

Preparation and Photochemistry of 3-Methoxyestra-1,3,5(10)-triene-17 β -yl cinnamates and 3-O-methylestra-1,3,5(10)-trien-17-one O-cinnamoyl-17-oximes

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Abstract: 3-Methoxyestra-1,3,5(10)-triene-17 β -yl (*E*)-cinnamates and 3-methoxyestra-1,3,5(10)-trien-17-one O-(*E*)-cinnamoyl-17-oximes were prepared from the reaction of cinnamic acids with 3-methoxyestra-1,3,5(10)-trien-17- β -ol and 3-methoxyestra-1,3,5(10)-trien-17-one 17-oxime, respectively, in the presence of PPh₃-CBrCl₃ in an Appel-type reaction. Under photolysis, the steroidal cinnamates underwent *E*-/*Z*-isomerization, while the steroidal O-cinnamoyloximes underwent *E*-/*Z*-isomerization concomitant with cleavage reactions.

Keywords: steroids, estradiol, cinnamates, O-cinnamoyl oximes, Appel reaction, photochemistry, *E*-/*Z*-isomerization, TDDFT calculations

Introduction: In our endeavor to find steroidal based breast cancer-active products,¹⁻³ we have engaged in the preparation of a number of O-cinnamoyl estrone-oximes of type **E-1**. A number of steroidal oxime esters^{4,5} and ethers^{5,6} have been documented to show activity against a variety of cancer cell lines. To augment our study, we have prepared the estradiol 17 β -cinnamates **E-2**, realizing that the *in vivo* cleavage of **E-2** would most likely be too rapid for it to find application as medication. As standard *in vitro* stability testing of our new compounds in the laboratory, we also investigate their light sensitivity. The cinnamoyl structure itself is photoactive. Previously, we have found an appreciable *E*-/*Z*-isomerization of the cinnamyl unit in estradiol cinnamide conjugates.³ Photochemical *E*-/*Z*-isomerization allows for the preparation of the less readily accessible *Z*-cinnamyl structures, if the *Z*-isomer is formed in significant amounts. In the following, the preparation of O-cinnamoyl estrone-oximes **E-1** and estradiol 17 β -cinnamates **E-2** will be detailed. The results of their photoirradiation will be discussed, aided, in the case of the estradiol 17 β -cinnamates **E-2**, by a computational study of the relative stabilities of the *E*- and *Z*-isomers and the electronic transitions for both *E*- and *Z*-isomers that contribute to the *E*-/*Z*-isomerization process.

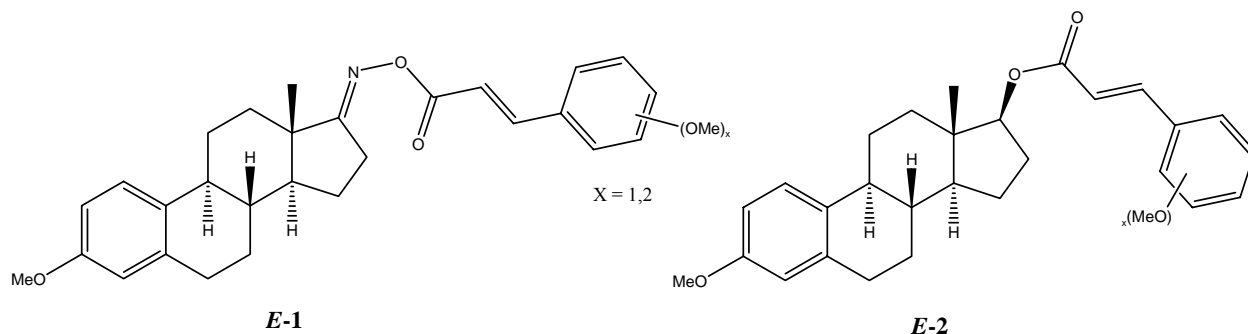


Figure 1. Study objects of this investigation: Estrone based cinnamoyloximes *E-1* and estadiol based steroidal cinnamates *E-2*

Experimental Part:

Melting points were measured with a Stuart SMP10 melting point apparatus and are uncorrected. ^1H NMR (at 400 MHz) and ^{13}C NMR (at 100.5 MHz) spectra were taken on a Varian 400 MHz spectrometer. Infrared spectra were taken on a spectrometer (solid samples as KBr pellets, liquid samples using NaCl plates). Column chromatography was carried out on silica gel S (0.2 – 0.5 mm and 0.063 – 0.1 mm, Riedel de Haen). Analytical thin layer chromatography (TLC) was carried out on silica on TLC Alu foils from Fluka (with fluorescent indicator at $\lambda = 254$ nm). For detection a UVGL-58 lamp was used from UYP (Upland, CA, USA). For the photoirradiation, a Luzchem LZC 4V photoreactor was used with 13 USHIO G8T5 lamps (7.2 W low pressure Hg lamp with a radiation peak at $\lambda = 253.7$ nm). In the photoirradiation, where the *E*- and *Z*-isomers of both **1** and **2** were to be separated chromatographically, 13 Sylvania s958 F8T5/CW lamps (8W, Hg lamp with $\lambda \geq 280$ nm) were used.

The cinnamic acids were prepared from the respective benzaldehydes in a one-pot Wittig reaction – hydrolysis.⁷ 3-Methoxyestra-1,3,5(10)-trien-17-one (3-*O*-Me-estrone, **4**) was prepared by reacting estra-1,3,5(10)-trien-3-ol-17-one (estrone, **3**) with methyl iodide in DMSO in the presence of KOH, analogous to a procedure of Johnstone.⁸ 3-*O*-Methylestra-1,3,5(10)-trien-3,17 β -diol (3-*O*-Me-estra-3,17 β -diol, **5**) was synthesized from 3-*O*-methylestra-1,3,5(10)-trien-3-ol-17-one (3-*O*-Me-estrone, **4**) (NaBH_4 , MeOH/Et₂O 1:1). 3-*O*-Methylestra-1,3,5(10)-trien-3-ol-17-one 17-oxime (3-*O*-Me-estrone oxime, **6**) was obtained from 3-*O*-methylestra-1,3,5(10)-trien-3-ol-17-one (3-*O*-Me-estrone, **4**) according to a general procedure by Regan.⁹

Esterification of 3-*O*-methylestra-1,3,5(10)-trien-3,17 β -diol (**5**) with cinnamic acids under Appel-type conditions

To a solution of triphenylphosphine (PPh₃, 582 mg, 2.22 mmol) in dry CH₂Cl₂ (7 mL) was given BrCCl₃ (460 mg, 2.32 mmol). The ensuing mixture was stirred at rt for 30 min., during which time it turned dark orange. Thereafter, 4-methoxycinnamic acid (360 mg, 2.02 mmol) was added portionwise, and the resulting reaction mixture was stirred under reflux for 45 min. Then, 3-*O*-methylestra-1,3,5(10)-trien-3,17 β -diol (275 mg, 0.96 mmol) was added, and the mixture was stirred under reflux for another 12h. At certain intervals, the reaction vessel is set under slight vacuum (alternatively 0.96 mmol dry DBU or dry Et₃N can be added to the reaction 15 min. after the addition of the steroid). Direct column chromatography of the cooled, concentrated solution on silica gel (CHCl₃/Et₂O/hexane 1:1:1) 3-methoxyestra-1,3,5(10)-trien-17 β -yl 4-(*E*)-methoxycinnamate (**E-2a**) (292 mg, 68%) as a colorless solid, mp. 126-128 °C; ν_{\max} (KBr/cm⁻¹) 2919, 2866, 2836, 1701, 1636, 1604, 1575, 1512, 1497, 1323, 1257, 1205, 1172, 1033, 984, 967, 828, 812; δ_{H} (400 MHz, CDCl₃) 0.90 (3H, s, CH₃), 1.25 – 2.31 (13H, m), 2.85 – 2.87 (2H, m), 3.77 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 4.82 (1H, dd, ³*J* = 9.2 Hz, ³*J* = 8.0 Hz), 6.32 (1H, d, ³*J* = 16.0 Hz), 6.63 (1H, d, ⁴*J* = 2.8 Hz), 6.70 (1H, dd, ³*J* = 8.8 Hz, ⁴*J* = 2.8 Hz), 6.90 (2H, d, ³*J* = 8.8 Hz), 7.20 (1H, d, ³*J* = 8.4 Hz), 7.48 (2H, d, ³*J* = 8.8 Hz), 7.62 (1H, d, ³*J* = 16.0 Hz); δ_{C} (100.5 MHz, CDCl₃) 12.2, 23.3, 26.2, 27.2, 27.7, 29.8, 37.0, 38.6, 43.2, 43.8, 49.8, 55.2 (OCH₃), 55.4 (OCH₃), 82.6 (OCH), 111.5 (CH), 113.8 (CH), 114.3 (2C, CH), 116.1 (CH), 126.4 (CH), 127.2 (C_{quat}), 129.7 (2C, CH), 132.5 (C_{quat}), 137.9 (C_{quat}), 144.0 (CH), 157.4 (C_{quat}), 161.3 (C_{quat}), 167.4 (C_{quat}, CO). Found: C, 78.14%; H, 7.44%. Calcd. for C₂₉H₃₄O₄ (446.58): C, 78.00%; H, 7.67%.

