Cycloaddition and one-carbon homologation studies in the synthesis of advanced iridoid precursors†

Anne T. Stevens,[a] Mino R. Caira,[a] James R. Bull[a] and Kelly Chibale*[a,b]

Received 5th February 2009, Accepted 4th June 2009
First published as an Advance Article on the web 8th July 2009
DOI: 10.1039/b902452b

A Diels–Alder cycloaddition approach to the sweroside aglycone intermediate of iridoids was explored using silylated butenolides and levoglucosenone as dienophiles under both Lewis acid and thermal conditions. Results of this study reveal no evidence that using less sterically demanding derivatives compromise the diastereofacial selectivity of the cycloaddition using silylated butenolides. Further chemistry performed on cycloadducts concentrated on the identification and management of methodologies suitable for its conversion into sweroside aglycone. During the course of these studies, a dehydrative cyclisation onto a preformed tetrahydrofuran ring to a bis-tetrahydrofuranoid moiety was unravelled. In addition studies on levoglucosenone-derived cycloadducts provide extensive insight into the conformational behaviour and reactivity. Further, the X-ray crystal structure of an alcohol intermediate from one-carbon homologation studies provided the first structural evidence confirming the diastereoselectivity of the cycloaddition procedure.

Introduction

Chiral α,β-butenolides or 2–5(*H*)-furanones have frequently been utilised as chiral synthons in the enantioselective synthesis of natural products. Examples include the synthesis of an aflatoxin[1] and the preparation of the ABC ring of paclitaxel (Taxol™).[2] Although the use of acrylic acid derivatives as dienophiles in enantioselective Diels–Alder cycloadditions has been extensively explored,[3] that of butenolides (as cyclic acrylate equivalents) is limited. We reasoned that the high degree of stereoselectivity imparted by Diels–Alder methodology combined with the high density of functionality associated with butenolides make this an attractive option for the synthesis of sweroside aglycone **1** (Fig. 1) as part of our continuing efforts in iridoid synthesis.[4,5] For this synthesis, the cycloadduct obtained from the reaction of 4-*tert*-butyldiphenylsilyloxymethyl substituted butenolide **2** with butadiene was identified as a suitable chiral intermediate.

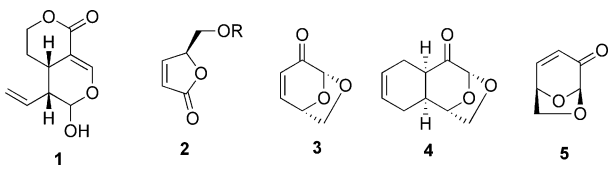
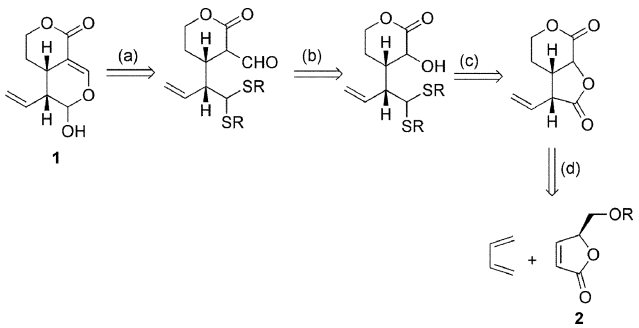


Fig. 1 Chemical structures of sweroside aglycone, butenolide, levoglucosenone *ent*-levoglucosenone and cycloadduct.

Key structures identified during the retrosynthetic analysis are depicted in Scheme 1. Deprotection of the thioacetal with concomitant ring closure to form the dihydropyran moiety [step (a)] would deliver the target, sweroside aglycone **1**. The one-carbon homologation represented in step (b) is an overall conversion of hydroxyl functionality into a formyl group. Ring opening of the butenolide residue, by reducing the lactone to a lactol, followed by aldehyde trapping to give the thioacetal-alcohol intermediate is depicted in step (c). The cycloaddition reaction of a silylated butenolide followed by a series of functional group interconversions involving oxidation and chemoselective lactonization is depicted in step (d).



Scheme 1 Retrosynthetic steps identified for the synthesis of **1** from **2**.

Many enantioselective syntheses of the hydroxymethyl butenolides, from which **2** can be accessed in a simple silylation step, are known. These are based on (i) transformation of intermediates from the chiral pool, and (ii) asymmetric transformations on achiral starting materials. From the chiral pool, the desired (4*S*)-enantiomer has been synthesised from (*S*)-glutamic acid,[6] D-ribonolactone,[7] D-mannitol[8] and serine-derived isopropylidineglycelaldehyde.[9] The latter procedure was selected for this work because it is well described and the starting material is inexpensive.

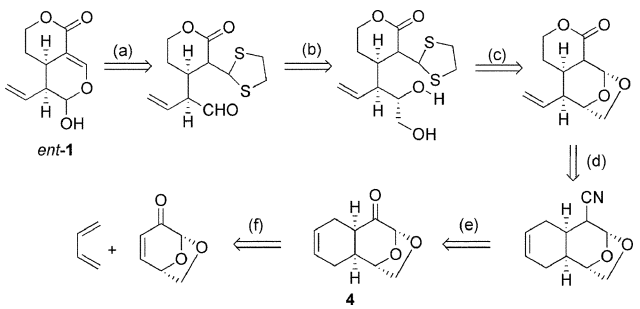
[a]*Department of Chemistry, University of Cape Town, Rondebosch, 7701, South Africa. E-mail: Kelly.Chibale@uct.ac.za; Fax: 27 21 689 7499; Tel: 27 21 650 2553*
[b]*Institute of Infectious Disease and Molecular Medicine, University of Cape Town Medical School, Cape Town, South Africa. E-mail: Kelly.Chibale@uct.ac.za; Fax: 27 21 689 7499; Tel: 27 21 650 2553*

† Electronic supplementary information (ESI) available: Experimental section, spectroscopic and crystallographic data. CCDC reference number 731873. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b902452b

The Diels–Alder adduct arising from the reaction between **2** and butadiene was first reported by Mann *et al.*[8] who performed a Lewis-acid catalysed cycloaddition to give the corresponding cycloadduct in 76% yield. The product was then used in the enantioselective synthesis of a prostaglandin analogue.[10,11] The Mann report prompted a publication by Ortuño *et al.*[12] in which thermal cycloadditions with non-silylated analogues of **2** are reported. Further work by this group includes studies on the regio- and *endo*/*exo*-selectivities of the reactions of these butenolides with isoprene and cyclopentadiene.[13] The latter diene results in polyfunctional norbornene-type derivatives that have been used in synthesis of several biologically active compounds.[13]

On the other hand levoglucosenone **3** has been used as a chiral template in natural product synthesis and its chemistry has been extensively explored and documented.[14] More recently levoglucosenone has been employed in the synthesis of chiral cyclopropanecarboxylic acids.[15,16] For our work we selected levoglucosenone from the chiral pool as a useful dienophile for the synthesis at hand because the cycloadduct **4**, obtained from the Diels–Alder reaction with butadiene, is highly functionalised. If the internal acetal moiety is unravelled, the conversion of **4** into the enantiomer of the desired hydrocarbon skeleton can be envisaged. Levoglucosenone could thus provide access to the *ent*-series of secoiridoid intermediates, thus expanding the scope for biological testing, whilst also providing a model for the synthesis of the natural secoiridoid series, starting from *ent*-levoglucosenone **5** which is available synthetically.

A retrosynthetic analysis of the proposed model synthesis using levoglucosenone is illustrated in Scheme 2. Deprotection of the thioacetal in step (a) would provide the enolic participant for the formation of the dihydropyran moiety in *ent*-sweroside aglycone, whilst the electrophilic carbonyl participant would be expected to arise from oxidative cleavage of the vicinal diol as shown in step (b). Access to the glycol moiety of levoglucosenone derivatives by trapping of the carbonyl group as a cyclic thioacetal [step (c)] has been described.[17] In step (d) oxidative cleavage of the cyclohexenyl olefin followed by reduction of the termini to give hydroxyethyl groups was envisaged. Hydrolysis of the nitrile moiety to give a carboxyl group, followed by chemoselective δ-lactone formation would allow selective functionalisation of the remaining hydroxyl group to give the required terminal olefin. Step (e) represents a one-carbon homologation at C-8 on **4**. The presence of carbonyl functionality provides wide scope for one-carbon homologation. The scope for direct carboxylation is limited so the introduction of a nitrile group, from which the carboxyl functionality could be revealed by acid hydrolysis at an appropriate stage, was planned.



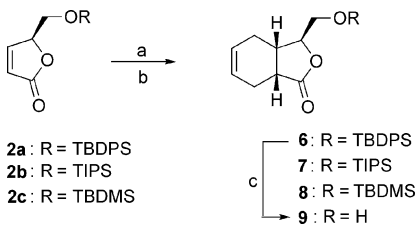
Scheme 2 Retrosynthetic plan for the synthesis of *ent*-**1** from the known cycloadduct **4**.

Results and discussion

Cycloaddition of silylated butenolides

Of the hydroxymethyl protecting groups utilised in the cycloaddition reactions cited above, a silylated version was selected as a starting point for this synthesis. The facility with which chemoselective desilylation can be achieved using the fluoride ion under conditions that are compatible with most functional groups was an important consideration. In order to increase the scope for applying chemoselective differentiation of similar functionality should this be required later, an investigation of the Diels–Alder reaction of butadiene with butenolides bearing alternative silyl groups was planned. The more robust examples of commonly used silyl protecting groups, triisopropylsilyl (TIPS) and *tert*-butyldimethylsilyl (TBDMS) were thus included with *tert*-butyldiphenylsilyl (TBDPS) in the investigation.

