which were filtered off, washed with water, and dried; mp 225 °C.

NMR Spectra. ^1H and ^{13}C spectra were recorded on a Varian XL-100-12 WG spectrometer. ^1H and ^{13}C shifts were measured with Me_4Si as an internal reference. ^1H spectra (100 MHz, 5-mm tubes, ^1H lock) were studied by using the CW mode. ^{13}C spectra (25.17 MHz, 10-mm tubes, ^2H lock) were collected by using the Fourier transform technique. The instrument was equipped with a 620 L-100-16 K on-line computer. Spectral widths of 5000 or 2500 Hz were used (digital resolution 1.25 or 0.68 Hz/point). The sample concentration was about 0.33 M.

Acknowledgment. We are indebted to Dr. J. Y. Lallemand for the ^1H spectra of **3a** recorded at 250 MHz with a CAMECA instrument.

Registry No. 1, 58-61-7; 1-H^+, 18475-49-5; **2a**, 74792-78-2; **3a**, 50827-00-4; **3a**-H^+, 74684-32-5.

Synthesis of 19-Norprogesterone and 19-Nordeoxycorticosterone

Chang-Yon Byon and Marcel Gut*

The Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts 01545

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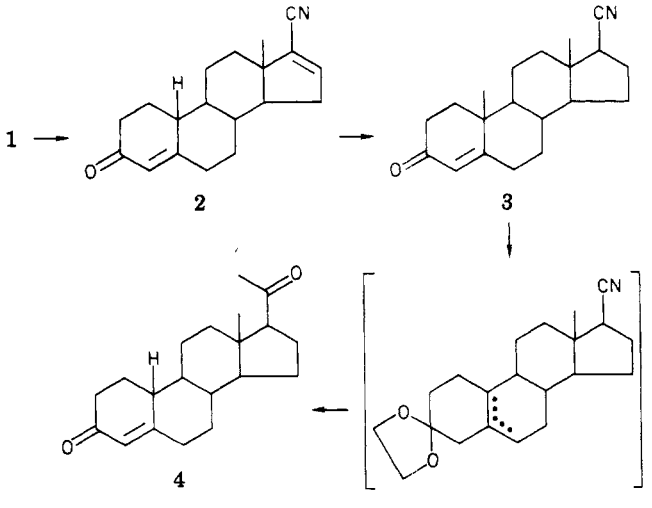
19-Norprogesterone was obtained by a synthesis similar to the one used for the transformation of androst-4-ene-3,17-dione to progesterone. 19-Norandrost-4-ene-3,17-dione was converted to its 17-cyanohydrin and dehydrated and the 16,17 double bond catalytically reduced. The 3-ketone was protected by ketalization with ethylene glycol and the crude product was reacted with methylmagnesium iodide to give the desired 19-norprogesterone in an overall yield of 15%. The starting material for 19-nordeoxycorticosterone was 19-norandrost-4-ene-3,17-dione 3-ethylene ketal which was transformed via a Wittig reaction and hydrolysis to 17β-formyl-19-norandrost-4-en-3-one and 3-oxoestr-4-en-17-al 3-ethylene ketal. Reaction of the keto aldehyde with propane-1,3-dithiol gave the bis(thioketal), the anion of which was treated with formaldehyde. The resulting 19-nordeoxycorticosteroid 3,20-bis(thioketal) was hydrolyzed to the desired 19-nordeoxycorticosterone in an overall yield of 10%.

17-Hydroxy-17-cyanoestr-4-en-3-one (1)[1] was dehydrated with phosphorus oxychloride in pyridine to give the conjugated nitrile **2**. Selective catalytic reduction with palladized charcoal gave 17β-cyanoestr-4-en-3-one (**3**) which was ketalized with ethylene glycol. The crude produce was reacted with methylmagnesium iodide and hydrolyzed to yield the desired 19-norprogesterone[2] (**4**) in a yield of 15% (from estr-4-ene-3,17-dione) (Scheme I).

