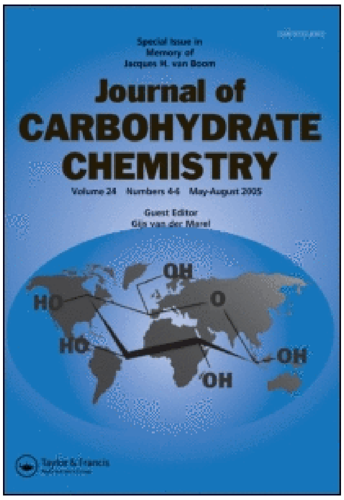

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BRANCHED-CHAIN SUGARS AS PUSH-PULL BUTADIENES

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ABSTRACT

Treatment of methyl 4,6-*O*-benzylidene-2-(dicyanomethylene)-2,3-dideoxy-α-D-*erythro*-hexopyranoside (**2**) with 3-benzyl-2-methylthio-2-thiazolinium iodide (**3**), 4,5-dihydro-3-methyl-2-methylthio-1,3-thiazinium iodide (**5**) and 3-benzyl-4,5-dihydro-2-methylthio-1,3-thiazinium iodide (**6**), respectively, gave methyl 4,6-*O*-benzylidene-3-[(*2Z*)-3-benzyl-2-thiazolidinylidene, 3-methyl-1,3-thiazinan-2-ylidene and 3-benzyl-1,3-thiazinan-2-ylidene]-2-(dicyanomethylene)-2,3-dideoxy-α-D-*erythro*-hexopyranoside (**4**), (**7**), (**8**), respectively.

INTRODUCTION

Recently we reported the synthesis of branched chain sugars[1,2] and C-extended sugars[3] with push-pull functionality. These compounds may serve as precursors for the synthesis of C-nucleoside analogues and for monosaccharides bearing an amino group in the branching.

In earlier studies[4] we found, that arylalkylidenemalononitrile reacted with carbon disulfide in the presence of sodium ethanolate and methyl iodide to yield the 3-aryl-2-

cyano-5,5-bis(methylthio)-2,4-pentadienenitriles. Similarly, cyclohexylidenemalononitrile gave 2,6-bis[bis(alkylthio)methylene]cyclohexylidenemalononitriles.[5] These types of push-pull butadienes could be converted to substituted nicotinonitriles, pyrazolo[3,4-b]pyridines, isoquinolinecarbonitriles and diazaphenalenes, respectively.[6,7]

In order to prepare monosaccharides with an integrated push-pull butadiene structure we carried out reactions between methyl 4,6-*O*-benzylidene-2-(dicyanomethylene)-2,3-dideoxy-α-D-*erythro*-hexopyranoside (**2**) and 3-benzyl-2-methylthio-2-thiazolinium iodide (**3**), prepared from 3-benzyl-thiazolidin-2-thione[8] and excessive methyl iodide, 4,5-dihydro-3-methyl-2-methylthio-1,3-thiazinium iodide (**5**) and 3-benzyl-4,5-dihydro-2-methylthio-1,3-thiazinium iodide (**6**), respectively. Compounds **5** and **6** were prepared from the corresponding thiazinan-2-thiones with an excess of methyl iodide[9] and could also be isolated as completely characterized compounds in nearly quantitative yields.[10]

RESULTS AND DISCUSSION

The Knoevenagel type reaction of uloses is not well known.[11] Treatment of methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*erythro*-hexopyranosid-2-ulose[12] (**1**) under usual conditions with malononitrile in benzene in the presence of acetic acid and ammonium acetate gave only poor yield of expected **2**. However, the reaction was completed using basic alumina[13,14] in dichloromethane at room temperature.

