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Synthesis of the tetrasaccharide residue of clarhamnoside, a novel glycosphingolipid isolated from the marine sponge *Agelas clathrodes*

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Abstract—A tetrasaccharide, α-L-Rha*p*-(1→3)-β-D-Gal*p*NAc-(1→6)-α-D-Gal*p*-(1→2)-α-D-Gal*p*, the carbohydrate moiety of clarhamnoside isolated from the marine sponge *Agelas clathrodes*, was synthesized as its propyl glycoside via a convergent approach. The key steps to the synthetic strategy were the stereoselective construction of the reducing-end disaccharide α-D-Gal*p*-(1→2)-D-Gal*p* (**5**) and efficient coupling with the terminal disaccharide α-L-Rha*p*-(1→3)-D-Gal*p*NAc building block, in which the *N*-phthalimido-protected trifluoroacetimidate **13** was proved to be an effective donor.

Keywords: Clarhamnoside; Glycosphingolipids; Immuno-modulating; Glycosylation; Synthesis; Trifluoroacetimidate

1. Introduction

It is well established that sponges of the genus *Agelas* and *Axinella* produce α-galactoglycosphingolipids (α-GalGSLs).[1] The distinguishing feature of these glycosphingolipids is the α-anomeric linkage of the inner galactose to the lipid, unlike the ubiquitous β-glycosidic bond in nearly all known natural glycosphingolipids from higher animals and plants.[2] Natural and synthetic α-GalGSLs have recently attracted increasing attention as interesting immunomodulators, which may prove useful for treatment of immune related diseases.[3] Recent studies have demonstrated the importance of both the lipid and sugar structures to the overall immunogenicity. For example, modifications in the ceramide part of a marine-sponge-derived glycolipid agelasphin-9b led to the discovery of KRN7000.[4] Extensive investigations showed that KRN7000 is a highly potent immunostimulatory agent and is shown to act as a specific ligand presented by CD1d to the invariant mouse $V_\alpha14$ or human $V_\alpha24$ antigen receptor of nature killer T-cells (NKT cells) to activate the immune system.[5] A truncated analogue of KRN7000, OCH, was found to selectively induce IL-4, as opposed to IFNγ, and to offer protection in mice against experimental autoimmune encephalomyelitis (EAE).[6] More recently it has been shown to offer protection against diabetes in NOD mice[7] and against collagen-induced arthritis.[8] The structure of the sugar moiety is also very important, mostly because the T-cell receptors (TCR) establish cognate interactions with parts of the hydrophilic moiety of the glycolipid.[9] Now substitutions on the galactose 2-OH group have received more attention in developing the structure–activity relationships (SAR) for the sugar part of α-GalGSLs.[2,9–11]

Clarhamnoside, recently isolated from new specimens of *Agelas clathrodes* by the Mangoni group, has quite a unique structure containing α-L-Rha*p*-(1→3)-β-D-Gal*p*-NAc-(1→6)-α-D-Gal*p*-(1→2)-α-D-Gal*p*.[12] It is one of the few natural α-GalGSLs glycosylated at the inner galactose 2-OH group and is the only α-GalGSL so far identified that bears an L-rhamnose unit in the sugar

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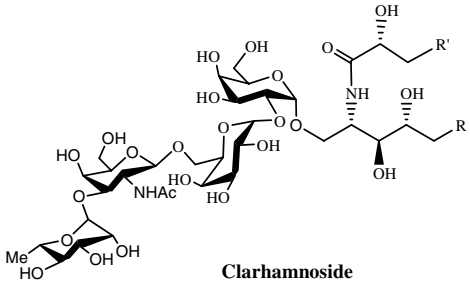
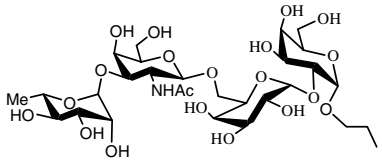
head.[12] In addition, the sequential two 1,2-*cis*-α-D-galactopyranosidic linkages [Galα-(1″→2′)-Galα-(1′→1)-Cer] are also an extraordinary feature and are rare among naturally occurring glycolipids. As part of our effort to understand the mechanism of CD1-mediated T-cell activation, we are interested in developing a general and effective strategy for the synthesis of α-GalGSLs with a glycosylated 2′-OH. The unique structure and potent bioactivities make clarhamnoside a suitable goal for synthesis. Herein, we describe the concise construction of the carbohydrate moiety of clarhamnoside as its propyl glycoside (**1**) via a convergent approach.