The hydroxy butenolide precursor was routinely prepared on a 10 g scale from D-mannitol[8,9] Silylation under standard conditions afforded the butenolides **6**, **7** and **8**. Earlier attempts to reproduce the catalytic efficiency of the aluminium trichloride catalysed cycloaddition between **2** and butadiene as described by Mann[8] provided erratic results. An alternative aluminium-based Lewis-acid catalyst, ethylaluminium dichloride was used in the reaction with **2a** to deliver **4**, Scheme 3. The successful outcome of this reaction was reproducible, but was however followed by less encouraging results with **2a** and **2b**.



Scheme 3 *Reagents and conditions*: (a) butadiene, $EtAlCl_2$ (0.3 mol equiv.), CH_2Cl_2, 55 °C, 7 d, 70% (**6**), 41% (**7**), 14% (**8**)/15% (**9**); (b) butadiene, 210 °C, 63% (**6**), 68% (**7**), 65% (**8**); (c) TBAF–HOAc, THF, 10 °C, 78% or HF–MeCN, MeCN, 25 °C, 75%.

The use of TBDPS as a protecting group in the original work[8] was based on the desire to maximise facial differentiation on the dienophile during the cycloaddition. Although the yields of cycloadducts **7** and **8** obtained in our work are poor, they were the only diastereomers detected. This study has thus given no evidence that using less sterically demanding derivatives compromised the diastereofacial selectivity of the cycloaddition. Although the yield of **6** was as expected, the lability of the TIPS and TBDMS ethers under these conditions was confirmed by the poor recoveries of **7** and **8** as well as the presence of a spirolactone and deprotected cycloadduct **9**. The spirolactone has been isolated previously from the thermal cycloaddition of the hydroxybutenolide precursor and its acetate to butadiene.[12]

The complexity of the product mixtures containing **7** and **8** render this option unattractive for the preparation of these cycloadducts as starting materials under Lewis acid conditions.

The thermal cycloaddition of these butenolides with butadiene was thus investigated. These reactions provided the desired cycloadducts exclusively and no decomposition products were detected. However, isolation of the products was difficult due to extensive butadiene polymerisation under thermal conditions and careful chromatography using large proportions of silica gel was required in order to isolate clean cycloadducts. The addition of hydroquinone, as described by Ortuño[12] did not inhibit polymerisation. This is probably attributable to the higher dilutions of the butenolide in butadiene used in that study. This dilution was considered excessive for the preparative scale conditions sought. Owing to the problems encountered during the isolation of products and the safety problems associated with the use of butadiene under thermal conditions, this approach was not considered suitable for the production of multigram quantities of the cycloadducts. The modified Mann procedure was thus used to react 5 g quantities of the TBDPS protected parent butenolide and further work towards the synthesis of sweroside aglycone **1** was made on the cycloadduct **4**.

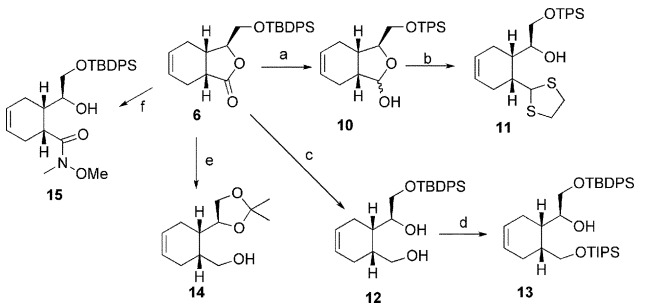
Treatment of **6** with tetrabutylammonium fluoride (TBAF) at room temperature gave an inseparable 85 : 15 (by NMR) mixture of **9**, and an unidentified by-product. Based on the duplication of signals in the NMR spectra of the mixture, the by-product was assumed to be the *trans* diastereomer of **9**, which had resulted from epimerisation α to the carbonyl group, *via* enolisation under the basic reaction conditions. Although this observation was unexpected, literature precedent for the abstraction of α-acidic protons in this reaction medium does exist.[18]

Reaction at 0 and −15 °C gave a similar diastereomeric mixture. Maintaining the temperature of the reaction mixture at −20 to −30 °C provided a single diastereomer, but the reaction was slow. In order to temper the basicity of TBAF, buffering of the reaction medium with acetic acid has been reported.[19] The reaction of **6** with equimolar quantities of TBAF and acetic acid at 10 °C provided a single diastereomer, but **9** could only be recovered in 78% yield. Hydrogen fluoride was also used as a fluoride source for deprotection, although large excesses of HF were required in order to achieve complete reaction. After 20 min at 40 °C, 55% of the desired product was recovered. This was improved to 75% by decreasing the reaction temperature to 25 °C for 24 h. At 0 °C, no reaction was observed.

The relative ease with which C-7a was deprotonated during deprotection of **6** indicated that reduction of the lactone moiety was required prior to deprotection. The formyl level of oxidation was required in any event, so **6** was reduced with DIBAH at low temperature to the diastereomeric lactol mixture **10**, Scheme 4.

A radical deoxygenation process on **11** was envisaged, which after appropriate transformation would allow an enolate-mediated one-carbon homologation step. All attempts to produce a radical deoxygenation precursor (xanthate ester, thiocarbonyl imidazole or phenoxythiocarbonyl)[20] failed, possibly due to limited reagent access to the hydroxyl which was α to a tertiary carbon and β to the bulky TBDPS moiety.

The exhaustive reduction of **6** to **12** with $LiBH_4$[8] was followed by the selective protection of the primary hydroxyl group as a triisopropyl silyl ether **13**. In this instance, tosylation of the secondary hydroxyl group, followed by an S_N2 substitution with CN^-,[21] to give the corresponding nitrile was planned. The nitrile, after hydrolysis at an appropriate point, would provide the desired carboxyl moiety in sweroside aglycone. Once again, no reaction occurred at the free hydroxyl group under standard tosylation conditions.



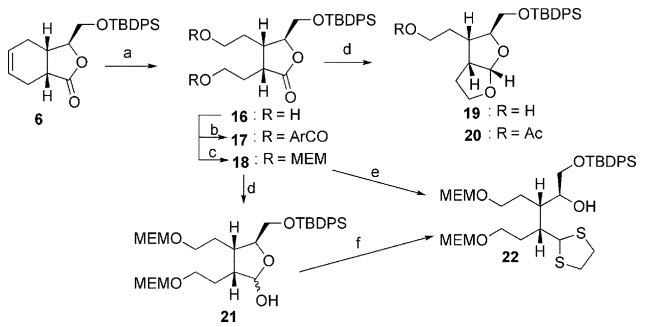
Scheme 4 *Reagents and conditions*: (a) DIBAH, toluene, −78 °C, 91%; (b) ethanedithiol, $TiCl_4$, CH_2Cl_2, −78 °C, 80%; (c) $LiBH_4$, THF, RT, 85 h, 63%; (d) TIPSCl, imidazole, MeCN, 96%; (e) (i) LAH, Et_2O, reflux, 1 h, (ii) acetone, *p*-TsOH, $CuSO_4$ (anhydrous), reflux, 28% (over two steps); (f) MeONHMe·HCl, Me_2AlCl, CH_2Cl_2.

When the reduction of **6** to **12** was attempted with $NaBH_4$, DIBAH, or LAH, silyl deprotection accompanied reduction. An excess of LAH in refluxing diethyl ether for 60 min provided complete conversion into a single product that was assumed to be the triol. Because the extraction and purification of the triol were hampered by its polarity, the 1,2-diol moiety in the crude reduction product was subjected to acetonide formation conditions[22] to give **14**, Scheme 4. However, the yield of this compound was too low to be useful in a total synthesis and, despite numerous attempts using different work-up and extraction procedures for the reduction, it could not be optimised.

Although the reduction–aldehyde trapping sequence applied above was successful, its timing in the synthetic route is problematic owing to the susceptibility of sulfur to oxidation under the conditions for oxidative cleavage of the olefin. Another possibility examined was the opening of the lactone to the Weinreb amide **15**. Chemoselective reduction of the Weinreb amide to an aldehyde (as was targeted) in an excess of DIBAH is well known.[23] Treatment of **6** with Weinreb's salt and dimethylaluminium chloride gave complete reaction to a single product. The amide appeared to relactonise during work up, chromatography, and in $CDCl_3$, and could not be isolated and characterised, Scheme 4.

Ozonolysis of **6** followed by a reductive work up with $NaBH_4$ proceeded efficiently to give diol **16**. The analytical and spectral data gathered could not preclude the possibility of formation of the alternative γ-lactone or the δ-lactone. The diol **16** was thus bis-esterified with 3,5-dinitrobenzoyl chloride in pyridine to give **17**, Scheme 5.

