Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 4287–4295

TETRAHEDRON

A new approach toward the synthesis of C,D-*cis* coupled steroid and C,D-*cis* coupled D-homosteroid skeletons

Svetlana Dratch,[a,b] Tanya Charnikhova,[a,b] Florence C. E. Sarabèr,[a] Ben J. M. Jansen[a] and Aede de Groot[a,*]

[a]*Laboratory of Organic Chemistry, Wageningen University, Dreijenplein 8, 6703 HB Wageningen, The Netherlands*
[b]*Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Kuprevich str. 5/2, 220141 Minsk, Belarus*

Received 10 February 2003; revised 27 March 2003; accepted 16 April 2003

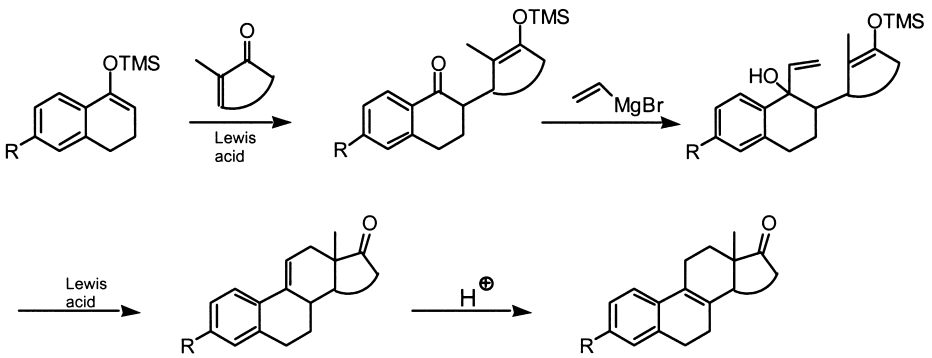
Abstract—A short and efficient procedure has been developed for the synthesis of C,D-*cis* coupled steroid and D-homo steroid skeletons. A Mukaiyama reaction with transfer of the silyl group of the starting silyl enol ether to the enol of the adduct followed by addition of vinyl magnesium bromide to the unprotected carbonyl group leads to adducts which can be cyclized with $ZnBr_2$. The synthesis of functionalized steroid skeletons in overall yields of about 50% in four steps can be achieved in this way.

1. Introduction

The construction of ring C as the final step in total syntheses of steroid skeletons is well known because of the good results that have been obtained using the Torgov reaction.[1–12] In this approach the formation of the 8–14 bond completes the synthesis of the steroid skeleton. Many other methods, based on other reaction types for the closing of ring C have been employed in later steroid syntheses, but to the best of our knowledge only one report has been published in which the construction the 12–13 bond was the final step in the closure of ring C.[13–16] We now report a second example of such an approach, which is depicted in Scheme 1.

The strategy relies on a Mukaiyama–Michael reaction in which the silyl group of the silyl enol ether of methoxy tetralone is transferred to the carbonyl group of the receiving enone e.g. carvone or methyl cyclopentenone. A selective Grignard reaction of vinyl magnesium bromide with the unprotected carbonyl group of methoxy tetralone becomes possible, leading to a Torgov type intermediate. This can be converted easily into a carbocation, which than reacts with the silyl enol ether to close ring C, thus completing the synthesis of the (homo)steroid skeleton.

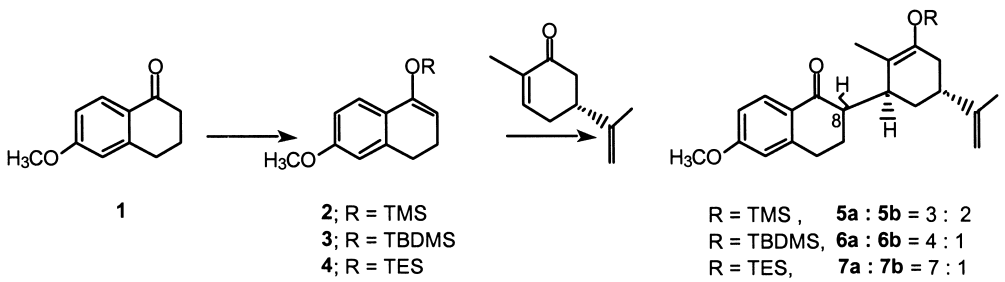
It is clear that the use of cyclopentenone as receptor in the Mukaiyama–Michael reaction will lead to racemic reaction products in which equilibration at C14 will not be straightforward. For this reason *R*-carvone was investigated as receptor, which should lead to enantiomerically pure products with the natural steroid configuration at C14.



Scheme 1.

Keywords: Mukaiyama–Michael addition; homo-steroid synthesis; C,D-*cis* steroids; carvone.
* Corresponding author. Tel.: +31-317-482370; fax: +31-317-484914; e-mail: aede.degroot@wur.nl

0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00629-X



Scheme 2.

