6-*O*-Glycosylation of Morphine Derivatives Using Thioglycosides as Glycosyl Donors

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Abstract: A novel approach was developed for the synthesis of the pharmaceutically important morphine and dihydromorphine 6-β-D-glucuronides. The key step involves a selective 6-*O*-glycosylation of 3-*O*-protected morphines and dihydromorphines with thioglycosides that serve as glycosyl donors in the presence of thiophilic promoters. This novel approach may be useful for the *O*-glycosylation of other alkoloid derivatives.

Key words: alkaloid glycosides, glycosylation, thioglycosides, morphine 6-β-D-glucuronide, dihydromorphine 6-β-D-glucuronide

Morphine and other opioid analogs[1] are used as powerful analgesics. It has been shown[1] that the major pathway for their detoxification in 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).

It has been demonstrated,[2,3] that much of the analgesic effect after dosing morphine is due not to morphine itself, but rather to one of its main metabolites, M6G. Furthermore, it has been shown that morphine's other main metabolite, M3G antagonizes the analgesic effect of morphine. This potential pharmaceutical importance of M6G as a powerful analgetic and replacement for morphine prompted several researchers to explore ways for its selective synthesis.

Several methods for M6G preparation have been reported: The first method is based on the Koenigs–Knorr reaction and was originally used by Yoshimura[4] and subsequently by others.[5,6] However, this approach leads to variable yields (from 0% to 70%) of the conjugate and difficulties in purification. The trace amounts of heavy metal ions are very difficult to remove in the intermediate conjugate and also in the final product.

The second approach is based on the adopted protocol of Shmidt and Grundler,[7] patented by Scheinmann et al.[8a] and improved by Brown et al.[8b] Although the latter reported yields of up to 50–70%, several researchers had difficulties in reproducing these results.[6,9] In our attempts to adopt this method, using either boron trifluoride-diethyl ether complex or trimethylsilyl trifluoromethanesulfonate (TMSOTf)[8a] as catalysts, similar difficulties[6,9] were encountered and in all cases the yield of the desired glycoside was below 30%.

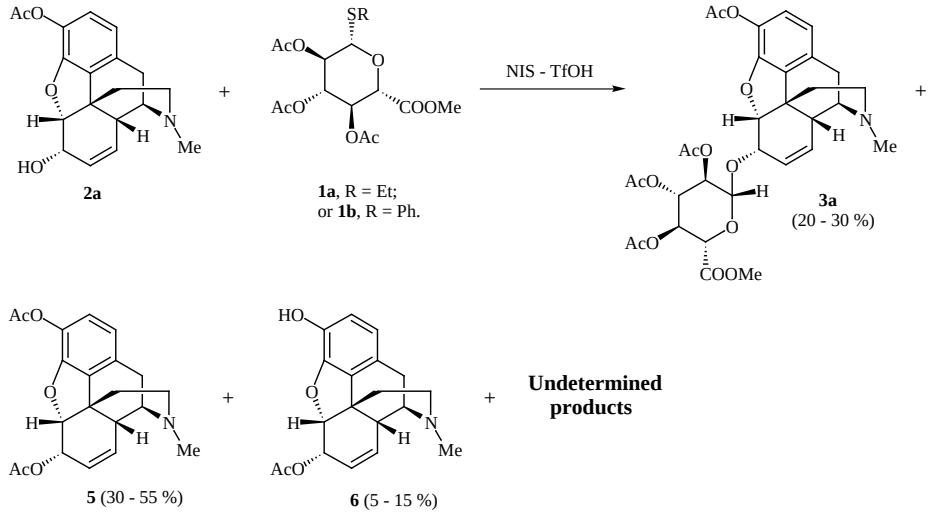
In view of these difficulties, we tried to devise a synthetic method, which avoids toxic and/or expensive reagents, and which cleanly produces the fully protected morphine 6-β-D-glucuronide. This intermediate should then be hydrolysed to the analgesic agent morphine 6-β-D-glucuronide, avoiding tedious and expensive purification steps. Our idea was based on literature reports that iodonium ion or other thiophilic promoters like dimethyl(methylthio)sulfonium triflate (DMTST)[10] promote highly stereoselective glycoside preparation. In particular, it was reported that action of *N*-iodosuccinimide (NIS) together with triflic acid (TfOH)[11–13] or DMTST[14–18] on 2-*O*-esterified thioglycosides caused the rapid, high yielding and stereoselective 1,2-trans-glycosylation of glycosyl acceptors.

