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Selective synthesis of both isomers of morphine 6-β-D-glucuronide and their analogs

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Abstract—A stereoselective synthesis of both isomers of the pharmaceutically important morphine 6-β-D-glucuronide (M6G) and its analogs was developed. The method is based on the use of $ZnBr_2$ for the key coupling reaction. It was shown that the α/β stereoselectivity of the reaction can be directed and controlled by the amount of $ZnBr_2$. This paper describes the synthesis, analysis and characterization of the α-isomer of M6G, useful as a reference marker for testing purity and stability of the morphine 6-β-D-glucuronide (M6G). © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Morphine and other opioid analogs[1] are used as powerful analgesics. It has been shown[1] that the major pathway for detoxification of morphine and analogs in the human body is conjugation with D-glucuronic acid in the liver to produce several glucuronides: morphine 3-β-D-glucuronide (M3G), morphine 6-β-D-glucuronide (M6G) and morphine 3,6-β-D-diglucuronide (M3,6-diG) (Fig. 1).

It has been demonstrated,[2,3] that much of the analgesic effect is due not to morphine itself but rather to one of its main metabolites, morphine 6-β-D-glucuronide. Furthermore, is has been shown that morphine's other main metabolite,

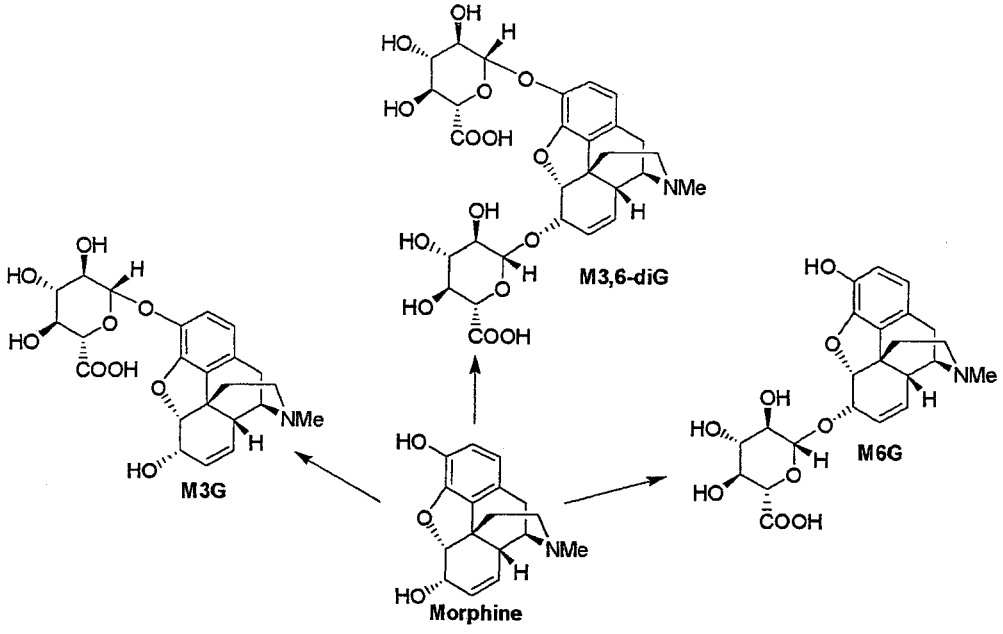

Figure 1.

Keywords: alkaloids; α/β stereocontrol; glycosidation; orthoesters.

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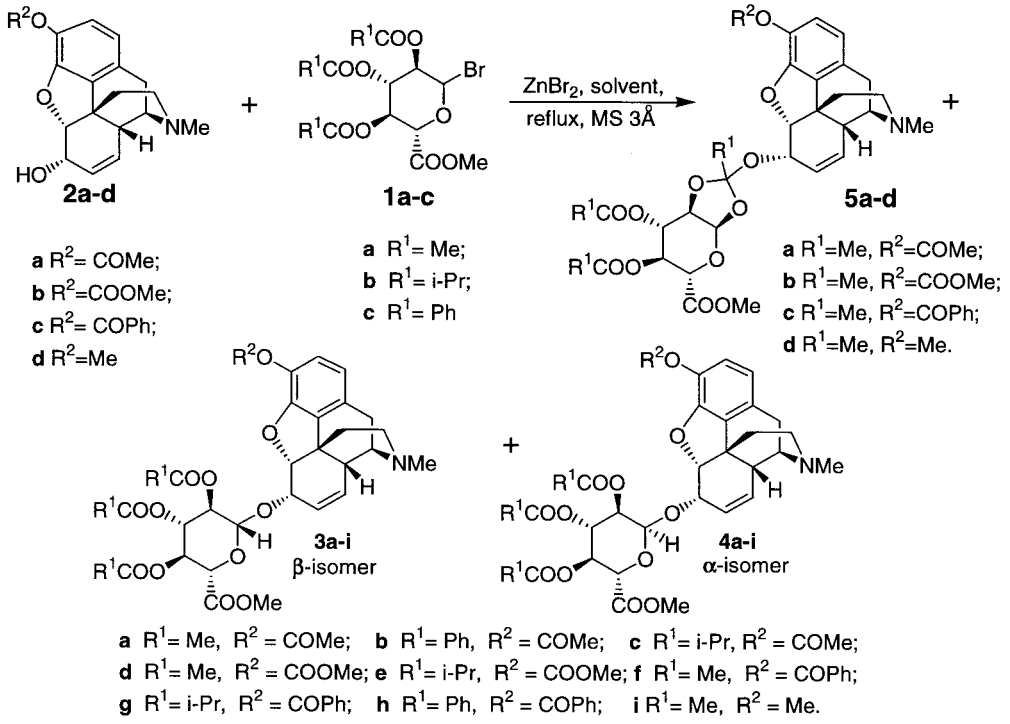


Scheme 1.

M3G, antagonizes the analgesic effect of morphine. This potential pharmaceutical importance of M6G as a powerful analgesic and replacement to morphine prompted several researchers to explore ways for its selective synthesis.

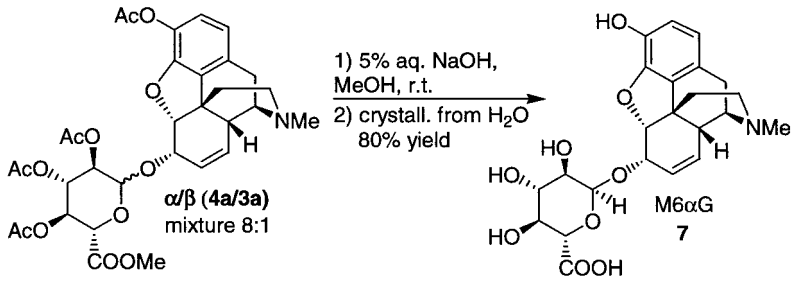
All literature-reported methods 4,5,6,7a,b,8,16 of M6G preparation are highly β stereoselective, but in several publications[7a,16] the presence of the α-isomer was noticed after glycosylation. However, this α-isomer was never isolated and characterized.[11]

In the present paper we report a high-yielding and stereoselective synthesis that enables us at will to obtain either morphine 6-β-D-glucuronide **6** (M6G) or morphine 6-α-D-glucuronide **7** (M6αG).

Table 1. The α/β selectivity (reaction conditions: CH_2Cl_2, reflux 48–72 h, MS 4 Å)

Glucuronate ester, **1a–c**	3-*O*-protected morphine, **2a–d**	$ZnBr_2$, equiv.	Ratio, α/β[b]
1a	**2a**	0.7	1:7[a]
1a	**2a**	0.8	1:7[a]
1a	**2a**	0.9	1:5[a]
1a	**2a**	1.0	1:2[a]
1a	**2a**	1.1	1:1.5[a]
1a	**2a**	1.2	2:1[a]
1a	**2a**	1.5	4:1[a]
1a	**2a**	1.7	6:1[a]
1a	**2a**	2.0	8:1[a]
1a	**2a**	2.5	~8:1[a]
1a	**2b**	1.0	1:8
1a	**2b**	1.4	1:5
1a	**2c**	1.0	1:6
1a	**2d**	2.0	5:95
1a	**2d**	1.0	1:99
1b	**2a**	1.0	1:2.5
1b	**2b**	1.0	1:9
1b	**2b**	1.5	1:6
1b	**2c**	0.8	1:18
1b	**2c**	1.0	1:7
1b	**2c**	1.5	1:4
1c	**2a**	1.0	1:3
1c	**2c**	1.0	1:10
1c	**2c**	0.8	1:25

[a] Ratio was determined by ^{1}H NMR spectroscopy.
[b] Ratio was determined by HPLC.



