Aqueous [6 + 4] cycloadditions of tropone with 1-(glucopyranosyloxy)buta-1,3-diene

André Lubineau,[a] Giliane Bouchain[a] and Yves Queneau[a,b]

[a] *Laboratoire de Chimie Organique Multifonctionnelle, CNRS URA 462, Institut de Chimie Moléculaire d'Orsay, Université de Paris-Sud, Bat. 420, 91405 Orsay Cedex, France*

[b] *Present address: Unité Mixte de Sucrochimie, CNRS-Béghin-Say (UMR 143), c/o Eridania Béghin-Say, CEI, 27 Bd du 11 novembre 1918, BP 2132, 69603 Villeurbanne Cedex, France*

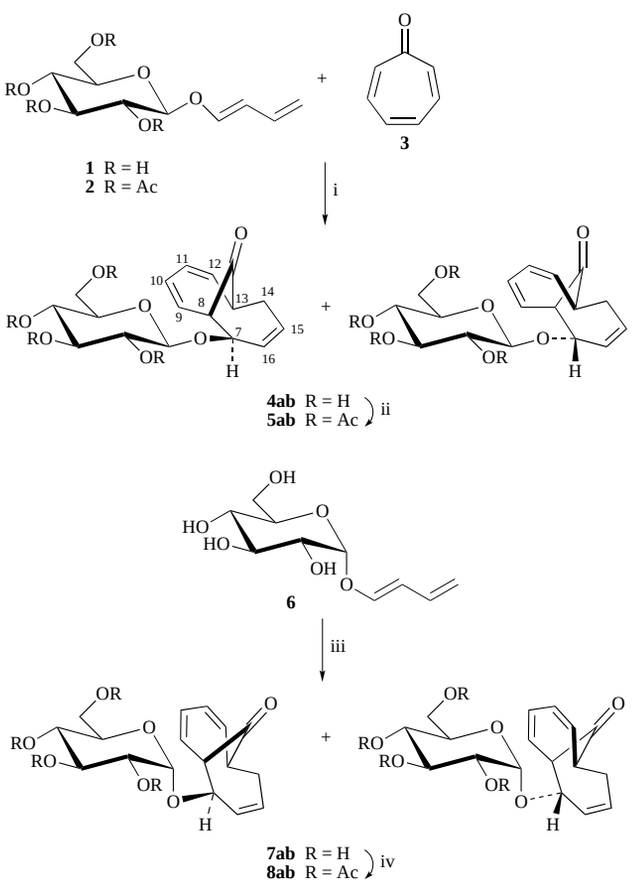
The first aqueous [6 + 4] cycloaddition reaction is reported. Starting from tropone and glucopyranosyloxybuta-1,3-diene, bicyclic adducts arising from the expected *exo*-transition state have been obtained in fair yields under much milder conditions than those usually required, thus preventing side-[4 + 2] adduct formation by limiting the reversibility of the [6 + 4] process. Influence of the solvent is clearly demonstrated as the reaction in methanol is much slower compared with that in water. The best yields are obtained in buffered solutions or in concentrated aq. sugar solutions.

Introduction

The [6 + 4] cycloaddition reaction of tropone with dienes allows the construction of the bicyclo[4.4.1]undecanone backbone, which can serve as the starting point for the synthesis of complex polycyclic compounds such as troponophanes, cyclodecenes, and some diterpenes in the ingenol series.[1] This reaction was first reported in the mid 60s in the case of cyclopentadiene which provided *exo*-oriented adducts[2] as predicted by the Woodward–Hoffmann rules.[3] The condensation of non-substituted tropone with simple dienes is not an easy process as confirmed by the high temperature and long reaction time which are often necessary.[4] Owing to the greater reversibility of the [6 + 4] cycloaddition pathway compared with the [4 + 2] one, [4 + 2] adducts can be the major products upon prolongation of the reaction time.[5] It is therefore useful to investigate new conditions for such reactions. A possibility is to catalyse the reaction using transition metal catalysts.[6] Based on our experience in cycloadditions using water as the solvent,[7] we studied the outcome of the reaction of tropone in aqueous medium using the water-soluble 1-(β-D-glucopyranosyloxy)-buta-1,3-diene **1**.[8] Indeed, we showed that, in water, such a diene could provide [4 + 2] cycloaddition adducts with both rate and selectivity increase compared with other solvents.[9] Widening the scope of the use of this diene in aqueous medium, we report herein the synthesis of 2-(glucopyranosyloxy)-bicyclo[4.4.1]undecanones, as the first [6 + 4] cycloaddition reaction performed in water.

Results and discussion

Cycloaddition of β-D-glucopyranosyloxybuta-1,3-diene **1** with cyclohepta-2,4,6-trienone (tropone) **3** was performed in aqueous medium to provide adducts **4ab** as a mixture of two diastereoisomers in nearly equivalent amounts (Scheme 1) which were characterized as their per-acetylated derivatives **5ab**. The relative stereochemistry in adducts **4ab** was assigned by comparison with known derivatives after reduction and hydrolysis (*vide infra*). Reaction conditions and yields are given in Table 1. The necessity of keeping the temperature below 60 °C to prevent substantial hydrolysis of the starting diene led to quite long reaction times. This had a positive consequence for the [6 + 4] process whose reversibility was inhibited, therefore preventing side-[4 + 2] cycloadditions to occur. Nevertheless, moderate to fair yields of adducts **4ab** could be obtained at 40 or 50 °C which is an exceptionally low temperature for a [6 + 4] cycloaddition. For example, a temperature of 80 °C is necessary for reaction of cyclopentadiene,[2a] although a much more reactive diene, and refluxing xylene during 5 days is necessary for the cycloaddition with 1-acetoxybuta-1,3-diene.[4a] The reaction