With the oxidative cleavage product in hand, the reduction–aldehyde trapping sequence was attempted. The unprotected diol **16** in toluene at −78 °C was treated with 3 equivalents of DIBAH. The product **19** was extremely polar and full characterisation was hampered by a minor co-eluting impurity. Acetylation of product **19** provided internal acetal **20**. The formation of **19** was rationalised as a dehydration of the reduced product under the acidic work up conditions. This bis-tetrahydrofuranoid moiety is present in a number of natural products, in particular the aflatoxins. Although dehydrative cyclisation onto a preformed tetrahydrofuran ring has been used in the total synthesis of aflatoxins,[24,25] this result produces a useful synthon, easily derived



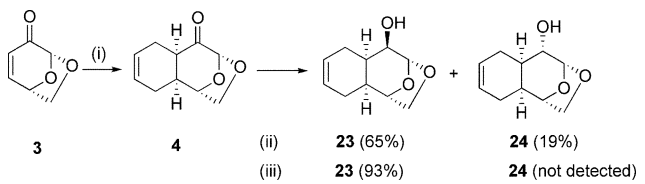
Scheme 5 *Reagents and conditions*: (a) O_3, MeOH, −78 °C, then $NaBH_4$, RT, 88%; (b) ArC(O)Cl, pyr, 80%; (c) MEMCl, iPr_2NEt, CH_2Cl_2, 92%; (d) DIBAH, toluene, −78 °C, (ii) Ac_2O, DMAP, pyr; (e) DIBAH, toluene, −78 °C, 93%; (f) ethanedithiol, $TiCl_4$, CH_2Cl_2, −84 °C, 32%.

from the chiral pool for the enantioselective synthesis of similar systems. This route was deemed unsuitable for the synthesis at hand and was accordingly abandoned. Nevertheless it proved useful (albeit serendipitously) for unravelling a bis-tetrahydrofuran moiety

In order to prevent the observed dehydration, the free hydroxyl groups in **16** were protected as methoxyethoxymethyl (MEM) ethers to give **18**. The DIBAH reduction of **18** produced a diastereomeric mixture of the hemiacetals **21**. Treatment of **21** with ethanedithiol and $TiCl_4$ gave a very poor yield of the dithiolane **22**, Scheme 5. The MEM protection was selected because it would allow chemoselective TBAF-mediated deprotection of the TBDPS moiety in a more advanced intermediate although the labile nature of MEM acetals in Lewis acidic conditions was recognised.[26]

Model studies using levoglucosenone

Printed newspaper was used as the source of cellulose for producing levoglucosenone.[3] The paper was treated as described in a literature procedure.[27] The recovery of **3** was variable and averaged 0.8%. Following literature procedures,[28] the thermal cycloaddition of levoglucosenone was performed at 160 °C for 3 h to give after chromatography a product (72%) that was assigned as the expected cycloadduct **4** (Scheme 6). To prepare intermediates for possible 8-homologation studies, hydride-mediated reduction of **4** was attempted. The reaction with sodium borohydride afforded the diastereomeric alcohols **23** and **24** in 65 and 19% yields respectively. A more sterically demanding reducing agent was used in an attempt to improve the diastereoselectivity of the reduction. Reduction with L-Selectride in THF at −78 °C afforded only **23** in 93% yield.



Scheme 6 *Reagents and conditions*: (i) butadiene, 160 °C; (ii) butadiene, $EtAlCl_2$ (0.3 mol equiv.), CH_2Cl_2, 0 °C; (ii) $NaBH_4$, MeOH, 0 °C, (iii) L-Selectride, THF, −78 °C.

The rationalisation of the stereochemical outcome of this reaction requires insight into the conformation of the starting material **4**. It has been shown that the oxacyclohexanone ring adopts a chair-like conformation. Ignoring pendant functionality, stereoelectronic control analogous to that demonstrated in cyclohexanone could be expected, where the hydride is delivered from the *exo* face leading to an equatorial hydroxy substituent on the *endo* face of the oxacyclohexanoid ring,[29] Fig. 2.

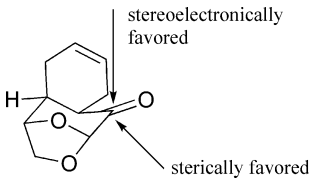


Fig. 2 Hydride approach to the 8-keto group of **4**.

On this basis, **24** should have been the favoured alcohol. However, the presence of the cyclohexenoid ring introduces a steric factor to this reduction. The hydride was preferentially delivered from the α-face, which is less sterically hindered, thus resulting in the axially substituted hydroxyl group on the β-face that was observed in the major product, **23**. This argument is supported by the fact that the stereoselectivity improved when hydride delivery took place from the more sterically demanding reducing agent L-Selectride.

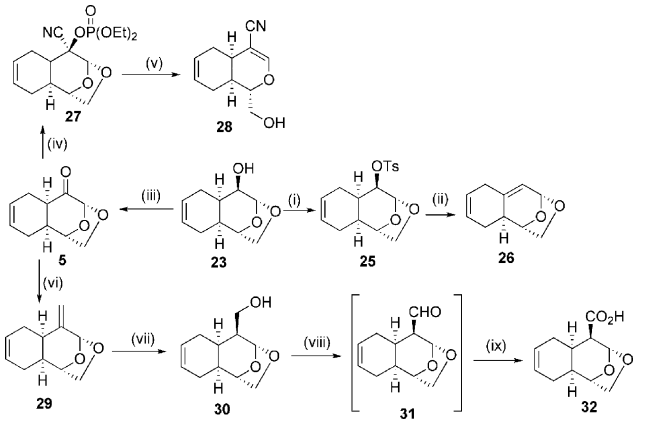
One-carbon homologation

Although the carbonyl functionality at C-8 in **4** provided a functional handle for one-carbon homologation, a suitable method for the direct conversion of the carbonyl group into a carboxylic acid was not obvious. However, the one-step conversion of ketones into nitriles in a reductive cyanation reaction with tosylmethyl isocyanide (TosMIC) is known and was envisaged to lead to the corresponding carboxylic acid on pyrolysis.[30,31]

The conditions described[32] were applied to the reductive cyanation of **4**, and produced a mixture so complex that neither starting material nor any single product could be isolated from it. A similar scenario was encountered when the traditional reaction conditions of van Leusen[30,33] were used. The reaction outcome could not be improved despite extensive efforts using varying rates of reagent addition and reaction temperatures.

In the light of the failure of the reductive cyanation reaction, displacement chemistry was considered for the introduction of the nitrile group. The alcohol **23** was available in high yield from the stereoselective reduction of **4**. Although the hydroxyl moiety on the oxacyclohexane in **23** ring was axial, which is the preferred orientation for leaving groups in S_N2 reactions, it was recognised that the approach trajectory of the nucleophile would be *syn* to the oxymethylene bridge and steric hindrance could compromise the substitution reactivity. Several procedures utilising S_N2 methodology have been developed for the introduction of cyanide.[34] The most common of these is the displacement of sulfonic acid esters by the cyanide anion. A non-aqueous cyanation procedure using lithium cyanide has been described to be more reactive than the traditional sodium and potassium variants that frequently require the use of phase transfer catalysts and extreme temperatures to achieve reaction. The hydroxyl group in **23** was converted into the tosylate **25**, to act as a more electrophilic partner. Heating of **25** at 80 °C in the presence of LiCN in DMF produced a single product.

Instead of substitution, the competing elimination reaction had occurred exclusively to give the olefin **26** (Scheme 7).



Scheme 7 *Reagents and conditions*: (i) *p*TsCl, DMAP, pyr, 97%; (ii) LiCN, DMF, 80 °C, 70%; (iii) Dess–Martin periodinane; (iv) LiCN, $(EtO)_2P(O)Cl$, DMF–THF, (v) SmI_2, HMPA, *t*BuOH, THF, 69%; (vi) Ph_3PCH_3I, *n*BuLi, THF, 0–25 °C, 85%; (vii) 9-BBN, THF, then 1 M NaOH, H_2O_2; (iv) 8 M CrO_3, acetone, –4 °C, 32%; (viii) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, then Et_3N, –78 to 25 °C.

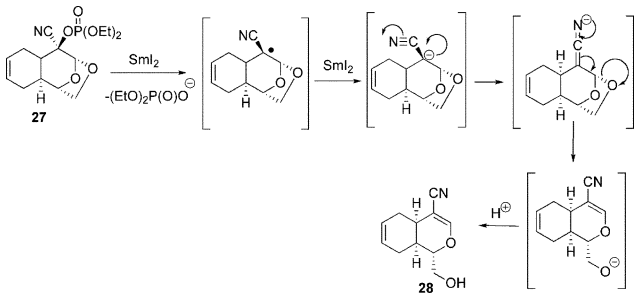
Alternative procedures for this substitution, which make use of NaCN and KCN in the presence of crown ethers or phase-transfer catalysts are used for this transformation,[34] but in the light of the facility with which elimination appears to have occurred in **25**, these were not considered. In the light of these factors, alternative homologation procedures were investigated preferentially.

The addition of cyanide to a carbonyl group to give a cyanohydrin was first reported in 1832[35] and numerous efficient procedures for this transformation have since been developed.[36] Reaction conditions whereby the cyanohydrin hydroxyl group is trapped as a phosphate ester[37,38] to give a cyanohydrin *O*,*O*′-diethyl phosphate (cyanophosphate) were attractive here because there is literature precedent for the reductive elimination of the phosphate group to give a nitrile.[39] The reaction of **4** with diethylchlorophosphate and lithium cyanide[38] afforded cyanophosphate **27** as a single diastereomer. Surprisingly, the treatment of **27** with SmI_2 in the presence of *tert*-butyl alcohol gave **28** as the major product instead of the expected nitrile.

The conversion of **27** into **28** appears to be one of overall β-elimination as opposed to reductive elimination. However, the accepted mechanism[40] for the reductive elimination of cyanophosphates does not allow for this outcome.

