Monatshefte für Chemie 135, 1129–1136 (2004)
DOI 10.1007/s00706-004-0203-9

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

The *Mitsunobu* Inversion Reaction of Sterically Hindered 17-Hydroxy Steroids

Pál Tapolcsányi, János Wölfling, Erzsébet Mernyák, and **Gyula Schneider***

Department of Organic Chemistry, University of Szeged, H-6720 Szeged, Hungary

Received March 4, 2004; accepted March 29, 2004
Published online June 30, 2004

Summary. The *Mitsunobu* inversion reaction of 3-methoxyestra-1,3,5(10)-trien-17β-ol is dramatically influenced by the acidic component. There appears to be a relationship between the dissociation constant of the electron-withdrawing substituent on the aryl acid and the overall effectiveness of the reaction, with more acidic species generally providing a higher yield of inverted product.

Keywords. Steroids; Estrone derivatives; *Mitsunobu* reaction; Carboxylic acids; Isomers.

Introduction

The *Mitsunobu* reaction is widely employed for the inversion of configuration in secondary alcohol derivatives [1, 2]. In general, this method proves efficacious for a variety of substrates, furnishing useful yields of inverted products under mild, essentially neutral reaction conditions. One of the most frequent goals of the application of the *Mitsunobu* reaction is the epimerization of optically active secondary alcohols, and most of the published papers have reported and discussed such transformations [3]. In these procedures, the optically active alcohol is reacted with different carboxylic acids under *Mitsunobu* conditions. In most cases, the acid strength is not the determining factor in the reaction, but for sterically hindered alcohols, application of a strong acid is recommended [4]. Early references to this observation included primary and secondary substrates such as nucleosides, carbohydrates, and alkaloids [5–7]. 4-Nitrobenzoic acid has been shown to be a particularly effective coupling reagent for sterically encumbered alcohols [8, 9], a finding which has led to practical modifications of the *Mitsunobu* reaction

* Corresponding author. E-mail: schneider@chem.u-szeged.hu
Dedicated to Professor *Sándor Antus* on the occasion of his 60th birthday

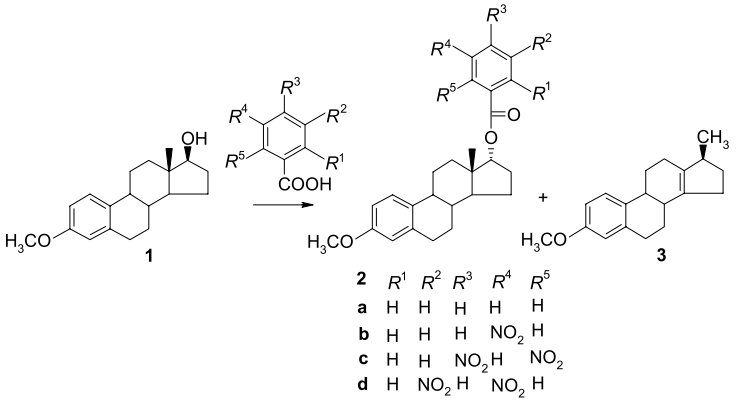
[10, 11]. Despite these observations, the origins of this interesting phenomenon have received little attention [12].

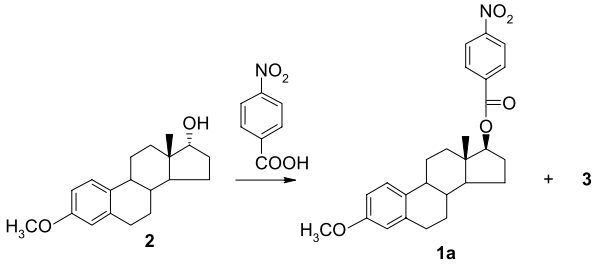
Dodge et al. have recently investigated the role of the carboxylic acid in the *Mitsunobu* inversion of menthol [13], and other sterically hindered hydroxyl functions on different sterane skeletons [14]. They found that, with different acids as nucleophilic reagents, the relatively acidic 4-nitrobenzoic acid proved to be the most convenient coupling partner. We have studied the *Mitsunobu* inversion of the 17β- and 17α-hydroxy groups of 3-methoxyestra-1,3,5(10)-trien-17-ol (**1**, **2**), using different carboxylic acids and solvents. Moreover, we have investigated the reactions of 16β-methyl- and 16α-methyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (**4**, **5**) in order to establish whether the *Mitsunobu* reaction is suitable for the inversion of strongly hindered alcohols which have two adjacent substituents.