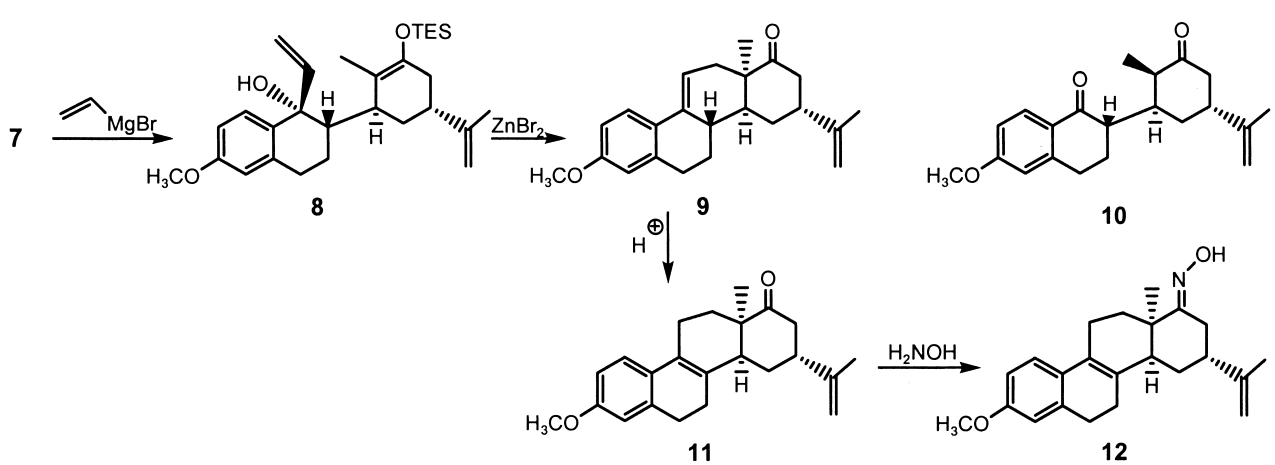
Starting from *R*-carvone, D-homo steroids will be obtained as end products but handles are available in ring D for ring-contraction to a normal steroid skeleton. The D-homo steroids may also have interesting biological properties. Since both enantiomers of carvone are available from nature, it is possible to determine the configuration of C14 by choosing the correct enantiomer as starter, thus making the normal 14-α D-homo steroids and their 14-β isomers accessible. The $\Delta^{9,11}$ double bond in the ring-closed products, will allow an easy functionalization of C11. In this paper we would like to report on this approach and on aspects of its scope and stereochemistry.

2. Results and discussion

The silyl enol ether of methoxy tetralone has been used before to generate the corresponding enolate for a Michael reaction with cyclopentenone.[17] The resulting enolate has been reacted further with suitable electrophilic reagents, with the ultimate purpose of constructing steroid skeletons. Silyl dienol ethers have been reacted with methyl cyclopentenone, with transfer of the silyl group to form a new silyl enol ether of the accepting enone.[18] This new silyl enol ether has been used as a substrate for further alkylation to give ultimately steroid skeletons.

To the best of our knowledge no Mukaiyama–Michael reaction of the silyl enol ether of methoxy tetralone with methyl cyclopentenone, accompanied by transfer of the silyl group to the carbonyl group of methyl cyclopentenone, has been reported. Preliminary results showed that such a reaction can proceed in high yield, leading to inseparable mixtures of diastereomers of the new silyl enol ether. To minimize these complications in product separation and identification, our efforts were concentrated first on carvone as acceptor in the Mukaiyama–Michael reaction. It was expected that the asymmetric center in carvone would direct the addition to the enone from the least hindered side, opposite to the isopropenyl group, thus leading to just one adduct. It appears that diastereomeric mixtures of adducts are formed, which differ in configuration at C8.[19] This stereoselectivity proved to be dependent on the nature of the starting silyl enol ether. When the trimethyl silyl enol ether **2** was used, a 3:2 ratio of diastereomers **5a** and **5b** was obtained in 56% yield. With the *tert*-butyl dimethyl silyl enol ether **3**, the ratio of **6a**:**6b** could be improved to 4:1 and the yield was quantitative. When the triethyl silyl enol ether **4** was the starting compound a 7:1 ratio of diastereomers was obtained in 88% yield (Scheme 2). The yields of these reactions were influenced by the stoichiometry of the reagents, a 2:1 molar ratio of enol ether and carvone gave the best results. Several Lewis acids and reaction conditions were tried out but ultimately tritylantimonyhexachloride ($TrSbCl_6$) as catalyst and methylene chloride as solvent at −78 to −40°C were used for all the Mukaiyama–Michael reactions.

Since the diastereomeric mixtures of **5a** and **5b** and of **6a** and **6b** could be separated only with difficulties or not at all, further reactions were first carried out with the pure major diastereomer of triethyl silyl enol ether **7a** (see Scheme 3). The addition of vinyl magnesium bromide to **7** proceeded in a reasonable 70% yield to give only one stereoisomer of the adduct **8**, which tentatively was assigned the indicated configuration[13] (vide infra). About 10% of non-converted



Scheme 3.

starting material could be recovered. Complete conversion of **7** proved to be difficult to achieve, probably because of competing enolization. Unfortunately enol ether **7** and adduct **8** could not be separated by column chromatography in our hands. Therefore cyclization of the mixture of **8** and **7** with $ZnBr_2$[20] was undertaken and went smoothly to give **9** in good yield, together with the desilylated diketone **10**. In a separate reaction it was shown that desilylation of **7** to **10** indeed takes place with $ZnBr_2$ under the applied reaction conditions.

