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Synthesis of active principles from the leaves of *Moringa oleifera* using *S*-pent-4-enyl thioglycosides

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Abstract

α-L-Rhamnosides of 4-hydroxy-benzyl compounds with nitrile, carbamate, and thiocarbamate groups occurring in *Moringa oleifera* leaf extracts and the α-L-rhamnoside of anisaldehyde derivatives were synthesised. Electrophilic activation of *S*-pent-4-enyl thiorhamnosides was applied for the construction of glycosidic linkages. © 1998 Elsevier Science Ltd. All rights reserved

Keywords: Aryl rhamnopyranosides; *Moringa oleifera* Lam.; *S*-Pent-4-enyl thioglycosides; O-Glycosides of 4-hydroxy-benzyl carbamates,-thiocarbamates

1. Introduction

Moringa oleifera Lam. belonging to the single-genus family Moringaceae is a small fast-growing ornamental tree widespread over the tropical regions of Africa and Asia [1]. All parts of this tree are applied in traditional medicine for the treatment of human diseases, whereby the leaves enriched in vitamins A and C are used as vegetables [1–3]. Because of its coagulating and antimicrobiotic properties, the powdered seeds are utilised for water purification [4,5].

The crude ethanolic extract of fresh uncrunched leaves exhibits (in vivo and in vitro) strong hypotensive and spasmolytic effects [6]. Phytochemical studies on this extract led to the isolation of 4-(α-L-rhamnopyranosyloxy)-benzyl compounds containing isothiocyanate, nitrile, carbamate or thiocarbamate groups and a benzaldehyde derivative [2,7–9] (Table 1).

Moreover, the L-rhamnose portions always α-glycosidically linked to the aglycone, possesses either free, 4′-*O*-acetylated and per-*O*-acetylated hydroxy groups. In addition, thiocarbamates occur as *E* and *Z* isomers which show typical differences in the chemical shifts of the NH protons in deuterated dimethyl sulfoxide [2,10] (Fig. 1).

Hypotensive effects of several compounds from the ethanolic extract of leaves were studied in vivo through intravenous administration to anaesthetised rats. These studies identified the rhamnosylated 4-hydroxy-benzyl isothiocyanates, carbamates and thiocarbamates as the pharmacologically active principles of the extract. The effects of all of these compounds were similar, reversible

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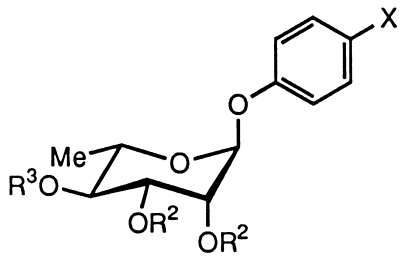
Table 1
Constituents of fresh ethanolic *Moringa oleifera* leaf extract [2,7–9]



X	R^1	R^2	R^3	Comp.	Name
$CH_2N{=}C{=}S$	—	H	H		—
	—	H	Ac		—
CH_2CN	—	H	H		niazirin
	—	H	Ac		niazirinin
	—	Ac	Ac	**1**	—
CHO		H	Ac		—
$CH_2N(H)C(=O)OR^1$	Me	H	Ac		—
	Me	Ac	Ac	**2**	—
	Et	H	Ac		niazimin A + B
	Et	Ac	Ac	**3**	—
$CH_2N^+(H)=C(OR^1)S^-$ (*E*)	Me	H	H	**4a**	niazinin A
	Me	H	Ac		niazicin A
	Me	Ac	Ac	**5a**	—
	Et	H	H	**6a**	niazimicin
	Et	H	Ac		niaziminin A
$CH_2N^+(H)=C(S^-)OR^1$ (*Z*)	Me	H	H	**4b**	niazinin B
	Me	H	Ac		niazicin B
	Me	Ac	Ac	**5b**	—
	Et	H	H	**6b**	—
	Et	H	Ac		niaziminin B
	Et	Ac	Ac	**7b**	—

and dose-dependent. Nitriles did not show any hypotensive effect. Investigations on organs of several animals indicated spasmolytic properties of thiocarbamates in vitro along with the hypotensive effects [9]. Nevertheless, these results showed so far that no specific mechanism can be supposed for the hypotensive and spasmolytic effects of these thiocarbamates.

Here, we report on the synthesis of pharmacologically active constituents of *Moringa oleifera* leaf extract with nitrile, aldehyde, carbamate and thiocarbamate functionalities according to the retrosynthetic strategy shown in Scheme 1: Following pathway A, the *Moringa oleifera* compounds are synthesised via rhamnosylation of the phenolic hydroxy group of the aglycone. This concept should be successful if no side reactions on the aglycone, e.g. on its thiocarbonyl group of thiocarbamates, interfere with the glycosylation. According to pathway B rhamnosylation of a

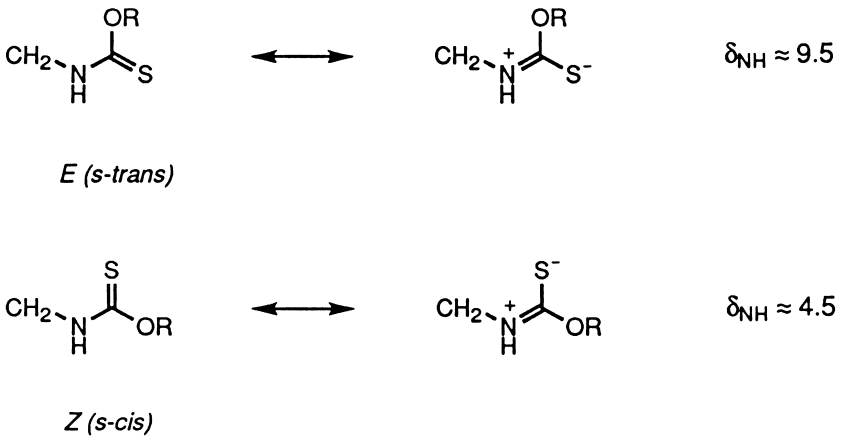
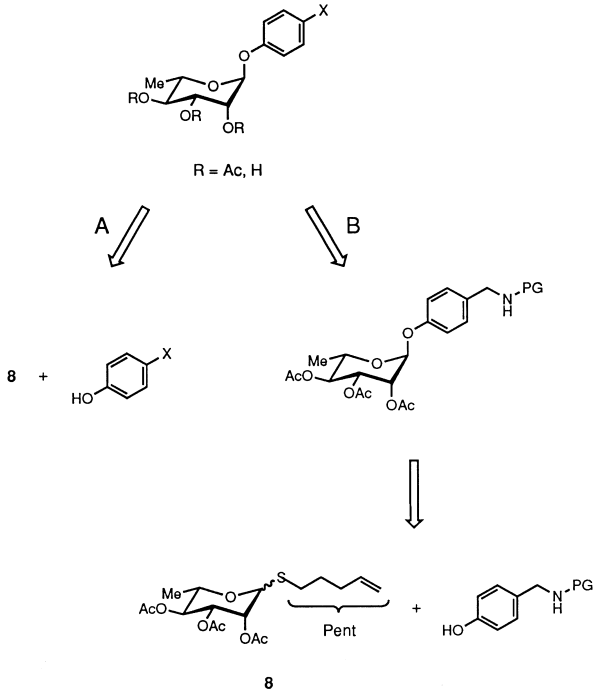


Fig. 1. Chemical shifts of the NH protons of thiocarbamate rotational isomers in Me_2SO-d_6 [2].

protected 4-hydroxy-benzylamine is carried out first. After deprotection of the rhamnosylated 4-hydroxy-benzylamine building block, subsequent conversion of the amine into the functional group of the *Moringa oleifera* compound is carried out. Side reactions on the functional group can be avoided by this strategy. For the construction of glycosidic linkages, *S*-pent-4-enyl thiorhamnoside **8** is used. Anomeric activation of this thioglycoside can be achieved by the reaction with soft electrophiles.