Compound **2** underwent subsequent treatment with 3-benzyl-2-methylthio-2-thiazolinium iodide (**3**) in presence of potassium carbonate in dichloromethane at room temperature to give methyl 4,6-*O*-benzylidene-3-[(2*Z*)-3-benzyl-2-thiazolidinylidene]-2-(dicyanomethylene)-2,3-dideoxy-α-D-*erythro*-hexopyranoside (**4**) as red crystals in 32 % yield. In accordance with the push-pull character of **4**, CN-vibrations appeared within the range of 2183-2159 cm^{-1} (for **2** : 2240 cm^{-1}) and the resonance of C-2' (46.6 ppm) compared with **2** (87.3 ppm) was shifted upfield. Similarly, resonances of C-2 (152.5 ppm), C-3 (95.1 ppm) and C-3' (182.1 ppm) indicated clearly the expected shifts for such push-pull butadienes.[15,16] On the other hand, these NMR data showed concordance with a polymethine structure.

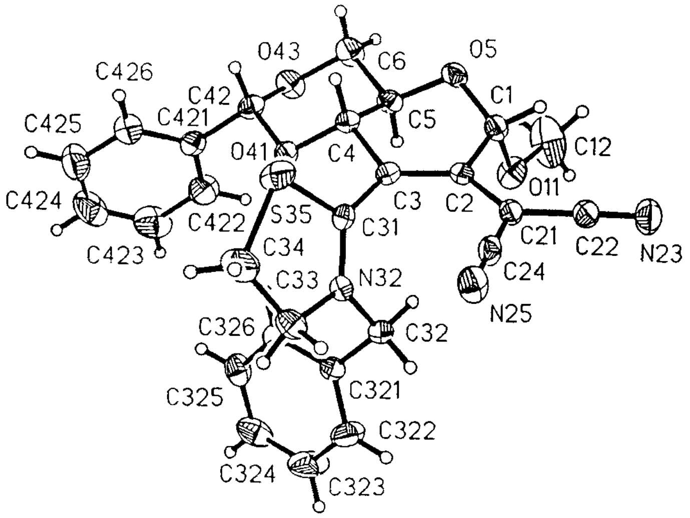
Furthermore, compound **4** was subjected to X-ray analysis at 293 K. The relevant crystallographic data for **4** are given in Table 1. The structure was solved by direct methods in the usual way with the help of the program SHELXS90,[17] and refined with SHELXL93.[18] All atoms (hydrogens introduced at theoretical positions) were refined. An ORTEP drawing of **4** is shown in Figure 1, which gives the numbering scheme of the atoms.

Table 1 Crystallographic data for Methyl 4,6-*O*-Benzylidene-3-[(2*Z*)-3-benzyl-2-thiazolidinylidene]-2-(dicyanomethylene)-2,3-dideoxy-α-D-*erythro*-hexopyranoside (**4**) and Methyl 4,6-*O*-Benzylidene-3-[(2*Z*)-3-benzyl-1,3-thiazinan-2-ylidene]-2-(dicyanomethylene)-2,3-dideoxy-α-D-*erythro*-hexopyranoside (**8**).[a]

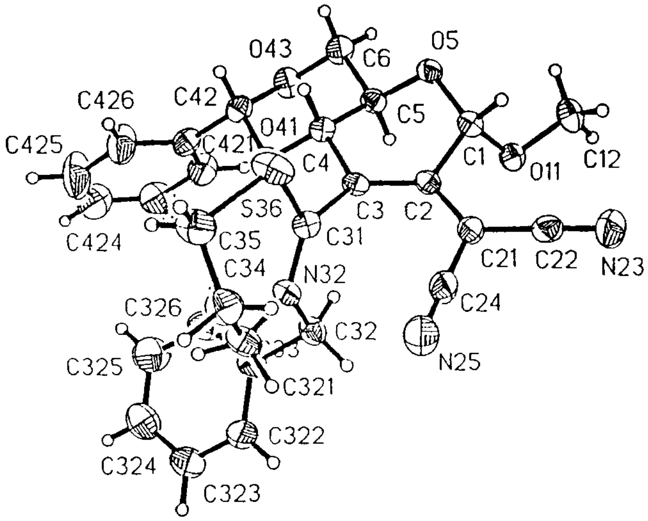
Compound	**4**	**8**
Crystal size (mm)	0.5 x 0.4 x 0.3	0.7 x 0.4 x 0.4
Space group	$P2_12_12_1$	$P2_1$
Cell parameters (Å, degrees)		
a	9.667(2)	10.447(1)
b	9.978(3)	9.448(1)
c	25.616(8)	26.705(3)
β		96.48(1)
Volume (Å^3)	2471(1)	2619(5)
Z	4	4
F(000)	1024	1056
Density D_X (Mg m^{-3})	1.311	1.272
λ (Mo *K*α) (Å)	0.71073	0.71073
μ (cm^{-1})	1.69	1.62
2 Θ range (degrees)	55	50
Symmetry independent reflections	5697	9236
Observed reflections with $I > 2\ \sigma(I)$	3855	6332
Number of refined parameters	343	706
Ratio of parameters to valued reflections	16.6	13.0
R1	0.0519	0.0714
Diffractometer	Hilger & Watts (Y290)	