The proposed mechanism is as depicted in Scheme 8. There is initial dissociative electron transfer to an easily reducible α-substituent. Subsequent reduction by a second equivalent of SmI_2 generates an enolate that becomes protonated to give the carbonyl product. It is speculated here that when **27** interacts with SmI_2, the reaction proceeds along a similar path to produce the product of β-elimination as illustrated in Scheme 8.

As an alternative, the obvious option of Wittig olefination methodology was applied to the conversion of the carbonyl group in **4** into a chain-extended carboxyl moiety. A stepwise approach of methylenation, followed by further functionalisation was adopted. The methylenated product **29** was afforded by the reaction of **4** with the methyltriphenylphosphorane (Scheme 7).



Scheme 8 Mechanism for the SmI_2-mediated reductive elimination in cyanophosphates.

The crystalline nature of alcohol **30** provided an opportunity for crystal structure determination (see ESI†). A search of the Cambridge Crystal Database[41] showed that no compounds bearing the levoglucosenone cycloadduct motif had been registered. The crystal structure obtained as shown in Fig. 3 confirmed the relative stereochemistry at the bridgehead positions C-2 and C-7, thus confirming the diastereoselectivity that had been assumed for the cycloaddition reaction. Calculated bond lengths and angles are consistent with the structural assignment. Puckering analysis confirmed that the six-membered ring C2→C7 adopts the expected half-chair conformation (puckering parameters $Q = 0.398(2)$ Å, $\theta = 130.7(3)°$, $\phi = 138.4(4)°$) while the six-membered ring containing atom O10 assumes a twist-chair form (puckering parameters $Q = 0.635(2)$ Å, $\theta = 18.4(2)°$, $\phi = 2.8(6)°$). The five-membered ring has an envelope conformation (flap at O10). An intermolecular hydrogen bond O2′-H2′···O11[a] (a = $1 - x$, $-\frac{1}{2} + y$, $\frac{1}{2} - z$) links molecules into infinite spirals parallel to the crystallographic *b*-axis. The configuration at C-8, where the hydroxymethyl substituent was axially orientated on the α-face of the oxacyclohexane ring, confirmed the deduction (argued for the hydride reduction of **4**) that reactions at C-8 were under steric rather than stereoelectronic control.

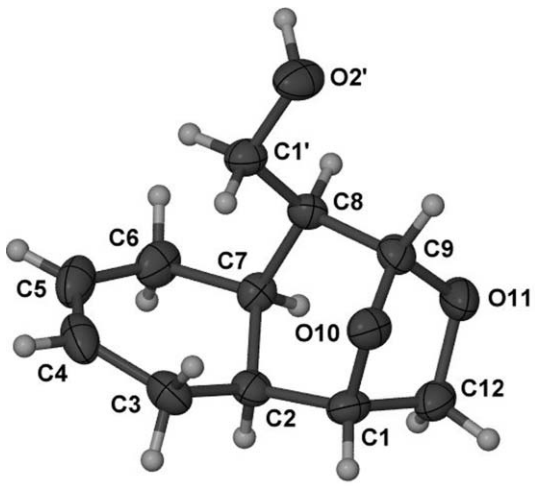
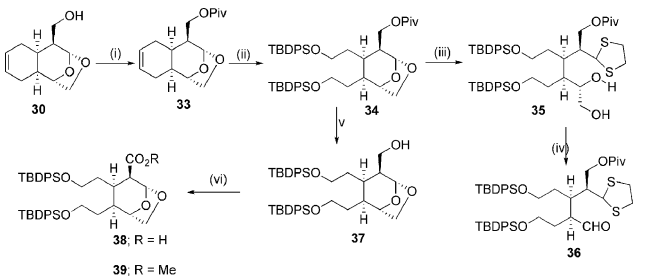


Fig. 3 X-Ray crystal structure of **30** (thermal ellipsoids are drawn at the 50% probability level).

In order to proceed to the required carboxyl level of oxidation at C-1′, Jones oxidation of **30** was investigated. In a reaction carried out at –4 °C the aldehyde **31** proved to be a discrete and isolable intermediate. However, under the prolonged reaction

times required to achieve complete consumption of the aldehyde, extensive decomposition intervened, as evidenced by TLC monitoring, and yields of **32** were poor. This behaviour was presumed to be due to the acid-labile nature of the internal acetal functionality. Other methods of achieving direct oxidation of the primary alcohol, including reactions with pyridinium dichromate and ruthenium tetroxide were attempted, but in both cases chemoselective reaction could not be achieved owing to the presence of the acetal and olefin moieties respectively. The conversion of **30** into the aldehyde **31** was most efficiently achieved using Swern oxidation conditions. However, the oxidation of **31** with sodium chlorite gave a complex mixture from which the carboxylic acid could not be isolated.

The hydroxymethyl group in **30** was pivaloylated, to give the ester **33** (Scheme 9). The ozonolysis and *in situ* reduction followed by silylation gave **34** in excellent yield. The acetal trapping was however beset by a deprotection problem. The poor yield of thioacetal **35** was accompanied by the recovery of TBDPSOH. This indicated that, although TBDPS ethers are reported to be stable to $BF_3{\cdot}OEt_2$ in dichloromethane at room temperature,[26] silyl cleavage had been induced under the reaction conditions applied here. A chemoselective transformation could not be achieved by varying the temperature or concentration of the reaction.



Scheme 9 *Reagents and conditions*: (i) PvCl, Et_3N, CH_2Cl_2, 95%; (ii) O_3, MeOH, −78 °C, then $NaBH_4$, 25 °C followed by TBDPSCl, imidazole, DMF, CH_2Cl_2,97%; (iii) ethanedithiol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C; (iv) $Pb(OAc)_2$, 69%; (v) LAH, THF, 0 °C, (vi) RuO_2 (cat.), $NaIO_4$, CCl_4–MeCN–H_2O, 0 °C, 93%; (vii) MeI, K_2CO_3, DMF, 0 °C, 99%.

Despite the poor yield of the thioacetal, and the attendant necessity to improve these steps for a practical synthesis, the available material sufficed to demonstrate the oxidative cleavage of the glycol moiety. Treatment of **35** with lead tetraacetate afforded a cleavage product that was purified by flash chromatography to give the aldehyde **36** in excellent yield. No epimerisation α to the aldehyde carbonyl group could be detected in the NMR spectra of **36**.

In the light of the observed instability of the TBDPS ethers in **34**, an alternative approach to this portion of the synthesis was embarked on. The pivaloate protection on **34** was removed by reduction with LAH to give the alcohol **37**. The alcohol was treated with ruthenium tetroxide to give the carboxylic acid **38**, which was characterised as its methyl ester **39** (Scheme 9).

Conclusion

The oxidative cleavage and functionalisation of the termini to hydroxyl groups has been achieved in high yields. One-carbon homologation and functionalisation to a carboxylic acid were achieved in a stepwise, but efficient process. The opening of the internal acetal to reveal the vicinal diol, and the oxidative cleavage of that diol to give the required aldehyde functionality have also been successfully demonstrated. Considerable progress has been made in determining the sequence in which these methodologies should be applied in the final synthetic route, as well as in the identification of protecting groups that complement these chemoselective processes.

In addition, the reduction studies have provided extensive insight into the conformational behaviour and reactivity of the tricyclic cycloadduct **4**, and allowed the identification of an artifact from the cycloaddition reaction as a *trans* epimer of the primary cycloadduct. Further, the X-ray crystal structure of **30** has provided the first structural evidence confirming the diastereoselectivity of the cycloaddition procedure, and of further transformations at C-8 in **30**. Although **28** was not the expected product, it does contain a dihydropyran ring as well as the masked carboxyl group in the form of a nitrile. Hydrolytic cleavage of the enol ether in **28**, thereby releasing the vicinal diol for oxidative cleavage, followed by reclosure of the dihydropyran moiety *via* hemiacetal formation, could be envisaged.

Experimental

Hydride reduction of 16

Diisobutylaluminium hydride (1.5 M in toluene, 1.66 cm^3, 2.49 mmol) was added to a stirred solution of **16** (275 mg, 0.62 mmol) in toluene (20 cm^3) at −78 °C. After 5 min 1 M HCl was added until pH 1 was reached and the mixture was warmed to 25 °C. The toluene was removed under reduced pressure and the mixture was extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give a residue (274 mg) which was further purified by column chromatography on silica gel (12 g) using ethyl acetate as eluent to give crude **19** (242 mg, ~88%) which required derivatisation to allow complete characterisation.

