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Naphthyl 3,4,6-tri-*O*-methyl-β-D-glucopyranoside as a chiral auxiliary in an asymmetric 1,4-addition reaction

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Abstract: Naphthyl 3,4,6-tri-*O*-methyl-β-D-glucopyranoside, easily synthesized from tri-*O*-acetyl-D-glucal, has been applied as a chiral auxiliary in an asymmetric Michael addition to the 2-*O*-crotonate. A very high facial diastereoselection (>95%) was obtained. No diastereoselection was observed when 1,3,4,6-tetra-*O*-methyl-β-D-glucopyranoside was used as the chiral auxiliary. A stereochemical model, taking into account steric shielding and π-stacking effects, is proposed on the basis of the observed results. © 1997 Elsevier Science Ltd

Carbohydrates are inexpensive natural products, simple to obtain in pure form, in which numerous functional groups and stereogenic centers are combined in one molecule. Even if the chiral information they contain is not always easily exploited in stereodifferentiating selection processes, they can be converted by regio- and stereoselective formation of derivatives into efficient chiral auxiliaries for controlling asymmetric syntheses.[1] Stereoelectronic effects, pre-orientation of the reagents through formation of complexes or hydrogen bonds, and shielding groups have been often used for effective diastereofacial differentiation.[1] The coordinating effect of a free hydroxyl group, for example, predominantly determines the facial differentiation observed in electrophilic additions to allylic alcohols bonded to the anomeric position of glycopyranosides,[2–4] while steric shielding generally characterizes the function of diacetone glucose, in the absence of coordinating Lewis acids, in the addition reactions to π-systems attached at the 3-position.[5] Steric shielding can be, however, obtained also in the glicopyranosides by introducing bulky groups in the proper positions. In particular, it is noteworthy that the introduction of aromatic substituents as bulky group can affect the reaction diastereoselection not only through steric effects but also via π–π interactions between the aromatic ring and prochiral carbon(s).

π–π interactions, or "π-stacking" effects, between a pendant aromatic nucleus and an adjacent π system have been invoked as stereochemical control elements in a broad range of stereodifferentiating organic reactions.[6] However, although the intermolecular through-space π–π overlap is undeniably involved in several fundamental phenomena, such as tertiary structures of proteins, double helical DNA structure,[7] there is only little indisputable evidence for the participation of such an interaction in the transtion states controlling the stereoselectivity of organic processes.[8] The experimental evidence that the presence of a phenyl group is essential for high diastereoselectivity does not indeed imply the presence of an electronic effect, but only that some property of the phenyl ring, size, shape or electronic character, is essential for a high stereodiscrimination. Furthermore, also the exact nature of the "π-stacking" effect (dipole–dipole and van der Waals attractions, or charge transfer interactions) is still a subject of some debate in the synthetic organic and computational areas.[9] However, independently of the controversy surrounding the precise nature of the effect, aromatic rings have been successfully utilized for some of the most important C–C bond forming reactions in organic asymmetric synthesis.[6]

In this paper we report a simple procedure for obtaining naphthyl 3,4,6-tri-*O*-methyl-β-D-glucopyranoside, having an aromatic nucleus adjacent to a free hydroxy group, to which the prochiral

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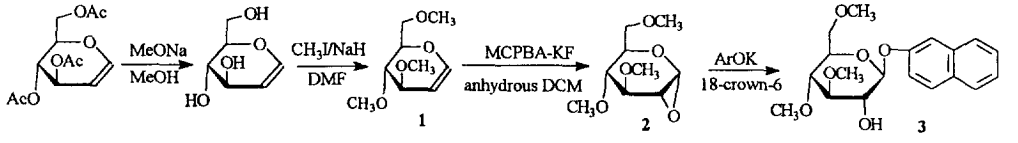
π-system can be linked, while all the other positions are protected by methylation, and its synthetic application in the asymmetric 1,4-addition reactions, showing that this compound can be a valid alternative to the use of 8-aryl menthol derivatives as chiral auxiliaries.