Scheme 1.

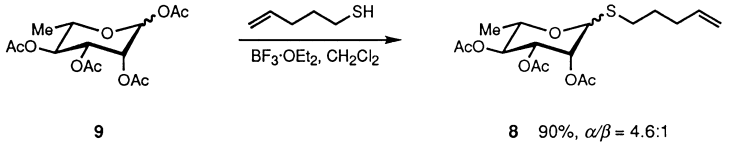
2. Results and discussion

S-*Pent-4-enyl thiorhamnoside*.—*S*-Pent-4-enyl thioglycosides have proved to be efficient in the construction of O-glycosyl amino acid and saccharide building blocks applied in the syntheses of T_N and T antigen glycopeptide sequences of tumor-associated MUC-1 [11]. Attack of electrophiles at the C–C double bond of *S*-pent-4-enyl thioglycosides induces an intramolecular cyclisation generating the corresponding thiolane as the anomeric leaving group. Alternatively, the reaction of electrophiles with the anomeric sulfur also leads to the activation of these thioglycosides. As the soft activating electrophile, a mixture of *N*-iodosuccinimide (NIS) and trifluoromethanesulfonic acid, has been applied advantageously for this purpose. For the preparation of the *S*-pent-4-enyl thiorhamnopyranoside **8**, tetra-*O*-acetyl-L-rhamnopyranose **9** [12] was reacted with 4-pentene-1-thiol [11,13] in the presence of borontrifluoride (Scheme 2). The thiorhamnoside **8** was obtained as a mixture of anomers ($\alpha/\beta = 4.6 : 1$).

Synthesis of Moringa *compounds via rhamnosylation of the aglycone*.—The *Moringa oleifera* derivatives with nitrile and aldehyde functionalities were prepared according to the retrosynthetic pathway A. To prevent side reactions of iodonium ions with the reactive phenols, the mixture of thiorhamnoside **8** and 4-hydroxy-benzonitrile **10** or anisaldehyde **11**, respectively, was treated with *N*-iodosuccinimide/trifluoromethanesulfonic acid at −40 °C to yield the nitrile derivative **1**, occurring in *Moringa oleifera* leaf extract and the benzaldehyde compound **12** (Scheme 3). Removal of the *O*-acetyl groups from **12** by Zemplén transesterification led

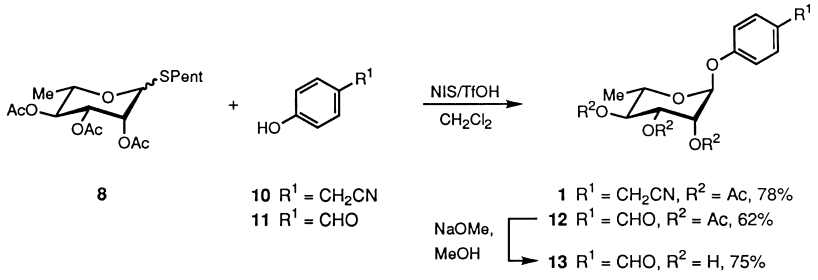
to 4-(α-L-rhamnopyranosyloxy)-benzaldehyde **13**. Alternative syntheses of the aldehydes **12** and **13** have already been reported [14]. For the synthesis of thiocarbamate derivatives contained in *Moringa oleifera* leaf extract, the thiocarbamate aglycone had to be prepared first (Scheme 4). As the starting material 4-hydroxy-benzonitrile **14** was used. Its phenolic hydroxy group was protected as the allyl ether. In a two-step process, the nitrile function of **15** was reduced to give the amine which without further purification was thioacylated applying Mukaiyama's conditions [15,16]. For this purpose, the crude amine was reacted with *O*-ethyl-*S*-(1-methyl-2-pyridinium)-dithiocarbonate generated in situ from pyridinium derivative **16** and potassium ethylxanthogenate in the presence of 1,8-diazabicylo[5.4.0]undec-7-ene (DBU) to yield the thiocarbamate **17**. Palladium(0)-catalyzed removal of the allyl ether [17] furnished the aglycone **18**.

To prevent side reactions at the thiocarbonyl group during glycosylation using electrophilic activators, the rhamnosylation of aglycone **18** was



9 **8** 90%, α/β = 4.6:1

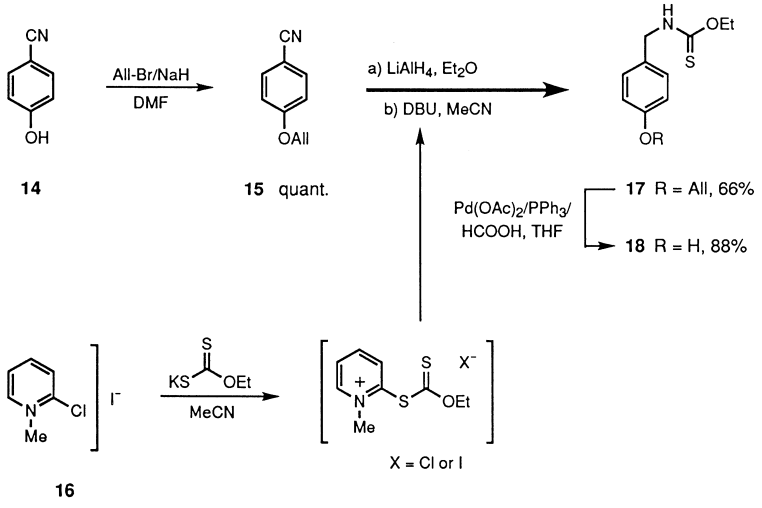
Scheme 2.



8 **10** $R^1 = CH_2CN$; **11** $R^1 = CHO$

1 $R^1 = CH_2CN$, R^2 = Ac, 78%; **12** $R^1 = CHO$, R^2 = Ac, 62%; **13** $R^1 = CHO$, R^2 = H, 75%

Scheme 3.