3-Methoxyestra-1,3,5(10)-trien-17 β -yl 2,5-(*E*)-dimethoxycinnamate (**E-2c**) as a colorless solid, mp. 139-140 °C; ν_{\max} (KBr/cm⁻¹) 3008, 2923, 2867, 2835, 1709, 1629, 1499, 1464, 1447, 1335, 1294, 1258, 1227, 1178, 1040, 997, 859, 819, 702, 560; δ_{H} (400 MHz, CDCl₃) 0.91 (3H, s, CH₃), 1.32 – 2.32 (13H, m), 2.84 – 2.87 (2H, m), 3.77 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 3.84 (3H, s, OCH₃), 4.84 (1H, dd, ³*J* = 8.8 Hz, ³*J* = 8.0 Hz, OCH), 6.50 (1H, d, ³*J* = 16.0 Hz), 6.63 (1H, d, ⁴*J* = 2.8 Hz), 6.71 (1H, dd, ³*J* = 8.8 Hz, ⁴*J* = 2.8 Hz), 6.84 (1H, d, ³*J* = 9.2 Hz), 6.90 (1H, dd, ³*J* = 9.2 Hz, ⁴*J* = 3.2 Hz), 7.06 (1H, d, ⁴*J* = 3.2 Hz), 7.21 (1H, d, ³*J* = 8.8 Hz), 7.97 (1H, d, ³*J* = 16.0 Hz); δ_{C} (100.5 MHz, CDCl₃) 12.2, 23.3, 26.3, 27.3, 27.7, 29.8, 37.0, 38.6, 43.2, 43.8, 49.8, 55.2 (OCH₃), 55.8 (OCH₃), 56.1 (OCH₃), 82.7 (OCH), 111.5, 112.4, 113.2, 113.8, 117.0, 119.2, 124.0, 126.4, 132.6, 137.9, 139.6, 152.8 (C_{quat}), 153.5 (C_{quat}), 157.4 (C_{quat}), 167.5 (C_{quat}, CO).

3-Methoxyestra-1,3,5(10)-trien-17 β -yl 3,4-(*E*)-dimethoxycinnamate (**E-2b**) as a colorless solid, mp. 162-165 °C; ν_{\max} (KBr/cm⁻¹) 3010, 2953, 2863, 2843, 2805, 2698, 1612, 1596, 1510, 1445, 1417, 1294, 1257, 1155, 1139, 1024, 848, 812, 782, 616, 570; δ_{H} (400 MHz, CDCl₃) 0.90 (3H, s, CH₃), 2.84 – 2.88 (2H, m), 1.25 – 2.31 (13H, m), 3.77 (3H, s, OCH₃), 3.91 (3H, s, OCH₃), 3.92 (3H, s, OCH₃), 4.83 (1H, dd, ³*J* = 8.0, ³*J* = 7.6 Hz, OCH), 6.32 (1H, d, ³*J* = 16.0 Hz), 6.63 (1H, d, ⁴*J* = 2.8

Hz), 6.70 (1H, dd, $^3J = 8.4$ Hz, $^4J = 2.8$ Hz), 6.86 (1H, d, $^3J = 8.4$ Hz), 7.05 (1H, d, $^4J = 2.0$ Hz), 7.10 (1H, dd, $^3J = 8.4$ Hz, $^4J = 2.0$ Hz), 7.20 (1H, d, $^3J = 8.4$ Hz), 7.61 (1H, d, $^3J = 16.0$ Hz); δ_c (100.5 MHz, CDCl₃) 12.2, 23.3, 26.2, 27.2, 27.7, 29.8, 37.0, 38.6, 43.2, 43.8, 49.8, 55.2 (OCH₃), 55.9 (OCH₃), 56.0 (OCH₃), 82.7 (OCH), 109.5, 111.0, 111.5, 113.8, 116.2, 122.6, 126.4, 127.5, 132.5, 137.9, 144.3, 149.2 (C_{quat}), 151.0 (C_{quat}), 157.4 (C_{quat}), 167.3 (C_{quat}, CO). Found: C, 75.76%; H, 7.32%. Calcd. for C₃₀H₃₆O₅ (476.60): C, 75.60%; H, 7.61%.

Acylation of 3-*O*-methylestra-1,3,5(10)-trien-3-ol-17-one-17-oxime (6) with cinnamic acids under Appel type conditions

To a solution of triphenylphosphine (PPh₃, 910 mg, 3.47 mmol) in dry CH₂Cl₂ (10 mL) was given BrCCl₃ (715 mg, 3.61 mmol). The ensuing mixture was stirred at rt for 30 min., during which time it turned dark orange. Thereafter, 4-methoxycinnamic acid (510 mg, 2.87 mmol) was added portionwise, and the resulting reaction mixture was stirred under reflux for 45 min. Then, 3-methoxyestra-1,3,5(10)-trien-17-one-17-oxime (450 mg, 1.50 mmol) was added, and the mixture was stirred under reflux for another 12h. At certain intervals, the reaction vessel is set under slight vacuum (alternatively 1.50 mmol dry DBU or dry Et₃N can be added to the reaction 15 min. after the addition of the steroid). Direct column chromatography of the cooled, concentration solution on silica gel (CHCl₃/Et₂O/hexane 1:1:1) gave 3-methoxyestra-1,3,5(10)-trien-17-one-17-oxime *N*-4-(*E*)-methoxycinnamate (**E-1a**) (515 mg, 71%) as a colorless solid; mp. 172 – 175 °C (isopropanol/diethyl ether); ν_{\max} (KBr/cm⁻¹) 2976, 2939, 2869, 2836, 2810, 1720, 1602, 1512, 1238, 1176, 1021, 824; δ_H (400 MHz, CDCl₃) 1.04 (3H, s, CH₃), 1.39 – 2.89 (15H, m), 3.77 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 6.38 (1H, d, $^3J = 16.0$ Hz), 6.63 (1H, d, $^4J = 2.1$ Hz), 6.71 (1H, dd, $^3J = 8.4$ Hz, $^4J = 2.1$ Hz), 6.90 (2H, d, $^3J = 8.8$ Hz), 7.21 (1H, d, $^3J = 8.4$ Hz), 7.49 (2H, d, $^3J = 8.8$ Hz), 7.72 (1H, d, $^3J = 16.0$ Hz); δ_c (100.5 MHz, CDCl₃) 17.1, 22.8, 26.1, 27.2, 27.3, 29.6, 33.7, 38.2, 43.8, 45.5, 50.9, 55.4 (OCH₃), 55.8 (OCH₃), 111.5, 113.5, 113.8, 114.3 (2C), 126.4, 127.1, 129.8 (2C), 132.1, 137.7, 145.2, 157.5 (C_{quat}), 161.4 (C_{quat}), 165.3 (C_{quat}), 178.7 (C_{quat}, CO).