The thioglycosides **1a–f** were prepared in two steps by a modification of a published procedure[19] in 85–95% overall yield (see experimental part). We prefered this method because the direct action of thiols and boron trifluoride-diethyl ether complex on the methyl 1,2,3,4-tetra-*O*-acyl-D-glucopyranuronates was less productive and resulted in maximum 60–70% yields[14,20] of thioglycosides **1a–f**.

In our tentative experiments we tested conjugation between 3-*O*-acetylmorphine (**2a**) and thioglycosides **1a** and **1b** under various reaction conditions. It was found from these experiments that while NIS/TfOH and DMTST as promoters afforded similar results, in the case of the latter more than a 5-fold excess was required. On the other hand, 1.5 equivalents of *N*-iodosuccinimide together with 1.1–1.2 equivalents of the trifluoromethanesulfonic acid facilitated the reaction. However, the initial experiments showed that the acetyl protecting group does not hold well under the reaction conditions which leads to a complicated mixture of undesirable products like morphine (**6**), di-*O*-acetylmorphine (**5**) and undetermined side products (Scheme 1). Decreasing of the reaction temperature did not cause significant improvement in the yield of the desired β-isomer (Scheme 1).

In an attempt to reduce the extent of the hydrolytic side reactions we investigated a broad range of substrates with more stable protecting groups, 3-*O*-protected morphines **2a–c** and thioglucosides **1a–f** and tested their coupling under various conditions (Scheme 2).

The best results were achieved when phenyl thioglycosides **1d–f** protected by isobutyryl, benzoyl or pivaloyl groups reacted with 3-*O*-benzoylmorphine (**2c**) to provide the desired glycosides **3f–h** with high stereoselectivity (α/β ratio from 5:95 to 1:99) and good to high yield without undesirable side reactions (Table 1).



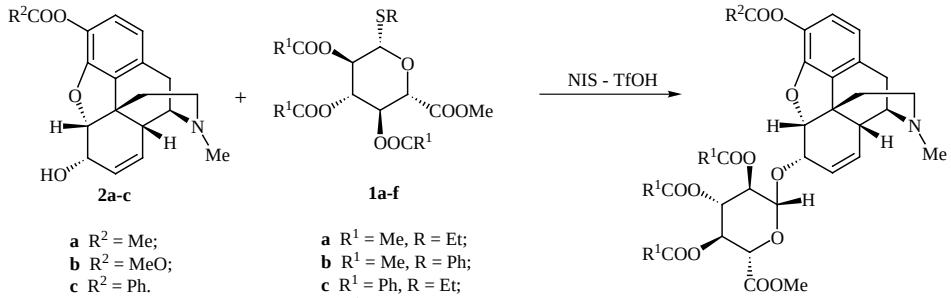
Scheme 1

The developed method could be used as a general approach to *O*-glycosylation of other morphine derivatives. Thus, we prepared the dihydro analog **9** by reacting 3-*O*-benzoyldihydromorphine (**8**) with thioglycoside **1d** and the obtained α/β ratio was 3:97. The purification by crystallization afforded the desired β-isomer **9** in 87% isolated yield (Scheme 3).

Glycosides **3a−h** and **9** were purified by crystallization from EtOH or *i*-PrOH. The ^{1}H NMR spectra of all compounds showed doublet resonance of anomeric protons at about δ = 4.9 with an axial-axial coupling in agreement with the β-configurations (Table 2). Alkaline hydrolysis[8] of **3a−h** and **9** gave morphine 6-β-D-glucuronide or dihydromorphine 6-β-D-glucuronide (**10**) respectively, in good yields. The structures of M6G and **10** were confirmed by NMR experiments and IR measurements and the spectroscopic data were consistent with the literature.[4-6,21]

In conclusion, a novel simple method for the stereoselective synthesis of morphine and dihydromorphine 6-β-D-glucuronides was developed. The method is based on the glycosylation of 3-*O*-protected morphine or dihydromorphine with thioglycosides in the presence of thiophilic promoters. The process provides both high stereoselectivity and up to 90% yields. The synthesis avoids toxic and/or expensive reagents, cleanly produces the desired product avoiding tedious purification and can be easily scaled up for M6G preparation in pharmaceutically sufficient quantities. This novel approach may be useful for *O*-glycosylation of other alkaloid derivatives.

