Induction of a Preferred Sense of Twist in Flexible Diphenyls by Carbohydrate Scaffolds. Synthesis of Two "Naked" Ellagitannin Analogous

Giuseppe Capozzi,[†] Cinzia Ciampi,[†] Giovanna Delogu,*[,‡] Stefano Menichetti,[§] and Cristina Nativi*[,†]

Centro CNR "Chimica e Struttura dei Composti Eterociclici", Dipartimento di Chimica Organica, Universita' di Firenze. Via G. Capponi, 9 I-50121 Firenze, Italy; Istituto CNR "Applicazione Tecniche Chimiche Avanzate ai Problemi Agrobiologici", Via Vienna, 2 I-07100 Sassari, Italy; and Dipartimento di Chimica Organica e Biologica, Università di Messina, Salita Sperone 31, I-98166 Messina, Italy

cristina.nativi@unifi.it

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The synthesis of "naked " ellagitannin analogues **1** and **2**, having a preferred sense of twist of the diphenyl moiety, with a rhamnose and a glucose template, is reported. A clear induction in the chirality of the diphenyl moiety, mediated through a 10-membered ring via ester linkages, was observed. The chiral scaffold of glucose (diequatorial 2,3-hydroxyl groups) exerts a remarkable stronger atropdiastereoselective effect onto the diphenoyl group than the rhamnose ring (axial−equatorial 2,3-hydroxyl groups), according to the Schmidt−Haslam hypothesis.

Introduction

Diphenyl−sugar moieties are present in a large number of naturally occurring biologically active compounds.[1,2] Due to their important pharmaceutical[3] and agrochemical proprieties,[4] diphenyl−sugar units constitute attractive synthetic leads. Many efforts devoted to prepare analogues of molecular receptors[5] and redox[6] and antimalaria agents[7] have been reported in the past decade. Among them, the most attractive syntheses of diphenyl−sugar core-containing molecules regard the preparation of new antibiotics related to ristocetin A and teicoplanin,[8] two glycopeptides that belong to the family of ristocetin-type antibiotics.[9] The structure of these challenging molecules shows a conformationally stable axially chiral ortho trisubstituted diphenyl unit, glycosylated to a mannopyranoside.

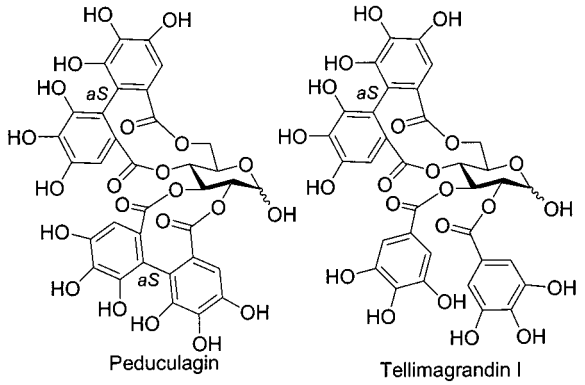

Figure 1. Structure of two naturally occurring ellagitannins.

The ellagitannins are another vast family of biologically active compounds that gained a top position in research fields engendered by recent disclosures of their promising anticancer and antiviral activities. The structures of most ellagitannins are characterized by the presence of one or more axially chiral hexahydrodiphenoyl (HHDP) residues connected to a glucopyranose scaffold by ester functions. The axially chiral HHDP moieties located at the 2,3- or 4,6-positions of the glucopyranose ring of the natural ellagitannins exhibit, except few cases, the *aS* configuration, while the 2,4- or 3,6-HHDP-substituted ellagitannins present the *aR* configuration (Figure 1).

* Corresponding author. Phone:+39-055-275-7633. Fax:+39-055-247-6964.

[†] Universita' di Firenze.

[‡] Istituto CNR "Applicazione Tecniche Chimiche Avanzate ai Problemi Agrobiologici".

[§] Università di Messina.

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Table 1. Selectivity in the Preparation of 2,3-*O*-Diphenoyl-α-D-rhamnopyranoside 1

entry	conditions	% yield (conversion) of **1**	% yield of **8**−**10**	ratio **1**/**8**−**10**
1	NaH, toluene (0.02 M), 0 °C to rt	15 (34%)	8	1.9/1
2	NaH, DMF (0.02 M), 0 °C to reflux			
3	DMAP, CH_2Cl_2 (0.01 M), 0 °C to rt	20 (48%)	7.8	2.6/1

Chemo-, regio-, and stereoselective construction of a pyranose-linked diaryl unit requires effective solutions of several synthetic problems, but paramount is the development of an efficient method to control the stereochemistry of the diaryl moiety.

In diphenyl−sugar core-containing molecules the role of the carbohydrate unit seems to be 2-fold: it influences some biological properties, such as cell penetration and pharmacokinetics, and it exerts a strong atropdiastereoselective control onto diphenyl bond formation.[10]

Such steric control was earlier proposed by Haslam[11] and Schmidt,[12] who tried to rationalize the stereocontrol of the biosynthesis of monomeric ellagitannins, and was more recently strengthened by conformational analysis of atropdiasteroisomeric D-glucose diphenoyl derivatives, which enable one to explain the diasteroselective formation of 2,3- and 4,6-(*aS*)-HHDP-bridged glucosides relying on the tendency of the ester groups to maintain their characteristic U-shape.[13]

A plethora of articles appeared in the literature dealing with the synthesis and characterization of ellagitannis in order to study the reaction mechanisms as well as the opposite configuration observed at the stereogenic axis in different natural compounds.[14] All papers, however, relate to ortho tetrasubstituted, and therefore conformationally stable, diphenyls. Indeed, as far as we know, only one example of ortho disubstituted diphenyl−sugar compound has been prepared, and no mention about the diphenyl stereochemistry was made.[15]