3-Methoxyestra-1-3,5(10)-trien-17-one-17-oxime *N*-2,5-(*E*)-dimethoxycinnamate (**E-1c**) as a slowly crystallizing colorless solid, mp. 118 – 120 °C (isopropanol/diethyl ether); ν_{\max} (KBr/cm⁻¹) 3056, 2933, 2836, 1732, 1628, 1497, 1465, 1317, 1283, 1252, 1131, 1046, 987, 944, 857, 735, 700; δ_H (400 MHz, CDCl₃) 1.50 – 2.90 (15H, m), 1.61 (3H, s, CH₃), 3.77 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 3.85 (3H, s, OCH₃), 6.58 (1H, d, $^3J = 16.4$ Hz), 6.63 (1H, d, $^4J = 2.8$ Hz), 6.72 (1H, dd, $^3J = 8.4$ Hz, $^4J = 2.8$ Hz), 6.85 (1H, d, $^3J = 9.2$ Hz), 6.91 (1H, dd, $^3J = 9.2$ Hz, $^4J = 2.8$ Hz), 7.06 (1H, d, $^4J = 2.8$ Hz), 7.22 (1H, d, $^3J = 8.4$ Hz), 8.03 (1H, d, $^3J = 16.4$ Hz); δ_c (100.5 MHz, CDCl₃) 17.1, 22.9, 26.1, 27.2, 27.3, 29.7, 33.7, 38.2, 43.8, 45.4, 52.8, 55.2 (OCH₃), 55.8 (OCH₃), 56.1 (OCH₃), 111.5, 112.4, 113.4, 113.9, 116.9, 117.2, 123.9, 126.4, 132.1, 137.7, 140.7, 152.9, 153.4, 157.5, 165.2, 178.8 (C_{quat}, CO).

3-Methoxyestra-1,3,5(10)-trien-17-one-17-oxime *N*-3,4-(*E*)-dimethoxycinnamate (**E-1b**) as a colorless solid, mp. 152 – 154 °C (isopropanol/diethyl ether); ν_{\max} (KBr/cm⁻¹) 3061, 2930, 2864, 2837, 1734, 1627, 1597, 1513, 1465, 1420, 1307, 1266, 1236, 1162, 1124, 1021, 979, 863, 816; δ_{H} (400 MHz, CDCl₃) 0.83 – 2.91 (15H, m), 1.05 (3H, s, CH₃), 2.91 (3H, s, OCH₃), 3.77 (3H, s, OCH₃), 3.92 (3H, s, OCH₃), 6.37 (1H, d, ³*J* = 16.0 Hz), 6.63 (1H, d, ⁴*J* = 2.8 Hz), 6.71 (1H, dd, ³*J* = 8.8 Hz, ⁴*J* = 2.8 Hz), 6.87 (1H, d, ³*J* = 8.4 Hz), 7.06 (1H, d, ⁴*J* = 2.0 Hz), 7.13 (1H, dd, ³*J* = 8.4 Hz, ⁴*J* = 2.0 Hz), 7.21 (1H, d, ³*J* = 8.8 Hz), 7.71 (1H, d, ³*J* = 16.0 Hz); δ_{C} (100.5 MHz, CDCl₃) 17.1, 22.9, 26.1, 27.2, 27.3, 29.6, 33.7, 38.2, 43.8, 45.5, 52.8, 55.2 (OCH₃), 55.9 (OCH₃), 56.0 (OCH₃), 109.7, 111.0, 111.5, 113.8, 113.9, 122.7, 126.4, 127.4, 132.1, 137.6, 145.4, 149.2, 151.2, 157.5, 165.1, 178.7 (C_{quat}, CO). Found: C, 73.69%; H, 7.37%; N, 2.73%. Calcd. for C₃₀H₃₅NO₅ (489.60): C, 73.59%; H, 7.21%; N, 2.86%.

Photoirradiation of 3-methoxyestra-1,3,5(10)-trien-17 β -yl cinnamates (**E-2**)

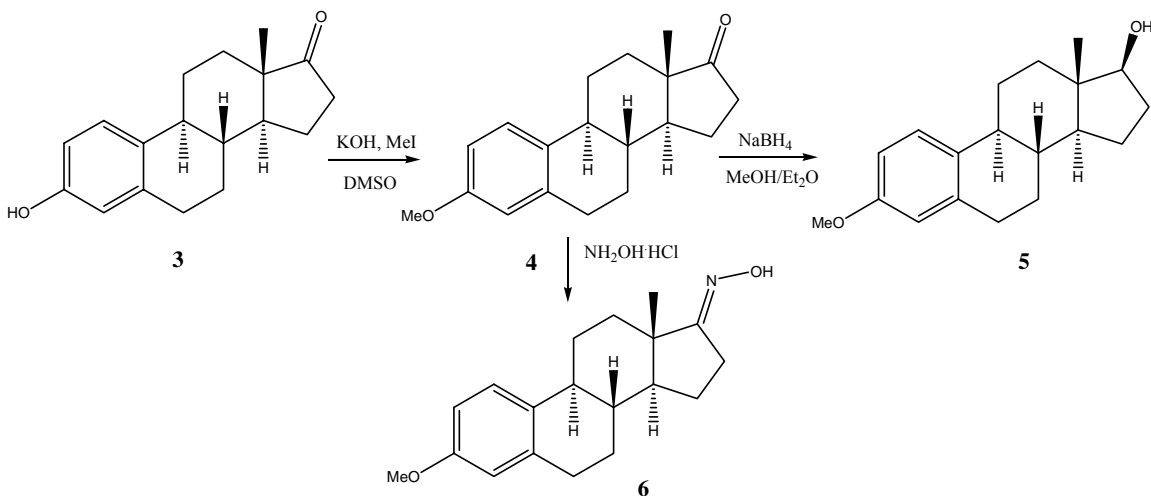
3-*O*-Methoxyestra-1,3,5(10)-trien-17 β -yl 3,4-(*E*)-dimethoxycinnamate (**E-2b**) in chloroform was placed in quartz tubes and photoirradiated until an *E*/*Z*-equilibrium was reached as monitored by ¹H-NMR spectroscopy. Column chromatography of the photoirradiated mixture on silica gel (Et₂O/CHCl₃/hexane 1:1:2) gave 3-*O*-methoxyestra-1,3,5(10)-trien-17 β -yl 3,4-(*Z*)-dimethoxycinnamate (**Z-2b**) as a slowly crystallizing, colorless solid; ν_{\max} (neat/cm⁻¹) 2929, 1515, 1464, 1257, 1171, 1144, 1026; δ_{H} (400 MHz, CDCl₃) 0.78 (3H, s, CH₃), 1.24 – 2.87 (15H, m), 3.77 (3H, s, OCH₃), 3.90 (3H, s, OCH₃), 3.91 (3H, s, OCH₃), 4.74 (1H, dd, ³*J* = 9.2 Hz, ³*J* = 7.6 Hz), 5.85 (1H, d, ³*J* = 13.2 Hz), 6.62 (1H, d, ⁴*J* = 2.8 Hz), 6.70 (1H, dd, ³*J* = 8.4 Hz, ⁴*J* = 2.8 Hz), 6.81 (1H, d, ³*J* = 13.2 Hz), 7.18 – 7.22 (2H, m), 7.63 (1H, d, ⁴*J* = 2.0 Hz); δ_{C} (100.5 MHz, CDCl₃) 12.1, 23.3, 26.2, 27.2, 27.6, 29.8, 36.9, 38.6, 43.0, 43.8, 49.8, 55.2, 55.8, 55.9, 82.6, 110.3, 111.4, 113.1, 113.7, 117.7, 124.5, 126.4, 127.8, 132.5, 137.9, 143.1, 148.2, 149.9, 157.4, 166.6.

Photoirradiation of 3-*O*-methoxyestra-1,3,5(10)-trien-17-one-17-oxime *N*-cinnamates (**E-1**)