(3a*R*,6a*S*)-2-[(*S*)-*tert*-Butyldiphenylsilyloxymethyl]-3-[(*S*)-2-acetoxyethyl]hexahydrofuro[2,3-*b*]furan 20. Acetic anhydride (0.41 cm^3, 443 mg, 4.34 mmol) and 4-dimethylaminopyridine (20 mg, 0.16 mmol) were added sequentially to a stirred solution of **19** (480 mg, 1.08 mmol) in dry pyridine (10 cm^3). After stirring for 1 h at 25 °C toluene was added and the volume was reduced under reduced pressure. The resultant slurry was dissolved in ethyl acetate, washed with water and brine, dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue (497 mg) was purified by column chromatography on silica gel (50 g) using ethyl acetate–hexane (3 : 7) an eluent to give the *acetate* **20** (456 mg, 90%) as an oil, $[\alpha]_D$ +16.9 (*c* 2.0 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1733 (CO); δ_H (400 MHz, $CDCl_3$) 1.06 [9H, s, $C(CH_3)_3$], 1.59–1.74 (1H, m, 1″-H_A), 1.76–1.98 (3H, m, 4-H_2 and 1″-H_B), 2.03 [3H, s, $C(O)CH_3$], 2.39–2.50 (1H, m, 3-H), 2.87–2.96 (1H, m, 3a-H), 3.63–3.78 (2H, m, 2-H, 1′-H_A), 3.80–3.98 (2H, m, 5-H_2 and 1′-H_B), 4.03–4.19 (2H, m, 2″-H_2), 5.75 (1H, d, *J* 5.0 Hz, 6a-H), 7.35–7.43 (6H, m, Ar-H), 7.62–7.75 (4H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 19.5 [*C*$(CH_3)_3$], 21.1 [C(O)*C*H_3], 25.4 (C-4), 26.8 (C-1″), 27.0 [C(*C*$H_3)_3$], 39.9 (C-3), 46.1 (C-3a), 63.4 (C-2″), 64.2 (C-1′), 68.9 (C-5), 83.4 (C-2), 108.7 (C-6a), 127.9(0) and 127.9(3), 129.8(9) and 129.9(1), 133.4(8) and 133.7(0), 135.8(1) and 135.9(0) (Ar-C)

and 171.2 [C(O)CH_3] (Found: $M^+ - C_4H_9$, 411.1642. Calc. for $C_{23}H_{27}O_5Si$: M, 411.1628)

Reduction of cycloadduct 4

(a) L-Selectride (1.0 M in tetrahydrofuran, 2.7 cm^3) was added to a stirred solution of **4** (400 mg, 2.22 mmol) in toluene (100 cm^3) at −78 °C. After 2 h at −78 °C, saturated aqueous ammonium chloride was added and the mixture was warmed to 25 °C with stirring. Sodium hydroxide (1 M, 50 cm^3) was added, followed by hydrogen peroxide (30%, 50 cm^3) and the mixture was stirred for 60 min. The aqueous phase was extracted with dichloromethane, the organic extract was washed with aqueous saturated sodium hydrogen carbonate and brine, dried ($MgSO_4$) and the solvent was removed under reduced pressure to give a residue (507 mg) which was chromatographed on silica gel (50 g) using ethyl acetate–hexane (3 : 17) as eluent, to give (1*S*,2*S*,7*R*,8*R*,9*R*)-10,12-dioxatricyclo[7.2.1.0^{2,7}]dodec-4-en-8-ol **23** (376 mg, 93%), $[\alpha]_D$ −9.3 (*c* 1.0 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3525 (OH); δ_H (400 MHz, $CDCl_3$), 1.78–1.89 (2H, m, OH and 2-H), 2.01–2.10 (1H, m, 6-H$_A$), 2.11–2.21 (1H, m, 3-H$_A$), 2.27–2.43 (2H, m, 6-H$_B$ and 7-H), 2.43–2.55 (1H, m, 3-H$_B$), 3.40 (1H, br s, 8-H), 3.85 (1H, dd, *J* 7.2 and 5.2 Hz, 11-H$_A$), 3.93 (1H, dd, *J* 7.2 and 1.2 Hz, 11-H$_B$), 4.33 (1H, m, 1-H), 5.33 (1H, d, *J* 2.2 Hz, 9-H) and 5.78 (2H, m, 4-H and 5-H); δ_C (100 MHz, $CDCl_3$), 26.0 and 26.1 (C-3 and C-6), 26.9 (C-7), 34.4 (C-2), 67.0 (C-11), 72.6 (C-8), 76.5 (C-1), 103.1 (C-9), 125.7 and 126.3 (C-4 and C-5) (Found: M^+ 182.0964. Calc. for $C_{10}H_{14}O_3$: M, 182.0943).

(b) Sodium borohydride (90 mg, 2.44 mmol) was added to a stirred solution of **4** (400 mg, 2.22 mmol) in methanol (10 cm^3) at 0 °C. The mixture was stirred at 0 °C for 1 h after which saturated ammonium chloride was added and the volatile material was removed under reduced pressure. The aqueous residue was extracted with ethyl acetate, dried ($MgSO_4$) and the solvent was removed under reduced pressure to give a mixture of the alcohols (500 mg). Chromatography on silica gel (50 g) using ethyl acetate–hexane (3 : 17) as eluent afforded **23** (262 mg, 65%), followed by (1*S*,2*S*,7*R*,8*S*,9*R*)-8-hydroxy-10,12-dioxatricyclo[7.2.1.0^{2,7}]dodec-4-ene **24** (78 mg, 19%), mp 92–93 °C (from ethyl acetate–hexane); $[\alpha]_D$ −82.4 (*c* 0.4 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3574 (OH); δ_H (400 MHz, $CDCl_3$), 1.61 (1H, br d, OH), 1.87–2.60 (3H, m, 2-H, 3-H$_A$, 7-H), 2.09–2.20 (1H, m, 6-H$_A$), 2.30–2.45 (2H, m, 3-H$_B$, 6-H$_B$), 3.38 (1H, dd, *J* 9.7 and 1.3 Hz, 8-H), 3.85 (1H, dd, *J* 7.2 and 4.8 Hz, 11-H$_A$), 3.90 (1H, dd, *J* 7.2 and 0.8 Hz, 11-H$_B$), 4.29 (1H, d, *J* 5.2 Hz, 1-H), 5.32 (1H, d, *J* 1.3 Hz, 9-H), 5.55–5.63 (1H, m, 5-H) and 5.65–5.75 (1H. m. 4-H); δ_C (100 MHz, $CDCl_3$), 23.8 (C-6), 24.2 (C-3), 33.7 (C-7), 35.7 (C-2), 67.9 (C-11), 70.1 (C-8), 77.3 (C-1), 103.0 (C-9), 123.8 (C-5) and 125.0 (C-4) (Found: C, 65.9, H, 7.7%, M^+ 182. Calc. for $C_{10}H_{14}O_3$: C, 65.5, H, 7.8%, M, 182).

(1*S*,2*S*,7*R*,8*S*,9*R*)-8-Hydroxy-10,12-dioxatricyclo[7.2.1.0^{2,7}]-dodec-4-en-8-carbonitrile diethylphosphate 27. Diethyl chlorophosphate (1.12 cm^3, 1.34 g, 7.75 mmol) and lithium cyanide (0.5 M in *N,N*-dimethylformamide, 22.0 cm^3) were added to a stirred solution of **4** (1.00 g, 5.56 mmol) in tetrahydrofuran (30 cm^3). After stirring at 25 °C for 60 min, water was added and the mixture was concentrated under reduced pressure. The aqueous residue was extracted with ethyl acetate, the organic extract was washed with water and brine, dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a solid residue (1.02 g). Chromatography on silica gel (100 g) using ethyl acetate–hexane (1 : 1) as eluent afforded the *cyanophosphate* **27** (1.17 g, 61%), mp 85–86 °C (from ethyl acetate–hexane); $[\alpha]_D$ −37.8 (*c* 1.3 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1273 (PO); δ_H (400 MHz, $CDCl_3$), 1.30–1.37 (6H, m, 2 × OCH_2CH_3), 1.84–1.93 (1H, m, 2-H), 1.97–2.07 (1H, m, 3-H$_A$), 2.24–2.34 (1H, m, 6-H$_A$), 2.41–2.54 (2H, m, 3-H$_B$ and 6-H$_B$), 2.60–2.68 (1H, m, 7-H), 3.92 (1H, dd, *J* 7.6 and 5.0 Hz, 11-H$_A$), 4.01 (1H, dd, *J* 7.6 and 0.8 Hz, 11-H$_B$), 4.09–4.20 (4H, m, 2 × OCH_2CH_3), 4.42 (1H, dd, *J* 4.4 and 0.8 Hz, 1-H), 5.52–5.55 (2H, m, 4-H and 5-H) and 5.95 (1H, s, 9-H); δ_C (100 MHz, $CDCl_3$), 15.9 (d, *J* 6.0 Hz, OCH_2CH_3), 16.0 (d, *J* 9.2 Hz, OCH_2CH_3), 24.8 and 25.1 (C-3 and C-6), 32.7 (C-7), 34.1 (C-2), 64.5 (d, *J* 24 Hz, OCH_2CH_3), 64.8 (d, *J* 24 Hz, OCH_2CH_3), 67.8 (C-11), 75.8 (C-8), 76.7 (C-1), 100.0 (C-9), 116.8 (CN), 124.0 and 125.1 (C-4 and C-5) (Found: C, 52.6, H, 6.6, N, 4.0%, M^+, 343. Calc. for $C_{15}H_{22}NO_6P$: C, 52.5, H, 6.5, N, 4.1%, M, 343).