Clarhamnoside



1

2. Results and discussion

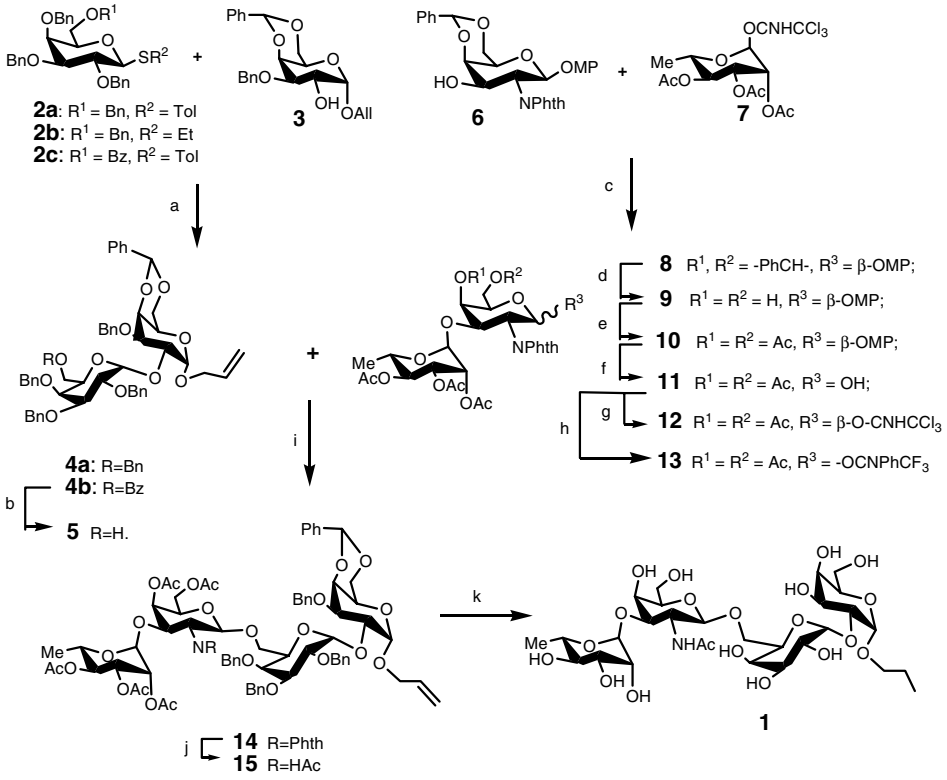
The β-linkage [GalNAcβ-(1‴→6″)-Gal] in the target molecule can be readily formed by using a neighboring bulky group at the 2-amino position of the D-galactosamine. Thus the first disconnection of **1** leads to two disaccharide building blocks. It was our intention to execute the synthesis in a 2+2 fashion from the reducing-end disaccharide α-D-Gal*p*-(1→2)-D-Gal*p* and the terminal disaccharide α-L-Rha*p*-(1→3)-D-Gal*p*NAc building blocks (Scheme 1).

For preparation of the reducing-end disaccharide (α-D-Gal*p*-(1→2)-D-Gal*p*), a major effort was to construct the glycosidic bond in high α-selectivity and in good yield.

Thioglycosides are commonly used as α-selective donors, and several reports[13] have emphasized that the nature of a protecting group remote to the anomeric center may influence the stereochemical outcome of glycosylations. Therefore, a thiogalactoside, equipped with a 6-*O*-benzoyl and 2,3,4-tri-*O*-benzyl groups, could be employed as the donor in the stereocontrolled glycosylation, leaving ample choices for a distinguishable protective group on the 6-OH. As shown in Table 1, to find appropriate reaction conditions including the catalytic systems and solvents, we first explored the glycosylation of acceptor **3** with easily prepared thioglycoside donors **2a**,**b.** In some cases, iodonium-ion mediated glycosylations of thioglycosides in 1,4-dioxane–toluene gave higher α-selectivities compared to similar couplings in the most frequently used Et_2O–CH_2Cl_2.[14] Accordingly, 1,4-dioxane–toluene was chosen as the solvent for the first investigation. However, only a complex mixture of the products and unreacted **3** were obtained, presumably due to the low solubility of acceptor **3**. The glycosylation of **2a** with **3** was next carried out in 4:1 Et_2O–CH_2Cl_2, but the reaction was too sluggish when promoted with IDCP, and was better when promoted with NIS/AgOTf, giving disaccharide **4a** as an anomeric mixture (α/β = 10:1) and in moderate yield (62%). Under these conditions, the more reactive donor of ethyl thioglycoside **2b** failed to further improve the glycosylation (α/β = 10:1, 64% yield). Thus, thiogalactoside **2c** was applied to the glycosylation for obtaining **4b** under the action of NIS/AgOTf in 4:1 Et_2O–CH_2Cl_2. As expected, a significant improvement in α-selectivity from α:β = 10:1 to α only and in yield from 62% to 71% was demonstrated. After removing the benzoate temporary protecting group in **4b**, **5** was expected as the acceptor for elaboration of the target molecule via coupling with a disaccharide donor.

To synthesize the terminal disaccharide (α-L-Rha*p*-(1→3)-D-Gal*p*NAc) building block, 2-*N*-phthalimido-substituted **6** turned out to be a crucial intermediate. The 2-*N*-phthalimido protecting group was planned to ensure the stereoselective formation of the required β-linkage and to avoid the oxazoline intermediate[15] during the course of later glycosylation. Thus coupling of peracetylated rhamnosyl trichloroacetimidate **7** with the hindered 3-OH of acceptor **6**[16] gave the expected disaccharide **8** quantitatively when TMSOTf (0.1 equiv) was employed as the promoter. Cleavage of the anomeric OMP group in the presence of the labile 4,6-*O*-benzylidene was viewed as potentially problematic. Furthermore, synchronization of the protective groups at an earlier stage would facilitate the final deprotection. Therefore, the 4,6-*O*-benzylidene group on **8** was removed with 80% HOAc, followed by protection with acetates and removal of the anomeric OMP group on **10** with CAN in CH_3CN–H_2O to afford **11**.

Two disaccharide donors **12** and **13** were designed for the investigation of the later coupling of two disaccharide building blocks. Trifluroacetimidate donor[17] **13** was obtained in 98% yield by treatment of the 1-hydroxy sugar **11** with *N*-phenyl trifluoroacetimidoyl chloride (5.5 equiv) in the presence of easily removed inorganic



Scheme 1. Reagents and conditions: (a) NIS/AgOTf, 4 Å MS, 4:1 Et_2O–CH_2Cl_2; (b) CH_3ONa, CH_3OH–CH_2Cl_2, 83%; (c) TMSOTf, 4 Å MS, CH_2Cl_2, −40 °C, quant.; (d) 80% HOAc, 90 °C, 85%; (e) Ac_2O, pyridine, 91%; (f) CAN, CH_3CN–H_2O, 94%; (g) DBU, CCl_3CN, CH_2Cl_2, 74%; (h) K_2CO_3, PhN=CClCF$_3$, CH_2Cl_2, 98%; (i) TMSOTf, 4 Å MS, CH_2Cl_2, −20 °C; (j) ethylenediamine, *n*-BuOH, 90 °C, then Ac_2O, pyridine, 64%; (k) $Pd(OH)_2$, 3:1 EtOAc–MeOH, then 0.02 M CH_3ONa in CH_3OH, 80%.