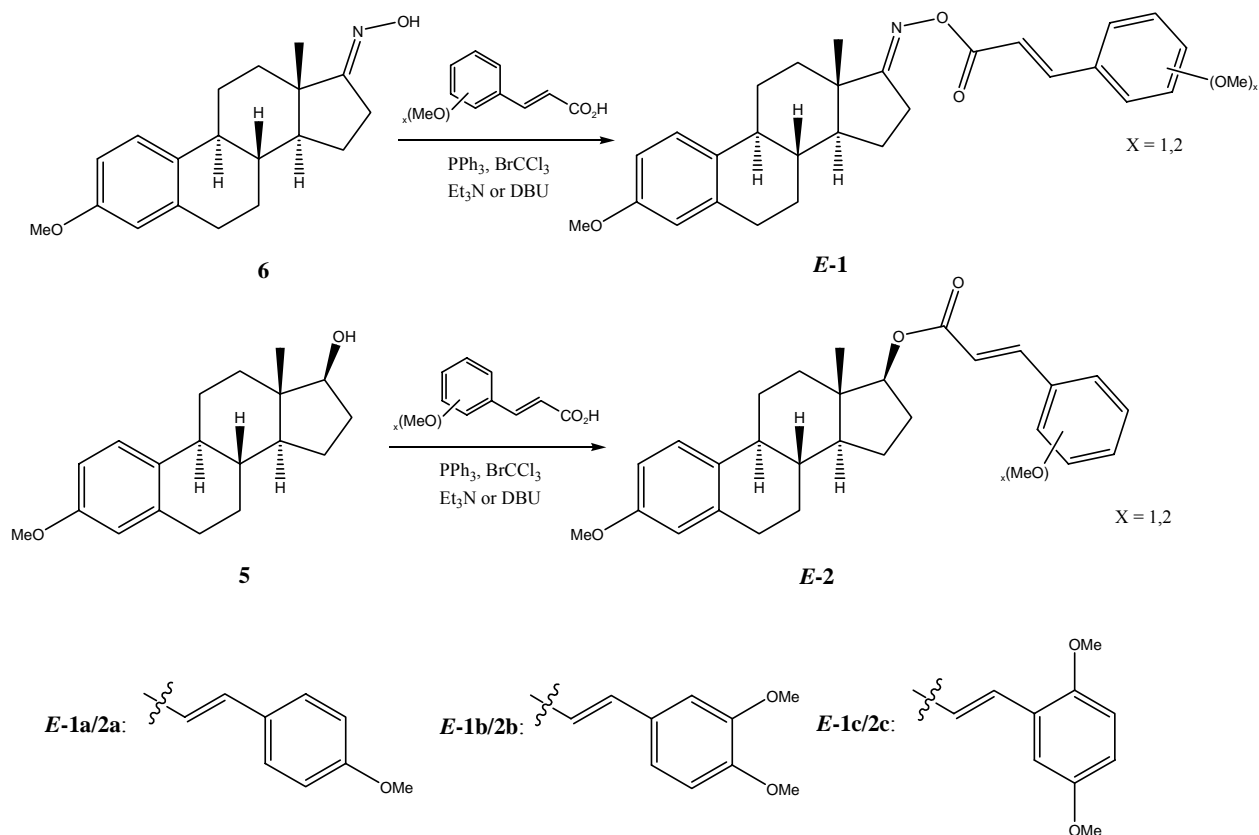
3-*O*-Methoxyestra-1,3,5(10)-trien-17-one-17-oxime *N*-3,4-(*E*)-dimethoxycinnamate (**E-1b**, 50 mg, 0.10 mmol) in chloroform (3.6 mL) [in two quartz tubes having 25 mg **E-1b** and 1.8 mL CHCl₃, each] was photoirradiated for 9 h. Column chromatography of the photoirradiated mixture on silica gel (hexane/CHCl₃/diethyl ether 3:1:1, then 2:1:1) gave 3-*O*-methylestra-1,3,5(10)-trien-17-one-17-oxime *N*-3,4-(*Z*)-dimethoxycinnamate **Z-1b** (12 mg, 24%) as a slowly crystallizing colorless oil; ν_{\max} (neat/cm⁻¹) 2930, 2826, 1744, 1620, 1514, 1257, 1118; δ_{H} (400 MHz, CDCl₃) 1.02 (3H, s, CH₃), 1.28 – 2.57 (13H, m), 2.87 – 2.89 (2H, m), 3.78 (3H, s, OCH₃), 3.91 (3H, s, OCH₃), 3.94 (3H, s, OCH₃), 5.88 (1H, d, ³*J* = 13.2 Hz), 6.64 (1H, d, ³*J* = 2.8 Hz), 6.72 (1H, dd, ³*J* = 8.4 Hz, ³*J* = 2.8 Hz), 6.83 (1H, d, ³*J* = 8.4 Hz), 6.89 (1H, d, ³*J* = 13.2 Hz), 7.20 – 7.24 (2H, m), 7.82 (1H, d, ⁴*J* = 2.0 Hz); δ_{C} (100.5 MHz, CDCl₃) 17.0 (CH₃), 22.8, 26.1, 27.1, 27.2, 29.6, 33.7, 38.1, 43.8, 45.4, 52.8, 55.2 (OCH₃), 55.9 (OCH₃), 56.0 (OCH₃), 110.2, 111.5, 113.3, 113.8, 114.8, 125.1, 126.4, 127.7, 132.0, 139.6, 144.5, 148.3, 150.3 (C_{quat}), 157.5 (C_{quat}), 164.4 (C_{quat}), 178.7 (C_{quat}).

Results and Discussion:

The Appel reagent tetrachlorocarbon – triphenylphosphine ($\text{CCl}_4\text{-PPh}_3$) is a versatile reagent for amidation and esterification reactions.¹⁰ In recent times, it was understood that CCl_4 is an ozone depletor. Therefore, it is of interest to replace CCl_4 with a suitable alternative reagent. Already, L. E. Barstow and V. J. Hruby noted that for the reactive system CX_4/PPh_3 , CCl_4 can be exchanged for the environmentally more benign bromotrichloromethane (BrCCl_3) in the synthesis of amides from carboxylic acids and amines. This approach was tested successfully in the preparation of the simple dipeptide, ethyl *N*-benzyloxycarbonyl-L-phenylalanyl-glycinate.¹¹ More recently, the authors have used the reagent $\text{BrCCl}_3\text{-PPh}_3$ for a number of reactions, including the preparation of nitriles¹² from oximes, the preparation of anhydrides and of esters from carboxylic acids.¹³ It was found that this reaction can also be used for the acylation of oximes. Thus, cinnamic acids were treated with $\text{PPh}_3\text{-CBrCl}_3$ in refluxing CH_2Cl_2 to give *in situ* the particular cinnamoyl halides. These were reacted in one-pot with either 3-*O*-methylestra-1,3,5(10)-trien-3,17 β -diol **5** or 3-methoxyestra-1,3,5(10)-trien-17-one-17-oxime **6** to give after column chromatographic purification the 3-methoxyestra-1,3,5(10)-trien-17 β -yl cinnamates **E-2** and 3-methoxyestra-1,3,5(10)-trien-17-one-17-oxime *N*-cinnamates **E-1**, respectively (Scheme 2).



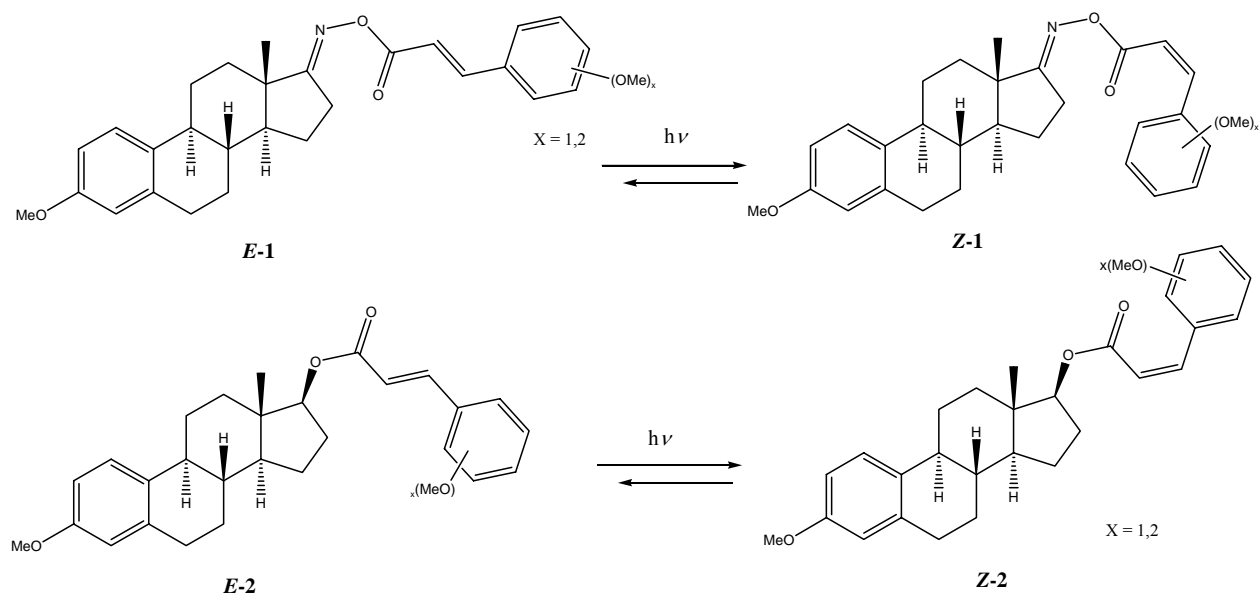
Scheme 1. Reaction sequences to the starting materials for the esterification reactions