Two configurations at the stereogenic axis have to be expected for an ortho tetrasubstituted diphenyl.[16] Generally, if the synthetic process chosen for the preparation of this type of biphenyl−sugar-containing compound is stereoselective, the exclusive or predominant formation of the configurationally more stable diphenyl derivative can be reached. The situation would be likely different whether the diphenyl moiety is not conformationally stable.[17]

In this paper we describe the diasteroselective synthesis of two "naked" ellagitannin-type molecules, **1** and **2** (vide infra), inducing a preferred sense of twist in flexible diphenyls by carbohydrate scaffolds by reacting the axially chiral and *conformationally flexible* diphenoyl chloride (**3**), via ester cyclization with a rhamnose and glucose template, respectively. The choice of the rhamnose derivative **4** and the glucose derivative **5** (vide infra) as model sugars was dictated by their different conformations (**4**, $^1C_4$; **5**, $^4C_1$) and different configuration at the hydroxyl group at C-2 (**4**, *axial*−equatorial 2,3-hydroxyl groups; **5**, *diequatorial* 2,3-hydroxyl groups).

The investigation herein reported can furnish useful insight into the stereochemical problems encountered in the synthesis of diphenyl derivatives of carbohydrates and represents the first example of the induction of central chirality (sugar scaffold) onto the configuration of the stereogenic axis of a *conformationally flexible* diphenyl unit.[18]

Results and Discussion

The rhamnose template **4**, prepared in three steps from β-rhamnose **6**, was reacted under different conditions with the conformationally flexible diphenoyl chloride (**3**). Independently of reaction conditions, five different products were formed: two cyclic diesters **1** and the flexible open-chain diesters[19] **8**−**10** (Scheme 1, Table 1).

Compounds **1**, deriving from an intramolecular diesterification, were obtained as a atropdiasteroisomeric mixture (1.8:1 with DMAP, 1.7:1 with NaH as base) that was easily separated from intermolecular diesters **8**−**10** by silica gel flash chromatography. Use of toluene as solvent (0.02 M) in the presence of NaH as base (entry 1) gave results (yield, selectivity, and inter/intra ratio) closely related to those obtained in dichloromethane (0.01 M) with (dimethylamino)pyridine (DMAP) (entry 3). The use of NaH in dimethylformamide (DMF) (entry 2) ended up with the recovery of unaltered starting material (room temperature) or with the formation of undesired side products (reflux).

Although moderate, an interesting atropdiasteroselectivity was observed during the formation of cyclic derivative **1**, suggesting that the rhamnose template exerts to some extent chiral induction onto the diphenoyl moiety.

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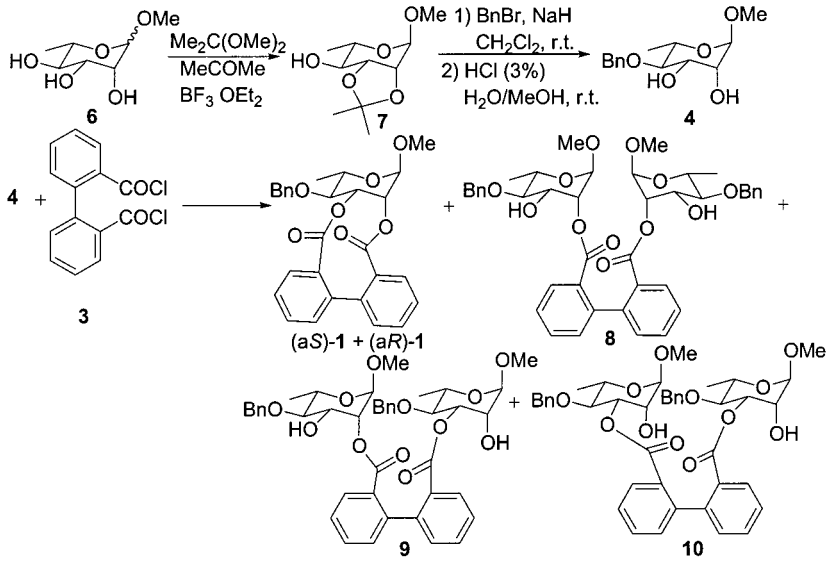
Scheme 1



Since diasteroselectivity was not excellent and diastereomers (*aR*)-**1** and (*aS*)-**1** were not easily separable, we prepared derivatives **11** and **12**, which presented at C-3 a *p*-methoxybenzyl (PMB) group and a pivaloyl (Piv) group, respectively (Figure 2).

Compounds **11** and **12**, prepared following a standard procedure (see the Experimental Section), were reacted with **3** in dichloromethane and in the presence of DMAP, affording the cyclic diesters **13** (20%) and **14** (17%), respectively, both as inseparable atropdiastereoisomers in a 1.7:1 and 1.8:1 ratio.

The presence of different protecting groups at C-4 did not influence the diasteroselectivity of the cyclization, and as reported for diol **4**, diesterification of **11** also gave a mixture of three open-chain diesters, in a 2.2:1 inter/intramolecular ratio, while in the case of **12**, diester **14** was formed together with side products. Thus we repeated the reaction of **3** with a conformationally more rigid template. To this purpose the methyl 4,6-*O*-benzylideneglucopyranoside **5**, prepared by treatment of methyl glucose **15** with benzaldehyde in the presence of *p*-toluenesulfonic acid (PTSA), was reacted with **3** and DMAP in dry dichloromethane (0.01 M) at room temperature (Scheme 2).