Scheme 2.

2. Results and discussion

For tentative experiments methyl 2,3,4-tri-*O*-acetyl-D-glucopyranosyluronate bromide (**1a**) and 3-*O*-acetylmorphine (**2a**) were prepared by known protocols[15] and coupling was tested under various reaction conditions and with different catalysts.[9,10] It was found that with $ZnBr_2$ glycosylation proceeded to completion with minimal undesired products. Interestingly, use of $MgBr_2$[9] instead of $ZnBr_2$ under similar reaction conditions led to formation of orthoester **5a** (40% isolated yield) without any traces of the glycosides **3a** or **4a**. Based on these initial results, future investigation concentrated around $ZnBr_2$ as catalyst (Scheme 1).

It was found, that the stereochemical outcome of glycosylation was strongly influenced by the amount of $ZnBr_2$: thus, use of two and more equivalents of $ZnBr_2$ in the reaction between 3-*O*-acetylmorphine **2a** and glucopyranosyl bromide **1a** afforded a mixture of isomers with an α/β ratio of 8:1, while use of 0.8 equiv. of $ZnBr_2$ in this reaction led to the opposite ratio of isomers, α/β=1:8. As can be seen in Table 1, the dependency of stereoselectivity of glycosylation on the amount of $ZnBr_2$ was observed in all cases for various acyl-protecting groups both on morphine and glucopyranosyl bromide.

In the present work the chemical and physical properties of M6αG were studied and a significant difference in the solubility between the two isomers was detected. Thus, M6αG was poorly soluble in cold water and only slightly soluble in warm water. Therefore, when a mixture of isomers **4a/3a** (α/β ratio 8:1) was hydrolyzed and cooled, only pure M6αG **7** crystallized from the aqueous solution (Scheme 2). M6αG and M6G were analyzed by HPLC and under conditions described in our previous paper[12] it appeared as two baseline-separated peaks. Thus, the developed HPLC method permitted the detection of trace amounts of M6αG in the pharmaceutical grade M6G.

In a previous publication[12] we also reported a detailed ^{1}H NMR spectroscopic investigation of M6αG that has been conducted in order to ascertain the chemical identity and anomeric configuration of the glycosidic linkage. All signals were fully assigned on the basis of two-dimensional COSY spectra and by comparison with spectra of reference compounds obtained under identical conditions.

In our synthetic study, we also investigated the dependence of stereoselectivity on different protecting groups on morphine as well as on the glucopyranosyl bromide. For morphine protecting groups, it was found that the use of methoxycarbonyl[17] **2b** as protecting group afforded best selectivity in the acetyl **2a**, benzoyl **2c**, and methoxycarbonyl series (see Table 1). For glucopyranosyl bromide protecting groups the best results were obtained with the benzoyl protecting group[15] **1b**. However, changes in protecting groups on the sugar moiety did not result in a significant improvement in the α/β stereoselectivity (Table 1). Interestingly, very high stereoselectivity and good yield (85%) were observed with codeine (Table 1), even when excess of $ZnBr_2$ was used.

Based on results described above, we speculated that two different pathways take place in this reaction[13a]: (1) a catalytic amount of $ZnBr_2$ initially forms the dioxolanylium cation[13a] that may be stereoselectively opened to the 1,2-*trans*-product[13b] **3a–i** and/or may form the orthoester[13b] **5a–d**, which may then transform into desired β-isomer **3a–i** after addition of a catalytic amount of $ZnBr_2$;[13f,g] (2) the presence of excess of $ZnBr_2$ (Br^- source) together with

Table 2. The influence of the solvent on the orthoester's formation and the stereoselectivity

Glucuronate ester, **1a–c**	3-*O*-protected morphine, **2a–d**	$ZnBr_2$, equiv.	Solvent	Ratio
1a	**2a**	1.7	CH_2Cl_2/EtOAc	**4a**(α)/**3a**(β)=1:2[a]
1a	**2a**	1.7	CH_3CN	**4a**(α)/**3a**(β)=1:1[a,b]
1a	**2a**	1.0	CH_2Cl_2/EtOAc	**4a**(α)/**3a**(β)=1:4[a,b]
1a	**2b**	1.0	$CHCl_3$	**4d**(α)/**3d**(β)=1:8[b]
1a	**2b**	1.0	$CHCl_3$/EtOAc	**5b**(ortho)/**3d**(β)=2:1[a,b]
1a	**2b**	1.0	THF	**5b**(ortho) only[a,b]
1a	**2c**	1.0	CH_2Cl_2/EtOAc	**5c**(ortho)/**3f**(β)=1:1[a,b]

[a] Ratio was determined by ^{1}H NMR spectroscopy.
[b] Ratio was determined by HPLC.

Table 3. The optimized glycosidation procedure ($ZnBr_2$: 0.6 equiv. then 0.3 equiv.)

Glucuronate ester, **1a–c**	3-*O*-protected morphines, **2a–d**	Solvent	Ratio[a,b]	Yield[c]
1a	**2a**	CH_2Cl_2	only β	80%
1a	**2a**	$CHCl_3$	only β	82%
1b	**2a**	$CHCl_3$	only β	76%
1a	**2b**	$CHCl_3$	only β	85%
1b	**2b**	$CHCl_3$	only β	75%
1a	**2c**	$CHCl_3$	only β	72%
1b	**2c**	$CHCl_3$	only β	74%

[a] Ratio was determined by ^1H NMR spectroscopy.
[b] Ratio was determined by HPLC.
[c] Isolated yield.

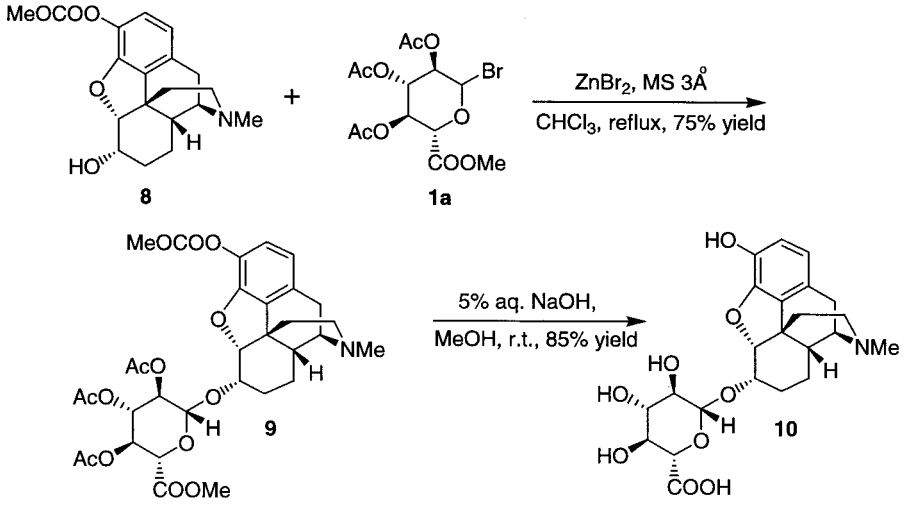
3-*O*-protected morphine (amino function) may result in the formation of the highly reactive β-glucopyranosyl bromide (in situ anomerization)[13d,e] that reacts much faster than α-glucopyranosyl bromide to give α-isomer **4a–i** via ionic intermediates.[13c] This assumption would explain well the α-isomer/β-isomer/orthoester selectivity in the glycosylation.