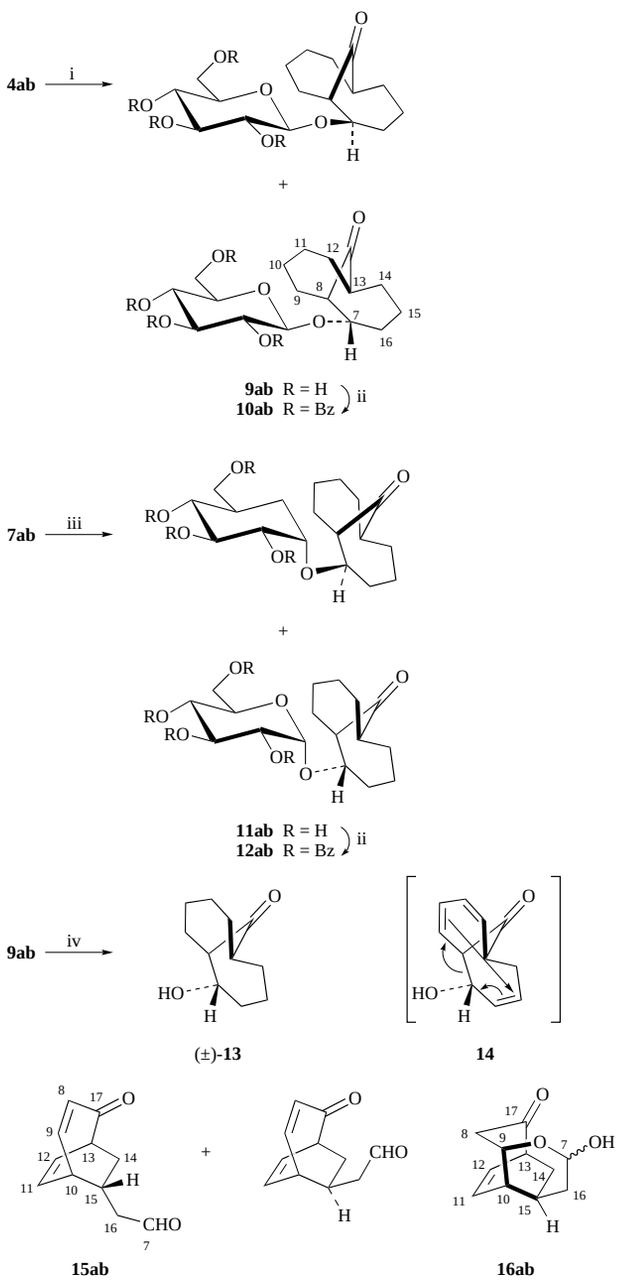
Scheme 1 *Reagents and yields*: i, see Table 1; ii, Ac_2O, Py (96%); iii, **3**, water (66%); iv, Ac_2O, Py (92%). Arbitrary NMR numbering scheme is shown for structures **4** and **5**.

Table 1 Reaction conditions and yields for adducts **4ab** and **7ab** (Scheme 1)

Entry	Diene (mol equiv.)	Solvent	*T*/°C	*t*/days	Yield (%)
1	**1** (0.5)	water	40	9.5	45
2	**1** (0.5)	methanol	40	12	28
3	**2** (0.5)	toluene	110	10	44
4	**1** (0.5)	water	50	3.5	46
5	**1** (0.5)	pH 7 buffer	50	6.5	54
6	**1** (2.0)	pH 7 buffer	50	6.5	58
7	**1** (1.8)	pH 7 buffer + hydroquinone	50	6.5	62
8	**1** (0.5)	4 M glucose	40	9.5	62
9	**1** (0.5)	2.5 M sucrose	40	9.5	59
10	**6** (1.8)	pH 7 buffer + hydroquinone	50	6.5	66

of diene **1** with tropone **3** was shown to be very sensitive to the nature of the solvent, as a much lower yield was obtained in methanol (entry 2) and a much slower reaction was observed for the acetylated diene **2** in toluene (entry 3). Yields could be improved by conducting the reaction in water at 50 °C in the presence of additives (entries 5–7) such as (i) pH 7 phosphate buffer in order to prevent competitive hydrolysis of diene, and (ii) hydroquinone to inhibit polymerization of diene. Concentrated glucose and sucrose as aqueous solutions were also used (entries 8 and 9) for which yields of ~60% were obtained. We have already described the use of such a solvent mixture for Diels–Alder reactions and other transformations.[10] It was shown that the rate increase was due to enforced hydrophobic effects. The α-glucosyl diene **6** was also shown to provide similar adducts **7ab** which were characterized as their per-acetylated derivatives **8ab**. In order to establish the stereochemistry (*exo*) of the glycosylated bicyclo[4.4.1]undecanones, compounds **4ab** were submitted to hydrolysis. As alcohol **13** has already been described in the literature,[4a] adducts **4ab** were hydrogenated under classical conditions (10% Pd/C, 14 psi H_2), to provide compounds **9ab** which were characterized as their benzoylated derivatives **10ab** (Scheme 2). It is to be noted that, at this stage, the two diastereoisomers **9ab** could be separated by flash chromatography, but attempts to establish the absolute configuration at the newly created chiral centres were unsuccessful. The same synthetic sequence was applied to the α-anomers **7ab**, allowing isolation of hydrogenated glycosides **11ab** and their benzoylated derivatives **12ab**. Acidic hydrolysis (0.5 M H_2SO_4; 100 °C) of glycosides **9ab**, albeit in moderate yield (47%), allowed us to identify keto alcohol **13** (by comparison with literature NMR data) as the sole product, thus confirming the total *exo* selectivity of the cycloaddition. Similar treatment of each of the two compounds **9a** and **9b** as pure isomers allowed us to obtain (+)-**13** and (−)-**13** for which an α_D value of +9 and −9 were measured. Hydrogenated adducts in the α series **7ab** could be hydrolysed to provide **13** in similar yield (42%).

Direct hydrolysis of adducts without previous hydrogenation of the three double bonds appeared to be a much more complicated process. Indeed, intermediate keto alcohols (such as that having structure **14**) could not be isolated before subsequent oxy-Cope[3,3] sigmatropic rearrangement as shown by isolation of structures **15ab** (31%) after acidic treatment (0.5 M H_2SO_4; 80 °C), together with hemiacetals **16ab** (13%) arising from hydration of one of compounds **15ab**, having a *cis* relationship between the oxoethyl chain and the enone bridge. Their structures were determined by ^{1}H COSY NMR analysis. A similar oxycope rearrangement has already been described in the literature.[5b]



Scheme 2 *Reagents and yields*: i, H_2, Pd/C, MeOH (98%); ii, BzCl, Py; iii, H_2, Pd/C, MeOH (97%); iv, 0.5 M H_2SO_4

Conclusions

In this paper, we have reported the first aqueous [6 + 4] cycloaddition of tropone using water-soluble dienes derived from carbohydrates. The reaction was shown to proceed at much lower temperature compared with the usual conditions, providing fair yields of glycosylated bicyclo[4.4.1]undecanones.

The *exo* selectivity was confirmed after hydrogenation and hydrolysis, and pure enantiomers of 7-hydroxybicyclo[4.4.1]-undecanone **13** could be isolated.