Table 1. Glycosylation of galactosyl donors **2a**–**c** with **3**

Entry	Donor	Promoter	Solvent	Product	Yield (α:β)
1	**2a**	—	4:1 1,4-Dioxane–toluene	**4a**	—
2	**2a**	IDCP	4:1 Et_2O–CH_2Cl_2	**4a**	[a]
3	**2a**	NIS/AgOTf	4:1 Et_2O–CH_2Cl_2	**4a**	62% (10:1)
4	**2b**	NIS/AgOTf	4:1 Et_2O–CH_2Cl_2	**4a**	64% (10:1)
5	**2c**	NIS/AgOTf	4:1 Et_2O–CH_2Cl_2	**4b**	71% (α only)

[a] Glycosylation was too sluggish when promoted with IDCP.

base K_2CO_3 (5 equiv); meanwhile trichloroacetimidate donor **12** was prepared in 74% yield by treating **11** with trichloroacetonitrile (15 equiv) in the presence of DBU (0.5 equiv). When 1.3 equiv of trichloroacetimidate donors **12** or **13** were employed in the presence of TMSOTf in CH_2Cl_2, tetrasaccharide **14** was obtained smoothly in 55% and 73% yield, respectively, both with a slight amount of unreacted acceptor **5**. Applying 1.7 equiv of **12** or **13** under the same coupling conditions generated **14** in an enhanced 83% or 82% yield, respectively, with no unreacted acceptor detected in either case. The results revealed that trifluoroacetimidate donor **13** was more efficient than trichloroacetimidate donor **12** when a low equivalent of donor was used. It is also noteworthy that the yield for preparation of trifluoroacetimidate donor **13** is much higher than that for the corresponding trichloroacetimidate **12**. In addition, donor **13** was much more thermally stable than **12** toward air and silica gel (data not shown). All the above indicated that trifluoroacetimidate donor **13** is a valuable alternative to the corresponding trichloroacetimidate **12**, which would be successfully employed in the total synthesis of clarhamnoside in our later work.

That which remained was to deprotect **14** en route to the intended target **1**. Transformation of the phthalimido group into an acetamido group was accomplished using ethylenediamine, followed by acetylation to give **15**. Hydrogenolysis of the benzylidine and benzyl ether groups using Pd–C (10%) in several solvents resulted in complex mixtures. However, using palladium hydroxide (75%) in 3:1 EtOAc–MeOH proved successful, affording the desired tetrasaccharide. After deesterification with sodium methoxide in methanol, the intended target **1** was obtained.

In summary, a 2+2 strategy was developed to synthesize the carbohydrate moiety of clarhamnoside. The α-D-Gal*p*-(1→2)-D-Gal*p* linkage was constructed with complete stereocontrol using thioglycoside donor **2c.** Trifluoroacetimidate **13** showed advantages over the corresponding trichloroacetimidate **12** both in donor preparation and in glycosylation with **5** to construct the corresponding tetrasaccharide. Our strategy developed for the synthesis of **1** will be useful for total synthesis of clarhamnoside, the synthesis of which is currently under pursuit in our laboratory.

3. Experimental

3.1. General methods

Solvents were purified in a conventional manner. Thin-layer chromatography (TLC) was performed on pre-coated E. Merck Silica Gel 60 F_{254} plates. Flash column chromatography was performed on silica gel (200–300 mesh, Qingdao, China). Optical rotations were determined with a Perkin–Elmer Model 241 MC polarimeter. ^{1}H NMR and ^{13}C NMR spectra were taken on a Jeol JNM-ECP 600 spectrometer with tetramethylsilane (Me_4Si) as the internal standard, and chemical shifts are recorded in δ values. Mass spectra were recorded on a Q-TOF Global mass spectrometer.

3.2. Allyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranoside (4a)

To a mixture of galactosyl donor **2b** (73.3 mg, 0.11 mmol), galactosyl acceptor **3** (36.9 mg, 0.1 mmol), and 4 Å molecular sieves (100 mg) in 4:1 CH_2Cl_2–Et_2O (15 mL) were added NIS (34.4 mg, 0.15 mmol) and AgOTf (2.4 mg, 0.01 mmol) at 0 °C under Ar. After 4 h of stirring, the reaction mixture was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 (30 mL), washed with 10% aq $Na_2S_2O_3$ (10 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (3:1 petroleum ether–EtOAc) to give product **4a** (59.3 mg, 64.2%) as an amorphous solid: R_f 0.42 (2:1 petroleum ether–EtOAc); $[\alpha]_D^{22}$ +70.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.51–7.24 (m, 30H, Ph), 5.87 (m, 1H, $OCH_2CH{=}CH_2$), 5.47 (s, 1H, PhC*H*), 5.25 (dd, 1H, *J* 17.4, 1.5 Hz, $OCH_2CH{=}CHH$), 5.19 (d, 1H, *J* 3.2 Hz, H-1), 5.13 (dd, 2H, *J* 10.6, 1.5 Hz, $OCH_2CH{=}CHH$), 5.08 (d, 1H, *J* 3.7 Hz, H-1′), 4.90–4.52 (8H, 4C*H*HPh), 4.37 (dd, 1H, *J* 10.1, 3.2 Hz, H-2), 4.33 (d, 1H, *J* 11.9 Hz, C*H*HPh), 4.30 (dd, 1H, *J* 6.9, 6.4 Hz, H-5′), 4.22 (d, 2H, *J* 12.4 Hz, C*H*HPh, H-6a), 4.17 (d, 1H, *J* 3.2 Hz, H-4), 4.14 (dd, 1H, *J* 11.5, 5.0 Hz, H-3), 4.03 (m, 5H, H-2′, H-3′, H-6b, OCH_2), 3.91 (br s, 1H, H-4′), 3.64 (s, 1H, H-5), 3.52 (dd, 1H, *J* 9.2, 8.2 Hz, H-6′a), 3.42 (dd, 1H, *J* 9.2, 5.5 Hz, H-6′b). ESIMS (*m*/*z*): 959.5 $[M+K]^+$ (calcd 959.4).