After 1.5 h, the reaction was stopped and the diphenoyl derivative **2** (18%) was easily separated from unreacted glucopyranoside **5** (40% conversion) and byproducts (20%). Longer reaction times caused the formation of greater amounts of side products. Spectroscopic data

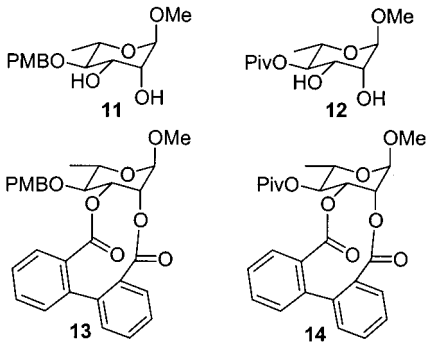
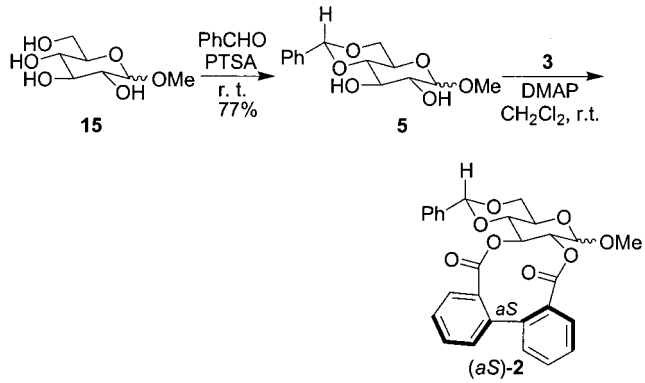


Figure 2. Stuctures of compounds **11**−**14**.

Scheme 2



unambiguously showed that compound **2** was a mixture of two anomers (α/β = 1.4/1) and that only one atropdiasteroisomer was formed, meaning that the diesterification of **5** had occurred with total diasteroselectivity. The separation of the anomeric mixture was accomplished by HPLC (see the Experimental Section), and the configuration of the axially chiral derivatives **2α** and **2*β*** was determined by UV and CD spectra. The absorption and CD spectra, recorded in THF, are reported in Figure 3. The most important observations that can be made are as follows: (1) the absorption spectra are almost superimposable. In fact they both show three main regions of absorption centered at 280 nm ($\epsilon \approx 5000$), 245 nm ($\epsilon \approx 20\,000$), and 210 nm ($\epsilon \approx 60\,000$), related to the ^1L_b, ^1L_a, and ^1B transitions of a substituted benzene chromophore. This is a strong indication that the same chromophore (i.e. the diphenic moiety) determines the shape of the spectra. (2) As far as the CD spectra are concerned, **2α** and **2*β*** show the same sequence of four Cotton effects, the signs of which are (moving from longer to shorter wavelengths) negative, positive, negative, positive. These Cotton effects occur at the same wavelengths position, with the same width and intensity. All these facts demonstrate that the diphenic moiety chromophore is twisted in the same sense in the two compounds. (3) To deduce the preferred sense of twist induced in the diphenic moiety by the carbohydrate core, the well-known method of empirical comparison of the CD spectra of the unknown compound with one of a configurationally

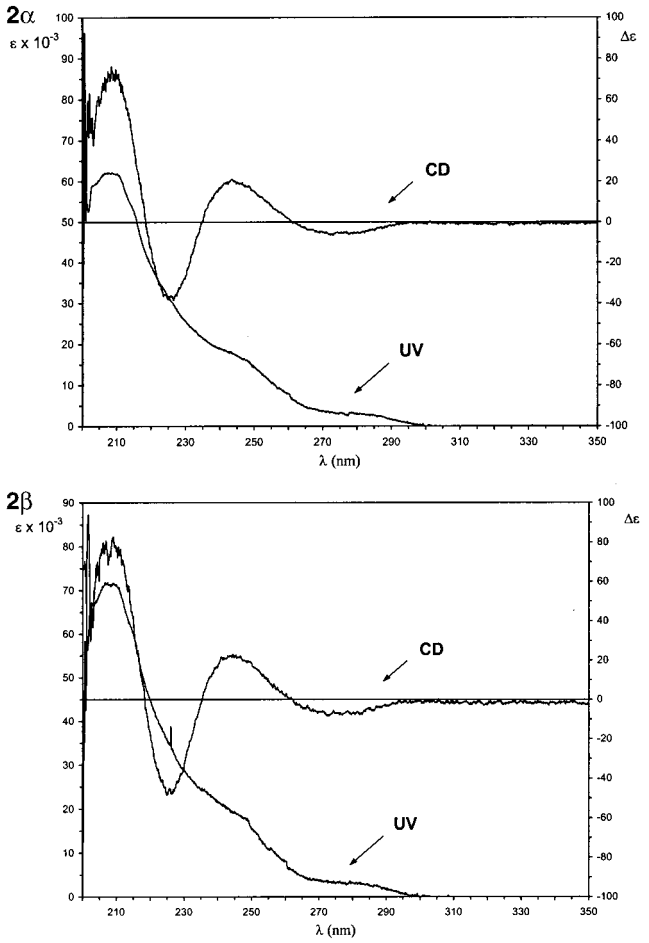


Figure 3. UV and CD spectra of diesters **2α** and **2*β***.

defined molecule having similar structure can be employed.[20] Thus, the known mahtabin A and pariin B[14b] can be safely chosen as external references. In fact, in these molecules, a substituted diphenic moiety is linked through ester bonds to the C-2 and C-3 of a D-glucopyranoside core. This should guarantee that **2α** and **2*β*** are structurally very similar to the references mahtabin A and pariin B.[14b,21] Since the CD spectra of the latter compounds, where the diphenic moiety has *aR* absolute configuration, are in a mirror image relationship with those of **2α** and **2*β***, we can empirically but with a reasonable confidence conclude that in **2α** and **2*β*** the same moieties are *aS*-configurated.