Since we were unable to even approximate the published[3] yields for the Serini reaction on 17β-hydroxy-20,21-diacetoxy-19-norpregn-4-en-3-one to give 19-nordeoxycorticosterone acetate, we searched for another route to the desired 19-nordeoxycorticosterone. The following sequence, shown in Scheme II, led to the desired product. The known[1] 3-ethylene ketal of estr-4-ene-3,17-dione (**5**)[4] was reacted with (methoxymethylene)triphenylphosphonium chloride under Wittig conditions[5] to give the $\Delta^{5(6)}$ and $\Delta^{5(10)}$ mixture of 17-ξ-(methoxymethylene)-estr-4-en-3-one 1,2-ethanediyl acetal (**6**).[6] Hydrolysis with dilute perchloric acid gave 3-oxoestr-4-ene-17β-carboxaldehyde (**7**) and also the 3-oxoestr-4-en-17-al 3-(1,2-ethanediyl acetal) (**8**), a product arising from trans-

Scheme I



acetalization. The mixture of these two compounds was treated with propane-1,3-dithiol to give 3-oxoestr-4-ene-17-carboxaldehyde 3,20-bis(1,3-propanedithiylacetal) (**9a**). The anion of the thioacetal **9a**, produced with *n*-butyllithium, was alkylated with formaldehyde to give 21-hydroxy-19-nordeoxycorticosterone 3,20-bis(1,3-propanedithiyl acetal) (**9b**). Deacetalization with mercuric chloride and calcium carbonate gave the desired 19-nordeoxycorticosterone (**10**)[7] in an overall yield of ca. 10% (from **5**).

Another, albeit aborted, approach to 19-nordeoxycorticosterone (**10**) was initiated by the acetoxylation of

(1) P. de Ruggieri, *Gazz. Chim. Ital.*, 87, 795 (1957).

(2) For previous preparations of 19-norprogesterone see, e.g., J. S. Mills, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 6118 (1958); A. Bowers, R. Vilotti, J. A. Edwards, E. Donot, and O. Halpern, *ibid.*, 84, 3204 (1962).

(3) A. Sandoval, G. H. Thomas, C Djerassi, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, 77, 148 (1955).

(4) For an analysis of the ratio of $\Delta^{5(6)}$ and $\Delta^{5(10)}$ of a cyclic 3-(1,2-ethanediyl acetal) see F. T. Bond, W. Weyler, B. Brunner, and J. E. Stemke, *J. Med. Chem.*, 19, 255 (1976).

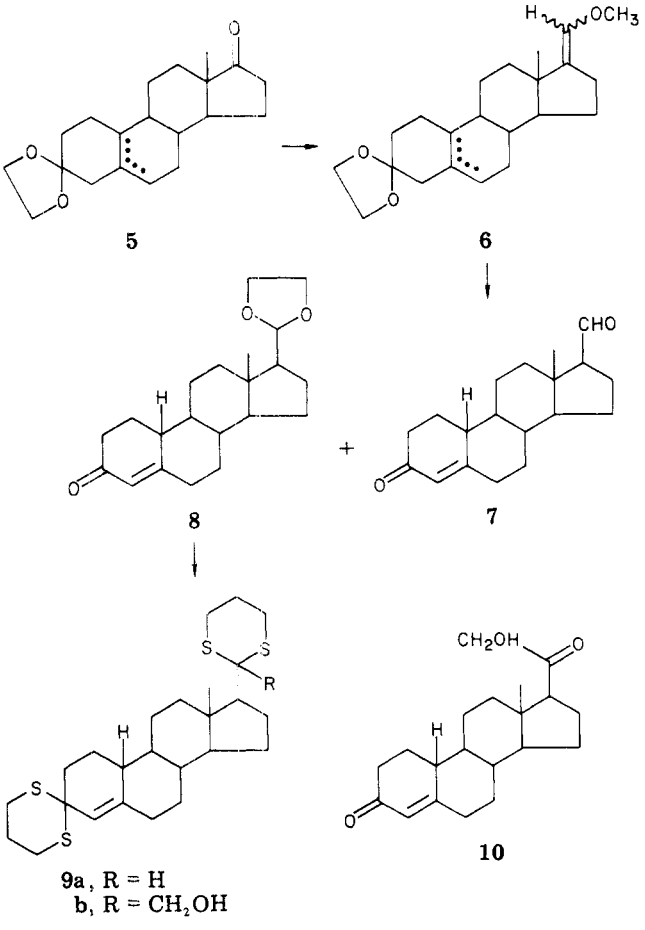
(5) S. Danishefsky, K. Nagasawa, and K. N. Wang, *J. Org. Chem.*, **40**, 1989 (1975).