Results and Discussion

Since literature reveals that both the carboxylic acid and the solvent used for the *Mitsunobu* inversion process exert a considerable influence on the outcome of the reaction, we performed the *Mitsunobu* inversion of 3-methoxyestra-1,3,5(10)-trien-17β-ol (**1**) with various carboxylic acids in three different solvents: toluene, chlorobenzene, and hexamethylphosphorus triamide (*HMPT*). The results demonstrated that the more acidic aromatic carboxylic acids gave better yields in the *Mitsunobu* reaction. The traditionally used relatively weak benzoic acid ($pK_a =$ 4.16) is one of the least attractive coupling partners. 4-Nitrobenzoic acid ($pK_a =$ 3.41) gave a similar result to that reported by *Dodge and Lugar* [14]. Despite being more acidic, 3,5-dinitrobenzoic acid ($pK_a = 2.82$) led to a yield similar to that with 4-nitrobenzoic acid. The best result was achieved with 2,4-dinitrobenzoic acid, which has the highest dissociation constant ($pK_a = 1.42$). Among the solvents, toluene and chlorobenzene proved convenient. *HMPT* is suitable for the S_N2 exchange reactions of steroid-oxyphosphonium species with nucleophilic aryl acids. In the present systems, however, *HMPT* furnished only lower yields and the work-up of the reaction mixture was more difficult, too. In each case, besides the desired product we isolated an unsaturated side-product, 3-methoxy-17β-methylestra-1,3,5(10),13-tetraene (**3**). Evidence of the structure of compound **3** was provided by the exchange reaction of 17α-chloro-3-methoxyestra-1,3,5(10)-triene with sodium acetate [15] and by the acetolysis of 17β-*p*-tolylsulfonyloxy-3-methoxyestra-1,3,5(10)-triene with potassium acetate [16]. The formation of this compound can be explained by the *Wagner-Meerwein* rearrangement of steroid-oxyphosphonium species in parallel with the nucleophilic exchange reaction. The first *Wagner-Meerwein* rearrangement under *Mitsunobu* reaction conditions had been found for the rigid bicyclo[3.1.1.]heptanol system by *Evans et al.* [17] (Scheme 1).

To compare the reactivities of the 17β- and 17α-hydroxy groups, we carried out the *Mitsunobu* reaction of 3-methoxyestra-1,3,5(10)-trien-17α-ol (**2**) with 4-nitrobenzoic acid in toluene and in chlorobenzene. 3-Methoxyestra-1,3,5(10)-trien-17β-yl (4-nitrobenzoate) (**1a**) was obtained in only 10% and 12% yield. The main product in both cases was **3**. The *pseudo axial* 17α-hydroxy group exhibits low



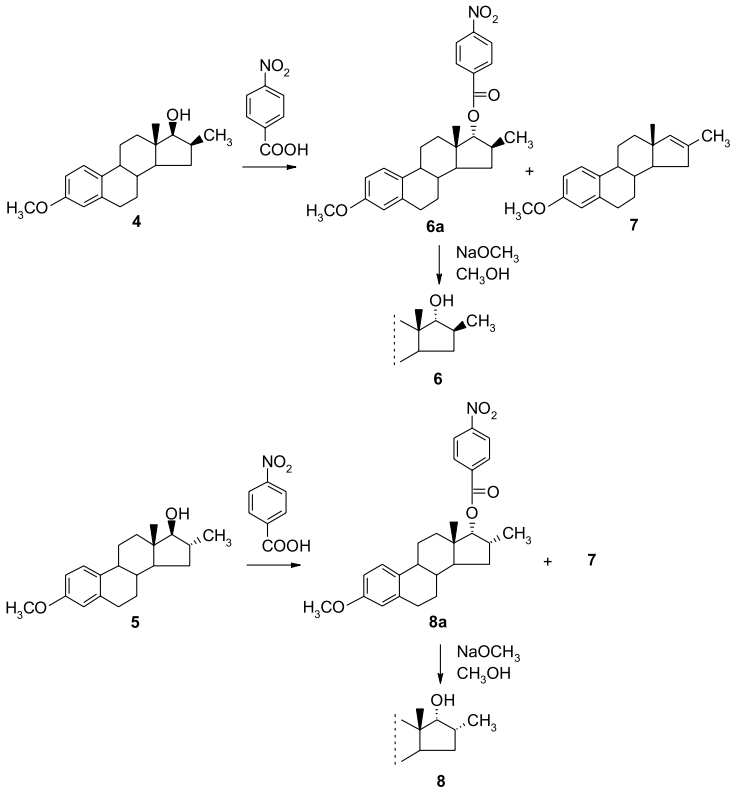


Scheme 1

reactivity, in agreement with the general behaviour of the *axial* hydroxy group of steroids [3].