To test the configurational stability of **2α** and **2*β***, they were separately heated to 60 °C in $CDCl_3$ for 48 h and a possible interconversion monitored by ^{1}H NMR spectra. Both **2α** and **2*β*** were kinetically and thermodynamically stable under these conditions.[22]

As reported for rhamno derivatives **1**, different reaction conditions were followed to prepare **2** (see Table 2). When using NaH as base (entry 1), higher yields were obtained (40%, 63% conversion), while LiH afforded the best α/*β* selectivity (only traces of *β* anomer were detected; see entry 2) but in a lower yield (12%, 34% conversion).

Table 2. Reaction Conditions and Selectivity for the Synthesis of Diphenoyl Derivative 2

entry	conditions	% yield (conversion) of **2**	α/*β* ratio of **2**
1	NaH, toluene (0.02 M), 0 °C to rt	40 (63%)	3/1
2	LiH, toulene (0.02 M), 0 °C to rt	12 (34%)	>20/1
3	DMAP, CH_2Cl_2 (0.01 M), 0 °C to rt	18 (40%)	1.4/1
4	DBU, CH_2Cl_2 (0.02 M), rt		

The total diasteroselectivity observed for the synthesis of the diphenoylglucopyranose **2** could be likely explained by considering the more rigid environment offered by the trans C-2 and C-3 hydroxyl groups in the glucopyranose ring with respect to the corresponding *cis*-hydroxyls of the rhamnopyranose template. The rather rigid glucopyranose scaffold works as a "chiral straitjacket"[13] to which only a (*aS*)-diphenoyl moiety can be suitably attached. The present result, in line with Feldman[14l,n] and Immel's[13] works, confirms the Haslam[11]–Schmidt[12] hypothesis, which concerns the structural basis for stereochemical control in the biosynthesis of ellagitannins and related compounds.

The results clearly show the induction by central chirality (sugar scaffold) onto the configuration of the stereogenic axis of the diphenyl unit of final diesters,[18,24] and noteworthy, in the case of compound **2** the induction is complete and therefore the reaction is completely diasteroselective. Likely, the geometrical constrains imposed by the glucopyranose ring and geometry around the diester groups of the diphenyl–sugar derivatives made the esterification diasteroselective also with the conformationally flexible diphenyl derivative **3**.

In conclusion, the chiral induction in the *conformationally flexible* axially chiral diphenoyl derivative **3** was successfully obtained and the enantiopure "naked" ellagitannin analogue (*aS*)-**2** was synthesized. Two main aspects emerged from the present work: (1) a suitable carbohydrate scaffold seems to be fundamental to achieve optical resolution, and (2) the total induction and the *aS* conformational preference of the 10-membered diphenoyl ring unit observed for the gluco derivative **5** might depend on the rather rigid trans-type linkage of the diphenoyl moiety to the pyranose template, thus confirming the Haslam–Schmidt hypothesis.

Experimental Section

General Procedure. Reagents were purchased from commercial suppliers and used without purification. Biphenyl-2,2′-dicarbonyl dichloride **3** was prepared according to a known procedure.[25] DMF was distilled under a nitrogen atmosphere prior to use, toluene was dried over Na and benzophenone, and CH_2Cl_2 was dried over $LiAlH_4$. Unless otherwise noted, all air and moisture sensitive reactions were performed under an argon or nitrogen atmosphere. Analytical thin-layer chromatography (TLC) was conducted on glass-backed silica gel (Macherey-Nagel, Durasil-25-UV_{254}) with detection by a solution of vanillin (3 g) and H_2SO_4 (4 mL) in EtOH (250 mL). Flash chromatography was carried out on silica gel (Macherey-Nagel, 60M). ^{1}H NMR spectra are obtained at 200 MHz on a

(20) The CD spectra of the two compounds described in the literature are red-shifted with respect to those of **2α** and **2*β***, but this is certainly due to the lack in **2α** and **2*β*** of the auxchromic hydroxy substituents.

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Varian Gemini 2000 spectrometer. Chemical shifts are reported in part per million (δ) relative to $CHCl_3$ (7.26 ppm) for spectra run in $CDCl_3$. ^{13}C NMR spectra were obtained at 50 MHz on a Varian Gemini 2000 and are reported in δ relative to $CDCl_3$ (77.0 ppm). Melting points are uncorrected. High performance liquid chromatography (HPLC) was performed on a Gilson HPLC system using an Alltech Silica Sp Berisorb 5 μm column. Optical rotations were determined at 25 °C with a JASCO DIP-370 polarimeter (1 dm cell). Elemental analyses were performed on a Perkin-Elmer elemental analyzer 2400 II. Absorption and CD spectra were recorded on a JASCO J600 spectropolarimeter at room temperature in THF ($c \sim 6 \times 10^{-3}$M) in 0.1 and 1.0 mm cells. During the measurement the instrument was thoroughly purged with N_2.

Methyl α,β-L-Rhamnopyranoside (6). To a solution of 300 mg (1.65 mmol) of L-rhamnose monohydrate in 5 mL of MeOH was added 150 mg of Amberlist IR-120 (H^+). The reaction mixture was refluxed for 48 h and then filtered over Celite and purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 5:1) to give 287.8 mg (98%) of methyl derivative **6** as a yellow syrup.