To examine this proposition, solvents like THF or ethyl acetate, which complex with $ZnBr_2$ were added to the reaction mixture. In the case of 3-*O*-(methoxycarbonyl)morphine (**2b**), addition of ethyl acetate led to the partial formation of 1,2-orthoester **5b** with a final **5b/3d** ratio of 2:1 without detectable traces of the α-isomer **4d**. Use of THF as reaction solvent led only to formation of orthoester **5b** in 87% yield. This product was isolated and characterized. For 3-*O*-benzoyl morphine (**2c**), addition of ethyl acetate afforded a 1:1 **5c/3f** ratio without the presence of α-isomer **4f** (see Scheme 1 and Table 2). For 3-*O*-acetylmorphine (**2a**) we could not detect the presence of orthoester **5a** in the reaction mixture because no separation between the orthoester **5a** and the β-isomer **3a** was obtained by HPLC or other analytical methods, except NMR spectroscopy. However, the orthoesters **5a** and **5d** were prepared by another procedure (see Experimental part).

These results indicated that according to the first reaction path some minimal amount of $ZnBr_2$ is needed for formation of 1,2-orthoester **5a–d** and that a further amount of $ZnBr_2$ transfers it to the desired β-isomer. To check this, we carried out the following experiments: coupling between 3-*O*-methoxycarbonyl morphine (**2b**) and glucopyranosyl bromide **1a** was performed in chloroform gradually increasing the amount of $ZnBr_2$. It was found that after addition of 0.6 equiv. of $ZnBr_2$ the main reaction product was the orthoester **5b**. Addition of another 0.3 equiv. of $ZnBr_2$ at this stage, cleanly transferred all orthoester into the desired β-isomer **3d** without traces of α-isomer. Using this procedure, we prepared other derivatives (Table 3) with different protecting groups on morphine and glucopyranosyl bromide. In all cases very high stereoselectivity (>99% β-isomer by HPLC) was obtained.

We adopted the above procedure also for the preparation of the protected dihydromorphine 6-β-D-glucuronide (dihydroM6G) **9** by reaction between 3-*O*-(methoxycarbonyl)-dihydromorphine (**8**) and **1a** (Scheme 3). The desired β-isomer **9** was isolated in 75% yield.

After alkaline hydrolysis of **3a–h** by a modification of a published procedure[7] followed by crystallization, pure M6G **6** (or in the case of **9**, the dihydroM6G **10**) was obtained in good yields. The structures of M6G and dihydroM6G were confirmed by NMR and IR measurements, which showed that the spectroscopic data were consistent with the literature.[4–6,14]



Scheme 3.

Table 4. Physical data of the compounds **3a–i**, **5a–d** and **9**

Product[a,e,f]	$[\alpha]_D$ (*c* 1, $CHCl_3$)[c]	Melting point[b] (°C)	MS (CI) (*m/z*) ($M^+ + 1$)
3a[d]	−131.6	178–179	645
3b	−84.6	115–116	831
3c	−112.0	188–189	729
3d	−138.9	176–177	660
3e	−108.8	184–185	745
3f	−25.6	201–202	706
3g	−114.4	144–147	791
3h	−84.2	158–163	893
3i[g]	−132.5	115–116	617
9	−122.2	158–159	662
5a	−96.3	99–100	645
5b	−105.3	99–100	660
5c	−34.3	103–104	706
5d	−97.4	86–88	617

[a] All compounds appeared as white to light yellow solids.
[b] Melting points are uncorrected.
[c] Recorded at 20°C.
[d] Lit.[4b] ($C_{32}H_{37}O_{13}N\times1/2H_2O$) $[\alpha]_D^{26}$ −140 (*c* 0.5, $CHCl_3$), mp 186–188°C.
[e] Satisfactory microanalyses obtained: C ±0.39; H ±0.30; N ±0.23.
[f] Characteristic IR data were obtained for all compounds: FT-IR (KBr) 2900, 1630–1780, 1450 cm^{-1}.
[g] Lit.[4b] ($C_{32}H_{37}O_{13}N\times2H_2O$) $[\alpha]_D^{26}$ −140 (*c* 0.5, $CHCl_3$), mp 112–114°C.

In conclusion, a stereoselective synthesis of both isomers of M6G was developed. The method is based on use of $ZnBr_2$ and the selectivity of this reaction may be controlled by amount of $ZnBr_2$ added. The process provided both high stereoselectivity and good yields. The synthesis avoids expensive reagents, cleanly produces the desired products avoiding tedious purification and can be easily scaled up for M6G preparation in pharmaceutically sufficient quantities without losses in stereoselectivity. Synthesis and analysis of α-M6G makes it possible to verify its content in the pharmaceutical grade M6G.

3. Experimental

CH_2Cl_2 and $CHCl_3$ were distilled over CaH_2 and stored over 4 Å molecular sieves. Anhydrous Et_2O from Bio-Lab Ltd. (Jerusalem, Israel) was used without additional purification. All 3-*O*-protected morphines were crystallized and vacuum dried overnight at 40°C. Silica gel 60 (Merck, 230–400 mesh) was used for column chromatography. Silica gel 60 F_{254} plates (Merck) were used for TLC. All NMR spectra were recorded on a Bruker AM-400 spectrometer. Melting points were determined in open capillary tubes with Electrothermal IA 9300 Digital melting point apparatus. Chemical-ionization (CI) mass spectrometry was performed with a Varian Matt-71. Elemental analyses were performed by the Microanalytical Laboratory of the Institute of Chemistry (The Hebrew University, Jerusalem). HPLC was carried out on a Merck–Hitashi Lachrom Series 7000 apparatus with 284 nm UV detector. HPLC analyses were performed at 25°C and a flow rate of 1 mL min^{-1} on the column LiChrospher 100 RP-18 by using the following system: A: 0.1% aq. solution of sodium heptanesulfonate (1000 mL), adjusted to pH5.5 with HOAc (2 mL) and 25% aq. NH_3 (2.4 mL): B: MeOH. Gradient: 0 min, 90% A, 10% B; 5 min, 90% A, 10% B; 10 min, 50% A. 50% B; 15 min, 50% A, 50% B; 25 min, 10% A, 90% B; 45 min, 10% A, 90% B. Optical rotations were measured at 589 nm with a JACSO DIP-370 polarimeter.

3.1. 3-*O*-Methoxycarbonyl morphine 2b and dihydromorphine 8: typical procedure

To the solution of pre-dried dihydromorphine (2.88 g, 10 mmol) in water (60 mL) and MeOH (5 mL) the solution of $NaHCO_3$ (4.20 g, 50 mmol) in water (42 mL) was added in one portion. The resulting suspension was stirred for 1 h at ambient temperature and then cooled to 0°C. A solution of methyl chloroformate (1.89 g, 20 mmol) in CH_2Cl_2 (20 mL) was added during 30 min and after complete dissolution of precipitate, the two-phase mixture was heated to room temperature and stirred for an additional 1 h. Then the layers were separated and the aqueous layer was washed with CH_2Cl_2 (2×30 mL). The combined organics were re-extracted twice with a solution of citric acid (8.00 g) in water (100 mL). The aqueous phase was washed with CH_2Cl_2, then basified with solid $NaHCO_3$ to pH9 and extracted with CH_2Cl_2 (2×50 mL). The organic phase was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated in vacuo, affording the title compound **8** (3.42 g, quantitative yield) as a white powder. FT-IR (Nujol) ν_{max} cm^{-1} 3520, 2930, 1750, 1452; ^1H NMR ($CDCl_3$) δ 6.79, 6.62 (2d, 2H, *J*=8.4 Hz, H_{arom}), 4.57 (d, 1H, *J*=5.1 Hz), 4.11 (m, 1H), 3.88 (s, 3H, C-3 OCO_2*Me*), 3.48 (m, 1H), 3.08 (m, 1H), 2.99 (d, 1H, *J*=18.7 Hz), 2.51 (dd, 1H, *J*=4.4, 12.1 Hz), 2.38 (m, 1H), 2.37 (s, 3H, N*Me*), 2.18 (m, 2H), 1.81 (m, 2H), 1.63 (dd, 1H, *J*=3.1, 10.2 Hz), 1.38 (m, 1H), 1.25 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 152.8, 133.6, 131.9, 130.2, 128.4, 92.2, 66.6, 59.7, 56.6, 46.9, 42.8, 42.5, 40.0, 36.6, 28.2, 20.5, 18.2; MS (CI): *m/z* 346 ($M^+ + 1$); Anal. calcd for $C_{19}H_{23}NO_5$ (345.39): C 66.07; H 6.71; N 4.06. Found: C 66.02; H 6.62; N 4.05.