We performed the *Mitsunobu* inversion of the very encumbered 16β-methyl and 16α-methyl-3-methoxyestra-1,3,5(10)-trien-17β-ols (**4**, **5**). The two methyl functionalities cause strong steric hindrance about the adjacent alcohol moiety. For compounds unsubstituted at position C-16 (**1**, **2**), the most acidic 2,4-dinitrobenzoic acid has proved to be the most effective. In the case of 16β-methyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (**4**), 2,4-dinitrobenzoic acid and 4-nitrobenzoic acid gave similar yields. For the *Mitsunobu* reaction we chose the less bulky 4-nitrobenzoic acid, which resulted in 17% 16β-methyl-3-methoxyestra-1,3,5(10)-trien-17α-yl (4-nitrobenzoate) (**6a**), 15% 16-methyl-3-methoxyestra-1,3,5(10),16-tetraene (**7**), and 65% unreacted starting compound **4**. A surprisingly high yield was achieved in the *Mitsunobu* inversion of 16α-methyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (**5**). 16α-Methyl-3-methoxyestra-1,3,5(10)-trien-17α-yl (4-nitrobenzoate) (**8a**) was obtained in 60%, **7** in 5%, and unreacted **5** in 31% yield (Scheme 2).

The great difference in reactivity of the two isomers **4** and **5** can be explained by steric reasons. The formation of the oxyphosphonium salt at the β-hydroxy group is probably much more hindered by the two adjacent methyl groups, also in the β-position, than in the case of **5**, where the methyl group is situated far from the reaction center. The formation of 16-methyl-3-methoxyestra-1,3,5(10),16-tetraene (**7**) can easily be explained by the elimination of the oxyphosphonium species preceding the last step of the *Mitsunobu* reaction.



Scheme 2

Experimental

Melting points were determined on a *Kofler* block. Optical rotations were measured in chloroform ($c = 1$) on a Polamat-A (Zeiss, Jena) polarimeter at 23°C, and $[\alpha]_D$ values are given in 10^{-1} °cm^2 g^{-1}. NMR spectra were recorded on a Bruker AM 400 instrument. Chemical shifts (δ) are given in ppm, and coupling constants (J) in Hz. For the determination of multiplicities, the J-MOD pulse sequence was used. Elemental analysis data were determined with a Perkin-Elmer CHN analyser model 2400. For all new compounds satisfactory elemental analyses were obtained. Thin-layer chromatography: silica gel 60, layer thickness 0.2 mm (Merck); solvent system (ss): (A) chloroform, (B) ethyl acetate:chloroform (5:95, v/v); detection with iodine or UV (365 nm) or by spraying with 50% phosphoric acid and heating at 100–120°C for 10 min. Flash chromatography: silica gel 60, 40–63 μm.

General Procedure

3-Methoxyestra-1,3,5(10)-trien-17-ol (**1**, **2**; 1 mmol, 286 mg) or 3-methoxy-16-methylestra-1,3,5(10)-trien-17-ol (**4**, **5**; 1 mmol, 300 mg), 656 mg of triphenylphosphine (2.5 mmol), and 305 mg of benzoic acid (2.5 mmol) or substituted benzoic acid (2.5 mmol) were suspended in 15 cm^3 of dry toluene in a 50 cm^3, three-necked, round-bottomed flask equipped with a thermometer, a dropping funnel, and a reflux condenser with a $CaCl_2$-tube. The flask was placed on a heating magnetic stirrer and stirred for 2 min, and 436 mg of diethyl azodicarboxylate (2.5 mmol) were then added dropwise at room temperature. The suspension cleared to give a yellow-orange solution and became slightly warm. The reaction mixture was kept at 80°C for 1.5 h, the solvent was then removed under vacuum, and the residue was subjected to chromatography and eluted with $CHCl_3$. With *HMPT* as solvent, the work-up

was as follows: at the end of the reaction, the reaction mixture was poured into water and allowed to stand overnight. A dense oil formed, which was then separated from H_2O and dissolved in $CHCl_3$. After drying and evaporation of the solvent, the residue was chromatographed on a silica gel column with $CHCl_3$.