CH_2Cl_2 and $CHCl_3$ were distilled over CaH_2 and stored over molecular sieves 4 Å. Anhyd. 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) for column chromatography was used. Silica gel 60 F_{254} plates (Merck) were used for TLC. All NMR spectra were recorded on a Bruker AM-400 spectrometer using $CDCl_3$ as a solvent. Mps were determined in open capillary tubes with Electrothermal IA 9300 Digital melting point apparatus and are uncorrected. Chemical ionization (CI) mass spectrometry was



a R^2 = Me;
b R^2 = MeO;
c R^2 = Ph.

a R^1 = Me, R = Et;
b R^1 = Me, R = Ph;
c R^1 = Ph, R = Et;
d R^1 = i-Pr, R = Ph;
e R^1 = Ph, R = Ph;
f R^1 = t-Bu, R = Ph.

a R^1 = Me, R^2 = Me;
b R^1 = Ph, R^2 = Me;
c R^1 = i-Pr, R^2 = Me;
d R^1 = Me, R^2 = MeO;
e R^1 = i-Pr, R^2 = MeO;
f R^1 = i-Pr, R^2 = Ph;
g R^1 = Ph, R^2 = Ph;
h R^1 = t-Bu, R^2 = Ph.

Scheme 2

Table 1 6-***O***-Glycosylation of Morphine Derivatives **2a−c** and **8** Using Thioglycosides **1a−f** as Glycosyl Donors

Morphine Derivative	Thioglycoside	Reaction Temp. (ºC)	Promoter	Product[a]	Yield[b] (%)	$[\alpha]_D$ (*c* = 1, $CHCl_3$)[c]	Mp[d] (ºC)	MS (CI) *m/z* ($M^+ + 1$)
2a	**1a**[21]	−15	NIS/TfOH	**3a**[e]	26	−131.6	178−179	645
2a	**1a**	−15	DMTST	**3a**	20			
2a	**1a**	−40	NIS/TfOH	**3a**	32			
2a	**1b**[23]	−12	NIS/TfOH	**3a**	35			
2a	**1c**[24]	−15	NIS/TfOH	**3b**	24	−84.6	115−116	831
2a	**1c**	−15	DMTST	**3b**	22[f]			
2a	**1c**	−23	NIS/TfOH	**3b**	32			
2a	**1e**[24]	−12	NIS/TfOH	**3b**	41			
2c	**1c**	−12	DMTST	**3g**	61	−84.2	158−163	893
2c	**1c**	−12	NIS/TfOH	**3g**	73			
2c	**1c**	−23	NIS/TfOH	**3g**	78			
2c	**1e**	−12	NIS/TfOH	**3g**	87			
2a	**1d**	−12	NIS/TfOH	**3c**	36[f]	−112.0	188−189	729
2b	**1b**	−12	NIS/TfOH	**3d**	42	−138.9	176−177	661
2b	**1d**	−12	NIS/TfOH	**3e**	70	−108.8	184−185	745
2c	**1d**	−12	NIS/TfOH	**3f**	85	−114.4	144−147	791
2c	**1d**	−23	NIS/TfOH	**3f**	87			
2c	**1f**	−12	NIS/TfOH	**3h**	93	−104.8	190−191	833
8	**1d**	12	NIS/TfOH	**9**	87	−88.0	70−72	793

[a] Satisfactory microanalyses obtained: C, ±0.39; H, ±0.30; N, ±0.23. Exception, **3a**: C, +0.47.
[b] Isolated yield.
[c] Recorded at 20ºC.
[d] Mps are uncorrected.
[e] Lit.[4b] $[\alpha]_D^{26}$ –140 (*c* = 0.5, $CHCl_3$), mp 186−188ºC.
[f] Determined by HPLC.

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 on the column LiChrospher 100 RP-18 by using the following system: A: 0.1% aq solution of sodium heptanesulfonate (1 L), adjusted to pH 5.5 with AcOH (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 JACSO DIP-370 polarimeter. The structures of all compounds were consistent with their spectroscopic data.