3.1.1. 3-*O*-(Methoxycarbonyl)morphine (2b). Compound **2b** (a white solid) was prepared as described above from morphine hydrochloride trihydrate in quantitative yield. $[\alpha]_D^{20}$ −193.0 (*c* 1, $CHCl_3$), mp 118–119°C (dec.) [Lit.[17] 116–120°C (dec.)]; FT-IR (Nujol) ν_{max} cm^{-1} 3500, 2900, 1750, 1448; ^1H NMR ($CDCl_3$) δ 6.84, 6.62 (2d, 2H,

Table 5. ^{1}H NMR data for compounds **3a–i** and **9**

Product	^{1}H NMR ($CDCl_3$), δ, J (Hz) H-1′ ($J_{1',2'}$)	H-2′ ($J_{1',2'}$, $J_{2',3'}$)	H-5′ ($J_{4',5'}$)	H-6 m	Others
3a	4.88 d (7.2)	5.07 dd (7.2, 7.7)	4.09 d (8.8)	4.28	6.69, 6.52 (2d, 2H, J=8.0, H_{arom}), 5.65 (d, 1H, J=9.5, 8-H), 5.25 (m, 3H, 3′-H, 4′-H, 7-H), 4.86 (d, 1H, J=6.5), 3.72 (s, 3H, CO_2Me), 3.33 (m, 1H), 3.02 (d, 1H, J=18.9), 2.61 (m, 1H), 2.56 (m, 1H), 2.40 (s, 3H, NMe), 2.29–2.39 (m, 2H), 2.28 (s, 3H, C-3 Ac), 2.08 (s, 3H, Ac), 2.03 (s, 6H, 2 Ac), 1.93–2.03 (m, 1H), 1.90 (m, 1H)
3b	4.96 d (6.4)	5.57 dd (6.4, 6.2)	4.46 d (8.1)	4.49	7.97, 7.91, 7.87 (3d, 6H, J=7.7, 3 COPh), 7.27–7.52 (m, 9H, 3 COPh), 6.64, 6.50 (2d, 2H, J=8.1, H_{arom}), 5.82 (m, 2H, 3′-H, 4′-H), 5.72 (d, 1H, J=10.0, 8-H), 5.31 (d, 1H, J=10.0, 7-H), 5.28 (d, 1H, J=5.8), 3.63 (s, 3H, CO_2Me), 3.36 (m, 1H), 3.03 (d, 1H, J=18.8), 2.69 (br s, 1H), 2.57 (m, 1H), 2.42 (s, 3H, NMe), 2.28–2.43 (m, 2H), 2.10 (s, 3H, C-3 Ac), 2.02 (m, 1H), 1.87 (m, 1H)
3c	4.91 d (7.6)	5.10 dd (7.6, 8.0)	4.10 d (9.2)	4.28	6.68, 6.50 (2d, 2H, J=8.0, H_{arom}), 5.63 (d, 1H, J=10.0, 8-H), 5.28 (m, 3H, 3′-H, 4′-H, 7-H), 4.87 (d, 1H, J=5.6), 3.69 (s, 3H, CO_2Me), 3.32 (m, 1H), 3.02 (d, 1H, J=18.8), 2.42–2.60 (m, 5H), 2.41 (s, 3H, NMe), 2.27–2.40 (m, 2H), 2.26 (s, 3H, C-3 Ac), 2.01 (m, 1H), 1.88 (m, 1H), 1.05–1.13 (m, 18H, 3 *i*-PrCO)
3d	4.91 d (7.7)	5.04 dd (7.7, 8.5)	4.08 d (9.5)	4.33	6.77, 6.52 (2d, 2H, J=8.2 Hz, H_{arom}), 5.64 (d, 1H, J=9.7 Hz, 8-H), 5.22–5.29 (m, 3H, 3′-H, 4′-H, 7-H), 4.93 (d, 1H, J=5.8 Hz), 3.87 (s, 3H, C-3 OCO_2CH_3), 3.72 (s, 3H, CO_2CH_3), 3.33 (m, 1H), 3.03 (d, 1H, J=19.7 Hz), 2.62 (s, 1H), 2.56 (m, 1H), 2.40 (s, 3H, NCH_3), 2.20–2.38 (m, 2H), 2.10 (s, 3H, Ac), 2.01–2.10 (m, 1H), 2.01 (s, 6H, 2 Ac), 1.89 (d, 1H, J=9.7 Hz)
3e	4.92 d (7.2)	5.11 dd (7.2, 7.5)	4.10 d (9.3)	4.27	6.69, 6.51 (2d, 2H, J=7.6 Hz, H_{arom}), 5.64 (d, 1H, J=9.5 Hz, 8-H), 5.27 (m, 3H, 3′-H, 4′-H, 7-H), 4.87 (d, 1H, J=6.3 Hz), 3.80 (s, 3H, C-3 OCO_2CH_3), 3.70 (s, 3H, CO_2CH_3), 3.32 (m, 1H), 3.02 (d, 1H, J=18.8 Hz), 2.45–2.61 (m, 5H), 2.44 (s, 3H, NCH_3), 2.29–2.43 (m, 2H), 2.26 (m, 1H), 1.99 (m, 1H), 1.87 (d, 1H), 1.04–1.16 (m, 18H, 3×CO*i*-Pr)
3f	4.87 d (7.1)	4.97 dd (7.1, 7.5)	4.02 d (8.7)	4.30	8.17 (d, 2H, J=7.6, C-3 Bz), 7.58 (t, 1H, J=7.6, C-3 Bz), 7.48 (t, 2H, J=7.6, C-3 Bz), 6.83, 6.57 (2d, 2H, J=8.5, H_{arom}), 5.72, 5.33 (2d, 2H, J=9.8, 8-H, 7-H), 5.19 (m, 2H, 3′-H, 4′-H), 4.92 (d, 1H, J=5.7), 3.70 (s, 3H, CO_2Me), 3.36 (m, 1H), 3.06 (d, 1H, J=18.9), 2.64 (br s, 1H), 2.60 (m, 1H), 2.42 (s 3H, NMe), 2.30–2.43 (m, 1H), 1.99 (m, 1H), 1.97 (s, 3H, Ac), 1.95 (s, 6H, 2 Ac), 1.87 (d, 1H)
3g	4.95 d (7.5)	5.01 dd (7.5, 8.1)	4.05 d (9.3)	4.31	8.17 (d, 2H, J=7.6, C-3 Bz), 7.58 (t, 1H, J=7.1, C-3 Bz), 7.48 (td, 2H, J=7.6, 7.1, C-3 Bz), 6.84, 6.56 (2d, 2H, J=8.2, H_{arom}), 5.67 (d, 1H, J=9.1, 8-H), 5.25 (m, 3H, 3′-H, 4′-H, 7-H), 4.92 (d, 1H, J=5.5), 3.68 (s, 3H, CO_2Me), 3.34 (m, 1H), 3.06 (d, 1H, J=18.8), 2.63 (br s, 1H), 2.56 (m, 1H), 2.26–2.53 (m, 7H), 2.20 (m, 1H), 2.02 (m, 1H), 1.93 (d, 1H, J=10.8), 1.00–1.07 (m, 12H, 2 *i*-PrCO), 0.84, 0.80 (2d, 6H, J=6.7 Hz, *i*-PrCO)
3h	5.00 d (6.2)	5.44 dd (6.2, 6.0)	4.37 d (8.0)	4.49	8.10 (d, 2H, J=7.7), 7.86 (d, 4H, J=7.7), 7.75 (d, 2H, J=7.7), 7.19–7.51 (m, 12H), 6.81, 6.56 (2d, 2H, J=8.5, H_{arom}), 5.77 (m, 3H, 3′-H, 4′-H, 8-H), 5.35 (d, 1H, J=10.0, 7-H), 5.31 (d, 1H, J=6.0), 3.57 (s, 3H, CO_2Me), 3.36 (m, 1H), 3.06 (d, 1H, J=18.8), 2.68 (br s, 1H), 2.56 (dd, 1H, J=12.0, 3.9), 2.42 (s, 3H, NMe), 2.30–2.41 (m, 2H), 2.02 (td, 1H, J=12.0, 4.6), 1.91 (m, 1H)
3I	4.96 d (7.5)	5.07 dd (7.5, 8.8)	4.09 d (9.5)	4.35	6.60, 6.48 (d, 1H, J=8.0, H_{arom}), 5.65 (d, 1H, J=9.9, 8-H), 5.30 (m, 2H, 3′-H, 7-H), 5.23 (dd, 1H, J=9.5, 8.8, 4′-H), 4.90 (d, 1H, J=5.9), 3.75 (s, 3H, C-3 OMe), 3.73 (s, 3H, CO_2Me), 3.31 (q, 1H, J=5.9, 3.1), 3.00 (d, 1H, J=18.8), 2.61 (br s, 1H), 2.53 (dd, 1H), 2.41 (s, 3H, NMe), 2.38 (td, 3H), 2.26 (dd, 1H), 2.13 (s, 6H, 2 Ac), 2.02 (m, 1H), 2.00 (s, 3H, Ac), 1.85 (d, 1H, J=12.3), 1.74 (m, 1H)
9	4.82 d (7.1)	4.77 dd (7.1, 8.0)	4.04 d (9.3)	4.00	6.83, 6.60 (2d, 2H, J=8.0, H_{arom}), 5.17 (m, 2H, 3′-H, 4′-H), 4.66 (d, 1H, J=4.2), 3.84 (s, 3H, C-3 OCO_2Me), 3.70 (s, 3H, CO_2Me), 3.07 (m, 1H), 2.95 (d, 1H, J=18.8), 2.49 (dd, 1H, J=12.2, 4.4), 2.37 (m, 1H), 2.35 (s, 3H, NMe), 2.19 (m, 2H), 2.05 (s, 3H, Ac), 1.97 (s, 3H, Ac), 1.95 (s, 3H, Ac), 1.88 (td, 1H), 1.70 (d, 1H, J=11.7), 1.55 (m, 1H), 1.44 (m, 2H), 1.24 (m, 1H), 0.95 (m, 1H)

