PERKIN 2

Conformation of chiral alkoxyallenes by proton NMR spectroscopy

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A comparison of steady-state NOE coefficients measured for 3-*O*-allenyl-substituted furanoses in [$^2H_8$]toluene solution with conformations generated by a molecular mechanics program allowed characterisation of the most favourable ground state conformations. The geometry assigned from NOE coefficients corresponds well to that obtained by X-ray structure analysis of allene **1**.

Introduction

Alkoxyallenes represent an interesting class of compounds which offer a variety of synthetic applications.[1,2] Reactions involving lithiated alkoxyallenes,[3] additions of organometallic compounds to alkoxyallenes,[4] [4 + 2]cycloadditions to electrophilic dienes,[5] and (1,3)dipolar cycloadditions[6] are particularly interesting. Despite the synthetic usefulness of alkoxyallenes there is little information on their conformation.[7]

Recently, we initiated a synthetic project aimed at transforming chiral vinyl ethers derived from sugars and from readily available hydroxy acids into clavams and 5-dethia-5-oxacephams.† [8,9] The crucial step of the synthesis involved a highly exothermic [2 + 2]cycloaddition of vinyl ethers and isocyanates. We have proposed a stereochemical model of the transition state for [2 + 2]cycloaddition of chlorosulfonyl isocyanate to vinyl ethers, based on the lowest energy ground-state conformation derived from nuclear Overhauser effect (NOE) coefficients.[10] This conformation agreed well with the experimental facts and provided a sound explanation of the direction of asymmetric induction.

Application of the NOE method, successfully performed for chiral vinyl ethers, to chiral alkoxyallenes should make it possible to ascribe the most favourable ground-state conformation of these cumulenes. Consequently, it would be reasonable to use the ground-state conformation of alkoxyallenes to reflect their conformation in the transition state of a variety of exothermic reactions such as [2 + 2]cycloaddition to chlorosulfonyl isocyanate.

Results and discussion

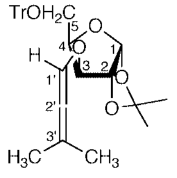
For the present study we selected three allenes **1**, **2** and **3**, readily available from the respective pentafuranoses **4**, **5** and anhydrohexitol **6** by standard methods (*cf.* Experimental).

gem Dimethyl-substituted alkoxyallenes **1**–**3** were chosen as they are more stable than unsubstituted congeners in the presence of strong electrophiles such as chlorosulfonyl isocyanate.

X-Ray crystallography

X-Ray structure analysis of compound **1**[11] provided information about the location of the allene fragment in relation to the rigid bicyclic ring system. As evidenced from the analysis of intracyclic torsion angles both the furanoid and the dioxolane ring adopt the twist conformation shown in Fig. 1 along with the crystallographic labelling scheme. Large substituents located at the C4 and C3 atoms are both placed on the same side of the furanoid moiety. The linear allene fragment points outwards from the ring system, perhaps due to steric overcrowding of the trityl group, and it is located below the ring system in close proximity to the hydrogen atom attached to the C3 carbon. Two torsion angles define the spatial location of the former: C1′–O3–C3–C2 and C2′–C1′–O3–C3 being −90.6(3) and 15.5(6)°, respectively.

The geometry of the crystal-state conformation of **1** was used



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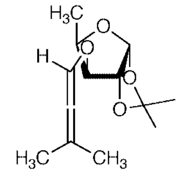

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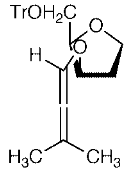

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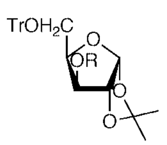
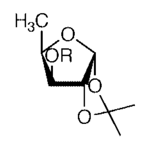


4: R = H
7: R = $CH_2C{\equiv}CH$



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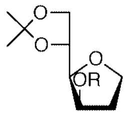
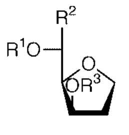
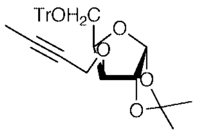
8: R = $CH_2C{\equiv}CH$



6: R = H
9: R = $CH_2C{\equiv}CH$



10: R^1 = H, R^2 = CH_2OH,
R^3 = $CH_2C{\equiv}CH$
11: R^1 = R^2 = H, R^3 = $CH_2C{\equiv}CH$
12: R^1 = Tr, R^2 = H,
R^3 = $CH_2C{\equiv}CH$



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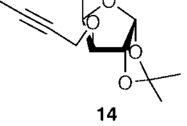

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† IUPAC Recommendations, *Pure Appl. Chem.*, 1999, **71**, 587.

Table 1 Experimental steady-state NOEs (%) for allene **1** in [$^2H_8$]toluene solution. NOEs calculated for the best-fitted conformer are shown in parentheses. Estimated precision of experimental NOEs is ±1%

Irradiated proton	Observed proton H-1′	H-1	H-4	H-2	H-3
H-1′		−0.2 (0.0)	−0.4 (0.0)	1.2 (1.1)	1.9 (0.9)
H-1	−0.2 (0.0)		0.4 (0.9)	11.6 (13.5)	−0.5 (−0.3)
H-4	−0.9 (0.0)	0.9 (1.2)		−0.8 (0.2)	13.6 (11.1)
H-2	2.6 (1.5)	16.0 (16.4)	0.3 (0.2)		1.4 (4.3)
H-3	4.1 (1.5)	−0.8 (−0.4)	11.3 (11.5)	3.9 (5.1)	

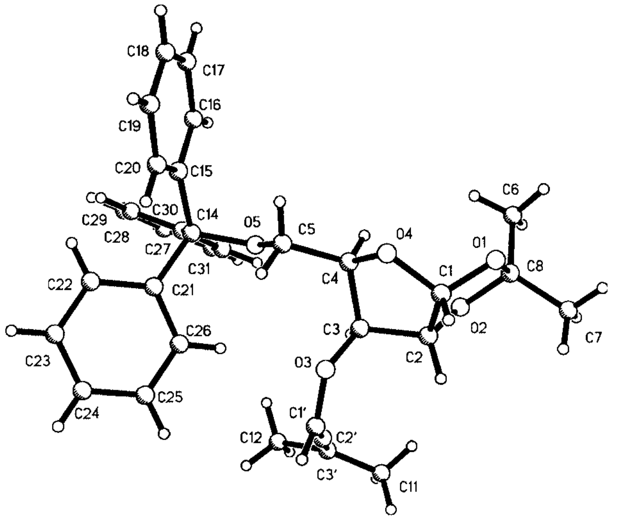

Fig. 1 X-Ray molecular structure of compound **1**.

by us as a base for determination of possible conformations in solution not only for **1** but also for the related compounds **2** and **3**.