Experimental

General

NMR spectra were recorded with Bruker AC200 and 250 spectrometers. δ-Values are given in ppm downfield from internal

tetramethylsilane and *J*-values are given in Hz. Carbohydrate entities are described with the classical numbering. Position 7 is arbitrarily assigned to the bicyclic ring's carbon linked to oxygen. Positions 8 and 13 are assigned to the ring junction. IR spectra were recorded using a Bruker FT instrument. Flash chromatography was performed using 6–35 μm silica gel (60) purchased from S.D.S. TLC was performed using Merck 60 F_{254} plates, and visualized first with UV light and then by heating after treatment with alcoholic sulfuric acid. Elementary analyses were performed at the Service Central de Microanalyse du C.N.R.S. Optical rotations were measured on a JASCO (DIP-370) spectrometer, with $[\alpha]_D$-values given in units of 10^{-1} deg cm^2 g^{-1}.

(1*R,6*R**,7*R**)-7-(β-D-Glucopyranosyloxy)bicyclo[4.4.1]-undeca-2,4,8-trien-11-one 4ab**

β-D-Glucopyranosyloxybuta-1,3-diene **1**[8] (1.89 g, 8.1 mmol), tropone **3** (1.42 cm^3, 14.65 mmol) and hydroquinone (10 mg, 0.09 mmol) were heated in phosphate buffer (1 M, pH 7; 16.2 cm^3) at 50 °C for 6 days. After being cooled to room temperature, the mixture was diluted with water (3 cm^3) and extracted with dichloromethane (2 × 3 cm^3). The aqueous layer was concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2–MeOH, 94:6) to give compounds **4ab** (1.7 g, 62%) as a syrup (Found: C, 58.1; H, 6.7. $C_{17}H_{22}O_7$·0.66H_2O requires C, 58.3; H, 6.7%).

Isomer **4a**, δ_H(250 MHz; D_2O) 2.52–2.74 (2 m, 2 H, 14-H_2), 3.22–4.0 (m, 8 H, 2-, 3-, 4-, 5-, 8- and 13-H and 6-H_2), 4.52 (d, *J* 8, 1 H, 1-H), 4.94–5.05 (m, 1 H, 7-H), 5.69–6.02 (m, 4 H, 9-, 12-, 15- and 16-H) and 6.12–6.36 (m, 2 H, 10- and 11-H); δ_C(62 MHz; D_2O) 29.23 (C-14), 54.94 (C-13), 60.64 (C-6), 62.47 (C-8), 69.58, 72.95, 74.18, 75.74, 75.87 (C-2, -3, -4, -5 and -7), 100.96 (C-1), 124.25, 125.71, 127.53, 130.22, 130.38 and 131.41 (C-9, -10, -11, -12, -15 and -16) and 209.73 (CO).

Isomer **4b**, δ_H(250 MHz; D_2O) 2.56–2.67 (2 m, 2 H, 14-H_2), 3.15–3.97 (m, 8 H, 2-, 3-, 4-, 5-, 8- and 13-H and 6-H_2), 4.61 (d, *J* 8, 1 H, 1-H), 4.95–5.09 (m, 1 H, 7-H), 5.74–5.90 (m, 4 H, 9-, 12-, 15- and 16-H) and 6.18–6.36 (m, 2 H, 10- and 11-H); δ_C(62 MHz; D_2O) 29.25 (C-14), 54.76 (C-13), 60.59 (C-6), 61.62 (C-8), 69.53, 73.18, 75.50 and 76.0 (C-2, -3, -4, -5 and -7), 102.28 (C-1), 124.95, 126.53, 128.14, 129.65, 130.65 and 132.21 (C-9, -10, -11, -12, -15 and -16) and 208.17 (CO).

(1*R,6*R**,7*R**)-7-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyrano-syloxy)bicyclo[4.4.1]undeca-2,4,8-trien-11-one 5ab**

To a stirred solution of glucosylated compounds **4ab** (45 mg, 0.13 mmol) in pyridine (0.16 cm^3), cooled to 0 °C and under nitrogen, was added acetic anhydride (0.11 cm^3, 1.22 mmol). The reaction mixture was stirred for 12 h, before removal of the solvent under reduced pressure to leave a crude product as a yellow oil. This oil was recrystallized in diethyl ether to give compounds **5ab** (63 mg, 96%) as a solid (Found: C, 59.0; H, 6.1. $C_{25}H_{30}O_{11}$ requires C, 59.3; H, 6.0%). The two diastereoisomers have been partially separated, then deacetylated to give tetraols **4a** and **4b**.

Isomer **5a** (Found: C, 58.8; H, 6.1%); mp 116–117 °C; ν_{max}(neat)/cm^{-1} 3022, 1758, 1709, 1522, 1427, 1368, 1215, 1041 and 929; $[\alpha]_D^{27}$ 14 (*c* 0.45, CH_2Cl_2); δ_H(250 MHz; $CDCl_3$) 2.0, 2.01 and 2.10 (4 s, 12 H, CH_3), 2.35–2.52 (m, 1 H, 14-H), 2.59–2.75 (m, 1 H, 14-H′), 3.40–3.50 (m, 1 H, 13-H), 3.59–3.69 (m, 1 H, 5-H), 3.70–3.79 (dt, *J* 1 and 8, 1 H, 8-H), 4.15 (dd, *J* 2 and 12, 1 H, 6-H), 4.20 (dd, *J* 5 and 12, 1 H, 6-H′), 4.51 (d, *J* 8, 1 H, 1-H), 4.72–4.82 (m, 1 H, 7-H), 4.91–5.23 (m, 3 H, 2-, 3- and 4-H), 5.49–5.60 and 5.61–5.86 (2 m, 4 H, 9-, 12-, 15- and 16-H) and 6.01–6.13 (m, 2 H, 10- and 11-H); δ_C(62 MHz; $CDCl_3$) 20.56 and 20.69 (4 × CH_3), 31.30 (C-14), 54.49 (C-13), 60.07 (C-6), 62.96 (C-8), 68.46, 71.26, 71.79 and 72.73 (C-2, -3 -4 and -5), 74.39 (C-7), 99.12 (C-1), 125.68, 125.77, 126.88, 130.07, 131.30 and 132.20 (C-9, -10, -11, -12, -15 and -16), 169.03, 169.32, 170.27 and 170.51 (CO_2) and 203.21 (CO).

