# Model Steroid Glycoside Synthesis via a Glycosyl Transfer Mediated by Heterocycloaddition

War Ward Win* and Richard W. Franck*

*Department of Chemistry, Hunter College/CUNY, 695 Park Avenue, New York, New York 10021*

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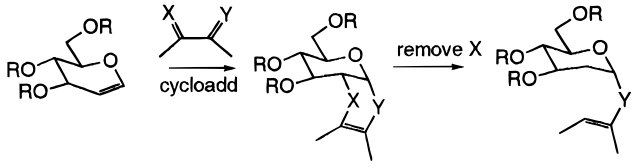
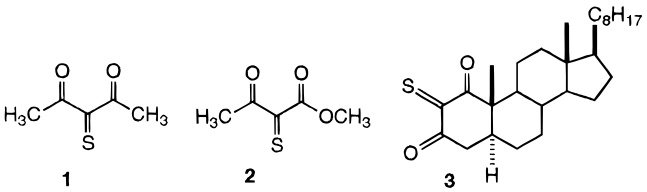
Steroid glycosides have been a subject of study for the synthetic chemist for many years.[1] The construction of the glycoside−steroid linkage has been successfully accomplished by several groups. Every recorded synthesis used the most common method of glycoside bond formation, namely electrophilic activation of the anomeric carbon of the carbohydrate followed by its trapping with a steroidal alcohol. Our laboratory has been exploring an alternate approach to glycosyl transfer,[2] shown by the general cycloaddition in Scheme 1.

**Scheme 1**



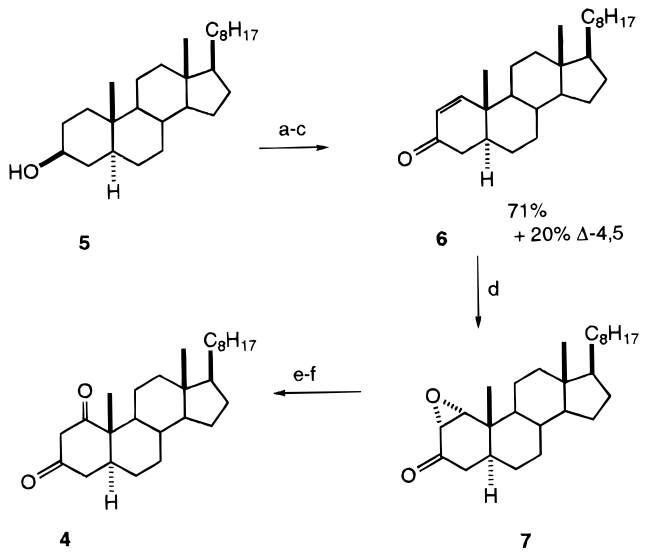

We were interested to discover if our concept could be applied to the glycosidation of steroids. Our planning was based on our earlier demonstration that the structural element required for a successful heterocycloaddition was a 1,3-dioxo-2-thiono assembly such **1**, which is symmetrical, and **2**, where the carbonyls were differentiated electronically. Thus, our proposed steroid heterodiene **3** led to an interesting question: would there be selectivity between the carbonyls at C-1 and C-3 in the cycloaddition?




## Results

The first task was to prepare cholestane-1,3-dione (**4**), which was to be the precursor to heterodiene **3**. Dione **4** had been reported by Tamm,[3] using the sequence shown in Scheme 2. We repeated the work with one significant change. In our hands, the Grieco modification of the Yang method using *t*-BuOOH for the epoxidation of the enone **6** produced the desired **7** in 53% yield, compared to 16% yield in our hands, when alkaline hydrogen peroxide was the reagent.[4]

**Scheme 2**[a]




[a] Key: (a) oxidation: Swern 72%, TPAP 87%, Jones 97%; (b) bromination: $Br_2$-HBr 62%, $CuBr_2$ 92% (2α/2β 95:5); (c) $CaCO_3$−DMF, reflux 30 min 71% + 20% Δ-4,5; (d) $H_2O_2$/NaOH 16%, Triton B-TBHP 53%; (e) LAH, ether, reflux 99%; (f) Jones 81%.

