 5.55–5.50

(1H, m), 4.82 (2H, dd, $^2J_{H-F}$ 46.1 ^4J 1.2), 1.69 (6H, s); δ_C ($CDCl_3$, 75 MHz) 164.9 (d, $^2J_{C-F}$ 21.7), 160.1, 107.5, 93.7 (d, $^3J_{C-F}$ 6.0), 79.7 (d, $^1J_{C-F}$ 174.7), 24.95, 24.85; δ_F ($CDCl_3$, 282 MHz) −230.5 (t, $^2J_{F-H}$ 46.1); HRMS (EI$^+$, M$^+$) Found: 160.05360, Calc. for $C_7H_9FO_3$ 160.05357; *m/z* (EI): 160 (M$^+$, 4%), 159 (40), 141 (95), 77 (100); t_R (GC) 13.85 min.

6-(Difluoromethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one 11

6-Fluoro-2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **8** (312 mg, 1.95 mmol) was added to a freshly prepared solution of LDA (2.92 mmol) in THF (10 mL) at −78 °C. The yellow solution was stirred for 30 minutes at this temperature. A solution of NFSi (1.23 g, 3.9 mmol) in THF (10 mL) was added slowly over 30 min. The mixture darkened from light yellow to orange and was stirred at −78 °C over 2 hours. The reaction was quenched by the addition of ammonium chloride (20 mL of a saturated aqueous solution). The mixture was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), concentrated *in vacuo*, and purified by flash chromatography on silica gel to afford 6-(difluoromethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one **11** as a light yellowish oil (190 mg, 55%); R_f (20% ethyl acetate in light petroleum) 0.4; δ_H ($CDCl_3$, 300 MHz) 6.01 (1H, t, $^2J_{H-F}$ 53.5), 5.68 (1H, s), 1.68 (6H, s); δ_C ($CDCl_3$, 75 MHz) 159.5, 159.5 (t, $^2J_{C-F}$ 25.9), 108.5, 108.4 (t, $^1J_{C-F}$ 243.0), 95.7 (t, $^3J_{C-F}$ 4.8), 24.85, 24.80; δ_F ($CDCl_3$, 282 MHz) −127.0 (d, $^2J_{F-H}$ 53.5); HRMS (EI$^+$, M$^+$) Found: 178.04411, Calc. for $C_7H_8F_2O_3$ 178.04415; *m/z* (EI): 178 (M$^+$, 21%), 51 (100); t_R (GC) 15.52 min.

Trace amounts of known[20] **12** were also detected.

n-Butyl-β-DL-olivoside 15

Luche reduction procedure. Sodium borohydride (0.85 g, 23.0 mmol) was added slowly to a stirred mixture of **5** (4.3 g, 23.0 mmol), cerium(III) chloride heptahydrate (8.21 g, 23.0 mmol) and dry ether (150 mL) at −78 °C. After 2 hours, the reaction mixture was warmed to room temperature and stirred at this temperature for one hour. The mixture was cooled to 0 °C and quenched with potassium acetate (50 mL of a saturated aqueous solution) and sodium bicarbonate (50 mL of a saturated aqueous solution) and then stirred at 0 °C for 15 minutes. The mixture was poured into a mixture of brine (50 mL) and ether (100 mL).§ The organic layer was separated and the aqueous phase was extracted with ether (60 mL). The combined organic extracts were washed with sodium bicarbonate (50 mL of a saturated aqueous solution) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford alcohol **14** (4.0 g, 97% theoretical) as an unstable yellow oil which was used in the next step without further purification; R_f (50% ethyl acetate in hexane) 0.53; the data were in agreement with those reported by Coleman and Fraser.[4]

Hydroboration–oxidation–hydrolysis procedure. Crude **14** (4.0 g, 20 mmol) was taken up in dry THF (45 mL) under N_2 and cooled to 0 °C. A solution of $BH_3{\cdot}SMe_2$ (20 mL of a 2.0 M solution in THF, 40.0 mmol) was added slowly *via* syringe pump over 30 minutes. The reaction mixture was allowed to reach room temperature and was stirred for a further 19 hours. The reaction mixture was quenched with water (40 mL), solid $NaBO_3{\cdot}H_2O$ (15.28 g, 100.0 mmol) was added and the slurry was stirred vigorously at room temperature overnight. The mixture was extracted with ethyl acetate (4 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography and then recrystallised (ethyl acetate–hexane) to pyranoside **15** as a white solid (3.2 g, 68% over the 2 steps); R_f (50% ethyl acetate in light petroleum) 0.11; mp 102–105 °C; ν_{max} (film)/cm^{-1}: 3500 br, 1420 m, 1247 m, 1116 w, 956 w; δ_H ($CDCl_3$, 300 MHz); 4.48 (1H, dd, *J* 9.6, 2.0), 3.87 (1H, dt, ^2J 9.3, *J* 6.6), 3.60 (1H, ddd, *J* 11.7, 8.4, 5.0), 3.44 (1H, dt, ^2J 9.3, *J* 6.9), 3.28 (1H, dq, *J* 9.0, 6.0), 3.10 (1H, m incl. app. t, *J* 8.9), 2.28 (2H, br s), 2.21 (1H, ddd, ^2J 12.6, 5.0, 2.0), 1.68–1.53 (3H, m), 1.44–1.31 (2H, m), 1.34 (3H, d, *J* 6.0), 0.92 (3H, t, *J* 7.5); δ_C ($CDCl_3$, 75 MHz) 99.6, 77.9, 71.7, 71.6, 69.3, 39.1, 31.7, 19.2, 17.8, 13.9; HRMS (EI$^+$, M$^+$) Found: 203.12840, Calc. for $C_{10}H_{19}O_4$ 203.12833; *m/z* (EI): 203 (M$^+$ − H, 2%), 160 (M$^+$ − H − Et, 6), 83 (100). The data were in agreement with those reported by Coleman and Fraser.[4]

