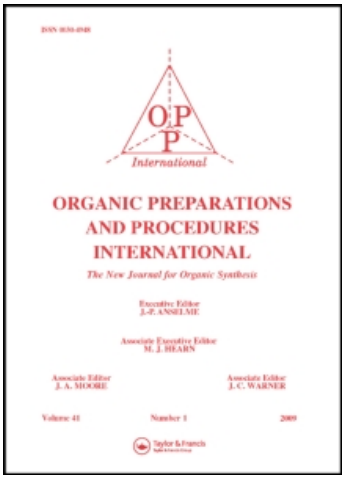

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SYNTHESIS OF ESTRIOL 16α-4',5'-DEHYDROGLUCURONIDE

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(1986). The yield for the last two steps was 72%. No yield was given for the first step.

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SYNTHESIS OF ESTRIOL 16α-4',5'-DEHYDROGLUCURONIDE

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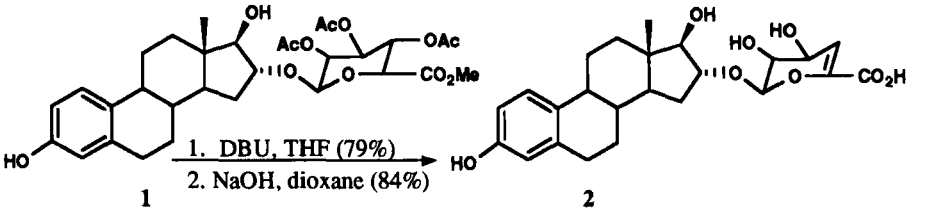
Glucuronides of biologically active compounds are essential as reference standards for analytical procedures and in basic research. For a total estriol immunoassay, we needed analytically-pure estriol 16α-glucuronide; HPLC analysis of commercial as well as our own synthetic estriol 16α-glucuronide[1] revealed that the material contained two components. The unknown material was tentatively identified as estriol-16α-4',5'-dehydroglucuronide **2**. We undertook the synthesis of **2** to confirm the structure of the unknown material and evaluate its cross-reactivity in our immunoassay. As shown below, elimination of acetic acid from glucuronate **1**[2] gave an intermediate α,β-unsaturated glucuronate which was hydrolyzed to the desired estriol 16α-4',5'-dehydroglucuronide **2** in 66% overall yield. The purity of other glucuronides has recently come under scrutiny[3] and this procedure should facilitate the identification of 4',5'-dehydroglucuronide "impurities" present in either synthetic or commercial preparations.



1 **2**

EXPERIMENTAL SECTION

Proton (500 MHz) and carbon (125 MHz) spectra were recorded on a GE-500 NMR spectrometer and mass spectra (FAB) were recorded on a Nermag 3010 spectrometer. Melting points were determined in open capillaries in a Thomas melting point apparatus and are uncorrected. All solvents were HPLC grade and used as is except for tetrahydrofuran (THF) which was distilled from sodium benzophenone ketyl immediately prior to use. Silica gel (EM grade 60) was purchased from Aldrich.

Estriol 16α-4',5'-Dehydroglucuronide 2.- 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 53 µL, 0.35 mmol) was added to a solution of **1**[2] (65 mg, 0.11 mmol) in 3.0 mL THF and stirred for 2 hrs to afford a clear yellow solution with complete disappearance of **1** by tlc. The reaction was quenched by adding glacial acetic acid (14 µL, 0.25 mmol) followed by removal of the volatile solvents *in vacuo*. The residue was dissolved in 0.5 mL chloroform and purified by flash chromatography (50% ethyl acetate/50% hexanes; v/v) to yield 46.4 mg (79%) of the intermediate α,β-unsaturated glucuronate as an off-white solid, mp. 155-157°.

^{1}H NMR ($CDCl_3$ + 2 drops CD_3OD): δ 7.13 (d, *J* = 8.60 Hz, 1H), 6.62 (dd, *J* = 8.17, 2.58 Hz, 1H), 6.56 (d, *J* = 2.58 Hz, 1H), 6.11 (*vinyl* H, d, *J* = 3.44 Hz, 1H), 5.42 (t, *J* = 4.30 Hz, 1H), 5.20 (t, 5.59 Hz, 1H), 5.11 (β-*anomeric* H[4], d, *J* = 6.02 Hz, 1H), 4.01-3.96 (m, 1H), 3.85 (s, 3H), 3.61 (d, *J* = 6.02 Hz, 1H), 2.83-2.76 (m, 2H), 2.29-2.14 (m, 2H), 2.10 (s, 3H), 2.09 (s, 3H), 2.02-1.86 (m, 2H), 1.83-1.77 (m, 1H), 1.72-1.67 (m, 1H), 1.56-1.25 (m, 5H), 0.82 (s, 3H); ^{13}C NMR($CDCl_3$ + 2 drops CD_3OD): δ 170.24, 169.52, 162.45, 153.56, 142.26, 138.02, 132.31, 126.37, 115.25, 112.74, 108.12, 99.73, 90.85, 87.32, 69.12, 66.77, 52.98, 47.78, 44.00, 43.81, 38.14, 36.70, 32.29, 29.51, 27.21, 25.88, 20.87, 20.75, 12.17; HRMS: m/z $(M+H)^+$ calcd 544.2308, obsd 544.2308.