J=8.2 Hz, H_{arom}), 5.78, 5.24 (2d, 2H, J=10.0 Hz, 8-H, 7-H), 4.98 (d, 1H, J=6.4 Hz), 4.18 (m, 1H), 3.90 (s, 3H, C-3 OCO_2*Me*), 3.62 (m, 1H), 3.03 (d, 1H, J=18.9 Hz), 2.66 (m, 1H), 2.55 (dd, 1H, J=11.6, 3.8 Hz), 2.40 (s, 3H, N*Me*), 2.34 (m, 2H), 2.12 (m, 2H), 1.90 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 153.5, 144.2, 134.0, 133.0, 132.5, 132.3, 127.7, 92.4, 65.8, 58.8, 55.6, 46.3, 42.9, 42.6, 40.3, 35.1, 20.7; MS (CI): *m*/*z* 344 (M^++1); Anal. calcd for $C_{19}H_{21}NO_5$ (343.37): C 66.46; H 6.16; N 4.08. Found: C 66.82; H 6.52; N 3.87.

3.1.2. Morphine 6-α-D-glucuronide (7). A suspension of the vacuum pre-dried 3-*O*-acetylmorphine (**2a**) (3.27 g, 10 mmol), **1a** (5.95 g, 15 mmol) and molecular sieves 4Å (9.00 g) in dry CH_2Cl_2 (70 mL) was stirred for 30 min at room temperature. Then $ZnBr_2$ (25 mmol) was added and the resulting suspension was refluxed for 48 h with stirring (TLC monitoring). More CH_2Cl_2 (80 mL) was added and the suspension was filtered through Celite and stirred for 20 min with saturated aqueous solution of $NaHCO_3$ (80 mL). The aqueous phase was separated, washed with CH_2Cl_2, the organics were combined, washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated. The residue (9.10 g) was passed through a short silica gel column (CH_2Cl_2/MeOH, 97:3) to give 6.20 g of the crude product as slight yellow solid (mixture of α and β isomers in ratio of 8:1, respectively). The mixture was dissolved in 50 mL of MeOH, 5% aqueous solution of NaOH (35 mL) was added dropwise and the resulting slight yellow solution was stirred overnight at room temperature. Then the mixture was acidified to pH5 with acetic acid, cooled to 0°C and diluted with EtOH (150 mL). The milky suspension was stirred for 4 h at 0°C, filtered and the white powder was washed with EtOH, recrystallized from hot water and

Table 6. ^{13}C NMR data for compounds **3a–i** and **9**

Product	^{13}C NMR (400 MHz, $CDCl_3$), δ		
	C-1′	C-5	Others
3a	118.9	99.0	169.9, 169.1, 168.5, 167.2, 149.9, 132.2, 131.5, 131.3, 130.1, 128.7, 121.7, 89.3, 73.2, 72.6, 71.9, 71.1, 69.2, 58.6, 52.7, 46.2, 43.4, 42.9, 40.9, 35.6, 20.8, 20.5, 20.4, 20.3
3b	118.9	98.1	168.6, 167.8, 165.4, 165.0, 164.8, 151.2, 133.2, 133.05, 133.0, 131.9,131.6, 131.0, 130.3, 129.7, 129.6, 129.4, 128.9, 128.6, 128.2, 128.1, 121.8, 89.4, 72.6, 72.4, 71.7, 71.6, 69.2, 58.7, 58.6, 46.2, 43.4, 42.8, 40.8, 23.3, 20.9, 20.3
3c	118.9	98.9	175.8, 175.1, 175.0, 168.6, 167.3, 150.0, 132.2, 131.4, 130.2, 128.7, 121.6, 89.6, 73.0, 72.7, 71.5, 70.8, 69.0, 58.6, 52.6, 46.1, 43.6, 43.0, 41.0, 35.6, 33.7, 20.8, 20.6, 18.8, 18.75, 18.7, 18.6
3d	119.0	98.0	169.8, 169.5, 169.3, 154.5, 150.3, 132.6, 132.1, 131.7, 130.0, 128.7, 121.4, 89.1, 89.0, 72.7, 72.6, 72.2, 72.1, 71.9, 71.0, 69.4, 58.6, 58.5, 55.4, 53.1, 46.1, 43.6, 42.9, 41.0, 40.9, 35.6, 20.8, 20.5, 20.4
3e	118.9	98.8	175.8, 175.1, 175.0, 168.6, 167.3, 150.0, 132.2, 131.1, 130.2, 128.7, 121.6, 89.6, 73.0, 72.7, 71.5, 70.8, 69.0, 58.5, 52.6, 46.1, 43.6, 42.9, 41.0, 35.6, 33.7, 20.8, 20.6, 18.9, 18.8, 18.7, 18.6
3f	119.3	97.8	170.0, 169.8, 169.4, 168.3, 164.3, 150.6, 133.0, 132.5, 131.7, 131.6, 130.4, 129.7, 129.4, 128.4, 122.4, 92.0, 77.6, 70.8, 69.5, 69.4, 68.3, 58.6, 52.4, 46.1, 43.9, 43.0, 41.4, 35.7, 21.0, 20.6, 20.5, 20.0.
3g	119.0	98.4	175.8, 175.2, 175.1, 170.2, 167.3, 152.3, 133.4, 132.4, 131.3, 130.4, 130.3, 129.4, 128.9, 128.5, 121.9, 89.7, 71.5, 70.8, 69.3, 58.6, 52.7, 46.2, 44.0, 43.1, 41.2, 35.8, 33.8, 33.6, 21.0, 18.8, 18.5
3h	119.0	98.1	167.8, 165.3, 165.0, 164.3, 164.0, 150.2, 133.2, 133.1, 132.8, 132.2, 131.7, 131.6, 130.4, 130.2, 129.75, 129.7, 129.6, 129.2, 129.16, 128.9,128.85, 128.2, 128.1, 128.0, 121.9, 90.1, 72.9, 72.4, 71.6, 71.4, 69.2, 58.7, 52.6, 46.2, 43.8, 43.0, 41.1, 35.5, 20.9
3I	118.9	98.0	172.1, 170.0, 169.4, 167.4, 149.2, 147.4, 142.1, 130.6, 130.2, 128.8, 127.1, 113.4, 88.1, 72.8, 72.1, 71.9, 71.3, 69.6, 58.9, 56.3, 52.9, 46.5, 43.5, 43.1, 41.1, 36.0, 20.6, 20.5.
9	118.9	98.6	169.9, 169.3, 169.2, 167.4, 154.8, 149.4, 132.6, 131.8, 129.8, 121.9, 88.7, 73.5, 72.4, 72.2, 71.4, 69.3, 59.5, 55.5, 52.7, 46.1, 43.0, 42.9, 38.0, 37.2, 29.6, 23.2, 20.6, 20.4, 19.8.