Isomer **5b** (Found: C, 59.0; H, 5.95%); $[\alpha]_D^{28}$ −29 (*c* 0.7, CH_2Cl_2); mp 166–167 °C; ν_{max}(neat)/cm^{-1} 3022, 1757, 1711, 1522, 1424, 1366, 1215, 1040 and 929; δ_H(250 MHz; $CDCl_3$) 2.0, 2.04 and 2.10 (4 s, 12 H, CH_3), 2.37–2.52 (m, 1 H, 14-H), 2.58–2.75 (m, 1 H, 14-H′), 3.43–3.54 (m, 1 H, 13-H), 3.58–3.72 (2 m, 2 H, 5- and 8-H), 4.12 (dd, 1 H, *J* 2 and 12, 6-H), 4.26 (dd, 1 H, *J* 5 and 12, 6-H′), 4.59 (d, *J* 8, 1 H, 1-H), 4.73–4.84 (m, 1 H, 7-H), 4.97 (dt, *J* 8 and 10, 1 H, 2-H), 5.08 (t, 1 H, *J* 10, 4-H), 5.20 (t, 1 H, *J* 10, 3-H), 5.55–5.78 and 5.80–5.92 (2 m, 4 H, 9-, 12-, 15- and 16-H) and 6.03–6.19 (m, 2 H, 10- and 11-H); δ_C(62 MHz; $CDCl_3$) 20.59, 20.61, 20.71 and 20.74 (CH_3), 30.98 (C-14), 54.55 (C-13), 61.87 (C-6), 62.27 (C-8), 68.34, 71.18, 71.74 and 72.62 (C-2, -3, -4 and -5), 75.65 (C-7), 100.62 (C-1), 125.71, 127.60, 128.22, 132.15 and 133.32 (C-9, -10, -11, -12, -15 and -16), 169.27, 169.39, 170.30 and 170.65 (CO_2) and 202.58 (CO).

Starting from the acetylated diene **2**[7b] (20 mg, 0.05 mmol) as a solution in toluene (0.1 cm^3) with tropone (0.01 cm^3, 0.1 mmol), the reaction mixture was heated at reflux for 10 days. Removal of the solvent followed by flash chromatography (hexane–ethyl acetate, 7:3) yielded adducts **5ab** (11 mg, 44%).

(1*R,6*R**,7*R**)-7-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl-oxy)bicyclo[4.4.1]undeca-2,4,8-trien-11-one 8ab**

The same procedure described for anomers **4ab** was used, starting from α-D-glucopyranosyloxybuta-1,3-diene **6**[8] (2 g, 8.6 mmol) and tropone **3** (1.5 cm^3, 15.8 mmol) in phosphate buffer (17.2 cm^3). Compounds **7ab** {7-(α-D-glucopyranosyloxy)-bicyclo[4.4.1]undeca-2,4,8-trien-11-one} (1.9 g, 66%) were obtained as a syrup (ratio 55:45) (Found: C, 57.5; H, 6.4. $C_{17}H_{22}O_7$·0.83H_2O requires C, 57.8; H, 6.7%); ν_{max}(KBr)/cm^{-1} 3388, 3031, 2929, 1698, 1407, 1338, 1259, 1145, 1076 and 1026; δ_H(250 MHz; D_2O) 2.57–2.67 (2 m, 4 H, 14-H_2), 3.35–3.90 (m, 16 H, 2-, 3-, 4-, 5-, 8- and 13-H and 6-H_2), 4.80–4.94 (m, 2 H, 7-H), 4.98 (d, 1 H, *J* 4, 1-H), 5.10 (m, 1 H, *J* 4, 1-H), 5.63–5.96 (m, 8 H, 9-, 12-, 15- and 16-H) and 6.15–6.32 (m, 4 H, 10- and 11-H); δ_C(62 MHz; D_2O) 29.44 and 31.17 (C-14), 53.85 and 54.83 (C-13), 60.16 and 60.35 (C-6), 61.80 and 62.30 (C-8), 69.27, 69.50, 70.05, 71.01, 71.34, 72.0, 72.38, 72.91 and 73.36 (C-2, -3, -4, -5 and -7), 96.09 and 98.58 (C-1), 124.70, 125.30, 126.16, 128.05, 128.47, 129.70, 130.64, 131.61, 131.95 and 132.42 (C-9, -10, -11, -12, -15 and -16) and 208.81 (CO).

Further acetylation using the same procedure as for anomers **5ab** led, starting from tetraols **7ab** (1.7 g, 5 mmol), to acetylated derivatives **8ab** (2.33 g, 92%) as a powder (Found: C, 58.4; H, 6.0. $C_{25}H_{30}O_{11}$·0.5H_2O requires C, 58.3; H, 6.1%); ν_{max}(KBr)/cm^{-1} 1762, 1760, 1753, 1749, 1741, 1254, 1246, 1239, 1236, 1229, 1225, 1217 and 1046; δ_H(250 MHz; $CDCl_3$) 1.99–2.18 (m, 24 H, CH_3), 2.33–2.55 (m, 2 H, 14-H), 2.64–2.85 (m, 2 H, 14-H′), 3.42–3.58 (m, 2 H, 13-H), 3.60–3.68 (dt, 1 H, *J* 2 and 8, 8-H), 3.70–3.80 (dt, *J* 2 and 8, 1 H, 8-H), 3.96–4.35 (m, 6 H, 5-H and 6-H_2), 4.68–4.89 (m, 2 H, 7-H), 4.98–5.53 (m, 8 H, 1-, 2-, 3- and 4-H), 5.53–5.90 (m, 8 H, 9-, 12-, 15- and 16-H) and 6.02–6.20 (m, 4 H, 10- and 11-H); δ_C(62 MHz; $CDCl_3$) 20.63 (8 × CH_3), 30.58 and 31.32 (C-14), 54.29 and 54.81 (C-13), 61.64 (2 × C-6), 61.98 and 62.40 (C-8), 67.48, 67.70, 68.27, 68.49, 70.03 and 70.70 (2 × C-2, -3, -4 and -5), 72.59 and 73.86 (C-7), 94.45 and 95.62 (C-1), 125.09, 125.43, 125.73, 127.68, 129.75, 131.60, 132.10 and 132.55 (C-9, -10, -11, -12, -15 and -16), 169.56, 169.98 and 170.53 (8 × CO_2) and 202.60 and 202.71 (CO).

(1*R,2*R**,6*S**)-2-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyrano-syloxy)bicyclo[4.4.1]undecan-11-one 10a and 10b**

A solution of adducts **4ab** (250 mg, 0.74 mmol) and 150 mg of 10% palladium on carbon in 5 cm^3 of methanol were placed under 14 psi of hydrogen and the mixture was shaken for 24 h. The suspension was filtered through Celite and the filtrate was concentrated under reduced pressure. Separation of diastereoisomers was achieved by flash chromatography (CH_2Cl_2–

MeOH, 94:6) to provide purified samples of compounds **9a** and **9b** {2-(β-D-glucopyranosyloxy)bicyclo[4.4.1]undecan-11-one} (250 mg, 98%) as a powder in a 55:45 ratio.