Methyl 2,3-*O*-Isopropylidene-α-L-rhamnopyranoside (7). To a suspension of 1.33 g (7.5 mmol) of methyl α,β-L-rhamnopyranoside (**6**) in 10 mL of acetone was added 1.56 mL (12.8 mmol) of dimethoxypropane. The mixture was cooled to 0 °C, and 138.4 μL (1.1 mmol) of BF_3•Et_2O was added. After 30 min, the reaction mixture was warmed to room temperature and stirred for 12 h. Then the reaction mixture was neutralized with Py (155 μL, 2.0 mmol) and after removal of solvent, the crude product obtained (2.1 g, α:β = 11:1) was purified by flash column chromatography on silica gel (eluant EtOAc/hexane, 3:1) to give **7** (α diastereoisomer, 1.4 g, 86%) as a yellowish oil [130 mg (8%) of the β diastereoisomer was also isolated]. α-**7**: $[\alpha]_D$ −290.7° (*c* 0.22, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 (d, J = 6.2 Hz, 3H), 1.34 (s, 3H), 1.51 (s, 3H), 2.51 (bs, 1H, OH), 3.30−3.41 (m, 1H, H-4), 3.37 (s, 3H), 3.59−3.66 (m, 1H, H-5), 4.02−4.13 (m, 2H, H-2, H-3), 4.83 (s, 1H, H-1);^{13}C NMR (50MHZ, $CDCl_3$) δ 17.34, 26.02, 27.88, 54.79, 65.57, 74.32, 75.71, 78.46, 98.06 (C-1), 109.41. Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.02; H, 8.32. Found: C, 54.82; H, 8.30. β-**7**: ^1H NMR (200 MHz, $CDCl_3$) δ 1.32 (d, J = 5.8 Hz, 3H), 1.35 (s, 3H), 1.53 (s, 3H), 3.24−3.35 (m, 1H, H-5), 3.41−3.50 (m, 1H, H-4), 3.56 (s, 3H), 4.01 (at, J = 5.4 Hz, 1H, H-3), 4.23 (dd, J = 2.2 Hz, J = 5.4 Hz, 1H, H-2), 4.62 (d, J = 2.2 Hz, 1H, H-1); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.55, 26.08, 27.80, 57.45, 70.88, 74.41, 74.60, 80.08, 99.50 (C-1), 110.64.

Methyl 4-*O*-Benzyl-α-L-rhamnopyranoside (4). To a solution of 500 mg (2.3 mmol) of methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**7**) in DMF (4 mL) was added 0.545 mL (4.6 mmol) of benzyl bromide. The reaction mixture was cooled to 0 °C and treated with 137.4 mg (4.6 mmol) of NaH (80%), and the suspension obtained was warmed to rt and stirred for 6 h. After this time, the reaction was diluted with CH_2Cl_2 (10 mL) and washed with saturated NH_4Cl (3 × 5 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue (923 mg) was purified by flash chromatography on silica gel (eluant hexane/EtOAc, 2:1) to give methyl 4-*O*-benzyl-2,3-isopropylidene-α-L-rhamnopyranoside (657 mg, 93%) as a pale yellow oil: $[\alpha]_D$ −55.2° (*c* 0.22, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.31 (d, J = 6.2 Hz, 3H), 1.378 (s, 3H), 1.52 (s, 3H), 3.23 (dd, J = 7.0 Hz, J = 10.0 Hz, 1H, H-4); 3.35 (s, 3H), 3.64−3.72 (m, 1H, H-5), 4.13−4.30 (m, 2H, H-2, H-3), 4.64 (A part of an AB system, J = 11.6 Hz, 1H), 4.86 (s, 1H, H-1), 4.92 (B part of an AB system, J = 11.8 Hz, 1H), 7.24−7.41 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.75, 26.22, 27.91, 54.66, 64.33, 72.81, 76.96, 78.60, 80.99, 97.99 (C-1), 109.10, 127.56, 127.90, 128.21, 138.36. Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.32; H, 7.79. A solution of 657 mg (2.1 mmol) of methyl 4-*O*-benzyl-2,3-isopropylidene-α-L-rhamnopyranoside in MeOH (5 mL) and H_2O (500 μL) was treated with HCl (3.7%) until pH ∼3 and stirred for 96 h at rt. Then the reaction mixture was diluted with EtOAc (10 mL) and washed with saturated Na_2CO_3 (2 × 5 mL), and the organic layer was dried (Na_2SO_4). After concentration, the residue (503 mg, 89%) obtained as white solid **4** was used without any other purification: mp 101−102 °C; $[\alpha]_D$ −69.4° (*c* 0.16, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.36 (d, J = 6.2 Hz, 3H); 2.22 (bs, 2H, OH), 3.28−3.37 (m, 1H, H-4), 3.35 (s, 3H), 3.65−3.85 (m, 1H, H-5), 3.86−3.93 (m, 2H, H-2, H-3), 4.66 (s, 1H, H-1), 4.74 (s, 2H), 7.30−7.38 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.92, 54.75, 66.98, 71.03, 71.44, 74.91, 81.55, 100.36 (C-1), 127.89, 128.56, 138.28. Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.73; H, 7.50.