DL-Olivose 1

Glycoside hydrolysis procedure with conventional heating. Olivoside **15** (70 mg, 0.34 mmol) was dissolved in D_2O (1 mL). DCl (0.12 mL of a 9.8 M solution) was added and the reaction mixture was heated at 60 °C for 30 minutes. The solution was neutralised with $NaHCO_3$ and freeze-dried. The resulting solid was taken up with methanol and purified on silica gel to afford DL-olivose (±)-**1** (41 mg, 82%) as a white solid, as a 52 : 48 mixture of α- and β-anomers; mp 102–103 °C (lit.[24] 125.5–127 °C); R_f (20% methanol in DCM) 0.5; ν_{max} (film)/cm^{-1}: 3272 s, 2935 w, 1647 w, 1372 w, 1116 m, 1050 s, 981 m, 899 w; δ_H (MeOD, 300 MHz) α-anomer: 5.10 (1H, d, *J* 3.2), 3.86–3.64 (2H, m), 2.85 (1H, m incl. app. t, *J* 9.3), 1.95 (1H, dd, ^2J 12.3, *J* 4.2), 1.51 (1H, td, ^2J 12.3, *J* 3.2), 1.13 (3H, d, *J* 6.3), δ_H (MeOD, 300 MHz) β-anomer: 4.67 (1H, dd, *J* 9.6, 1.8), 3.51–3.31 (1H, m), 3.22–3.13 (1H, m), 2.81 (1H, m incl. app. t, *J* 9.5), 2.05 (1H, ddd, ^2J 12.3, *J* 4.8, 1.8), 1.46–1.30 (1H, m), 1.18 (3H, d, *J* 6.3); δ_C (MeOD, 75 MHz) α-anomer: 92.6, 78.4, 72.2, 68.7, 39.8, 18.3, δ_C (MeOD, 75 MHz) β-anomer: 94.8, 79.2, 73.2, 69.4, 42.0, 18.3; HRMS (EI$^+$, M$^+$) Found: 149.08131, Calc. for $C_6H_{13}O_4$ 149.08138; *m/z* (FAB$^+$): 149 (M + H$^+$, 12%), 131 (24), 95 (50), 57 (100). The data were in agreement with those reported by Roush and Brown,[24] apart from the mp (lit. 125.5–127 °C). However, Roush and Brown prepared enantiomerically enriched material.

n-Butyl-3,4-(*O*-dimethyl)-2,6-dideoxy-β-DL-arabino-hexapyranoside 16

Methylation procedure. NaH (120 mg, 60% suspension in oil, 3.0 mmol) was added slowly at 0 °C to a solution of **15** (204 mg, 1.0 mmol) in THF (50 mL). The reaction mixture was stirred for 30 minutes at this temperature. MeI (568 mg, 4.0 mmol) was added to the mixture and the reaction was stirred at room temperature overnight. Water (20 mL) was added slowly to stop the reaction. The mixture was then extracted with ethyl acetate (3 × 50 mL), and the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil

§ A very dense white precipitate can form at this stage; filtration through Celite assists decisively with phase separation.

which was used in the next step without any further purification: *O*-dimethylated pyranoside **16** (229 mg, 99%); R_f (20% ethyl acetate in light petroleum) 0.38; ν_{max} (film)/cm^{-1}: 2932 w, 1266 w, 1157 w, 1094 m, 1060 m, 990 w, 736 s; δ_H ($CDCl_3$, 300 MHz) 4.32 (1H, dd, *J* 9.9, 1.8), 3.78 (1H, dt, ^2J 9.6, *J* 6.6), 3.48 (3H, s), 3.39–3.31 (1H, m), 3.34 (3H, s), 3.23–3.13 (2H, m), 2.66 (1H, m incl. app. t, *J* 8.7), 2.22 (1H, ddd, ^2J 12.6, 5.1, 1.8), 1.53–1.48 (2H, m), 1.41–1.25 (3H, m), 1.24 (3H, d, *J* 6.3), 0.84 (3H, t, *J* 7.2); δ_C ($CDCl_3$, 75 MHz) 99.5, 85.5, 80.9, 71.2, 70.0, 60.6, 56.6, 36.3, 31.7, 19.1, 17.9, 13.8; HRMS (EI$^+$, M – H$^+$) Found: 231.15966, Calc. for $C_{12}H_{23}O_4$ 231.15963; *m*/*z* (EI): 231 (M – H$^+$, 6%), 188 (6), 161 (28), 132 (37), 88 (100); t_R (GC) 14.26 min.