14 **15** quant. **17** R = All, 66%; **18** R = H, 88%

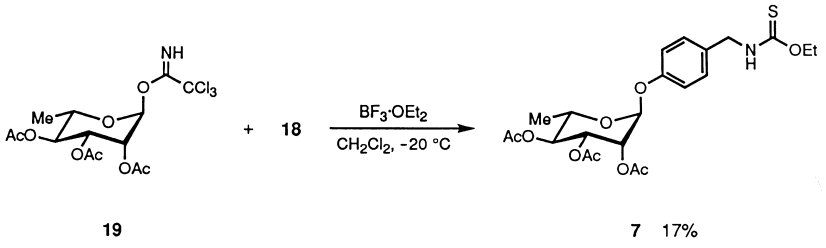
16

Scheme 4.

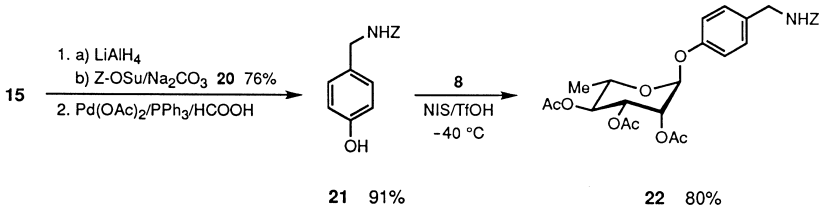
carried out with rhamnosyl trichloroacetimidate **19** [18] in the presence of catalytic amounts of boron-trifluoride (Scheme 5). However, even under these conditions, rhamnosylation to give the thiocarbamate compound **7** was accompanied by the formation of a number of by-products.

Synthesis of Moringa *compounds via (thio)-acylation of the 4-rhamnosyloxy-benzylamine.*—As an alternative, the conversion of a rhamnosyloxy-benzylamine building block precedingly prepared by rhamnosylation of a protected 4-hydroxy-benzylamine into the functional group of the active principle should prevent such side reactions described above. According to this strategy, *N*-benzyloxy-carbonyl-protected 4-hydroxy-benzylamine **21** was synthesised by reduction of the nitrile **15**, subsequent introduction of the benzyloxycarbonyl group and final removal of the allyl ether (Scheme 6). Rhamnosylation of **21** was achieved using *N*-iodosuccin-imide/trifluoromethanesulfonic acid to yield the protected rhamnosyloxy-benzylamine **22**.

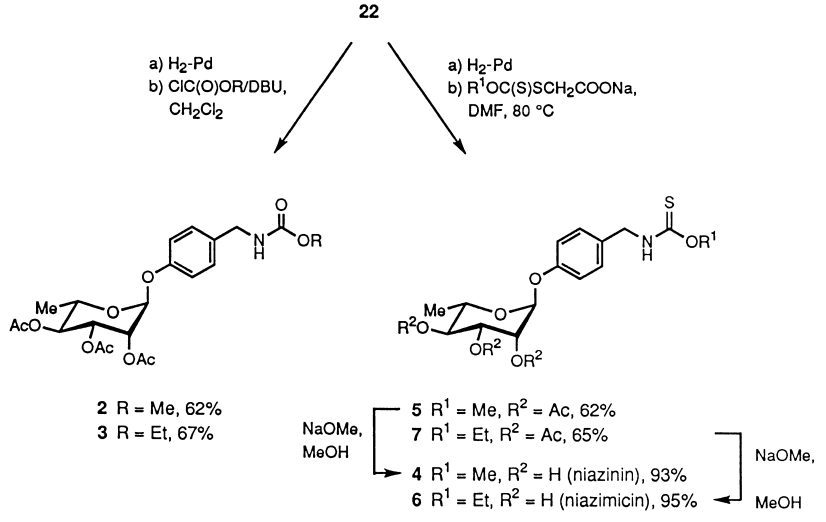
Acylation of the crude amine obtained by hydrogenolytic removal of the benzyloxycarbonyl group from **22** was carried out using methyl and ethyl chloroformate in the presence of 1,8-diazabi-cyclo[5.4.0]undec-7-ene to furnish *O*–methyl carbamate **2** or *O*-ethyl carbamate **3**, respectively (Scheme 7). Reaction of the crude amine with the corresponding sodium salt of *O*-alkyl-*S*-carboxy-methyl dithiocarbonate at elevated temperature



Scheme 5.



Scheme 6.



Scheme 7.

[19] led to the *O*-methyl thiocarbamate **5** and the *O*-ethyl thiocarbamate **7** in good yields. The obtained active principles **5** and **7** were subjected to Zemplén transesterification in order to remove the *O*-acetyl groups and gave the natural products niazinin **4** and niazimicin **6**.

The structures of the synthesised compounds which show correct analytical data were unequivocally ascertained by FD mass spectrometry and by high field NMR spectroscopy. In the ^{1}H NMR spectrum of thiocarbamates **4–7** recorded in deuterated dimethyl sulfoxide, the NH signals appeared at δ 9.6. This indicates that in dimethyl sulfoxide only the *E* isomer is present (Fig. 1). The NMR data are in accordance with reported data of compounds isolated from *Moringa oleifera* [2,7–9].

The described syntheses make the *Moringa oleifera* constituents accessible in preparative scale for pharmacological investigations of their spasmolytic and hypotensive properties. Not only *O*-alkyl but also *O*-acetyl protected *S*-pentenyl thioglycosides proved to be efficient glycosyl donors useful for a stereoselective glycosylation of hydroxyamino acid and saccharide derivatives [11] as well as that of phenols, even such ones of reduced nucleophilicity, e.g. **11**. The applied strategies also are useful for the search and the construction of more effective and specific analogs of the natural drugs.

3. Experimental

General methods.—Melting points were measured on a Büchi apparatus and are uncorrected. ^{1}H NMR (200 or 400 MHz) and ^{13}C NMR (50.3 or 100.6 MHz) spectra were recorded on a Bruker AC 200 or a Bruker AM 400 spectrometer. Chemical shifts (δ) are given relative to the signal of Me_4Si. Mass spectra were recorded on a Varian CH7A (EI) or a Finnigan MAT-95 (FD) spectrometer. Flash-chromatography was carried out using Silica Gel 30–60 μm (Baker). For column chromatography, Silica Gel 0.063–0.200 mm (Baker) was used. TLC was performed on aluminium foil coated with Silica Gel 60 F_{254} (E. Merck, Darmstadt). Optical rotation values were measured on a Perkin–Elmer polarimeter 241. If not indicated otherwise, reactions were carried out at room temperature.