Compound **9a**, mp 60–62 °C; ν_{max}(KBr)/cm^{-1} 3409, 2927, 2868, 1681, 1650, 1445, 1365, 1278, 1162, 1076, 1039 and 1010; $[\alpha]_D^{28}$ −69 (*c* 1.04, CH_2Cl_2); δ_H(250 MHz; D_2O) 1.15–2.29 (m, 14 H, 9-, 10-, 11-, 12-, 14-, 15- and 16-H_2), 2.70–2.87 (m, 1 H, 13-H), 2.92–3.05 (m, 1 H, 8-H), 3.20–3.57 (m, 4 H, 2-, 3-, 4- and 5-H), 3.72 (dd, *J* 5 and 12, 1 H, 6-H), 3.85 (dd, 1 H, *J* 2 and 12, 6-H′), 4.19–4.30 (m, 1 H, 7-H) and 4.60 (d, *J* 8, 1 H, 1-H); δ_C(62 MHz; D_2O) 21.09, 25.54, 25.75, 27.30, 28.85 and 33.52 (C-9, -10, -11, -12, -14, -15 and -16), 54.93 (C-13), 60.12 (C-8), 60.76 (C-6), 69.65, 73.41, 75.62 and 75.99 (C-2, -3, -4 and -5), 78.91 (C-7), 102.65 (C-1) and 219.58 (CO).

Compound **9b**, mp 68–70 °C; ν_{max}(KBr)/cm^{-1} 3409, 2918, 2867, 1684, 1456, 1361, 1186, 1160, 1078 and 1037; $[\alpha]_D^{26}$ −23 (*c* 1, CH_2Cl_2); δ_H(250 MHz; D_2O) 1.15–2.30 (m, 14 H, 9-, 10-, 11-, 12-, 14-, 15- and 16-H_2), 2.70–2.92 (m, 2 H, 13-H), 3.25 (t, *J* 8, 1 H, 8-H), 3.18–3.56 (m, 4 H, 2-, 3-, 4- and 5-H), 3.74 (dd, *J* 5 and 12, 1 H, 6-H), 3.92 (dd, *J* 1 and 12, 1 H, 6-H′), 4.32 (br t, *J* 8, 1 H, 7-H) and 4.52 (d, *J* 8, 1 H, 1-H); δ_C(62 MHz; D_2O) 20.98, 25.39, 25.78, 26.35, 27.85, 28.67 and 32.09 (C-9, -10, -11, -12, -14, -15 and -16), 54.79 (C-13), 60.66 (C-6), 60.96 (C-8), 69.67, 72.93, 75.82 and 75.92 (C-2, -3, -4 and -5), 76.31 (C-7), 100.41 (C-1) and 219.41 (CO).

To a stirred solution of tetraol **9a** (90 mg, 0.26 mmol) in pyridine (0.53 cm^3) was added benzoyl chloride (0.17 cm^3, 1.44 mmol). The reaction mixture was stirred for 2.5 h at room temperature under nitrogen. Benzoyl chloride in excess was quenched by 0.3 cm^3 of methanol, and then dichloromethane (5 cm^3) and water (3 cm^3) were added. The organic phase was washed successively with dil. aq. hydrochloric acid (3 cm^3) and saturated aq. $NaHCO_3$ (3 cm^3) and was then dried over $MgSO_4$. After filtration the solution was concentrated under reduced pressure to give a pale yellow syrup. Flash chromatography of the residue (toluene–diethyl ether, 95:5) provided tetrabenzoate **10a** (175 mg, 88%). Using the same procedure starting from the diastereoisomer **9b** (96 mg, 0.28 mmol), compound **10b** (117 mg, 56%) was obtained.

Compound **10a**, mp 87–89 °C (Found: C, 71.1; H, 5.8. $C_{45}H_{44}O_{11}$ requires C, 71.0; H, 5.8%); ν_{max}(KBr)/cm^{-1} 3630, 3536, 3440, 3063, 2928, 2857, 1729, 1692, 1602, 1584, 1492, 1452, 1365, 1267, 1177, 1111, 1069 and 1027; $[\alpha]_D^{23}$ +23 (*c* 1.1, CH_2Cl_2); δ_H(200 MHz; $CDCl_3$) 0.80–1.85 and 2.10–2.27 (2 m, 14 H, 9-, 10-, 11-, 12-, 14-, 15- and 16-H_2), 2.50–2.67 (m, 1 H, 13-H), 2.74–2.88 (m, 1 H, 8-H), 4.10–4.28 (m, 2 H, 5- and 7-H), 4.50 (dd, *J* 6 and 12, 1 H, 6-H), 4.63 (dd, *J* 3 and 12, 1 H, 6-H′), 5.04 (d, *J* 8, 1 H, 1-H), 5.50 (dd, *J* 8 and 10, 1 H, 2-H), 5.60 (t, *J* 10, 1 H, 4-H), 5.93 (t, *J* 10, 1 H, 3-H) and 7.14–7.61 and 7.79–8.08 (2 m, 20 H, 4 × Ph); δ_C(62 MHz; $CDCl_3$) 21.55, 25.90, 26.17, 26.98, 27.15, 30.0, 34.60 (C-9, -10, -11, -12, -14, -15 and -16), 53.89 (C-13), 59.73 (C-8), 63.16 (C-6), 69.82, 71.97, 72.12 and 72.73 (C-2, -3, -4 and -5), 78.16 (C-7), 100.90 (C-1), 128.17, 128.27, 128.58, 128.64, 129.09, 129.43, 129.55, 129.62, 129.69, 133.09 and 133.38 (4 × Ph), 164.89, 165.15, 165.67 and 165.87 (CO_2) and 215.82 (CO).

Compound **10b**, mp 90–92 °C (Found: C, 71.1; H, 6.0%); ν_{max}(KBr)/cm^{-1} 3630, 3550, 3063, 2928, 2855, 1736, 1685, 1602, 1584, 1492, 1452, 1358, 1264, 1177, 1094, 1061 and 1026; $[\alpha]_D^{27}$ −5 (*c* 1.05, CH_2Cl_2); δ_H(250 MHz; $CDCl_3$) 0.95–2.17 (m, 14 H, 9-, 10-, 11-, 12-, 14-, 15- and 16-H_2), 2.55–2.68 (m, 1 H, 13-H), 2.70–2.82 (m, 1 H, 8-H), 4.15–4.32 (m, 2 H, 5- and 7-H), 4.54 (dd, *J* 6 and 12, 1 H, 6-H), 4.63 (dd, *J* 3 and 12, 1 H, 6-H′), 4.92 (d, *J* 8, 1 H, 1-H), 5.49 (dd, *J* 8 and 10, 1 H, 2-H), 5.63 (t, *J* 10, 1 H, 4-H), 5.93 (t, *J* 10, 1 H, 3-H) and 7.01–7.60 and 7.79–8.09 (2 m, 20 H, 4 × Ph); δ_C(62 MHz; $CDCl_3$) 21.80, 25.67, 26.16, 27.51, 30.95 and 33.19 (C-9, -10, -11, -12, -14, -15 and -16), 53.93 (C-13), 60.47 (C-8), 63.28 (C-6), 69.86, 71.75, 72.05 and 72.84 (C-2, -3, -4 and -5), 75.30 (C-7), 98.53 (C-1), 128.10, 128.17, 128.26, 128.60, 128.64, 128.90, 129.12, 129.52, 129.60, 129.70, 133.08 and 133.37 (4 × Ph), 164.75, 165.15, 165.68 and 165.90 (CO_2) and 216.57 (CO).