The yield of the vinyl magnesium bromide addition could be improved by repeating the addition twice or three times after workup and drying of the mixture of **7** and **8**. This worked well for the TES and TBDMS silyl enol ethers because these are stable compounds. The TMS silyl enol ether is less stable and some decomposition leading to desilylated product **10** and its stereoisomers, was observed.

The cyclization of pure **8** with $ZnBr_2$ proceeded in 66% yield, and in this way D-homo steroid **9** was obtained as an enantiopure product in just four steps starting from methoxy tetralone in 40% overall yield. It is known that the $\Delta^{9,11}$ double bond in steroids like **9** can be isomerized easily by treatment with mild acid.[21] It indeed proved to be the case that **9** could be converted smoothly into its $\Delta^{8,9}$ isomer **11** by treatment with hydrochloric acid at room temperature in quantitative yield. All compounds were obtained as oils, but the oxime **12**, derived from **11**, could be obtained in crystalline form, so an X-ray became possible.[22] In this way the stereochemistry of **12** was determined unambiguously, and turned out to be as indicated in Scheme 3. This stereochemistry can be explained by a selective approach of the bulky triethyl silyl enol ether **4** to *R*-(−)-carvone from the top face, opposite to the isopropenyl group. The carvone substituent ends up in a favorable axial position next to the carbonyl group in the tetralone portion of the molecule and consequently the addition of vinyl magnesium bromide occurs from the top face.[14] The closure of ring C then leads to a *cis* fused CD-ring system in the steroid skeleton.

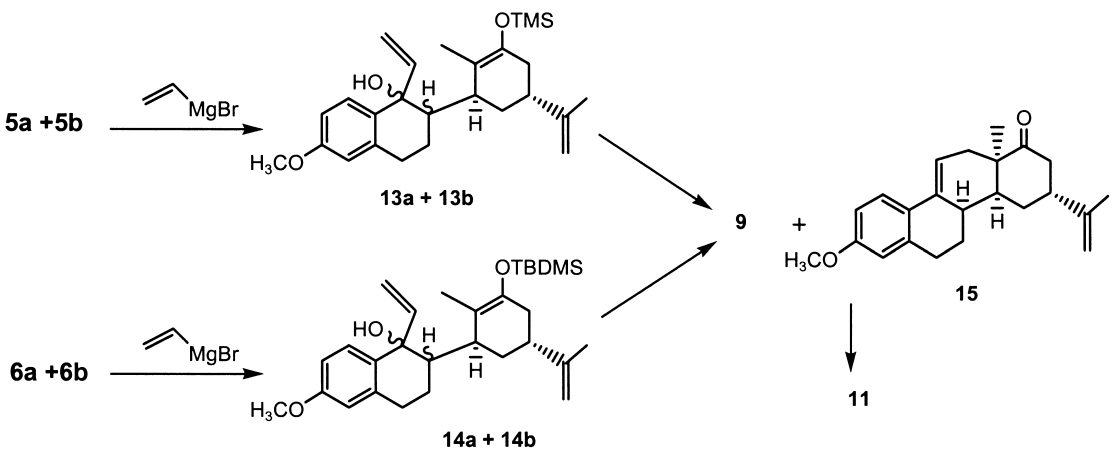
The reaction of the mixture of TMS silyl enol ethers **5a** and **5b** with vinyl magnesium bromide gave a mixture of two adducts **13a** and **13b** in good yield, and in a similar way the mixture of **6a** and **6b** could be converted into **14a** and **14b** in 75% yield (see Scheme 4). The ratio of the diastereomers varied slightly with the enol ether that was used, and again the reaction was not complete after one run but a good yield could be achieved by performing several repetitions of the reaction without purification of the intermediate mixtures. The ratio of the unreacted silyl enol ethers **5** and **6** and the ratio of the corresponding adducts **13** and **14**, respectively, differed from that of the starting mixture of silyl enol ethers **5** and **6**, which can be explained either by different rates of enolization and reprotonation of the enols, or by different rates of adduct formation.

The adducts **13** and **14** could be cyclized to a mixture of **9** and its C8 epimer **15** with $ZnBr_2$. The fact that the two compounds in the mixture were epimeric at C8 was proven again by acid catalyzed isomerization of the mixture to one compound **11**.