a Standard deviations in parentheses.

Fractional atomic coordinates, thermal displacement factors, bond lengths, bond angles and torsion angles are given in Tables 1-6 , which have been deposited with the Cambridge Crystallographic Data Centre.

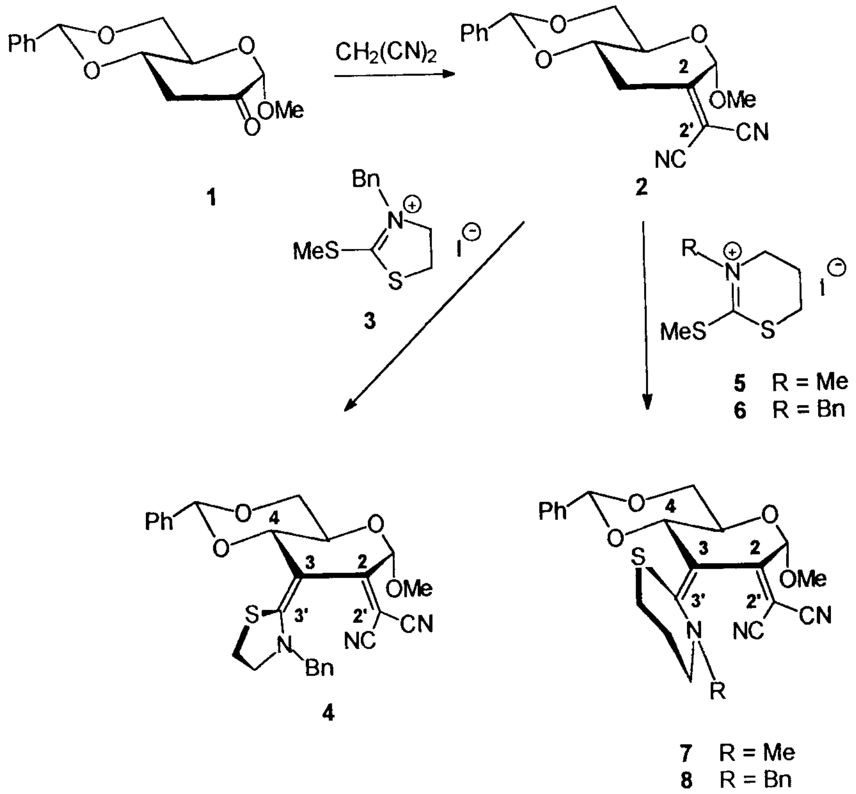


Compound **4**



Compound **8**

Fig. 1. ORTEP drawings of **4** and **8**



The crystallographic data were in agreement with (*Z*)-configuration of **4**. Although the thiazolidine ring was out of plane (Θ (C-4,C-3)-(C-3',S): -49.8°), the C-C distances showed the push-pull butadiene character: the exceptionally reduced distance of C-2-C-3-bond (1.373 Å) and increased bond lengths of C-2'-C-2- and C-3-C-3' (1.421 and 1.438 Å). Similar results were found by Viehe and coworkers for the 2-cyano-5,5-bis(dimethylamino)-2,4-pentadienenitrile.[19]