dried under reduced pressure at 100°C to give the title compound **7** as a white solid (2.80 g, 63% yield). Melting point of approx. 310°C (dec.), $[\alpha]_D^{20}$ −86.9 (*c* 1, DMSO); FT-IR (KBr) cm^{-1} 1600 (COO^-), 2400–2800 (−(H)N^+Me); ^1H NMR (D_2O) δ 6.58, 6.50 (2d, 2H, *J*=8.1 Hz, H_{arom}), 5.67 (d, 1H, *J*=9.5 Hz, 8-H), 5.27 (d, 1H, *J*=9.5 Hz, 7-H), 5.01 (d, 1H, *J*=5.7 Hz), 4.93 (d, 1H, *J*=2.8 Hz, 1′-H), 4.21 (m, 1H), 4.15 (d, 1H, *J*=9.5 Hz, 5′-H), 4.00 (m, 1H), 3.63 (t, 1H, *J*=9.5 Hz, 3′-H), 3.45 (dd, 1H, *J*=2.8, 9.5 Hz, 2′-H), 3.36 (t, 1H, *J*=9.5 Hz, 4′-H), 3.09 (m, 2H), 2.95 (m, 1H), 2.79 (s, 3H, NMe), 2.77 (m, 2H), 2.17 (m, 1H), 1.96 (d, 1H, *J*=14.3 Hz); ^{13}C NMR (D_2O) δ 175.4, 148.4, 140.9,129.8, 127.5, 126.0, 123.1, 119.8, 117.3, 98.4, 90.0, 73.1, 72.5, 72.4, 71.5, 70.7, 59.5, 46.7, 42.3, 40.3, 38.2, 32.8, 20.5; FAB-MS: Calcd for $C_{23}H_{27}NO_9$ *m/z* 461.1762. Found: [M^+] 461.1773, (M^++1) 462.1749. Anal. calcd for $C_{23}H_{27}NO_9 \times H_2O$ (479.48): C 57.61; H 6.10; N 2.92. Found: C 57.79; H 6.32; N 2.73.

3.2. Glycosylation of 3-*O*-protected morphines. Typical procedure: 3-*O*-Benzoyl-6-*O*-(methyl 2′,3′,4′-tri-*O*-benzoyl-β-D-glucopyranosyluronate)morphine (3g)

A suspension of 3-*O*-benzoylmorphine **2c** (10.0 g, 25.7 mmol), **1c** (16.1 g, 33.5 mmol) and 4 Å molecular sieves (25 g) in dry CH_2Cl_2 (150 mL) was stirred for 30 min at room temperature. Then $ZnBr_2$ (5.8 g, 25.7 mmol) was added and the resulting suspension was refluxed for 60 h with stirring (TLC monitoring). After disappearance of the starting material, reflux was stopped and more CH_2Cl_2 (200 mL) was added. The suspension was filtered through Celite and stirred for 20 min with 150 mL of saturated aqueous solution of $NaHCO_3$. The aqueous phase was separated, washed once with CH_2Cl_2, the organics were combined, washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated. The residue (25.5 g) was chromatographed on a short silica gel column (CH_2Cl_2/MeOH, 40:1) to give 19.7 g of the crude product that was recrystallized from EtOH to afford the desired β isomer **3g** as a light yellow solid (14.2 g, 70%) (Tables 4–6).

3.2.1. Methyl [3′,4′-di-*O*-acetyl-1′,2′-*O*-(3-*O*-acetylmorphine-6α-yl)ethylidene-D-gluco-pyranosid]uronate (5a) and methyl [3′,4′-di-*O*-acetyl-1′,2′-*O*-(codeine-6α-yl) ethylidene-D-glucopyranosid]uronate (5d). A solution of **2a** or **2b** (1.00 g, 3.1 mmol), **1a** (1.93 g, 4.6 mmol) and tetrabutylammonium bromide (0.52 g, 1.5 mmol) in dry collidine (6 mL) was stirred overnight under nitrogen at 55°C. After this time, collidine (≈5.5 mL) was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (25 mL), washed successively with saturated aqueous solution of $NaHCO_3$, water and brine and dried over anhydrous Na_2SO_4. After removing CH_2Cl_2 in vacuo the residue was chromatographed on a silica gel column to give the title compound **5a** as a white powder (1.4 g, 71%) or the title compound **5d** as a light yellow solid (1.5 g, 76%) (Tables 7 and 8).

3.2.2. Methyl [3′,4′-di-*O*-acetyl-1′,2′-*O*-(3-*O*-(methoxycarbonyl)morphine-6α-yl)ethylidene-D-glucopyranosid]-uronate (5b). A suspension of the vacuum pre-dried 3-*O*-(methoxycarbonyl)morphine **2b** (3.00 g, 8.8 mmol), **1a** (5.20 g, 13.1 mmol) and 4 Å molecular sieves (8.00 g) in dry THF (60 mL) was stirred for 30 min at room temperature. Then $ZnBr_2$ (1.97 g, 8.8 mmol) was added and the resulting suspension was refluxed for 3 h with stirring (TLC monitoring). CH_2Cl_2 (100 mL) was added and the suspension was filtered through Celite and stirred for 20 min with saturated aqueous solution of $NaHCO_3$ (60 mL). The aqueous phase was separated, washed once

Table 7. ^{1}H NMR data for compounds **5a–d**

Product	^{1}H NMR ($CDCl_3$), δ, J (Hz) H-1′ ($J_{1',2'}$)	H-2′ ($J_{1',2'}$, $J_{2',3'}$)	H-3′ ($J_{2',3'}$, $J_{3',4'}$)	H-4′ ($J_{3',4'}$, $J_{4',5'}$)	H-5′ ($J_{4',5'}$)	H-6 m	Others
5a	5.89 d (4.8)	4.50 dd (4.8, 3.9)	5.23 t (3.9)	5.13 dd (3.9, 8.3)	4.26 d (8.3)	4.10	6.70, 6.50 (2d, 2H, J=8.0, H_{arom}), 5.58 (d, 1H, J=9.6, 8-H), 5.29 (d, 1H, J=9.6, 7-H), 4.82 (d, 1H, J=5.9), 3.74 (s, 3H, CO_2Me), 3.33 (m, 1H), 3.02 (d, 1H, J=18.8), 2.62 (br s, 1H), 2.55 (dd, 1H), 2.40 (s, 3H, NMe), 2.37–2.24 (m, 2H), 2.17 (s, 3H, C-3, Ac), 2.09, 2.08 (2 s, 6H, 2 Ac), 2.02 (m, 1H), 1.88 (d, 1H, J=11.0), 1.77 (s, 3H, ortho Me).
5b	5.88 d (5.0)	4.51 dd (5.0, 3.0)	5.23 dd (3.0, 3.5)	5.13 dd (3.5, 7.8)	4.26 d (7.8)	4.10	6.77, 6.50 (2d, 2H, J=8.0, H_{arom}), 5.58 (d, 1H, J=9.0, 8-H), 5.28 (d, 1H, J=9.0, 7-H), 4.84 (d, 1H, J=5.5), 3.84 (s, 3H, C-3 OCO_2Me), 3.74 (s, 3H, CO_2Me), 3.35 (m, 1H), 3.02 (d, 1H, J=18.8), 2.63 (m, 1H), 2.57 (dd, 1H), 2.40 (s, 3H, NMe), 2.32 (m, 2H), 2.11, 2.10 (2s, 6H, 2 Ac), 2.04 (m, 1H), 1.90 (d, 1H, J=11.0), 1.75 (s, 3H, ortho Me).
5c	5.33 d (3.5)	4.80 dd (3.5, 5.3)	5.54 dd (5.3, 6.0)	5.02 dd (6.0, 8.2)	4.77 d (8.2)	4.01	8.22 (d, 2H, J=7.7, C-3 Bz), 7.55 (t, 1H, J=7.7, C-3 Bz), 7.46 (t, 2H, J=7.7, C-3 Bz), 6.80, 6.57 (2d, 2H, J=8.1, H_{arom}), 5.69 (d, 1H, J=10.0, 8-H), 5.31 (d, 1H, J=10.0, 7-H), 4.96 (d, 1H, J=5.6), 3.50 (s, 3H, CO_2Me), 3.35 (m, 1H), 3.06 (d, 1H, J=18.9), 2.60 (m, 1H), 2.54 (dd, 1H), 2.41 (s, 3H, NMe), 2.34 (m, 2H), 1.99, 1.98 (2s, 6H, 2 Ac), 1.96 (m, 2H), 1.49 (s, 3H, ortho-Me).
5d	5.92 d (4.7)	4.52 dd (4.7, 3.3)	5.24 dd (3.3, 3.6)	5.13 dd (3.6, 7.9)	4.27 d (7.9)	4.12	6.59, 6.48 (2d, 2H, J=8.2, H_{arom}), 5.61 (d, 1H, J=9.7, 8-H), 5.29 (d, 1H, J=9.6, 7-H), 4.78 (d, 1H, J=6.0), 3.80 (s, 3H, C-3 OMe), 3.78 (s, 3H, CO_2Me), 3.42 (m, 1H), 3.00 (d, 1H, J=18.6), 2.75 (m, 1H), 2.65 (dd, 1H), 2.45 (s, 3H, NMe), 2.33 (m, 2H), 2.09 (s, 6H, 2 Ac), 2.05 (m, 1H), 1.87 (d, 1H, J=12.3), 1.77 (s, 3H, ortho-Me).