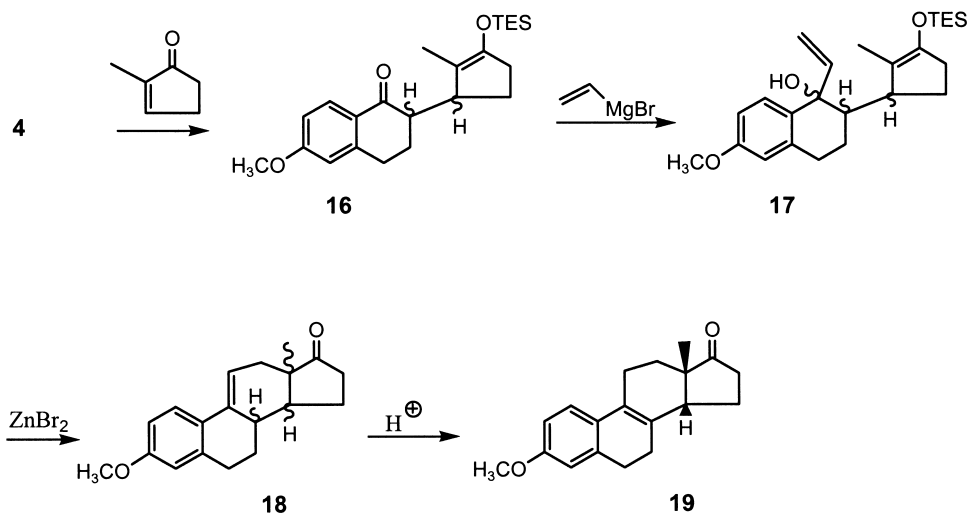
The reactions with methyl cyclopentenone as acceptor also proceeded smoothly, this was performed with silyl enol ether **4**. In this case the Mukaiyama–Michael reaction also gave diastereomeric mixtures of the new silyl enol ether **16**. The addition of vinyl magnesium bromide also went smoothly and again the reaction was not complete after one run. A good yield could be achieved by performing several repetitions of the reaction without purification of the intermediate mixtures. The cyclization of the adducts **17** with $ZnBr_2$ gave a lower yield of the cyclised diastereomeric mixture of the steroid skeleton **18**. Dehydration was a major side reaction in these cases. Finally acid catalyzed isomerization of this mixture gave the known racemic **19**[23] in about 30% overall yield starting from **4** (Scheme 5).

3. Conclusions

A short and efficient synthesis has been developed of CD *cis* coupled steroid and CD *cis* coupled D-homo steroid skeletons. A Mukaiyama–Michael reaction with transfer of the silyl group of the starting silyl enol ether to the enol of the adduct is the key feature in this approach. Addition of vinyl magnesium bromide to the unprotected carbonyl group followed by cyclization of the adduct with $ZnBr_2$ completes the synthesis of the (homo)steroid skeleton.



Scheme 4.



Scheme 5.

Overall yields of about 50% in four steps leading to functionalized steroid skeletons, make this approach easy and attractive.

4. Experimental

4.1. General

All reagents were purchased from Aldrich or Arcos, except for carvone which was donated by Quest, and were used without further purification unless otherwise stated. Melting points are uncorrected. Infrared spectra were recorded on a FTIR Biorad FTS7 spectrometer and only characteristic absorptions are reported. NMR experiments were conducted with Bruker AC-E 200 or DPX 400 instruments; signals are reported in ppm (δ), referenced to $CHCl_3$. HRMS data were obtained with a Finnigan MAT 95 spectrometer. Solvents were freshly distilled by common practice. Product solutions were dried over $MgSO_4$ prior to evaporation of the solvent under reduced pressure by using a rotary evaporator. Reactions were monitored by GC with a DB-17 column (30 m×0.25 mm i.d.) or by TLC on silica gel plate and visualization of compounds was accomplished by UV detection and by spraying with a molybdate solution and subsequent heating.

4.1.1. [(6-Methoxy-3,4-dihydro-1-naphthalenyl)oxy](trimethyl)silane (2).[24] To a solution of 8.8 g (50 mmol) of 6-methoxytetralone in 60 ml of acetonitrile were added 6.1 g (60 mmol) of triethylamine, 6.5 g (60 mmol) of chlorotrimethylsilane and 9 g (60 mmol) of sodium iodide. The reaction mixture was stirred overnight at room temperature. Then 100 ml of petroleum ether and 50 ml of a saturated solution of sodium bicarbonate were added. After extraction the petroleum ether solution was dried over Na_2SO_4. After evaporation of the solvent, bulb to bulb distillation afforded silyl enol ether **2** (11.4 g, 92%).

IR (CCl_4) 2958, 2835, 1683, 1639, 1607, 1252 cm^{-1}. ^1H NMR δ: 0.31 (s, 9H); 2.24–2.35 (m, 2H); 2.79 (t, J=7.8 Hz, 2H); 3.83 (s, 3H); 5.12 (t, J=4.6 Hz, 1H); 6.74 (s, 1H); 6.76 (d, J=8.6 Hz, 1H); 7.41 (d, J=8.2 Hz, 1H). ^{13}C NMR δ: 0.21 (3q); 22.20 (t); 28.66 (t); 55.14 (q); 102.86 (d); 110.68 (d); 113.18 (d); 123.10 (d); 126.61 (s); 138.91 (s); 147.95 (s); 158.94 (s). HRMS: M^+, found 248.1229. $C_{14}H_{20}O_2Si$ requires 248.1233. MS *m/e* (%) 248 (M^+, 100), 247 (64), 233 (30), 217 (13), 73 (21).