Results and discussion

The tri-*O*-methyl-D-glucal **1**, used as the starting material in this synthetic approach, was prepared from commercial tri-*O*-acetyl-D-glucal by deacetylation[10] followed by exhaustive methylation.

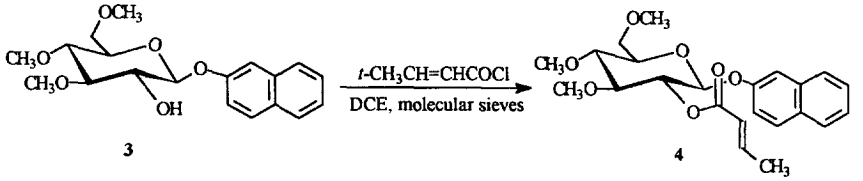
The glucal **1** was transformed into the corresponding 1,2-anhydro-3,4,6-tri-*O*-methyl-α-D-glucopyranose (**2**) by epoxidation with MCPBA–KF in anhydrous CH_2Cl_2, a reaction which has been shown[11] to give the corresponding *anti* and *syn* epoxidation products, in a *ca.* 95:5 ratio, and practically quantitative yield. The crude epoxide mixture **2** was then subjected to oxirane ring opening, under basic conditions, by addition of the preformed potassium salt of 2-naphthol in THF at 0°C in the presence of 18-crown-6 to give, after purification by column chromatography, pure **3** (>90% yield), which was characterized by ^1H and ^{13}C NMR spectra.



It must be remarked that, although 1,2-anhydro sugar derivatives have been proved to be very good glycosyl donors for oligosaccharide and other glycoside syntheses in the presence of a Lewis acid,[12] the reaction generally proceeding with a high *anti*-stereoselection, it has recently been reported[13] that with phenols, under these conditions, the reaction gives, with moderate yield, α and β-aryl glycoside mixtures, and a high *anti*-stereoselection can be achieved only under basic conditions.[13,14]

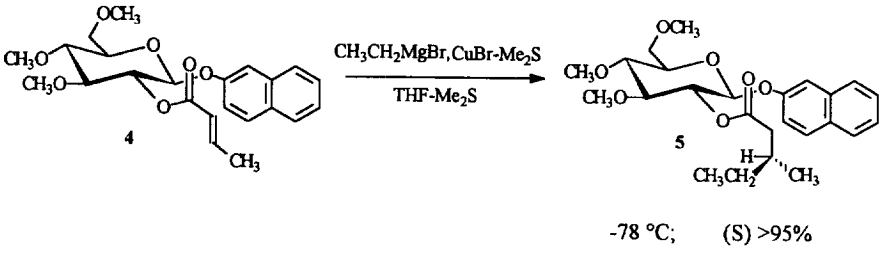
In order to verify the potential use of **3** as a chiral auxiliary for asymmetric conversions of prochiral substrates linked to the 2-OH group, we chose as a model the crotonyl group and its conversion to 3-methylpentanoyl through a Michael addition of the ethyl Grignard reagent. This choice was dictated by the fact that previous data were available on the use in the same or similar reactions of other auxiliares containing aryl groups, such as 8-aryl menthols[15] and 5-deoxy-5-phenyl-1,2-*O*-isopropylidene-α-D-xilofuranose,[16] thus allowing a comparison of efficiencies, and, possibly, of the facial stereoselection of the induction. Furthermore, it was hoped to establish the effective role played by the aryl group.

Esterification of **3** was efficiently carried out in 1,2-dichloroethane by refluxing with *trans*-crotonyl chloride. The yield of **4** was much better (90%) when 3 Å molecular sieves were used instead of the traditional pyridine or triethylamine.



The 1,4-addition reaction of EtMgBr to **4**, catalyzed by $CuBr \cdot Me_2S$, was carried out at −78°C in THF.[16] It is noteworthy that, an anhydrous, freshly distilled and peroxide free solvent was necessary in order to obtain **5** in a satisfactory yield, around 65% after purification by column chromatography.