*Mitsunobu Esterification of **1** with Benzoic Acid*

In toluene: A mixture of 286 mg of **1** (1 mmol) and 305 mg of benzoic acid (2.5 mmol) was treated in 15 cm^3 of toluene as described in the general procedure. The resulting crude product was chromatographed on a silica gel column with $CHCl_3$. The separation resulted in 83 mg of **3** (31%), mp 108–110°C (Ref. [15] 107–109°C), $R_f = 0.85$ (ss A); $[\alpha]_D^{20} = -54\,10^{-1}\,°cm^2\,g^{-1}$ ($c = 1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si): $\delta = 1.01$ (d, $J = 7.0$ Hz, 17-CH_3), 1.30–2.65 (overlapping multiplets, 13H), 2.90 (m, 6-H_2), 3.78 (s, 3-OCH_3), 6.66 (d, $J = 2.6$ Hz, 4-H), 6.72 (dd, $J = 8.6$, 2.6 Hz, 2-H), 7.26 (d, $J = 8.6$ Hz, 1-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si): $\delta = 19.5$ (17-CH_3), 24.1, 26.9, 27.2, 30.1, 31.3, 32.1, 39.8 (C-8), 41.3 (C-9), 41.7 (C-17), 55.2 (3-OCH_3), 111.2 (C-2), 113.9 (C-4), 125.9 (C-1), 133.0 (C-10), 136.9 (C-13), 138.3 (C-14), 138.9 (C-5), 157.5 (C-3) ppm. Continued elution resulted in 148 mg of **2a** (38%), mp 98–101°C, $R_f = 0.60$ (ss A); $[\alpha]_D^{20} = -17\,10^{-1}\,°cm^2\,g^{-1}$ ($c = 1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si): $\delta = 0.86$ (s, 18-H_3), 1.30–2.40 (overlapping multiplets, 13H), 2.87 (m, 6-H_2), 3.77 (s, 3-OCH_3), 5.11 (d, $J = 6.0$ Hz, 17-H), 6.64 (d, $J = 2.6$ Hz, 4-H), 6.71 (dd, $J = 8.6$, 2.6 Hz, 2-H), 7.20 (d, $J = 8.6$ Hz, 1-H), 7.45 (m, 3′- and 5′-H), 7.55 (t, $J = 7.3$ Hz, 4′-H), 8.06 (d, $J = 7.9$ Hz, 2′- and 6′-H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, Me_4Si): $\delta = 16.8$ (C-18), 24.5, 26.2, 28.1, 29.9, 30.3, 32.2, 39.1 (C-8), 43.7 (C-9), 45.4 (C-13), 49.5 (C-14), 55.2 (3-OCH_3), 82.6 (C-17), 111.5 (C-2), 113.8 (C-4), 126.4 (C-1), 128.3 (2C, C-3′ and C-5′), 129.5 (2C, C-2′ and C-6′), 130.9 (C-1′), 132.6 (C-10), 132.7 (C-4′), 137.9 (C-5), 157.5 (C-3), 166.1 (C=O) ppm. Further elution yielded 72 mg of unreacted **1** (25%).

In chlorobenzene: A mixture of 286 mg of **1** (1 mmol) and 305 mg of benzoic acid (2.5 mmol) was treated in 15 cm^3 of chlorobenzene as described in the general procedure. The resulting crude product was chromatographed on a silica gel column with $CHCl_3$. The separation resulted in 94 mg of **3** (35%), 117 mg of **2a** (30%), and 92 mg of **1** (32%).

In *HMPT*: A mixture of 286 mg of **1** (1 mmol) and 305 mg of benzoic acid (2.5 mmol) was treated in 15 cm^3 of *HMPT* as described in the general procedure. The resulting crude product was chromatographed on a silica gel column with $CHCl_3$. The separation resulted in 32 mg of **3** (12%), 141 mg of **2a** (36%), and 137 mg of **1** (48%).

*Mitsunobu Esterification of **1** with 4-Nitrobenzoic Acid*

In toluene: A mixture of 286 mg of **1** (1 mmol) and 418 mg of 4-nitrobenzoic acid (2.5 mmol) was treated in 15 cm^3 of toluene as described in the general procedure. The resulting crude product was chromatographed on a silica gel column with $CHCl_3$. The separation resulted in 16 mg of **3** (6%). Continued elution resulted in 357 mg of **2b** (82%), mp 154–155°C, $R_f = 0.55$ (ss A); $[\alpha]_D^{20} = -31\,10^{-1}\,°cm^2\,g^{-1}$ ($c = 1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si): $\delta = 0.88$ (s, 18-H_3), 1.35–1.85 (overlapping multiplets, 8H), 1.95 (m, 2H), 2.38 (m, 3H), 2.88 (m, 6-H_2), 3.78 (s, 3-OCH_3), 5.15 (d, $J = 6.1$ Hz, 17-H), 6.64 (d, $J = 2.7$ Hz, 4-H), 6.71 (dd, $J = 8.6$, 2.7 Hz, 2-H), 7.20 (d, $J = 8.6$ Hz, 1-H), 8.22 (d, $J = 8.8$ Hz, 2′- and 6′-H), 8.30 (d, $J = 8.8$ Hz, 3′- and 5′-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si): $\delta = 16.8$ (C-18), 24.4, 26.1, 28.1, 29.9, 30.2, 32.2, 39.1 (C-8), 43.7 (C-9), 45.5 (C-13), 49.6 (C-14), 55.2 (3-OCH_3), 83.9 (C-17), 111.5 (C-2), 113.8 (C-4), 123.5 (2C, C-3′ and C-5′), 126.3 (C-1), 130.6 (2C, C-2′ and C-6′), 132.3 (C-10), 136.2 (C-1′), 137.9 (C-5), 150.5 (C-4′), 157.5 (C-3), 164.2 (C=O) ppm. Further elution yielded 28 mg of unreacted **1** (10%).