Table 8. ^{13}C NMR data for compounds **5a–d**

Product	^{13}C NMR (400 MHz, $CDCl_3$), δ C-1′	Ortho (C-7′)	Others
5a	119.0	122.3	169.2, 168.8, 168.7, 168.3, 149.9, 132.2, 131.6, 131.5, 130.7, 129.4, 121.6, 96.4, 91.9, 91.8, 72.9, 68.9, 68.8, 68.3,, 58.7, 52.7, 46.2, 43.6, 43.0, 41.0, 35.5, 21.6, 20.9, 20.7, 20.6
5b	118.9	122.2	169.1, 168.8, 168.6, 153.4, 149.7, 132.4, 131.7, 130.7, 129.1, 121.2, 96.3, 92.0, 72.7, 68.8, 68.7, 68.6, 68.3, 58.6, 55.3, 52.6, 46.1, 43.5, 42.9, 40.9, 35.4, 21.5, 20.8, 20.6.
5c	119.0	121.7	169.2, 168.8, 168.7, 168.6, 148.9, 134.0, 133.7, 133.6, 132.4, 130.4, 129.7, 128.4, 122.4, 96.4, 92.5, 69.4, 69.3, 68.3, 68.2, 58.8, 52.5, 46.1, 43.3, 43.0, 41.0, 35.4, 21.7, 20.9, 20.8, 20.5.
5d	119.2	121.9	168.8, 168.7, 168.4, 167.6, 149.7, 148.3, 132.5, 131.3, 129.4, 127.2, 115.8, 97.3, 92.1, 69.5, 69.4, 68.7, 67.0, 58.6, 56.7, 52.9, 46.4, 43.0, 42.9, 41.5, 36.0, 20.9, 20.8.

with CH_2Cl_2, the organics were combined, washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated. The residue (8.00 g) was passed through a short silica gel column (CH_2Cl_2/MeOH, 35:1) to give the title compound **5b** (5.00 g, 70%) as a pure white solid by HPLC and NMR (Tables 4, 7 and 8).

3.2.3. Methyl [3′,4′-di-*O*-acetyl-1′,2′-*O*-(3-*O*-benzoylmorphine-6α-yl)ethylidene-D-glucopyranosid]uronate (5c). A suspension of 3-*O*-benzoylmorphine **2c** (1.00 g, 2.57 mmol), **1a** (1.35 g, 3.41 mmol) and 4 Å molecular sieves (2.20 g) in dry CH_2Cl_2 (20 mL) was stirred for 30 min at room temperature, then a solution of $ZnBr_2$

(0.58 g, 2.58 mmol) in EtOAc (2.1 ml) was added dropwise and the resulting suspension was refluxed for 60 h with stirring (TLC monitoring). More CH_2Cl_2 (20 mL) was added, the suspension was filtered through Celite and stirred for 20 min with saturated aqueous solution of $NaHCO_3$ (20 mL). The aqueous phase was separated, washed with CH_2Cl_2, the organics were combined, washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated. The residue (2.20 g) was chromatographed on a short silica gel column (CH_2Cl_2/MeOH, 40:1) to give 1.70 g of the crude product (1:1 mixture of orthoester **5c** and β-isomer **3c** by ^{1}H NMR). The mixture was crystallized from EtOH to give the pure orthoester **5c** (0.68 g, 37.5%) as a white solid (Tables 4, 7 and 8).

3.2.4. Optimized procedure of glycosylation: 3-*O*-(methoxycarbonyl)-6-*O*-(methyl 2′,3′,4′-tri-*O*-acetyl-β-D-glucopyranosyluronate)morphine (3d). A suspension of the 3-*O*-(methoxycarbonyl)morphine (**2b**) (30.0 g, 87.5 mmol), **1a** (52.0 g, 131.2 mmol) and molecular sieves 4 Å (60 g) in dry $CHCl_3$ (500 mL) was stirred for 30 min at room temperature, $ZnBr_2$ (11.8 g, 52.5 mmol) was added and the resulting suspension was refluxed for 24 h with stirring and TLC monitoring. Then the second portion of $ZnBr_2$ (5.9 g, 26.3 mmol) was added, and the resulting slightly red-yellow suspension was refluxed for an additional 48 h. $CHCl_3$ was added (400 mL), the suspension was filtered through Celite and stirred for 20 min with saturated aqueous solution of $NaHCO_3$ (600 mL). The aqueous phase was separated, washed with $CHCl_3$, the organics were combined, washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated. The residue (81 g) was dissolved in EtOAc (700 mL) and extracted with 1% aqueous HCl (5×300 mL). The combined aqueous solution was washed twice with EtOAc and basified up to pH9 with solid $NaHCO_3$ (added in small portions!). The resulting suspension was extracted with CH_2Cl_2 (2×500ml), combined organics were washed with water and brine and dried over anhydrous Na_2SO_4. Filtration and evaporation of solvent afforded 53.0 g of **3d** (only β-isomer by HPLC). After crystallization from EtOH, *the* title compound **3d** was obtained as white crystals (48.5 g, 85% yield) (Tables 4–6).

3.2.5. Hydrolysis. Modified procedure: dihydromorphine 6-β-D-glucuronide (10). 6.6 g of **9** was dissolved in MeOH (80 mL) and 5% aqueous solution of NaOH (15 mL) was added dropwise at room temperature. The resulted solution was stirred overnight, filtered, acidified with acetic acid to pH5.0, cooled to 0°C and the crude product was precipitated after addition of EtOH (100 mL) and acetone (400 mL). The precipitate was filtered off, washed twice with EtOH and crystallized from mixture EtOH/water 5:3. The white solid was filtered, washed twice with a mixture EtOH/water 1:1 and dried for 4 h under reduced pressure at 100°C to give the title compound **10** (3.9 g, 85%). $[\alpha]_D^{20}$ −168 (*c* 1, D_2O), mp 270–272°C (dec.) [Lit.[16] for $C_{23}H_{27}O_9N\times CH_3OH\times H_2O$ mp>260°C (dec.)]; FT-IR (KBr) cm^{-1} 1600 (COO^-), 2400–2800 (—(H)N$^+$Me), 3500; ^{1}H NMR (D_2O) δ 6.65, 6.57 (2d, 2H, *J*=8.3 Hz), 4.77 (d, 1H, *J*=4.8 Hz), 4.40 (d, 1H, *J*=7.8 Hz, 1′-H), 4.04 (m, 1H), 3.70 (br s, 1H), 3.49 (d, 1H, *J*=9.5 Hz, 5′-H), 3.29 (dd, 1H, *J*=8.6, 9.3 Hz, 3′-H), 3.26 (dd, 1H, *J*=9.3, 9.5 Hz, 4′-H), 3.05 (m, 1H), 3.03 (dd, 1H, *J*=7.8, 8.6 Hz, 2′-H), 2.86 (m, 2H), 2.74 (s, 3H, NMe), 2.30 (m, 1H), 2.04 (td, 1H), 1.75 (br d, 1H, *J*=12.9 Hz), 1.39–1.51 (m, 2H), 1.29 (m, 1H), 0.84 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 172.7, 146.0, 138.3, 128.7, 123.6, 118.7, 117.1, 102.1, 86.5, 76.0, 74.8, 74.3, 73.6, 71.8, 59.2, 45.6, 41.7, 41.1, 35.1, 30.6, 22.8, 20.4,19.4; HRMS: Calcd for $C_{23}H_{29}NO_9$ *m/z* 463.1815. Found: [M$^+$] 463.1813; [M$^+$+1] 464.1834. Anal. calcd for $C_{23}H_{29}NO_9\times H_2O$ (481.49): C 57.37; H 6.49; N 2.91. Found: C 57.30; H 6.65; N 2.58.