Pent-4′-enyl 2,3,4-tri-O-*acetyl-1-thio*-L-*rhamnopyranoside* (**8**).—Tetra-*O*-acetyl-L-rhamnopyranose **9** [12] (3.32 g, 10.0 mmol), 4-pentene-1-thiol [11,13] (2.04 g, 20.0 mmol) and 4 Å molecular sieves (2 g) in CH_2Cl_2 (60 mL) were stirred for 1 h with exclusion of light. BF_3 etherate (1.9 mL, 15.0 mmol) was added dropwise. After stirring for 20 h, TLC monitoring showed incomplete conversion. Therefore, additional pentenethiol (1.60 g, 15.7 mmol) and BF_3 etherate (1.9 mL, 15.0 mmol) were added dropwise. After stirring for 24 h, the mixture was neutralized by addition of satd $NaHCO_3$ and filtered through Celite. The organic phase was washed with water, dried with $MgSO_4$, and concentrated in vacuo. Flash-chromatography (5:1 petroleum ether–EtOAc) gave **8** (3.38 g, 90%) as a yellow oil: R_f 0.35 (α anomer) and 0.24 (β anomer), petroleum ether–EtOAc; α/β 4.6:1 (according to ^{1}H NMR); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.74 (ddt, 1 H, J_{tr} 17.0, J_{cis} 10.2, J_{vic} 6.7 Hz, –CH=), 5.47 (dd, 0.18 H, $J_{1\beta,2\beta}$ 0.9, $J_{2\beta,3\beta}$ 3.0 Hz, H-2β), 5.31 (dd, 0.82 H, $J_{1\alpha,2\alpha}$ 1.3, $J_{2\alpha,3\alpha}$ 3.3 Hz, H-2α), 5.21 (dd, 0.82 H, $J_{3\alpha,4\alpha}$ 10.1 Hz, H-3α), 5.14 (d, 0.82 H, H-1α), 5.06 (t, 0.82 H, J 9.7 Hz, H-4α), 5.06–4.94 (m, 2.36 H, H-3β,4β, $=CH_2$), 4.69 (d, 0.18 H, H-1β), 4.20 (dq, 0.82 H, $J_{4\alpha,5\alpha}$ 9.4, $J_{5\alpha,6\alpha}$ 6.2 Hz, H-5α), 3.59–3.45 (m, 0.18 H, H-5β), 2.72–2.44 (m, 2 H, SCH_2), 2.22–2.07 (m, 2 H, CH_2CH=), 2.16, 2.13, 2.03, 1.96, and 1.95 (5 s, 9 H, Ac), 1.76–1.61 (m, 2 H, SCH_2CH_2), 1.25 (d, 0.54 H, $J_{5\beta,6\beta}$ 6.2 Hz, H-6β), 1.20 (d, 2.46 H, H-6α); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 169.81 and 169.67 (C=O), 137.23 (–CH=), 115.30 (=CH_2), 82.22 (C-1), 74.75, 71.75, 70.65, and 70.22 (C-2β,3β,4β,5β), 71.34, 71.08, 69.29, and 66.81 (C-2α,3α,4α,5α), 32.37, 31.82, 30.62, 28.66, and 28.42 (CH_2-Pent), 20.76, 20.62, and 20.49 (CH_3-Ac), 17.53 (C-6β), 17.17 (C-6α).

4-(2′,3′,4′-Tri-O-*acetyl*-α-L-*rhamnopyranosyloxy)-phenylacetonitrile* (**1**).—A mixture of **8** (1460 mg, 3.9 mmol), 4-hydroxy-phenylacetonitrile **10** (346 mg, 2.6 mmol) and 4 Å molecular sieves (0.5 g) in CH_2Cl_2 (40 mL) was stirred for 30 min and then cooled to −40 °C. A cooled (−40 °C) solution of NIS (877 mg, 3.9 mmol) and HOTf (0.09 mL, 1.0 mmol) in 3:1 CH_2Cl_2–MeCN (8 mL) was added. After stirring for 2 h at −40 °C, Et_3N (2 mL) and CH_2Cl_2 (50 mL) were added, and the mixture was filtered through Celite. The filtrate was washed with aq 10% $Na_2S_2O_3$ (50 mL) and brine (50 mL), dried with $MgSO_4$, and concentrated in vacuo. Purification by flash-chromatography (2.4:1 petroleum ether–EtOAc) gave **1** (822 mg, 78%) as colourless crystals: mp 103 °C; R_f 0.20 (2:1 petroleum ether-EtOAc). For analytical data, see Tables 2, 3, 5 and 7–9.

Table 2
^{1}H NMR chemical shifts (δ in ppm) for compounds **1–7**, **12**, **13** and **22** [a]

Proton	**1** $CDCl_3$	**2** $CDCl_3$	**3** $CDCl_3$	**4** Me_2SO-d_6	**5** Me_2SO-d_6	**6** Me_2SO-d_6	**7** Me_2SO-d_6	**12** $CDCl_3$	**13** Me_2SO-d_6	**22** $CDCl_3$
H-2,6	7.03, d	6.97, d	6.98, d	6.98, d (B) 6.97, d (A)	7.07, d	6.98, d (B) 6.96, d (A)	7.08, d (B) 7.07, d (A)	7.16, d	7.21, d	6.98, d
H-3,5	7.21, d	7.17, d	7.18, d	7.21, d (A) 7.15, d (B)	7.23, d (A) 7.18, d (B)	7.20, d (A) 7.15, d (B)	7.23, d (A) 7.18, d (B)	7.81, d	7.86, d	7.18, d
H-7	3.66, s	4.25, d	4.26, d	4.56, d (A) 4.24, d (B)	4.57, d (A) 4.25, d (B)	4.54, d (A) 4.21, d (B)	4.56, d (A) 4.23, d (B)	9.86, s	9.87, s	4.28, d
H-1′	5.41, d	5.38, d	5.39, d	5.33, d	5.64, d	5.32, d	5.63, d	5.53, d	5.54, d	5.39, d
H-2′	5.37, dd	5.36, dd	5.37, dd	3.81, ddd	5.30, dd	3.79, ddd	5.30, dd	5.39, dd	3.85, ddd	5.38, dd
H-3′	5.45, dd	5.45, dd	5.45, dd	3.63, ddd	5.27, dd	3.61, ddd	5.27, dd	5.45, dd	3.65, ddd	5.46, dd
H-4′	5.10, t	5.09, t	5.10, t	3.27, dt	4.95, t	3.25, dt	4.95, t	5.12, t	3.30, dt	5.11, t
H-5′	3.90, dq	3.91, dq	3.92, dq	3.45, dq	3.90, dq	3.44, dq	3.90, dq	3.88, dq	3.39, dq	3.92, dq
H-6′	1.15, d	1.14, d	1.15, d	1.08, d	1.06, d	1.07, d	1.06, d	1.15, d	1.09, d	1.16, d
HO-2′	—	—	—	5.03, d	—	5.02, d	—	—	5.15, d	—
HO-3′	—	—	—	4.73, d	—	4.72, d	—	—	4.81, d	—
HO-4′	—	—	—	4.86, d	—	4.85, d	—	—	4.93, d	—
OCH_3	—	3.63, s	—	3.88, s (B) 3.87, s (A)	3.88, s (B) 3.86, s (A)	—	—	—	—	—
OCH_2CH_3	—	—	4.09, q	—	—	4.38, q (A) 4.37, q (B)	4.38, q (A) 4.37, q (B)	—	—	—
OCH_2CH_3	—	—	1.20, t	—	—	1.23, t (A) 1.19, t (B)	1.23, t (A) 1.18, t (B)	—	—	—
CH_2Ph	—	—	—	—	—	—	—	—	—	5.08,s
CH_2Ph	—	—	—	—	—	—	—	—	—	7.32–7.25, m
NH	—	5.14, s_b	5.04, s_b	9.62, t (B) 9.58, t (A)	9.63, t(B) 9.60, t (A)	9.55, t	9.56, t	—	—	5.19, s_b
Ac	2.15, 2.01, 1.98, 3s	2.14, 2.01, 1.97, 3s	2.14, 2.01, 1.98, 3s	—	2.13, 2.04, 1.96, 3s	—	2.13, 2.04, 1.96, 3s	2.15, 2.01, 1.99, 3s	—	2.15, 2.02, 1.99, 3s

[a] Recorded at 400 MHz.