3,4-(*O*-Dimethyl)-2,6-dideoxy-β-DL-arabino-hexapyranoside 17

Glycoside hydrolysis procedure with microwave heating. *n*-Butyl pyranoside **16** (250 mg, 1.08 mmol) was taken up in a mixture of THF (3 mL) and HCl (3 mL of a 1 N solution). The mixture was heated in the microwave at 80 °C (300 W) for 2 hours. The tube was cooled and opened carefully, and water was added. The mixture was extracted with ethyl acetate (3 × 10 mL), and the combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The acidic aqueous phase was neutralised with $NaHCO_3$ and freeze-dried. The colourless residue was suspended in methanol (20 mL) and filtered. The original organic phase and filtrate were combined and purified on silica gel to afford 3,4-(*O*-dimethyl)-2,6-dideoxysugar **17** (94 mg, 48%) as a colourless oil, and as a 62 : 38 mixture of α- and β-anomers; R_f (50% ethyl acetate in light petroleum) 0.38; ν_{max} (film)/cm^{-1}: 3393 m, 2935 w, 1446 w, 1266 w, 1089 s, 995 m, 734 s; δ_H ($CDCl_3$, 300 MHz) α-anomer: 5.22 (1H, br d, *J* 2.7), 3.80 (1H, dq, *J* 9.2, 6.3), 3.63–3.45 (4H, m (including 3.49 (3H, s))), 3.37 (3H, s), 2.68 (1H, m incl. app. t, *J* 9.2), 2.18 (1H, ddd, ^2J 13.0, 5.1, 1.5), 1.45 (1H, ddd, ^2J 13.0, 11.4, 3.6), 1.19 (3H, d, *J* 6.3), δ_H ($CDCl_3$, 300 MHz) β-anomer: 4.73 (1H, dd, *J* 9.6, 2.0), 3.49 (3H, s), 3.35 (3H, s), 3.26–3.17 (2H, m), 2.68 (1H, m incl. app. t, *J* 9.2), 2.30 (1H, ddd, ^2J 12.6, 5.1, 2.0), 1.41–1.37 (1H, m), 1.24 (3H, d, *J* 6.3); δ_C ($CDCl_3$, 75 MHz) α-anomer: 91.7, 86.3, 77.9, 67.2, 60.6, 57.2, 35.2, 18.0, δ_C ($CDCl_3$, 75 MHz) β-anomer: 93.8, 85.3, 80.6, 71.4, 60.8, 57.2, 37.6, 18.0; HRMS (EI$^+$, M$^+$) Found: 176.10488, Calc. for $C_8H_{16}O_4$ 176.10486; *m*/*z* (EI): 176 (M$^+$, 6%), 159 (7), 144 (29), 88 (100); t_R (GC) 11.48 min.

n-Butyl-4-(*O*-methyl)-2,6-dideoxy-β-DL-arabino-hexapyranoside 26

Hydrogenolysis procedure. 10% Palladium-on-carbon (45 mg, 0.04 mmol) was added to a solution of **25** (130 mg, 0.42 mmol) in absolute ethanol (10 mL). The vessel atmosphere was replaced with a hydrogen atmosphere following successive flushes with argon, and the reaction was stirred vigorously at room temperature overnight. The vessel atmosphere was then exchanged for argon with successive flushes and the mixture was filtered through a pad of Celite which was washed copiously with DCM (5 × 10 mL). The combined filtrates were concentrated *in vacuo* and purified by flash chromatography on silica gel to afford *n*-butyl-4-(*O*-methyl) pyranoside **26** (70 mg, 77%) as a white solid; R_f (50% ethyl acetate in light petroleum) 0.45; mp 52 °C; ν_{max} (film)/cm^{-1}: 3349 m, 2958 m, 1464 m, 1369 m, 1169 m, 1115 m, 1096 m, 1073 m, 1020 m, 974 m; δ_H ($CDCl_3$, 300 MHz) 4.38 (1H, dd, *J* 9.6, 2.1), 3.79 (1H, dt, ^2J 9.6, *J* 6.6), 3.57 (1H, ddd, *J* 11.7, 8.9, 5.1), 3.51 (3H, s), 3.36 (1H, dt, ^2J 9.6, *J* 6.9), 3.18 (1H, dq, *J* 9.0, 6.5), 2.65 (1H, m incl. app. t, *J* 8.9), 2.36 (1H, br s), 2.11 (1H, ddd, ^2J 12.6, *J* 5.1, 2.1), 1.60–1.48 (3H, m), 1.35–1.17 (2H, m), 1.27 (3H, d, *J* 6.5), 0.85 (3H, t, *J* 6.2); δ_C ($CDCl_3$, 75 MHz) 99.5, 87.7, 71.2, 71.1, 66.9, 60.9, 37.7, 29.7, 19.2, 18.2, 13.9; HRMS (EI$^+$, M$^+$) Found: 218.15178, Calc. for $C_{11}H_{22}O_4$ 218.15181; *m*/*z* (EI): 217 (M – H$^+$, 1%), 145 (3), 126 (17), 111 (21), 74 (100); t_R (GC) 14.17 min.

