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Catalytic tin radical mediated tricyclisations. Part 1. Monocyclisation studies †

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Received (in Cambridge, UK) 24th January 2000, Accepted 16th March 2000
Published on the Web 27th April 2000

A general strategy for catalytic tin radical mediated, radical cascade reactions is proposed in which three rings are constructed in a single step. The initial step in the tricyclisation process has been examined using 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosides bearing unsaturated substituents at the 1-*O* and/or 4-*O*-positions. Substrates for cyclisation of substituents at the 1-*O*-position were prepared by a novel zinc chloride catalysed Ferrier rearrangement of tri-*O*-acetyl-D-glucal with unsaturated alcohols, whereas substrates for cyclisation of substituents at the 4-*O*-position were prepared by alkylation or acylation of ethyl 6-*O*-protected 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosides. Propargyl substituents cyclise efficiently, but propenyl substituents less so. Propioloyl substituents undergo hydrostannylation without cyclisation.

Tin hydride reagents are often rightly criticised because reagents such as tri-*n*-butyltin hydride[1] (TBTH; MW 291) and triphenyltin hydride (TPTH; MW 351) have a low equivalence and consequently a large amount of spent and excess reagent has to be separated from the product. The higher equivalence of trimethyltin hydride (MW 165) is an advantage, however trimethyltin compounds are extremely toxic and hence they must be handled with elaborate precautions. Tin hydride reagents can be used catalytically if a co-reductant is present (*e.g.* sodium borohydride[2] or polymethyl hydrosiloxane (PMHS), potassium fluoride[3]), but this reduces their inherent chemoselectivity.

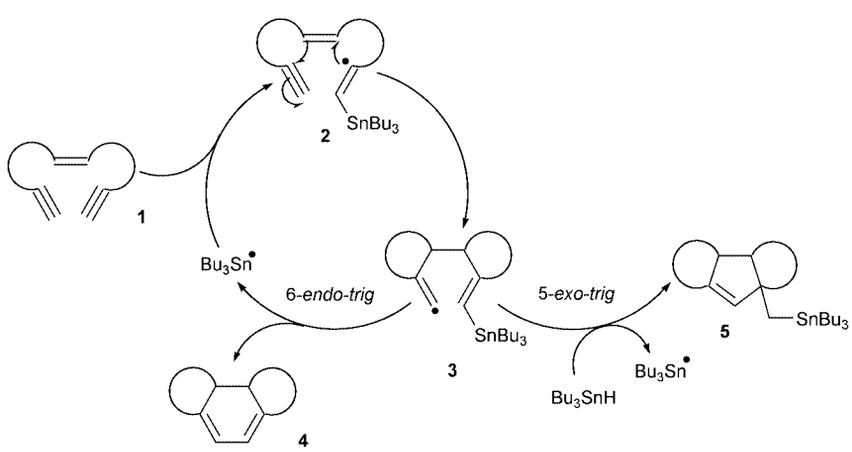
This situation has resulted in a wealth of prescriptions for removing "tin residues",[4] and the development of alternative reagents such as the fluorous[5] and polar[6] derivatives which can be removed by extraction. The fluorous reagents have not been widely adopted as yet, but the benefits for clean extraction of the reagents are manifest. However, the molecular weights are even higher than the hydrocarbon analogues, which reduces their effectiveness on a weight for weight basis.

On the other hand, organotin radicals are excellent radical abstractors and tin hydrides are excellent hydrogen radical donors to alkyl radicals (*vide infra*), which results in reactions of high selectivity and fidelity.[7] It would be of great benefit if the chemoselectivity of radicals generated using tin hydrides could be utilised in a wholly catalytic process.

Results and discussion

This *a priori* requires a process in which the tin radical adds to a system, effects some change and is then released. We envisaged a process in which a tin radical adds to an unsaturated system **1** and initiates a series of addition reactions such that the radical is translocated to a position at which it can cause elimination of the stannyl radical (*cf.* **3**). Since radicals do not easily effect S_H reactions at saturated centres[8] this requires that the stannyl group is temporarily attached to an unsaturated moiety and substitution proceeds *via* radical addition followed by β-elimination.[9] Since the tin radical must undergo addition to a moiety of the system which is unsaturated both before and after the addition of the tin radical, an alkyne group is one possibility. The next requirement is to construct a series of unsaturated bonds capable of translocating the radical back to the desired position. 5-*exo*-*trig* Radical cyclisations are an

† Full experimental and spectroscopic data for all compounds prepared by methods other than free radical cyclisation are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b0/b000661k/ (this includes the following compounds in order of appearance: **7a**, **8a**, **7b**, **7d**, **10e**, **7c**, **8c**, **7d**, **7f**, **7g**, **7h**, **10h**, **7f**, **9**, **13a**, **13b**, **13c**, **13d**, **14**, **18**, **21**, **22**, **23**, **25b**, **25c**, **26**, **28**, **29b**, **31a**, **31b**, **33a**, **33b**, **35a**, **35b**, **35c**, **36b**).

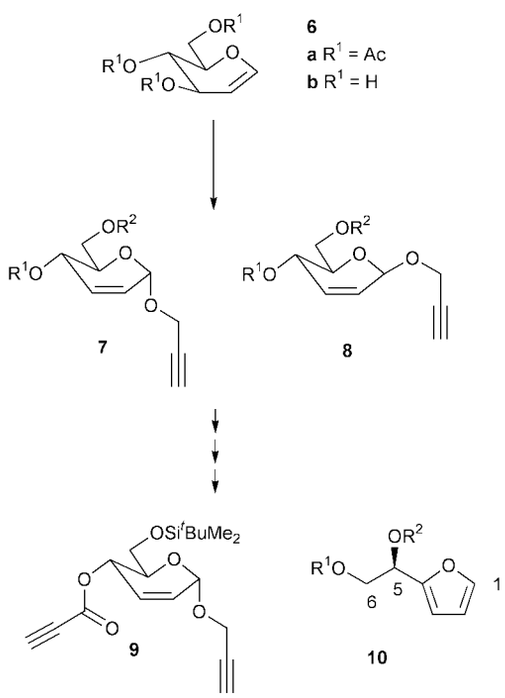


Scheme 1

obvious choice because of their predictable stereochemistry and reliability.

Any number of radical translocations *via* additions to alkene bonds will translocate the radical by an even number of carbons. Hence the final cyclisation at the original site of attack must always be *via* a cyclisation with an even number of carbons between the radical and the original site of attack. In the current case the final desired cyclisation is 6-*endo*-*trig*, with the possibility of an undesirable 5-*exo*-*trig* cyclisation.[10] It was envisaged that the desired regiochemistry of cyclisation could be enforced by the geometry of the vinyl radical and the rigidity of the ring system created in the earlier steps. Radical cascades are now commonly used in synthesis,[11,12] but processes in which the initiating radical is subsequently eliminated are rare. Subsequent to our preliminary disclosure[13] there have been only three other examples as far as we are aware. Pancrazi and co-workers[14] achieved elimination of the initiating tri-*n*-butyltin radical in an alkyne–alkene monocyclisation as did Spino and Barriault with the tricyclisation of an acyclic alkynone diene.[15] Marco-Contelles accomplished tricyclisation of an alkynic diene sugar[16] closely resembling our original report. Palladium catalysed cyclisation of similar substrates has only yielded bisannulation products thus far.[17]

We conceived that the idea summarised in Scheme 1 could be implemented by appending two unsaturated side chains to a rigid ring system. This would hold the side chains in the correct orientation to favour the formation of single stereoisomers. The combination of a Ferrier rearrangement[18] of an acylated glucal *e.g.* **6a** (Scheme 2), followed by attachment of an unsaturated chain at the 4-*O*-position (to give *e.g.* **9**) offered the prospect



7, **8**, **10**
a $R^1 = R^2 = Ac$
b $R^1 = R^2 = H$
c $R^1 = H$, $R^2 = Pv$
d $R^1 = R^2 = Pv$
e $R^1 = Pv$, $R^2 = H$
f $R^1 = H$, $R^2 = Si^tBuMe_2$
g $R^1 = Si^tBuMe_2$; $R^2 = H$
h $R^1 = R^2 = Si^tBuMe_2$
i $R^1 = H$, $R^2 = Si^tBuPh_2$
j $R^1 = Si^tBuPh_2$, $R^2 = H$
k $R^1 = R^2 = Si^tBuPh_2$

Scheme 2

that the proposal in Scheme 1 could be rapidly tested and moreover the products would be single enantiomers. In practice, this sequence requires deprotection of the unsaturated sugar **7a**, selective derivatisation at the more accessible primary 6-hydroxy group, followed by 4-*O*-substitution. The alkynyl alkene **7a** could also be used to test the single step components of the multiple cyclisation. Unsaturated sugars have been heavily investigated by Fraser-Reid[19] and others[20] and exploited in innumerable free radical cyclisations[21] and total syntheses.

It was anticipated that the propiolic ester moiety would react preferentially with tri-*n*-butyltin radical due to the strongly electron withdrawing effect of the carboxy group. A propiolic ester would also provide the correct side chain length to allow a favourable initial 5-*exo*-*trig* cyclisation. Similar considerations apply to a propargyl ether at the anomeric centre, but a propiolic ester at this position would be too reactive to survive the intermediate synthetic manipulations. Although it was envisaged that attack of the radical should occur initially at the propiolic ester, this is not a requirement for success. The reverse sequence of radical translocations would also give the same product.

This publication describes our initial foray into this area and some model studies with monocyclisations.