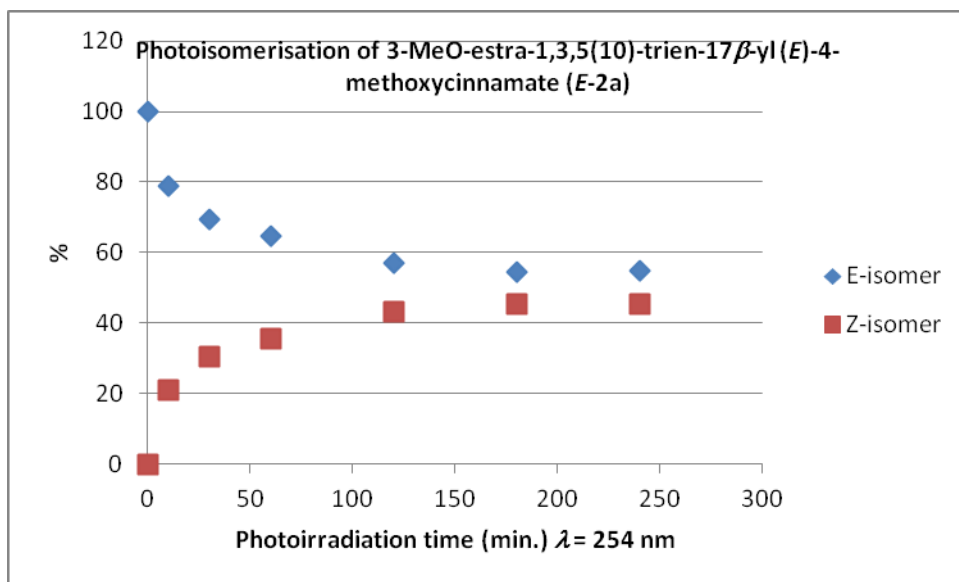
Scheme 2. Esterification of 5 and 6 with cinnamic acids with $\text{BrCCl}_3\text{-PPh}_3$ under Appel-type conditions.

Next, the photostability of **E-1** and **E-2** was studied. 3-Methoxyestra-1,3,5(10)-trien-17 β -yl 3,4-dimethoxycinnamate (**E-2b**) was photoirradiated at $\lambda = 253.7$ nm (peak intensity). Photoirradiation of **E-2b** in deuterated chloroform showed a rapid *E/Z*-isomerization: *E/Z* 77/23 (10 min.), *E/Z* 57.5/42.5 (30 min.), *E/Z* 51/49 (1h), *E/Z* 47/53 (2h), *E/Z* 45/55 (4h). The *E/Z*-isomerization was monitored by ^1H NMR assessing the integrals of the doublet of the olefinic proton at δ 5.82 ppm (*Z*-isomer) and of the doublet of the olefinic proton at δ 6.28 ppm (*E*-isomer). First, the photoreaction was also carried out in deuterated DMSO. Here again, a rapid *E/Z*-isomerization occurred. However, after 2h the steroidal system seemed to have oligomerized, so that no identifiable signals from the steroidal framework could be detected any longer. For the irradiation in chloroform, *E*- and *Z*-isomers could be separated. The *Z*-isomer **Z-2b**, thus obtained, was subjected to photoirradiation in CDCl_3 , to again obtain a mixture of *E/Z*-isomers – *E/Z* 25/75 (10 min.), *E/Z* 40.5/59.5 (30 min.), *E/Z* 50/50 (1h), *E/Z* 50/50 (2h). Photoirradiation of 3-methoxyestra-1,3,5(10)-trien-17 β -yl 4-(*E*)-methoxycinnamate (**E-2a**) was also carried out in deuterated chloroform to obtain a mixture of *E/Z*-isomers – *E/Z* 79/21 (10

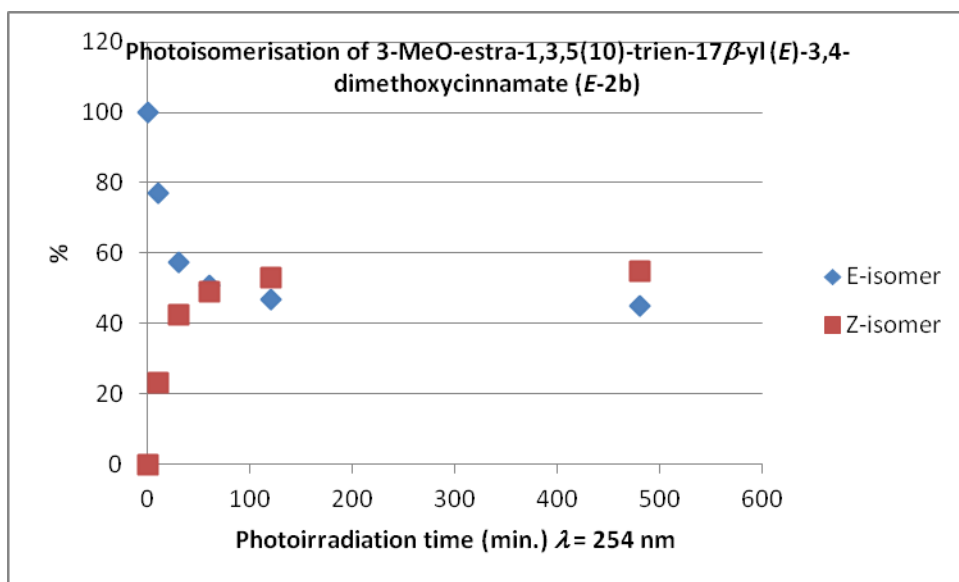
min.), *E/Z* 69.5/30.5 (30 min.), *E/Z* 64.5/35.5 (1h), *E/Z* 57/43 (2h), *E/Z* 54.5/45.5 (3h), 54.8/45.2 (4h). Photoirradiation of 3-methoxyestra-1,3,5(10)-trien-17 β -yl 2,5-(*E*)-dimethoxycinnamate (**E-2c**) in CDCl₃ gave a mixture of *E/Z* 87.5/12.5 (10 min.), *E/Z* 76/24 (30 min.), *E/Z* 69/31 (1h), *E/Z* 72/28 (2h), *E/Z* 73/27 (3h), indicating that after an initial build-up of *Z*-isomer with a maximum after 1h irradiation a pseudo-equilibrium is reached in the *E/Z*-isomerization, where any further change in the mixture is due to secondary reactions, the products of which were not studied further. Again, all the evaluation of the *E/Z*-ratios was carried out by ¹H NMR spectroscopy, now in CDCl₃ (400 MHz), by evaluating the olefinic proton on the carbon α to the ester group. In all cases, longer photoirradiation times in CHCl₃(CDCl₃) lead to significant deterioration of the materials in part due to the occurrence of chloro radicals and hydrogen chloride from the homolytic C-Cl bond cleavage in the solvent.



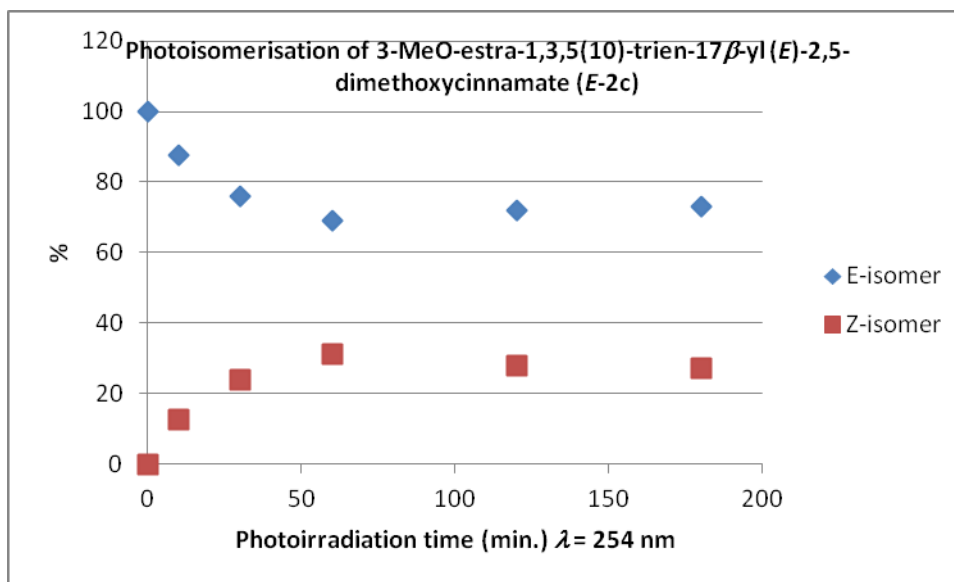
Scheme 3. Photoisomerization of 3-MeO-estra-1,3,5(10)-trien-17- β -yl cinnamates (**2**) and 3-MeO-estra-1,3,5(10)-trien-17-one – 17-oxime N-cinnamates (**1**).