4-(*O*-Methyl)-2,6-dideoxy-β-DL-arabino-hexapyranoside 27

Glycoside hydrolysis: Ace tube procedure. A solution of 4-(*O*-methyl) pyranoside **26** (70 mg, 0.32 mmol) in THF (3 mL) and HCl (3 mL of a 1 N solution) was heated in an Ace tube at 80 °C for 2 hours. The organic phase was separated and concentrated *in vacuo* and the residue set aside. The aqueous phase was neutralised with $NaHCO_3$ and freeze-dried. The solid residue, and the residue from the original organic phase were taken up in acetone (20 mL) and filtered. The filtrate was concentrated *in vacuo* and the residue purified on silica gel to afford 4-(*O*-methyl) pyranose **27** (27 mg, 52%) as a colourless oil, as a 63 : 37 mixture of α- and β-anomers; R_f (50% ethyl acetate in light petroleum) 0.06; mp 52 °C; ν_{max} (film)/cm^{-1}: 3385 m, 2935 m, 1724 m, 1242 m, 1093 s, 1023 s, 989 s, 976 s, 729 m; δ_H ($CDCl_3$, 300 MHz) α-anomer: 5.23 (1H, br. d, *J* 3.5), 3.96 (1H, ddd, *J* 11.9, 9.0, 5.0), 3.81 (1H, dq, *J* 9.6, 6.3), 3.52 (3H, s), 2.65 (1H, m incl. app. t, *J* 9.0), 2.08 (1H, ddd, ^2J 12.9, *J* 5.0, 0.6), 1.62 (1H, ddd, ^2J 12.9, *J* 11.9, 3.5), 1.22 (3H, d, *J* 6.3), δ_H ($CDCl_3$, 300 MHz) β-anomer: 4.75 (1H, dd, *J* 9.6, 1.8), 3.60 (1H, ddd, *J* 12.0, 9.0, 4.9), 3.52 (3H, s), 3.25 (1H, dq, *J* 9.3, 6.3), 2.66 (1H, m incl. app. t, *J* 9.0), 2.21 (1H, ddd, ^2J 12.3, *J* 4.9, 1.8), 1.57–1.44 (1H, m), 1.27 (3H, d, *J* 6.3); δ_C ($CDCl_3$, 75 MHz) α-anomer: 91.8, 88.2, 68.0, 67.1, 60.9, 37.6, 18.2, δ_C ($CDCl_3$, 75 MHz) β-anomer: 93.9, 87.3, 71.4, 70.8, 61.1, 40.2, 18.2; HRMS (EI$^+$, M$^+$) Found: 162.08922, Calc. for $C_7H_{14}O_4$ 162.08921; *m*/*z* (EI): 161 (M – H$^+$, 1%), 144 (4), 126 (18), 74 (100); t_R (GC) 11.56 min.

2-Butoxy-6-(fluoromethyl)-2,3-dihydro-4*H*-pyran-4-one 29

Was prepared as for **5** from 6-(fluoromethyl) dioxinone **8** (0.3 g, 1.86 mmol) in dry toluene (5 mL), and butyl vinyl ether (1.3 mL, 10 mmol) in dry toluene (15 mL). Work-up and isolation described for **5** and chromatography on silica gel (20% diethyl ether in hexane) afforded fluoromethyl pyranone **29** as an orange oil (0.205 g, 55%); R_f (20% ethyl acetate in light petroleum) 0.35; ν_{max} (film)/cm^{-1}: 2960 w, 1680 s, 1633 m, 1318 w, 1118 w, 1058 m, 971 s, 810 m; δ_H ($CDCl_3$, 300 MHz) 5.56 (1H, s), 5.40 (1H, dd, *J* 5.0 3.7), 4.80 (2H, m incl. app. d, $^2J_{H-F}$ 46.1), 3.75 (1H, part of an ABX_2 system, ^2J 9.4, 6.6), 3.52 (1H, part of an ABX_2 system, ^2J 9.4, 6.6), 2.72 (1H, part of an ABX system, ^2J 16.8 *J* 5.0), 2.60 (1H, part of an ABX system, ^2J 16.8 *J* 3.7), 1.55–1.45 (2H, m), 1.35–1.22 (2H, m), 0.84 (3H, t, *J* 7.2); δ_C ($CDCl_3$, 75 MHz) 190.5, 166.1 (d, $^2J_{C-F}$ 20.2), 103.9 (d, $^3J_{C-F}$ 4.5), 102.2, 79.4 (d, $^1J_{C-F}$ 174.0), 69.6, 42.3, 31.4, 19.1, 13.7; δ_F ($CDCl_3$, 282 MHz) –228.5 (t, $^2J_{F-H}$ 46.1); HRMS (EI$^+$, M$^+$) Found: 202.10052, Calc. for $C_{10}H_{15}FO_3$ 202.10052; *m*/*z* (EI): 203 (M + H$^+$, 2%), 202 (100), 128 (80), 169 (50), 113 (85); t_R (GC) 14.44 min.