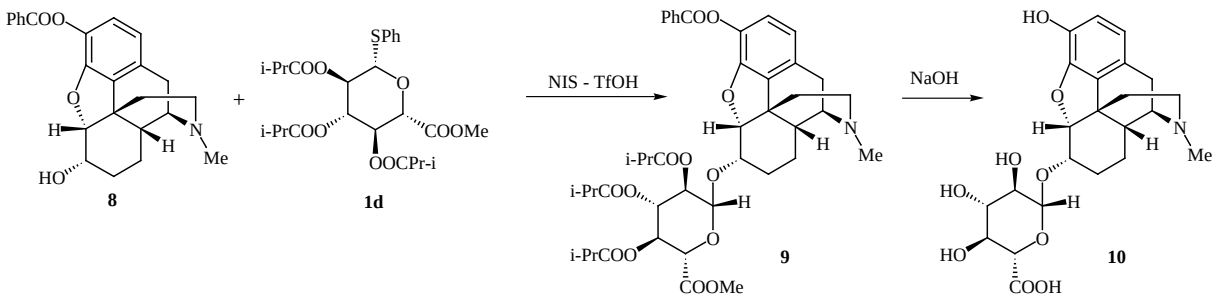
3-*O*-Benzoylmorphine (2c); Typical Procedure

To a solution of morphine hydrochloride trihydrate (7.52 g, 20 mmol) in H_2O (100 mL) was added solid $NaHCO_3$ (8.40 g, 100 mmol) in three portions and the mixture was stirred for 2 h. Benzoyl chloride (1.83 g, 13 mmol) in CH_2Cl_2 (20 mL) was added dropwise and the mixture was stirred for 24 h at r.t. A second portion of benzoyl chloride (1.83 g, 13 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 2 h, and the resulting suspension was stirred for an additional 48 h at r.t.(monitored by HPLC). More CH_2Cl_2 (80 mL) was added, the aqueous layer was separated and washed with CH_2Cl_2 (60 mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was crystallized from EtOH to give 6.90 g of **2c** (95% yield); mp 180−182 °C (Lit.[22] mp 178−184 °C).

3-*O*-Benzoyldihydromorphine (8)

In analogy to the above procedure, compound **8** was obtained from dihydromorphine (6.20 g, 20 mmol) and benzoyl chloride (3.66 g, 26 mmol) as a white solid in 90% yield; $[\alpha]_D^{20}$ −166.5 (*c* = 1, $CHCl_3$); mp 308−310 ºC (dec.)

^{1}H NMR ($CDCl_3$): δ = 8.18 (d, 1 H, *J* = 7.8 Hz, C-3 Bz), 7.61 (t, 1 H, *J* = 7.5 Hz, C-3 Bz), 7.48 (t, 2 H, *J* = 7.5 Hz, C-3 Bz), 6.86, 6.69 (2 d, 2 H, *J* = 8.5 Hz, H_{arom}), 4.56 (d, 1 H, *J* = 5.1 Hz), 4.15 (t, 1 H, *J* = 4.9 Hz), 3.69 (br s, 1 H), 3.09 (d, 1 H, *J* = 4.2 Hz), 3.03 (d, 1 H, *J* = 18.6 Hz), 2.53 (dd, 1 H, *J* = 12.0, 4.2 Hz), 2.42 (m, 1 H), 2.40