3.3. Allyl 6-*O*-benzoyl-2,3,4-tri-*O*-benzyl-α-D-galactopyranosyl-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranoside (4b)

To a mixture of galactosyl donor **2c** (220.0 mg, 0.33 mmol), galactosyl acceptor **3** (110.8 mg, 0.28 mmol), and 4 Å molecular sieves (400 mg) in 4:1 CH_2Cl_2–Et_2O (20 mL) were added NIS (103.1 mg, 0.45 mmol) and AgOTf (7.20 mg, 0.03 mmol) at 0 °C under Ar. After 4 h of stirring, the reaction mixture was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 (50 mL), washed with 10% aq $Na_2S_2O_3$ (30 mL) and brine (30 mL). The organic phase was dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (3:1 petroleum ether–EtOAc) to give product **4b** (434.2 mg, 71.1%) as an amorphous solid: R_f 0.32 (3:1 petroleum ether–EtOAc); $[\alpha]_D^{22}$ +80.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.91–7.17 (m, 30H, Ph), 5.94 (m, 1H, $OCH_2CH{=}CH_2$), 5.38 (s, 1H, PhC*H*), 5.31 (dd, 1H, *J* 17.2, 1.5 Hz, $OCH_2CH{=}CHH$), 5.26 (d, 1H, *J* 3.7 Hz, H-1), 5.12 (m, 2H, $OCH_2CH{=}CHH$, C*H*HPh), 4.99 (d, 1H, *J* 11.8 Hz, C*H*HPh), 4.83 (d, 1H, *J* 11.7 Hz, C*H*HPh), 4.81 (d, 1H, *J* 11.0 Hz, C*H*HPh), 4.74 (m, 2H, C*H*HPh, H-1′), 4.67 (d, 1H, *J* 12.1 Hz, C*H*HPh), 4.64 (d, 1H, *J* 11.3 Hz, C*H*HPh), 4.51 (d, 1H, *J* 12.4 Hz, C*H*HPh), 4.36 (m, 2H, H-6′), 4.29 (dd, 1H, *J* 9.9, 3.7 Hz, H-2), 4.21 (dd, 1H, *J* 12.4, 1.1 Hz, H-6a), 4.16 (dd, 1H, *J* 14.6, 5.5 Hz, $OCHCH{=}CH_2$), 4.12 (dd, 1H, *J* 13.2, 5.9 Hz, $OCHCH{=}CH_2$), 4.08 (d, 1H, *J* 3.7 Hz, H-4), 4.05 (dd, 1H, *J* 10.3, 3.7 Hz, H-3), 3.97 (dd, 1H, *J* 6.0, 1.1 Hz, H-6b), 3.93 (dd, 1H, *J* 9.5, 1.8 Hz, H-2′), 3.82 (d, 1H, *J* 2.2 Hz, H-4′), 3.68 (dd, 1H, *J* 6.8, 6.6 Hz, H-5′), 3.65 (s, 1H, H-5), 3.53 (dd, 1H, *J* 9.9, 2.9 Hz, H-3′); ^{13}C NMR ($CDCl_3$): δ 166.0, 139.0, 138.7, 138.4, 138.3, 137.8, 134.2, 133.0, 129.6, 129.5, 128.7, 128.4, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 127.5, 127.4, 127.2, 126.3, 116.9, 104.7, 101.1, 98.8, 82.0, 79.2, 76.0, 75.5, 74.7, 74.4, 73.7, 73.5, 72.0, 69.4, 69.0, 63.4, 62.4. HRMS: calcd for $C_{57}H_{58}O_{12}Na^+$ 957.3826; found 957.3854.

3.4. Allyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranosyl-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranoside (5)

To a stirred solution of **4** (150.0 mg, 0.16 mmol) in CH_3OH (2 mL) and CH_2Cl_2 (2 mL) was added solid $NaOCH_3$ (30 mg, 50%). After stirring for 6 h at rt, the solution was neutralized with ion-exchange resin (H^+)

and then filtered and concentrated. The residue was purified by column chromatography (3:1 petroleum ether–EtOAc) to afford **5** (110.0 mg, 82.9%) as an amorphous solid: R_f 0.12 (3:1 petroleum ether–EtOAc); $[\alpha]_D^{22}$ +116.0 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.51–7.26 (m, 25H, PhCH and 4Ph), 5.87 (m, 1H, $OCH_2CH{=}CH_2$), 5.26 (dd, 1H, *J* 17.2, 1.5 Hz, $OCH_2CH{=}CHH$), 5.13 (d, 1H, *J* 3.2 Hz, H-1), 5.13 (dd, 1H, *J* 12.0, 1.5 Hz, $OCH_2CH{=}CHH$), 5.04 (d, 1H, *J* 3.7 Hz, H-1′), 4.92–4.56 (m, 8H, $4PhCH_2$), 4.35 (dd, 1H, *J* 10.3, 3.3 Hz, H-2), 4.23 (m, 2H, H-6a, H-4), 4.16 (m, 1H, $OCHHCH{=}CH_2$), 4.07–4.01 (m, 5H, H-3, H-2′, $OCHHCH{=}CH_2$, H-5′, H-6b), 3.97 (dd, 1H, *J* 9.9, 2.9 Hz, H-3′), 3.71 (d, 1H, *J* 1.8 Hz, H-4′), 3.66 (s, 1H, H-5), 3.50 (m, 1H, H-6′a), 3.26 (m, 1H, H-6′b), 1.72 (s, 1H, 6′-OH); ^{13}C NMR ($CDCl_3$): δ 138.7, 138.6, 138.4, 138.3, 137.7, 133.8, 128.9, 128.4–127.5, 126.3, 126.1, 118.3, 100.8 (Ph*C*H), 95.6 (C1), 95.3 (C1′), 79.1 (C3′), 75.9, 75.1 (C5), 74.7, 74.4, 73.9 (C4), 73.0, 72.9, 71.6, 70.9 (C2), 70.4, 69.3 (C6), 68.8 (OCH_2), 62.7, 62.4. HRMS: calcd for $C_{50}H_{54}O_{11}Na^+$ 853.3564; found 853.3528.