Scheme 3 illustrates the cycloaddition chemistry. Thus, steroid dione **4** was cleanly phthalimidosulfenylated to afford sulfenyl dione **8**, the ultimate precursor to our heterodiene **3**, which was generated and trapped *in situ* in the presence of 0.5 equiv of tribenzyl glucal **9**. Two cycloadducts were obtained in identical yield and were separable by flash chromatography on silica gel. That both adducts had arisen from heterodiene attack on the bottom or α face of the glucal was clear from proton NMR data. In particular, the axial H at C-2′ ($\delta$ 3.2), adjacent to sulfur, is quite diagnostic in all our cycloadducts. In order to differentiate between the two adducts, an undecoupled $^{13}C$ NMR spectrum of each material was used. Thus, the product assigned structure **10** exhibited a triplet for the resonance at $\delta$ 162.1 assigned to the vinyl carbon at C-3, whereas the material assigned structure **11** revealed a distorted triplet for the C═O at $\delta$ 194.7. Desulfurization of **10** and **11** with Raney nickel in benzene afforded the novel steroid glycosides **12** and **13** in 57% and 21% yield, respectively.

## Discussion

The absence of regioselectivity in the cycloaddition step of diene **3** was surprising at first glance since the 2-D representation implies that congestion might exist near the C-1 carbonyl. However, a simple calculation of the ground-state geometry of heterodiene **3** corrected our naive first impression. Figure 1 shows that, indeed, the C-1 carbonyl carbon is somewhat blocked by the angular methyl. But, the A ring is quite twisted, presumably to avoid eclipsing of the carbonyls and thiocarbonyl, so that the oxygen at C-1, which is the terminus of the diene, is not near any group that might have provided some steric hindrance to approach of the tribenzyl glucal. Our cycloaddition method is novel, and it does provide a 2-deoxyglycoside without electrophilic glycosyl transfer

(1) Randolph, J. T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5693−5700. This recent paper has a good bibliography.

(2) (a) Capozzi, G.; Franck, R. W.; Menichetti, S.; Mattioli, M.; Nativi, C.; Valle, G. *J. Org. Chem.* **1995**, *60*, 6416−6426. (b) Capozzi, G.; Dios, A.; Franck, R. W.; Geer, A.; Marzabadi, C.; Menichetti, S.; Nativi, C.; Tamarez, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 777−779.

(3) Tamm, C.; Albrecht, R. *Helv. Chim. Acta* **1960**, *43*, 768−782

(4) (a) Grieco, P. A.; Nishizawa, M.; Oguri, T.; Burke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *99*, 5773−5780. (b) Yang, N. C.; Finnegan, R. A. *J. Am. Chem. Soc.* **1958**, *80*, 5845−5848.

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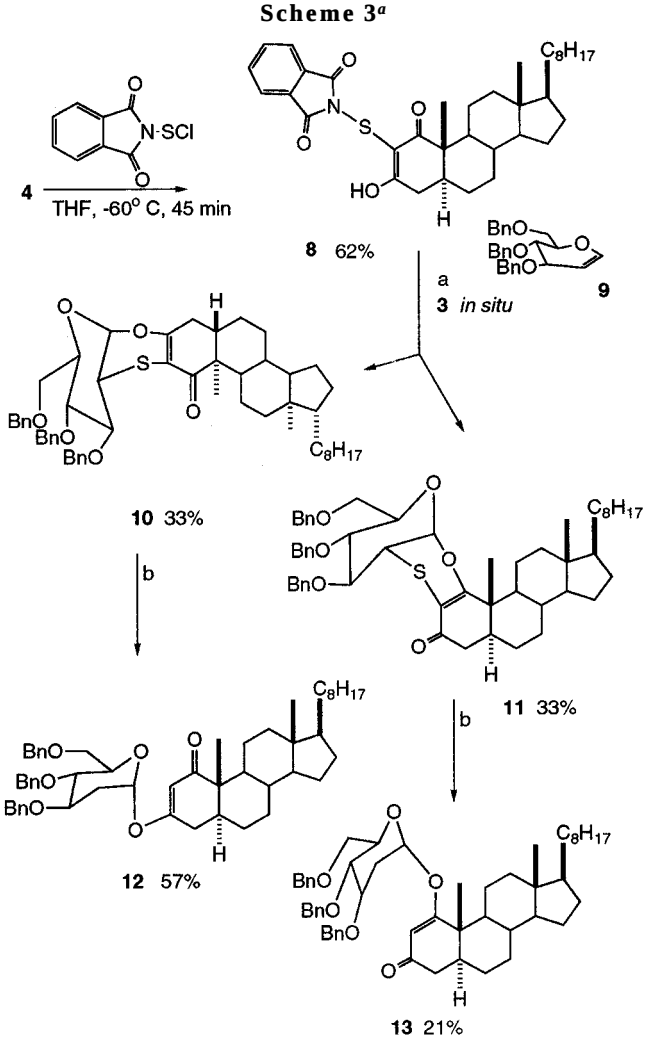
**Scheme 3**[a]