Likewise, methyl 4,6-*O*-benzylidene-2-(dicyanomethylene)-2,3-dideoxy-3-[(2*Z*)-3-methyl-1,3-thiazinan-2-ylidene]-α-D-*erythro*-hexopyranoside (**7**) and methyl 4,6-*O*-benzylidene-3-[(2*Z*)-3-benzyl-1,3-thiazinan-2-ylidene]-2-(dicyanomethylene)-2,3-dideoxy-α-D-*erythro*-hexopyranoside (**8**), respectively, were synthesised by reaction of **2** with 4,5-dihydro-3-methyl-2-methylthio-1,3-thiazinium iodide (**5**) and 3-benzyl-4,5-dihydro-2-methylthio-1,3-thiazinium iodide (**6**), respectively, in presence of potassium carbonate in dichloromethane at room temperature. The IR and NMR data were in agreement with the proposed structures.

The crystallographic data for **8** are given in Table 1. An ORTEP drawing of **8** is shown in Figure 1. The crystallographic data were in agreement with (*Z*)-configuration of

8. Similarly for the structure **4** (Figure 1), the thiazinane ring was out of plane [Θ (C4,C3)-(C3',S): -70.1°], the C-C distances showed the expected reduced distance of C-2-C-3-bond (1.367 Å) and increased bond lengths of C-2'-C-2- and C-3-C-3' (1.430 and 1.472 Å).

CONCLUSION

In this paper, we have described the syntheses and X-ray crystal structures of branched chain sugars with an integrated push-pull butadiene structure. These compounds will be evaluated in substitution reactions with N-nucleophiles to give pyranosides with anellated heterocylic rings as new types of C-nucleoside analogues (cf. [6,7]).

EXPERIMENTAL

General Procedures. Melting points were determined with a BOËTIUS melting point apparatus and are corrected. Specific rotations were determined with a Gyromat HP (Dr. Kernchen). IR spectra were recorded with a Nicolet 205 FT-IR spectrometer. ^{1}H NMR (300,133 and 250.133 MHz, respectively) and ^{13}C NMR (75.466 MHz and 62.896 MHz, respectively) spectra were obtained on Bruker instruments WM 300 and AC 250, respectively, with $CDCl_3$ as solvent. The ^{13}C NMR spectra were determined by DEPT and/or ^{1}H, ^{13}C COSY experiments. ^{1}H and ^{13}C chemical shifts (δ) are given in ppm relative to that of chloroform. The mass spectra were recorded on an AMB 402/3 spectrometer. For chromatography Merck Silica gel 60 230-400 mesh was used. TLC was performed on silica gel 60 GF_{254} (Merck) with detecting by charring with sulphuric acid.

Methyl 4,6-*O*-Benzylidene-2-(dicyanomethylene)-2,3-dideoxy-α-D-*erythro*-hexopyranoside (2). To a suspension of methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*erythro*-hexopyranosid-2-ulose[12] (**1**, 2.6 g, 10.0 mmol) and alumina (10 g, typ T, Merck 150, activated 3 h at 350 °C) in dry dichloromethane (30 mL) was added dropwise, in the course of 1.5 h with stirring at room temperature, a solution of malononitrile (0.73 g, 11.0 mmol) in dry dichloromethane (20 mL). The mixture was filtered and the residue washed with dichloromethane (2 x 20 mL). The filtrate was washed with water (3 x 20 mL) and dried (sodium sulfate). The solvents were evaporated to leave a solid. Recrystallization of the product from methanol gave white crystals of **2** (2.56 g, 82%): mp 137-139 °C; $[\alpha]^{25}_D$ -6.0° (*c* 1.0, chloroform); IR (Nujol) 2240 (CN), 1615 cm^{-1} (C=C); ^{1}H NMR (Bruker WM 300) δ 2.91 (dd, 1H, $J_{3a,4}$ = 11.9 Hz, H-3a), 3.33 (dd, 1H, $J_{3a,3e}$ = 14 Hz,