Conformational analysis by ^{1}H NMR

Determination of the conformational behaviour of alkoxyallenes **1**–**3** was performed at room temperature in [$^2H_8$]toluene. Vicinal proton–proton coupling constants $^3J_{2,3}$ for both 1,2-*O*-isopropylidene compounds **1** and **2** are below resolution. This is in accordance with the X-ray geometry of **1** in which the torsion angle H2–C2–C3–H3 is equal to −85(8)° and also with respective crystallographic and NMR data obtained for a great number of 1,2-*O*-isopropylidene-α-D-gluco- and xylofuranoses. We assumed, therefore, that the bicyclic fragment exists as a single rigid conformation in solution with well-defined interproton distances that can be taken from the X-ray structure of **1**.

Conformation analysis of allenes **1** and **2** in solution was based on steady-state nuclear Overhauser effects (NOEs) and molecular modelling. For both compounds the analysis was done in the same way, in several steps. The first step involved generation of a set of low-energy conformers by near-random rotations around all rotatable exocyclic bonds (*cf.* Experimental). Then, for each conformer from the set, theoretical steady-state NOEs were calculated (scaled using an external relaxation parameter[12]) using the recently reported computer program *NOE*.[13] As a measure of fit of calculated to experimental NOEs, root-mean-square deviation factors $\mathrm{rms}_{\mathrm{NOE}}$ were used (for definition see Experimental). Finally, the statistical test was applied to assess if the conformation with the lowest $\mathrm{rms}_{\mathrm{NOE}}$ factor was significantly better fitted to the NOE data than any other conformer from the set. In this approach computed energies of individual conformers were ignored and all structures from the conformational set were treated as equally probable.

Proton NMR spectral assignments for **1** and **2** were accomplished by means of chemical shifts, coupling patterns and qualitative analysis of NOEs. The signal assignments for **3** required few additional decoupling experiments.

Table 1 shows steady-state NOEs measured for **1**. Parameters of low-energy conformers of **1** generated by the computer program PCMODEL[14] are presented in Table 2, entry 1. The lowest value of $\mathrm{rms}_{\mathrm{NOE}} = 0.206$. On the basis of statistical analysis (at a 10% significance level) of the values of the $\mathrm{rms}_{\mathrm{NOE}}$ factors, we can assume that all conformers given in bold in Table 2 (entry 1) including the X-ray conformation, are equally well fitted to the data (for details of statistical calculations see Experimental). All best-fitted conformers are s-*cis* type (or *(±)sp* according to Klyne–Prelog notation) around the C1′–O3 bond (torsion angle C2′–C1′–O3–C3 of 0 ± 30°). Furthermore, the best fitted conformers have the same sign of torsion angle C1′–O3–C3–C2 and all values, with one exception, amount to *ca.* −90°.

In order to verify our conformational analysis of **1** based on the steady-state NOEs, we have run a series of one-dimensional transient DPFGSE NOE (double-pulsed-field gradient spin echo)[15] experiments for the same sample. The signal of the H3 proton was inverted by a selective π-pulse and the fractional enhancements of the H1′ and H4 were observed as a function of mixing time (Table 3). Assuming rigidity of the furanoid ring, the distance between the H4 and H3 protons of *ca.* 2.40 Å can be used for estimation of the distance between H1′ and H3 which is clearly different for the s-*cis* and the s-*trans* conformers (Table 2). For the s-*trans* conformers the distance between H1′ and H3 is expected to be around 2.50 Å. Therefore using two-spin-approximation the ratio of transient NOEs H4{H3} to H1′{H3} should be around 1. Experiment shows that for all mixing times applied, this ratio is about 5 (Table 3), corresponding to a distance between H1′ and H3 of around 3.2 Å. These findings unequivocally testify to the s-*cis* conformation of **1** in solution and are in agreement with the steady-state NOE data.

A similar conformational analysis was done for compound **2** on the basis of the crystallographic data found for **1** and of the same assumptions as used for **1**. The same sequence of experiments and calculations was applied. The results for **2** are presented in Tables 2–4. The conformational space modelled by PCMODEL for allene **2** is more diverse than for allene **1**. In particular, the torsion around the C1′–O3 bond in the majority of conformations is of the s-*cis* type (torsion angle C2′–C1′–O3–C3 of 0 ± 20°) but few have *(+)sc* type conformation including the one with the lowest $\mathrm{rms}_{\mathrm{NOE}}$. In the majority of cases the torsion around the O3–C3 bond is of *(−)sc* type having values of *ca.* −80° but some have this torsion of *ca.* −160°. However, all these conformations have the $\mathrm{rms}_{\mathrm{NOE}}$ values lying inside the 10% significance interval for the lowest $\mathrm{rms}_{\mathrm{NOE}}$ value (0.189, 0.337) and hence they cannot be treated as different models. Therefore the same arguments, as deduced for **1** (Table 2, entry 2), lead us to the conclusion that the preferred conformation of **2** is also s-*cis*, being locally isostructural with the X-ray conformation of **1**. The ratio of transient NOEs H4{H3} to H1′{H3} in the case of **2** is about 4 (Table 3) which is again in accordance with the s-*cis* model.