Table 3
^{1}H NMR coupling constants (J in Hz) for compounds **1–7**, **12**, **13** and **22**

Coupling constant	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**12**	**13**	**22**
$J_{2,3}=J_{5,6}$	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.8	8.5	8.4
$J_{7,NH}$	—	5.9	5.6	5.9 (A) 6.2 (B)	5.9 (A) 6.2 (B)	5.9 (A) 6.2 (B)	5.9 (A) 6.2 (B)	—	5.6	
$J_{1',2'}$	1.8	1.8	1.8	1.8	1.8	1.8	1.5	1.8	1.8	1.8
$J_{2',3'}$	3.4	3.4	3.5	3.2	3.5	3.4	3.5	3.5	3.8	3.2
$J_{3',4'}$	10.1	10.0	10.0	9.1	10.0	9.4	10.3	10.0	9.1	10.0
$J_{4',5'}$	9.8	10.0	10.0	9.1	9.7	9.4	9.7	9.7	9.4	10.0
$J_{5',6'}$	6.2	6.2	6.2	6.2	6.2	6.2	6.2	6.2	6.2	6.2
$J_{2',OH}$	—	—	—	4.4	—	4.1	—	—	4.4	—
$J_{3',OH}$	—	—	—	5.6	—	5.6	—	—	5.3	—
$J_{4'OH}$	—	—	—	5.6	—	5.6	—	—	5.3	—
J_{vic}(OEt)	—	—	7.0	—	—	7.1	7.0	—	—	

4-(2′,3′,4′-Tri-O-*acetyl-α*-L-*rhamnopyranosyloxy)-benzaldehyde* (**12**).—Compound **12** was obtained from **8** (1460 mg, 3.9 mmol), 4-hydroxy-benzaldehyde **11** (318 mg, 2.6 mmol) and a mixture of NIS (877 mg, 3.9 mmol) and HOTf (0.09 mL, 1.0 mmol) under warming up to −20 °C within 16 h, as described for **1**. Flash-chromatography (4:1 petroleum ether–EtOAc) yielded **12** (635 mg, 62%) as colourless crystals: mp 161 °C; R_f 0.32 (2:1 petroleum ether–EtOAc). For analytical data, see Tables 2, 3, 5 and 7–9.

4-(α-L-*Rhamnopyranosyloxy)-benzaldehyde* (**13**).—A solution of **12** (1.00 g, 2.5 mmol) in MeOH (20 mL) was stirred with 0.75 M NaOMe in MeOH (0.8 mL) for 3 h and, subsequently, neutralised with Amberlite IR-120. After filtration, the solvent was evaporated in vacuo. Flash-chromatography (1.5:1 petroleum ether–acetone) gave **13** (503 mg,

Table 4
^{1}H NMR chemical shifts (δ in ppm) and coupling constants (J in Hz) in $CDCl_3$ for compounds **15**, **17**, **18**, **20**, and **21** [a]

Proton	**15**	**17**	**18**	**20**	**21**
H-2,6	6.97–6.90, m	6.87, d $J_{2,3}$ 8.6	6.97, d $J_{2,3}$ 8.5	6.85, d $J_{2,3}$ 8.5	6.73, d $J_{2,3}$ 8.5
H-3,5	7.59–7.52, m	7.23, d (A) 7.15, d (B) $J_{5,6}$ 8.6	7.17, d (A) 7.05, d (B) $J_{5,6}$ 8.4	7.18, d $J_{5,6}$ 8.5	7.09, d $J_{5,6}$ 8.5
H-7	—	4.65, d (A) $J_{7,NH}$ 5.4 4.36, d (B) $J_{7,NH}$ 5.6	4.63, d (A) $J_{7,NH}$ 5.5 4.32, d (B) J_{7NH} 5.7	4.29, d $J_{7,NH}$ 5.8	4.27, s_b
HO-1	—	—	5.28, s_b	—	5.12, s_b
CH_2CH_3	—	4.56, q (B) 4.49, q (A) J_{vic} 7.1	4.55, q (B) 4.48, q (A) J_{vic} 7.1	—	—
CH_2CH_3	—	1.36, t (B) 1.30, t (A)	1.35, t (B) 1.29, t (A)	—	—
$CH_2CH=CH_2$	4.56, dt J_{vic} 5.3 J_{all} 1.4	4.53, dt $J_{vic\ 5.3}$ J_{all} 1.4	—	4.50, dt J_{vic} 5.3 J_{all} 1.4	—
$CH_2CH=CH_2$	6.01, ddt J_{tr} 17.3 J_{cis} 10.5	6.04, ddt J_{tr} 17.3 J_{cis} 10.5	—	6.03, ddt J_{tr} 17.3 J_{cis} 10.5	—
$CH_2CH=CH_2$	5.39, dq (CH_{tr}) 5.31, dq (CH_{cis})	5.40, dq (CH_{tr}) 5.28, dq (CH_{cis})	—	5.38, dq (CH_{tr}) 5.27, dq (CH_{cis})	—
CH_2Ph	—	—	—	5.11, s	5.12, s
CH_2Ph	—	—	—	7.33, s	7.33, s
NH	—	6.75, s_b (B) 6.36, s_b (A)	6.85, s_b (B) 6.39, s_b (A)	5.00, s_b	5.12, s_b

[a] Spectra of compounds **15**, **17**, **20** and **21** were recorded at 200 MHz; the spectrum of compound **18** was recorded at 400 MHz.

75%) as colourless crystals: mp 105 °C; R_f 0.23 ($CHCl_3$–MeOH). For analytical data, see Tables 2, 3, 5 and 7.