$J_{3e,4}$ = 4.6 Hz , H-3e) , 3.53 (s, 3H, MeO), 3.66 (m, 1H, H-4), 3.73 (t, 1H, $J_{5,6a}$ = 10.4 Hz, H-6a), 4.04 (m, 1H, $J_{4,5}$ = 9.5 Hz, H-5), 4.32 (dd, 1H, $J_{5,6e}$ = 4.9 Hz, $J_{6a,6e}$ = 10.4 Hz, H-6e), 5.41 (s, 1H, H-1), 5.54 (s, 1H, CHPh), 7.3-7.5 (m, 5H, Ph); ^{13}C NMR (Bruker WM 300) δ 169.7 (C-2), 136.5, 129.4, 128.4, 126.1 (Ph), 110.2, 109.8 (CN), 101.9 (*C*HPh), 96.6 (C-1), 87.3 (C-2'), 76.8 (C-4), 68.7 (C-6), 64.5 (C-5), 56.1 (MeO), 34.3 (C-3). Mass spectrum: *m/z* = 313 $[M + H]^{+\cdot}$.

Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.10; H, 5.30; N, 8.61.

Methyl 4,6-*O*-Benzylidene-3-[(2*Z*)-3-benzyl-2-thiazolidinylidene]-2-(dicyanomethylene)-2,3-dideoxy-α-D-*erythro*-hexopyranoside (4). A suspension of methyl 4,6-*O*-benzylidene-2-(dicyanomethylene)-2,3-dideoxy-α-D-*erythro*-hexopyranoside (**2**, 939 mg, 3.0 mmol), 3-benzyl-2-methylthio-2-thiazolinium iodide[8] (**3**, 1124 mg, 3.2 mmol) and potassium carbonate (828 mg) in dry dichloromethane (20 mL) was stirred at room temperature while the course of reaction was monitored by TLC (toluene/acetone 5:1). After 48 h the starting material nearly disappeared. The mixture was filtered and the residue washed with dichloromethane (2 x 20 mL). The filtrate was washed with water (20 mL) and dried (sodium sulfate). The solvents were evaporated to leave a syrup. The product was chromatographed on a column of silica gel (100 g) with 6:1 toluene/acetone to give, after recrystallization from methanol, red crystals of **4** (468 mg, 32%): mp 243-247 °C; $[\alpha]^{22}_D$ 10.5° (*c* 1.0, chloroform); IR (Nujol) 2183, 2159 (CN), 1567 cm^{-1} (C=C); ^{1}H NMR (Bruker AC 250) δ 2.82-3.12 (m, 2H, SCH_2), 3.30 (s, 3H, MeO), 3.55-3.76 (m, 2H, $J_{6a,6e}$ = 9.7 Hz, $J_{5,6a}$ = 9.8 Hz, H-6a, NC*H*H), 3.95-4.13 (m, 3H, $J_{4,5}$ = 8.9 Hz, $J_{5,6e}$ = 4.5 Hz, H-5, H-6e, C*H*HPh), 4.32-4.50 (m, 2H, H-4, NC*H*H), 4.70 (d, 1H, $J_{gem.}$ = 14.5 Hz, CH*H*Ph), 4.90 (s, 1H, H-1), 5.50 (s, 1H, C*H*Ph), 7.00-7.35 (m, 10H, 2 x Ph); ^{13}C NMR (Bruker AC 250) δ 182.1 (C-3'), 152.5 (C-2), 137.5, 133.1, 129.3, 129.2, 129.1, 128.5, 128.3, 126.1 (Ph), 120.5, 119.1 (CN), 101.2 (*C*HPh), 98.0 (C-1), 95.1 (C-3), 77.7 (C-4), 68.9 (C-6), 64.5 (C-5), 56.4 (MeO), 55.5 (Ph*C*H_2), 52.8 (NCH_2), 46.6 (C-2'), 28.1 (SCH_2). Mass spectrum: *m/z*(%) = 487 (34, $M^{+\cdot}$) , 91 (100) .