(6) This product is a mixture of the two 17(20) double bond isomers as shown by the splitting of the 18-methyl and of the methoxy NMR signals.

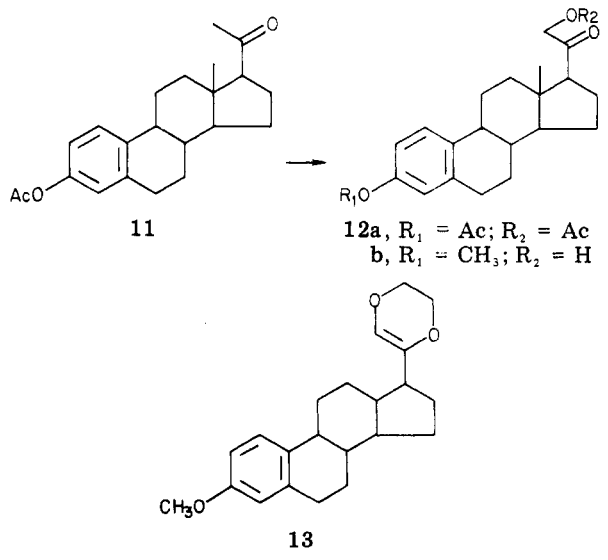
(7) A. Sandoval, L. Miramontes, G. Rosenkranz, C. Djerassi, and F. Sondheimer, *J. Am. Chem. Soc.*, **75**, 4117 (1953).

0022-3263/80/1945-4404$01.00/0

Scheme II



Scheme III



3-acetoxy-19-norpregna-1,3,5(10)-trien-20-one (11)[8] to give in fair yield 3,21-diacetoxy-19-norpregna-1,3,5(10)-trien-20-one (**12a**)[9]. The diacetate **12a** was hydrolyzed and the phenol fraction converted to its methyl ether to give the desired **12b**. Prior to the Birch reduction, we attempted to protect the 20-oxo group by ketalization. However, the only product isolated was the useless 3-methoxyestra-1,3,5(10)-triene-17-(1,2-ethanediol) cyclic 1,2-ethanediyl acetal (**13**) (Scheme III).

It is noteworthy that an attempted alkaline hydrolysis of the nitrile of 17β-cyanoestr-4-en-3-one (**3**) did not allow the isolation of any product.

Experimental Section

Melting points were determined on a Kofler melting-point apparatus and are uncorrected. The UV spectra were determined in methanolic solutions on a Cary Model 14 recording spectrophotometer. The NMR spectra were obtained in deuteriochloroform solution, using tetramethylsilane as an internal reference, and the positions of the proton signals are expressed in parts per million downfield from tetramethylsilane.

17-Cyanoestra-4,16-dien-3-one (2) from 17-Cyano-17-hydroxyestr-4-en-3-one (1). To a solution of 3.4 g of the cyanohydrin 1 in 20 mL of pyridine was added 2 mL of phosphorus oxychloride and the solution heated under reflux in a nitrogen atmosphere. After cooling to room temperature the brown solution was poured on ice, acidified with concentrated hydrochloric acid, and washed with water until neutral. Drying and evaporation of the solvent gave 3.1 g of crude product which was chromatographed on alumina and gave, after recrystallization from ethanol, 2.1 g of pure conjugated nitrile **2**: mp 127-128 °C; IR ν 2200 (CN), 1660 and 1600 cm^{-1} (conjugated ketone); NMR (60 MHz) δ 1.00 (s, 3 H, 18-CH_3), 5.80 (br s, 1 H, 4-H), 6.60 (t, 1 H, 16-H).

Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.82; H, 8.50; N, 4.52.