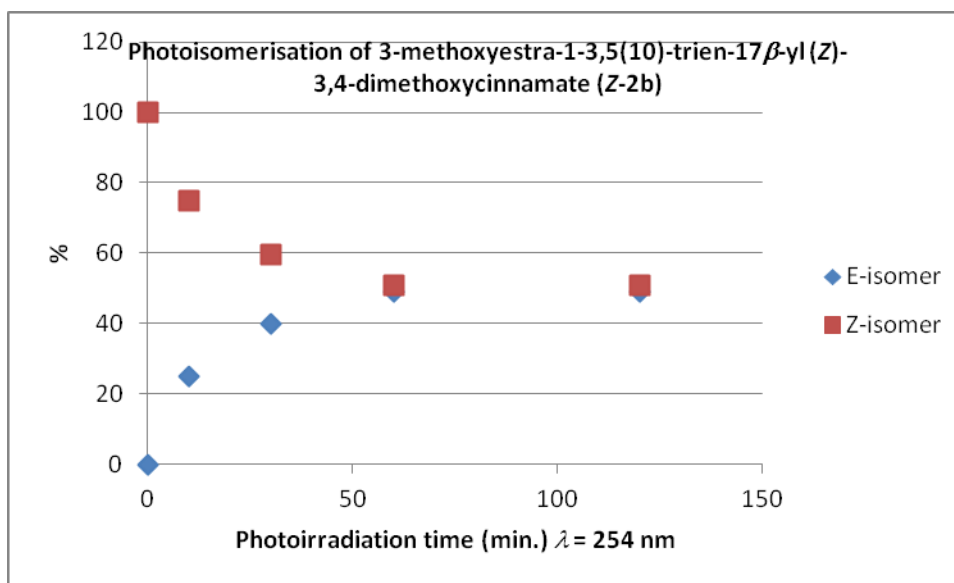
Graph 1.



Graph 2.



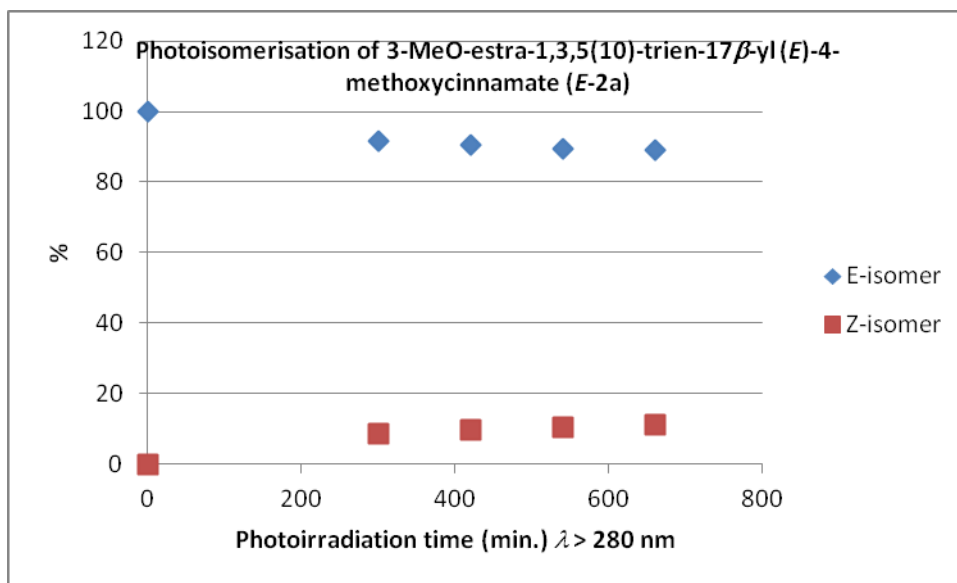
Graph 3.



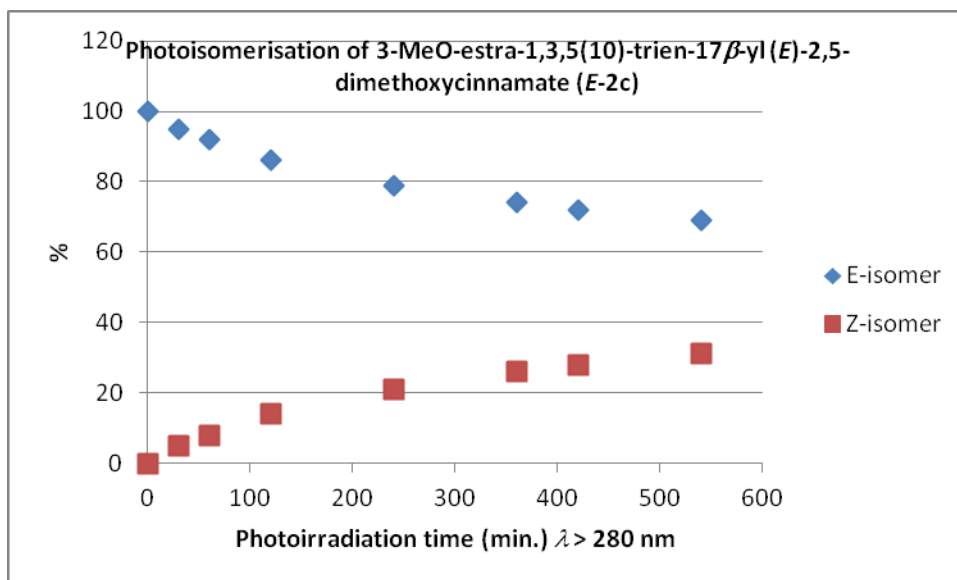
Graph 4.

Further, the photoirradiation of the cinnamates **E-2** and *NO*-oxime cinnamates **E-1** was carried out at a longer wavelength using a Hg lamp ($\lambda \geq 280$ nm). Here, photoirradiation of 3-methoxyestra-1,3,5(10)-trien-17 β -yl 2,5-(*E*)-dimethoxycinnamate (**E-2c**) in CDCl_3 gave *E/Z* 95/5 (30 min.), *E/Z* 92/8 (1h), *E/Z* 86/14 (2h), *E/Z* 79/21 (4h), *E/Z* 74/26 (6h), *E/Z* 72/28 (7h), and *E/Z* 69/31 (9h). Photoirradiation of 3-methoxyestra-1,3,5(10)-trien-17 β -yl 4-(*E*)-methoxycinnamate (**E-2a**) in CDCl_3 gave *E/Z* 91.5/8.5 (5h), *E/Z* 90.5/9.5 (7h), *E/Z* 89.5/10.5 (9h), and *E/Z* 89/11 (11h). Photoirradiation of 3-methoxyestra-1,3,5(10)-trien-17 β -yl 3,4-(*E*)-dimethoxycinnamate (**E-2b**) in CDCl_3 gave *E/Z* 96/4 (30 min), *E/Z* 93/7 (1h), *E/Z* 88.5/11.5 (2h), *E/Z* 84/16 (4h), *E/Z* 81/19 (6h), *E/Z* 79.5/20.5 (7h) and *E/Z* 78.3/21.7 (9h). Photoirradiation of 3-methoxyestra-1,3,5(10)-trien-17-one-17-oxime -2,5-(*E*)-dimethoxycinnamate (**E-1c**) using a Hg lamp gave *E/Z* (