In chlorobenzene: A mixture of 286 mg of **1** (1 mmol) and 418 mg of 4-nitrobenzoic acid (2.5 mmol) was treated in 15 cm^3 of chlorobenzene as described in the general procedure. The resulting

crude product was chromatographed on a silica gel column with $CHCl_3$. The separation resulted in 27 mg of **3** (10%), 340 mg of **2b** (78%), and 28 mg of **1** (10%).

In *HMPT*: A mixture of 286 mg of **1** (1 mmol) and 418 mg of 4-nitrobenzoic acid (2.5 mmol) was treated in 15 cm^3 of *HMPT* as described in the general procedure. The resulting crude product was chromatographed on a silica gel column with $CHCl_3$. The separation resulted in 13 mg of **3** (5%), 270 mg of **2b** (62%), and 74 mg of **1** (26%).

*Mitsunobu Esterification of **1** with 3,5-Dinitrobenzoic Acid*

In toluene: A mixture of 286 mg of **1** (1 mmol) and 530 mg of 3,5-dinitrobenzoic acid (2.5 mmol) was treated in 15 cm^3 of toluene as described in the general procedure. The resulting crude product was chromatographed on a silica gel column with $CHCl_3$. The separation resulted in 27 mg of **3** (10%). Continued elution yielded 389 mg of **2c** (81%), mp 174–175°C, $R_f = 0.70$ (ss A); $[\alpha]_D^{20} = -5\,10^{-1}\,°cm^2\,g^{-1}$ ($c = 1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si): $\delta = 0.90$ (s, 18-H_3), 1.30–2.50 (overlapping multiplets, 13H), 2.88 (m, 6-H_2), 3.77 (s, 3-OCH_3), 5.23 (d, $J = 6.2$ Hz, 17-H), 6.63 (d, $J = 2.7$ Hz, 4-H), 6.69 (dd, $J = 8.6$, 2.7 Hz, 2-H), 7.18 (d, $J = 8.6$ Hz, 1-H), 9.14 (d, $J = 2.3$ Hz, 2′- and 6′-H), 9.22 (t, $J = 2.3$ Hz, 4′-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si): $\delta = 16.7$ (C-18), 24.5, 26.1, 28.0, 29.8, 30.1, 32.4, 39.1 (C-8), 43.6 (C-9), 45.7 (C-13), 49.6 (C-14), 55.2 (3-OCH_3), 85.2 (C-17), 111.5 (C-2), 113.8 (C-4), 122.2 (C-4′), 126.3 (C-1), 129.3 (2C, C-2′ and C-6′), 132.1 (C-10), 134.4 (C-1′), 137.8 (C-5), 148.7 (2C, C-3′ and C-5′), 157.5 (C-3), 162.1 (C=O) ppm. Further elution yielded 14 mg of **1** (5%).

In chlorobenzene: A mixture of 286 mg of **1** (1 mmol) and 530 mg of 3,5-dinitrobenzoic acid (2.5 mmol) was treated in 15 cm^3 of chlorobenzene as described in the general procedure. The resulting crude product was chromatographed on a silica gel column with $CHCl_3$. The separation resulted in 27 mg of **3** (10%) and 404 mg of **2c** (84%).