Anal. Calcd for $C_{29}H_{36}O_{10}$: C, 63.96; H, 6.66. Found: C, 63.93; H, 7.01

The intermediate α,β-unsaturated glucuronate (30.8 mg, 0.058 mmol) was dissolved in 3 mL dioxane and 2.5 mL water whereupon 2N NaOH (0.47 mL, 0.94 mmol) was added; the reaction mixture was stirred for 2 hrs then adjusted to pH 7 with 1N HCl. After removing the volatile solvents *in vacuo*, purification by semi-preparative HPLC [methanol/water/acetic acid (55/45/1); v/v] afforded the desired estriol 16α-4',5'-dehydroglucuronide **2** (21.2 mg, 84%) as an off-white solid, mp. 182-183.5°(dec.).

^{1}H NMR (CD_3OD): δ 7.26 (d, *J* = 8.19 Hz, 1H), 6.73 (dd, *J* = 9.01, 2.46 Hz, 1H), 6.67 (d, *J* = 2.46 Hz, 1H), 6.23 (*vinyl* H, d, *J* = 3.28 Hz, 1H), 5.12 (β-*anomeric* H[4], d, *J* = 6.55 Hz, 1H), 4.37 (dd, *J* = 5.74, 3.28 Hz, 1H), 4.33-4.26 (m, 1H), 3.86-3.78 (m, 2H), 3.03-2.90 (m, 2H), 2.52-2.46 (m, 1H), 2.43-2.34 (m, 1H), 2.20-1.98 (m, 4H), 1.79-1.68 (m, 1H), 1.67-1.46 (m, 4H), 1.02 (s, 3H); ^{13}C NMR(CD_3OD): δ 165.75, 155.97, 142.41, 138.76, 132.46, 127.11, 116.06, 113.77, 113.54, 103.17, 88.92, 88.84, 72.73, 69.17, 49.13, 45.28, 44.92, 39.91, 38.03, 32.49, 30.63, 28.56, 27.18, 12.87; HRMS: m/z $(M+H)^+$ calcd 446.1940, obsd 446.1941.

Anal. Calcd for $C_{24}H_{30}O_8 \cdot 0.7\ H_2O$: C, 62.78; H, 6.89. Found: C, 62.75; H, 7.02

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SYNTHESIS OF CYCLOPROPANES USING S-ETHENYLSULFILIMINES†

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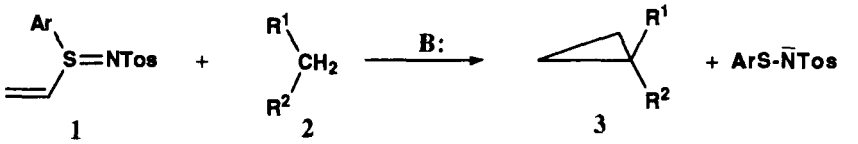
Cyclopropanes are useful compounds for transforming and enlarging carbon skeleton.[1] The main methods for their preparation involve the reaction of olefins with carbene and carbenoid sources,[2] of active methylene compounds with 1,2-dihaloalkanes[3] and with S-ethenylsulfonium compounds,[4] and of olefins with dimsyl anion and its analogues.[5] In recent years, heterogeneous reactions under PTC condition have been reported to give cyclopropanes in higher yields.[6] In a series of studies on the synthesis of ethenyl[7] and cyclic compounds[8] using S-ethenylsulfilimines, we have developed an efficient preparation of cyclopropanes using S-ethenylsulfilimines (**1**).

The method comprises three steps, Michael-type addition, prototropy (γ to α) followed intramolecular substitution.



1 **2** **3**

a) Ar = C_6H_5 b) Ar = 4-MeC_6H_4

S-Ethenyl-S-phenyl- (**1a**) and S-ethenyl-S-(4-methylphenyl)-N-tosylsulfilimines (**1b**) were used as S-ethenylsulfilimines. Seven compounds, whose pKa's values are different, were selected as active methylene compounds (**2**). The reaction of compounds **2** (in slight excess) with **1a** or **1b** were carried out in the presence of equimolar amount of sodium hydride in tetrahydrofuran (THF) at room temperature. The results are listed in Table 1. The reactions of both **1a** and **1b** with **2** gave the corresponding cyclopropanes (**3**) and the highest yields were obtained with **1b**. Moreover, the present method yields the target molecule **3e** from **1** and **2e**, while the PTC method[7] which affords the