Table 2 Parameters of low energy conformers of allenes **1** and **2**. Conformers best-fitted to steady-state NOE data are give in bold

Energy[a]/kcal mol^{-1}	Torsion angle/° C2′–C1′–O3–C3	Torsion angle/° C1′–O3–C3–C2	Type of conformation	d(H-3, H-1′)/Å	rms$_{NOE}$[b]
Entry 1: allene **1**					
60.18	**0.62**	**−149.29**	***(±)sp(−)ac***	**3.67**	**0.258**
62.18	**−24.92**	**−95.31**	***(±)sp(−)sc***	**3.69**	**0.211**
63.96	**−9.10**	**−88.77**	***(±)sp(−)sc***	**3.69**	**0.206**
65.57	−178.90	−81.64	*(±)ap(−)sc*	2.54	0.453
X-ray	**15.5**	**−90.6**	***(±)sp(−)sc***	**3.40**	**0.239**
Entry 2: allene					
−19.92	**−5.38**	**−73.70**	***(±)sp(−)sc***	**3.74**	**0.261**
−19.09	168.21	−75.60	*(±)ap(−)sc*	2.51	0.439
−18.86	**−1.89**	**−155.26**	***(±)sp(−)ac***	**3.69**	**0.299**
−18.64	−153.92	−163.31	*(±)ap(±)ap*	2.42	0.540
−18.54	168.33	−156.87	*(±)sp(−)ac*	2.49	0.460
−18.34	134.30	−66.63	*(+)ac(−)sc*	2.61	0.360
−17.95	**−18.36**	**−118.56**	***(±)sp(−)sc***	**3.65**	**0.272**
−15.68	**42.87**	**−79.01**	***(+)sc(−)sc***	**3.39**	**0.241**
−14.39	−131.84	−118.21	*(−)ac(−)sc*	2.56	0.393
−14.35	**56.59**	**−156.04**	***(+)sc(±)ap***	**3.55**	**0.291**
[c]	**15.5**	**−90.6**	***(±)sp(−)sc***	**3.40**	**0.292**

[a] Calculated for minimised structures using MM3 force field. [b] For definition see Experimental. [c] The model was obtained by replacement of trityloxy group by a hydrogen atom in the X-ray structure of **1**.

Table 3 Experimental transient NOEs (%) for allenes **1**–**3** as a function of mixing time

Mixing time/ms	Allene **1** H-4{H-3}	Allene **1** H-1′{H-3}	Allene **2** H-4{H-3}	Allene **2** H-1′{H-3}	Allene **3** H-4{H-3}	Allene **3** H-1′{H-3}
500	2.6	0.5	1.3	0.4	1.9	0.4
750			2.0	0.5	2.9	0.5
1000	4.0	0.7	2.4	0.6	3.6	0.6
1500	4.4	0.9				
2000	4.3	0.9				

Table 4 Experimental steady-state NOEs (%) for allene **2** in [^{2}H$_8$]toluene solution. NOEs calculated for the best fitted conformer are shown in parentheses. Estimated precision of experimental NOEs is ±1%

Irradiated proton	Observed proton H-1′	H-1	H-2	H-4	H-3
H-1′		0.1 (0.5)	1.1 (0.5)	0.1 (−0.1)	2.2 (1.6)
H-1	−1.0 (0.1)		9.9 (11.4)	−0.2 (0.8)	−1.0 (−0.2)
H-2	2.2 (0.8)	14.5 (14.0)		−4.7[a] (0.2)	3.8 (4.5)
H-4	−1.5 (−0.1)	0.3 (0.9)	−5.0[a] (0.2)		14.9 (11.1)
H-3	5.1 (2.5)	−2.2 (−0.2)	2.7 (4.0)	9.5 (11.0)	

[a] Direct saturation due to nonselective irradiation. These values were omitted in calculation of rms$_{NOE}$.

The assumption of rigidity of the furanoid ring cannot be directly transferred from **1** and **2** to **3** since in this case the dioxolane ring was removed and the conformational behaviour of the furanoid ring has obviously changed. However, the distance between the H-3 and H-4 protons in **3** is not sensitive to changes of conformation of the five-membered ring and therefore it can be used as a calibration distance. The ratio of transient NOEs H4{H3} to H1′{H3} in the case of **3** is about 5 (Table 3) testifying to the s-*cis* conformation around the C1′–O3 bond. The steady-state NOE data for **3** are presented in Table 5 and are compared to NOEs calculated for the model built on the basis of the X-ray geometry of **1** by deleting the dioxolane ring atoms. It must be stressed that the 'real' conformation of the five-membered ring in **3** was not assigned and the torsion angle C1′–O–C3–C2 which was taken from compounds **1** and **2**, most likely does not reflect the true value.

Our NOE studies on compounds **1**–**3** show with high confidence that the s-*cis* conformation should dominate in solution. We cannot rigorously exclude the possibility that studied molecules exist in solution as conformational mixtures of the s-*cis* and s-*trans* conformers. However, low rms$_{NOE}$ factors for the s-*cis* models together with DPFGSE NOE results provide sound evidence that the presence of the s-*trans* conformer in solution is negligible in modelling ground-state conformations of studied molecules.