[a] Key: (a) benzene-$d_6$, 2,6-lutidine, rt 21 h; (b) Raney nickel, toluene.

chemistry. However, it is not a practical alternative to the classical methods for steroid glycoside synthesis because of the several steps needed to prepare the steroidal heterodiene precursor.

## Experimental Section

Pulsed Fourier transform 300 MHz $^1$H and 75 MHz $^{13}$C spectra were obtained with deuterated chloroform (99.8%, 0.03% v/v TMS, Sigma−Aldrich). Chemical shifts are in $\delta$ or ppm units downfield from $Me_4Si$ as internal reference. Coupling constants are reported in hertz (J values). The assignment of the $^{13}$C was confirmed by single-frequency off-resonance decoupled and proton-coupled spectra. TLC analyses were done on silica gel 60 F254 plates available from EM Science and visualized by dipping them in a cerium sulfate or polymolybdic acid solution. All regular and flash column chromatography separations were performed using 230−400 mesh, 60 Å silica gel, available from EM Science. Optical rotations were recorded on an automatic polarimeter using a 1 dm cell at the reported temperatures and concentrations.

**Phthalimidosulfenyl Chloride.** Into an ice-chilled suspension of potassium phthalimide (73 g, 0.4 mol) in dry $CH_2Cl_2$ (400 mL) was added a solution of sulfur monochloride (26 g, 0.2 mol, 15.4 mL) in dry $CH_2Cl_2$ (15 mL) via a dropping funnel over a period of 10 min. The reaction mixture was stirred mechanically. After being stirred for 15 min at 0 °C, it was allowed to warm to rt for 18 h. The insoluble material was filtered. After the solvent was removed under reduced pressure, 22.8 g (33%, mp 235−236 °C) of *N,N′*-dithiobis(phthalimide) was obtained:

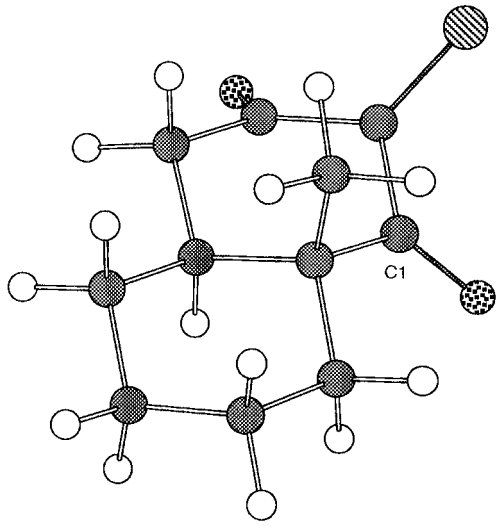



**Figure 1.** Chem3D+ representation of an AM1 calculation (Spartan software) of the A and B rings of **3**.

$^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.5−8.7 (m, 8H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 124.3, 132.2, 134.9, 166.5.

To a solution of *N,N′*-dithiobis(phthalimide) (3.4 g, 9.6 mmol) in 150 mL of HPLC-grade $CH_2Cl_2$ were added dry pyridine (0.2 mL) and sulfuryl chloride (8.3 g, 5.0 mL, 62 mmol) via a dropping funnel at rt. The yellow reaction mixture was stirred for 2 days, and all volatile materials were removed under vacuum, affording the title compound in 90% yield (3.7 g): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.8−8.0 (m, 4H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 124.8, 131.6, 135.7, 165.3.