17β-Cyanoestr-4-en-3-one (3) from 17-Cyanoestra-4,16-dien-3-one (2). The solution of 280 mg of the diene **2** in 25 mL of ethyl acetate containing 100 mg of 10% palladium-on-charcoal was hydrogenated at 1 atm and after 10 min 1.3 equiv were taken up. Celite was added, the catalyst was filtered, and the filtrate was evaporated. The major product was isolated by preparative thin-layer chromatography to yield 170 mg of the saturated nitrile **3**, after recrystallization from methanol: mp 193-195 °C; IR ν 2220 (CN), 1660 and 1605 cm^{-1} (conjugated ketone); NMR (60 MHz) δ 1.00 (s, 3 H, 18-CH_3), 5.82 (br s, 1 H, 4-H).

Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.39; H, 9.09; N, 4.54.

19-Norprogesterone (4) from 17β-Cyanoestr-4-en-3-one (3). To a solution of 100 mg of enone **3** in 20 mL of benzene containing 20 mg of *p*-toluenesulfonic acid was added 0.1 mL of ethylene glycol and the resulting mixture was heated to reflux for 18 h. The water formed during the reaction was collected in a Dean-Stark apparatus. After cooling to room temperature the mixture was poured into a saturated sodium bicarbonate solution and extracted into benzene. The organic phase was washed three times with bicarbonate and then dried and the solvent was removed. There remained 103 mg of crude ketal which was dissolved in 1 mL of anhydrous benzene and added to a methyl Grignard solution, prepared from 15 mg of magnesium shavings. After the addition, the mixture was heated for 5 h under reflux, then cooled, and decomposed with ice cold saturated ammonium chloride solution. After workup the residue was dissolved in 5 mL of tetrahydrofuran, 2 drops of concentrated hydrochloric acid was added, and the solution was kept at 50 °C for 2 h. Evaporation under a stream of nitrogen at room temperature gave a residue of 86 mg which was purified by preparative thin-layer chromatography to give, after recrystallization from acetone-hexane, 38 mg of 19-norprogesterone (**4**): mp 140-143 °C; identical in mixture melting point, IR, TLC, and UV with an authentic sample; NMR (60 MHz) δ 0.70 (s, 3 H, 18-CH_3), 2.13 (s, 3 H, 21-CH_3), 5.83 (br s, 1H, 4-H).

17ε-(Methoxymethylene)estr-5-en-3-one 3-(1,2-Ethanediyl acetal) (6) from 5. A mixture of 4 g of 54.3% sodium hydride–mineral oil dispersion in 70 mL of anhydrous dimethyl sulfoxide was stirred at 55 °C under a nitrogen atmosphere until no hydrogen evolution could be detected. The mixture was cooled to room temperature and a solution of (methoxymethylene)triphenylphosphonium chloride in 150 mL of anhydrous dimethyl sulfoxide was added. Then 4.9 g of **5** in 50 mL of anhydrous dimethyl sulfoxide was added, and the resulting mixture was stirred at 70 °C for 10 h. The reaction mixture was extracted with methylene chloride and the combined extracts were washed with water and saturated sodium chloride solution, dried (Na_2SO_4), and evaporated. The residue was purified by column chroma-

(8) C. Djerassi, G. Rosenkranz, J. Iriarte, J. Berlin, and J. Romo, *J. Am. Chem. Soc.*, **73**, 1523 (1951).
(9) C. Djerassi and C. T. Lenk, *J. Am. Chem. Soc.*, **76**, 1722 (1954).

tography on alumina. Elution with 5% methylene chloride in hexane gave 3.4 g of **5**. An analytical sample was prepared by recrystallization from acetone: mp 166–168 °C; NMR (60 MHz) δ 0.82 and 0.90 (s, 3 H, 18-CH_3), 3.47 and 3.55 (s, 3 H, OCH_3), 3.95 and 3.98 (uneven d, 4 H, OCH_2CH_2O), 5.47 (m, 1 H, 6-H proton), 5.73 (m, 1 H, =C**H**OCH_3).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.56; H, 9.15.