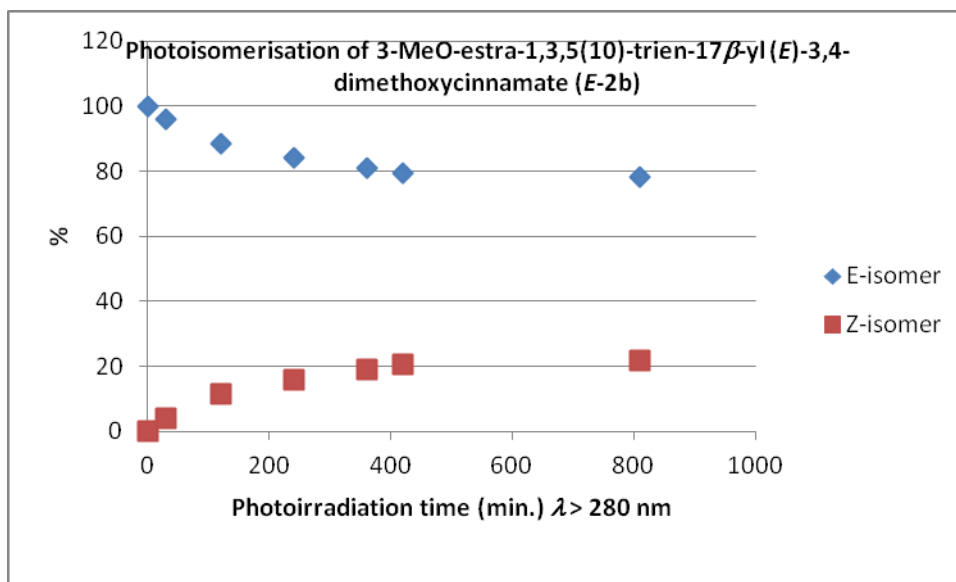
(2h) 81.9/14.9, *E/Z* (3h) 75.2/8.3, *E/Z* (5h) 67.5/22.8, *E/Z* (7h) 61.9/23.1, and (9h) 63.4/15.8. All the *Z*-cinnamates, obtained as photoproducts from the reactions above, could be purified by column chromatography on silica gel except for 3-methoxyestra-1,3,5(10)-trien-17 β -yl 2,5-(*E*)-dimethoxycinnamate (**Z-2c**), and 3-methoxyestra-1-3,5(10)-trien-17-one-17-oxime-2,5-(*E*)-dimethoxycinnamate (**Z-1c**), which could not be separated by column chromatography, where in the latter two cases the best result was achieved with hexane/ether/CH₂Cl₂ 3.5:1:1, which led to fractions with an enrichment of the *Z*-isomer.



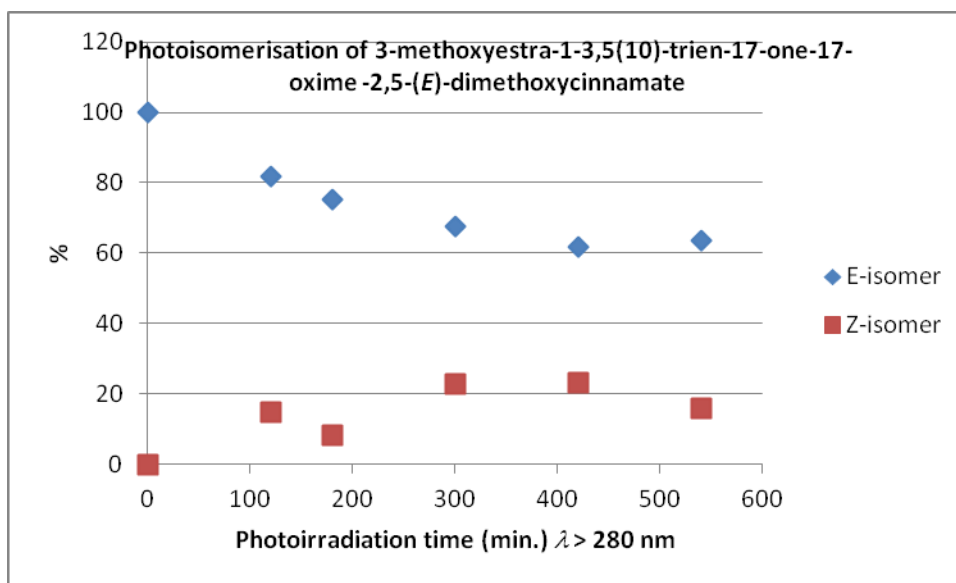
Graph 5.



Graph 6.



Graph 7.



Graph 8.

It must be noted that the steroidal cinnamoyl-oximes **1**, while surprisingly stable under photoirradiation at $\lambda \geq 280$ nm, showed on top of the *E*-/*Z*-isomerization cleavage products as the photoirradiation progressed. Not all cleavage products could be identified yet, but the free *E*- and *Z*-cinnamic acids could be detected after longer irradiation times. This would not be unusual as it is known that the N-O acyloxime bond is prone to photochemical cleavage.^{14,15} Hydrogen abstraction from the solvent would then lead from the cinnamic radical to the cinnamic acid. Other pathways such as decarboxylation of the primary radical can be envisaged that would lead to further side-products that still need to be identified experimentally.

To understand better the process of the photochemical *E*-/*Z*-isomerization of the cinnamates **2**, the photoisomerization was looked at computationally. Computational studies on the photoisomerization of cinnamates have been carried out previously by other groups.¹⁶ It has been noted that the photoisomerization is affected by the substitution in the aromatic system.^{17,18} From the experimental results, it was evident that 4-methoxycinnamate **E-2a** and 3,4-dimethoxycinnamate **E-2b** undergo rapid isomerization at $\lambda = 254$ nm, while 2,5-dimethoxycinnamate **E-2c** does not. At $\lambda \geq 280$ nm, the situation was reversed. Thus, it was deemed to be of interest to have a better understanding of the effect of the methoxy substitution pattern on the photoisomerization of the cinnamates **2**. Further calculations with a different basis set as well as calculated energies of **E-2** and **Z-2** can be found in the separate addendum.

Computational Details: All calculations were performed using the Gaussian 09W¹⁹ program and all compounds were modeled in the gas phase. Geometry optimizations of the model compounds were performed using the B3LYP hybrid functional^{20,21} and 6-31G(d) basis set. Time dependent density functional theory (TDDFT) calculations were used to determine the 6 lowest lying excited states of each model compound, using the B3LYP functional and 6-31G(d) basis set. Transition state structures for E-Z isomerization were determined using the Synchronous Transit-Guided Quasi-Newton (STGQN) method employing starting structures and a transition state guess QST3^{22,23} and the Hartree-Fock ab initio method and 6-31G(d) basis set. Total energies of the transition states were calculated using the B3LYP functional and 6-31G(d) basis set. The energies of transition states in the S_1 excited state were calculated using the Hartree-Fock optimized transition state geometries and TDDFT at the B3LYP/6-31G(d) level.

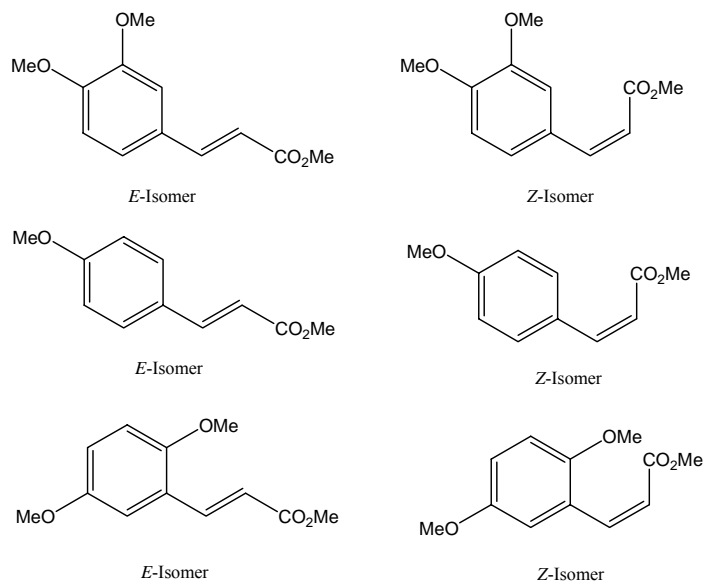


Figure 2. Methyl methoxycinnamates used as model compounds

Structure: The structure of each compound was modeled by replacing the steroidal group with a methyl group. The structure of each model compound in *E*- and *Z*- conformations was optimized at the B3LYP/6-31G(d) level. In all cases it was found that the energy of the *E*-isomer was lower, but the energy

difference between *E*- and *Z*- isomers was greatest for the 2,6-dimethoxy model compound (Table 1). This greater energy difference for the 2,6-dimethoxy compound appears to arise from steric hindrance in the *Z*-form, which inhibits planarity (Figure 3). The *Z*-isomers of the 4-methoxy, 2-5-dimethoxy and 3,-4-dimethoxy compounds do not exhibit this distortion from planarity.

Compound	Energy difference (E-Z) kJ/mole
4-MeO(model)	17.3
3,4-MeO (model)	14.3
2,5-MeO (model)	20.1
2,6-MeO (model)	27.2

Table 1. Energy differences between *E*- and *Z*- isomers for model compounds.