(1*S*,4a*R*,8a*S*)-1-Hydroxymethyl-4a,5,8,8a-tetrahydro-1*H*-isochromene-4-carbonitrile 28. 1,2-Diiodoethane (564 mg, 2.0 mmol) in tetrahydrofuran (20 cm^3) was slowly added to samarium (451 mg, 3.0 mmol) with rapid stirring. The solution was refluxed until a deep blue colour developed (~60 min) after which it was cooled and hexamethylphosphoramide (0.01 cm^3, 0.06 mmol) was added. To this was added a solution of **27** (200 mg, 0.58 mmol) and *tert*-butyl alcohol (43 mg, 0.58 mmol) in tetrahydrofuran (6 cm^3). After stirring at 25 °C for 4 h, 1 M HCl was added (till pH 2 was reached). The mixture was diluted with ethyl acetate, washed with aqueous sodium thiosulfate (1 M), dried ($MgSO_4$), and the solvent was removed under reduced pressure to give an oily residue (140 mg). Chromatography on silica gel (15 g) using ethyl acetate–hexane (2 : 3) as eluent yielded the *carbonitrile* **28** as a colourless oil (76 mg, 69%), $[\alpha]_D$ +18.6 (*c* 1.3 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3425 (OH), 2212 (CN); δ_H (400 MHz, $CDCl_3$), 1.80 (1H, br s, OH), 1.99–2.13 (2H, m, 5-H$_A$. and 8-H$_A$), 2.16–2.31 (2H, m, 8a-H and 8-H$_B$), 2.42–2.51 (1H, m, 5-H$_B$), 2.52–2.59 (1H. m, 4a-H), 3.74 (1H, dd, *J* 12.4 and 5.6 Hz, 1′-H$_A$), 3.80 (1H, dd, *J* 12.4 and 3.4 Hz, 1′-H$_B$), 4.08 (1H, ddd, *J* 7.6, 5.6 and 3.4 Hz, 1-H), 5.59–5.62 (2H, m, 6-H and 7-H) and 7.10 (1H, s, 3-H); δ_C (100 MHz, $CDCl_3$), 24.4 (C-8), 27.9 (C-4a), 28.3 (C-5), 29.0 (C-8a), 62.7 (C-1′), 78.6 (C-1), 92.5 (C-4), 118.4 (CN), 123.2 and 124.3 (C-6 and C-7) and 155.6 (C-3) (Found: M^+, 191.0948. Calc. for $C_{11}H_{13}NO_2$: M, 191.0946)

(1*S*,2*S*,7*R*,9*R*)-8-Methylene-10,12-dioxatricyclo[7.2.1.0^{2,7}]-dodec-4-ene 29. *n*-Butyllithium (10 M solution in hexane, 2.40 cm^3) was added to a stirred slurry of methyltriphenylphosphonium iodide (9.42 g, 23.3 mmol) in tetrahydrofuran (50 cm^3) at 0 °C. The resulting solution was warmed to 25 °C and stirred for 2 h. The solution was cooled to 0 °C and a solution of **4** (2.10 g, 11.7 mmol) in tetrahydrofuran (20 cm^3) was slowly added. The reaction was warmed to 25 °C and stirred for 18 h. The mixture was acidified with 1 M HCl and concentrated. The aqueous residue was extracted with dichloromethane, the organic extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The yellow residue (10.90 g) was adsorbed onto silica gel (25 g) and then chromatographed on silica gel (200 g) using ethyl acetate–hexane (1 : 9) as eluent to yield *olefin* **29** (1.77 g, 85%), mp 88–90 °C (from hexane); $[\alpha]_D$ 32.9 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$), 1.92–1.96 (1H, m, 3-H$_A$), 1.97–2.06 (1H, m, 2-H), 2.22–2.33 (2H,

m, 6-H_2), 2.34–2.49 (1H, m, 3-H_B), 2.93–3.00 (1H, m, 7-H), 3.89 (1H, dd, *J* 7.2 and 4.9 Hz, 11-H_A), 4.06 (1H, dd, *J* 7.2 and 0.8 Hz, 11-H_B), 4.35 (1H, dd, *J* 4.9 and 2.1 Hz, 1-H), 4.70 (1H, d, *J* 2.3 Hz, 1′-H_A), 4.96 (1H, d, *J* 2.3 Hz, 1′-H_B), 5.53 (1H, s, 9-H) and 5.58–5.66 (2H, m, 4-H and 5-H); δ_C (100 MHz, $CDCl_3$), 23.7 (C-3), 24.4 (C-6), 30.2 (C-7), 38.4 (C-2), 67.7 (C-11), 77.2 (C-1), 105.0 (C-9), 107.6 (C-1′), 123.2 and 125.0 (C-4 and C-5) and 146.4 (C-8) (Found: C, 73.9, H, 8.0%, M^+ 178. Calc. for $C_{11}H_{14}O_2$: C, 65.5, H, 7.8%, *M*, 178).

(1*S*,2*S*,7*R*,8*S*,9*R*)-8-Hydroxymethyl-10,12-dioxatricyclo[7.2.1.0^{2,7}]dodec-4-ene 30. 9-Borabicyclo[3.3.1]nonane (4.93 g, 40.4 mmol) was added to a stirred solution of **29** (3.60 g, 20.2 mmol) in tetrahydrofuran (100 cm^3). After 6 h of stirring at 25 °C 1 M NaOH (50 cm^3) was slowly added, followed by hydrogen peroxide (30%, 50 cm^3). The mixture was diluted with water and extracted with ethyl acetate. The extract was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue (6.72 g) was chromatographed on silica gel (100 g) using ethyl acetate–hexane (4 : 1) as eluent to yield the *alcohol* **30** (3.83 g, 97%), mp 80–82 °C (from ethyl acetate–hexane); $[\alpha]_D$ 67.4 (*c* 1.0 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3626 (OH); δ_H (400 MHz, $CDCl_3$), 1.65–1.95 (4H, m, 2-H, 6-H_A, 8-H and OH), 2.00–2.12 (1H, m, 3-H_A), 2.24–2.39 (2H, m, 3-H_B and 6-H_B), 2.50–2.59 (1H, m, 7-H), 3.64 (1H, dd, *J* 10.5 and 4.4 Hz, 1′-H_A), 3.76 (1H, t, *J* 2 × 10.5 Hz, 1′-H_B), 3.83 (1H, dd, *J* 7.0 and 5.3 Hz, 11-H_A), 3.97 (1H, dd, *J* 7.0 and 0.7 Hz, 11-H_B), 4.30 (1H, dd, *J* 5.3 and 0.7 Hz, 1-H) and 5.62–5.75 (3H, m, 4-H, 5-H and 9-H); δ_C (100 MHz, $CDCl_3$), 24.7 (C-7), 26.2 (C-3), 27.0 (C-6), 35.1 (C-2), 48.3 (C-8), 61.3 (C-1′), 67.8 (C-11), 77.1 (C-1), 103.2 (C-9), 125.5 and 126.2 (C-4 and C-5) (Found: C, 67.1, H, 8.3%, M^+ 196. Calc. for $C_{11}H_{16}O_3$: C, 67.3, H, 8.2%, *M*, 196).

(1*S*,2*S*,7*R*,8*S*,9*R*)-8-Pivaloyloxymethyl-10,12-dioxatricyclo-[7.2.1.0^{2,7}]dodec-4-ene 33. Triethylamine (5.0 cm^3, 3.63 g, 35.9 mmol) and pivaloyl chloride (1.0 cm^3, 0.98 g, 8.1 mmol) were added to a solution of the alcohol **30** in dichloromethane (20 cm^3). The resulting mixture was stirred for 3 h after which it was acidified with 1 M HCl and extracted with dichloromethane. The organic phase was washed with brine, dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue (2.09 g) was chromatographed on silica gel (100 g) using ethyl acetate–hexane (1 : 9) as eluent to give the *pivaloate* **33** (1.79 g, 95%) as an oil, $[\alpha]_D$ +52.3 (*c* 1.7 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1719 (CO); δ_H (400 MHz, $CDCl_3$), 1.10 (9H, s, $C(CH_3)_3$), 1.67–1.79 (1H, m, 2-H), 1.81–1.95 (2H, m, 6-H_A and 8-H), 1.96–2.10 (1H, m, 3-H_A), 2.20–2.37 (2H, m, 3-H_B and 6-H_B), 2.47–2.56 (1H, m, 7-H), 3.76 (1H, dd, *J* 7.0 and 5.2 Hz, 11-H_A), 3.91 (1H, d, *J* 7.0 Hz, 11-H_B), 3.98 (1H, t, *J* 3 × 11.2 Hz, 1′-H_A), 4.12 (1H, dd, *J* 11.2 and 4.1 Hz, 1′-H_B), 4.24 (1H, d, *J* 5.1 Hz, 1-H), 5.44 (1H, s, 9-H) and 5.57–5.67 (2H, m, 4-H and 5-H); δ_C (100 MHz, $CDCl_3$), 24.7 (C-7), 26.0 (C-6), 26.8 (C-3), 27.1 [C(*C*H_3)$_3$], 34.9 (C-2), 38.7 [*C*(CH_3)$_3$], 45.2 (C-8), 63.1 (C-1′), 67.9 (C-11), 77.1 (C-1), 102.9 (C-9), 125.4 and 126.0 (C-4 and C-5) and 178.2 (C=O) (Found (FAB): M^+ + Rb, 365.0812. Calc. for $C_{16}H_{24}O_4Rb$: *M*, 365.0793).