The diastereoisomeric ratio was evaluated as >95%, there being practically the signals of only one diastereoisomer detectable in the ^1H and ^{13}C NMR spectra. A significantly lower diastereoselection, around 70:30, determined on the basis of the intensities of the signals of the anomeric carbons in the ^{13}C NMR spectrum, respectively at 99.11 and 98.51, was instead obtained when the reaction was carried out at a higher temperature (−20°C).

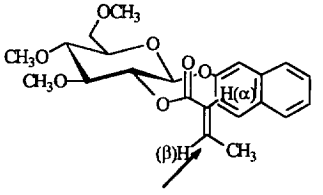


-78 °C; (S) >95%

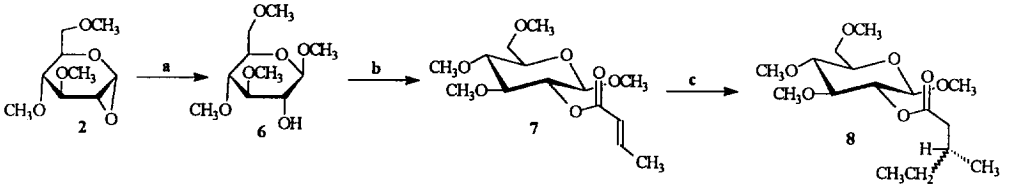
The S configuration at the new stereogenic center of the major product was established on the basis of the positive optical rotation of the 3-methylpentanoic acid obtained by treatment of **5** in THF, containing 5% of H_2O, with KOH(s) and 18-crown-6 at reflux temperature for 2 h. It should be emphasized that the chiral auxiliary, cleaved under these conditions, is recovered in a practically quantitative yield, and can be used for further reactions.

The S configuration of the newly created stereogenic center in **5** corresponds to the preferred approach of the cuprate reagent from the sterically less congested π-face of the crotonate moiety, represented in its *s-trans,syn* conformation (as was observed in 1,4-additions to crotonate derivatives of 8-phenylmenthol).[15]

Although this stereochemical finding appears to be in contradiction with the *s-cis,syn* conformation exhibited[17] by the crotonic ester of *trans*-2-[1(2-naphthyl)-1-methylethyl]-cyclohexane at the solid state and with the conformations calculated[18] for acrylates, it has been already stressed[17,18] that the trans conformation, having a higher dipole moment, is surely the more stable form in solution. Furthermore, the same ab initio calculations have shown[18] that the Lewis acid complexed acrylates prefer the *s-trans,syn* conformation also in the absence of solvent, so confirming the conformational hypothesis made[8,19] to rationalize the stereoselectivity of 1,4-additions to crotonates which, occur not only in solution, but also in the presence of metal ions capable to complex the carbonyl group.



In order to obtain information about the role actually played by the aromatic part in the asymmetric process, the stereochemical behaviour of the Michael addition to **4** was compared with the 1,4-addition of the cuprate reagent on crotonate double bonds to the 1-*O*-methyl analogue (**7**), which was synthesized from the same 1,2-anhydro sugar **2** by oxirane ring opening to **6** with MeONa in methanol, followed by esterification.



Conditions: a: MeONa/MeOH; b: *t*-CH_3CH_2=CHCOCl/DCE, Molecular sivies; c: CH_3CH_2MgBr/CuBr-Me_2S, THF, -78 °C.

The crotonyl derivative **7** was subjected to the 1,4-addition under conditions identical to those employed to prepare **5**. The product **8**, isolated after column chromatography, showed a diastereoisomeric

Table 1. Chemical shifts (δ) and coupling constants (Hz) of crotonic and C1 and C2 protons

	7		4	
	18 °C	-60 °C	18 °C	-60 °C
Hα	5.83 (15.5)	5.80 (15.5)	5.87 (15.5)	5.87(15.5)
Hβ	7.00 (15.5)	6.97 (15.5)	7.15 (15.5)	7.13(15.5)
CH_3	1.85 (6.9)	1.84 (6.9)	1.87 (6.9)	1.89 (6.9)
H1	4.25 (8.0)	4.19 (8.0)	5.09 (7.9)	5.16[a]
H2	4.87 (8.0)	4.70 (8.0)	5.30 (7.9)	5.16[a]

[a] Higher order analysis

ratio around 50:50, determined on the basis of the signals related to the carbon atoms of the new stereogenic centre of the two diastereoisomers which appeared at different chemical shifts.