*Mitsunobu Esterification of **1** with 2,4-Dinitrobenzoic Acid*

In toluene: A mixture of 286 mg of **1** (1 mmol) and 530 mg of 2,4-dinitrobenzoic acid (2.5 mmol) was treated in 15 cm^3 of toluene as described in the general procedure. The resulting crude product was chromatographed on a silica gel column with $CHCl_3$. The separation resulted in 8 mg of **3** (3%). Continued elution yielded 461 mg of **2d** (96%), mp 86–89°C, $R_f = 0.70$ (ss A); $[\alpha]_D^{20} = -77\,10^{-1}\,°cm^2\,g^{-1}$ ($c = 1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si): $\delta = 0.85$ (s, 18-H_3), 1.35–2.40 (overlapping multiplets, 13H), 2.84 (m, 6-H_2), 3.77 (s, 3-OCH_3), 5.12 (d, $J = 5.9$ Hz, 17-H), 6.62 (d, $J = 2.5$ Hz, 4-H), 6.69 (dd, $J = 8.6$, 2.5 Hz, 2-H), 7.18 (d, $J = 8.6$ Hz, 1-H), 7.98 (d, $J = 8.6$ Hz, 6′-H), 8.52 (dd, $J = 8.6$, 2.2 Hz, 5′-H), 8.73 (d, $J = 2.2$ Hz, 3′-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si): $\delta = 16.6$ (C-18), 24.2, 26.1, 28.0, 29.7, 29.8, 31.8, 39.0 (C-8), 43.4 (C-9), 45.3 (C-13), 49.1 (C-14), 55.2 (3-OCH_3), 86.0 (C-17), 111.5 (C-2), 113.8 (C-4), 119.5 (C-3′), 126.3 (C-1), 127.2 (C-5′), 131.5 (C-6′), 132.3 (C-10), 133.0 (C-1′), 137.9 (C-5), 148.4 and 148.9 (2C, C-2′ and C-4′), 157.5 (C-3), 163.1 (C=O) ppm.

In chlorobenzene: A mixture of 286 mg of **1** (1 mmol) and 530 mg of 2,4-dinitrobenzoic acid (2.5 mmol) was treated in 15 cm^3 of chlorobenzene as described in the general procedure. The resulting crude product was chromatographed on a silica gel column with $CHCl_3$, yielding 471 mg of **2d** (98%).

In *HMPT*: A mixture of 286 mg of **1** (1 mmol) and 530 mg of 2,4-dinitrobenzoic acid (2.5 mmol) was treated in 15 cm^3 of *HMPT* as described in the general procedure. The resulting crude product was chromatographed on a silica gel column with $CHCl_3$, yielding 355 mg of **2d** (74%) and 34 mg of **1** (12%).

*Mitsunobu Esterification of **2** with 4-Nitrobenzoic Acid*

In toluene: A mixture of 286 mg of **2** (1 mmol) and 418 mg of 4-nitrobenzoic acid (2.5 mmol) was treated in 15 cm^3 of toluene as described in the general procedure. The resulting crude product was

chromatographed on a silica gel column with $CHCl_3$. The separation resulted in 190 mg of **3** (71%). Continued elution yielded 52 mg of **1a** (12%), mp 159–162°C, $R_f = 0.65$ (ss A); $[\alpha]_D^{20} = +86\,10^{-1}\,°cm^2\,g^{-1}$ ($c = 1$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, Me_4Si): $\delta = 0.99$ (s, 18-H_3), 1.30–2.50 (overlapping multiplets, 13H), 2.89 (m, 6-H_2), 3.78 (s, 3-OCH_3), 4.97 (m, 17-H), 6.64 (d, $J = 2.7$ Hz, 4-H), 6.71 (dd, $J = 8.6$, 2.7 Hz, 2-H), 7.20 (d, $J = 8.6$ Hz, 1-H), 8.21 (d, $J = 8.8$ Hz, 2′- and 6′-H), 8.29 (d, $J = 8.8$ Hz, 3′- and 5′-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si): $\delta = 12.4$ (C-18), 23.4, 26.2, 27.2, 27.7, 29.8, 37.0, 38.6 (C-8), 43.4 (C-13), 43.8 (C-9), 49.8 (C-14), 55.2 (3-OCH_3), 84.3 (C-17), 111.5 (C-2), 113.8 (C-4), 123.5 (2C, C-3′ and C-5′), 126.3 (C-1), 130.6 (2C, C-2′ and C-6′), 132.3 (C-10), 136.1 (C-1′), 137.8 (C-5), 150.4 (C-4′), 157.5 (C-3), 164.6 (C=O) ppm. Further elution yielded 43 mg of unreacted **2** (15%).

In chlorobenzene: A mixture of 286 mg of **2** (1 mmol) and 418 mg of 4-nitrobenzoic acid (2.5 mmol) was treated in 15 cm^3 of chlorobenzene as described in the general procedure. The resulting crude product was chromatographed on a silica gel column with $CHCl_3$, yielding 204 mg of **3** (76%), 52 mg of **1a** (12%), and 25 mg of **2** (9%).