Anal. Calcd for $C_{27}H_{25}N_3O_4S$: C, 66.51; H, 5.17; N, 8.62; S, 6.57. Found: C, 66.50 H, 5.19; N, 8.77; S, 6.55.

Methyl 4,6-*O*-Benzylidene-2-(dicyanomethylene)-2,3-dideoxy-3-[(2Z)-3-methyl-1,3-thiazinan-2-ylidene]-α-D-*erythro*-hexopyranoside (7). Treatment of methyl 4,6-*O*-benzylidene-2-(dicyanomethylene)-2,3-dideoxy-α-D-*erythro*-hexopyranoside (**2**, 939 mg, 3.0 mmol), 4,5-dihydro-3-methyl-2-methylthio-1,3-thiazinium iodide[9] (**3**, 925 mg, 3.2 mmol) and potassium carbonate (828 mg) as described above for the preparation of **4** gave, after recrystallization from methanol, yellow crystals of **7** (255 mg, 20%): mp 202-204 °C ; $[\alpha]^{24}_D$ 602° (*c* 0.3, chloroform); IR (Nujol) 2178, 2151 (CN), 1600, 1571 cm^{-1} (C=C); ^{1}H NMR (Bruker AC 250) δ 2.09-2.29, 2.45-2.62 (2 x m, 2H, $CH_2CH_2CH_2$), 3.03-3.27 (m, 2H, SCH_2), 3.42 (s, 1H, NMe), 3.51 (s, 3H, MeO), 3.52-3.68 (m, 1H, NC*H*H), 3.83 (t, 1H, $J_{6a,6e}$ = 10.1 Hz, $J_{5,6a}$ = 10.1 Hz, H-6a), 4.04-4.20 (m, 2H, H-5, NCH*H*), 4.26 (dd, 1H, $J_{5,6e}$ = 4.6 Hz, H-6e), 4.5 (d, 1H, $J_{4,5}$ = 8.8 Hz, H-4), 5.02 (s, 1H, H-1), 5.58 (s, 1H, C*H*Ph), 7.30-7.45 (m, 5H, Ph); ^{13}C NMR (Bruker AC 250) δ 179.5 (C-3'), 147.7 (C-2), 137.4, 129.0, 128.2, 125.9 (Ph), 122.0 (CN), 101.2 (*C*HPh), 98.5 (C-3), 98.0 (C-1), 78.2 (C-4), 68.9 (C-6), 64.4 (C-5), 56.4 (MeO), 51.4 (NCH_2), 45.7 (NMe), 40.1 (C-2'), 27.6 (SCH_2), 21.2 ($CH_2CH_2CH_2$). Mass spectrum: *m/z* = 425 ($M^{+\cdot}$).

Anal. Calcd for $C_{22}H_{23}N_3O_4S$: C, 62.10; H, 5.45; N, 9.87; S, 7.35. Found: C, 62.19 H; 5.44; N, 10.04; S, 7.53.