(1*R,2*R**,6*S**)-2-(α-D-Glucopyranosyloxy)bicyclo[4.4.1]-undecan-11-one 11ab**

The same procedure described for compounds **9ab** was used, starting from α compounds **7ab** (250 mg, 0.74 mmol), to yield two diastereoisomers separated by flash chromatography (CH_2Cl_2–MeOH, 94:6), tetraols **11a** and **11b** (247 mg, 97%) as a gum in the ratio 55:45.

Compound **11a**, ν_{max}(KBr)/cm^{-1} 3419, 2929, 2872, 1732, 1682, 1470, 1445, 1412, 1361, 1279, 1200, 1185, 1147, 1112, 1076, 1050, 1026 and 990; $[\alpha]_D^{30}$ +157 (*c* 0.4, CH_2Cl_2); δ_H(250 MHz; D_2O) 1.15–2.23 (m, 14 H, 9-, 10-, 11-, 12-, 14-, 15- and 16-H_2), 2.73–2.90 (m, 1 H, 13-H), 2.95–3.12 (m, 1 H, 8-H), 3.39 (dd, *J* 10 and 10, 1 H, 6-H), 3.51 (dd, *J* 4 and 10, 1 H, 6-H′), 3.60–3.92 (m, 4 H, 2-, 3-, 4- and 5-H), 4.01–4.17 (m, 1 H, 7-H) and 5.01 (d, *J* 4, 1 H, 1-H); δ_C(62 MHz; D_2O) 21.15, 25.16, 25.39, 25.84, 26.37, 29.85 and 32.97 (C-9, -10, -11, -12, -14, -15 and -16), 55.01 (C-13), 59.77 (C-8), 60.57 (C-6), 69.63, 71.81, 72.33 and 73.22 (C-2, -3, -4 and -5), 77.44 (C-7), 98.55 (C-1) and 219.40 (CO).

Compound **11b**, mp 65–68 °C (foam with CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3379, 2928, 2865, 1687, 1451, 1412, 1358, 1275, 1233, 1197, 1183, 1147, 1101, 1066, 1050 and 1028; $[\alpha]_D^{28}$ +95 (*c* 1.0, CH_2Cl_2); δ_H(250 MHz; D_2O) 1.27–2.19 (m, 14 H, 9-, 10-, 11-, 12-, 14-, 15- and 16-H_2), 2.71–2.84 (m, 1 H, 13-H), 2.85–2.96 (m, 1 H, 8-H), 3.35–3.94 (m, 6 H, 2-, 3-, 4- and 5-H and 6-H_2), 4.24 (t, *J* 4, 1 H, 7-H) and 5.06 (d, *J* 4, 1 H, 1-H); δ_C(62 MHz; D_2O) 21.07, 25.41, 25.80, 26.71, 27.95, 28.86 and 31.09 (C-9, -10, -11, -12, -14, -15 and -16), 54.77 (C-13), 60.53 (C-8), 61.05 (C-6), 69.62, 71.23, 72.47 and 72.96 (C-2, -3, -4 and -5), 73.94 (C-7), 95.74 (C-1) and 219.44 (CO).

(1*R,2*R**,6*S**)-2-(2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl-oxy)bicyclo[4.4.1]undecan-11-one 12a and 12b**

Using the same procedure which allowed us to obtain benzoylated compound **10a**, the diastereoisomers **11a** (90 mg, 0.26 mmol) and **11b** (80 mg, 0.23 mmol) gave, respectively, compounds **12a** (159 mg, 81%) and **12b** (110 mg, 63%), each as a powder.

Compound **12a**, mp 169–170 °C (Found: C, 70.7; H, 6.0. $C_{45}H_{44}O_{11}$ requires C, 71.0; H, 5.8%); ν_{max}(KBr)/cm^{-1} 3432, 3063, 2927, 2855, 1719, 1692, 1602, 1584, 1492, 1451, 1315, 1273, 1177, 1095, 1069 and 1027; $[\alpha]_D^{25}$ +69 (*c* 1.0 25, CH_2Cl_2); δ_H(250 MHz; $CDCl_3$) 0.99–1.89 and 2.18–2.33 (2 m, 14 H, 9-, 10-, 11-, 12-, 14-, 15- and 16-H_2), 2.53–2.67 (m, 1 H, 13-H), 2.87–2.99 (m, 1 H, 8-H), 4.03–4.16 (br t, *J* 8, 1 H, 7-H), 4.42–4.62 (m, 3 H, 5-H and 6-H_2), 5.23 (dd, *J* 4 and 10, 1 H, 2-H), 5.59 (d, *J* 4, 1 H, 1-H), 5.56–5.70 (m, 1 H, 4-H), 6.14 (t, *J* 10, 1 H, 3-H) and 7.20–7.60 and 7.81–8.08 (2 m, 20 H, 4 × Ph); δ_C(62 MHz; $CDCl_3$) 21.80, 25.66, 26.29, 26.73, 27.40, 30.37 and 34.50 (C-9, -10, -11, -12, -14, -15 and -16), 53.94 (C-13), 60.40 (C-8), 63.17 (C-6), 68.17, 69.48, 70.20 and 72.33 (C-2, -3, -4 and -5), 79.13 (C-7), 96.81 (C-1), 128.28, 128.38, 128.73, 128.81, 129.10, 129.66, 129.83, 129.89, 133.13 and 133.45 (4 × Ph), 165.36, 165.70, 165.88 and 166.09 (CO_2) and 216.05 (CO).