4-Allyloxy-benzonitrile (**15**).—To a stirred mixture of NaH (0.72 g, 24 mmol; 80% dispersion in mineral oil) in DMF (20 mL) was added slowly a solution of 4-hydroxy–benzonitrile **14** (2.38 g, 20 mmol) in DMF (5 mL) at 0 °C. After the evolution of H_2 had deceased, allyl bromide (3.5 mL, 40 mmol) was added. The mixture was allowed to warm up to room temperature and the stirring was continued for 16 h. MeOH (20 mL) was added in order to solvolyse the excess of NaH. The mixture was subsequently poured into 1:1 Et_2O–water (300 mL). After separation, the water solution was extracted twice with Et_2O (150 mL). The combined organic solutions were dried with $MgSO_4$ and concentrated in vacuo. Flash-chromatography (6:1 petroleum ether–EtOAc) gave **15** (3.15 g, quant) as colourless crystals: mp 43 °C, lit. mp 43.6–44.4 °C [20]; R_f 0.46 (6:1 petroleum ether–EtOAc); EIMS: m/z 159 (19) [$M^{+\cdot}$], 119 (5) [$C_7H_5NO^{+\cdot}$], 41 (100) [$C_3H_5^+$]. For further analytical data, see Tables 4, 6 and 9.

N-*Ethoxythiocarbonyl-4-allyloxy-benzylamine* (**17**).—(a) Reduction of the nitrile **15**: A solution of **15** (2.55 g, 16 mmol) in Et_2O (20 mL) was added to a stirred mixture of $LiAlH_4$ (0.91 g, 24 mmol) in Et_2O (70 mL). The mixture was heated under reflux for 24 h. After cooling to 0 °C, water (20 mL) was added dropwise under stirring. After dilution with CH_2Cl_2 (200 mL), the mixture was filtered through Celite. The filtrate was washed with brine (200 mL), dried with $MgSO_4$, and concentrated in vacuo to yield the crude amine as a colourless liquid. (b) Thioacylation of the amine: To a mixture of 2-chloro-1-methyl–pyridinium iodide **16** (4.91 g, 19.2 mmol) in MeCN (60 mL) was added potassium ethylxanthogenate (3.08 g, 19.2 mmol). After stirring for 70 min, a solution of the amine in MeCN (15 mL) and DBU (2.9 mL, 19.2 mmol) was added, and the mixture was stirred for additional 12 h and, subsequently, poured into 1:1 Et_2O–water (400 mL). The organic layer was separated

Table 5
^{13}C NMR data for compounds **1–7**, **12**, **13** and **22**

Carbon [a]	**1** $CDCl_3$	**2** $CDCl_3$	**3** $CDCl_3$	**4** Me_2SO-d_6	**5** $CDCl_3$	**6** Me_2SO-d_6	**7** $CDCl_3$	**12** $CDCl_3$	**13** Me_2SO-d_6	**22** $CDCl_3$
C-1	155.51	155.15	155.18	155.20	156.43	155.14	155.39	160.43	160.84	155.17
C-2,6	116.98	116.50	116.55	116.36 116.27	116.69 116.63	116.28 116.22	116.60	116.50	116.49	116.53
C-3,5	129.18	128.77	128.79	128.65 128.52	129.26 129.03	128.64 128.61	129.24 129.03	131.78	131.57	~128 [b]
C-4	124.10	132.94	133.07	131.44 131.28	131.31 130.89	131.50 131.32	131.29 130.95	131.55	130.44	132.82
C-7	22.76	44.43	44.39	47.42 45.09	48.68 46.55	47.11 45.03	48.43 46.41 37.37	191.54	191.26	44.46
C-8	117.76	156.97	156.58	190.89 188.86	191.45 190.61	189.98 187.94	190.55 189.72	—	—	156.32
C-1′	95.68	95.72	95.78	98.48	95.72	98.44	95.68	95.46	98.16	95.73
C-2′–C-5′	70.82 69.55 68.80 67.24	70.92 69.65 68.87 67.11	70.98 69.69 68.91 67.14	71.78 70.44 70.15 69.36	70.90 69.65 68.90 67.18	71.75 70.39 70.12 69.33	70.89 69.60 68.84 67.14	70.70 69.40 68.71 67.63	71.63 70.33 69.89 69.81	70.93 69.65 68.88 67.11
C-6′	17.32	17.30	17.35	17.79	17.36	17.76	17.31	17.35	17.75	17.32
C=O, Ac	169.89 169.86 169.79	169.90 169.86 169.83	169.92 169.87 169.84	—	169.96 169.87	—	169.92 169.89 169.82	169.87 169.77	—	169.89 169.86 169.83
Ch_3, Ac	20.71 20.61 20.57	20.71 20.61 20.55	20.73 20.63 20.58	—	20.76 20.67 20.61	—	20.70 20.61 20.55	20.70 20.61 20.57	—	20.70 20.61 20.55
Other signals	—	52.07 (OMe)	60.88 14.55 (OEt)	57.17 56.42 (OMe)	58.28 57.11 (OMe)	66.02 65.22 14.14 13.93 (OEt)	70.60 67.83 66.37 14.14 14.10 13.54 (OEt)	—	—	136.48 128.79 128.40 128.01 66.75 (CH_2Ph)

[a] Recorded at 100.6 MHz; all signals with the exception of these of compound **13** were assigned by DEPT-135 spectra.
[b] Signal lies below the signals of the CH_2Ph group.

and the aqueous solution was extracted with Et_2O (200 mL). The combined organic layers were washed with water (400 mL), dried with $MgSO_4$, and concentrated in vacuo. Flash-chromatography (10:1 petroleum ether–EtOAc) gave **17** (2.65 g, 66%) as a yellow oil: R_f 0.40 (10:1 petroleum ether–EtOAc); ratio of rotamers 1.7:1 (according to ^1H NMR); EIMS: *m/z* 251 (80) [$M^{+\cdot}$], 222 (82) [$C_{11}H_{12}NO_2S^+$], 179 (42) [$C_{10}H_{11}$ OS^+], 162 (32) [$C_{10}H_{12}NO^+$], 147 (41) [$C_{10}H_{11}$ O^+], 121 (19) [$C_8H_9O^+$], 107 (29) [$C_7H_7O^+$], 84 (19), 83 (31), 41 (100) [$C_3H_5^+$]. For further analytical data, see Tables 4, 6 and 9.

N-*Ethoxythiocarbonyl-4-hydroxy-benzylamine* (**18**).—To a stirred solution of **17** (1.83 g, 7.3 mmol), formic acid (0.42 mL, 11.0 mmol) and triphenylphosphine (1.15 g, 4.4 mmol) in THF (50 mL) palladium acetate (90 mg, 0.4 mmol) was added under strict exclusion of O_2. After the mixture was heated under reflux for 20 h, the solvent was evaporated in vacuo and the residue diluted with 1:1 Et_2O–water (200 mL). After separation, the water solution was extracted twice with Et_2O (100 mL). The combined organic solutions were washed with water (300 mL), dried with $MgSO_4$, and concentrated in vacuo. Purification by flash-chromatography (3:1 petroleum ether–EtOAc) yielded **18** (1.36 g, 88%) as colourless crystals: mp 83 °C; R_f 0.37 (3:1 petroleum ether–EtOAc); ratio of rotamers A:B 1.4:1 (according to ^1H NMR); EIMS: *m/z* 211 (60) [$M^{+\cdot}$], 182 (44) [$C_8H_8NO_2S^+$], 139 (29) [$C_7H_7OS^+$], 122 (57) [$C_7H_8NO^+$], 107 (100) [$C_7H_7O^+$], 95 (26) [$C_6H_7O^+$], 77 (36) [$C_6H_5^+$]. For further analytical data, see Tables 4, 6 and 9.