(2*S,4*S**)-2-*n*-Butoxy-6-(fluoromethyl)-4-hydroxy-2,3-dihydro-2*H*-pyran-4-ol 30a, (2*R**,4*S**)-2-*n*-butoxy-6-(fluoromethyl)-4-hydroxy-2,3-dihydro-2*H*-pyran-4-ol 30b and 2-*n*-butoxy-6-(fluoromethyl)-tetrahydropyran-4-ol 31**

Prepared as for **14** (see procedure for **15**) from **29** (1.01 g, 4.9 mmol), sodium borohydride (0.38 g, 10 mmol), cerium(III) chloride heptahydrate (3.72 g, 10 mmol) and dry ether (60 mL) at −78 °C over 2 hours. Work-up and isolation as described for **14** and chromatography on silica gel (20% EtOAc in hexane) afforded *cis*-dihydropyranol **30a** (0.43 g, 44%) as a pale yellow oil; R_F (20% EtOAc in hexane) 0.37; δ_H (300 MHz, $CDCl_3$) 5.32–5.29 (1H, m), 5.25–5.24 (1H, m), 4.65 (1H, part of an ABX system, $^2J_{H-F}$ 47.7, ^2J 11.1), 4.61 (1H, part of an ABX system, $^2J_{H-F}$ 47.3, ^2J 11.1), 3.95 (1H, br. s), 3.70 (1H, dt, ^2J 9.3, J 6.3), 3.42 (1H, dt, ^2J 9.3, J 6.3), 3.16–2.96 (1H, br. s), 2.23–2.15 (1H, m incl. app. dq, ^2J 14.7, J 1.8), 1.92 (1 H, part of an ABMX system, ^2J 14.7, J 5.1, 2.7), 1.57–1.42 (2H, m), 1.28 (2H, m incl. app. sextet, J 7.2), 0.84 (3H, t, J 7.2); δ_C (75.5 MHz, $CDCl_3$) 146.3 (d, $^2J_{C-F}$ 15.8), 105.8 (d, $^3J_{C-F}$ 7.6), 97.3, 81.9 (d, $^1J_{C-F}$ 169.1), 68.6, 59.0, 34.3, 31.5, 19.3, 13.7; δ_F (282 MHz, $CDCl_3$) −218.6 (t, $^2J_{H-F}$ 47.4); ν_{max} (film) 2933 w, 1678 w, 1058 m, 1013 m, 991 m, 869 m; *m*/*z* (EI) 205 (M + H^+, 10%), 187 (19), 159 (20), 145 (25), 128 (46), 105 (88) 57 (100); [HRMS (EI, M + H^+) Found 205.12411. Calc. for $C_{10}H_{18}FO_3$ 205.12400]; t_R (GC) 13.40 min and *trans*-dihydropyranol **30b** (0.104 g, 10%); R_F (20% EtOAc in hexane) 0.2; δ_H (300 MHz, $CDCl_3$) 5.07 (1H, br. t, J 3.0), 4.99 (1H, dd, J 6.6, 2.7), 4.63 (2H, app. d, $^2J_{H-F}$ 47.4), 4.41–4.30 (1H, m), 3.81 (1H, dt, ^2J 9.6, J 6.6), 3.48 (1H, dt, ^2J 9.6, J 6.6), 2.00–1.81 (2H, m (including 1.86 (1H, app. ddd, ^2J 13.5, J 5.4, 2.7))), 1.80–1.62 (1H, br. s), 1.58–1.43 (2H, m), 1.40–1.23 (2H, m), 0.85 (3H, t, J 7.2); δ_C (75.5 MHz, $CDCl_3$) 148.8 (d, $^2J_{C-F}$ 17.4), 103.6 (d, $^3J_{C-F}$ 7.5), 98.1, 81.4 (d, $^1J_{C-F}$ 169.1), 69.1, 60.9, 36.2, 34.8, 19.2, 13.8; δ_F (282 MHz, $CDCl_3$) −219.8 (t, $^2J_{H-F}$ 47.4); ν_{max} (film) 3380 w, 2934 w, 1680 w, 1141 m, 1118 m, 1039 m, 1015 m, 979 m; *m*/*z* (EI) 205 (M + H^+, 8%), 187 (13), 153 (20), 57 (100); [HRMS (EI, [M + H]$^+$) Found 205.12412. Calc. for $C_{10}H_{18}FO_3$ 205.12400] and tetrahydropyranol **31** (0.054 g, 6%); R_F (20% EtOAc in hexane) 0.08; δ_H (300 MHz, $CDCl_3$) 4.40 (1H, part of an ABMX system, $^2J_{H-F}$ 47.7, ^2J 9.6, J 5.7), 4.36 (1H, dd, J 9.0, J 2.1), 4.35 (1H, part of an ABMX system, $^2J_{H-F}$ 47.1, ^2J 9.6, J 3.9), 3.89–3.74 (2H, m), 3.65–3.49 (1H, m), 3.40 (1H, dt, J 9.5, J 6.9), 2.23–2.06 (2H, m), 1.89–1.79 (1H, m), 1.57–1.43 (2H, m), 1.40–1.14 (4H, m), 0.85 (3H, t, J 7.5); δ_C (75.5 MHz, $CDCl_3$) 100.2, 84.8 ($^1J_{C-F}$ 172.1), 70.7 ($^2J_{C-F}$ 20.4), 69.2, 66.5, 40.7, 35.4 ($^3J_{C-F}$ 5.3), 31.7, 19.2, 13.8; δ_F (282 MHz, $CDCl_3$) −227.1 (td, $^2J_{H-F}$ 47.4, J_{H-F} 18.0); ν_{max} (film) 3404 w, 2958 w, 2934 w, 1374 w, 1073 m, 1041 m, 1014 m, 990 m, 946 w; t_R 13.8 min (100%); *m*/*z* (EI) 206 (M^+, 10%), 205 (15), 173 (25), 149 (30), 133 (100), 103 (70, $C_5H_8FO^+$) (see text), 57 (20); [HRMS (EI, [M + H]$^+$) Found 206.13183. Calc. for $C_{10}H_{19}FO_3$ 206.13182]; t_R (GC) 13.84 min.