Comparison of the steric courses of the 1,4-additions to **4** and **7** shows that the presence of the naphthyl group is essential for the diastereofacial discrimination, even if this gives no information about the nature of the effect, noncovalent interaction (π-stacking effect) and/or steric effects. Since it has been established[8] that, at least for 8-aryl crotonates derived from menthol, a convincing support of the existence of an intramolecular π-stacking interaction is furnished by their ^1H NMR analysis, indeed the protons of the crotonate moiety are shielded by the ring current of the neighboring aromatic nucleus, the ^1H NMR spectra of **4**, in $(CD_2Cl)_2$ at 18 and −60°C, were compared with those of **7**. Independently of the temperature, which instead markedly affects the diastereoselectivity of the process, no significant shift of the signals of the crotonate moiety of **4** with respect to those of **7**, was observed both at 18 and −60°C (Table 1).

In view of the ability of the naphthyl group to induce facial diastereoselection, the latter results can be rationalized considering that the two π-systems of **7** are not engaged in a stacked geometry and induction arises only from steric shielding. Alternatively, one may hypothesize that the origin of diastereoselectivity cannot be simply related to a preferred ground state conformation, but it should be connected to the transition state geometry in which the complexation with the metal and the formation of the adduct can be relevant.

Finally, at variance with the 8-aryl derivatives of menthol, in which the aromatic group is bonded to the cyclohexane ring by a methylene bridge, in **4** the aromatic substituent is a naphthol connected to the anomeric position of the sugar moiety by β bond. The ability of the oxygen to favor a dipole in the aromatic ring by mesomeric effect could affect not only the ring current in the aromatic nucleus, but also the nature of the interaction between the two π-systems, dipole–dipole or dipole-induced dipole interactions instead of dispersion energy, which primarily contributes to the π-stacking effect in the 8-aryl derivatives of menthol,[8] and this could affect the NMR spectra of **4**.

In conclusion, independent of the origin of the diastereoselection, **3** presents, at least in 1,4 addition reactions, the same efficiency as a chiral inducer as -(2-naphthyl)menthol and the same diastereofacial selectivity. Thus, taking into account the limitations in the use of 8-(2-naphthyl)menthol as chiral auxiliary owing to purification problems during its preparation from (+)-pulegone, **3** could represent a valid alternative. On the other hand, 5-deoxy-5-phenyl-1,2-*O*-isopropylidene-α-D-xylofuranose, the other sugar proposed as a chiral auxiliary in asymmetric 1,4-addition reactions gives products with opposite stereochemistry at the new stereogenic centre.

Work is in progress in our laboratory in order to further evaluate the efficiency of **3** as a chiral auxiliary in other asymmetric synthesis.

Experimental

All melting points were measured on a Kofler apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ solution (c=1.0±0.2) at 20±2°C with a Perkin–Elmer 241 polarimeter. NMR spectra were registered with a Bruker AC 200 instrument using tetramethylsilane as internal standard. All reactions were followed by TLC Alugram^R sil G/UV_{254} with detection by UV or with

ethanolic 10% sulphuric acid and heating. Kieselgel Macherey–Nagel (70–230) was used for column chromatography. Solvents were distilled and stored over 4 Å molecular sieves activated by heating for 24 h at 400°C. Reactions under anhydrous conditions were carried out under an argon atmosphere. $MgSO_4$ was used as the drying agent for solutions. Anhydrous KF was obtained by heating at 120°C and 0.1 mmHg for 2 h. $CuBrMe_2S$ was crystallized from hexane–Me_2S immediately before use.