4.1.2. [(6-Methoxy-3,4-dihydro-1-naphthalenyl)oxy](dimethyl-*tert*-butyl)silane (3). To a solution of 10 g (56.8 mmol) of 6-methoxytetralone in 90 ml of acetonitrile were added 6.9 ml (68.2 mmol) of triethylamine, 10.3 g (68.2 mmol) of chlorodimethyl-*tert*-butylsilane and 10.2 g (68.2 mmol) of sodium iodide. The reaction mixture was stirred overnight at room temperature. Then 100 ml of petroleum ether and 50 ml of a saturated solution of sodium bicarbonate were added. After separation the petroleum ether solution was dried over Na_2SO_4. After evaporation of the solvent, bulb to bulb distillation afforded silyl enol ether **3** (16.55 g, 100%).

^1H NMR δ: 0.21 (s, 6H), 1.02 (s, 9H), 2.30 (m, 2H), 2.74 (t, J=7.8 Hz, 2H), 3.80 (s, 3H), 5.06 (t, J=4.6 Hz, 1H), 6.72 (m, 2H), 7.40 (d, J=8.2 Hz, 1H). ^{13}C NMR δ: −4.43 (2q), 18.36 (s), 22.27 (t), 25.95 (3q), 28.74 (t), 55.22 (q), 102.58 (d), 110.68 (d), 113.24 (d), 123.19 (d), 126.81 (s), 139.04 (s), 148.16 (s), 158.92 (s). HRMS: M^+, found 290.1704. $C_{17}H_{26}O_2Si$ requires 290.1702. MS *m/e* (%) 290 (M^+, 54), 275 (5), 234 (28), 233 (100), 203 (38), 73 (8).

4.1.3. [(6-Methoxy-3,4-dihydro-1-naphthalenyl)oxy](triethyl)silane (4). To a solution of 8.8 g (50 mmol) of 6-methoxytetralone in 60 ml of acetonitrile were added 8.3 ml (60 mmol) of triethylamine, 9.1 g (60 mmol) of chlorotriethylsilane and 9 g (60 mmol) of sodium iodide. The reaction mixture was stirred overnight at room temperature. Then 100 ml of petroleum ether and 50 ml of a saturated solution of sodium bicarbonate were added. After extraction the petroleum ether solution was dried over Na_2SO_4. After evaporation of the solvent, bulb to bulb distillation afforded silyl enol ether **4** (12.0 g, 83%).

IR (CCl_4) 2956, 2877, 1682, 1600, 1271 cm^{-1}. ^1H NMR δ: 0.78 (q, J=7.6 Hz, 6H); 1.06 (t, J=7.6 Hz, 9H); 2.30–2.38 (m, 2H); 2.73–2.81 (t, J=7.8 Hz, 2H), 3.81 (s, 3H); 5.11 (t,

J=4.2 Hz, 1H); 6.72–6.77 (m, 2H); 7.45 (d, J=8.2 Hz, 1H). ^{13}C NMR δ: 5.15 (3t); 6.85 (3q); 22.31 (t); 28.74 (t); 55.14 (q); 102.18 (d); 110.71 (d); 113.22 (d); 123.11 (d); 126.79 (s); 138.98 (s); 148.19 (s); 158.99 (s). HRMS: M^+, found 290.1707. $C_{17}H_{26}O_2Si$ requires 290.1702. MS *m/e* (%) 290 (M^+, 100); 261 (81); 233 (9); 232 (9); 231 (38); 159 (8).

4.1.4. 2-{(1*R*,5*S*)-5-Isopropenyl-2-methyl-3-[(triethylsilyl)oxy]-2-cyclohexen-1-yl}-6-methoxy-3,4-dihydro-1(2H)-naphthalenone (7a and 7b). To a solution of 2.03 g (7 mmol) of triethylsilylenol ether **4** and 0.525 g (3.5 mmol) of *R*-carvone in 15 ml CH_2Cl_2 was added 0.035 g (0.06 mmol) of $TrSbCl_6$ at −78°C and the reaction mixture was allowed to warm to −40°C. After 1 h some drops of pyridine were added to destroy the catalyst, and the yellow color of the reaction mixture immediately disappeared. The reaction mixture was allowed to warm to room temperature, washed with brine, dried (Na_2SO_4), and the solvent was evaporated. The adducts **7a** and **7b** (1.36 g, ratio 7:1) were isolated by chromatography on SiO_2 (light petroleum/ethyl acetate/pyridine, 98:1:1) as an oil in 88% yield.

^{1}H NMR δ: 0.69 (q, J=7.9 Hz, 6H); 1.00 (t, J=7.9 Hz, 9H); 1.61 (s, 3H); 1.67 (s, 3H); 1.50–2.40 (m, 7H); 2.76 (dt, J=13.0, 3.7 Hz, 1H), 2.92 (m, 2H); 3.22 (br s, 1H); 3.83 (s, 3H); 4.66 (d, J=5.6 Hz, 2H); 6.66 (d, J=2.4 Hz, 1H); 6.82 (dd, J=8.6, 2.4 Hz, 1H); 8.02 (d, J=8.6 Hz, 1H).