Ferrier rearrangements are usually performed with boron trifluoride–diethyl ether as the Lewis acid catalyst. Photo-induced electron transfer,[22] lithium tetrafluoroborate,[23] ceric ammonium nitrate,[24] iodine,[25] and NIS treatment of 3-*O*-pentenyl glycals[26] have been also been advocated, but only the last two have found wide acceptance. In our experience, zinc chloride gives cleaner products which require less purification, than boron trifluoride–diethyl ether.[27] Thus tri-*O*-acetyl-D-glucal **6a** was treated with propargyl alcohol and zinc chloride under otherwise standard Ferrier reaction conditions. As with the boron trifluoride–diethyl ether catalysed reaction, complete conversion is signalled by the sudden appearance of a purple colouration. Quenching and work up of the reaction at this time afforded the propargyl α-glycoside **7a** in good yield (87%). TLC analysis of the product indicated a small amount of the β-glycoside **8a** which was confirmed by ^{1}H-NMR of the crude product to be present in the ratio 89:11, **7a**:**8a**. Delay in quenching the reaction resulted in the formation of an approximately equal amount of α- and β-glycosides and a discoloured crude product. The diacetates **7a**, **8a** were readily converted to the corresponding diols **7b**, **8b** by reaction with sodium methoxide in methanol. Selective protection of the primary C-6 hydroxy group was then required to permit acylation at the secondary C-4 hydroxy group.

Reaction of the diols **7b**, **8b** with pivaloyl chloride, triethylamine and DMAP[28] at −30 °C gave a complex mixture, which was separated by column chromatography to give the dipivalate **7d** (25%), the furan **10e** (22%), the desired monopivalate **7c** (6%), the monopivalate β-glycoside **8c** (2%) and recovered starting material **7b** (2%). The collected unseparated fractions contained an approximately 50:50 mixture of the monopivalate anomers **7c**, **8c** (12%) to give a total recovery of 69%.

The ^{1}H-NMR spectrum of the furan **10e** in deuteriochloroform showed coincident chemical shifts for the protons attached to C-6, but these were resolved in benzene-d_6. ^{1}H–^{1}H-COSY experiments indicated two isolated spin systems each containing three protons (δ 4.79, 4.41, 4.36; 7.11, 6.18, 6.12; C_6D_6). The upfield spin system was readily identified as a methine adjacent to a methylene group with vicinal and geminal coupling constants (J 4.8, 6.5 and 11.4 respectively) typical of those expected for 5-H and 6-H_2 of a hexopyranose. The downfield spin system had rather small vicinal coupling constants ($^3J_{1,2}$ *ca.* 1 Hz, $^3J_{2,3}$ 3.1 Hz) which are typical of furans. This material failed to react with tetracyanoethylene at room temperature which excludes a number of other conceivable

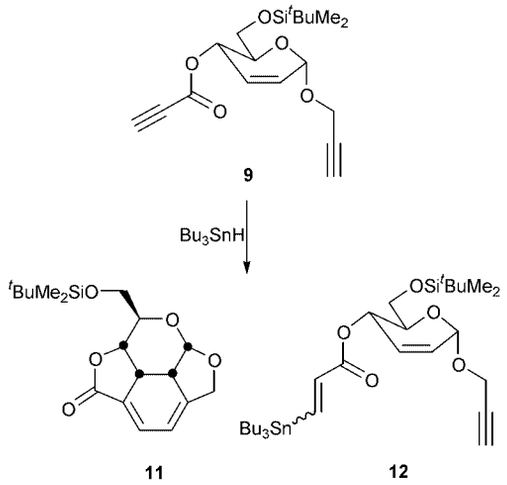
diene structures. The furan **10e** is a known compound which was prepared by pivaloylation of the diol **10b**.[29] The reported ^{1}H-NMR spectrum of this compound in deuteriochloroform has couplings which are similar to those reported here, but the chemical shifts for the ring protons are some 0.4–0.5 ppm upfield, relative to those which we measured in the same solvent. The signal for 5-H has a chemical shift (δ 4.86) which is almost identical to that which we measured, but 6-H_2 is reported at the inconceivable value of δ 3.1 (δ 4.38, our work). Comparison of our ^{1}H-NMR and ^{13}C-NMR data for the furan **10e** with those reported for furfuryl alcohol[30] reveals only minor differences and hence we conclude that errors were made in the cited work. The furan diol **10b** has been prepared by mercuric sulfate[31] or copper sulfate[32] catalysed rearrangement of D-glucal **6b** and the 6-*O*-silyl furan **10j** by treatment of the pyranoside **7i** with iodine.[33] Presumably, triethylamine hydrochloride or an acylium species acts as a Lewis acid in a similar way on the diol **7a** or the monopivaloate **7c**.

More practical results were obtained when the diol **7b** was reacted with pivaloyl chloride in pyridine at room temperature[34] to give a mixture of the monopivalate **7c** (41%) and the dipivalate **7d** (22%) plus the β-anomer of the monopivalate **8c** (0.3%).

We next turned to the *tert*-butyldimethylsilylation as a means to achieve selective 6-*O*-protection. Treatment of the diol **7b** with *tert*-butyldimethylsilyl chloride, triethylamine, DMAP and dichloromethane (Hernandez's conditions[35]) gave a mixture comparable to that produced by pivaloylation. Column chromatography yielded the 6-*O*-silyl ether **7f** (26%), the 4-*O*-silyl ether **7g** (4%), the 4,6-di-*O*-silyl ether **7h** (8%), recovered starting material **7b** (4%) and a trace of the furan disilyl ether **10h**. However, by using *tert*-butyldimethylsilyl chloride and imidazole in DMF (Corey's conditions[36]) at room temperature an easily separated mixture of the 6-*O*-silyl ether **7f** (75%) and starting material **7b** (7%) was produced in only 6 hours.

Simple propiolic esters can be easily prepared by treatment of propiolic acid with an excess of the alcohol,[37] but this is not applicable to valuable alcohols. Moreover propiolyl chloride is highly unstable,[38] and indeed we found that when propiolic acid was refluxed with thionyl chloride, no acid chloride could be detected by IR analysis. Consequently, we decided to investigate the DMAP catalysed DCC esterification.[39,40] Addition of the alcohol **7f** and propiolic acid to DMAP and DCC resulted in polymerisation However dropwise addition of a solution of DMAP and DCC to a mixture of a large excess of propiolic acid and the alcohol **7f** at 0 °C minimised polymerisation.[41] The reaction mixture containing the propiolate **9** was highly unstable. Removal of solvent at >30 °C caused the yellow tinged ester solution to rapidly change to dark green and the single spot product became a multi-product mixture on analysis by TLC. However by keeping the material below 30 °C, and working quickly, a pure product could be isolated by column chromatography, albeit in poor yield (10%). In other studies we have found that the most efficient means for generating stannyl radicals is TBTH with AIBN initiation. This of course means that there is the potential for reduction before full cyclisation. On the other hand use of hexabutylditin with various initiators is much less efficient as has been noted by others.[15]

TBTH (1.3 equiv.) in benzene was added dropwise from a syringe pump to a refluxing solution containing the enediyne **9** and AIBN (0.04 equiv.) under nitrogen.[42] The crude reaction mixture contained a complex mixture of products by TLC and the ^{1}H-NMR spectrum of the crude reaction mixture suggested that one of the major reaction products was the hydrostannylation product **12**. Column chromatography yielded an impure fraction containing the major product plus tin residues. In the ^{1}H-NMR spectrum the signal for the alkynic proton of the propiolyl group (δ 2.9) was absent but that of the propargyl group (δ 2.44) was present. Low field doublets with very large coupling constants indicated the presence of *cis*- and



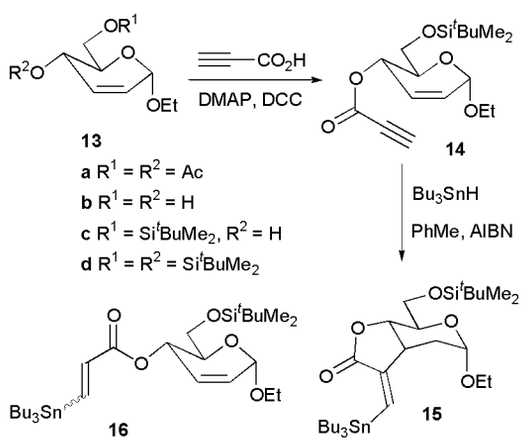
Scheme 3

trans-stannyl acrylates (δ 7.22, 6.65 *J* 16 and δ 7.73, 6.28, *J* 22 respectively).

This reaction although disappointing was instructive. The regiochemistry of stannyl radical addition had proceeded as predicted and the presence of *cis*- and *trans*-isomers indicates that stannyl radicals had been generated efficiently. The lack of cyclisation could be attributed to the intermediate vinyl radical having an inappropriate conformation, however, given the poor yield of the hydrostannylation product **12**, there was also the suspicion that the dialkynyl alkene **9** or a cyclisation product might have decomposed before it could be isolated. We therefore turned our attention to a simpler analogue, which would enable us to study the cyclisation of the 4-*O*-propiolate alone and provide a route to α-methylene-γ-lactones.

Monocyclisations of side chains at the 4-*O*-position

Reaction of tri-*O*-acetyl-D-glucal **6a** with ethanol and zinc chloride gave the glycoside **13a** (67% yield; α : β ratio 89 : 11), which upon treatment with sodium methoxide in methanol readily underwent hydrolysis to give the diol **13b** (91% yield).[18,22] Selective silylation of the primary hydroxy group occurred without incident to give the 6-*O*-silyl ether **13c** (49% yield), plus starting material (28% yield) and a trace of the 4,6-di-*O*-silyl ether **13d** (3%). Treatment of the 6-*O*-silyl ether **13c**

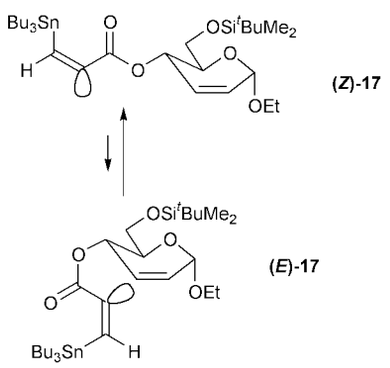


Scheme 4

with propiolic acid and a solution of DCC and DMAP gave a complex mixture of products as before, from which the desired product **14** was isolated in poor yield (10%) by column chromatography. The presence of a propiolate ester was confirmed by ^{1}H-NMR singlet signal for the alkynic proton (δ 2.92), the shift of the signal for 4-H from δ 4.15 in the starting material **13c** to

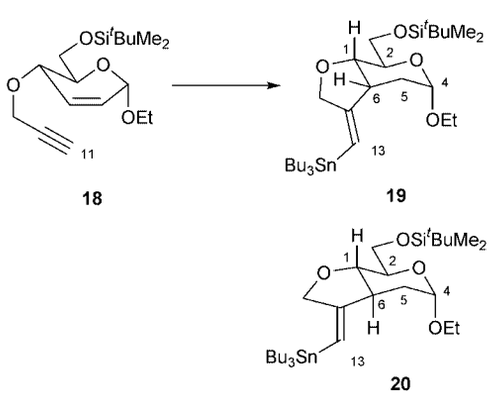
δ 5.40 and a very strong acetylenic stretch at 2100 cm^{-1} in the IR spectrum.