Naphthyl 3,4,6-tri-O-methyl-β-D-glucopyranoside 3

Tri-*O*-methylglucal **1**, prepared from commercial tri-*O*-acetylglucal by deacetylation[10] followed by methylation according to the general alkylation procedure,[20] was subjected to epoxidation with MCPBA–KF complex,[11] to give essentially epoxide **2**.[13] To a solution of crude **2**, containing *ca.* 5% of its β-anomer, (300 mg, 1.47 mmol) in anhydrous THF (6 ml) at 0°C the previously prepared potassium salt of naphthol (4.4 mmol) and 18-crown-6 (0.22 mmol) were added. The reaction mixture was then allowed to warm to room temperature, stirred for 15 h, and finally diluted with water ed extracted with ethyl ether. The organic phase, washed and dried ($MgSO_4$), was eporated *in vacuo* and the residue was chromatographed over silica gel (6:4 hexane–AcOEt) to give pure **3** in a 90% yield. $[\alpha]_D=-64.1$ (c 1.30, $CHCl_3$). M.p. 135–137°C. ^1H NMR ($CDCl_3$): 3.40 (s, 3 H, OCH_3), 3.57 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 3.31–3.75 (m, 6 H), 4.98 (d, 1 H, J=7.7 Hz, H-1), 7.21–7.79 (7 aromatic H). ^{13}C NMR ($CDCl_3$) δ: 59.36 (OCH_3); 60.39 (OCH_3); 60.86 (OCH_3); 70.97; 73.76; 75.17; 79.10; 85.90; 100.85 (C-1); 111.31, 118.93, 124.33, 126.33, 127.15, 127.59 and 129.41 (7 aromatic CH); 129.89, 134.20 e 154.91 (3 aromatic >C<). Anal. Calcd. for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.42; H, 7.0%.

Naphthyl 2-O-crotonyl-3,4,6-tri-O-methyl-β-D-glucopyranoside 4

To a 1,2-dichloroethane solution (7 ml) of **3** (600 mg, 1.7 mmol) containing molecular sieves 3 Å (800 mg), 0.2 ml (225 mg, 2.15 mmol) of *trans*-crotonyl chloride were added. The mixture was heated under reflux for 48 h, then diluted with 1,2-dichloroethane and washed with a saturated aqueous solution of $NaHCO_3$. The organic phase was dried ($MgSO_4$) and evaporated *in vacuo*. The crude product (820 mg) was purified by column chromatography over silica gel (6:4, hexane/AcOEt) to give 680 mg of pure **4**, 95% yield. $[\alpha]_D=+11.2$ (c 1.52, $CHCl_3$). M.p. 108–110°C. ^1H NMR ($CDCl_3$) δ: 1.86 (dd, 3H, J=6.9 and 1.6 Hz, CH_3); 3.41 (s, 3 H, OCH_3), 3.55 (s, 3 H, OCH_3), 3.58 (s, 3 H, OCH_3), 3.40–3.72 (m, 6 H), 5.09 (d, 1 H, J=7.9 Hz, H-1), 5.30 (t, 1H, J=7.9 Hz, H-2); 5.87 (dd, $J_{trans}=15.5$ and $J_{1,4}=1.6$ Hz, =CH); 7.15 (dq, $J_{trans}=15.5$ and $J_{1,2}=6.9$ Hz, =CH); 7.33–7.77 (m, 7 aromatic H). ^{13}C NMR ($CDCl_3$) δ: 18.11 (CH_3); 59.4 (OCH_3); 60.25 (OCH_3); 60.48 (OCH_3); 71.17 (C-6); 72.56, 75.26, 78.90, 84.77 (C2, C3, C4 and C5); 99.38 (C-1); 122.06 (CH=); 111.72, 119.02, 124.25, 126.27, 127.07, 127.54 e 129.29 (7 aromatic CH); 129.82 e 134.12 (2 aromatic >C>); 143.76 (=CH); 155.11 (1 aromatic >C<); 164.19 (C=O). Anal. Calcd. for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78. Found: C, 66.58; H, 6.91.