3.5. *p*-Methoxyphenyl *O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-galactopyranoside (8)

To a mixture of **6** (336.1 mg, 0.67 mmol), **7** (376.0 mg, 0.87 mmol), and 4 Å molecular sieves (400 mg) in dried CH_2Cl_2 (10 mL) was added TMSOTf (15.6 mg, 0.07 mmol) at −40 °C under Ar protection. The mixture was stirred under these conditions for 1 h, then neutralized with Et_3N. The solid was filtered off, and the filtrate was concentrated under vacuum to give a yellow syrup, which was purified by column chromatography (2:1 petroleum ether–EtOAc) to give compound **8** (517.5 mg, 100%) as a white solid: R_f 0.20 (1:1 petroleum ether–EtOAc); $[\alpha]_D^{22}$ +43.6 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.96–6.71 (m, 13H, Ph), 5.68 (d, 1H, *J* 8.3 Hz, H-1), 5.59 (s, 1H, PhC*H*), 5.10 (dd, 1H, *J* 10.1, 3.2 Hz, H-3′), 5.01 (dd, 1H, *J* 11.5, 8.7 Hz, H-2), 4.91 (dd, 1H, *J* 10.1, 9.6 Hz, H-4′), 4.86 (d, 1H, *J* 1.9 Hz, H-1′), 4.79 (dd, 1H, *J* 3.7, 1.9 Hz, H-2′), 4.75 (dd, 1H, *J* 11.5, 3.7 Hz, H-3), 4.48 (d, 1H, *J* 3.2 Hz, H-4), 4.40 (d, 1H, *J* 12.4 Hz, H-6a), 4.13 (m, 2H, H-5′, H-6b), 3.72 (s, 3H, OCH_3), 3.68 (s, 1H, H-5), 1.98 (s, 3H, $COCH_3$), 1.96 (s, 3H, $COCH_3$), 1.84 (s, 3H, $COCH_3$), 0.98 (d, 3H, *J* 6.4 Hz, CH_3-6′); ^{13}C NMR ($CDCl_3$): δ 170.0, 169.7, 169.2, 167.4, 155.5, 150.8, 137.3, 134.3, 134.1, 131.6, 131.3, 129.1, 128.2, 126.3, 124.1, 123.2, 119.1, 114.3, 101.1 (Ph*C*H), 98.9 (C1′), 98.4 (C1), 76.5 (C3), 74.9 (C4), 70.7 (C4′), 69.6 (C2′), 69.2 (C6), 68.8 (C3′), 67.0 (C5′), 66.5 (C5), 55.5 (OCH_3), 51.4 (C2), 20.7 ($2COCH_3$), 20.5 ($COCH_3$), 17.3 (CH_3-6′). HRMS: calcd for $C_{40}H_{41}NO_{15}Na^+$ 798.2374; found 798.2363.

3.6. *p*-Methoxyphenyl 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→3)-2-deoxy-2-phthalimido-β-D-galactopyranoside (9)

Compound **8** (250.0 mg) was added to 80% HOAc–H_2O (10 mL), and the mixture was heated at 90 °C for 8 h, then concentrated and co-evaporated with toluene (5 mL) three times. The residue was purified by column chromatography (20:1 $CHCl_3$–CH_3OH) to give compound **9** (188.6 mg, 85.1%) as a white solid: R_f 0.5 (20:1 $CHCl_3$–CH_3OH); $[\alpha]_D^{22}$ +36.6 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.93–6.71 (m, 8H, Ph), 5.66 (d, 1H, *J* 8.8 Hz, H-1), 5.20 (dd, 1H, *J* 9.9, 3.3 Hz, H-3′), 4.97 (dd, 1H, *J* 9.9, 9.5 Hz, H-4′), 4.84 (dd, 1H, *J* 11.0, 8.4 Hz, H-2), 4.79 (m, 1H, H-2′), 4.77 (d, 1H, *J* 1.8 Hz, H-1′), 4.63 (dd, 1H, *J* 11.0, 3.3 Hz, H-3), 4.23 (br s, 1H, H-4), 4.12 (m, 1H, H-5′), 4.04 (dd, 1H, *J* 11.7, 5.9 Hz, H-6a), 3.94 (dm, 1H, *J* 12.1 Hz, H-6a), 3.81 (dd, 1H, *J* 5.5, 5.2 Hz, H-5), 3.71 (s, 3H, OCH_3), 3.09 (br s, 1H, O*H*-4), 2.37 (br s, 1H, O*H*-6), 2.03 (s, 3H, $COCH_3$), 1.94 (s, 3H, $COCH_3$), 1.89 (s, 3H, $COCH_3$), 1.20 (d, 3H, *J* 6.2 Hz, CH_3-6′); ^{13}C NMR ($CDCl_3$): δ 170.0, 169.6, 169.5, 155.4, 150.6, 134.2, 131.4, 118.3, 114.5, 98.7 (C1′), 97.8 (C1), 77.0 (C3), 74.3 (C5), 70.9 (C4′), 69.7 (C2′), 69.2 (C4), 68.5 (C3′), 67.4 (C5′), 62.6 (C6), 55.6 (OCH_3), 51.7 (C2), 20.8 ($COCH_3$), 20.6 ($COCH_3$), 20.6 ($COCH_3$), 17.4 (CH_3-6′). HRMS calcd for $C_{33}H_{37}NO_{15}K^+$ 726.1800; found 726.1801.