NOE studies performed on chiral vinyl ethers led us to the assignment of the lowest energy conformation which corresponded to the conformation in which the plane consists of the s-*trans* vinyl group, the stereogenic centre, and the methyl substituent antiperiplanar to the C1′–O bond (Fig. 2). The ligand bearing an electronegative group was located out of plane, synclinal to C1′ of the vinyl group. The torsion angle C1′–O–C1–C2 of *ca.* 75° was explained in terms of the stereoelectronic interaction of the conjugated π electrons of the double bond, and the lone pair of electrons of the oxygen atom, from one side and the antibonding σ*-orbital of the C1–C2 bond from the

Table 5 Experimental steady-state NOEs (%) for allene **3** in [$^2H_8$]toluene solution. NOEs calculated for molecular model built by deleting dioxolane ring atoms in the X-ray structure of allene **1** are shown in parentheses. Estimated precision of experimental NOEs is ±1%. Root-mean-square NOE factor is equal to 0.260

Irradiated proton	Observed proton					
	H-1′	H-3	H-4	H-1	H-1	H-2
H-1′		1.7 (1.3)	−0.1 (−0.1)	0.1 (0.0)	0.0 (0.2)	0.7 (0.0)
H-3	5.5 (3.3)		13.0 (13.1)	0.1 (−0.5)	−0.2 (0.4)	1.1 (5.0)
H-4	−0.5 (−0.2)	13.6 (13.3)		−1.4[a] (1.0)	2.0 (0.3)	−0.4 (2.8)
H-1	0.5 (−0.1)	0.4 (−0.7)	−1.9[a] (1.3)		27.3 (26.5)	5.8 (9.7)
H-1	−0.2 (0.6)	−0.2 (0.5)	3.1 (0.4)	30.0 (26.4)		−1.3 (−1.1)
H-2	3.2 (0.1)	2.6 (7.3)	0.2 (4.1)	6.4 (11.2)	0.3 (−1.2)	

[a] Direct saturation due to nonselective irradiation. These values were omitted in calculation of rms_{NOE}.

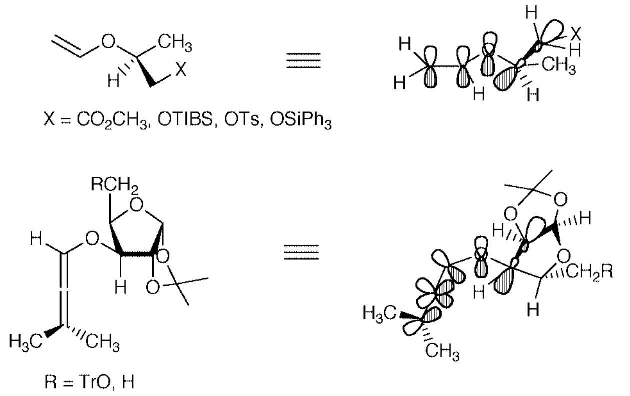

Fig. 2 Illustration of stereoelectronic effects operating in vinyl and allenyl ethers.

other side. For compounds **1** and **2** we observe the steric arrangement which allows similar stereoelectronic interaction between the π electrons of the vinyloxy fragment and the σ*-orbital of the C3–C2 bond (Fig. 2); in both cases the C3–C4 bond, bearing the furanoid ring-oxygen atom does not display a similar arrangement.

Experimental

Melting points were determined on a Kofler hot-stage apparatus with microscope and are uncorrected. Optical rotations were measured using a JASCO P 3010 polarimeter at ambient temperature. ^1H NMR spectra were obtained with Varian Gemini AC-200, Bruker AM-500 and Varian INOVA 500 spectrometers. Chemical shifts are given in ppm and *J* values in Hz; chemical shifts of trityl protons are not reported. IR Spectra were recorded on a Perkin Elmer FT-IR Spectrum 2000 spectrophotometer. Mass spectra were determined with an AMD 604 Inectra GmbH spectrometer. Column chromatography was performed on Merck Kiesel Gel (230–400 mesh).

1,2-*O*-Isopropylidene-5-*O*-trityl-α-D-xylofuranose (4) was obtained according to the known procedure (72%).[16]

5-Deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (5) was obtained from 1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose[17] according to the literature procedure (78%).[18]

1,4-Anhydro-2-deoxy-5,6-*O*-isopropylidene-D-*arabino*-hexitol (6)

A stirred solution of 1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-D-*arabino*-hex-1-enitol[19] (10 g, 53.70 mmol) in anhydrous ethanol (400 cm^3) was hydrogenated over 10% palladium on activated charcoal (50 mg of catalyst per 1 g; FLUKA) for 6 h. Subsequently, the solution was passed through Florisil and evaporated. The residue was purified on a silica gel column using hexane–ethyl acetate 1 : 1 v/v as an eluent to afford **6** as an oil (8.8 g, 87%) (Found: C, 57.27; H, 8.71. $C_9H_{16}O_4$ requires C, 57.43; H, 8.57%); $[\alpha]_D$ −26.1 (0.74 in CH_2Cl_2); ν_{max} (CH_2Cl_2)/cm^{-1} 3589 (OH); δ_H (500 MHz, $CDCl_3$ + D_2O) 1.36, 1.43 (2s, 6H, isoprop.); 1.99 (dddd, 1H, *J* 1.7, 3.9, 6.7 and 13.3, H-2a); 2.14 (dddd, 1H, *J* 5.5, 8.8, 8.8 and 13.3, H-2b); 3.66 (dd, 1H, *J* 3.8 and 8.4, H-4); 3.82–3.86 (m, 1H, H-1a); 3.96 (dd, 1H, *J* 5.2 and 8.5, H-6a); 4.01–4.06 (m, 1H, H-1b); 4.16 (dd, 1H, *J* 6.2 and 8.5, H-6b); 4.28 (ddd, 1H, *J* 5.2, 6.2 and 8.5, H-5); 4.50 (ddd, 1H, *J* 1.7, 3.8 and 5.4, H-3) [Found: HRMS (EI) *m*/*z* (M − CH_3)$^+$, 173.0827. $C_8H_{13}O_4$ requires 173.0814].