Compound **12b**, mp 89–90 °C (Found: C, 71.2; H, 6.0%); ν_{max}(KBr)/cm^{-1} 3442, 3063, 2928, 2859, 1731, 1692, 1602, 1584, 1492, 1452, 1315, 1273, 1177, 1094, 1068 and 1026; $[\alpha]_D^{27}$ +73 (*c* 0.95, CH_2Cl_2); δ_H(250 MHz; $CDCl_3$) 1.20–1.90 (m, 14 H, 9-, 10-, 11-, 12-, 14-, 15- and 16-H_2), 2.71–2.87 (m, 1 H, 13-H), 2.98–3.12 (m, 1 H, 8-H), 3.95–4.08 (m, 1 H, 7-H), 4.50 (dd, *J* 5 and 12, 1 H, 6-H), 4.68 (dd, *J* 2 and 12, 1 H, 6-H′), 4.68–4.83 (m, 1 H, 5-H), 5.25 (dd, *J* 8 and 10, 1 H, 2-H), 5.46 (d, *J* 8, 1 H, 1-H), 5.71 (t, *J* 10, 1 H, 4-H), 6.10 (t, *J* 10, 1 H, 3-H) and 7.15–7.62 and 7.82–8.14 (2 m, 20 H, 4 × Ph); δ_C(62 MHz; $CDCl_3$) 21.31, 25.90, 26.15, 26.79, 28.20, 29.23 and 32.57 (C-9, -10, -11, -12, -14, -15 and -16), 54.20 (C-13), 60.76 (C-8), 62.97 (C-6), 68.40, 69.17, 70.46 and 72.11 (C-2, -3, -4 and -5), 77.60 (C-7),

95.59 (C-1), 128.24, 128.35, 128.82, 129.68, 129.67, 129.75, 129.95, 133.05 and 133.43 (4 × Ph), 165.36, 165.59, 165.83 and 166.19 (CO_2) and 215.72 (CO).

2-Hydroxybicyclo[4.4.1]undecan-11-one 13[4a]

Compounds **9ab** (154 mg, 0.447 mmol) and sulfuric acid (0.5 M; 4.5 cm^3) were heated at 100 °C for 8 h. After the mixture had cooled to room temperature, aq. $KHCO_3$ (10%) was added to neutralize it. The aqueous phase was extracted with dichloromethane (3 × 5 cm^3) and the combined organic extract was washed with water (5 cm^3), dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography of the residue (hexane–ethyl acetate, 7:3) gave keto alcohol **13** (38 mg, 47%). Using the same methodology, acidic hydrolysis of glycosides **11ab** (210 mg, 0.61 mmol) for 11 h gave the same keto alcohol **13** (46 mg, 42%).

Similar treatment for each of the two diastereoisomers **11a** and **11b** allowed us to measure the rotation of enantiomerically pure materials. Isomer **11a** gave compound (−)-**13**, $[\alpha]_D^{26}$ −9 (*c* 0.6, CH_2Cl_2) and isomer **11b** gave compound (+)-**13**, $[\alpha]_D^{27}$ +9 (*c* 0.55, CH_2Cl_2); (+)-**13**, ν_{max}(neat)/cm^{-1} 3446, 3019, 2932, 2858, 1684, 1518, 1441, 1215, 1122 and 1035; δ_H(200 MHz; $CDCl_2$) 1.22–1.98 (m, 14 H, 3-, 4-, 5-, 7-, 8-, 9- and 10-H_2), 2.04–2.30 (br s, 1 H, OH), 2.68–2.87 (m, 2 H, 1- and 6-H) and 4.04 (m, 1 H, 2-H); δ_C(50 MHz; $CDCl_3$) 21.0, 26.0, 26.34, 26.40, 27.60, 29.24 and 35.23 (C-3, -4, -5, -7, -8, -9 and -10), 54.69 (C-6), 62.49 (C-1), 69.33 (C-2) and 217.78 (CO).

2-(2-Oxobicyclo[3.2.2]nona-3,8-dien-6-yl)acetaldehyde 15ab

A solution of compounds **4ab** (400 mg, 1.18 mmol) in sulfuric acid (0.5 M; 15 cm^3) was heated at 80 °C for 2.5 h. After cooling to room temperature, the reaction mixture was neutralized with aq. $KHCO_3$ (10%). The aqueous phase was extracted with dichloromethane (2 × 10 cm^3) and the combined organic phase was washed with water (5 cm^3), dried over $MgSO_4$, and concentrated. This oil was purified by flash chromatography over silica gel (hexane–ethyl acetate, 6:4) to give compounds **15ab** (57 mg, 31%) (in a 70:30 ratio) and hemiacetals **16ab** (25 mg, 13%) (in a 25:75 ratio).

Compounds **15ab** (Found: C, 73.1; H, 7.0. $C_{11}H_{12}O_2 \cdot 0.25\ H_2O$ requires C, 73.1; H, 7.0%); ν_{max}(neat)/cm^{-1} 3020, 2930, 1736, 1710, 1677, 1668, 1520, 1422, 1215 and 1022.

Compound **15a**, δ_H(250 MHz; $CDCl_3$) 1.50 (ddd, *J* 4, 6 and 14, 1 H, 14-H^{exo}), 2.27 (ddd, *J* 1, 10 and 14, 1 H, 14-H^{endo}), 2.50–2.59 (m, 2 H, 16-H_2), 2.77–2.90 (m, 1 H, 15-H), 3.16 (br t, 1 H, *J* 8, 10-H), 3.48 (m, 1 H, 13-H), 5.79 (dd, *J* 2 and 11, 1 H, 8-H), 6.20 (t, 1 H, 12-H), 6.42 (t, 1 H, 11-H), 7.12 (dd, *J* 9 and 11, 1 H, 9-H) and 9.75 (t, *J* 1, 1 H, CHO); δ_C(50 MHz; $CDCl_3$) 28.92 (C-14), 33.14 (C-15), 41.53 (C-10), 52.08 (C-13 and -16), 128.35 and 129.86 (C-11 and -12), 135.55 (C-8), 152.87 (C-9), 197.57 (CO) and 200.99 (CHO).

Compound **15b**, δ_H(250 MHz; $CDCl_3$) 1.38 (ddd, *J* 3, 6 and 14, 1 H, 14-H^{endo}), 2.44 (ddd, *J* 1, 7 and 14, 1 H, 14-H^{exo}), 2.50–2.59 (m, 2 H, 16-H_2), 2.77–2.90 (m, 1 H, 15-H), 3.31 (br t, *J* 8, 1 H, 10-H), 3.48 (m, 1 H, 13-H), 5.90 (dd, *J* 2 and 11, 1 H, 8-H), 6.05 (t, *J* 8, 1 H, 12-H), 6.60 (t, *J* 8, 1 H, 11-H), 6.86 (dd, *J* 9 and 11, 1 H, 9-H) and 9.80 (t, *J* 1, 1 H, CHO); δ_C(50 MHz; $CDCl_3$) 28.04 (C-14), 34.26 (C-15), 41.27 (C-10), 49.86 (C-16), 51.79 (C-13), 125.69 and 131.44 (C-11 and -12), 139.49 (C-8), 149.70 (C-9), 196.64 (CO) and 200.74 (CHO).