Treatment of the propiolate ester **14** with TBTH under standard cyclisation conditions afforded a complex mixture of products as determined by TLC intensities The ^{1}H-NMR spectrum of the crude reaction mixture provided no evidence for the presence of the desired cyclised product **15**, however the distinctive alkenic signals of the vinyl stannane **16** were present. Despite repeated chromatography, this product could not be purified adequately and the only product actually isolated was the silyl ether **13c** (20% yield), albeit containing trace amounts of impurities. Given that no starting material remained in the crude reaction mixture, this seemingly indicates that the stannyl ester **16** was cleaved during column chromatography. We attribute the lack of cyclisation products from both propiolates **9** and **14** to unfavourable conformational factors. α-Acrylate radicals undergo reactions which are fairly typical of vinyl radicals and organic radicals in general.[43] However, allyl esters of propiolic acid undergo radical addition induced cyclisation comparatively slowly[44] compared to the corresponding ketones.[45] This observation and our results reflect the preference for the (*Z*)-conformer over the (*E*)-conformer of the ester group (*ca.* 12 kJ mol^{-1}) and the barrier to rotation of the corresponding radical **17**.[46] This conformational preference was circumvented by



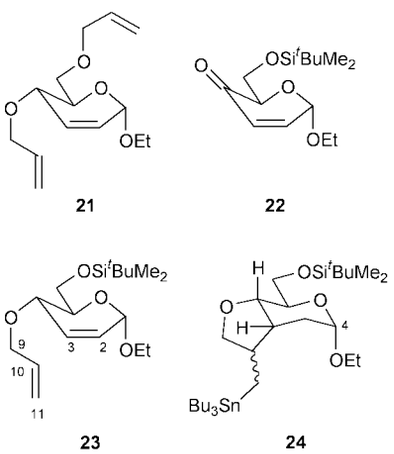
using the corresponding propargyl ether **18**, which was prepared in good yield (57%) by treatment of the 6-*O*-silyl ether **13c** with sodium hydride and propargyl bromide.

Initial attempts at the cyclisation gave mixtures of products which were difficult to separate from "tin residues". TLC monitoring indicated that the initial stages of the reaction occurred with clean conversion, but in the later stages small amounts of a host of by-products accumulated which made purification difficult. The intractable mixtures produced by prolonged reaction times were avoided by running the reaction with incomplete conversion, at the expense of reduced product yields, although starting material could be recovered. This protocol was utilised subsequently on many occasions. Cyclisation in toluene with slow addition of TBTH gave a single product **19** plus starting material **18** as determined by TLC. Purification by column chromatography gave clean products. The lowest field signal in



the ^{1}H-NMR spectrum was a broad doublet (δ 5.77, J 1.9, 13-H) with coupling to tin ($^2J_{Sn,H}$ 57.2 Hz) although the resolution was insufficient to distinguish ^{117}Sn and ^{119}Sn couplings. The second furthest downfield signal was assigned to the anomeric proton, 4-H (δ 4.77, dd, J 5.9, 5.9), which was used as the origin for the assignment of a ^{1}H–^{1}H-COSY NMR experiment. 1-H appeared as an apparent triplet (δ 3.89, dd, J 7.6, 7.6, with a broadened centre line) and 6-H as a doublet of doublets of doublets (δ 2.65, J 11.3, 6.3, 5.0). This indicates that the true value of $^3J_{1,6}$ is about 6.3 Hz. Typical line broadening is about 1.5 Hz which is sufficient to meld couplings of 7.6 and 6.3 Hz plus weak long range couplings into an apparent triplet. The rough equivalence of $^3J_{1,2}$ and $^3J_{1,6}$ suggests at first sight that both 1-H and 2-H and 1-H and 6-H might have a *trans*-diaxial relationship (*cf.* **20**) and this idea is reinforced by the large value for $^3J_{ax\text{-}5,6}$ (11.3 Hz). However molecular modelling and coupling constant calculations with Haasnoot's equation (**19** $^3J_{1,eq\text{-}6}$ 5.9 Hz; **20** $^3J_{1,ax\text{-}6}$ 11 Hz), indicate *cis*-fusion with *ax*-5-H in a position which is close to eclipsed with 6-H. The 6-*O*-trityl analogue of compound **19** has been previously prepared by similar means and was characterised by ^{1}H-NMR and IR spectra. The data is in satisfactory agreement with that reported here.[47]

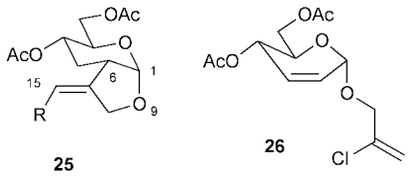
With the propargyl cyclisation secured (albeit in low yield), we turned to the corresponding allyl cyclisation. Allylation of the silyl alcohol **13c** under standard conditions (sodium hydride, allyl iodide) gave a mixture of three products which were separated by column chromatography (**21**, 8%; **22**, 3%; **23**,



21% yield). We had expected that the 4-*O*-*tert*-butyldimethylsilyl-6-*O*-allyl isomer of **23** might be formed due to silyl migration, but this was not identified amongst the products. We suspect that transsilylation occurred under the strongly basic conditions to give the diol **13b** plus the disilyl ether **13d** and the latter underwent retro-hydrosilylation to give the enone **22**. Treatment of the prop-2-enyl ether **23** with TBTH gave the expected reaction mixture, and purification by column chromatography afforded a single spot fraction containing equal amounts of two components **24**. The anomeric protons (δ 4.79, 0.5H, dd J 8.5, 5.6, 4-H and δ 4.74, 0.5H, dd, J 4.3, 4.3, 4′-H) were clearly adjacent to two protons as required for the cyclisation product and these could be located in a ^{1}H-^{1}H *J*-COSY NMR spectrum. Rigorous analysis of ^{1}H-NMR spectra was not possible due to poor dispersion, nevertheless all of the spectroscopic data was in agreement with the proposed structure.

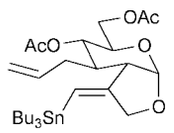
Monocyclisations of side chains at the 1-*O*-position

The compounds prepared in the course of the synthesis of the dialkyne alkene **9** provided an opportunity to examine the cyclisation of side chains attached to the anomeric position. Treatment of the alkyne **7a** with TBTH in refluxing toluene under the standard conditions gave an excellent yield of the



25
a R = Bu_3Sn
b R = I
c R = H

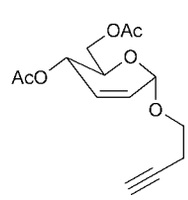
26



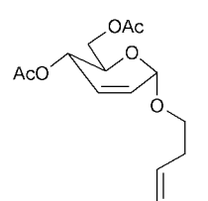
27

vinyl stannane **25a** (65%) as previously reported by Chapleur's group[47] in refluxing benzene. Free radical induced cyclisation with diphenylphosphine is reported to give a mixture of cyclic (37%) and acyclic products (29%).[48] The reaction was monitored by ^{1}H-NMR which indicated steady conversion to the vinylstannane **25a** by the disappearance of the characteristic signals for the alkenic protons at C-2, C-3 (δ 5.92, 5.85) and the alkyne (δ 2.48) and the appearance of a single alkenic signal at δ 5.88. Iodo- and protio-destannylation with iodine and wet silica gel gave the iodoalkene **25b** and the alkene **25c** respectively. In each of these three compounds the ^{1}H-NMR signal for 6-H was too broad to interpret, however 1-H appeared as a clean doublet J 4.6, 4.6 and 6.2 Hz (for **25a**, **b**, **c** respectively), indicating *cis*-fusion. The alkene **25c** was also prepared independently by cyclisation of the vinyl chloride **26** in refluxing toluene. This proceeded in good chemical yield (50%), considering that the abstraction step is not particularly facile, and as expected starting material **26** was recovered (8%). Encouraged by these comparatively good yields we attempted to trap the radical intermediate formed by the alkyne **7a** with allyl tri-*n*-butyltin (2.5 equiv.)[49] using TBTH (10 mol%) as a propagation catalyst and AIBN initiation (3 mol%). The allylation product **27** was not formed, but the monocyclisation product **25a** was produced (28%), plus starting material **7a** (10%). Only part of the reduced product can be accounted for by TBTH added to the reaction. The most likely explanation for the remainder is retro-hydrostannylation of allyl tri-*n*-butyltin to give allene and TBTH; a process which is well precedented for crotyltri-*n*-butyltin.[50]

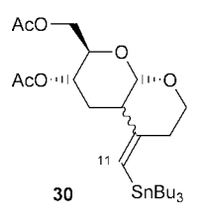
Given the success of these cyclisations, we next attempted to apply them to the next higher homologue. Zinc chloride catalysed Ferrier reaction of tri-*O*-acetyl-D-glucal **6a** with but-3-yn-1-ol gave exclusively the butynyl α-glycoside **28** in 30 minutes in excellent yield, compared with the boron trifluoride–diethyl ether catalysed reaction (31%).[51] When the reaction



28



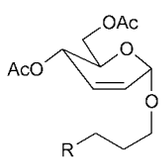
29
a R = $SnBu_3$
b R = H



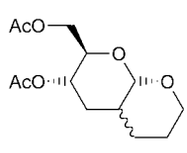
30

time was extended, (*e.g.* 1 hour) the β-anomer was detected. In the ^{1}H-NMR spectrum of the reaction mixture, signals for the β- and α-anomeric protons appeared at δ 5.13, 5.08 (ratio 21 : 79). Attempted cyclisation of the α-anomer **28** with TBTH gave a mixture of two products of very similar polarity. From TLC intensities it appeared that the less polar component was by far the major product and it was isolated by column chromatography. ^{1}H-NMR spectra showed signals characteristic of the starting material except for the absence of the alkynic proton (δ 2.00), plus the presence of a tri-*n*-butylstannyl group and two down field alkenic signals (δ 6.45, 5.86) with a common coupling constant of 12 Hz.