17β-Formylestr-4-en-3-one 3,20-Bis(1,3-propanedithiyl Acetal) (9a) from 6. To the solution of 3 g of **6** in 150 mL of ether was added 15 drops of 70% aqueous perchloric acid while cooling in an ice bath. After being stirred at 0 °C for 5 min and at room temperature for 50 min, the reaction mixture was poured into ice water. To this mixture was added ethyl acetate and the organic phase was washed successively with saturated sodium bicarbonate solution and water. After the solution was dried over sodium sulfate, the solvent was evaporated to give 2.7 g of crude compound. An aliquot was cleaned on TLC (15% acetone in hexane, multiple runs) to yield **7** and **8**. The former is more polar than the latter; **7**: NMR (60 MHz) δ 0.83 (s, 3 H, 18-CH_3), 5.85 (m, 1 H, 4-H), 9.77 (d, J = 2 Hz, 1 H, CHO), **8**: 0.80 (s, 3 H, 18-CH_3), 3.85 (m, 4 H, OCH_2CH_2O), 4.73 (m, 1 H OCHO).

To the solution of 2.5 g of the crude mixture in 50 mL of $CHCl_3$ containing 2.8 mL of 1,3-propanedithiol was added 0.3 mL of BF_3–Et_2O at 0 °C. After being stirred at room temperature for 20 h, the mixture was poured into ice water. The methylene chloride extracts were washed with water, 10% potassium hydroxide solution, water, and saturated sodium chloride solution, and the extract was dried over sodium sulfate. The residue was purified by column chromatography on alumina. Elution with hexane and 2% ethyl acetate in hexane gave 2.3 g of **9a**. An analytical sample was prepared by recrystallization from methylene chloride and methanol: mp 166–169 °C; NMR (90 MHz) δ 0.83 (s, 3 H, 18-CH_3), 2.81 (m, 12 H, $SCH_2CH_2CH_2S$), 4.00 (d, J = 10 Hz, 1 H, SCHS), 5.48 (br s, 1 H, 4-H).

Anal. Calcd for $C_{25}H_{38}S_4$: C, 64.36; H, 8.21; S, 27.44. Found: C, 64.47; H, 8.01; S, 27.29.

19-Nordeoxycorticosterone 3,20-Bis(1,3-propanedithiyl Acetal) (9b) from 9a. To 2.6 g of **9a** in 5 mL of anhydrous THF was added 5.3 mL of n-butyllithium (1.5 M) dropwise at −40 °C. The mixture was stirred at −20 °C for 3.5 h. After addition of 40 mL of anhydrous ether, paraformaldehyde gas was introduced into this solution by a slow flow of nitrogen while cooling in a dry ice–acetone bath, and the mixture was stirred at room temperature overnight. Then the mixture was poured into ice water and extracted with methylene chloride, and the extract was washed with saturated sodium chloride and water, and dried over sodium sulfate. Evaporation of the solvent yielded 2.7 g of crude **9b**. The purification of 61 mg of crude product on TLC gave 21 mg of pure alcohol **9b**: mp 87-90 °C (MeOH); NMR (60 MHZ) δ 1.00 (s, 3 H, 18-CH_3), 2.78 (m, 12 H, $SCH_2CH_2CH_2S$), 4.17 (br s, 1 H, CH_2OH), 5.43 (br s, 1 H, 4-H); mass spectrum, m/e 496 (M^+), 478 (M^+ − 18), 465 (M^+ − 31), 404 (M^+ − 92).

19-Nordeoxycorticosterone (10) from 9b. To a mixture of 1.1 g of the dithiane adduct **9b** in 200 mL of methanol and 48 mL of water were added 2.6 g of mercuric chloride and 960 mg of calcium carbonate and then the mixture was heated to reflux for 5 h. The precipitate was filtered off and washed with methylene chloride. The filtrate was transferred into a separatory funnel containing three times the volume of water. The methylene chloride extracts were washed with ammonium chloride solution and water and then dried over sodium sulfate. Evaporaton of the solvent furnished 600 mg of **10**, identical in all respects with authentic 19-nordeoxycorticosterone (IR, melting point, NMR, TLC): NMR (60 MHz) δ 0.73 (s, 3 H, 18-CH_3), 4.17 and 4.20 (br d, 2 H, CH_2OH), 5.85 (br s, 1 H, 4 H).