3.7. *p*-Methoxyphenyl 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→3)-4,6-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-galactopyranoside (10)

Compound **9** (120.0 mg, 0.18 mmol) was dissolved in pyridine (2 mL) and Ac_2O (1 mL), and the mixture was stirred overnight. Excess Ac_2O was destroyed by addition of CH_3OH (5 mL). The mixture was concentrated and purified by chromatography (1:1 petroleum ether–EtOAc) to afford compound **10** (122.3 mg, 90.8%) as a foamy solid: R_f 0.4 (3:2 petroleum ether–EtOAc); $[\alpha]_D^{22}$ +42.6 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.93–6.71 (m, 8H, Ph), 5.61 (d, 1H, *J* 8.5 Hz, H-1), 5.51 (br s, 1H, H-4), 5.07 (dd, 1H, *J* 9.9, 3.7 Hz, H-3′), 4.95 (dd, 1H, *J* 9.9, 9.8 Hz, H-4′), 4.81 (m, 2H, H-2, H-3), 4.70 (dd, 1H, *J* 3.3, 1.9 Hz, H-2′), 4.67 (d, 1H, *J* 1.9 Hz, H-1′), 4.20 (m, 2H, H-6), 4.12 (dd, 1H, *J* 6.6, 6.2 Hz, H-5), 3.92 (dq, 1H, *J* 9.5, 6.2 Hz, H-5′), 3.72 (s, 3H, OCH_3), 2.30 (s, 3H, Ac), 2.08 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 1.89 (s, 3H, $COCH_3$), 1.86 (s, 3H, $COCH_3$), 1.94 (d, 3H, *J* 6.2 Hz, CH_3-6′); ^{13}C NMR ($CDCl_3$): δ 170.6, 170.5, 170.1, 169.5, 169.4, 155.6, 150.6, 134.2, 118.6, 114.4, 98.8 (C1′), 98.0 (C1), 73.6 (C3), 71.5 (C5), 70.7 (C4′), 70.0 (C2′), 68.5 (C4), 68.1 (C3′), 67.5 (C5′), 62.0 (C6), 55.6 (OCH_3), 52.8 (C2), 20.9 ($COCH_3$), 20.8

($CO\mathit{C}H_3$), 20.7 ($CO\mathit{C}H_3$), 20.6 ($2CO\mathit{C}H_3$), 17.3 ($\mathit{C}H_3$-6′). HRMS calcd for $C_{37}H_{41}NO_{17}Na^+$ 794.2272; found 794.2302.

3.8. 2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→3)-4,6-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-galactopyranose (11)

To a solution of **10** (111.0 mg, 0.144 mmol) in CH_3CN (5 mL) and water (1 mL) was added ammonium cerium(IV) nitrate (394.7 mg, 0.72 mmol), and the mixture was stirred for 2 h at rt. The reaction mixture was diluted with EtOAc, successively washed with satd aq $NaHCO_3$, dried, and concentrated. Purification by flash column chromatography (1:1 petroleum ether–EtOAc) gave **11** (89.8 mg, 93.8%) as an amorphous solid. The pure compound **11** was used directly for the preparation of donors **12** and **13**.

3.9. 2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→3)-4,6-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-galactopyranosyl trichloroacetimidate (12)

To a solution of **11** (89.8 mg, 0.14 mmol) in dry CH_2Cl_2 (5 mL) were added trichloroacetonitrile (295.5 mg, 2.1 mmol) and DBU (10.3 mg, 0.068 mmol). The mixture was stirred for 5 h, at the end of which time TLC indicated the reaction was complete. The mixture was concentrated and then purified by flash chromatography (2:1 petroleum ether–EtOAc) to afford the donor **12** (81.2 mg, 74.4%) as a foamy solid: R_f 0.30 (3:2 petroleum ether–EtOAc); $[\alpha]_D^{22}$ +43.9 (*c* 0.22, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.59 (s, 1H, N*H*), 7.86–7.71 (4H, Phth), 6.40 (d, 1H, *J* 8.8 Hz, H-1), 5.54 (d, 1H, *J* 3.3 Hz, H-4), 5.07 (dd, 1H, *J* 9.9, 3.7 Hz, H-3′), 4.95 (t, 1H, *J* 9.9 Hz, H-4′), 4.89 (dd, 1H, *J* 11.0, 3.3 Hz, H-3), 4.83 (dd, 1H, *J* 11.0, 8.8 Hz, H-2), 4.70 (dd, 1H, *J* 3.3, 1.8 Hz, H-2′), 4.68 (d, 1H, *J* 1.8 Hz, H-1′), 4.26 (dd, 1H, *J* 10.6, 5.8 Hz, H-6a), 4.23 (dd, 1H, *J* 7.0, 6.2 Hz, H-5), 4.17 (dd, 1H, *J* 10.6, 6.2 Hz, H-6b), 3.94 (dq, 1H, *J* 9.6, 6.2 Hz, H-5′), 2.31 (s, 3H, $COC\mathit{H}_3$), 2.09 (s, 3H, $COC\mathit{H}_3$), 2.04 (s, 3H, $COC\mathit{H}_3$), 1.89 (s, 3H, $COC\mathit{H}_3$), 1.85 (s, 3H, $COC\mathit{H}_3$), 1.20 (d, 3H, *J* 6.2 Hz, $C\mathit{H}_3$-6′); ^{13}C NMR ($CDCl_3$): δ 170.7, 170.5, 170.1, 169.5, 134.2, 131.5, 123.8, 98.8, 93.4, 73.5, 71.7, 70.7, 69.9, 68.7, 68.2, 67.5, 62.3, 54.7, 20.8, 20.5, 17.3. ESIMS: calcd for $[M-CCl_3CN+Na]^+$ *m*/*z* 688.2; found: *m*/*z* 688.3.