Scheme 3

Table 2 ^{1}H NMR Data for Compounds **3a–h** and **9**

Product	^{1}H NMR ($CDCl_3$), δ, *J* (Hz)				
	H-1' ($J_{1',2'}$)	H2' ($J_{1',2'}$, $J_{2',3'}$)	H-5' ($J_{4',5'}$)	H-6 m	Others
3a[9]	4.88 d (7.2)	5.07 dd (7.2, 7.7)	4.09 d (8.8)	4.28	6.69, 6.52 (2 d, 2 H, *J* = 8.0, H_{arom}), 5.65 (d, 1 H, *J* = 9.5, 8-H), 5.25 (m, 3 H, 3'-H, 4'-H, 7-H), 4.86 (d, 1 H, *J* = 6.5), 3.72 (s, 3 H, CO_2CH_3), 3.33 (m, 1 H), 3.02 (d, 1 H, *J* = 18.9), 2.61 (m, 1 H), 2.56 (m, 1 H), 2.40 (s, 3 H, NCH_3), 2.29–2.39 (m, 2 H), 2.28 (s, 3 H, C-3 $COCH_3$), 2.08 (s, 3 H, $COCH_3$), 2.03 (s, 6 H, 2 $COCH_3$), 1.93–2.03 (m, 1 H), 1.90 (m, 1 H)
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 (3 d, 6 H, *J* = 7.7, 3, C_6H_5), 7.27-7.52 (m, 9 H, 3 C_6H_5), 6.64, 6.50 (2 d, 2 H, *J* = 8.1, H_{arom}), 5.82 (m, 2 H, 3'-H, 4'-H), 5.72 (d, 1H, *J* = 10.0, 8-H), 5.31 (d, 1 H, *J* = 10.0, 7-H), 5.28 (d, 1 H, *J* = 5.8), 3.63 (s, 3 H, CO_2CH_3), 3.36 (m, 1 H), 3.03 (d, 1 H, *J* = 18.8), 2.69 (br s, 1 H), 2.57 (m, 1 H), 2.42 (s, 3 H, NCH_3), 2.28–2.43 (m, 2 H), 2.10 (s, 3 H, C-3 $COCH_3$), 2.02 (m, 1 H), 1.87 (m, 1 H)
3c	4.91 d (7.6)	5.10 dd (7.6, 8.0)	4.10 d (9.2)	4.28	6.68, 6.50 (2 d, 2 H, *J* = 8.0, H_{arom}), 5.63 (d, 1 H, *J* = 10.0, 8-H), 5.28 (m, 3 H, 3'-H, 4'-H, 7-H), 4.87 (d, 1 H, *J* = 5.6), 3.69 (s, 3 H, CO_2CH_3), 3.32 (m, 1 H), 3.02 (d, 1 H, *J* = 18.8), 2.42–2.60 (m, 5 H), 2.41 (s, 3 H, NCH_3), 2.27–2.40 (m, 2 H), 2.26 (s, 3 H, C-3 $COCH_3$), 2.01 (m, 1 H), 1.88 (m, 1 H), 1.05–1.13 [m, 18 H, 3 $CH(CH_3)_2$]
3d	4.91 d (7.7)	5.04 dd (7.7, 8.5)	4.08 d (9.5)	4.33	6.77, 6.52 (2 d, 2 H, *J* = 8.2, H_{arom}), 5.64 (d, 1 H, *J* = 9.7, 8-H), 5.22–5.29 (m, 3 H, 3'-H, 4'-H, 7-H), 4.93 (d, 1 H, *J* = 5.8), 3.87 (s, 3 H, C-3 OCO_2CH_3), 3.72 (s, 3 H, CO_2CH_3), 3.33 (m, 1 H), 3.03 (d, 1 H, *J* = 19.7), 2.62 (s, 1 H), 2.56 (m, 1 H), 2.40 (s, 3 H, NCH_3), 2.20–2.38 (m, 2 H), 2.10 (s, 3 H, $COCH_3$), 2.01–2.10 (m, 1 H), 2.01 (s, 6 H, 2 $COCH_3$), 1.89 (d, 1 H, *J* = 9.7)
3e	4.92 d (7.2)	5.11 dd (7.2, 7.5)	4.10 d (9.3)	4.27	6.69, 6.51 (2 d, 2 H, *J* = 7.6, H_{arom}), 5.64 (d, 1 H, *J* = 9.5, 8-H), 5.27 (m, 3 H, 3'-H, 4'-H, 7-H), 4.87 (d, 1 H, *J* = 6.3), 3.80 (s, 3 H, C-3 OCO_2CH_3), 3.70 (s, 3 H, CO_2CH_3), 3.32 (m, 1 H), 3.02 (d, 1 H, *J* = 18.8), 2.45–2.61 (m, 5 H), 2.44 (s, 3 H, NCH_3), 2.29-2.43 (m, 2 H), 2.26 (m, 1 H), 1.99 (m, 1 H), 1.87 (d, 1 H, *J* = ? Hz), 1.04-1.16 [m, 18 H, 3 $CH(CH_3)_2$]