General procedure for the preparation of propargyl ethers 7–9

To a solution of the optically active alcohol (15 mmol) in dry DMF (25 cm^3) cooled at 0 °C NaH (60% dispersion in mineral oil, 0.72 g, 18 mmol) was added. The suspension was stirred at 0 °C for 30 min prior to addition of propargyl‡ bromide (1.35 cm^3, 18 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 40 min and then at room temperature for another 1 h. Subsequently, the reaction mixture was poured into water and extracted with *tert*-butyl methyl ether (4 × 70 cm^3). The extract was washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography using 8–10% of ethyl acetate in hexanes gave respective propargyl ethers, **7**–**9**.

1,2-*O*-Isopropylidene-3-*O*-propargyl-5-*O*-trityl-α-D-xylofuranose (7) (95%). White crystals; mp 124.5–127 °C (from AcOEt–hexane) (Found: C, 76.75; H, 6.24. $C_{30}H_{30}O_5$ requires C, 76.57; H, 6.42%); $[\alpha]_D$ −43.1 (*c* 1.0 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 2115 (C≡C), 3269 (H–C≡); δ_H (200 MHz, $CDCl_3$) 1.32, 1.54 (2s, 6H, isoprop.); 2.35 (t, 1H, *J* 2.4, H–C≡); 3.25 (dd, 1H, *J* 7.6 and 9.1, H-5a); 3.48 (dd, 1H, *J* 5.5 and 9.1, H-5b); 4.05 (dd, 1H, *J* 2.4 and 16.0, H-1′a); 4.15 (dd, 1H, *J* 2.4 and 16.0, H-1′b); 4.17 (d, 1H, *J* 3.0, H-3); 4.37 (ddd, 1H, *J* 3.0, 5.5 and 7.6, H-4); 4.60 (d, 1H, *J* 3.8, H-2); 5.84 (d, 1H, *J* 3.8, H-1) [Found: HRMS (EI) *m*/*z* M$^+$, 470.2068. $C_{30}H_{30}O_5$ requires 470.2093].

5-Deoxy-1,2-*O*-isopropylidene-3-*O*-propargyl-α-D-xylofuranose (8) (80%). Oil (Found: C, 62.20; H, 7.70. $C_{11}H_{16}O_4$ requires C, 62.25; H, 7.60%); $[\alpha]_D$ −57.9 (*c* 0.9 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 2118 (C≡C), 3270 (H–C≡); δ_H (200 MHz, $CDCl_3$) 1.30 (d, 3H, *J* 6.4, Me); 1.32, 1.50 (2s, 6H, isoprop.); 2.46 (t, 1H, *J* 2.4, H–C≡); 3.90 (d, 1H, *J* 3.0, H-3); 4.21 (dd, 1H, *J* 2.4 and 16.0, H-1′a); 4.28 (dd, 1H, *J* 2.4 and 16.0, H-1′b); 4.36 (dq, 1H, *J* 3.0 and 6.4, H-4); 4.61 (d, 1H, *J* 3.8, H-2); 5.88 (d, 1H, *J* 3.8, H-1) [Found: HRMS (EI) *m*/*z* (M − CH_3)$^+$, 197.0833. $C_{10}H_{13}O_4$ requires 197.0814].

1,4-Anhydro-2-deoxy-5,6-*O*-isopropylidene-3-*O*-propargyl-D-*arabino*-hexitol (9) (83%). Oil (Found: C, 63.35; H, 7.80; $C_{12}H_{18}O_4$ requires C, 63.70; H, 8.02%); $[\alpha]_D$ −36.3 (*c* 0.6 in CH_2Cl_2); ν_{max} (CH_2Cl_2)/cm^{-1} 2120 (C≡C), 3303 (H–C≡); δ_H (500

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‡ Propargyl is prop-2-ynyl.

MHz, $CDCl_3$) 1.36, 1.43 (2s, 6H, isoprop.); 2.01–2.14 (m, 2H, H-2a, H-2b); 2.41 (t, 1H, *J* 2.4, H–C≡); 3.82 (dd, 1H, *J* 3.8 and 6.4; H-4); 3.83–3.87 (m, 1H, H-1a); 3.94 (dd, 1H, *J* 6.1 and 8.4, H-6a); 3.94–3.99 (m, 1H, H-1b); 4.06 (dd, 1H, *J* 6.4 and 8.4, H-6b); 4.20 (dd, 1H, *J* 2.4 and 16.0, H-1′a); 4.24 (dd, 1H, *J* 2.4 and 16.0, H-1′b); 4.25–4.28 (m, 1H, H-3); 4.31 (q, 1H, *J* 6.4, H-5) [Found: HRMS (EI) *m*/*z* $(M - CH_3)^+$, 211.0981. $C_{11}H_{15}O_4$ requires 211.0970].

1,4-Anhydro-2-deoxy-3-*O*-propargyl-D-*threo*-pentitol (11)

Compound **11** was obtained from **9** by the standard reaction sequence[20] involving deprotection of the isopropylidene grouping, glycolic cleavage of the terminal diol **10** and reduction of the aldehyde to the pentitol **11**. The crude product was purified by column chromatography on silica gel using hexane–ethyl acetate 2:3 v/v as an eluent to give **11** (85%). Syrup (Found: C, 61.83; H, 7.88. $C_8H_{12}O_3$ requires C, 61.52; H, 7.74%); $[\alpha]_D$ −82.8 (*c* 0.92 in CH_2Cl_2); ν_{max} $(CH_2Cl_2)/cm^{-1}$ 2120 (C≡C), 3302 (H–C≡), 3580 (OH); δ_H (500 MHz, $CDCl_3$ + D_2O) 2.03–2.15 (m, 2H, H-2a, H-2b); 2.45 (t, 3H, *J* 2.4, H–C≡); 3.78–3.85 (m, 3H, H-1a, H-5a, H-5b); 3.96 (q, 1H, *J* 5.3, H-4); 4.02 (m, 1H, H-1b); 4.12 (dd, 1H, *J* 2.4 and 16.0, H-1′a); 4.26 (dd, 1H, *J* 2.4 and 16.0, H-1′b); 4.40–4.43 (m, 1H, H-3).