Methyl 4-*O*-Benzyl-2,3-*O*-diphenoyl-α-L-rhamnopyranoside (1). To a solution of 92.4 mg (0.3 mmol) of **4** in CH_2Cl_2 (17.6 mL) was added 252.9 mg (2.1 mmol) of DMAP. The reaction mixture was cooled to 0 °C, and a solution of 95.9 mg (0.3 mmol) of diphenoyl chloride in CH_2Cl_2 (15 mL) was added in 1 h. After 30 min at 0 °C, the mixture was warmed at rt, stirred for 1 h, diluted with CH_2Cl_2 (15 mL), and washed with H_2O (2 × 10 mL). The organic layer was dried (Na_2SO_4), and the crude product obtained after concentration (390 mg) was purified by flash column chromatography on silica gel (eluant hexane/EtOAc, 2:1) to give the white solid diphenoyl derivatives **1** (33 mg, 23%), as an inseparable 1.8:1 atropdiastereomeric mixture, and the inseparable open chain diphenoyl derivatives **8**−**10** (7.8%). **1**: ^1H NMR (200 MHz, $CDCl_3$) δ 1.20 (d, J = 6.4 Hz, 3H, minor diast), 1.36 (d, J = 6.2 Hz, 3H, major diast), 2.56 (at, J = 9.2 Hz, 1H, H-4, minor diast), 2.94 (at, J = 9.6 Hz, 1H, H-4 major diast), 3.25 (s, 3H, minor diast), 3.28 (s, 3H, major diast), 3.51−3.72 (m, 1H, H-5), 3.94 (dd, J = 3.6 Hz, J = 9.2 Hz, 1H, H-3, minor diast), 4.02 (dd, J = 4.0 Hz, J = 9.4 Hz, 1H, H-3, major diast), 4.49−4.88 (m, 3H), 5.07 (dd, J = 1.8 Hz, J = 4.0 Hz, 1H, H-2, minor diast), 5.14 (dd, $J_{1,2}$ = 1.4 Hz, $J_{2,3}$ = 3.6 Hz, 1H, H-2, major diast), 7.18−8.16 (m, 13H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.65, 17.92, 54.73, 54.81, 66.71, 70.03, 74.85, 81.28, 66.93, 70.43, 75.00, 81.53, 73.40, 74.20, 127.61, 127.76, 127.83, 128.18, 128.42, 128.54, 128.67, 130.69, 131.02, 131.40, 132.11, 132.37, 138.52, 143.16, 143.47, 166.43, 167.29. Anal. Calcd for $C_{28}H_{26}O_7$: C, 70.87; H, 5.52. Found: C, 70.97; H, 5.59. **8**−**10**: ^1H NMR (200 MHz, $CDCl_3$) δ 1.21−1.35 (m, 9H), 2.59 (at, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.2 Hz, H-4), 3.01 (at, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.6 Hz, H-4), 3.23, 3.26, 3.30 (s, 9H, OCH_3), 3.57−3.80 (m, 4H, H-4, 3 H-5), 3.89−4.06 (m, 3H, H-3), 4.29−4.89 (m, 9H, H-1, OCH_2Ph), 5.02−5.27 (m, 3H, H-2), 7.15−8.15 (m, 39H, H_{arom}).

Methyl 4-*O*-*p*-Methoxybenzyl-α-L-rhamnopyranoside (11). To a solution of 323 mg (1.5 mmol) of **7** in DMF (4 mL) was added 400 μL (3.0 mmol) of *p*-methoxybenzyl bromide. The solution was cooled to 0 °C, and 111 mg (3.7 mmol) of NaH (80%) and a catalytic amount of tetrabutyl amonium iodide were added. The suspension was stirred at 0 °C for 30 min and at rt until starting material was consumed (TLC, 6 h). The reaction was diluted with CH_2Cl_2 (10 mL), washed with saturated NH_4Cl (3 × 10 mL), and dried (Na_2SO_4). The organic layer was concentrated and the crude product (525 mg) purified by flash chromatography on silica gel (eluant hexane/EtOAc, 7:1) to give methyl 2,3-*O*-isopropylidene-4-*O*-*p*-methoxybenzyl-α-L-rhamnopyranoside (375 mg, 75%) as yellow oil: ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (d, J = 6.6 Hz, 3H), 1.37 (s, 3H), 1.52 (s, 3H), 3.19 (dd, J = 7.0 Hz, J = 9.8 Hz, 1H, H-4), 3.34 (s, 3H), 3.60−3.68 (m, 1H, H-5); 3.78 (s, 3H), 4.27−4.10 (m, 2H, H-2, H-3), 4.55 (A part of an AB system, J = 11.0 Hz, 1H), 4.83 (B part of an AB system, J = 10.8 Hz), 4.84 (s, 1H, H-1), 6.87 (AA′ part of an AA′MM′ system, J = 8.8 Hz, 2H), 7.28 (MM′ part of an AA′MM′ system, J = 8.4 Hz, 2H). Methyl 2,3-*O*-isopropylidene-4-*O*-*p*-methoxybenzyl-α-L-rhamnopyranoside (360 mg, 1.1 mmol) in MeOH (4 mL), was treated with HCl (3.7%) until pH ∼3 and with H_2O (300 μL). The solution was stirred at rt for 100 h and processed as reported for **4**. The crude product (271 mg) was purified by flash chromatography on silica gel (eluant hexane/EtOAc, 1:3) to give **11** (200 mg, 64%) as white glassy solid: $[\alpha]_D$ −58.7° (*c* 0.18, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.34 (d, J = 6.2 Hz, 3H), 2.26 (bs, 1H, OH), 2.37 (bs, 1H, OH), 3.26−3.35 (m, 1H, H-4); 3.34 (s, 3H), 3.64−3.72 (m, 1H, H-5), 3.80 (s, 3H), 3.82−3.93 (m, 2H, H-2, H-3), 4.65 (s, 2H), 4.67 (s, 1H, H-1), 6.89 (AA′ part of an AA′MM′ system, J = 8.8 Hz, 2H) 7.28 (MM′ part of an AA′MM′ system, J = 9.2 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.88,54.69, 55.19, 66.99, 70.97, 71.39, 74.52, 81.13,

100.36 (C-1), 113.92, 129.58 130.38, 159.37. Anal. Calcd for $C_{15}H_{22}O_6$: C, 62.67; H, 7.51. Found: C, 62.47; H, 7.59.