Methyl 4,6-*O*-Benzylidene-3-[(2*Z*)-3-benzyl-1,3-thiazinan-2-ylidene]-2-(dicyano-methylene)-2,3-dideoxy-α-D-*erythro*-hexopyranoside (8). Treatment of methyl 4,6-*O*-benzylidene-2-(dicyanomethylene)-2,3-dideoxy-α-D-*erythro*-hexopyranoside (**2**, 939 mg, 3.0 mmol), 3-benzyl-4,5-dihydro-2-methylthio-1,3-thiazinium iodide[9] (**3**, 1.17 g, 3.2 mmol) and potassium carbonate (828 mg) as described above for the preparation of **4** gave, after recrystallization from methanol, yellow crystals of **8** (331 mg, 22%): mp 220-230 °C (decomp.); $[\alpha]^{24}_D$ 222° (*c* 0.5, chloroform); IR (Nujol) 2177, 2147 (CN), 1571, 1560 cm^{-1} (C=C); ^{1}H NMR (Bruker AC 250) δ 1.61-1.80, 2.26-2.44 (2 x m, 2H, $CH_2CH_2CH_2$), 2.96-3.24 (m, 2H, SCH_2), 3.33-3.45 (m, 1H, NC*H*H), 3.50 (s, 3H, MeO), 3.84-3.97 (m, 2H, $J_{6a,6e}$ = 9.8 Hz, $J_{5,6a}$ = 9.9 Hz, H-6a, NCH*H*), 4.12-4.33 (m, 3H, $J_{5,6e}$ = 4.5 Hz, H-5, H-6e, PhC*H*H), 4.69 (d, 1H, $J_{4,5}$ = 8.8 Hz, H-4), 5.05 (s, 1H, H-1), 5.57 (d, 1H, $J_{gem.}$= 14.3 Hz, PhCH*H*), 5.68 (s, 1H, PhC*H*), 7.05-7.50 (m, 10H, 2 x Ph); ^{13}C NMR (Bruker AC 250) δ 181.4 (C-3'), 147.8 (C-2), 137.4, 131.9, 129.3, 129.2, 129.1, 129.0, 128.3, 126.2 (Ph), 122.0 (CN), 101.4 (*C*HPh), 98.0 (C-1), 97.8 (C-3), 78.3 (C-4), 68.8 (C-6), 64.5 (C-5), 60.7 ($PhCH_2$), 56.4 (MeO), 47.5 (NCH_2), 39.5 (C-2'), 28.5 (SCH_2), 21.4 ($CH_2CH_2CH_2$). Mass spectrum: *m/z* (%) = 501 (13, $M^{+\cdot}$), 91 (100).

Anal. Calcd for $C_{28}H_{27}N_3O_4S$: C, 67.05; H, 5.43; N, 8.38; S, 6.39. Found: C, 67.01 H, 5.59; N, 8.28; S, 6.11.

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REFERENCES

1. K. Peseke, H. Feist, and E. Cuny, *Carbohydr. Res.*, **230**, 319 (1992).
2. H. Feist, K. Peseke, and P. Köll, *Carbohydr. Res.*, **247**, 315 (1993).
3. K. Peseke, H.-D. Ambrosi, and M. Michalik, *Carbohydr. Res.*, **194**, 87 (1989).
4. K. Peseke, *Z. Chem.*, **17**, 288 (1977).
5. K. Peseke, M. Michalik, and G. Heide, *Z. Chem.* **27**, 39 (1987).
6. K. Peseke, M. Michalik, and U. Schönhusen, *J. Prakt. Chem.*, **328**, 856 (1986).
7. K. Peseke, G. Heide, H. Feist, and M. Michalik, *J. Prakt. Chem.*, **333**, 119 (1991).
8. C. K. Bradsher, F. C. Brown, and E. F. Sinclair, *J. Am. Chem. Soc.*,**78**, 6189 (1956).
9. W. Hanefeld, *Archiv. Pharm. (Weinheim, Ger.)*, **310**, 409 (1977).
10. H. Harms, Thesis, Marburg 1994.
11. A. Fatiadi, *Synthesis*, 248 (1978).
12. A. Rosenthal and P. Catsoulacos, *Can. J. Chem.* **47**, 2747 (1969).
13. F. Texier-Boullet and A. Foucaud, *Tetrahedron Lett.* **23**, 4927 (1982).
14. J. F. Roudier and A. Foucaud, *Synthesis*, 159 (1984).
15. M. Michalik, K. Peseke, and R. Radeglia, *J. Prakt. Chem.*, **327**, 103 (1985).
16. M. Michalik and K. Peseke, *J. Prakt. Chem.*, **329**, 705 (1987).
17. G. M. Sheldrick, *Acta Crystallogr., Sect. A*, **46**, 467 (1990).
18. G. M. Sheldrick, SHELXL93, Crystal structure refinement, University of Göttingen, Germany 1993.
19. D. Boyvy, Z. Janousek, H. G. Viehe, B. Tinant, and J.-P. Declercq, *Tetrahedron Lett.*, **34**, 1779 (1993).