Naphthyl 2-O-(3-(S)-methylpentanoyl)-3,4,6-tri-O-methyl-β-D-glucopyranoside 5

To a mixture of $CuBrMe_2S$ (430 mg, 2.1 mmol) and 3 ml of (1:1) Me_2S–THF (THF was previously accurately anhydrified and treated in order to remove peroxides) a 1.0 M solution of EtMgBr in THF (2.1 ml) was added at −78°C with stirring under argon for 10 min. To this brownish solution compound **4** (210 mg, 0.5 mmol) in THF (2.5 ml) was added. After 2 h of stirring at −78°C the resulting dark green mixture was poured into aqueous NH_4Cl at 0°C and extracted with CH_2Cl_2. The organic phase, washed and dried ($MgSO_4$), was evaporated *in vacuo* to give a residue (400 mg), which was purified by column chromatography over silica gel (7:3 hexane–AcOEt) giving pure **5** (140 mg, 0.32 mmol) in a *ca.* 65% yield. $[\alpha]_D=-24.1$ (c 1.64, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.84 (t, 3H, J=7.3 Hz, CH_3); 0.94 (d, 3H, J=6.7 Hz, CH_3); 1.24 (m, 2H, CH_2); 1.9 (m, 1H, CH); 2.15 (dd, $J_{gem}=14.4$ and $J_{1,2}=8.0$ Hz, 1H, CH_2); 2.36 (dd, $J_{gem}=14.4$ and $J_{1,2}=6.3$ Hz, 1H, CH_2); 3.42 (s, 3 H, OCH_3); 3.57 (s, 3 H, OCH_3); 3.58 (s, 3 H, OCH_3); 3.40–3.8 (m, 6 H), 5.08 (d, 1 H, $J_{1,2}=7.9$ Hz, H-1), 5.25 (t, 1H, $J_{1,2}=7.9$ Hz, H-2); 7.12–7.78 (m, 7 aromatic H). ^{13}C NMR ($CDCl_3$) δ: 11.20 (CH_3); 19.10 (CH_3); 29.12 (CH); 31.93 (CH_2); 41.57 (CH_2); 59.47 (OCH_3); 60.25 (OCH_3); 60.49 (OCH_3); 71.04 (C-); 72.21, 75.32,

79.16, 84.51 (C2, C3, C4 and C5); 99.11 (C-1); 110.76, 118.87, 124.29, 126.34, 127.10, 127.59 e 129.35 (7 aromatic CH); 129.81, 134.20 e 155.98 (3 aromatic >C<); 171.79 (C=O). Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67. Found:C, 67.10; H, 7.60.

Methyl 2-O-crotonyl-3,4,6-tri-O-methyl-β-D-glucopyranoside 7

A solution of MeONa in MeOH (38 ml), prepared by dissolving 1.6 g of Na in 40 ml of MeOH, was added to crude **2**, containing *ca.* 5% of the β-anomer, (300 mg, 1.47 mmol). After 30 min at room temperature, the reaction mixture was diluted with CH_2Cl_2 (50 ml) and washed with water. The organic phase was dried ($MgSO_4$), eporated *in vacuo* to give, in a 90% yield, a 93:7 mixture of **6** and of the diastereomeric methyl 3,4,6-tri-*O*-methyl-α-D-mannopyranoside, arising from the oxirane ring opening of the minor epoxide. Methyl 3,4,6-tri-*O*-methyl-β-D-glucopyranoside **6**; ^{1}H NMR ($CDCl_3$) δ: 3.41 (s, 3 H, OCH_3), 3.52 (s, 3 H, OCH_3), 3.53 (s, 3 H, OCH_3), 3.65 (s, 3 H, OCH_3), 3.18–3.69 (m, 6 H), 4.13 (d, 1 H, $J_{1,2}$=7.6 Hz, H-1). ^{13}C NMR ($CDCl_3$) δ: 56.92 (OCH_3); 59.15 (OCH_3); 60.14 (OCH_3); 60.57 (OCH_3); 71.00 (C6); 73.76, 74.66, 79.16, 85.89, (C2, C3, C4 and C5); 103.56 (C1).