3f	4.95 d (7.5)	5.01 dd (7.5, 8.1)	4.05 d (9.3)	4.31	8.17 (d, 2 H, *J* = 7.6, C-3 C_6H_5), 7.58 (t, 1 H, *J* = 7.1, C-3 C_6H_5), 7.48 (td, 2 H, *J* = 7.6, 7.1, C-3 C_6H_5), 6.84, 6.56 (2 d, 2 H, *J* = 8.2, H_{arom}), 5.67 (d, 1 H, *J* = 9.1, 8-H), 5.25 (m, 3 H, 3'-H, 4'-H, 7-H), 4.92 (d, 1 H, *J* = 5.5), 3.68 (s, 3 H, CO_2CH_3), 3.34 (m, 1 H), 3.06 (d, 1 H, *J* = 18.8), 2.63 (br s, 1 H), 2.56 (m, 1 H), 2.26–2.53 (m, 7 H), 2.20 (m, 1 H), 2.02 (m, 1 H), 1.93 (d, 1 H, *J* = 10.8), 1.00–1.07 [m, 12 H, 2 $CH(CH_3)_2$], 0.84, 0.80 [2 d, 6 H, *J* = 6.7, $CH(CH_3)_2$]
3g	5.00 d (6.2)	5.44 dd (6.2, 6.0)	4.37 d (8.0)	4.49	8.10 (d, 2 H, *J* = 7.7), 7.86 (d, 4 H, *J* = 7.7), 7.75 (d, 2 H, *J* = 7.7), 7.19–7.51 (m, 12 H), 6.81, 6.56 (2 d, 2 H, *J* = 8.5, H_{arom}), 5.77 (m, 3 H, 3'-H, 4'-H, 8-H), 5.35 (d, 1 H, *J* = 10.0, 7-H), 5.31 (d, 1 H, *J* = 6.0), 3.57 (s, 3 H, CO_2CH_3), 3.36 (m, 1 H), 3.06 (d, 1 H, *J* = 18.8), 2.68 (br s, 1 H), 2.56 (dd, 1 H, *J* = 3.9, 12.0), 2.42 (s, 3 H, NCH_3), 2.30-2.41 (m, 2 H), 2.02 (td, 1 H, *J* = 12.0, 4.6), 1.91 (m, 1 H).
3h	4.92 d (7.3)	5.06 dd (7.3, 7.9)	4.07 d (9.3)	4.28	8.17 (d, 2 H, *J* = 7.7, C-3 C_6H_5), 7.58 (t, 1 H, *J* = 7.7, C-3 C_6H_5), 7.47 (t, 2 H, *J* = 7.7, C-3 C_6H_5), 6.82, 6.56 (d, 1 H, *J* = 8.0, H_{arom}), 5.68 (d, 1 H, *J* = 10.0, 8-H), 5.26 (m, 3 H, 3'-H, 4'-H, 7-H), 4.88 (d, 1 H, *J* = 5.8), 3.69 (s, 3 H, CO_2CH_3), 3.35 (m, 1 H), 3.06 (d, 1 H, *J* = 18.8), 2.63 (br s, 1 H), 2.58 (m, 1 H), 2.42 (s, 3 H, NCH_3), 2.30–2.40 (m, 2 H), 2.03 (m, 1 H), 1.92 (m, 1 H), 1.10, 1.06, 0.92 (3 s, 27 H, 3 *t*-C_4H_9)
9	4.94 d (7.5)	4.81 dd (7.5, 7.4)	3.93 d (9.2)	4.13	8.20 (d, 2 H, *J* = 7.7, C-3 C_6H_5), 7.59 (t, 1 H, *J* = 7.5, C-3 C_6H_5), 7.49 (td, 2 H, *J* = 7.7, 7.5, C-3 C_6H_5), 6.91, 6.64 (2 d, 2 H, *J* = 8.0, H_{arom}), 5.18 (m, 2 H, 3'-H, 4'-H), 4.71 (d, 1 H, *J* = 4.2), 3.66 (s, 3 H, CO_2CH3), 3.09 (m, 1 H), 3.01 (d, 1 H, *J* = 18.7), 2.51 (m, 1 H), 2.38 (m, 5 H), 2.24 (m, 3 H), 1.88 (m, 3 H), 1.76 (d, 1 H, *J* = 10.6), 1.51 (m, 3 H), 1.05 [m, 12 H, 2 $CH(CH_3)_3$], 0.89, 0.86 [d, 3 H, *J* = 7.0, $CH(CH_3)_3$]