**1,3-Dioxo-2-(thiophthalimido)cholestane (8).** A solution of phthalimidosulfenyl chloride (144 mg, 0.7 mmol) in dry THF (5 mL) was cooled to −60 °C. Into it was added a solution of cholestane-1,3-dione (**4**) (200 mg, 0.5 mmol; see Supporting Information for details of its preparation) in dry THF (5 mL) dropwise. After the white suspension was stirred for 45 min at −60 °C, the reaction mixture was allowed to warm to room temperature and then filtered. The filtrate was evaporated under vacuum to give the title compound in 62% yield (180 mg): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.67 (s, 3H,), 0.87 (d, 6H, $J$ = 6.6), 0.89 (m, 6H,), 7.76 (m, 4H), 11.00 (s, 1H).

**Regioisomeric Cyclic Oxathiines (10 and 11).** Into a suspension of 1,3-dioxo-2-(thiophthalimido)cholestane (**8**) (335 mg, 0.6 mmol) and tri-*O*-benzylglucal **(9)** (125 mg, 0.3 mmol) in benzene-$d_6$ (5 mL) was added 0.3 mL of 2,6-lutidine at rt under Ar. After being stirred for 21 h, the reaction mixture was diluted with $CH_2Cl_2$, washed first with aqueous saturated sodium bicarbonate solution and second with brine, dried over $Na_2SO_4$, and evaporated in vacuo to give 480 mg of crude product. The components were separated by column chromatography (silica gel, petroleum ether −10% ethyl acetate) to afford regioisomeric cyclic oxathiines **10** ($R_f$ = 0.76) and **11**($R_f$ = 0.24) each in 33% yield (80 mg). Data for **10**: $[\alpha]^{25} = +119.5$ ($c$ = 8.5, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.65 (s, 3H), 0.84 (d, 6H, $J$ = 6.6), 0.89 (d, 3H, $J$ = 6.5), 1.05 (s, 3H), 3.20 (dd, 1H, $J$ = 10.7, 2.9), 3.57−3.96 (m, 3H), 4.52−4.83 (m, 8H), 5.63 (d, 1H, $J$ = 2.8), 7.33 (m, 15H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 11.6, 12.6, 18.8, 22.8, 23.0, 23.7, 24.1, 24.5, 28.1, 28.2, 28.3, 29.9, 30.7, 34.0, 36.1, 36.4, 37.0, 39.8, 40.3, 41.5, 42.1, 42.7, 47.1, 48.2, 56.6, 68.3, 73.4, 73.8, 75.7, 78.5, 96.5, 102.8, 128.3, 128.4, 128.5, 128.7, 138.0, 162.1, 202.0. Anal. Calcd for $C_{48}H_{70}O_6S$: C 76.56, H 8.33, S 3.79. Found: C 76.22, H 8.55, S 3.72. Data for **11**: $[\alpha]^{25} = +112.4$ ($c$ = 9.25, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.67 (s, 3H), 0.86 (d, 6H, $J$ = 6.6), 1.15 (s, 3H), 3.25 (dd, 1H, $J$ = 10.8, 2.8), 3.71−3.90 (m, 3H), 4.56−4.92 (m, 8H), 5.57 (d, 1H, $J$ = 2.8, 1-H), 7.15−7.20 (m, 15H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 12.1, 12.2, 19.0, 22.5, 22.6, 23.5, 24.2, 25.5, 27.6, 27.9, 29.7, 30.1, 35.5, 35.7, 37.2, 39.8, 40.4, 40.6, 42.1, 42.3, 43.4, 44.9, 50.9, 56.2, 56.4, 68.2, 74.4, 74.6, 75.8, 76.2, 78.8, 100.5, 128.1, 128.2, 128.3, 128.4, 137.8, 137.9, 175.0, 194.7.