(1*S*,2*S*,3*R*,4*S*,5*R*)-2,3-Bis(2-*tert*-butyldiphenylsilanyloxyethyl)-4-pivaloyloxymethyl-6,8-dioxabicyclo[3.2.1]octane 34. Ozone was bubbled through a solution of **33** (140 mg, 0.50 mmol) in methanol (8 cm^3), at −78 °C until the solution turned blue. The ozone was replaced by oxygen which until the solution became colourless after which sodium borohydride (95 mg, 2.5 mmol) was added. The reaction mixture was warmed to 25 °C and then quenched with aqueous saturated ammonium chloride. The volatile material was removed under reduced pressure and the remaining mixture was extracted with chloroform, dried ($MgSO_4$) and the solvent was removed to give the diol (161 mg) which was dissolved in acetonitrile (10 cm^3). Imidazole (102 mg, 1.5 mmol) and *tert*-butyldiphenylsilyl chloride (0.29 cm^3, 1.1 mmol) were added and the solution was stirred for 60 min. The mixture was concentrated under reduced pressure and water was added to the residue. The aqueous mixture was extracted with dichloromethane, the organic extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue (550 mg) was chromatographed on silica gel (50 g) using ethyl acetate–hexane (1 : 9) as eluent to give the *bissilyl ether* **34** (385 mg, 97%) as an oil, $[\alpha]_D$ −10.4 (*c* 1.0 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1719 (CO); δ_H (300 MHz, $CDCl_3$), 1.03 [9H, s, TPS-C(CH_3)$_3$], 1.05 [9H, s, TPS-C(CH_3)$_3$], 1.16 [9H, s, Pv-C(CH_3)$_3$], 1.35–1.73 (5H, m, 2-H, 1′-H_2 and 1″-H_2), 1.80–1.91 (1H, m, 4-H), 2.50–2.64 (1H, m, 3-H), 3.55–3.82 (6H, m, 7-H_2, 2′-H_2 and 2″-H_2), 3.92–4.17 (2H, m, 1‴-H_2), 4.28 (1H, d, *J* 5.0 Hz, 1-H), 5.46 (1H, d, *J* 1.2 Hz, 5-H), 7.30–7.46 (12H, m, Ar-H) and 7.58–7.64 (8H, m, Ar-H); δ_C (75 MHz, $CDCl_3$), 19.1 and 19.2 [2 × TPS-*C*(CH_3)$_3$], 26.8 and 26.9 [2 × TPS-C(*C*H_3)$_3$], 27.2 [Pv-C(*C*H_3)$_3$], 27.3 (C-3), 29.4 and 32.0 (C-1′ and C-1″), 37.5 (C-2), 38.7 [Pv-*C*(CH_3)$_3$], 42.7 (C-4), 61.0 and 62.2 (C-2′ and C-2″), 62.4 (C-1‴), 68.1 (C-7), 75.5 (C-1), 102.1 (C-5), 127.6(7) and 127.6(9), 129.6(2) and 129.6(9), 133.6(5), 133.6(9), 133.7(2) and 133.7(6), 135.5(3), 135.5(6) and 135.5(8) (Ar-C) and 178.2 (C=O) (Found (FAB): M^+ + Rb, 877.3369. Calc. for $C_{48}H_{64}O_6Si_2Rb$: *M*, 877.3360).

(2*S*,3*S*,4*R*,5*S*)-3,4-Bis[2-(*tert*-butyldiphenylsilanyloxy)ethyl]-5-(1,3-dithiolan-2-yl)-6-pivaloyloxyhexane-1,2-diol 35. Ethanedithiol (0.40 cm^3, 4.8 mmol) followed by titanium tetrachloride (1.0 M in dichloromethane, 2.8 cm^3, 2.8 mmol) were added to a stirred solution of **34** (2.80 g, 3.5 mmol) in dichloromethane (60 cm^3) at 0 °C. The reaction was stirred at this temperature for 4 h and then quenched with aqueous saturated sodium hydrogen carbonate, extracted with dichloromethane, dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue (3.80 g) was chromatographed on silica (150 g) using ethyl acetate–hexane (1 : 9 to 3 : 7) to give the *thioacetal* **37**, (2.17 g, 69%), $[\alpha]_D$ −11.6 (*c* 1.6 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1718 (CO), 3566 (OH); δ_H (300 MHz, $CDCl_3$), 1.02 [9H, s, TPS-C(CH_3)$_3$], 1.03 [9H, s, TPS-C(CH_3)$_3$], 1.16 [9H, s, Pv-C(CH_3)$_3$], 1.49–1.66 (3H, m, 1′-H_2 and 1″-H_A), 1.73–1.90 (2H, m, 3-H and 1″-H_B), 1.94–2.12 (2H, m, 4-H and OH), 2.47–2.57 (1H, m, 5-H), 2.62–2.70 (1H, br d, OH), 2.98–3.27 (4H, m, 4‴-H_2 and 5‴-H_2), 3.45–3.75 (7H, m, 1-H_2, 2-H, 2′-H_2 and 2″-H_2), 4.21 (1H, dd, *J* 11.7 and 7.0 Hz, 6-H_A), 4.36 (1H, dd, *J* 11.7 and 3.6 Hz, 6-H_B), 4.73 (1H, d, *J* 3.8 Hz, 2‴-H), 7.30–7.45 (12H, m, Ar-H) and 7.60–7.70 (8H, m, Ar-H); δ_C (75 MHz, $CDCl_3$), 19.0 [2 × TPS-*C*(CH_3)$_3$], 26.8 [2 × TPS-C(*C*H_3)$_3$], 27.1 [Pv-C(*C*H_3)$_3$], 31.2 and 31.3 (C-1′ and C-1″), 37.0 (C-3), 38.0 and 39.3 (C-4‴ and C-5‴), 38.6 (C-4), 44.4 (C-5), 54.2 (C-2‴), 62.4 and 62.9 (C-2′ and C-2″), 65.1 (C-1), 65.2 (C-6), 73.1 (C-2), 127.5(8) and 127.6(4), 129.5(3) and 129.6(4), 133.2(9), 135.4(7) and 135.5(0) (Ar-C),

and 178.2 (C=O) (Found (FAB): M^+ + Rb, 971.3257. Calc. for $C_{50}H_{70}O_6S_2Si_2Rb$: *M*, 971.3270).

(2*S*,3*R*,4*S*)-2,3-Bis[2-(*tert*-butyldiphenylsilanyloxy)ethyl]-4-(1,3-dithiolan-2-yl)-5-pivaloyloxypentanal 36. Lead tetraacetate (0.90 g, 2.03 mmol) was added to a solution of **35** (1.50 g, 1.70 mmol) in toluene (100 cm^3) at 25 °C. After 15 min, ethylene glycol (5 drops) was added and the mixture was stirred for 10 min, then filtered through Celite and $MgSO_4$ layers and concentrated to give an oil (1.97 g). Flash chromatography on silica gel (100 g) using ethyl acetate–hexane (1 : 9) as eluent afforded the aldehyde **36** (1.37 g, 94%), $[\alpha]_D$ 4.4 (*c* 1.5 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1722 (CO); δ_H (300 MHz, $CDCl_3$), 1.04 [18H, s, 2 × TPS-C$(CH_3)_3$], 1.17 [9H, s, Pv-C$(CH_3)_3$], 1.47–1.63 (1H, m, 1′-H_A), 1.64–1.86 (2H, m, 1″-H_2), 1.96–2.12 (1H, m, 1′-H_B), 2.12–2.24 (1H, m, 4-H), 2.30–2.43 (1H, m, 3-H), 2.89–2.99 (1H, m, 2-H), 3.04–3.25 (4H, m, 4‴-H_2 and 5‴-H_2), 3.54–3.80 (4H, m, 2′-H_2 and 2″-H_2), 4.27 (2H, d, *J* 4.7 Hz, 5-H_2), 4.73 (1H, d, *J* 7.4 Hz, 2‴-H), 7.28–7.45 (12H, m, Ar-H), 7.57–7.70 (8H, m, Ar-H) and 9.66 (1H, d, *J* 1.9 Hz, 1-H); δ_C (75 MHz, $CDCl_3$), 19.0 [2 × TPS-*C*$(CH_3)_3$], 26.8 [2 × TPS-C(*C*$H_3)_3$], 27.1 [Pv-C(*C*$H_3)_3$], 31.4 and 32.0 (C-1′ and C-1″), 38.1 and 38.8 (C-4‴ and C-5‴), 38.4 (C-4), 38.6 [Pv-*C*$(CH_3)_3$], 46.1 (C-3), 48.1 (C-2), 54.3 (C-2‴), 61.5 and 61.8 (C-2′ and C-2‴), 63.9 (C-5), 127.5, 129.5, 133.5, 135.4(4) and 135.4(8) (Ar-C), 178.7 (C=O) and 204.2 (C-1) (Found (FAB): M^+ + Rb, 939.3021. Calc. for $C_{49}H_{66}O_5S_2Si_2Rb$: *M*, 939.3008).

(1*S*,2*S*,3*R*,4*S*,5*R*)-2,3-Bis(2-*tert*-butyldiphenylsilanyloxyethyl)-4-hydroxymethyl-6,8-dioxabicyclo[3.2.1]octane 37. Lithium aluminium hydride (134 mg, 3.5 mmol) was added to a solution of **34** (2.53 g, 3.2 mmol) in tetrahydrofuran (250 cm^3) at 0 °C. After 10 min, the reaction was quenched with water and the solvent removed under reduced pressure. The aqueous slurry was diluted with 1 M sodium hydroxide, extracted with chloroform, the organic extract was dried ($MgSO_4$) and the solvent was removed *in vacuo* to give the an oily residue (2.70 g). Chromatography on silica gel (250 g) using ethyl acetate–hexane (2 : 3) as eluent afforded the *alcohol* **37** (2.09 g, 93%) as an oil, $[\alpha]_D$ −18.7 (*c* 1.0 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450 (OH); δ_H (300 MHz, $CDCl_3$), 1.04 [9H, s, C$(CH_3)_3$], 1.06 [9H, s, C$(CH_3)_3$], 1.32–1.66 (6H, m, 2-H, 1′-H_2, 1″-H_2 and OH), 1.66–1.76 (1H, m, 4-H), 2.43–2.64 (1H, m, 3-H), 3.50–3.74 (7H, m, 7-H_A, 2′-H_2, 2″-H_2 and 1‴-H_2), 3.79 (1H, d, *J* 7.6 Hz, 7-H_B), 4.27 (1H, d, *J* 5.2 Hz, 1-H), 5.56 (1H, d, *J* 1.2 Hz, 5-H), 7.31–7.46 (12H, m, Ar-H) and 7.59–7.68 (8H, m, Ar-H); δ_C (75 MHz, $CDCl_3$), 19.2 [2 × *C*$(CH_3)_3$], 26.9 and 26.9 [2 × C(*C*$H_3)_3$], 27.6 (C-3), 29.5 and 32.1 (C-1′ and C-1″), 37.7 (C-2), 45.8 (C-4), 60.4 (C-1‴), 61.5 and 62.3 (C-2′ and C-2″), 68.0 (C-7), 75.5 (C-1), 102.5 (C-5), 127.7, 129.7, 133.7 and 135.6 (Ar-C) (Found: M^+ − C_4H_9, 651.2975. Calc. for $C_{39}H_{47}O_5Si_2$: *M*, 651.2962).