^{13}C NMR (main isomer) δ: 5.66 (3t); 6.84 (3q); 13.99 (q); 20.76 (q); 25.45 (t); 29.39 (t); 30.54 (t); 35.07 (t); 36.46 (d); 39.46 (d); 50.60 (d); 55.40 (q); 109.10 (t); 111.10 (s); 112.46 (d); 112.96 (d); 126.97 (s); 129.87 (d); 145.33 (s); 146.58 (s); 148.61 (s); 163.32 (s); 198.60 (s). (Minor isomer): 5.77 (3t); 6.59 (3q); 16.24 (q); 20.45 (q); 27.09 (t); 29.88 (t); 30.47 (t); 35.00 (t); 36.15 (d); 38.49 (d); 53.59 (d); 55.31 (q); 108.88 (t); 110.50 (s); 112.12 (d); 112.88 (d); 126.27 (s); 130.03 (d); 144.75 (s); 144.89 (s); 146.11 (s); 163.24 (s); 198.10 (s). HRMS: M^+, found 440.2749. $C_{27}H_{40}O_3Si$ requires 440.2747. MS *m/e* (%) 440 (M^+, 10); 290 (8); 265 (100); 223 (5); 176 (7); 115 (8); 87 (21).

4.1.5. (1*R*,2*S*)-2-{(1*R*,5*S*)-5-Isopropenyl-2-methyl-3-[(triethylsilyl)oxy]-2-cyclohexen-1-yl}-6-methoxy-1-vinyl-1,2,3,4-tetrahydro-1-naphthalenol (8). To a solution of 15 mmol of 1 M vinyl magnesium bromide in THF was added slowly a solution of 1.32 g (3 mmol) of ketone **7** in 15 ml of THF at 0°C. The reaction mixture was stirred under these conditions for 1 h and then at room temperature for 4–5 h. Then 25 ml of a saturated solution of NH_4Cl was added and the mixture was extracted with ethyl acetate (3×75 ml). The ethyl acetate solution was dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by chromatography on SiO_2 (light petroleum/ethyl acetate, grad., with 1% of pyridine) to give 0.95 g (68%) of **8** as a colorless oil.

IR (CCl_4) 3616, 2957, 2914, 2878, 1677, 1604, 1575, 1498, 1460, 1245, 1177 cm^{-1}. ^{1}H NMR δ: 0.69 (q, J=7.9 Hz, 6H); 1.00 (t, J=7.8 Hz, 9H); 1.56 (s, 3H); 1.72 (s, 3H), 1.50–2.85 (m, 11H); 3.77 (s, 3H); 4.69 (d, J=5.2 Hz, 2H); 5.40 (dd, J=10.2, 2.3 Hz, 1H); 5.62 (dd, J=17.1, 2.4 Hz, 1H); 5.84 (dd, J=17.1, 10.2 Hz, 1H); 6.61 (d, J=2.4 Hz, 1H); 6.71 (dd, J=8.7, 2.4 Hz, 1H); 7.29 (d, J=8.7 Hz, 1H). ^{13}C NMR δ: 5.45 (3t); 6.63 (3q); 14.24 (q); 19.88 (t); 20.85 (q); 28.92 (t); 31.04 (t); 34.34 (t); 37.53 (d); 38.32 (d); 43.71 (d); 55.02 (q); 104.78 (s); 108.33 (t); 112.24 (d); 112.57 (d); 113.06 (s); 113.57 (t); 129.25 (d); 133.77 (s); 137.92 (s); 143.56 (d); 144.50 (s); 148.93 (s); 158.60 (s). HRMS: M^+, found 468.3062. $C_{29}H_{44}O_3Si$ requires 468.3060. MS *m/e* (%) 468 (M^+, 4.5); 450 (10); 336 (10); 265 (100); 115 (6); 87 (17).

4.1.6. (3*R*,4a*S*,4b*S*,12a*R*)-3-Isopropenyl-8-methoxy-12a-methyl-3,4,4a,4b,5,6,12,12a-octahydro-1(2H)-chrysenone (9). A suspension 0.47 g (1 mmol) of adduct **8** and 0.22 g (1 mmol) of $ZnBr_2$ in 20 ml of dry CH_2Cl_2 was stirred under nitrogen for 1 h at −78°C. Then the reaction mixture was allowed to warm to room temperature and the solution became clear and green. After 2 h the mixture was poured into 50 ml of saturated sodium bicarbonate solution. The organic solution was separated and the aqueous solution was washed three times with 50 ml of CH_2Cl_2. The combined organic solution was dried over Na_2SO_4 and the solvent was carefully evaporated. The residue was chromatographed over silica gel (light petroleum/ethyl acetate, 9:1) to give 0.22 g (66%) of **9** as a colorless oil.