This material was assigned structure **29b** with a (*Z*)-stannylalkene moiety, which results from kinetic hydrostannylation of the alkyne group. The structure was verified by dissolving the adduct **29a** in wet ether containing silica gel (70–230 mesh) to give the alkene **29b** which was also prepared independently by Ferrier rearrangement of tri-*O*-acetyl-D-glucal **6a** with but-3-en-1-ol. Conventional silica gel flash column chromatography failed to separate the minor product **30** from the adduct **29a**, however chromatography using silica gel impregnated with silver nitrate gave an impure fraction containing the minor product (<5 mg). ^{1}H-NMR analysis indicated the presence of a single alkenic proton (δ 6.01, s, 11-H) consistent with the structure of the bicyclic adduct **30.** The Chapleur group, isolated the bicyclic stannane **30** (21%, *Z* : *E*, 3.5 : 1) and the vinyl stannanes **29a** (59%, *Z* : *E*, 18 : 82).[47] The thermodynamic ratio of vinylstannane stereoisomers **29a** obtained in this work is surprising, because the equilibration of non-conjugated vinylstannanes is usually only observed after protracted reaction times and/or with high concentrations of stannyl radicals.[52]



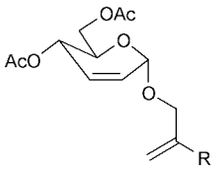
31
a R = Br
b R = H



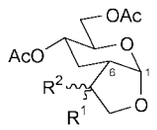
32

We also probed the 6-*exo*-*trig* mode[53] of cyclisation by the attempted cyclisation of the bromopropyl glycoside **31a**. Comparable cyclisations of bromoethyl glycosides give good yields.[49,54] Treatment of the bromopropyl glycoside **31a** with TBTH under a wide range of experimental conditions (temperature, high dilution) gave exclusively the reduced product **31b** (77% yield), which was also prepared independently by Ferrier rearrangement. The reluctance of radicals to undergo 6-*exo*-*trig* cyclisation is well known and these results confirm that such a cyclisation is unlikely to be a usable component of the proposed tricyclisation on the structural framework (Scheme 1).

A propenyl glycoside would lack the necessary degree of unsaturation required to both initiate and terminate the tandem cyclisation process. However a propenyl group could readily be used in the final cyclisation step if the tandem process was initiated by an alkyne. The propenyl **33a** and 2-methylpropenyl glycosides **33b** were prepared by Ferrier rearrangement as before and subjected to cyclisation with TBTH. The propenyl glycoside **33a** yielded two products with similar mobilities on TLC plus a plethora of minor products. Repeated chromatography eventually yielded material of adequate purity which was assigned the structures **34a**, **b**. Although the anomeric protons (δ 5.45, 5.35) could be easily assigned the remainder of the spectrum was too complex to permit rigorous interpretation. Similarly the 2-methylpropenyl glycoside **33b** reacted with TBTH to give a complex mixture of products. Separation by column chromatography gave a fraction containing three close running components in the ratio 50 : 35 : 15 as determined from



33
a R = H
b R = Me

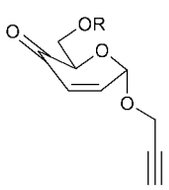


34
a $R^1 = CH_2SnBu_3$, R^2 = H
b R^1 =H, $R^2 = CH_2SnBu_3$
c $R^1 = CH_2SnBu_3$, R^2 = Me
d R^1 = Me, $R^2 = CH_2SnBu_3$

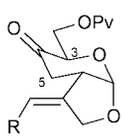
the integration of the anomeric protons in the ^{1}H-NMR spectrum (δ 5.39, 5.31, 5.24 all d J 4.8). No alkenic signals were present. A ^{1}H–^{1}H J-COSY NMR experiment enabled the 1-H signals to be correlated with the 6-H signals and other tentative assignments to be made. The $^3J_{1,6}$ coupling constant is consistant with *cis*-ring fusion as observed previously and the two major components are assigned as the epimers **34c**, **d**. The structure of the third component remains unassigned.

The work thus far established that both the propargyl glycoside **7a** and the chloropropenyl glycoside **26** readily undergo 5-*exo*-*trig* cyclisation, whereas alkenes **33a** and **33b** react poorly by this cyclisation mode. Difficulties in isolating closely running mixtures of epimers necessarily reduced the isolated yields. The poor 6-*exo*-*trig* cyclisation of the butynyl glycoside **28** indicates that cyclisations homologous to those originally proposed are unlikely to be viable.

Unsubstituted organic radicals react more readily with electron deficient alkenes than electron rich alkenes. Therefore it was anticipated that the enones **35** might cyclise even more



35
a R = H
b ^{t}BuMe$_2$Si
c Pv



36
a R = $SnBu_3$
b R = I

readily than the propargyl glycoside **7a** which had given a 65% yield of the bicycle **25a**. This of course would require revision of the original cyclisation plan, nevertheless it potentially offered the opportunity to incorporate otherwise unfavourable cyclisations into the cascade. Oxidation of the diol **7b** with manganese dioxide[55] gave the desired enone **35a**. However as reported,[56] treatment with the mildest bases or even storage initiated a retro-aldol reaction and decomposition. This precluded protection at the 6-*O*-position. However manganese dioxide oxidation of the 6-*O*-*tert*-butyldimethylsilyl **7b** and pivalate **7c** derivatives gave the desired enones **35b**, **c** in poor to fair yields.

Treatment of the 6-*O*-pivalate **7c** with the cyclisation standard conditions yielded a complex mixture from which the vinylstannane **36a** was isolated in low yield. To facilitate further purification this was treated with iodine to give the vinyl iodide **36b**. The small amount of material obtained only enabled the compound to be characterised by NMR. The ^{1}H-NMR spectrum of the vinyl stannane **36a** showed an alkenic peak (δ 5.88, dd, J 2.5, 2.5) at an identical chemical shift to the corresponding proton (δ 5.88, m) in the di-*O*-acetyl analogue **25a**. As anticipated, the 5-H protons which were well separated (δ 2.23 and 1.70) in the di-*O*-acetyl analogue **25a** were shifted down field to give a single multiplet (δ 2.77) in the ketone **36b**. The ^{1}H-NMR spectrum of the iodide **29b** was better dispersed than that of the stannane **29a**. The 5-H protons now appeared as a clean pair of doublet of doublets with a large geminal coupling (δ 2.78, dd, J 15.7, 5.7, *ax*-5-H; δ 2.63 dd, J 15.7, 2.7, *eq*-5-H).

Conclusions

The results clearly demonstrate that 1-*O* and 4-*O*-propargyl substituents act as good radical traps for tri-*n*-butyltin radicals and the intermediate vinyl radicals undergo the anticipated 5-*exo*-*trig* cyclisation. Radical trapping by alkenyl substituents is much less effective, but nevertheless cyclised products are also obtained, albeit in low yields. In contrast, propiolyl substituents exclusively undergo hydrostannylation, due to a preference for a conformation which is unfavourable to cyclisation. The following paper in this issue describes the successful exploitation of these observations.

We gratefully acknowledge sponsorship of this work by Warner-Lambert, Parke-Davis and the provision of spectrometer time by the EPSRC at the National Mass Spectrometry Service at the University of Swansea.

Experimental

General

Purified or dried solvents were freshly distilled under an argon or nitrogen atmosphere from a suitable drying agent.

All reactions were monitored by thin layer chromatography (TLC) using Merck aluminium backed precoated silica gel plates (0.2 mm, 60, F_{254}) with UV light or ethanolic phosphomolybdic acid (3%) and heat for visualisation. Virtually all products were purified by flash column chromatography using Merck silica gel 60 (70–230 mesh), eluted with a gradient starting with a low polarity solvent and then increasing amounts of a more polar solvent. All products were homogeneous as judged by TLC unless stated otherwise.

Infra red (IR) spectra were recorded on a Perkin-Elmer 1600 Series FTIR spectrophotometer, using sodium chloride cells. Elemental analyses were performed on a Perkin-Elmer 240c.

Low resolution mass spectra were recorded on VG Trio 1 and VG platform II spectrometers using electron impact (EI) or chemical ionisation (CI, CH_4). Some low resolution spectra, CI–NH_3 spectra and all accurate mass measurements were recorded at the EPSRC Mass Spectrometry Centre at Swansea. Mass spectra data for compounds with high molecular weights (particularly those containing tin and halogens) were simulated using the computer program HiMass.[57] This calculates the abundance of the ions in an ion cluster for a given elemental formula. This is termed cluster analysis.

NMR spectra were recorded on Perkin-Elmer R12B, Varian T-60, Bruker AMX-360, and Bruker Advance DPX-400 spectrometers. $CDCl_3$ was used as solvent unless indicated. Tetramethylsilane or residual solvent peaks (*e.g.* $CHCl_3$) were used as frequency standards. ^{13}C-NMR spectra were recorded with full and partial proton decoupling and using the DEPT technique.