***n*-Butyl-2,6-dideoxy-6-fluoro-β-DL-arabino-hexapyranoside 32a**

Pyranol **30a** (100 mg, 0.49 mmol) underwent hydroboration–oxidation–hydrolysis as for **14** in THF (10 mL) with $BH_3{\cdot}SMe_2$ (0.5 mL of a 2.0 M solution in THF, 1.0 mmol) and $Na_2BO_3{\cdot}H_2O$ (308 mg, 2.0 mmol). Work-up and isolation as described for **15** and chromatography on silica gel afforded pyranoside **32a** as colourless needles (40 mg, 37%, 98% by GC); mp 78–79 °C; R_f (50% ethyl acetate in light petroleum) 0.15; ν_{max} (film)/cm^{-1} 3373 w, 2958 w, 1458 w, 1422 w, 1378 m, 1160 m, 1066 s, 1008 s, 974 m, 889 m, 864 m; δ_H ($CDCl_3$, 300 MHz) 4.72–4.50 (2H, m incl. app. d, $^2J_{H-F}$ 47.2), 4.45 (1H, dd, J 9.6, 1.8), 3.83 (1H, dt, ^2J 9.3, J 6.6), 3.64–3.53 (1H, m), 3.45–3.15 (5H, m (including 3.25 (2H, br. s))), 2.14 (1H, ddd, ^2J 12.6, J 4.8, 1.8), 1.63–1.45 (3H, m), 1.37–1.23 (2H, m), 0.85 (3H, t, J 7.2); δ_C (75.5 MHz, $CDCl_3$) 100.0, 82.6 (d, $^1J_{C-F}$ 171.0), 74.6 (d, $^2J_{C-F}$ 18.1), 71.8, 71.3 (d, $^3J_{C-F}$ 6.0), 69.3, 38.6, 31.6, 19.2, 13.8; δ_F ($CDCl_3$, 282 MHz) −233.5 (td, $^2J_{F-H}$ 47.2, $^3J_{F-H}$ 23.8); HRMS (EI$^+$, M$^+$) Found: 221.11899, Calc. for $C_{10}H_{18}FO_4$ 221.11891; *m*/*z* (EI): 221 (M − H^+, 3%), 159 (28), 149 (54), 101 (62), 82 (51); t_R (GC) 16.3 min.

2,6-Dideoxy-6-fluoro-β-DL-arabino-hexapyranoside (6-fluoro-DL-olivose) 6

Was prepared as for **1** from a solution of **32a** (56 mg, 0.25 mmol) in D_2O (1 mL), with DCl (0.1 mL of a 9.8 M solution) heated at 60 °C for 30 minutes. Work-up and isolation as described for **1** afforded **6** (40 mg, 97%) as a pale yellow solid, as a 77 : 23 mixture of α- and β-anomers; R_f (20% methanol in DCM) 0.42; mp 107–109 °C, (lit. 102–104 °C); ν_{max} (film)/cm^{-1}: 3342 s, 2936 w, 1116 m, 1058 s, 1014 s, 658 m; δ_H (acetone d_6, 400 MHz) α-anomer: 5.29 (1H, br. s), 5.25 (1H, br. d, J 2.9), 4.72–4.46 (2H, m), 4.24 (1H, br. s), 3.99–3.89 (1H, m), 3.88 (1H, dddd, ^2J 27.4, J 10.0, 4.5, 1.7), 3.30–3.22 (1H, m), 2.05–1.98 (1H, m), 1.61–1.50 (1H, m), δ_H (acetone d_6, 400 MHz) β-anomer: 5.59 (1H, br. d, J 5.5), 4.81 (1H, br. s), 4.72–4.46 (2H, m), 4.27 (1H, br. s), 4.12 (1H, br. s), 3.59 (1H, br. s), 3.37 (1H, dddd, ^2J 25.1, J 9.7, 5.2, 1.7), 3.25–3.15 (1H, m), 2.18–2.08 (1H, m), 1.53–1.39 (1H, m); δ_C (acetone d_6, 75 MHz) α-anomer: 92.4, 83.7 (d, $^1J_{C-F}$ 169.6), 72.4 (d, $^3J_{C-F}$ 6.7), 72.0 (d, $^2J_{C-F}$ 18.0), 69.3, 39.4, δ_C (acetone d_6, 75 MHz) β-anomer: 95.1, 83.6 (d, $^1J_{C-F}$ 169.6), 76.0 (d, $^2J_{C-F}$ 16.2), 72.4, 71.9 (d, $^3J_{C-F}$ 7.0), 41.8; δ_F (acetone d_6, 282 MHz) α-anomer: −234.2 (td, $^2J_{F-H}$ 47.9, $^3J_{F-H}$ 27.4), δ_F (acetone d_6, 282 MHz) β-anomer: −233.2 (td, $^2J_{F-H}$ 47.9, $^3J_{F-H}$ 25.1); HRMS (EI$^+$, M$^+$) Found: 166.06409. Calc. for $C_6H_{11}FO_4$ 166.06414; *m*/*z* (EI): 167 (M^+, 4%), 149 (28), 57 (100); t_R (GC) 12.94 min. The data were in agreement with those reported by O'Hagan and Nieschalk,[10] apart from the mp (lit. 102–104 °C). However, O'Hagan and Nieschalk prepared enantiomerically enriched material.