*Mitsunobu Reaction of **4** with 4-Nitrobenzoic Acid*

A mixture of 300 mg of **4** (1 mmol) and 418 mg of 4-nitrobenzoic acid (2.5 mmol) was treated in 15 cm^3 of toluene as described in the general procedure. The resulting crude product was chromatographed on a silica gel column with $CHCl_3$. The separation resulted in 42 mg of **7** (15%), mp 95–98°C, $R_f = 0.85$ (ss A); $[\alpha]_D^{20} = +86\,10^{-1}\,°cm^2\,g^{-1}$ ($c = 1$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, Me_4Si): $\delta = 0.78$ (s, 18-H_3), 1.73 (s, 16-CH_3), 1.40–2.35 (overlapping multiplets, 11H), 2.87 (m, 6-H_2), 3.77 (s, 3-OCH_3), 5.48 (s, 17-H), 6.63 (d, $J = 2.6$ Hz, 4-H), 6.70 (dd, $J = 8.6$, 2.6 Hz, 2-H), 7.17 (d, $J = 8.6$ Hz, 1-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si): $\delta = 17.3$ and 17.6 (C-18 and 16-CH_3), 26.6, 28.0, 29.8, 36.3 (2C), 37.4 (C-8), 44.6 (C-9), 46.1 (C-13), 55.2 (3-OCH_3), 56.0 (C-14), 111.3 (C-2), 113.8 (C-4), 126.0 (C-1), 133.2 (C-10), 137.3 (C-17), 138.0 (C-5), 139.4 (C-16), 157.4 (C-3) ppm. Further elution yielded 76 mg of **6a** (17%), mp 145–147°C, $R_f = 0.65$ (ss A); $[\alpha]_D^{20} = -4\,10^{-1}\,°cm^2\,g^{-1}$ ($c = 1$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, Me_4Si): $\delta = 0.94$ (s, 18-H_3), 1.32 (d, $J = 7.0$ Hz, 16-CH_3), 1.10–2.40 (overlapping multiplets, 12H), 2.88 (m, 6-H_2), 3.78 (s, 3-OCH_3), 4.77 (s, 17-H), 6.64 (d, $J = 2.7$ Hz, 4-H), 6.71 (dd, $J = 8.6$, 2.7 Hz, 2-H), 7.19 (d, $J = 8.6$ Hz, 1-H), 8.22 (d, $J = 8.8$ Hz, 2′- and 6′-H), 8.30 (d, $J = 8.8$ Hz, 3′- and 5′-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si): $\delta = 17.4$ (C-18), 20.8 (16-CH_3), 25.9, 28.0, 29.9, 32.7, 34.4, 38.8 (C-8), 41.2 (C-16), 43.5 (C-9), 45.3 (C-13), 51.0 (C-14), 55.2 (3-OCH_3), 90.4 (C-17), 111.5 (C-2), 113.8 (C-4), 123.6 (2C, C-3′ and C-5′), 126.3 (C-1), 130.6 (2C, C-2′ and C-6′), 132.3 (C-10), 136.2 (C-1′), 137.9 (C-5), 150.4 (C-4′), 157.5 (C-3), 164.4 (C=O) ppm. Further elution resulted in 195 mg of **4** (65%).

3-Methoxy-16β-methylestra-1,3,5(10)-trien-17α-ol (**6**)

Compound **6a** (45 mg, 0.1 mmol) was dissolved in 5 cm^3 of methanol containing 10 mg of $NaOCH_3$ (0.184 mmol) and the solution was refluxed for 1 h, than diluted with 20 cm^3 of H_2O and extracted with 3×10 cm^3 of CH_2Cl_2. The CH_2Cl_2 solution was washed with H_2O, dried, and evaporated. The residual oil was chromatographed on a silica gel column with a mixture of ethyl acetate/$CHCl_3$ (5/95). The product was crystallized from $CHCl_3$/petrolether. This yielded 31 mg of **6** (70%), mp 52–54°C (Ref. [18] 53–56°C), $R_f = 0.40$ (ss B); $[\alpha]_D^{20} = +60\,10^{-1}\,°cm^2\,g^{-1}$ ($c = 1$, $CHCl_3$).