IR (CCl_4) 2935, 2837, 1711, 1644, 1608, 1571, 1234, 1177 cm^{-1}. ^{1}H NMR δ: 1.35 (s, 3H); 1.82 (s, 3H); 1.65–2.85 (m, 13H); 3.76 (s, 3H); 4.81 (s, 2H); 6.11 (m, 1H); 6.56 (d, J=2.6 Hz, 1H); 6.71 (dd, J=8.6, 2.4 Hz, 1H); 7.50 (d, J=8.6 Hz, 1H). ^{13}C NMR δ: 20.58 (q); 26.85 (t); 27.14 (q); 29.16 (t); 30.42 (t); 33.24 (t); 36.01 (d); 41.31 (d); 41.75 (t); 46.74 (d); 47.15 (s); 55.23 (q); 109.93 (t); 112.53 (d); 112.93 (d); 116.59 (d); 125.21 (d); 127.89 (s); 133.54 (s); 136.81 (s); 147.59 (s); 158.37 (s); 213.32 (s). HRMS: M^+, found 336.2096. $C_{23}H_{28}O_2$ requires 336.2089. MS *m/e* (%) 336 (M^+, 100); 321 (11); 239 (14); 225 (29); 187 (17); 186 (44); 174 (14).

4.1.7. (3*R*,4a*S*,12a*R*)-3-Isopropenyl-8-methoxy-12a-methyl-3,4,4a,5,6,11,12,12a-octahydro-1(2H)-chrysenone (11). Compound **9** (0.08 g, 0.24 mmol) was stirred in 12 ml of 5:1 MeOH/10N HCl for 1 h. The MeOH was removed and the remaining aqueous suspension was diluted with 12 ml NaH_2PO_4 buffer (pH 4) and extracted three times with 30 ml of ethyl acetate. The combined extracts were dried over Na_2SO_4, and the solvent was evaporated to give 0.08 g (100%) of **11** as a colorless oil.

IR (CCl_4) 2937, 2834, 1705, 1608, 1500, 1283 cm^{-1}. ^{1}H NMR δ: 1.19 (s, 3H); 1.74 (s, 3H); 2.05–2.73 (m, 14H); 3.78 (s, 3H); 4.68 (s, 1H); 4.80 (s, 1H); 6.69 (s, 1H); 6.73 (d, J=8.2 Hz, 1H); 7.10 (d, J=8.1 Hz, 1H). ^{13}C NMR δ: 21.11 (q); 22.96 (t); 24.48 (q); 26.61 (t); 28.93 (t); 30.34 (t); 40.14 (d); 43.15 (t); 45.99 (d); 47.13 (s); 55.28 (q); 110.60 (t); 110.89 (d); 113.20 (d); 123.17 (d); 128.25 (s); 129.47 (s); 131.53 (s); 136.89 (s); 147.33 (s); 158.12 (s); 215.60 (s). HRMS: M^+, found 336.2090. $C_{23}H_{28}O_2$ requires 336.2089. MS *m/e* (%) 336 (M^+, 100), 321 (16), 240 (18), 239 (16), 226 (36), 225 (43), 211 (14), 150 (10).

4.1.8. (1*E*,3*R*,4a*S*,12a*R*)-3-Isopropenyl-8-methoxy-12a-methyl-3,4,4a,5,6,11,12,12a-octahydro-1(2H)-chrysenone oxime (12). To a stirred solution of **11** (0.67 g,

2.0 mmol) in EtOH was added a hydroxylamine hydrochloride (1.39 g, 20 mmol) and anhydrous sodium acetate (1.64 g, 20 mmol) in portions, and the suspension was refluxed. After 30 min, TLC showed the reaction to be complete. The mixture was filtered and solvent was removed under vacuum. The residue was dissolved in $CHCl_3$ (100 ml) and extracted with H_2O (3×30 ml). Drying (Na_2SO_4), removal of solvent under vacuum, and column chromatography over silica gel (light petroleum/ethyl acetate, 9:1) provided 0.53 g (75%) of **25** as white crystals, mp 112°C (from hexane/Et_2O).

IR (CCl_4) 3602, 3267, 3086, 2936, 2833, 1645, 1608, 1573, 1500, 1284 cm^{-1}. ^1H NMR δ:1.24 (s, 3H), 1.55 (m, 1H), 1.77 (s, 3H), 1.93 (t, J=5.8 Hz, 2H), 2.23 (m, 6H), 2.74 (m, 5H), 3.81 (s, 3H), 4.80 (s, 2H), 6.73 (m, 2H), 7.15 (d, J=8.0 Hz, 1H), 9.20 (br s, 1H). ^{13}C NMR δ: 21.37 (q), 22.88 (t), 25.50 (t), 25.90 (q), 26.78 (t), 28.99 (t), 29.31 (t), 31.38 (t), 38.63 (d), 39.06 (s), 45.23 (d), 55.25 (q), 110.21 (t), 110.87 (d), 113.16 (d), 123.05 (d), 127.04 (s), 129.42 (s), 132.09 (s), 136.93 (s), 147.35 (s), 157.97 (s), 163.95 (s). HRMS: M^+, found 351.2191. $C_{23}H_{29}NO_2$ requires 351.2198. MS *m/e* (%) 351 (M^+, 100), 334 (57), 306 (4), 226 (12), 225 (19), 143 (16).