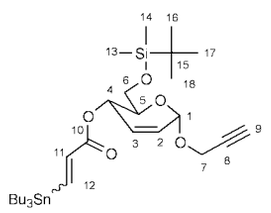
Coupling constants were determined using the computer program Multiplet[58] and are quoted in hertz (Hz). Multiplet uses peak positions from peak listings to calculate line spacings which are averaged to give putative couplings. These in turn are permutated to give possible coupling patterns. Thus the calculated coupling constants have an accuracy which is only limited by the digital resolution of the NMR machine and line broadening effects. Values are reported to 0.1 Hz, but have an uncertainty of ±*ca.* 0.3 Hz (at 360 MHz), due to the digital resolution of the FID accumulation and Fourier transformation. ^{1}H-NMR spectra were simulated using RACCOON.[59] Molecular modelling was performed with PC-Model[60] on a Compusys, 33 MHz, 80486 PC. The program implements Allinger's MM2 force field, version MM88 with several enhancements. Structures were routinely optimised using the

randomise option with typically 200–500 trials. The PMR option in PC-Model was used to calculate vicinal coupling constants. This implements modified versions of the Karplus equation[61] parameterised to take account of the effect of substituents on coupling constants. An average absolute error of 1 Hz for all the vicinal coupling constants of a given molecule, with no single value with an error of >±2 Hz constitutes a satisfactory fit between experimental data and calculated values. Vinylic ^{1}H- and ^{13}C-NMR chemical shifts were predicted using Shoolery's rules.[62]

Electronic data

The full experimental and spectroscopic data for all compounds prepared by free radical cyclisation are described in the Experimental section which follows. Data for compounds prepared by other means, are provided in the supplementary data for this paper. This includes the following compounds in order of appearance: **7a**, **8a**, **7b**, **7d**, **10e**, **7c**, **8c**, **7d**, **7f**, **7g**, **7h**, **10h**, **7f**, **9**, **13a**, **13b**, **13c**, **13d**, **14**, **18**, **21**, **22**, **23**, **25b**, **25c**, **26**, **28**, **29b**, **31a**, **31b**, **33a**, **33b**, **35a**, **35b**, **35c**, **36b**.

Attempted preparation of the tetracycle 11. Identification of vinylstannanes 12



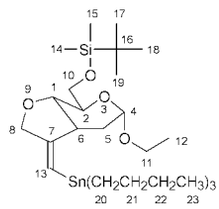
12

Prop-2-ynyl 2,3-dideoxy-4-*O*-propiolyl-6-*O*-*tert*-butyldimethylsilyl-α-D-*erythro*-hex-2-enopyranoside **9** (50 mg, 0.14 mmol) and AIBN (0.2 mg, 0.06 mmol, 0.04 equiv.) were dissolved in dry benzene (2 ml) and warmed to reflux under nitrogen. A solution of tri-*n*-butyltin hydride (55 mg, 0.19 mmol, 1.3 equiv.) was added dropwise from a syringe pump. The reaction was refluxed for 16 hours. TLC analysis indicated a very complicated mixture of products from which, despite repeated attempts at column chromatography, eluent hexane to 20% ethyl acetate in hexane, no fraction free from tin residues was isolated. ^{1}H-NMR analysis of the major fraction indicated that the characteristically sharp propiolic proton signal (δ 2.93, s, 12-H)) was absent, whereas, the propargyl alkynic proton (δ 2.44, t, *J* 2.4, 9-H) was present. ^{1}H-NMR spectra indicated a 50 : 50 mixture of vinyl stannanes **12**; δ_H (90 MHz) 7.73 (0.5H, d, *J* 22, 12-H), 7.22 (0.5H, d, *J* 16, 12-H), 6.65 (0.5H, d, *J* 16, 11-H), 6.28 (0.5H, d, *J* 22, 11-H), 5.82 (2H, br m, 2-H, 3-H), 5.30 (1H, m, 4-H), 5.18 (1H, br s, 1-H), 4.24 (2H, m, 7-H_2), 3.70 (3H, m, 5-H, 6-H_2), 2.44 (1H, dd, *J* 3, 3, 9-H), 1.32 (12H, m, 20-H_6, 21-H_6, $SnCH_2CH_2CH_2$), 0.85 (24H, m, 16-H_3, 17-H_3, 18-H_3, 19-H_6, 22-H_9, $(CH_3)_3CSi$, $SnCH_2(CH_2)_2CH_3$), 0.00 (6H, s, 13-H_3, 14-H_3, $(CH_3)_2Si$).

Attempted tri-*n*-butyltin hydride mediated cyclisation of ethyl 6-*O*-*tert*-butyldimethylsilyl-4-*O*-propiolyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside 14

Ethyl 6-*O*-*tert*-butyldimethylsilyl-4-*O*-propiolyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **14** (60 mg, 0.18 mmol), and AIBN (2 mg, 0.007 mmol, 0.04 equiv.) were dissolved in dry toluene (2 ml) and refluxed under nitrogen for 15 min. A solution of tri-*n*-butyltin hydride (77 mg, 0.26 mmol, 1.5 equiv.) in toluene (3 ml) was added dropwise over 3 hours *via* a syringe pump. The reaction solution was refluxed for 18 hours. TLC analysis indicated a complicated mixture. Column chromatography, eluent hexane to 10% ethyl acetate in hexane, afforded a fraction containing one of the major products, with two trace impurities as judged from TLC. It was identified by ^{1}H-NMR as the alcohol **13c** (10 mg, 20% yield), resulting from cleavage of the β-stannyl propenoate **16**. A more pure sample of the alcohol **13c** (3 mg, 7% yield) was obtained in another run.

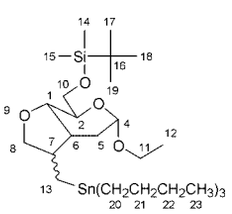
(1*S*,2*S*,4*S*,6*R*)-4-*endo*-Ethoxy-2-*exo*-*tert*-butyldimethylsilyloxymethyl-7-*exo*-(tri-*n*-butylstannylmethylene)-3,9-dioxabicyclo[4.3.0]nonane 19



19

Ethyl 6-*O*-*tert*-butyldimethylsilyl-4-*O*-prop-2-ynyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **18** (100 mg, 0.30 mmol), and AIBN (3 mg, 0.011 mmol, 0.04 equiv.) were dissolved in dry toluene (2 ml) and refluxed under nitrogen for 15 min. A solution of tri-*n*-butyltin hydride (123 mg, 0.43 mmol, 1.3 equiv.) in toluene (4 ml) was added over 3 hours *via* a syringe pump. The reaction solution was refluxed for 16 hours. TLC analysis indicated reaction product and starting material. Purification by column chromatography, eluent hexane to 10% diethyl ether in hexane afforded the title compound **19** (23 mg, 12%) and starting material **18** (24 mg, 24%), both as clear oils; δ_H 5.77 (1H, br d, *J* 1.9, $^2J_{Sn,H}$ 57.2, ^{117}Sn, ^{119}Sn not resolved, 13-H), 4.77 (1H, dd, *J* 5.9, 5.9, 4-H), 4.26 (1H, br d, *J* 13.0, 8a-H), 4.16 (1H, dd, *J* 12.9, 2.0, 8b-H), 3.89 (1H, dd, *J* 7.6, 7.6, 1-H), 3.75 (2H, m, 2-H, 11a-H), 3.63 (2H, m, 10-H_2), 3.36 (1H, dq, *J* 9.5, 7.1, 11b-H), 2.65 (1H, br ddd, *J* 11.3, 6.3, 5.0, 6-H), 1.96 (1H, ddd, *J* 14.2, 5.7, 5.7, 5a-H), 1.66 (1H, br m, 5b-H), 1.41 (6H, m, 22-H_6, $Sn(CH_2)_2CH_2$-), 1.21 (6H, m, 21-H_6, $SnCH_2$-CH_2), 1.10 (3H, dd, *J* 7.1, 7.1, 12-H_3), 0.83 (24H, m, 17-H_3, 18-H_3, 19-H_3, 20-H_6, 23-H_9, $(CH_3)_3CSi$, $SnCH_2(CH_2)_2CH_3$), 0.1 (6H, s, 14-H_3, 15-H_3, $(CH_3)_2Si$); ^{1}H–^{1}H *J*-COSY NMR 1-H to 2-H to 10-H_2, 1-H to 6-H, 4-H to 5a-H to 5b-H to 6-H, 2-H to 10-H_2, 4-H to 5b-H to 6-H to 13-H (weak), 8a-H to 8b-H to 13-H, 8a-H to 13-H, 11a-H to 11b-H to 12-H_3, 11b-H to 12-H_3, 20-H_6 to 21-H_6 to 22-H_6 to 23-H_9; δ_C 159.9 (C, 7-C), 117.3 (CH, 13-C), 97.3 (CH, 4-C), 77.4 (CH, 1-C), 72.9 (CH_2, 8-C), 71.2 (CH, 2-C), 64.7 (CH_2, 11-C), 62.9 (CH_2, 10-C), 42.1 (CH, 6-C), 31.9 (CH_2, 5-C), 29.5 (CH_2, 22-C, Sn-$(CH_2)_2CH_2$-), 27.7 (CH_2, 21-C, Sn-CH_2CH_2-), 26.3 (CH_3, 17-C, 18-C, 19-C, $(CH_3)_3CSi$), 18.8 (C, 16-C), 15.5 (CH_3, 12-C), 14.1 (CH_3, 23-C, $Sn(CH_2)_3CH_3$), 10.1 (CH_2, 20-C, $SnCH_2$); *m*/*z* (EI^+, peaks marked with * are tin cluster maxima) 614* (28%, $C_{29}H_{58}O_4SiSn$, M^+), 574* (23%, M − EtOH), 557* (51%, M − Bu), 513* (45%, M − EtOH − Bu), 329 (33%, M − Bu_3Sn), 288 (57%), 73 (100%); ν_{max} (neat)/cm^{-1} 2956, 2947, 2871, 2856, 1126, 1056, 837.