1,4-Anhydro-2-deoxy-3-*O*-propargyl-5-*O*-trityl-D-*threo*-pentitol (12)

Compound **12** was obtained from **11** according to the known procedure described for **4** (94%). Oil (Found: C, 81.20; H, 6.33; $C_{27}H_{26}O_3$ requires C, 81.38; H, 6.58%); $[\alpha]_D$ −27.5 (*c* 0.8 in CH_2Cl_2); ν_{max} $(CH_2Cl_2)/cm^{-1}$ 2120 (C≡C), 3309 (H–C≡); δ_H (500 MHz, $CDCl_3$) 2.00–2.10 (m, 2H, H-2a, H-2b); 2.31 (t, 1H, *J* 2.4, H–C≡); 3.27 (dd, 1H, *J* 6.3 and 9.4, H-5a); 3.38 (dd, 1H, *J* 6.0 and 9.4, H-5b); 3.80–3.84 (m, 1H, H-1a); 3.91–3.96 (m, 1H, H-1b); 3.99 (ddd, 1H, *J* 4.0, 6.0 and 6.3, H-4); 4.01 (dd, 1H, *J* 2.4 and 16.0, H-1′a); 4.10 (dd, 1H, *J* 2.4 and 16.0, H-1′b); 4.29–4.31 (m, 1H, H-3) [Found: HRMS (EI) *m*/*z* M^+, 398.1837. $C_{27}H_{26}O_3$ requires 398.1882].

3-*O*-(But-2′-ynyl)-1,2-*O*-isopropylidene-5-*O*-trityl-α-D-xylofuranose (13)

To a mixture of BuLi (2.5 M in hexane, 5.52 cm^3, 13.81 mmol) and dry THF (40 cm^3) under argon was added **7** (5.0 g, 10.62 mmol) in THF (20 cm^3) at −60 °C with stirring. The mixture was then allowed to warm up slowly to −20 °C and then treated with MeI (0.86 cm^3, 13.81 mmol). Stirring was continued for 1 h while warming up to room temperature. The mixture was diluted with *tert*-butyl methyl ether–hexane 1:1 v/v, washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was purified on a silica gel column using hexane–ethyl acetate 92:8 v/v as an eluent to give **13** (4.3 g, 84%). Oil (Found: C, 76.82; H, 6.60. $C_{31}H_{32}O_5$ requires C, 76.84; H, 6.65%); $[\alpha]_D$ −32.2 (*c* 0.6 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 2225 (C≡C); δ_H (200 MHz, $CDCl_3$) 1.32, 1.53 (2s, 6H, isoprop.); 1.76 (t, 3H, *J* 2.4, Me–C≡); 3.28 (dd, 1H, *J* 7.6 and 9.1, H-5a); 3.44 (dd, 1H, *J* 5.5 and 9.1, H-5b); 4.04 (dq, 1H, *J* 2.3 and 15.4, H-1′a); 4.14 (dq, 1H, *J* 2.3 and 15.4, H-1′b); 4.17 (d, 1H, *J* 3.0, H-3); 4.36 (ddd, 1H, *J* 3.0, 5.5 and 7.6, H-4); 4.58 (d, 1H, *J* 3.8, H-2); 5.85 (d, 1H, *J* 3.8, H-1) [Found: HRMS (LSIMS) *m*/*z* $(M + Na)^+$, 507.2168. $C_{31}H_{32}O_5Na$ requires 507.2147].

3-*O*-(But-2′-ynyl)-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (14)

Compound **14** was obtained from **8** according to the procedure described for **13** (75%). $[\alpha]_D$ −45.7 (*c* 0.13 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 2226 (C≡C); δ_H (200 MHz, $CDCl_3$) 1.31 (d, 3H, *J* 6.4, Me); 1.31, 1.50 (2s, 6H, isoprop.); 1.85 (t, 3H, *J* 2.3, Me–C≡); 3.89 (d, 1H, *J* 3.0, H-3); 4.15 (dq, 1H, *J* 2.3 and 15.4, H-1′a); 4.24 (dq, 1H, *J* 2.3 and 15.4, H-1′b); 4.35 (dq, 1H, *J* 3.0, 6.4, H-4); 4.60 (d, 1H, *J* 3.8, H-2); 5.89 (d, 1H, *J* 3.8, H-1) [Found: HRMS (EI) *m*/*z* $(M - CH_3)^+$, 211.0949. $C_{11}H_{15}O_4$ requires 211.0970].

1,4-Anhydro-3-*O*-(but-2′-ynyl)-2-deoxy-5-*O*-trityl-D-*threo*-pentitol (15)

Compound **15** was obtained from **12** according to the procedure described for **13** (79%) (Found: C, 81.65; H, 6.87. $C_{28}H_{28}O_3$ requires C, 81.52; H, 6.84%); $[\alpha]_D$ −24.3 (*c* 0.5 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 2224 (C≡C); δ_H (500 MHz, $CDCl_3$) 1.77 (t, 3H, *J* 2.4, Me–C≡); 2.00–2.09 (m, 2H, H-2a, H-2b); 3.29 (dd, 1H, *J* 6.2 and 9.4, H-5a); 3.36 (dd, 1H, *J* 6.0 and 9.4, H-5b); 3.79–3.84 (m, 1H, H-1a); 3.91–3.96 (m, 1H, H-1b); 3.98 (dq, 1H, *J* 2.3 and 15.4, H-1′a); 3.99 (ddd, 1H, *J* 4.0, 6.0 and 6.2, H-4); 4.07 (dq, 1H, *J* 2.3 and 15.4, H-1′b); 4.27–4.30 (m, 1H, H-3) [Found: HRMS (LSIMS) *m*/*z* $(M + Na)^+$, 435.1978. $C_{28}H_{28}O_3Na$ requires 435.1936].