N-*Ethoxythiocarbonyl-4-(2′,3′,4′-tri*-O-*acetyl*-α-L-*rhamnopyranosyloxy)-benzylamine* (**7**).—A mixture of tri-*O*-acetyl-α-L-rhamnopyranosyl trichloroacetimidate **19** [18] (1130 mg, 2.6 mmol), **18** (422 mg, 2.0 mmol) and 4 Å molecular sieves (0.5 g) in CH_2Cl_2

Table 6
^{13}C NMR data in $CDCl_3$ for compounds **15**, **17**, **18**, **20** and **21**

Carbon [a]	**15**	**17**	**18**	**20**	**21**
C-1	161.61	158.13	155.16	158.01	155.54
C-2,6	115.24	114.86	115.52	114.88	115.54
C-3,5	133.69	129.25	129.29	~128 [b]	~128 [b]
		129.04	129.11		
C-4	103.75	128.79	128.53	130.74	129.64
			128.10		
C-7	118.95	48.55	48.45	44.56	44.58
		46.49	46.47		
C-8	—	190.28	190.12	156.30	156.73
		189.41	189.03		
Other	131.87	133.09	68.10	136.55	136.12
signals	118.17	117.65	66.51	128.77	128.87
	68.74	68.74	14.07	128.41	128.48
	(OAll)	67.80	(OEt)	127.99	128.15
		66.35		68.80	67.02
		14.22		(CH_2Ph)	(CH_2Ph)
		(OAll, OEt)		133.23	
				117.48	
				66.69	
				(OAll)	

[a] Spectra of compounds **15**, **17**, **18**, and **21** were recorded at 50.3 MHz; the spectrum of compound **20** was recorded at 100.6 MHz.
[b] Signal lies below the signals of the CH_2Ph group.

(15 mL) was stirred for 30 min and then cooled to −20 °C. Then, a cooled (−20 °C) solution of BF_3 etherate (0.05 mL, 0.4 mmol) in CH_2Cl_2 (2 mL) was added dropwise. After stirring for 2 h at −20 °C, Et_3N (1 mL) and CH_2Cl_2 (50 mL) were added, and the mixture was filtered through Celite. The filtrate was washed with brine (50 mL), dried with $MgSO_4$, and concentrated in vacuo. Flash-chromatography (2.5:1 petroleum ether–EtOAc) gave **7** (169 mg, 17%) as amorphous material. Analytical data are in accordance with compound **7** obtained from thioacylation (vide infra).

N-*Benzyloxycarbonyl-4-allyloxy-benzylamine* (**20**).—Reduction of **15** (2.39 g, 15.0 mmol) with $LiAlH_4$ (0.85 g, 22.5 mmol) was carried out as described for **17**. To the crude amine dissolved in 1:1 acetone-water (50 mL) were added Na_2CO_3 (0.79 g, 7.5 mmol) and *N*-(benzyloxycarbonyloxy)-succinimide (3.74 g, 15.0 mmol). After stirring for 2.5 h, the mixture was poured into 1:1 Et_2O–water (200 mL). The separated aqueous solution was washed twice with Et_2O (100 mL). The combined organic solutions were washed with water, dried with $MgSO_4$, and concentrated in vacuo. Purification by flash-chromatography (5:1 petroleum ether–EtOAc) yielded **20** (3.38 g, 76%) as colourless crystals: mp 71 °C; R_f 0.20 (5:1 petroleum ether–EtOAc); EIMS: *m/z* 297 (1) [M^+·], 206 (100) [$C_{11}H_{12}NO_3^+$], 91 (43) [$C_7H_7^+$]. For further analytical data, see Tables 4, 6 and 9.

Table 8
Optical rotations for compounds **1–7**, **12**, **13**, and **22** [a]

Compound	$[\alpha]_D^{23}$	Compound	$[\alpha]_D^{23}$
1	−82.1°	**6**	−93.6°
2	−76.8°	**7**	−70.0°
3	−59.5°	**12**	−110.1° [b]
4	−97.3°	**13**	−154.5°
5	−69.5°	**22**	−61.5°

[a] *c* 1, $CHCl_3$.
[b] Lit. −37.8° (*c* 0.1, $CHCl_3$) [14].

N-*Benzyloxycarbonyl-4-hydroxybenzylamine* (**21**).—To a stirred solution of **20** (2.93 g, 9.9 mmol), formic acid (0.56 mL, 14.9 mmol) and triphenylphosphine (1.55 g, 5.9 mmol) in THF (60 mL) was added palladium acetate (112 mg, 0.5 mmol) under strict exclusion of O_2. After the mixture had been heated under reflux for 4.5 h, followed by work-up as described for **18** and flash-chromatography (2:1 petroleum ether–EtOAc), compound **21** (2.31 g, 91%) was obtained as colourless crystals: mp 90 °C; R_f 0.21 (2:1 petroleum ether–EtOAc); FDMS: *m/z* 257.1 [M^+·]. For further analytical data, see Tables 4, 6 and 9.

N-*Benzyloxycarbonyl-4-(2′,3′,4′-tri*-O-*acetyl*-α-L-*rhamnopyranosyloxy)-benzylamine* (**22**).—A mixture of **21** (515 mg, 2 mmol), NIS (675 mg, 3 mmol) and 4 Å molecular sieves (0.5 g) in CH_2Cl_2 (25 mL) was stirred for 30 min, then cooled to −40 °C, and HOTf (0.07 mL, 0.8 mmol) was added. Subsequently, a cooled (−40 °C) solution of **8** (1123 mg, 3 mmol) in CH_2Cl_2 (7 mL) was added. After stirring for 2 h at −40 °C, Et_3N (2 mL) was added. Work-up was carried out as described for **1** and flash-chromatography (2.7:1 petroleum ether–EtOAc) yielded **22**, 845 mg, 80%) as colourless crystals: mp 110 °C; R_f 0.22 (2:1 petroleum ether–EtOAc). For further analytical data, see Tables 2, 3, 5, 8 and 9.