3.2.6. Morphine 6-β-D-glucuronide (6). Compound **6** (a white solid) was prepared as described above from **3a–h** in 73–87% yield. $[\alpha]_D^{20}$ −198 (*c* 0.5, H_2O), mp 239–240°C (dec.) [Lit.4a,b for $C_{23}H_{27}O_9N\times 2H_2O$ $[\alpha]_D^{20}$ −172 (*c* 0.5, H_2O), mp 254–256°C (dec.)]; HRMS: Calcd for $C_{23}H_{27}NO_9$ *m/z* 461.1762. Found: [M$^+$] 461.1763; [M$^+$+1] 462.1749. Anal. calcd for $C_{23}H_{27}NO_9\times 0.2$ EtOH$\times 2H_2O$ (506.70): C 55.47; H 6.40; N 2.77. Found: C 55.81; H 6.40; N 2.75.

3.2.7. Codeine 6-β-D-glucuronide (12). Compound **12** (a white solid) was prepared as described above from **3i** in 84% yield. $[\alpha]_D^{20}$ −224 (*c* 1, H_2O), mp 274–275°C (dec.) [Lit.4a,b for $C_{24}H_{29}O_9N\times 1/2H_2O$ $[\alpha]_D^{20}$ −216 (*c* 0.5, H_2O), mp 276–278°C (dec.)]; FT-IR (KBr) cm^{-1} 1600 (COO^-), 2400–2800 (—(H)N$^+$Me), 3600; ^{1}H NMR (D_2O) δ 6.62, 6.48 (2d, 2H, *J*=8.2 Hz), 5.50 (d, 1H, *J*=9.5 Hz, 8-H), 5.22 (d, 1H, *J*=9.5 Hz, 7-H), 4.95 (d, 1H, *J*=5.9 Hz), 4.48 (d, 1H, *J*=7.7 Hz, 1′-H), 4.30 (q, 1H, *J*=2.7, 5.9 Hz), 3.60 (s, 3H, C-3 OMe), 3.50 (d, 1H, *J*=8.8 Hz, 5′-H), 3.32 (m, 2H, 3′-H, 4′-H), 3.25 (m, 1H), 3.17 (t, 1H, *J*=7.7 Hz, 2′-H), 2.89 (d, 1H, *J*=19.2 Hz), 2.46 (m, 1H), 2.39 (dd, 1H), 2.15–2.23 (m, 2H), 2.15 (s, 3H, NMe), 1.87 (td, 1H, *J*=4.9, 13.1 Hz), 1.65 (d, 1H, *J*=13.1 Hz); ^{13}C NMR (D_2O) δ 175.1, 148.9, 140.8, 130.4, 129.3, 129.0, 127.7, 119.3, 113.0, 101.1, 89.2, 75.6, 74.9, 73.0, 72.6, 71.2, 57.3, 56.0, 48.6, 46.0, 45.0, 42.4, 41.0, 37.0, 33.6, 19.8; HRMS: Calcd for $C_{24}H_{29}NO_9$ *m/z* 475.1812. Found: [M$^+$] 475.1823; [M$^+$+1] 476.1799. Anal. calcd for $C_{24}H_{29}NO_9\times 1/2H_2O$ (484.50): C 59.49; H 6.24; N 2.90. Found: C 59.67; H 6.11; N 3.01.

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References

1. Muhtadi, F. J. *Anal. Profiles Drug. Subs.* **1988**, *17*, 259–320.
2. Osborne, R.; Joel, S.; Trew, D.; Slevin, M. *Clin. Pharmacol. Ther.* **1990**, *47*, 12–19.
3. Rossi, G. C.; Parr, Y.-X.; Brown, G. P.; Pasternak, G. W. *FEBS Lett.* **1995**, *369*, 192–196.
4. (a) Yoshimura, H.; Oguri, K.; Tsukamoto, H. *Chem. Pharm. Bull.* **1968**, *16*, 2114–2117. (b) Yoshimura, H.; Oguri, K.; Tsukamoto, H. *Tetrahedron Lett.* **1968**, *4*, 483–486.
5. (a) Carrupt, P. A.; Testa, B.; Bechalany, A.; Tayar, N. E.; Descas, P. *J. Med. Chem.* **1991**, *34*, 1272–1275. (b) Mertz, A. A. H. Int. Patent WO 93/05057. *Chem. Abstr.* **1993**, *119*, 271612.

6. Lacy, C.; Sainsbury, M. *Tetrahedron Lett.* **1995**, *36*, 3949–3950.
7. (a) Scheinmann, F.; Lumbard, K. W.; Brown, R. T.; Mayalarp, S.P.; Carter, N. E. Int. Patent WO 93/03051, (PCT/GB92/01449), 1993; *Chem. Abstr.* **1993**, *119*, 226341. (b) Brown, R. T.; Lumbard, K. W.; Mayalarp, S.P.; Carter, N. E.; Scheinmann, F. *Tetrahedron Lett.* **1995**, *36*, 8661–8664.
8. Berrang, B.; Brine, G. A.; Carroll, F. I. *Synthesis* **1997**, 1165–1168.
9. Urban, F. J.; Moore, B. S. *Tetrahedron Lett.* **1990**, *31* (31), 4421–4424.
10. Banoub, J.; Bundle, D. R. *Can. J. Chem.* **1979**, *57*, 2091–2097.
11. Kovac, P.; Rice, K. C. *Heterocycles* **1995**, *41*, 697–707.
12. Rukhman, I.; Gutman, A. L. *Tetrahedron Lett.* **2000**, *41*, 6889–6893.
13. (a) Paulsen, H. In *Modern Methods in Carbohydrate Synthesis*, Khan, S. H., O'Neill, R. A., Eds.; Harwood Academic: Amsterdam, 1996; pp 1–20. (b) Isbell, H. S. *Am. Rev. Biochem.* **1940**, *9*, 65–68. (c) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2190–2199. (d) Paulsen, H. *Angew. Chem.* **1982**, *94*, 184–201. (e) Paulsen, H. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 155. (f) Kochetkov, N. K.; Bochkov, A. F.; Sokolovskaya, T. A.; Synyatkov, V. J. *Carbohydr. Res.* **1971**, *16*, 17–27. (g) Kochetkov, N. K.; Bochkov, A. F. *Carbohydr. Res.* **1975**, *39*, 355–357.
14. Scheinmann, F.; Stachulski, A. V.; Joel, S. US Patent 5977326, 1999; *Chem. Abstr.* **1999**, *131*, N 322871.
15. For preparation and complete data see: Mignat, C.; Heber, D.; Schlicht, H.; Ziegler, A. *J. Pharm. Sciences* **1996**, *85*, 691–694.
16. Rukhman, I.; Yudovich, L.; Nisnevich, G.; Gutman, A. L. *Synthesis* **2000**, 1241–1246.
17. *Beilsteins Handbuch Organischen Chemie*, *27*, E *II*, 131.