(1*S*,2*S*,4*S*,6*R*,7*S*)-4-*endo*-Ethoxy-2-*exo*-*tert*-butyldimethylsilyloxymethyl-7-*exo*-(tri-*n*-butylstannylmethyl)-3,9-dioxabicyclo[4.3.0]nonane 24

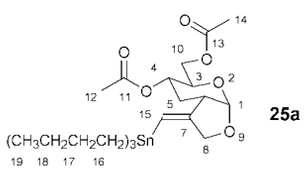


24

Ethyl 6-*O*-*tert*-butyldimethylsilyl-4-prop-2-enyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **23** (100 mg, 0.30 mmol) was dissolved in dry toluene (3 ml) and the solution warmed to reflux under nitrogen. AIBN (2 mg, 0.01 mmol, 0.04 equiv.) was added and the solution refluxed for a further ten minutes. A

solution of tri-*n*-butyltin hydride (135 mg, 0.46 mmol, 1.5 equiv.) in dry toluene (3 ml) was added over 3 hours from a syringe pump. The solution was refluxed for 15 hours. TLC analysis indicated partial reaction of the starting material. Purification of the crude reaction mixture by flash column chromatography, eluent hexane to 10% diethyl ether in hexane afforded the title compound **24** as a mixture of isomers (14 mg, 7%) and recovered starting material **23** (38 mg, 38%). δ_H 4.79 (0.5H, dd, *J* 8.5, 5.6, 4-H), 4.74 (0.5H, t, *J* 4.3, 4-H), 3.94 (0.5H, t, *J* 7.6, 8a-H), 3.90–3.47 (5H, m, 1-H, 2-H, 10-H_2, 11a-H), 3.41 (0.5H, dq, *J* 8.5, 7.0, 11b-H), 3.32 (1H, m), 3.17 (0.5H, t, *J* 8.3, 8b-H), 1.90 (0.5H, dt, *J* 13.5, 5.3, 5-H), 1.80 (0.5H, dt, *J* 13.5, 5.2, 5-H), 1.71 (0.5H + 0.5H, m, H-6), 1.38 (6H, m), 1.23 (6H, m), 1.14 (3H, t, *J* 6.9, 12a-H_3), 1.11 (3H, t, *J* 7.5, 12b-H_3), 0.85–0.70 (17-H_3, 18-H_3, 19-H_3, 20-H_6, 23-H_9), 0.00 (6H, s, 14-H_3, 15-H_3, $(CH_3)_2$Si); ^{1}H–^{1}H *J*-COSY NMR 4-H to 5-H to 6-H, 8a-H to 8b-H, 11-H_2 to 12a-H_3, 11-H_2 to 12b-H_3; δ_C 98.1, 97.0 (peak height ratio 42 : 58, 4-C), 78.3, 77.6, 76.2, 75.5, 74.8, 72.7, 70.4, 65.0, 64.6, 63.0, 62.8, 44.7, 42.1, 41.5, 39.6, 29.9, 29.6, 28.1, 27.8, 26.33, 26.30, 18.6, 15.5, 14.1, 11.2, 9.6, 9.5; *m*/*z* (EI) 620 ($C_{29}H_{60}O_4{}^{120}$SnSi, M, absent), 576 (1%, tin cluster, M − O-CH_2CH_3), 516 (100%, tin cluster, M − O-Si^{t}BuMe$_2$), 289 (35%, tin cluster), 175 (27%, tin cluster), 41 (56%); *m*/*z* (CI^+, NH_3) 638 (6%, $C_{29}H_{64}O_4Si^{120}SnN$, M + NH_4^+, cluster analysis correct), 592 (4%, M + NH_4 − EtOH), 575 (33%, tin cluster), 517 (24%, tin cluster), 308 (100%, Sn cluster); ν_{max} ($CDCl_3$)/cm^{-1} 2927, 1248.

(1*S*,3*R*,4*S*,6*S*)-4-*endo*-Acetoxy-3-*exo*-acetoxymethyl-7-(*Z*-tri-*n*-butylstannylmethylene)-2,9-dioxabicyclo[4.3.0]nonane 25a



25a

Prop-2-ynyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **7a** (500 mg, 1.86 mmol) and AIBN (13 mg, 0.079 mmol, 0.04 equiv.) were dissolved in dry toluene (10 ml) and warmed to reflux under argon. TBTH (597 mg, 2.05 mmol, 1.1 equiv.) was dissolved in dry toluene (1.5 ml) and added to the reaction solution over 4 hours using a syringe pump. The solution was allowed to reflux for a further 12 hours, cooled and evaporated to dryness. Purification by flash column chromatography; eluent hexane to 20% ethyl acetate in hexane, afforded the title compound **25a** (677 mg, 65%). Repetition of this reaction on 10 × scale: **7a** (5 g, 18.6 mmol), AIBN (0.13 g, 0.79 mmol, 0.04 equiv.), in toluene (100 ml) plus TBTH (5.97 g, 20.5 mmol, 1.1 equiv.) in toluene (5 ml) afforded TBTH (1.13 g, 19%), the title compound **25a** (2.75 g, 28%) and starting material **7b** (1.7 g, 34%). Combustion analysis: $C_{25}H_{44}O_6Sn$ requires C 53.69, H 7.93; found C 53.47, H 7.78%; δ_H 5.88 (1H, m, $^2J_{H\text{-}Sn117/119}$ 54, 15-H), 5.38 (1H, d, *J* 4.6, 1-H), 4.77 (1H, td, *J* 9.3, 5.0, 4-H), 4.57 (1H, ddd, *J* 13.2, 2.4, 1.5, 8a-H), 4.27 (1H, dd, *J* 12 0, 5.0, 10a-H), 4.22 (1H, dd, *J* 12.0, 3.0, 10b-H), 4.16 (1H, dd, *J* 12.1, 2.2, 8b-H), 4.01 (1H, ddd, *J* 9.1, 5.1, 2.3, 3-H), 2.77 (1H, br m, 6-H), 2.23 (1H, ddd, *J* 13.6, 6.7, 5.3, *eq*-5-H), 2.09 (3H, s, CH_3CO), 2.02 (3H, s, CH_3CO), 1.70 (1H, dt, *J* 13.4, 9.4, *ax*-5-H), 1.51 (6H, m, 18-H_6, $Sn(CH_2)_2CH_2$), 1.35 (12H, m, 16-H_6, 17-H_6, $SnCH_2CH_2$), 0.89 (9H, m, 19-H_9, $Sn(CH_2)_3CH_3$); δ_H (C_6D_6) 5.83 (1H, d, *J* 1.2, 15-H), 5.44 (1H, d, *J* 4.4, 1-H), 5.08 (1H, ddd, *J* 9.5, 9.5, 4.8, 4-H), 4.72 (1H, br m, 8a-H), 4.55 (1H, dd, *J* 12.1, 5.0, 10a-H), 4.35 (2H, m, 8b-H, 10b-H), 4.27 (1H, ddd, *J* 9.5, 4.9, 2.4, 3-H), 2.43 (1H, m, 6-H), 2.21 (1H, ddd, *J* 12.8, 7.2, 5.2, *eq*-5-H), 1.80 (3H, s, CH_3CO), 1.75 (3H, s, CH_3CO), 1.72 (1H, m, *ax*-5-H), 1.64. (6H, m, 18-H_6, $Sn(CH_2)_2CH_2$), 1.42 (12H, m, 16-H_6, 17-H_6, $SnCH_2CH_2$), 1.04 (9H, m, 19-H_9, $Sn(CH_2)_3CH_3$); ^{1}H-^{1}H *J*-COSY NMR 1-H to 6-H to *eq*-5-H to 4-H, 6-H to *ax*-5-H to 4-H, 4-H to 3-H to 10a-H to 10b-H, 3-H to 10b-H, 8a-H to 8b-H to 11-H, 8a-H to 15-H, 16-H_6 to 17-H_6 to 18-H_6 to 19-H_9; δ_C 171.3, 170.5 (2CO), 157.2 (C, 7-C, $^2J_{C\text{-}Sn117/119}$ 227), 119.8 (CH_2, 15-C), 101.1 (CH, 1-C), 70.9 (CH_2, 8-C), 70.1 (CH, 4-C), 66.6 (CH, 3-C), 63.4 (CH_2, 10-C), 43.8 (CH, 6-C), 31.70 (CH_2, 5-C), 29.5 (CH_2, 18-C, $Sn(CH_2)_2CH_2$-), 27.7 (CH_2, 17-C, $SnCH_2$-CH_2), 21.4 ($2CH_3$, 12-C, 14-C), 14.1 (CH_3, 19-C, $Sn(CH_2)_3CH_3$), 10.2 (CH_2, 16-C, $SnCH_2$); *m*/*z* (EI^+), only the highest intensity ions are reported for tin ion clusters 560 (0%, $C_{25}H_{44}O_6Sn$), 500 (56%, M − AcOH), 440 (43%, M − 2AcOH), 383 (76%, M − 2AcOH − Bu), 291 (71%, Bu_3Sn), 235 (51%), 231 (93%), 57 (100%); ν_{max} (neat)/cm^{-1} 3460 (weak), 2840, 1740 (str), 1625 (weak), 1460; ν_{max} ($CDCl_3$)/cm^{-1} 2956, 2919, 2872, 2852, 1744 (str, C=O), 1628 (weak), 1243; R_f 0.65 (hexane–EtOAc, 50 : 50).