N-*Methyloxycarbonyl-4-(2′,3′,4′-tri*-O-*acetyl*-α-L-*rhamnopyranosyloxy)-benzylamine* (**2**).—(a) Removal of the Z group from **22**: A solution of **22** (1.06 g, 2.0 mmol) in MeOH (50 mL) was hydrogenated under atmospheric pressure using Pd (black, 100 mg) for 6 h. Filtration through Celite, concentration of the filtrate in vacuo and drying in high vacuum gave the crude amine as an amorphous solid. (b) Acylation of the amine: To a solution of the amine in CH_2Cl_2 (20 mL) was added methyl chloroformate (0.23 mL, 3.0 mmol)

Table 9
Elemental analyses for compounds **1–8**, **12**, **13**, **17**, **18**, **20–22**

Comp.	Formula	Calcd:				Found:			
		%C	%H	%N	%S	%C	%H	%N	%S
1	$C_{20}H_{23}NO_8$	59.26	5.72	3.46	—	59.31	5.76	3.41	—
2	$C_{21}H_{27}NO_{10}$	55.63	6.00	3.09	—	55.60	6.09	2.97	—
3	$C_{22}H_{29}NO_{10}$	56.53	6.25	3.00	—	56.61	6.33	2.83	—
4	$C_{15}H_{21}NO_6S$	52.47	6.16	4.08	9.34	52.56	6.16	4.08	9.32
5	$C_{21}H_{27}NO_9S$	53.72	5.80	2.98	6.83	53.53	5.82	2.81	6.91
6	$C_{16}H_{23}NO_6S$	53.77	6.49	3.92	8.97	53.78	6.58	3.81	8.97
7	$C_{22}H_{29}NO_9S$	54.65	6.05	2.90	6.63	54.61	6.06	2.74	6.63
8	$C_{17}H_{26}O_7S$	54.53	7.00	—	8.56	54.37	7.00	—	8.51
12	$C_{19}H_{22}O_9$	57.87	5.62	—	—	57.79	5.66	—	—
13	$C_{13}H_{16}O_6$	58.20	6.01	—	—	58.06	6.07	—	—
17	$C_{13}H_{17}NO_2S$	62.12	6.82	5.57	12.76	62.04	6.95	5.62	12.69
18	$C_{10}H_{13}NO_2S$	56.85	6.20	6.63	15.18	56.88	6.25	6.57	15.21
20	$C_{18}H_{19}NO_3$	72.71	6.44	4.71	—	72.73	6.34	4.70	—
21	$C_{15}H_{15}NO_3$	70.02	5.88	5.44	—	69.94	5.92	5.30	—
22	$C_{27}H_{31}NO_{10}$	61.24	5.90	2.65	—	61.19	6.03	2.45	—

and DBU (0.45 mL, 3.0 mmol). After stirring for 2 h, the mixture was diluted with CH_2Cl_2 (100 mL), extracted twice with brine (100 mL), dried with $MgSO_4$, and concentrated in vacuo. Flash-chromatography (2:1 petroleum ether–EtOAc) yielded **2** (559 mg, 62%) as amorphous material: R_f 0.14 (2:1 petroleum ether–EtOAc). For further analytical data, see Tables 2, 3, 5 and 7–9.

N-*Ethoxycarbonyl-4-(2′,3′,4′-tri*-O-*acetyl*-α-L-*rhamnopyranosyloxy)-benzylamine* (**3**).—Removal of the Z group from **22** (1.06 g, 2.0 mmol) and subsequent acylation of the crude amine with ethyl chloroformate (0.29 mL, 3.0 mmol) were carried out as described for **2** and gave after flash-chromatography (2.5:1 petroleum ether–EtOAc) **3** (623 mg, 67%) as amorphous material: R_f 0.10 (2.5:1 petroleum ether–EtOAc). For further analytical data, see Tables 2, 3, and 7–9.

N-*Methoxythiocarbonyl-4-(2′,3′,4′-tri*-O-*acetyl*-α-L-*rhamnopyranosyloxy)-benzylamine* (**5**).—Removal of the Z group from **22** (1.91 g, 3.6 mmol) in MeOH (100 mL) with Pd (black, 180 mg) was carried out as described for **2**. A stirred solution of the crude amine in DMF (60 mL) was treated with sodium *S*-carboxymethyl-*O*-methyldithiocarbonate (1.36 g, 7.2 mmol) prepared by neutralisation of *S*-carboxymethyl-*O*-methyldithiocarbonate [21] with 2 M NaOH in acetone followed by recrystallisation from acetone–water. After heating this mixture at 80 °C for 2 h, it was poured into CH_2Cl_2 (300 mL), washed twice with brine (200 mL), dried with $MgSO_4$, and concentrated in vacuo. Flash-chromatography (2.4:1 petroleum ether–EtOAc) yielded **5** (1.04 g, 62%) as amorphous material: R_f 0.17 (2.5:1 petroleum ether–EtOAc); ratio of rotamers A:B 3.8:1 (according to ^{1}H NMR). For further analytical data, see Tables 2, 3, 5 and 7–9.

N-*Methoxythiocarbonyl-4-(*α-L-*rhamnopyranosyloxy)-benzylamine (niazinin)* (**4**).—A solution of **5** (939 mg, 2.0 mmol) in MeOH (20 mL) was treated with 0.75 M NaOMe in MeOH (0.6 mL). The mixture was stirred for 45 min and, subsequently, neutralised with Amberlite IR-120. After filtration, the solvent was evaporated in vacuo. Flash-chromatography (1.5:1 petroleum ether–acetone) gave **4** (640 mg, 93%) as amorphous material: R_f 0.16 (10:1 $CHCl_3$–MeOH); ratio of rotamers A:B 3.5:1 (according to ^{1}H NMR). For further analytical data, see Tables 2, 3, 5 and 7–9.

N-*Ethoxythiocarbonyl-4-(2′,3′,4′-tri*-O-*acetyl*-α-L-*rhamnopyranosyloxy)-benzylamine* (**7**).—Compound **7** was obtained by removal of the Z group from **22** (3.44 g, 6.5 mmol) in MeOH (150 mL) with Pd (black, 300 mg) and subsequent thioacylation of the crude amine with sodium *S*-carboxymethyl-*O*-ethyl dithiocarbonate (1.98 g, 9.8 mmol), prepared by neutralisation of *S*-carboxymethyl-*O*-ethyldithiocarbonate [21] with 2 M NaOH in acetone followed by recrystallisation from acetone-water. The reaction was conducted in DMF (70 mL) within 2.5 h according to the procedure described for **5** and gave after flash-chromatography (3.3:1 petroleum ether–EtOAc) **7** (2.05 g, 65%) as amorphous material: R_f 0.35 (2:1 petroleum ether–EtOAc); ratio of rotamers A:B 3.5:1 (according to

^{1}H NMR); ^{13}C NMR ($CDCl_3$, 50.3 MHz; gated-decoupled): δ 95.40 (d, $^1J_{C,H}$ 173.2 Hz, C-1′). For further analytical data, see Tables 2, 3, 5 and 7–9.

N-*Ethoxythiocarbonyl-4-(α-*L*-rhamnopyranosyl-oxy)-benzylamine (niazimicin)* (**6**).—Removal of the *O*-acetyl groups from **7** (1.32 g, 2.7 mmol) in MeOH (25 mL) was carried out as described for **4**. Purification by flash-chromatography (1:1 petroleum ether–acetone) gave **6** (920 mg, 95%) as amorphous material: R_f 0.21 (10:1 $CHCl_3$–MeOH); ratio of rotamers A:B 3.3:1 (according to ^{1}H NMR). For further analytical data, see Tables 2, 3, 5 and 7–9.

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