1,2-*O*-Isopropylidene-3-*O*-(3′-methylbuta-1′,2′-dienyl)-5-*O*-trityl-α-D-xylofuranose (1)

To a solution of **13** (2.0 g, 4.13 mmol) in dry THF (20 cm^3) at −45 °C under N_2 BuLi (2.5 M in hexane, 1.81 cm^3, 4.54 mmol) was added. After 25 min at −45 °C, MeI (0.28 cm^3, 4.54 mmol) was added, and the solution was warmed to 25 °C for 20 min. Subsequently, *tert*-butyl methyl ether (100 cm^3) and brine (25 cm^3) were added. The organic layer was separated, washed with water, dried ($MgSO_4$), and concentrated. The residue was purified on a silica gel column using hexane–ethyl acetate 9:1 v/v as an eluent to give **1** (1.24 g, 61%). Colourless crystals; mp 144–146.5 °C (Found: C, 77.03; H, 6.80. $C_{32}H_{34}O_5$ requires C, 77.08; H, 6.87%); $[\alpha]_D$ −1.6 (*c* 1.0 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 1958 (allene); δ_H (500 MHz, $CDCl_3$) 1.30, 1.52 (2s, 6H, isoprop.); 1.78 (d, 3H, *J* 2.0, Me); 1.84 (d, 3H, *J* 2.0, Me); 3.36 (dd, 1H, *J* 6.7 and 9.2, H-5a); 3.44 (dd, 1H, *J* 6.0 and 9.2, H-5b); 4.23 (d, 1H, *J* 3.1, H-3); 4.38 (ddd, 1H, *J* 3.1, 6.0 and 6.7, H-4); 4.52 (d, 1H, *J* 3.8, H-2); 5.84 (d, 1H, *J* 3.8, H-1); 6.33 (sept., 1H, *J* 2.0, H-1′); δ_H (500 MHz, $C_6D_5CD_3$) 1.08, 1.37 (2s, 6H, isoprop.); 1.59 (d, 3H, *J* 2.0, Me); 1.69 (d, 3H, *J* 2.0, Me); 3.64 (dd, 1H, *J* 6.2 and 9.2, H-5a); 3.76 (dd, 1H, *J* 6.2 and 9.2, H-5b); 4.35 (d, 1H, *J* 3.3, H-3); 4.43 (d, 1H, *J* 3.9, H-2); 4.66 (td, 1H, *J* 3.3 and 6.2, H-4); 5.80 (d, 1H, *J* 3.9, H-1); 6.34 (sept., 1H, *J* 2.0, H-1′) [Found: HRMS (LSIMS) *m*/*z* $(M + Na)^+$, 521.2328. $C_{32}H_{34}O_5Na$ requires 521.2304].

X-Ray structure determination of compound 1

Single crystals suitable for diffractometric measurements were obtained from Et_2O–hexane mixture. The $P2_12_12_1$ space group was assigned on the basis of systematic extinctions. Unit cell dimensions calculated for 15 reflections are: $a = 10.703(2)$, $b = 12.290(2)$, $c = 21.490(4)$ Å, $V = 2826.8(9)$ Å^3, $Z = 4$, $D_c = 1.172$ Mg m^{-3}, $\mu(\mathrm{CuK}\alpha) = 0.625$ mm^{-1}. 3276 Reflections were collected in the θ range 4.11–74.11° on a Nonius MACH3 diffractometer. 2416 unique reflections were corrected for Lorentz and polarisation factors. The structure was solved by direct methods with the use of SHELXS86 (Sheldrick, 1986)[21] and refined against F^2 using SHELXL97 (Sheldrick, 1997).[22] All H-atoms were placed in ideal positions and refined with the riding model and B_{iso} set at 1.2 of that of the parent atom. Final *R* indices $[I > 2\sigma(I)]$ are: $R_1 = 0.0391$, $wR_2 = 0.0996$, respectively. The absolute structure parameter was 0.2(3).

5-Deoxy-1,2-*O*-isopropylidene-3-*O*-(3′-methylbuta-1′,2′-dienyl)-α-D-xylofuranose (2)

Compound **2** was obtained from **14** according to the procedure described for **1** (65%). Oil; $[\alpha]_D$ −53.4 (1.09 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 1958 (allene); δ_H (200 MHz, $CDCl_3$) 1.30 (d, 3H, *J* 6.4, Me); 1.30, 1.50 (2s, 6H, isoprop.); 1.82 (d, 3H, *J* 2.0, Me); 1.84 (d, 3H, *J* 2.0, Me); 3.98 (d, 1H, *J* 3.0, H-3); 4.37 (dq, 1H, *J* 3.0 and 6.4, H-4); 4.57 (d, 1H, *J* 3.9, H-2); 5.85 (d, 1H, *J* 3.9, H-1); 6.45 (sept., 1H, *J* 2.0, H-1′); δ_H (500 MHz, $C_6D_5CD_3$) 1.30, 1.60 (2s, 6H, isoprop.); 1.52 (d, 3H, *J* 6.5, Me); 1.84 (d, 3H, *J* 2.0, Me); 1.90 (d, 3H, *J* 2.0, Me); 4.22 (d, 1H, *J* 2.8, H-3); 4.59 (dq, 1H, *J* 3.2 and 6.4, H-4); 4.66 (d, 1H, *J* 4.0, H-2); 6.0 (d, 1H, *J* 4.0, H-1); 6.67 (sept., 1H, *J* 2.0, H-1′) [Found: HRMS (EI) *m*/*z* M^+, 240.1374. $C_{13}H_{20}O_4$ requires 240.1361].