Compounds **16ab** (Found: C, 67.6; H, 7.0. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.3%); mp 102 °C; ν_{max}(KBr)/cm^{-1} 3389, 3019, 2932, 1700, 1685, 1216, 1157, 1085 and 1046; *m*/*z* 194 (M^+, 1.7%), 176 ($M^+ - H_2O$, 7.2), 150 (7), 105 (41), 91 (86), 79 (100), 78 (68) and 65 (12).

Compound **16a**, δ_H(250 MHz; $CDCl_3$) 1.60 (ddd, *J* 3, 13 and 13, 1 H, 14-H), 1.67 (ddd, *J* 5, 9 and 13, 1 H, 16-H), 1.89 (ddd, *J* 3, 5 and 13, 1 H, 16-H′), 2.26 (ddd, *J* 3, 6 and 13, 2 H, 14-H′ and 15-H), 2.53 (d, *J* 17, 1 H, 8-H), 2.86–3.02 (m, 1 H, 10-H), 3.13 (dd, *J* 8 and 17, 1 H, 8-H′), 3.23 (br t, *J* 6, 1 H, 13-H), 4.10 (br s, 1 H, OH), 4.47 (br t, *J* 8, 1 H, 9-H), 4.86 (dd, *J* 1 and 9, 1 H, 7-H), 6.17 (dt, *J* 6 and 8, 1 H, 12-H) and 6.34 (dt, *J* 6 and 8, 1 H, 11-H); δ_C(62 MHz; $CDCl_3$) 28.42 (C-15), 32.29 (C-14), 36.61 (C-10), 37.30 (C-16), 46.70 (C-8), 50.84 (C-13), 70.54 (C-9), 87.49 (C-7), 130.94 and 133.33 (C-11 and -12) and 211.75 (CO).

Compound **16b**, δ_H(200 MHz; $CDCl_3$) 1.51–1.71 (m, 1 H, 14-H), 1.82–2.12 (m, 2 H, 16-H_2), 2.34–2.42 (m, 2 H, 14-H′ and 15-H), 2.56 (d, *J* 17, 1 H, 8-H), 2.86–3.02 (m, 1 H, 10-H), 3.02 (dd, *J* 9 and 17, 1 H, 8-H′), 3.23 (br t, *J* 6, 1 H, 13-H), 3.81 (br s, 1 H, OH), 4.32 (br t, *J* 8, 1 H, 9-H), 5.30 (d, 1 H, 7-H), 6.17 (dt, *J* 6 and 8, 1 H, 12-H) and 6.34 (dt, *J* 6 and 8, 1 H, 11-H); δ_C(62 MHz; $CDCl_3$) 25.07 (C-15), 30.77 (C-14), 34.01 (C-16), 36.79 (C-10), 48.05 (C-8), 51.04 (C-13), 66.69 (C-9), 90.70 (C-7), 131.45 and 133.53 (C-11 and -12) and 210.21 (CO).

Acknowledgements

We thank C.N.R.S. and Université Paris-Sud for financial support.

References

1 J. H. Rigby, T. L. Moore and S. Rege, *J. Org. Chem.*, 1986, **51**, 2398; J. H. Rigby and S. V. Cuisiat, *J. Org. Chem.*, 1993, **58**, 6286; J. H. Rigby, [4 + 4] *and* [6 + 4] *Cycloadditions*, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, pp. 1063–1109.

2 (*a*) S. Itô, Y. Fujise, T. Okuda and Y. Inoue, *Bull. Chem. Soc. Jpn.*, 1966, **39**, 1351; (*b*) R. C. Cookson, B. V. Drake, J. Hudec and A. Morrison, *Chem. Comm.*, 1966, 15.

3 R. Hoffmann and R. B. Woodward, *J. Am. Chem. Soc.*, 1965, **87**, 2046, 4388.

4 (*a*) M. E. Garst, V. A. Roberts and C. Prussin, *J. Org. Chem.*, 1982, **47**, 3969; (*b*) M. E. Garst, V. A. Roberts, K. N. Houk and N. G. Rondan, *J. Am. Chem. Soc.*, 1984, **106**, 3882.

5 (*a*) S. Itô, K. Sakan and Y. Fujise, *Tetrahedron Lett.*, 1970, 2873; (*b*) M. E. Garst, V. A. Roberts and C. Prussin, *Tetrahedron*, 1983, **39**, 581 and references therein; (*c*) K. N. Houk and R. B. Woodward, *J. Am. Chem. Soc.*, 1970, **92**, 4145.

6 M. F. Neuman and D. Martina, *Tetrahedron Lett.*, 1977, 2293.

7 (*a*) A. Lubineau, J. Augé and N. Lubin, *J. Chem. Soc., Perkin Trans. 1*, 1990, 3011; (*b*) A. Lubineau and Y. Queneau, *J. Org. Chem.*, 1987, **52**, 1001.

8 A. Lubineau and Y. Queneau, *Tetrahedron Lett.*, 1985, **26**, 2653. For relevent studies on asymmetric Diels–Alder reactions using chiral diene derivatives from carbohydrates, see: R. C. Gupta, P. A. Harland and R. J. Stoodley, *J. Chem. Soc., Chem. Commun.*, 1983, 754; A. Lubineau, J. Augé, H. Bienaymé, N. Lubin and Y. Queneau, *Cycloaddition Reactions in Carbohydrate Chemistry*, ed. R. M. Giuliano, ASC Symposium Series, 1992, vol. 494, p. 147.

9 D. C. Rideout and R. Breslow, *J. Am. Chem. Soc.*, 1980, **102**, 7816; P. A. Grieco, P. Garner and Z. M. He, *Tetrahedron Lett.*, 1983, **24**, 1897; A. Lubineau, J. Augé and Y. Queneau, *Synthesis*, 1994, 741.

10 A. Lubineau, J. Augé, H. Bienaymé, Y. Queneau and M. C. Scherrmann, *Carbohydrates as Organic Raw Materials II*, ed. G. Descotes, VCH, Weinheim, Germany, 1993, p. 99; A. Lubineau, H. Bienaymé, Y. Queneau and M. C. Scherrmann, *New J. Chem.*, 1994, **18**, 279.

Paper 7/02447I
Received 10*th April* 1997
Accepted 2*nd June* 1997