3,21-Diacetoxy-19-norpregna-1,3,5(10)-trien-20-one (12a) from 3-Acetoxy-19-norpregna-1,3,5(10)-trien-20-one (11). To a stirred solution of 500 mg of the methyl ketone **11** in 25 mL of benzene and 1.4 mL of methanol was added 900 mg of lead tetraacetate. The solution was cooled and 3.4 mL of boron trifluoride etherate was added and then the solution was stirred at 25 °C for 5 h. After dilution with ethyl acetate the organic phase was washed with water, saturated aqueous sodium bicarbonate, and water and dried and the solvents were evaporated. The residue was chromatographed on 50 g of silica gel to give from the corresponding fractions 277 mg of acetoxy ketone **12a**, mp 124–125 °C (lit.[3] 124-125°C), identical in all respects with an authentic sample.

3-Methoxy-21-hydroxy-19-norpregna-1,3,5(10)-trien-20-one (12b) from Its 3,21-Diacetate 12a. To a solution of 400 mg of diacetate **12a** in 100 mL of methanol was added a solution of 1.2 g of potassium bicarbonate in 12 mL of water and the combined solutions were left at 25 °C for 20 h. Extraction with methylene chloride, followed by drying of the extract and evaporation of the solvent, gave, after two recrystallizations from methanol, 320 mg of prisms: mp 170-172 °C; IR ν 3500 (OH), 1750 cm^{-1} (ketone). This material was not further analyzed. To a solution of 300 mg of this diol in 30 mL of absolute ethanol were added 600 mg of anhydrous potassium carbonate and 2 mL of methyl iodide and the reaction mixture was heated at reflux temperature under a nitrogen atmosphere for 5 h. After 2 h an additional 2 mL of methyl iodide was added. The solution was cooled to room temperature and water and benzene were added. The organic phase was washed with 1 N sodium hydroxide solution, then washed to neutrality with water, and dried, and the solvents were evaporated. The residue was recrystallized from methanol to give 246 mg of methyl ether **12b**: mp 124-125 °C; IR ν 3600 (OH), 1750 cm^{-1} (ketone); UV = 286 nm (ϵ 2000), 278 (2100); NMR (60 MHz) δ 0.70 (s, 3 H, 18-CH_3), 3.78 (s, 3 H, OCH_3), 4.23 (s, 2 H, CH_2OH), 6.68-7.24 (m, 3 H, aromatic protons).

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.76; H, 8.38.

3-Methoxyestra-1,3,5(10)-triene-17β-(5,6-dihydro-2-dioxin) (13) from 12b. The solution of 200 mg of the ketol **12b** in 15 mL of benzene containing 0.1 mL of ethylene glycol and 15 mg of p-toluenesulfonic acid was heated under reflux with stirring 5 h with a water separator. Then the mixture was cooled, saturated sodium bicarbonate solution was added, and the organic phase was washed twice with water, dried, and evaporated. The residue was recrystallized from methanol to give 122 mg of dioxin **13**: mp 142-143 °C; NMR (60 MHz) δ 0.67 (s, 3 H, 18-CH_3), 3.73 (s, 3 H, OCH_3), 4.00 (s, 4 H, OCH_2CH_2O), 5.83 (s, 1 H, OCH=C), 6.60–7.18 (m, 3 H, aromatic).

Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.73; H, 8.34.

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Registry No. **1**, 17006-06-3; **2**, 74824-58-1; **3**, 40148-29-6; (5-ene)-**3** cyclic ethylene ketal, 74824-59-2; (5(10)-ene)-**3** cyclic ethylene ketal, 40148-28-5; **4**, 472-54-8; (5-ene)-**5**, 6193-98-2; (5(10)-ene)-**5**, 6193-99-3; (5-ene)-**6** (isomer 1), 74824-60-5; (5(10)-ene)-**6** (isomer 1), 74824-61-6; (5-ene)-**6** (isomer 2), 74824-62-7; (5(10)-ene)-**6** (isomer 2), 74824-63-8; **7**, 60124-24-5; **8**, 74824-64-9; **9a**, 74824-65-0; **9b**, 74824-66-1; **10**, 4682-70-6; **11**, 67530-18-1; **12a**, 74824-67-2; **12a** free alcohol, 74824-68-3; **12b**, 74867-49-5; **13**, 74824-69-4; 1,3-propanedithiol, 109-80-8.