2-(1-Butoxy)-6,6-difluoro-6-methyl-2,3-dihydro-4*H*-pyran-4-one 41

Was prepared as for **5** from 6-(difluoromethyl) dioxinone **11** (0.158 g, 0.89 mmol) in dry toluene (3 mL) and butyl vinyl ether (0.58 mL, 4.44 mmol) in dry toluene (15 mL). The work-up and isolation as described for **5** followed by chromatography on silica gel (20% ethyl acetate in hexane) afforded 6-(difluoromethyl) pyranone **41** as a pale yellow oil (62 mg, 32%); R_f (20% ethyl acetate in light petroleum) 0.37; δ_H ($CDCl_3$, 300 MHz) 6.00 (1H, t, $^2J_{H-F}$ 53.9), 5.71 (1H, s), 5.50 (1H, t, J 3.8), 3.77 (1H, dt, ^2J 9.4, 6.5), 3.53 (1H, dt, ^2J 9.4, 6.5), 2.77 (1H, part of an ABMX system, ^2J 16.8 J 3.8), 2.63 (1H, part of an ABMX system, ^2J 16.8 J 3.8 ^4J 0.4), 1.55–1.45 (2 H, m), 1.22–1.15 (2H, m), 0.83 (3H, t, J 7.2); δ_C ($CDCl_3$, 75 MHz) 190.3, 159.2 (t, $^2J_{C-F}$ 24.7), 108.7 (t, $^1J_{C-F}$ 241.5), 104.1 (t, $^3J_{C-F}$ 4.5), 101.5, 68.7, 41.4, 30.3, 18.1, 12.7; δ_F ($CDCl_3$, 282 MHz) −124.9 (1F, part of an ABX system, $^2J_{F-F}$ 308.0 $^2J_{F-H}$ 53.9), −125.7

(1F, part of an ABX system, $^2J_{F-F}$ 308.0 $^2J_{F-H}$ 53.9); HRMS (EI$^+$, M$^+$) Found: 220.09111. Calc. for $C_{10}H_{14}F_2O_3$ 220.09110; *m/z* (EI): 220 (M$^+$, 4%), 200 (2), 85 (100); t_R (GC) 13.07 min.