(s, 3 H, NCH_3), 2.21 (m, 2 H), 1.86 (m, 2 H), 1.66 (m, 1 H), 1.19–1.41 (m, 3 H).

^{13}C NMR ($CDCl_3$): δ = 133.6, 131.9, 130.3, 130.2, 128.4, 121.1, 119.2, 92.2, 66.6, 59.7, 46.9, 42.8, 42.5, 36.6, 28.2, 20.5, 18.2

MS (CI): *m*/*z* = 392 (M^+ + 1).

Anal. calcd for $C_{24}H_{25}NO_4$ (391.5): C 73.64; H 6.44; N 3.58. Found C 73.24; H 6.57; N 3.97.

Table 3 ^{13}C NMR Data for Compounds **3a–h** 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	119.0	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
3g	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
3h	118.9	98.7	176.8, 176.1, 175.9, 167.1, 164.2, 151.0, 133.3, 132.3, 131.5, 130.4, 129.5, 128.9, 128.4, 121.9, 89.9, 73.3, 72.9, 71.6, 70.9, 69.4, 58.6, 52.7, 46.2, 44.2, 43.1, 41.4, 38.6, 35.9, 27.1, 27.0, 26.9, 21.1
9	118.7	97.8	175.5, 175.0, 174.9, 167.3, 164.1, 149.6, 133.3, 132.2, 131.2, 130.5, 130.2, 129.2, 128.4, 122.1, 89.3, 72.4, 71.9, 71.7, 71.1, 69.1, 59.3, 52.5, 46.1, 43.1, 42.8, 38.4, 37.2, 33.6, 33.4, 29.5, 29.2, 23.5, 20.5, 19.7, 18.7, 18.6, 18.4

3-*O*-(Methoxycarbonyl)morphine (2b):
Compound **2b** was prepared from morphine hydrochloride trihydrate (7.52 g, 20 mmol) and methyl chloroformate (2.50 g, 26 mmol) as a white solid in 85% yield; $[\alpha]_D^{20}$ −193.0 (*c* = 1, $CHCl_3$), mp 118−119 ºC (dec.) [Lit.[23] mp 116−120 ºC (dec)].

^1H NMR ($CDCl_3$): δ = 6.84, 6.62 (2 d, 2 H, *J* = 8.2 Hz, H_{arom}), 5.78, 5.24 (2 d, 2 H, *J* = 10.0 Hz, 8-H, 7-H), 4.98 (d, 1 H, *J* = 6.4 Hz), 4.18 (m, 1 H,), 3.90 (s, 3 H, C-3 OCO_2CH_3), 3.62 (m, 1 H), 3.03 (d, 1 H, *J* = 18.9 Hz), 2.66 (m, 1 H), 2.55 (dd, 1H, *J* = 3.8, 11.6 Hz), 2.40 (s, 3 H, NCH_3), 2.34 (m, 2 H), 2.12 (m, 2 H), 1.90 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 153.5, 144.8, 134.0, 133.0, 132.5, 132.3, 127.7, 120.7, 119.7, 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 $C_{19}H_{21}NO_5$ (343.4): C 66.46; H 6.16; N 4.08. Found: C 66.82; H 6.52; N 3.87.

Thioglycosydes 1d and 1f; General Procedure
Methyl 1,2,3,4-tetra-*O*-acyl-D-glucopyranuronate[24] (28 mmol) was added in one portion to a precooled (−5 °C) 38% wt solution of HBr in AcOH (100 mL) and the resulting brown-red mixture was stirred for 1 h at 0°C and for 10 h at r.t. HBr and AcOH were removed under reduced pressure and the residue was partitioned between CH_2Cl_2 (100 mL) and sat. aq $NaHCO_3$ solution (60 mL). The phases were separated, the aqueous layer was washed with CH_2Cl_2 (50 mL) and the combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), filtered, and the solvent was removed under vacuo. The crude methyl 2,3,4-tri-*O*-acyl-D-glucopyranosyl bromide obtained was used in the next step without further purification.

Sodium (0.80 g., 35 mmol) was dissolved in anhyd MeOH (100 mL) under Ar and while stirring at r.t. thiophenol (4.53 mL, 40 mmol) was added dropwise and the solution was stirred for an additional 20 min. Then the above crude product was added in one portion and resulting suspension was stirred to completion of the reaction (monitored by TLC, mobile phase was hexane/EtOAc, 4:1). MeOH was evaporated under reduced pressure and the red-violet solid was dissolved in the mixture of CH_2Cl_2 (100 mL) and H_2O (100 mL). The phases were separated, the aqueous layer was washed with CH_2Cl_2 (50 mL) and the combined organics were washed with sat. aq $KHSO_4$ solution (2 × 80 mL), dried (Na_2SO_4), filtered, and the solvent was removed under vacuo. The crude product was crystallized from EtOH or *i*-PrOH to give **1d** or **1f** in 85−95% yield.