This crude product (290 mg, 1.2 mmol) was subjected to esterification under the same conditions employed for the preparation of **4**, and the resulting mixture was purified by column chromatography over silica gel (6:4, hexane/AcOEt) to give pure **7** in 95% yield. $[\alpha]_D$=+2.0 (c 1.47, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 1.83 (dd, 3H, J=6.9 and 1.6 Hz, CH_3), 3.37 (s, 3 H, OCH_3), 3.38 (s, 3 H, OCH_3), 3.42 (s, 3 H, OCH_3), 3.46 (s, 3 H, OCH_3), 3.23–3.63 (m, 6 H), 4.22 (d, 1 H, $J_{1,2}$=8.0 Hz, H1), 4.84 (t, 1H, $J_{1,2}$=8.0 Hz, H2), 5.80 (dd, J=15.4 and 1.6 Hz, =CH), 6.98 (dq, J=15.4 e 6.9 Hz, =CH). ^{13}C NMR ($CDCl_3$) δ: 17.81 (CH_3); 56.35 (OCH_3); 59.15 (OCH_3); 59.93 (OCH_3); 60.16 (OCH_3); 70.99 (C6); 72.40, 74.68, 78.87 e 84.54 (C2, C3, C4 and C5); 101.55 (C1); 122.09 (CH=); 145.27 (=CH); 164.85 (C=O). Anal. Calcd. for $C_{14}H_{24}O_7$: C, 55.25; H, 7.95. Found:C, 55.40; H, 7.65.

Methyl 2-O-(3-methylpentanoyl)-3,4,6-tri-O-methyl-β-D-glucopyranoside 8

Compound **7** (110 mg, 0.35 mmol) was subjected to 1,4 addition under the same conditions employed for the preparation of **5**, and the product was purified by column chromatography over silica gel (7:3 hexane–AcOEt) giving pure **8** (140 mg, 0.32 mmol) in a *ca.* 60% yield. ^{1}H NMR ($CDCl_3$) δ: 0.83 (t, 3H, J=7.7 Hz, CH_3); 0.95 (d, 3H, J=6.8 Hz, CH_3); 1.24 (m, 2H, CH_2); 1.9 (m, 1H, CH); 2.00–2.13 (two partially overlapped dd, due to 1H of the CH_2 group of the two diastereoisomers); 2.22–2.32 (two partially overlapped dd, due to 1H of the CH_2 group of the two diastereoisomers); 3.35 (s, 3H, CH_3O), 3.38 (s, 3H, CH_3O), 3.45 (s, 3 H, OCH_3), 3.47 (s, 3 H, OCH_3), 3.20–3.6 (m, 6 H), 4.17 (d, 1 H, J=7.8 Hz, H1), 4.81 (t, 1H, J=7.8 Hz, H2). ^{13}C NMR ($CDCl_3$) δ: 11.20 (CH_3); 18.98 (CH_3); 29.10 (CH_2, relative to one diastereoisomer) and 29.20 (CH_2, relative to the other diastereoisomer); 31.92 (CH, relative to one diastereoisomer) and 32.05 (CH relative to the other diastereoisomer); 41.58 (CH_2); 56.56 (OCH_3); 59.41 (OCH_3); 60.05 (OCH_3); 60.37 (OCH_3); 71.16 (C6); 72.23, 74.91, 79.29, 84.45 (C2, C3, C4 and C5); 101.83 (C1); 171.86 (C=O).

(+)-(S)-3-Methylpentanoic acid

To a solution of **5** (90 mg, 0.18 mmol) in THF (8 ml), containing 5% of H_2O, freshly powdered KOH (0.2 mmol) and 18-crown-6 (0.1 mmol) were added. After 4 h at the reflux temperature CH_2Cl_2 was added and the mixture was extracted with water. The organic phase, dried ($MgSO_4$) and evaporated *in vacuo* gave practically pure **3**, in quantitative yield. The aqueous phase was acidified with 1 N HCl and extracted with CH_2Cl_2. The extracts, washed with water, were dried ($MgSO_4$) and evaporated to give after evaporation *in vacuo* 20 mg (+)-(S)-3-methylpentanoic acid, which was identified by comparison of the FT-IR and FT-NMR spectra. $[\alpha]_D$=+8.7 (c 0.52, $CHCl_3$). Lit[21] $[\alpha]_D$=+8.92.

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