Methyl (1*S*,2*S*,3*R*,4*R*,5*R*)-2,3-bis(2-*tert*-butyldiphenylsilanyloxyethyl)-6,8-dioxabicyclo[3.2.1]octane-4-carboxylate 39. Sodium metaperiodate (10% solution in water, 12 cm^3) and ruthenium dioxide (19 mg, 0.14 mmol) were added sequentially to a vigorously stirred solution of **37** (1.00 g, 1.41 mmol) in carbon tetrachloride–acetonitrile (1 : 1) (100 cm^3) at 0 °C. Stirring was continued at this temperature for 18 h. The resulting mixture was poured into ethyl acetate–water and the aqueous layer was extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the acid (1.10 g) which was dissolved in *N,N*-dimethylformamide (10 cm^3). Potassium carbonate (390 mg, 2.82 mmol) and iodomethane (0.11 cm^3, 1.83 mmol) were added and the mixture was stirred at 0 °C for 2 h. The mixture was diluted with ethyl acetate (200 cm^3). The organic phase was washed twice with water, dried ($MgSO_4$) and the solvent removed under reduced pressure to give a residue (2.30 g) which was purified by chromatography on silica gel (50 g) using ethyl acetate–hexane (1 : 9) as eluent, to yield the *ester* **39** (1.03 g, 99%) as a gum, $[\alpha]_D$ −11.3 (*c* 1.5 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1740 (CO); δ_H (400 MHz, $CDCl_3$), 1.04 [9H, s, C$(CH_3)_3$], 1.06 [9H, s, C$(CH_3)_3$], 1.55 (1H, s, 2-H), 1.59–1.92 (4H, m, 1′-H_2, and 1″-H_2), 2.59–2.69 (2H, m, 3-H and 4-H), 3.61 (3H, s, OCH_3), 3.63–3.78 (5H, m, 7-H_A, 2′-H_2 and 2″-H_2), 3.81 (1H, d, *J* 7.1 Hz, 7-H_B), 4.37 (1H, d, *J* 5.7 Hz, 1-H), 5.67–5.72 (1H, br s, 5-H), 7.32–7.45 (12H, m, Ar-H) and 7.60–7.67 (8H, m, Ar-H); δ_C (100 MHz, $CDCl_3$), 19.1 [2 × *C*$(CH_3)_3$], 26.9 and 26.9 [2 × C(*C*$H_3)_3$], 27.5 (C-3), 28.7 and 32.4 (C-1′ and C-1″), 37.6 (C-2), 48.6 (C-4), 51.2 (OCH_3), 61.3 and 62.1 (C-2′ and C-2″), 68.4 (C-7), 75.6 (C-1), 100.5 (C-5), 127.6, 129.6, 133.8(0) and 133.8(2), 135.5(0), 135.5(3) and 135.5(6) (Ar-C) and 170.8 (C-1‴) (Found: M^+ − CH_3, 721.3387. Calc. for $C_{43}H_{53}O_6Si_2$: *M*, 721.3381).

Acknowledgements

We thank the South African National Research Foundation for financial support and Drs Gareth Arnott and Seanette Wilson for preliminary studies.

References

1 B. M. Trost and F. D. Toste, *J. Am. Chem. Soc.*, 1999, **121**, 3543.
2 G. Stork, K. Manabe and L. Liu, *J. Am. Chem. Soc.*, 1998, **120**, 1337.
3 W. Oppolzer, *Angew. Chem., Int. Ed.*, 1984, **23**, 876.
4 A. T. Stevens, J. R. Bull and K. Chibale, *Synlett*, 2007, 3175–3179.
5 A. T. Stevens, J. R. Bull and K. Chibale, *Org. Biomol. Chem.*, 2008, **6**, 586–595.
6 K. Tomioka, T. Ishiguro, Y. Iitaka and K. Koga, *Tetrahedron*, 1984, **40**, 1303.
7 P. Camps, J. Cardellach, J. Font, R. M. Ortuño and O. Ponsatí, *Tetrahedron*, 1982, **38**, 2395.
8 M. G. B. Drew, J. Mann and A. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 1986, 2279.
9 S. Takano, A. Kurotaki, M. Takahashi and K. Ogasawara, *Synthesis*, 1986, 403.
10 C. R. Schmid and J. D. Bryant, *Org. Synth.*, 1995, **72**, 6.
11 J. Mann and A. Thomas, *J. Chem. Soc. Perkin Trans. 1*, 1986, 2287.
12 R. M. Ortuño, J. Font and J. Corbera, *Tetrahedron Lett.*, 1986, **27**, 1081.
13 R. Batllori, J. Font, M. Monsalvatje, R. M. Ortuño and F. Sanchez-Ferrando, *Tetrahedron*, 1989, **45**, 1833.
14 *Levoglucosenone and Levoglocosans: Chemistry and Applications*, ed. Z. J. Witczak, A T L Pr. Scientific Pub., Washington DC, 1996 .
15 A. V. Samet, A.M. Shestopalov, D. N. Lutov, L. A. Rodinovskaya, A. A. Shestopalov and V. V. Semenov, *Tetrahedron: Asymmetry*, 2007, **18**, 1986.
16 A. V. Samet, D. N. Lutov, L. D. Konyushkin, Y. A. Strelenko and V. V. Semenov, *Tetrahedron: Asymmetry*, 2008, **19**, 691.
17 K. Mori, M. Mori, T. Chuman and K. Kato, *Tetrahedron Lett.*, 1982, **23**, 4593.
18 L. A. Paquette, A. M. Doherty and C. M. Rayner, *J. Am. Chem. Soc.*, 1992, **114**, 3910.
19 D. L. Boger, R. M. Borzilleri, S. Nukui and R. T. Beresis, *J. Org. Chem.*, 1997, **62**, 4721.
20 W. Hartwig, *Tetrahedron*, 1983, **39**, 2609.
21 S. Harusawa, R. Yoneda, Y. Omori and T. Kurihara, *Tetrahedron Lett.*, 1987, **28**, 4189.

22 P. Kocienski, *Protecting Groups*, Georg Thieme Verlag, Stuttgart, 1994, p. 104.
23 S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, 1981, **22**, 3815.
24 T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, 1999, p. 41. .
25 A. J. Castellino and H. Rapoport, *J. Org. Chem.*, 1986, **51**, 1006.
26 E. R. Civitello and H. Rapoport, *J. Org. Chem.*, 1994, **59**, 3775.
27 J. S. Swenton, J. N. Freskos, P. Dalidowicz and M. L. Kerns, *J. Org. Chem.*, 1996, **61**, 459.
28 D. D. Ward and F. Shafizadeh, *Carbohydr. Res.*, 1981, **95**, 155.
29 J. Seyden-Penne, *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, VCH Publishers, New York, 1991, p. 47.
30 O. H. Oldenziel and A. M. van Leusen, *Synth. Commun.*, 1972, **2**, 281.
31 J. March, *Advanced Organic Chemistry*, John Wiley & Sons, New York, 1992, p. 887.
32 J. R. Bull and A. Tuinman, *Tetrahedron*, 1975, **31**, 2151.
33 O. H. Oldenziel, D. van Leusen and A. M. van Leusen, *J. Org. Chem.*, 1977, **42**, 3114.
34 M. North, in *Comprehensive Organic Functional Group Transformations*, ed. A. R. Katritzky, O. Meth-Cohn and C. W. Rees, Elsevier, Oxford, 1995, p. 612.
35 F. W. Winkler, *Liebigs. Ann. Chem.*, 1832, **4**, 246.
36 M. North, in *Comprehensive Organic Functional Group Transformations*, ed. A. R. Katritzky, O. Meth-Cohn and C. W. Rees, Elsevier, Oxford, 1995, p. 615.
37 R. Yoneda, S. Harusawa, T. Kurihara, Y. Hamada and T. Shioiri, *Tetrahedron Lett.*, 1984, **25**, 427.
38 I. Micó and C. Nájera, *Tetrahedron*, 1993, **49**, 4327.
39 R. Yoneda, S. Harusawa and T. Kurihara, *J. Org. Chem.*, 1991, **56**, 1827.
40 G. A. Molander, *Org. React.*, 1994, **46**, 211.
41 Cambridge Structural Database and Cambridge Structural Database System, Version 5.21, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Cambridge, April 2001.