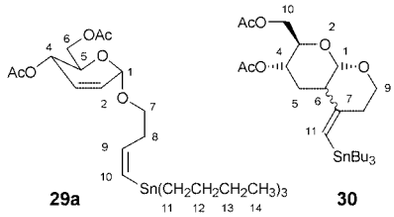
(1*S*,3*R*,4*S*,6*S*)-4-*endo*-Acetoxy-3-*exo*-acetoxymethyl-7-methylene-2,9-dioxabicyclo[4.3.0]nonane 25c by cyclisation of 26

1-(2-Chloroprop-2-enyl) 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **26** (100 mg, 0.31 mmol), was dissolved in dry toluene (3 ml) and heated to reflux under nitrogen. A catalytic amount of AIBN (3 mg, 0.01 mmol, 0.04 equiv.) was added and the solution refluxed for a further 10 min. A solution of tri-*n*-butyltin hydride (131 mg, 0.15 mmol, 1.5 equiv.) in dry toluene (3 ml) was added over 3 hours from a syringe pump and the reaction solution allowed to reflux for a further 16 hours. Purification by column chromatography, eluent hexane to 10% diethyl ether in hexane, afforded the title compound **25c** (27 mg, 30%) as a clear oil, with identical spectroscopy to previously prepared product, and unconverted starting material **26** (8 mg, 8.0%) plus a slightly impure fraction containing the product **26** (23 mg, <26%).

Attempted preparation of (1*S*,3*R*,4*S*,6*S*)-4-*endo*-acetoxy-3-*exo*-acetoxymethyl-5-prop-2-enyl-7-(*E*-tri-*n*-butylstannylmethylene)-2,9-dioxabicyclo[4.3.0]nonane 27

Prop-2-ynyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **7a** (2 g, 7.0 mmol), allyltri-*n*-butyltin (5.80 g, 17.5 mmol, 2.5 equiv.) and AIBN (51 mg, 0.2 mmol, 0.03 equiv.) were dissolved in dry benzene (60 ml) and warmed to reflux. Tri-*n*-butyltin hydride (210 mg, 0.72 mmol, 0.1 equiv.) was dissolved in dry benzene (5 ml) and added dropwise by a syringe pump. The solution was refluxed for 14 hours, evaporated to dryness, and purified by flash column chromatography, eluent hexane to 10% ethyl acetate in hexane, to yield (1*S*,3*R*,4*S*,6*S*)-4-*endo*-acetoxy-3-*exo*-acetoxymethyl-7-(*Z*-tri-*n*-butylstannylmethylene)-2,9-dioxabicyclo[4.3.0]nonane **25a** (1.1 g, 28%), starting material **7a** (400 mg, 10%) and a mixture of **25a** and **7a** (150 mg, 4%).

(*Z*)-(4-Tri-*n*-butylstannylbut-3-enyl) 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside 29a and (1*S*,3*R*,4*S*,6*S*)-4-*endo*-acetoxy-3-*exo*-acetoxymethyl-7-(*E*-tri-*n*-butylstannylmethylene)-2,10-dioxabicyclo[4.4.0]decane 30



29a **30**

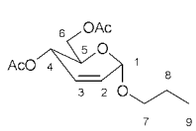
But-3-ynyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **28** (420 mg, 1.5 mmol) was dissolved in dry toluene (3 ml). The solution was warmed to reflux under nitrogen and AIBN (10 mg, 0.06 mmol, 0.04 equiv.) added in one

portion. Tri-*n*-butyltin hydride (0.66 g, 2.3 mmol, 1.5 equiv.) was dissolved in dry toluene (4 ml) and added dropwise from a syringe pump over 4 hours. The reaction solution was refluxed for 16 hours. TLC analysis of the reaction solution indicated a complex mixture of starting material **28** and two products, both of very similar polarity. The more polar product was present only at a very small amount. The reaction solution was concentrated to approximately 1 ml and purified by repeated column chromatography over silver nitrate impregnated silica gel, eluent hexane to 10% diethyl ether in hexane, to afford the title products **29a** (270 mg, 32%), **30** (<5 mg), a mixture of **29a** and **30** (50 mg, 6%) and starting material **28** (70 mg, 16%).

Spectroscopic data for (*Z*)-(4-tri-*n*-butylstannylbut-3-enyl) 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **29a**: combustion analysis: $C_{26}H_{46}O_6Sn$ requires C 54.47, H 8.09; found C 54.42, H 8.28%; δ_H 6.45 (1H, ddd, *J* 12.6, 6.9, 6.9, 9-H), 5.87 (1H, d, *J* 12.4, 10-H), 5.82 (1H, br d, *J* 10.8, 3-H), 5.76 (1H, ddd, *J* 10.2, 2.1, 2.1, 2-H), 5.25 (1H, dd, *J* 9.7, 1.3, 4-H), 4.97 (1H, br s, 1-H), 4.20 (1H, dd, *J* 12.1, 5.2, 6a-H), 4.10 (1H, dd, 12.0, 2.3, 6b-H), 4.05 (1H, ddd, *J* 9.6, 5.2, 2.2, 5-H), 3.75 (1H, ddd, *J* 9.4, 7.0, 7.0, 7a-H), 3.46 (1H, ddd, *J* 9.3, 6.9, 6.9, 7b-H), 2.29 (2H, app q, *J* 6.7, 8-H_2), 2.04 (3H, s, 16-H_3 or 18-H_3, CH_3CO), 2.02 (3H, s, 16-H_3 or 18-H_3, CH_3CO), 1.43 (6H, m, 13-H_6, $Sn(CH_2)_2CH_2$), 1.25 (6H, m, 12-H_6, $SnCH_2$-CH_2), 0.84 (15H, m, 11-H_6, 14-H_9, $SnCH_2(CH_2)_2CH_3$); ^1H–^1H *J*-COSY NMR 1-H to 2-H to 3-H, 4-H to 5-H to 6a-H, 5-H to 6b-H, 6a-H to 6b-H, 7a-H to 7b-H, 7a-H to 8-H_2, 7b-H to 8-H_2, 8-H_2 to 9-H (weak), 9-H to 10-H, 11-H_6 to 12-H_6 to 13-H_6 to 14-H_9; δ_H (C_6D_6) 6.61 (1H, dt, *J* 12.6, 6.9, 9-H), 6.08 (1H, d, *J* 12.5, 10-H), 5.73 (1H, d, *J* 10.3, 3-H), 5.53 (1H, m, 2-H), 5.50 (1H, dd, *J* 9.6, 1.4, 4-H), 4.79 (1H, s, 1-H), 4.31 (2H, m, 6-H_2), 4.23 (1H, ddd, *J* 9.5, 3.8, 3.8, 5-H), 3.80 (1H, dt, *J* 9.4, 6.9, 7a-H), 3.37 (1H, dt, *J* 9.3, 6.6, 7b-H), 2.39 (2H, m, 8-H_2), 1.67 (3H, 16-H_3, or 18-H_3, CH_3CO), 1.56 (6H, m, 13-H_6, $Sn(CH_2)_2CH_2$), 1.54 (3H, 16-H_3 or 18-H_3, CH_3CO), 1.35 (6H, m, 12-H_6, $SnCH_2$-CH_2), 1.01 (6H, m, 11-H_6, $SnCH_2$), 0.93 (9H, m, 14-H_9, $Sn(CH_2)_3CH_3$); δ_C 170.7, 170.2 (s, s, 15-C, 17-C, CO), 144.9 (d, 9-C), 131.5 (d, 10-C), 129.4 (d, 3-C), 128.2 (d, 2-C), 94.8 (d, 1-C), 68.6 (t, 7-C), 67.3 (d, 4-C), 65.6 (d, 5-C), 63.4 (t, 6-C), 37.6 (t, 8-C), 29.6 (t, 13-C, $Sn(CH_2)_2CH_2$), 27.6 (t, 12-C, $SnCH_2$-CH_2), 21.4, 21.2 (q, q, 16-C, 18-C), 14.1 (q, 14-C, $Sn(CH_2)_3$-CH_3), 10.6 (t, 11-C, $SnCH_2$); *m*/*z* (EI) 574 ($C_{26}H_{46}O_6{}^{120}Sn$, M, absent), 517 (9%, tin cluster, M − Bu), 457 (4%, tin cluster, M − Bu − AcOH), 415 (4%, tin cluster), 213 (100%, M − Bu_3Sn-CH=CH-CH_2-CH_2-OH), 153 (80%, M − Bu_3SnCH=CH-CH_2-CH_2-OH − AcOH), 110 (74%), 43 (65%); ν_{max} (Nujol)/cm^{-1} 1745 (C=O, str), 1595 (weak), 1230, 1040; R_f 0.55 (hexane–EtOAc, 75 : 25).

Spectroscopic data for (1*S*,3*R*,4*S*,6*S*)-4-*endo*-acetoxy-3-*exo*-acetoxymethyl-7-(*E*-tri-*n*-butylstannylmethylene)-2,10-dioxabicyclo[4.4.0]decane **30**: δ_H 6.01 (1H, s, 11-H), 5.15 (2H, m, 1-H, 4-H), 4.22, 3.95 (m, 3-H, 9-H_2, 11-H_2), 2.2 (m, H-6, 8-H_2), 2.1 (6H, s). The remainder of the spectrum indicated the presence of a large excess of non-stoichiometric tin residues; R_f 0.57 (hexane–EtOAc, 75 : 25).