Methyl 4-*O*-Pivaloyl-α-L-rhamnopyranoside (12). To a solution of **7** (400 mg, 1.8 mmol) in CH_2Cl_2 (4 mL) cooled to 0 °C were added 284 μL (3.6 mmol) of Py and 443 μL (3.6 mmol) of pivaloyl chloride. The reaction mixture was warmed to rt and stirred for 92 h. After this time the solvent was evaporated and the crude product (413 mg) purified by flash column chromatography on silica gel (eluant hexane/EtOAc, 7:1) to give the desired methyl 4-*O*-pivaloyl-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (446 mg, 82%) as yellow oil: $[\alpha]_D$ −18.6° (*c* 0.15, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12 (d, *J* = 6.2 Hz, 3H), 1.18 (s, 9H), 1.30 (s, 3H), 1.53 (s, 3H), 3.35 (s, 3H), 3.62−3.76 (m, 1H, H-5), 4.07−4.14 (m, 2H, H-2, H-3), 4.75−4.86 (m, 2H, H-4, H-1); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.92, 26.40, 27.04, 27.62, 38.71, 54.88, 63.84, 74.05, 75.82, 109.66, 177.43. A solution of methyl 4-*O*-pivaloyl-2,3-*O*-isopropilidene-β-L-rhamnopyranoside (135 mg, 0.45 mmol) in MeOH (3 mL) was treated with HCl (3.7%), until pH ∼3, and H_2O (100 μL). The solution was processed as reported for **4** to give **12** (111 mg, 94%) as a yellow oil, which was used without any other purification: $[\alpha]_D$ −92.7° (*c* 0.19, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22 (d, *J* = 6.4 Hz, 3H), 3.39 (s, 3H), 3.73−3.94 (m, 3H, H-5, H-3, H-2), 4.69−4.78 (m, 2H, H-4, H-1); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.26, 26.95, 38.86, 54.90, 65.55, 70.15, 70.77, 76.36, 100.61 (C-1), 179.34. Anal. Calcd for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45. Found: C, 55.03; H, 8.65.

Methyl 4-*O*-*p*-Methoxybenzyl-2,3-*O*-diphenoyl-α-L-rhamnopyranoside (13). To a solution of **11** (66 mg, 0.2 mmol) in CH_2Cl_2 (11 mL) was added 155.2 mg (1.3 mmol) of DMAP. The reaction mixture was cooled to 0 °C, treated (1 h) with a solution of diphenoyl chloride (61.4 mg, 0.2 mmol) in CH_2Cl_2 (9.5 mL), and then stirred for 30 min at 0 °C and for 3 h at rt. After this time the reaction was diluted with CH_2Cl_2 (10 mL) and washed with H_2O (3 × 15 mL) and the organic layer was dried (Na_2SO_4). The crude product (300 mg) was purified by flash chromatography on silica gel (eluant hexane/EtOAc, 2:1) to give **13** (20.2 mg, 20%) as a mixture of inseparable atropdiastereoisomers in a 1.7:1 ratio, and an inseparable mixture of three open chain intermolecular diesters (12%). **13**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.2 Hz, 3H, minor diast), 1.34 (d, 3H, *J* = 6.4 Hz, major diast), 2.56 (at, *J* = 9.4 Hz, 1H, H-4, minor diast), 2.93 (at, *J* = 9.4 Hz, 1H, H-4, major diast), 3.24 (s, 3H, minor diast), 3.27 (s, 3H, major diast), 3.52−3.70 (m, 1H, H-5), 3.80 (s, 3H), 3.92 (dd, *J* = 4.0 Hz, *J* = 8.8 Hz, 1H, H-3, minor diast); 4.01 (dd, *J* = 3.4 Hz, *J* = 9.2 Hz, 1H, H-3, major diast), 4.44−4.80 (m, 3H), 5.05 (dd, *J* = 4.0 Hz, 1H, H-2, minor diast), 5.13 (dd, *J* = 3.8 Hz, 1H, H-2, major diast), 6.86−8.16 (m, 12H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.67, 17.92, 54.81, 55.26, 66.75, 66.95, 70.01, 70.45, 73.38, 74.14, 81.02, 81.22, 74.58, 74.72, 97.81 (C-1, minor diast), 98.21 (C-1, major diast), 113.83, 127.60, 128.56, 128.71, 129.45, 129.53, 130.98, 131.37, 132.09, 132.33, 159.29, 143.63, 143.45, 166.41, 167.25. Anal. Calcd for $C_{29}H_{28}O_8$: C, 69.04; H, 5.59. Found: C, 69.44; H, 5.76. **Open chain diesters:** ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.21−1.33 (m, 9H); 2.55−2.63 (m, 1H), 3.03−3.08 (m, 1H), 3.22, 3.25, 3.29 (s, 9H); 3.55−4.75 (m, 16H), 4.80−5.25 (m, 3H), 6.72−8.16 (m, 36H).