3.10. 2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→3)-4,6-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-galactopyranosyl *N*-phenyl-2,2,2-trifluoroacetimidate (13)

To a solution of **11** (200.0 mg, 0.30 mmol) in dry CH_2Cl_2 (10 mL) were added *N*-phenyl trifluoroacetimidoyl chloride (267.7 mg, 1.65 mmol) and K_2CO_3 (207.3 mg, 1.50 mmol). The mixture was stirred for 20 h at rt, at the end of which time TLC indicated that the reaction was complete. The mixture was concentrated and then purified by flash chromatography (2:1 petroleum ether–EtOAc) to afford the donor **13** (232.8 mg, 98.2%) as a foamy solid: R_f 0.28 (3:2 petroleum ether–EtOAc); $[\alpha]_D^{22}$ +74.6 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.91–7.05 (9H, Ph), 6.60 (br s, 1H, H-1), 5.49 (br s, 1H, H-4), 5.30 (s, 1H), 5.05 (dd, 1H, *J* 9.6, 2.8 Hz, H-3′), 4.94 (dd, 1H, *J* 10.1, 9.6 Hz, H-4′), 4.79 (br s, 2H), 4.68 (br s, 1H, H-2′), 4.66 (br s, 1H, H-1′), 4.23 (m, 1H, H-6a), 4.12 (dd, 1H, *J* 14.2, 7.3 Hz, H-6b), 3.89 (m, 1H, H-5′), 2.31 (s, 3H, $COC\mathit{H}_3$), 2.05 (s, 3H, $COC\mathit{H}_3$), 2.03 (s, 3H, $COC\mathit{H}_3$), 1.89 (s, 3H, $COC\mathit{H}_3$), 1.86 (s, 3H, $COC\mathit{H}_3$), 1.18 (d, 3H, *J* 5.9 Hz, $C\mathit{H}_3$-6′); ^{13}C NMR ($CDCl_3$): δ 170.5, 170.4, 170.1, 169.5, 169.4, 134.3, 131.3, 128.7, 119.1 (C1), 98.8 (C1′), 73.3, 72.4, 70.6 (C3′), 69.9 (C2′), 68.2 (C4), 68.0 (C3′), 67.6 (C5′), 61.8 (C6), 51.9 (C2), 20.8 ($2CO\mathit{C}H_3$), 20.7 ($CO\mathit{C}H_3$), 20.6 ($2CO\mathit{C}H_3$), 17.3 ($C\mathit{H}_3$-6′). ESIMS: calcd for $[M-Ph+H]^+$ (*m*/*z* 760.2); found *m*/*z* 760.3.

3.11. Allyl 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→3)-4,6-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-galactopyranosyl-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranoside (14)

To a solution of compound **5** (53.5 mg, 0.064 mmol), donor **13** (100.0 mg, 0.11 mmol), and powdered 4 Å molecular sieves in dried CH_2Cl_2 (2 mL) was added TMSOTf (1.42 mg, 0.0064 mmol). The mixture was stirred at −20 °C for 1 h, and the reaction mixture was quenched with Et_3N. The solid was then filtered off, and the filtrate was concentrated under vacuum to give a yellow oil, which was purified by column chromatography (3:2 petroleum ether–EtOAc) to give compound **14** (77.8 mg, 82.4%) as a foamy solid: R_f 0.21 (1:1 petroleum ether–EtOAc); $[\alpha]_D^{22}$ +55.0 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.76–7.23 (24H, Phth, 5Ph), 5.80 (m, 1H, $OCH_2C\mathit{H}{=}CH_2$), 5.34 (s, 1H, PhC*H*), 5.31 (d, 1H, *J* 2.9 Hz, H-4^{III}), 5.19 (dd, 1H, *J* 17.2, 1.4 Hz, $OCH_2CH{=}C\mathit{H}H$), 5.08 (m, 2H), 5.01 (m, 2H), 4.97 (d, 1H, *J* 3.7 Hz), 4.92 (t, 1H, *J* 9.9 Hz, H-4^{IV}), 4.77–4.41 (m, 14H), 4.18–4.10 (m, 5H), 4.07–4.00 (m, 3H), 3.97 (m, 2H), 3.94–3.84 (m, 7H), 3.56 (br s, 1H), 3.53 (m, 2H), 2.18 (s, 3H, $COC\mathit{H}_3$), 2.02 (s, 3H, $COC\mathit{H}_3$), 1.98 (s, 3H, $COC\mathit{H}_3$), 1.86 (s, 3H, $COC\mathit{H}_3$), 1.83 (s, 3H, $COC\mathit{H}_3$), 1.18 (d, 3H, *J* 6.4 Hz, $C\mathit{H}_3$-6^{IV}); ^{13}C NMR ($CDCl_3$): δ 170.5, 170.1, 169.4, 169.3, 139.1, 138.6, 137.8, 128.8, 128.2, 128.1, 128.0, 127.8, 127.5, 127.2, 118.0, 101.1, 98.6, 97.5, 96.5, 96.2, 75.0, 74.9, 72.93, 71.9, 71.0, 69.9, 68.8, 68.1, 67.3, 53.0, 20.7, 20.5, 17.3. HRMS: calcd for $C_{80}H_{87}NO_{26}Na^+$ 1500.5414; found, 1500.5414.