**3-(3′,4′,6′-Tribenzyl-2′-deoxy-α-glucopyranosyl)cholest-2-en-1-one (12).** A teaspoonful of Raney nickel was washed first with absolute ethanol (4 × 5 mL) and then with toluene (4 × 5

mL). Into an ice-cooled suspension of Raney nickel in toluene (1 mL) was added cyclic oxathiine **18** (40 mg, 0.05 mmol) in HPLC-grade benzene (1 mL) under Ar. After being stirred at 0 °C for 2 h, the mixture was allowed to stir at rt for 29 h. The suspension was filtered through a Celite pad, which was then washed with ethyl acetate, and the filtrates were evaporated in vacuo and purified by flash chromatography over silica gel, eluting with petroleum ether −20% ethyl acetate, to give 23 mg (57% yield) of glycoside **12**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.67 (s, 3H), 0.87 (d, 6H, $J$ = 6.6), 0.89 (d, 3H, $J$ = 6.5), 1.00 (s, 3H), 2.33 (m, 2H), 2.52 (m, 1H), 3.63−3.98 (m, 3H), 4.47 (d, 2H, $J$ = 12.3), 4.55 (d, 2H, $J$ = 10.5), 4.67 (d, 2H, $J$ = 10.5), 4.90 (d, 2H, $J$ = 10.8), 5.48 (s, 1H), 5.54 (m, 1H, 1-H), 7.33 (m, 15H); $^{13}$C NMR ($CDCl_3$, 75 MHz) d 11.4, 12.6, 18.8, 22.8, 23.0, 23.8, 24.1, 24.5, 28.2, 28.3, 30.9, 33.3, 35.1, 36.1, 36.4, 37.0, 39.7, 40.4, 41.6, 42.7, 46.2, 48.1, 56.6, 68.5, 72.2, 72.5, 73.8, 75.3, 95.8, 104.7, 127.8, 127.9, 128.2, 128.6, 138.1, 138.5, 138.6, 170.2, 206.4. Anal. Calcd for $C_{54}H_{72}O_6$: C, 79.37; H, 8.88. Found: C, 79.22; H, 8.72.

**1-(3′,4′,6′-Tribenzyl-2′-deoxy-α-glucopyranosyl)cholest-2-en-3-one (13).** A teaspoonful of Raney nickel was washed first with absolute ethanol (4 × 5 mL) and then with toluene (4 × 5 mL). Into an ice-cooled suspension of Raney nickel in toluene (1 mL) was added cyclic oxathiine **19** (70 mg, 0.08 mmol) in HPLC-grade benzene (1.5 mL) under Ar. After being stirred at 0 °C for 2 h, the mixture was allowed to stir at rt for 18 h. The suspension was filtered through a Celite pad, which was washed repeatedly with ethyl acetate, and the filtrate was evaporated in vacuo and purified by flash chromatography over silica gel, eluting with petroleum ether −20% ethyl acetate, to give 14 mg (21% yield) of the title compound: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.65, (s, 3H), 0.86 (d, 6H, $J$ = 6.6), 0.88 (d, 3H, $J$ = 6.5), 1.14 (s, 3H), 3.60−3.96 (m, 4H), 4.47 (d, 2H, $J$ = 12.3), 4.55 (d, 2H, $J$ = 10.8), 4.88 (d, 2H, $J$ = 10.5), 5.56 (m, 1H), 5.58 (s, 1H), 7.38 (m, 15H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 11.9, 12.5, 12.7, 14.3, 18.8, 22.8, 23.0, 24.0, 24.4, 24.5, 26.0, 27.8, 28.1, 28.2, 28.3, 29.9, 31.0, 31.2, 35.2, 35.4, 35.98, 36.0, 36.3, 36.4, 37.7, 39.71, 39.74, 40.1, 40.7, 41.2, 42.7, 43.0, 44.1, 46.5, 46.8, 49.9, 56.5, 56.7, 57.2, 68.5, 70.3, 72.4, 73.2, 73.8, 75.5, 77.5, 78.4, 96.2, 105.0, 127.5, 127.9, 128.0, 128.1, 128.3, 128.6, 138.2, 138.4, 138.7, 184.7, 199.4.

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**Supporting Information Available:** The complete experimental procedures for the preparation of steroid materials **4**, **6**, and **7** plus the intermediates not shown in Scheme 2 along with copies of $^{13}$C and $^1$H NMR spectra for every compound in the schemes (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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