Methyl 2,3-*O*-Diphenoyl-4-*O*-pivaloyl-α-L-rhamnopyranoside (14). To a solution of **12** (55 mg, 0.2 mmol) in CH_2Cl_2 (10 mL) was added 141 mg (1.2 mmol) of DMAP. The mixture was cooled to 0 °C, treated for 1 h with a solution of diphenoyl chloride (53.4 mg, 0.2 mmol) in CH_2Cl_2 (9 mL), and stirred at 0 °C for 30 min and then for 2 h at rt. After this time the reaction was diluted with CH_2Cl_2 (10 mL) and washed with H_2O (3 × 10 mL), and the organic layer was dried (Na_2SO_4). The crude product (210 mg) was purified by flash chromatography on silica gel (eluant hexane/EtOAc, 2:1) to give **14** (15.6 mg, 17%) as inseparable atropdiasteromeric mixture, in a 1.8/1 ratio, and a inseparable mixture of side products (15 mg). **14**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.15−1.24 (m, 12H, two diast), 3.30 (s, 3H, two diast), 3.64−3.79 (m, 1H, H-5, two diast), 3.86 (dd, *J* = 4.0 Hz, *J* = 9.8 Hz, 1H, H-3, two diast), 4.26 (at, *J* = 9.8 Hz, 1H, H-4, minor diast), 4.43−4.53 (m, 2H, H-4, major diast and H-1 minor diast), 4.62 (d, *J* = 2.0 Hz, 1H, H-1, major diast), 5.09 (dd, *J* = 2.0 Hz, *J* = 4.0 Hz, 1H, H-2, major diast), 5.14 (dd, *J* = 2.0 Hz, *J* = 4.0 Hz, 1H, H-2, minor diast), 7.12−8.16 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.99, 17.15, 27.00, 38.84, 55.04, 65.53, 65.93, 68.21, 68.59, 73.38, 74.18, 98.17, 127.56, 128.34, 128.41, 130.31, 131.31, 131.75, 132.42, 143.34, 166.39, 178.48. Anal. Calcd for $C_{26}H_{28}O_8$: C, 66.66; H, 6.02. Found: C, 66.83; H, 6.18.

Methyl 4,6-*O*-Benzylidene-α,β-D-glucopyranoside (5). To a suspension of 1.4 g (7.2 mmol) of methyl D-glucopyranoside (**15**) in benzaldehyde (4.4 mL, 43.2 mmol) was added a catalytic amount of PTSA, and the mixture obtained was stirred at rt for 170 h. After this time the reaction was diluted with EtOAc (10 mL), washed with saturated $NaHCO_3$ (2 × 5 mL), and concentrated, and the organic layer was dried (Na_2SO_4). The crude product (4.1 g) was purified by flash column chromatography on silica gel (eluant hexane/EtOAc, 5:1) to give **5** (1.57 g, 77%) as white solid, in a 1/3 α/β ratio. The anomeric mixture was used for the subsequent reaction.^{1}H NMR (200 MHz, $CDCl_3$) δ 3.46 (s, 3H, α diast), 3.49−3.97 (m, 5H, α + β diast), 4.26−4.40 (m, 2H, H-1 β diast, H-2 α + β diast), 4.79 (d, *J* = 4.0 Hz, 1H, H-1 α diast), 7.35−7.52 (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.39, 57.32, 62.29, 66.18, 66.53, 68.82, 71.26, 72.63, 73.05, 74.34, 80.42, 80.88, 99.81, 101.81, 104.05, 126.30, 128.25, 128.94, 129.16, 129.71, 130.02, 134.42, 136.97, 137.04.

Methyl 4,6-*O*-Benzylidene-2,3-*O*-(*S*)-diphenoyl-D-glucopyranoside (2). To a solution of **5** (70 mg, 0.25 mmol) and DMAP (183 mg,1.5 mmol) in CH_2Cl_2 (25 mL) was added diphenoyl chloride (69.5 mg, 0.25 mmol) at 0 °C in 1 h. The reaction mixture was stirred for an additional 1.5 h at rt and after this time was diluted with CH_2Cl_2 (10 mL) and washed with H_2O (2 × 8 mL). The organic layer was dried (Na_2SO_4) and concentrated; the crude product (190 mg) was purified by flash column chromatography on silica gel (eluant CH_2Cl_2/MeOH, 30:1) to give **2** (22.1 mg, 18%) as an anomeric mixture (α:β = 1.4:1) separable by HPLC (hexane/EtOAc): ^{1}H NMR (200 MHz, $CDCl_3$) (α diast) δ 3.52 (s, 3H), 3.80−4.07 (m, 3H), 4.37 (dd, *J* = 4.0 Hz, *J* = 9.6 Hz, 1H, H-4), 5.01 (d, *J* = 3.4 Hz, 1H, H-1), 5.36 (dd, *J* = 3.8 Hz, *J* = 9.6 Hz, 1H, H-2), 5.59 (s, 1H), 5.76 (at, *J* = 9.6 Hz, 1H, H-3), 7.37−7.51 (m, 13H); (β diast) δ 3.62 (s, 3H), 3.50−3.67 (m, 1H, H-5), 4.43 (dd, *J* = 4.8 Hz, *J* = 10.2 Hz, 1H, H-4), 4.77 (d, *J* = 8.0 Hz, 1H, H-1), 5.18 (dd, *J* = 8.0 Hz, *J* = 9.6 Hz, 1H, H-2), 5.53 (at, *J* = 9.6 Hz, 1H, H-3), 5.59 (s, 1H), 7.38−7.58 (m, 13H);^{13}C NMR (50 MHz, $CDCl_3$) (α + β diast) δ 55.50, 57.29, 63.10, 67.25, 68.61, 68.93, 73.64, 74.59, 75.70, 76.02, 78.31, 98.34, 101.36, 101.76, 101.89, 125.91, 126.06, 126.17, 126.23, 126.33, 127.61, 127.72, 128.30, 129.28, 130.83, 130.96, 131.05, 132.75, 132.88, 132.97, 133.07, 133.23, 133.48, 134.42, 136.70, 136.84, 137.31, 137.40, 137.47, 137.54, 168.42, 168.83, 169.06. Anal. Calcd for $C_{28}H_{24}O_8$: C, 68.85; H, 4.95. Found: C, 68.54; H, 4.95.

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