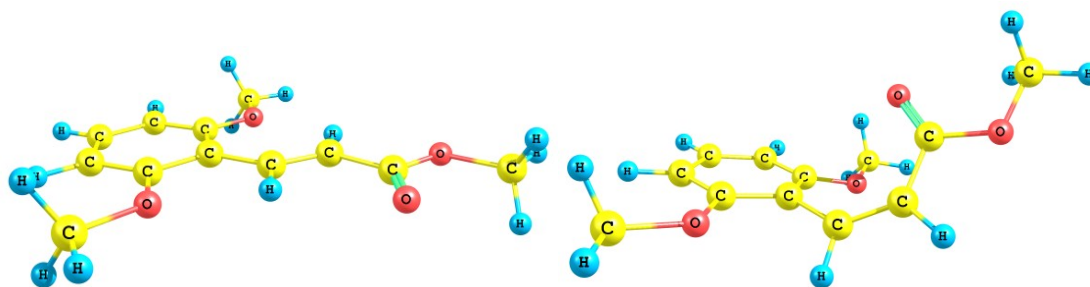


Figure 3. Optimized structure of *E*- and *Z*- 2,6-dimethoxy model compounds.

Electronic Spectra: TDDFT calculated spectra for each model complex indicate a transition in the range 270-320nm, which corresponds to weakening the C=C double bond. Figure 4 below shows isosurfaces of the orbitals involved in the transition for the 4-methoxy model compound (in this case, the HOMO and LUMO):

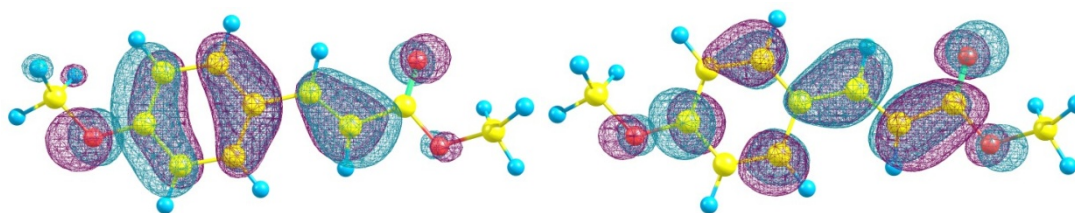


Figure 4: Isosurfaces of the HOMO and LUMO of the 4-methoxy model compound.

The calculated wavelengths and oscillator strengths for the relevant transition for each isomer are given in table 2:

	4-MeO (E)	4-MeO (Z)	3,4-MeO (E)	3,4-MeO (Z)	2,5-MeO (E)	2,5-MeO (Z)	2,6-MeO (E)	2,6-MeO (Z)
λ (nm)	295	302	273	283	275	281	293	318
f	0.82	0.67	0.47	0.37	0.54	0.44	0.58	0.06

Table 2. TDDFT calculated absorption wavelengths for transitions involving π - π^* of the C-C double bond in model compounds.

In each case the transition energy is higher in the *E*-isomer, arising due to slight destabilization of the C=C π orbital in the *Z*-isomer. In the case of the *Z*-2,6-di-MeO structure, the oscillator strength for the transition is significantly reduced as a result of the distortion of the structure from planarity.

Rotational Barrier: The *E-Z* rotational barrier for each model compound was determined by QST3 optimization of the transition state using HF/6-31G(d) calculations. The transition states identified were verified by vibrational frequency calculations which indicated one negative eigenvalue in each case. The calculated barriers are listed in Table 3.

	4-MeO	3,4-MeO	2,5-MeO	2,6-MeO
ΔE (<i>E-Z</i>) kJ/mole	300	299	298	313

Table 3. Thermal rotational barriers for *E-Z* isomerization for model compounds.

The structure of the transition state for the 4-MeO model compound is shown below in Figure 5. The C-C bond length has increased on rotation from 1.35Å to approximately 1.46Å, consistent with the reduced π overlap upon rotation:

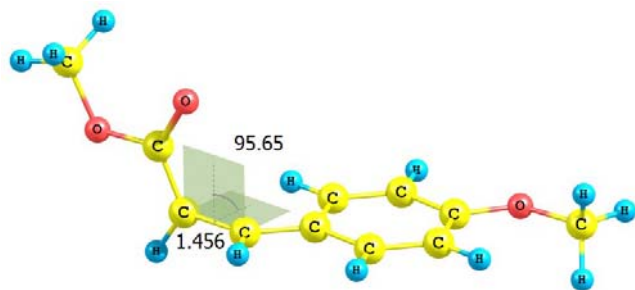


Figure 5. Structure of the optimized transition state for *E-Z* isomerization for the 4-methoxy model compound.

Photoisomerization: The π - π^* nature and high calculated oscillator strength for calculated transitions in the model compounds suggests that these excitations could result in *E-Z* isomerization. A possible Scheme for this process is illustrated in Figure 6 below, using the 2,6-dimethoxy model compound as an example. The energies of electronic transitions are derived from the TDDFT calculations discussed earlier and the rotational barrier for thermal rotation (TS-S₀) is that determined from the QST3 transition state.

The energy of the transition state in the first excited singlet state (S_1) was determined by TDDFT calculation of the electronic transition from the S_0 transition state.

While the *E*/*Z*-isomerization of the steroidal 2,6-cinnamate has not yet been attempted by us, it is possible that *Z*- to *E*- photoisomerization of the 2,6-dimethoxy compound could be inhibited due to the low oscillator strength of the S_0 - S_1 transition in the *Z*- isomer.

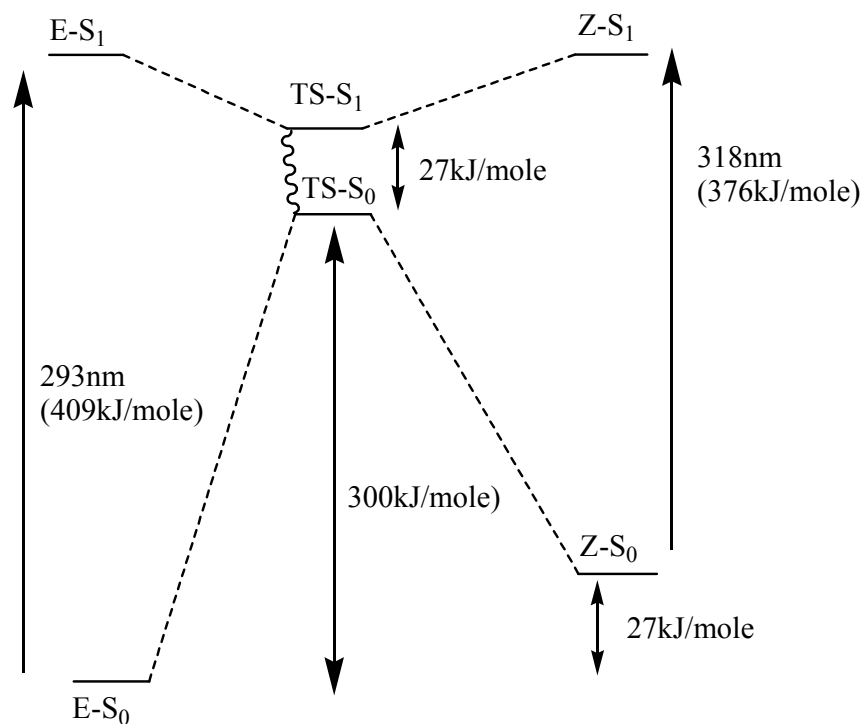


Figure 6. Possible scheme for the photoisomerization of the 2,6-dimethoxy model compound.

Conclusions. Estradiol-derived *E*-cinnamates **E-2** and *O*-(*E*)-cinnamoyl-estrone-oxime of type **E-1** by an Appel type esterification reaction using the novel reagent $\text{BrCCl}_3\text{-PPh}_3$. The (*E*)-4-methoxycinnamates **E-2a** and (*E*)-3,4-dimethoxycinnamate **2b** undergo rapid *E*/*Z*-isomerization when irradiated at $\lambda = 254$ nm, while (*E*)-2,5-dimethoxycinnamate **2c** does not. At $\lambda \geq 280$ nm, the cinnamates are more stable, and only isomerize appreciably after longer reaction times of some hours of direct irradiative exposure. Nevertheless, the photoisomerization at $\lambda \geq 280$ nm can be used to access the (*Z*)-cinnamates preparatively. The (*E*)-cinnamoyl oximes **E-1** also isomerize at $\lambda \geq 280$ nm. Additionally, they undergo N-O photocleavage reactions, but slowly.

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