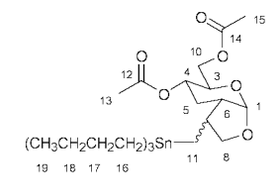
Propyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside 31b



31b

3-Bromopropyl 4,6-*O*-di-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **31a** (1.0 g, 2.8 mmol) was dissolved in dry benzene (5 ml) and warmed to reflux under nitrogen. AIBN (20 mg, 1.2 mmol, 0.04 equiv.) was added in a single portion and the reaction solution refluxed for 15 mins. A solution of tri-*n*-butyltin hydride (1.2 g, 4.2 mmol, 1.5 equiv.) in dry toluene (3 ml) was added dropwise from a syringe pump over 4 hours and the reaction solution refluxed for 12 hours. Analysis by TLC indicated the presence of a single product and starting material. Purification by column chromatography, eluent hexane to 30% EtOAc in hexane, afforded the reduction product **31b** (600 mg, 77%). None of the expected cyclised product was detected. Combustion analysis: $C_{13}H_{20}O_6$ requires C 57.34, H 7.40; found C 57.65, H 7.52%; δ_H 5.82 (1H, d, *J* 10.8, 3-H), 5.77 (1H, ddd, *J* 10.2, 1.9, 1.9, 2-H), 5.24 (1H, dd, *J* 9.6, 0.9, 4-H), 4.96 (1H, s, 1-H), 4.16 (2H, m, 6-H_2), 4.05 (1H, ddd, *J* 9.6, 5.4, 2.4, 5-H), 3.66 (1H, ddd, *J* 9.5, 6.8, 6.8, 7a-H), 3.42 (1H, ddd, *J* 9.5, 6.6, 6.6, 7b-H), 2.04, 2.02 (3H, 3H, s, s, 11-H_3, 13-H_3, $2CH_3CO$), 1.56 (2H, m, 8-H_2), 0.97 (3H, t, *J* 7.4, 9-H_3); δ_C 171.2, 170.7 (10-C and 12-C, 2CO), 129.4 (3-C), 128.4 (2-C), 94.8 (1-C), 71.0 (4-C), 67.3 (7-C), 65.7 (5-H), 63.5 (6-C), 23.4 (8-C), 21.4, 21.2 ($2CH_3$, 11-C, 13-C), 11.2 (CH_3, 9-C); *m*/*z* (EI^+) 272 (M, $C_{13}H_{20}O_6$, absent), 213 (100%, M − OPr), 170 (68%, M − $OHCCH_2OAc$, retro Diels–Alder), 153 (73%, M − OPr − AcOH), 128 (57%), 111 (54%, M − $OHCCH_2OAc$–OPr), 86 (65%), 57 (42%); *m*/*z* (CI^+, NH_3) 290 (18%, M + NH_4, $C_{13}H_{24}NO_6$), 230 (28%, M + NH_4 − AcOH), 213 (100%, M − OPr), 172 (15%), 153 (12%), 128 (11%); ν_{max} ($CDCl_3$)/cm^{-1} 2980, 1740 (str, C=O), 1220; R_f 0.75 (ether).

(1*S*,3*R*,4*S*,6*S*)-4-*endo*-Acetoxy-3-*exo*-acetoxymethyl-7-(tri-*n*-butylstannylmethyl)-2,9-dioxabicyclo[4.3.0]nonane 34a, b

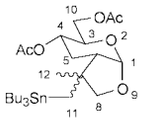


34a, b

Prop-2-enyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (100 mg, 0.54 mmol) **33a** was dissolved in dry toluene (3 ml) and warmed to reflux under nitrogen. AIBN (4 mg, 0.02 mmol, 0.04 equiv.) was added portionwise and the reaction refluxed for 15 min. A solution of tri-*n*-butyltin hydride (240 mg, 0.82 mmol, 1.5 equiv.) in dry toluene (3 ml) was added dropwise by a syringe pump over 3 hours. The reaction solution was refluxed for 16 hours. TLC analysis indicated a complex mixture containing two major products. Repeated column chromatography, eluent hexane to 10% ether in hexane, gave a mixture of two products **34a**, **b**, (10 mg, 5% yield), ratio 1 : 1 from analysis of the ^1H-NMR spectrum of the crude reaction mixture. δ_H 5.45 (0.5H, br d, 1-H), 5.35 (0.5H, br d, 1-H′), 4.79 (1H, m, 4-H), 4.25 (2H, m, 8a-H, 10a-H), 4.13 (1H, m, 10b-H), 3.93 (1H, m, 8b-H), 3.55 (0.5H, m, 3-H), 3.45 (1H, m, 7-H), 3.36 (0.5H, m, 3-H), 2.63 (0.5H, m, 6-H), 2.23 (0.5H, m), 2.12 (0.5H, m), 2.05 (6H, s, CH_3CO), 2.02 (3H, s, CH_3CO), 1.99 (3H, s, CH_3CO), 1.85 (1H, m, 5-H), 1.45 (6H, m, 18-H_6, $Sn(CH_2)_2CH_2$), 1.30 (12H, m, 16-H_6, 17-H_6, $SnCH_2(CH_2)_2$), 0.92 (11H, m, 11-H_2, 19-H_9, $CH_2Sn(CH_2)_3CH_3$); *m*/*z* (EI^+) 562 (M, $C_{25}H_{46}O_6{}^{120}Sn$, absent), 505 (24%, Sn cluster, M − Bu), 445 (11%, Sn cluster, M − AcOH), 385 (4%, M − Bu − AcOH − AcOH), 293 (53%, Sn cluster, Bu_3SnH), 179 (49%, BuSn), 57 (100%); ν_{max} ($CDCl_3$)/cm^{-1} 2927, 1739 (str, C=O), 1440, 1380, 1220, 1020.

(1*S*,3*R*,4*S*,6*S*)-4-*endo*-Acetoxy-3-*exo*-acetoxymethyl-7-methyl-7-(tri-*n*-butylstannylmethyl)-2,9-dioxabicyclo[4.3.0]nonane 34c, d

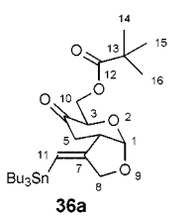
2′-Methylprop-2-enyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **33b** (500 mg, 1.76 mmol), was dissolved in dry benzene (8 ml) and warmed to reflux under nitrogen. AIBN (13 mg, 0.07 mmol, 0.04 equiv.) was added portionwise and the solution refluxed for 10 min. A solution of tri-*n*-butyltin hydride (560 mg, 1.9 mmol, 1.1 equiv.) was added dropwise over



34c, d

3 hours from a syringe pump. Reflux was maintained for 16 hours. TLC analysis indicated the presence of several products and starting material **33b**. Repeated column chromatography, eluent hexane to 10% diethyl ether in hexane, afforded an inseparable mixture (110 mg, 10%), and starting material **33b** (240 mg, 48%). Analysis of the mixture by ^{1}H-NMR indicated a mixture of three components **34c**, **d** and an unassigned compound. The ratio of components was 50 : 35 : 15, based on integration of signals at δ 5.39, 5.31 and 5.24 respectively; δ_H 5.39 (1H, d, *J* 4.9, 1a-H), 5.31 (1H, d, *J* 4.7, 1b-H), 5.24 (1H, d, *J* 4.8, 1c-H), 4.74 (2H, m), 4.24 (3H, m), 4.08 (3H, m), 3.87 (3H, m), 3.58 (1H, q, *J* 4.8, c-H), 3.49 (1H, dd, *J* 10.6, 8.2, b-H), 3.44 (1H, d, *J* 9.2, c-H), 3.32 (1H, dd, *J* 8.4, 4.7, a-H), 2.5 (2H, m, c-H_2), 2.18 (1H, m, c-H), 2.08 (2H, m, 2b-H, b-H), 2.02, 2.00, 1.997, 1.98 (3 × 6H, 4 × s, CH_3CO), 1.85 (1H, m, 2a-H), 1.4 (6H, m, $Bu_3Sn(CH_2)_2CH_2$-), 1.25 (6H, m $Bu_3SnCH_2CH_2$-), 0.78 (14H, m, 11-H_2, 12-H_3, Bu_3SnCH_2-, $Bu_3Sn(CH_2)_3$-CH_3); δ_C 171.3, 170.4, 170.3, 103.6, 102.4, 101.1, 75.0, 73.1, 73.0, 70.0, 69.8, 67.5, 66.9, 63.5, 63.1, 45.1, 42.3, 40.6, 40.0, 29.6, 29.5, 27.8, 27.5, 26.0, 21.5, 21.2, 14.1, 14.0, 9.6, 9.56, 5.20; *m*/*z* (EI$^+$) 588 (M, $C_{27}H_{48}O_6{}^{120}$Sn, absent), 505 (24%, Sn cluster), 445 (9%, Sn cluster, 505 − AcOH), 385 (3%, Sn cluster, 505 − AcOH − AcOH), 292 (Bu_3SnH), 57 (100%); ν_{max} (neat)/cm^{-1} 2958, 1738 (str), 1464, 1376, 1248, 1024; R_f 0.7 (hexane–EtOAc, 50 : 50).

(1*S*,3*R*,6*S*)-3-*exo*-Pivaloyloxymethyl-4-oxo-7-(*Z*-tri-*n*-butylstannylmethylene)-2,9-dioxabicyclo[4.3.0]nonane 36a



36a

Prop-2-ynyl-2,3-dideoxy-6-*O*-pivaloyl-α-D-*erythro*-hex-2-eno-pyran-4-uloside **35c** (50 mg, 0.19 mmol) and AIBN (2 mg, 0.008 mmol, 0.04 equiv.) were dissolved in dry toluene (1 ml) and warmed to reflux under argon. TBTH (66 mg, 0.23 mmol, 1.2 equiv.) was dissolved in dry toluene (2 ml) and added to the reaction solution over 3 hours *via* a syringe pump. The solution was allowed to reflux for a further 16 hours. TLC analysis of the reaction solution indicated a complex mixture of products and starting material. Purification by flash column chromatography, eluent hexane to 20% ethyl acetate in hexane, afforded the title compound **36a** (8 mg, 8%). δ_H 5.88 (1H, dd, *J* 2.5, 2.5, 11-H), 5.82 (1H, d, *J* 7.1, 1-H), 4.45 (2H, m, 10-H_2), 4.35 (2H, m, 8-H_2), 4.05 (1H, dd, *J* 3.7, 3.0, 3-H), 3.43 (1H, br m, 6-H), 2.77 (2H, m, 5-H_2), 1.46 (6H, m, 19-H_6, $Sn(CH_2)_2CH_2$-), 1.30 (6H, m, 18-H_6, $SnCH_2CH_2$), 1.18 (9H, s, 14-H_3, 15-H_3, 16-H_3, $C(CH_3)_3$), 0.92 (15H, m, 17-H_6, 20-H_6, $SnCH_2(CH_2)_2CH_3$); R_f 0.90 (hexane–EtOAc, 50 : 50).

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