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Notes and references

1 M. Q. Zhou and G. A. O'Doherty, *Org. Lett.*, 2008, **10**, 2283–2286.
2 F. E. McDonald and K. S. Reddy, *J. Organomet. Chem.*, 2001, **617**, 444–452.
3 W. R. Roush and R. J. Neitz, *J. Org. Chem.*, 2004, **69**, 4906–4912.
4 R. S. Coleman and J. R. Fraser, *J. Org. Chem.*, 1993, **58**, 385–392.
5 A. Kirschning, M. Jesberger and K. U. Schoning, *Synthesis*, 2001, 507–540.
6 For a recent review, see: R. M. De Lederkremer and C. Marino, *Adv. Carbohydr. Chem. Biochem.*, 2008, **61**, 143–216.
7 T. Tsuchiya, *Adv. Carbohydr. Chem. Biochem.*, 1990, **48**, 91–277.
8 K. Dax, M. Albert, J. Ortner and B. J. Paul, *Carbohydr. Res.*, 2000, **327**, 47–86.
9 K. Dax, M. Albert, J. Ortner and B. J. Paul, *Curr. Org. Chem.*, 1999, **3**, 287–307.
10 J. Nieschalk and D. O'Hagan, *J. Fluorine Chem.*, 1998, **91**, 159–163.
11 J. Junnemann, I. Lundt and J. Thiem, *Acta Chem., Scand.*, 1994, **48**, 265–268.
12 D. Crich and O. Vinogradova, *J. Am. Chem. Soc.*, 2007, **129**, 11756–11765 describes syntheses of various 6-deoxy 6-fluorinated sugars and their glycosylation reactions.
13 For syntheses of related *C*-arylglycosides, see: N. Q. Vu, S. Leconte, E. Brown, D. Grée, R. Grée and G. Dujardin, *J. Org. Chem.*, 2005, **70**, 2641–2650.
14 J. A. Ross, R. P. Seiders and D. M. Lemal, *J. Am. Chem. Soc.*, 1976, **98**, 4325–4327.
15 R. J. Clemens and J. S. Witzeman, *J. Am. Chem. Soc.*, 1989, **111**, 2186–2193 shows that acetoacetylations carried *via* dioxinone fragmentation have oxoketene formation as the rate determining step.
16 For a recent application of oxoketene methodology, see: I. Navarro, J. F. Basset, S. Hebbe, S. M. Major, T. Werner, C. Howsham, J. Brackow and A. G. M. Barrett, *J. Am. Chem. Soc.*, 2008, **130**, 10293–10298.
17 R. C. F. Jones and M. Tankard, *J. Chem. Soc., Perkin Trans. 1*, 1991, 240–241.
18 For a review of related electrophilic fluorinations, see: S. D. Taylor, C. C. Kotoris and G. Hum, *Tetrahedron*, 1999, **55**, 12431–12477.
19 T. Nakano, M. Makino, Y. Morizawa and Y. Matsumura, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1019–1021.
20 (*a*) T. Iwaoka, T. Murohashi, M. Sato and C. Kaneko, *Synthesis*, 1992, 977–981; (*b*) For a route to the trifluorinated dioxinones, see: J. Boivin, L. Elkaim and S. Z. Zard, *Tetrahedron*, 1995, **51**, 2585–2592.
21 J. L. Luche, *J. Am. Chem. Soc.*, 1978, **100**, 2226–2227.
22 O'Doherty has shown that dichloromethane can be used as an effective organic co-solvent for Luche reductions; see: M. H. Haukaas and G. A. O'Doherty, *Org. Lett.*, 2001, **3**, 401–404.
23 For a recent application of this methodology, see: J. N. Abrams, R. S. Babu, H. B. Guo, D. Le, J. Le, J. M. Osbourn and G. A. O'Doherty, *J. Org. Chem.*, 2008, **73**, 1935–1940.
24 W. R. Roush and R. J. Brown, *J. Org. Chem.*, 1983, **48**, 5093–5101.
25 M. Vogtherr and T. Peters, *J. Am. Chem. Soc.*, 2000, **122**, 6093–6099.
26 C. Zhou and D. M. Birney, *J. Am. Chem. Soc.*, 2002, **124**, 5231–5241.
27 W. Shumway, S. Ham, J. Moer, B. R. Whittlesey and D. M. Birney, *J. Org. Chem.*, 2000, **65**, 7731–7739.
28 E. M. Cabaleiro-Lago, J. Rodriguez-Otero, I. Gonzalez-Lopez, A. Pena-Gallego and J. M. Hermida-Ramon, *J. Phys. Chem. A*, 2005, **109**, 5636–5644.
29 Spartan′06, Wavefunction Inc., Irvine, CA, USA, 2006.
30 Y. Shao, L. F. Molnar, Y. Jung, J. Kussmann, C. Ochsenfeld, S. T. Brown, A. T. B. Gilbert, L. V. Slipchenko, S. V. Levchenko, D. P. O'Neill, R. A. DiStasio, R. C. Lochan, T. Wang, G. J. O. Beran, N. A. Besley, J. M. Herbert, C. Y. Lin, T. Van Voorhis, S. H. Chien, A. Sodt, R. P. Steele, V. A. Rassolov, P. E. Maslen, P. P. Korambath, R. D. Adamson, B. Austin, J. Baker, E. F. C. Byrd, H. Dachsel, R. J. Doerksen, A. Dreuw, B. D. Dunietz, A. D. Dutoi, T. R. Furlani, S. R. Gwaltney, A. Heyden, S. Hirata, C. P. Hsu, G. Kedziora, R. Z. Khalliulin, P. Klunzinger, A. M. Lee, M. S. Lee, W. Liang, I. Lotan, N. Nair, B. Peters, E. I. Proynov, P. A. Pieniazek, Y. M. Rhee, J. Ritchie, E. Rosta, C. D. Sherrill, A. C. Simmonett, J. E. Subotnik, H. L. Woodcock, W. Zhang, A. T. Bell, A. K. Chakraborty, D. M. Chipman, F. J. Keil, A. Warshel, W. J. Hehre, H. F. Schaefer, J. Kong, A. I. Krylov, P. M. W. Gill and M. Head-Gordon, *Phys. Chem. Chem. Phys.*, 2006, **8**, 3172–3191.
31 C. T. Lee, W. T. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785–789.
32 A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648–5652.
33 S. W. E. Eisenberg, M. J. Kurth and W. H. Fink, *J. Org. Chem.*, 1995, **60**, 3736–3742.
34 C. Møller and M. S. Plesset, *Phys. Rev.*, 1934, **46**, 5.
35 A. Pena-Gallego, J. Rodriguez-Otero and E. M. Cabaleiro-Lago, *Tetrahedron*, 2007, **63**, 11617–11621.
36 A. Pena-Gallego, J. Rodriguez-Otero and E. M. Cabaleiro-Lago, *Tetrahedron*, 2007, **63**, 4937–4943.