Methyl (Phenyl 2,3,4-tri-*O*-isobutyryl-1-thio-β-D-glucopyranosid)uronate (1d)
$[\alpha]_D^{20}$ −17.2 (*c* = 1, $CHCl_3$); mp 132.4−135.6 ºC.

^1H NMR ($CDCl_3$): δ = 7.45 (m, 2 H, SPh), 7.29 (m, 3 H, SPh), 5.30 (t, 1 H, *J* = 9.4 Hz, 3-H), 5.16 (dd, 1 H, *J* = 9.6, 9.4 Hz, 4-H), 4.99 (dd, 1 H, *J* = 9.8, 9.4 Hz, 2-H), 4.71 (d, 1 H, *J* = 9.8 Hz, 1-H), 4.03 (d, 1 H, *J* = 9.6 Hz, 5-H), 3.71 (s, 3 H, CO_2CH_3), 2.40−2.53 [m, 3 H, 3 C*H*$(CH_3)_3$], 1.16, 1.10 [2 d, 6 H, *J* = 7.2 Hz, CH(C*H*$_3)_3$], 1.02−1.07 [m, 12 H, 2 CH(C*H*$_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 175.7, 175.1, 174.8, 166.8, 133.1, 131.5, 128.9, 128.4, 86.5, 72.7, 69.0, 68,9, 52.7, 33.9, 33.8, 18.8, 18.7.

MS (CI): *m*/*z* = 511 (M^+ + 1).

Anal. calcd for $C_{25}H_{34}O_9S$ (510.6): C 58.81; H 6.71; S 6.28. Found: C 59.19; H 6.32; S 6.73.

Methyl (Phenyl 2,3,4-tri-*O*-pivaloyl-1-thio-β-D-glucopyranosid)uronate (1f)

$[\alpha]_D^{20}$ -21.0 (*c* = 1, $CHCl_3$), mp 130.8-131.6 °C

^{1}H NMR ($CDCl_3$): δ = 7.45 (m, 2 H, SC_6H_5), 7.29 (m, 3 H, SC_6H_5), 5.35 (t, 1 H, *J* = 9.3 Hz, 3-H), 5.19 (dd, 1 H, *J* = 10.0, 9.3 Hz, 4-H), 5.03 (t, 1 H, *J* = 9.8, 9.3 Hz, 2-H), 4.72 (d, 1 H, *J* = 9.8 Hz, 1-H), 4.04 (d, 1 H, *J* = 10.0 Hz, 5-H), 3.71 (s, 3 H, CO_2CH_3), 1.18, 1.09, 1,07 (3 s, 27 H, 3 *t*-C_4H_9).

^{13}C NMR ($CDCl_3$): δ = 177.1, 176.4, 176.1, 166.9, 133.0, 131.8, 129.0, 128.4, 86.8, 72.7, 69.1, 52.7, 38.7, 27.1, 27.0.

MS (CI): *m*/*z* = 553 (M^+ + 1).

Anal. Calcd for $C_{28}H_{40}O_9S$ (552.68): C 60.85; H 7.29; S 5.80. Found: C 60.83; H 7.51; S 5.93.

6-*O*-Glycosylation of Morphine Derivatives 2a-c and 8. General Procedure

A suspension of **1a−f** (3.4 mmol), NIS (0.90 g, 3.7 mmol), **2a−c** or **8** (2.6 mmol) and 4 Å molecular sieves (3.00 g) in anhyd CH_2Cl_2 (20 mL) was stirred for 10 min at r.t. and then cooled to −12° C to −40 °C. A solution of TfOH (0.27 mL, 2.7 mmol) in anhyd Et_2O (3 mL) was added during 15 min without changing the temperature. The resulting red-violet mixture was stirred to completion of the reacton (reaction was monitored by HPLC and/or TLC using as mobile phase CH_2Cl_2/MeOH/hexane/EtOAc, 6:1:2:1). Then the mixture was diluted with CH_2Cl_2 (30 mL), filtered, stirred for 20 min with sat. aq $NaHCO_3$ solution (30 mL) and the aqueous layer was separated. The organic layer was washed with 10% aq $Na_2S_2O_3$ solution (2 × 20 mL), dried (Na_2SO_4), filtered, and evaporated. The crude product was chromatographed on a short silica gel column and crystallized from EtOH or *i*-PrOH to give the desired glycosides **3a−h** and **9** (Table 1).

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