*Mitsunobu Reaction of **5** with 4-Nitrobenzoic Acid*

A mixture of 300 mg of **5** (1 mmol) and 418 mg of 4-nitrobenzoic acid (2.5 mmol) was treated in 15 cm^3 of toluene as described in the general procedure. The resulting crude product was chromatographed on a silica gel column with $CHCl_3$. The separation resulted in 42 mg of **7** (15%). Continued

elution yielded 270 mg of **8a** (60%), mp 161–163°C, $R_f = 0.70$ (ss A); $[\alpha]_D^{20} = +13\,10^{-1}\,°cm^2\,g^{-1}$ ($c = 1$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, Me_4Si): $\delta = 0.94$ (s, 18-H_3), 1.02 (d, $J = 7.2$ Hz, 16-CH_3), 1.40–2.40 (overlapping multiplets, 11H), 2.71 (m, 1H), 2.88 (m, 6-H_2), 3.77 (s, 3-OCH_3), 5.22 (d, $J = 5.8$ Hz, 17-H), 6.64 (d, $J = 2.6$ Hz, 4-H), 6.70 (dd, $J = 8.6$, 2.6 Hz, 2-H), 7.17 (d, $J = 8.6$ Hz, 1-H), 8.24 (d, $J = 8.8$ Hz, 2′- and 6′-H), 8.31 (d, $J = 8.8$ Hz, 3′- and 5′-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si): $\delta = 16.0$ (C-18), 17.2 (16-CH_3), 26.0, 28.0, 29.9, 32.3, 33.5, 34.3 (C-16), 39.0 (C-8), 43.7 (C-9), 46.7 (C-13), 48.8 (C-14), 55.2 (3-OCH_3), 85.3 (C-17), 111.5 (C-2), 113.8 (C-4), 123.6 (2C, C-3′ and C-5′), 126.3 (C-1), 130.6 (2C, C-2′ and C-6′), 132.3 (C-10), 135.9 (C-1′), 137.8 (C-5), 150.5 (C-4′), 157.5 (C-3), 164.3 (C=O) ppm. Further elution resulted in 63 mg of unreacted **5** (21%).

3-Methoxy-16α-methylestra-1,3,5(10)-trien-17α-ol (**8**)

Compound **8a** (90 mg, 0.2 mmol) was dissolved in 10 cm^3 of *Me*OH containing 15 mg of $NaOCH_3$ (0.276 mmol) and the solution was refluxed for 1 h, then diluted with 30 cm^3 of H_2O and extracted with 3×15 cm^3 of CH_2Cl_2. The CH_2Cl_2 solution was washed with H_2O, dried, and evaporated. The resulting crude product was chromatographed on a silica gel column with a mixture of ethyl acetate/$CHCl_3$ (5/95). The product was crystallized from $CHCl_3$/petrolether, yielding 44 mg of **8** (73%), mp 126–127°C (Ref. [18] 125–127°C), $R_f = 0.55$ (ss B).

Acknowledgements

We thank the Hungarian Scientific Research Fund (OTKA T042673) for financial support of this work. We also thank Dr. *M. Rózsa-Tarjáni* (University of Szeged, Hungary) for the NMR spectra.

References

[1] Mitsunobu O, Yamada M (1967) Bull Chem Soc Japan **40**: 2380
[2] Mitsunobu O, Eguchi M (1971) Bull Chem Soc Japan **44**: 3427
[3] Mitsunobu O (1981) Synthesis 1
[4] Brandstetter HH, Zbiral E (1978) Helv Chim Acta **61**: 1832
[5] Mitsunobu O, Kimura J, Fujisawa Y (1972) Bull Chem Soc Japan **45**: 245
[6] Jarosz S, Glodek J, Zamojski A (1987) Carbohydr Res **163**: 289
[7] Simon C, Hosztafi S, Makleit S (1997) J Heterocyclic Chem **34**: 349
[8] Eaton PE, Jobe PG, Reingold ID (1984) J Am Chem Soc **106**: 6437
[9] Kocienski PJ, Street SDA, Yeates C, Campbell SF (1987) J Chem Soc Perkin Trans 1: 2171
[10] Mori K, Ikunama I (1984) Tetrahedron **40**: 3471
[11] Mori K, Otsuka T, Oda M (1984) Tetrahedron **40**: 2929
[12] Martin SF, Dodge JA (1991) Tetrahedron **32**: 3017
[13] Dodge JA, Trujillo JI, Presnell M (1994) J Org Chem **59**: 234
[14] Dodge JA, Lugar CW (1996) Bioorg Med Chem Lett **6**: 1
[15] Johns WF (1961) J Org Chem **26**: 4583
[16] Schneider Gy, Hackler L, Sohár P (1988) Liebigs Ann Chem 679
[17] Evans PA, Nelson JD, Rheinhold AL (1997) Tetrahedron Lett **38**: 2235
[18] Meskó E, Schneider Gy, Dombi Gy, Zeigan D (1990) Liebigs Ann Chem 419