3.12. Allyl 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl-(1→3)-2-acetamido-4,6-di-*O*-acetyl-2-deoxy-β-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-galactopyranosyl-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranoside (15)

A solution of **14** (117.0 mg, 0.079 mmol) in ethylenediamine (3 mL) and *n*-BuOH (6 mL) was heated at 90 °C for 6 h. The reaction mixture was cooled and concentrated under diminished pressure. The residue was then dissolved in pyridine (3 mL) and Ac_2O (3 mL). The mixture was stirred at rt for 12 h, followed by addition of MeOH (5 mL) and concentration to give a residue, which was purified by column chromatography (3:2 petroleum ether–EtOAc) to give compound **15** (70.0 mg, 63.6%) as a foamy solid: R_f 0.28 (3:2 petroleum ether–EtOAc); $[\alpha]_D^{22}$ +42.5 (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.53–7.26 (20H, Ph), 5.86 (m, 1H, $OCH_2CH{=}CH_2$), 5.48 (s, 1H, PhC*H*), 5.28 (d, 1H, *J* 6.9 Hz, N*H*), 5.24 (dd, 1H, *J* 17.0, 1.4 Hz, $OCH_2CH{=}CHH$), 5.23 (d, 1H, *J* 3.7 Hz, H-4^{III}), 5.09 (m, 2H, H-2^{IV}, H-1), 5.03 (dd, 1H, *J* 10.1, 9.6 Hz, H-4^{IV}), 4.93 (d, 1H, *J* 11.5 Hz, C*H*HPh), 4.85 (d, 1H, *J* 12.4 Hz, C*H*HPh), 4.80–4.60 (m, 7H, H-1^{III}, H-1^{IV}, 5C*H*HPh), 4.63 (dd, 1H, *J* 11.0, 3.2 Hz, H-3^{III}), 4.60 (d, 1H, *J* 11.5 Hz, C*H*HPh), 4.24 (dd, 1H, *J* 10.6, 3.7 Hz, H-2), 4.23 (d, 1H, *J* 11.5 Hz), 4.18 (m, 2H), 4.12 (dd, 1H, *J* 12.4, 5.5 Hz), 4.07 (dd, 1H, *J* 10.1, 3.7 Hz, H-2^{II}), 4.05–3.91 (m, 6H, H-5^{IV}), 3.83 (m, 2H), 3.71 (t, 1H, *J* 6.4 Hz), 3.64 (br s, 1H, H-5), 3.47 (dd, 1H, *J* 10.1, 6.8 Hz), 2.86 (dd, 1H, *J* 11.4, 8.2 Hz), 2.16 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.00 (s, 3H, $COCH_3$), 1.98 (s, 3H, $COCH_3$), 1.65 (s, 3H, $COCH_3$); 1.18 (d, 3H, *J* 6.4 Hz, CH_3-6^{IV}); ^{13}C NMR ($CDCl_3$): δ 172.1, 170.4, 170.1, 170.0, 169.9, 139.0, 138.7, 138.6, 138.5, 137.8, 133.8, 129.0, 128.4, 128.3–128.2, 127.9, 127.6–127.3, 126.0, 118.0, 100.6, 99.4, 98.3, 95.8, 95.2, 78.8, 75.8, 75.0, 74.9, 74.8, 74.5, 72.9, 72.8, 72.6, 72.3, 71.6, 70.7, 70.6, 69.9, 69.7, 69.4, 69.3, 69.0, 68.7, 67.0, 62.8, 61.9, 55.5, 29.7, 23.2, 20.9, 20.7, 20.6, 17.3. HRMS: calcd for $C_{74}H_{88}NO_{25}^+$ 1390.5645; found 1390.5641.

3.13. Propyl α-L-rhamnopyranosyl-(1→3)-2-acetamido-2-deoxy-β-D-galactopyranosyl-(1→6)-α-D-galactopyranosyl-(1→2)-α-D-galactopyranoside (1)

To a solution of **15** (50.0 mg, 0.036 mmol) in MeOH (1 mL) and EtOAc (3 mL) was added $Pd(OH)_2/C$ (75% wt % Pd dry basis on charcoal, 12 mg), and the mixture was hydrogenated at rt for 3 h. The suspension was filtered through a Celite pad. The filter cake was rinsed with 5:1 $CHCl_3$–MeOH (10 mL). The combined filtrate and washings were concentrated in vacuo. The residue was then dissolved in a solution of MeONa in MeOH (0.02 M, 5 mL). After stirring at rt for 30 min, the solution was neutralized with ion-exchange resin (H^+), and then filtered and concentrated to afford **1** (21.2 mg, 80.3%) as a white solid: $[\alpha]_D^{22}$ +62.5 (*c* 1.0, $CHCl_3$); ^1H NMR (D_2O): δ 5.16 (d, 1H, *J* 3.9 Hz, H-1), 5.09 (d, 1H, *J* 3.8 Hz, H-1^{II}), 4.86 (br s, 1H, H-1^{IV}), 4.60 (d, 1H, *J* 9.0 Hz, H-1^{III}), 4.25 (t, 1H, *J* 6.4 Hz), 4.03–3.94 (m, 7H), 3.92 (dd, 1H, *J* 10.3, 3.2 Hz), 3.89 (dd, 1H, *J* 10.3, 3.8 Hz), 3.82 (m, 1H, H-2^{IV}), 3.81–3.73 (m, 10H), 3.69 (m, 2H), 3.52 (ddd, 1H, *J* 12.8, 6.4, 3.2 Hz, $OCHHCH_2CH_3$), 3.42 (t, *J* 9.6 Hz), 2.05 (s, 3H, $COCH_3$), 1.63 (m, 2H, $OCH_2CH_2CH_3$), 1.27 (d, 3H, *J* 6.4 Hz, CH_3-6^{IV}), 0.92 (dd, 3H, *J* 7.7, 7.0 Hz, $OCH_2CH_2CH_3$); ^{13}C NMR (D_2O): δ 174.6 ($COCH_3$), 102.3 (C-1^{IV}), 101.2 (C-1^{III}), 96.3 (C-1^{II}), 95.4 (C-1^{I}), 78.9, 75.2, 72.9, 71.9, 70.9, 70.4, 70.0, 69.9, 69.5, 69.3, 69.1, 69.0, 68.2, 68.1, 67.7, 61.2, 60.9, 51.6, 22.2 ($COCH_3$), 22.0 ($OCH_2CH_2CH_3$), 16.7 (CH_3-6^{IV}), 10.0 ($OCH_2CH_2CH_3$). HRMS: calcd for $C_{29}H_{52}NO_{20}^+$ 734.3083; found 734.3063.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2006.09.018.

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