1,4-Anhydro-2-deoxy-3-*O*-(3′-methylbuta-1′,2′-dienyl)-5-*O*-trityl-D-*threo*-pentitol (3)

Compound **3** was obtained from **15** according to the procedure described for **1** (48%). Oil; $[\alpha]_D$ +13.6 (0.3 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 1956 (allene); δ_H (200 MHz, $CDCl_3$) 1.73 (d, 3H, *J* 2.1, Me); 1.78 (d, 3H, *J* 2.1, Me); 1.95–2.1 (m, 2H, H-2a, H-2b); 3.31 (dd, 1H, *J* 5.6 and 9.6, H-5a); 3.37 (dd, 1H, *J* 6.3 and 9.6, H-5b); 3.76–4.06 (m, 3H, H-1a, H-1b, H-4); 4.3–4.37 (m, 1H, H-3); 6.39 (sept., 1H, *J* 2.1, H-1′); δ_H (500 MHz, $C_6D_5CD_3$) 1.57 (d, 3H, *J* 2.1, Me); 1.61 (d, 3H, *J* 2.1, Me); 1.66 (dddd, 1H, *J* 5.7, 8.5, 8.5 and 13.2, H-2a); 1.87 (dddd, 1H, *J* 2.1, 5.0, 7.6 and 13.2, H-2b); 3.53 (dd, 1H, *J* 4.8 and 9.5, H-5a); 3.56–3.61 (m, 1H, H-1a); 3.69 (dd, 1H, *J* 6.8 and 9.5, H-5b); 3.87–3.92 (m, 1H, H-1b); 4.00 (m, 1H, *J* 4.3, 4.8 and 6.8, H-4); 4.21 (ddd, 1H, *J* 2.1, 4.3 and 5.7, H-3); 6.28 (sept., 1H, *J* 2.1, H-1′) [Found: HRMS (EI) *m*/*z* M^+, 426.2176. $C_{29}H_{30}O_3$ requires 426.2195].

Calculation of low energy conformers

The program PCMODEL[14] was used to generate low energy conformations using the force field MM3. It was done by global optimisation of the structure by multiple, near random rotations about all rotatable bonds using a Monte Carlo-Metropolis approach to simulated annealing. Conformations obtained in this way were analysed using computer program MMXCOMP[23] to produce a conformational set within *ca.* 10 kcal mol^{-1} of the minimum energy conformer. This program orders the calculated conformations within a pre-set range of dihedral angles (30° of each other). It does it by setting the lowest energy conformer as a representative of the first cluster. The second lowest energy structure is added to the cluster if none of its dihedral angles differs by more than 30° from the first structure; if it does differ in at least one angle, it is taken as a representative of a second cluster. Each new structure is added in the same way.

Steady-state NOE experiments

Steady-state NOEs for **1**–**3** were measured in $[^2H_8]$toluene at room temperature on a Varian INOVA 500 spectrometer using a routine program for multiplet irradiation. The samples were degassed to minimise external relaxation. The longest ^1H T_1 determined for the samples were used for setting up the total irradiation time necessary to produce steady-state NOEs. The experimental conditions were as follows: 15 s total irradiation, 4 s acquisition using a 5000 Hz spectral window and 64 k data points. 32 Transients in blocks of 8 were acquired without interleaving the irradiated multiplets. Line broadening of 1 Hz was used for processing the FIDs and the same phase parameters were used for reference and NOE enhanced spectra. The spectra were calibrated using the reference signal unaffected by the irradiation. Irradiation power was kept minimal to avoid the direct saturation effects of closely lying multiplets. The experimental NOEs were calculated by the program NOE[13] which takes into account the saturation coefficients for irradiated multiplets. The estimated precision of all experimental NOEs was ±1%.

Calculations of the theoretical steady-state NOEs

The theoretical steady-state NOEs were calculated using the computer program *NOE*[13] which is available on request from the authors. A best fit value for the external relaxation parameter (which corresponds to the effective distance of the relaxation sink) was equal to 2.25, 2.1, 2.4 Å for the samples **1**–**3** respectively. The program *NOE* is based on steady-state equations in the presence of external relaxation. As a measure of the goodness of fit of the calculated to observed NOEs, we used rms_{NOE} factors, defined in eqn. (1), in a manner similar to its use in crystallography.

$$rms_{NOE} = \sqrt{\frac{\sum_{i=1}^{N} (NOE_i^{cal} - NOE_i^{exp})^2}{\sum_{i=1}^{N} (NOE_i^{exp})^2}} \qquad (1)$$

Statistical calculations

The determination of the best conformational model in solution (either single conformer or conformational mixture) on the basis of experimental and calculated steady-state NOE data cannot be made with absolute confidence. This is due to imperfections of NOE measurements, possible errors in the local geometry of generated low energy conformers and simplifications used in calculations of the theoretical NOEs. Therefore it is necessary to test if the difference between ‘a best-fit conformational model’ (a model with the lowest rms_{NOE} factor) and the other models is *statistically significant.* For the best-fitted conformer a residual sum of squares of the difference between calculated and observed NOEs was calculated. The 10% significance intervals for the residual sum of squares and for rms_{NOE} were calculated assuming a χ^2 distribution with the appropriate number of degrees of freedom equal to the number of NOEs measured minus one (the external relaxation parameter fitted to experimental data). In such an approach problems related to *multiple comparison* (*i.e.* simultaneous comparisons between a large number of possible models) were ignored.

Ten percent significance intervals for the lowest rms_{NOE} factors, corresponding to **1** and **2**, are (0.164, 0.282) and (0.189, 0.337), respectively.

DPFGSE NOE measurements

DPFGSE NOE (double-pulsed-field gradient spin echo) experiments were run using a pulse sequence published by Stott and co-workers[15] using a shaped selective π soft-pulse generated using a standard Varian program on a Varian INOVA 500 spectrometer. For the sample of **1** mixing times of 500, 1000, 1500 and 2000 ms were applied. For the samples of **2** and **3** mixing times of 500, 750 and 1000 ms were used. For each mixing time the spectra were acquired using a 5000 Hz spectral window and 64 k data points. 512 Transients in blocks of 16 were accumulated using a 4 s delay after each pulse sequence and the data were processed with 1 Hz line broadening to enhance the S/N ratio.

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