4.1.9. (2*S*)-2-[(1*R*,5*R*)-Isopropenyl-2-methyl-3-oxocyclohexyl]-6-methoxy-3,4-dihydro-1(2H)-naphthalenone (10). A suspension 0.22 g (0.5 mmol) of enol ether **7** and 0.11 g (0.5 mmol) of $ZnBr_2$ in 15 ml of dry CH_2Cl_2 was stirred under nitrogen for 1 h at −78°C. Then the reaction mixture was allowed to warm to room temperature and the solution became clear and green. After 2.5 h the mixture was poured into 25 ml of saturated sodium bicarbonate solution. The organic solution was separated and the aqueous solution was washed three times with 30 ml of CH_2Cl_2. The combined organic solution was dried over Na_2SO_4 and the solvent was evaporated. The residue was chromatographed over silica gel (light petroleum/ethyl acetate, 4:1) to give 0.168 g (100%) of two isomers (in ratio 15:1) of diketone **10** as white crystals (mp 118–119°C for main isomer).

Main isomer: IR (CCl_4) 2938, 1712, 1678, 1601, 1476, 1252, 1177 cm^{-1}. ^1H NMR δ: 1.02 (d, J=6.5 Hz, 3H); 1.50–1.72 (m, 1H), 1.80 (s, 3H); 1.82–2.71 (m, 9H); 2.93–2.98 (m, 2H); 3.81 (s, 3H); 4.73 (s, 1H); 4.89 (s, 1H); 6.66 (d, J=2.4 Hz, 1H); 6.77 (dd, J=8.6, 2.4 Hz, 1H); 7.96 (d, J=8.6 Hz, 1H). ^{13}C NMR δ: 11.71 (q); 22.04 (q); 22.85 (t); 28.90 (t); 29.97 (t); 37.52 (d); 40.70 (d); 44.57 (t); 46.72 (d); 48.67 (d); 55.44 (q); 112.42 (d); 112.47 (t); 113.15 (d); 126.67 (s); 129.81 (d); 146.13 (s); 146.54 (s); 163.48 (s); 197.38 (s); 212.55 (s). HRMS: M^+, found 326.1879. $C_{21}H_{26}O_3$ requires 326.1882. MS *m/e* (%) 326 (M^+, 6); 176 (100); 161 (4); 150 (15); 135 (3).

4.1.10. 2-{(1*R*,5*S*)-5-Isopropenyl-2-methyl-3-[(trimethylsilyl)oxy]-2-cyclohexen-1-yl}-6-methoxy-3,4-dihydro-1(2H)-naphthalenone (5a and 5b). To a solution of 5.7 g (23 mmol) of trimethylsilylenol ether **2** and 1.7 g (11.5 mmol) of *R*-carvone in 50 ml CH_2Cl_2 was added 0.11 g (0.2 mmol) of $TrSbCl_6$ at −78°C and the reaction mixture was allowed to warm to −40°C. After 1 h some drops of pyridine were added to destroy the catalyst, and the yellow color of the reaction mixture immediately disappeared. The reaction mixture was allowed to warm to room temperature, washed with brine, dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by chromatography on SiO_2 (light petroleum/ethyl acetate/pyridine, 98:1:1). A mixture of two isomers **5a** and **5b** in the ratio of 3:2 was obtained (2.6 g, 56%) as white crystals (mp 55–56°C from pentane).

IR (CCl_4) 2939, 1680, 1602, 1252 cm^{-1}. ^1H NMR δ: 0.15, 0.19 (s, s, 9H); 1.39, 1.58 (s, s, 3H); 1.68, 1.73 (s, s, 3H); 1.45–2.65 (m, 6H); 2.75 (dt, J=13.0, 3.7 Hz, 1H), 2.92 (m, 2H); 3.23, 3.35 (br s, br s, 1H); 3.83 (s, 3H); 4.73 (m, 2H); 6.67 (br s, 1H); 6.80 (dd, J=8.7, 2.5 Hz, 1H); 8.02 (d, d, J=8.7 Hz, 1H). ^{13}C NMR (isomer 1) δ: 1.35 (3q); 11.90 (q); 21.38 (q); 25.53 (t); 27.24 (t); 28.11 (t); 34.36 (d); 40.63 (d); 42.16 (t); 46.60 (d); 55.43 (q); 77.05 (s); 111.70 (t); 112.35 (d); 113.36 (d); 125.88 (s); 129.88 (d); 145.63 (s); 146.73 (s); 163.50 (s); 198.95 (s); 213.78 (s). (Isomer 2) 1.95 (3q); 12.23 (q); 21.07 (q); 26.83 (t); 29.06 (t); 29.50 (t); 36.51 (d); 42.41 (d); 44.11 (t); 47.99 (d); 55.43 (q); 77.69 (s); 111.04 (t); 112.35 (d); 113.22 (d); 125.18 (s); 130.05 (d); 145.77 (s); 147.03 (s); 163.50 (s); 198.85 (s); 213.78 (s). HRMS: M^+, found 398.2275. $C_{24}H_{34}O_3Si$ requires 398.2277. MS *m/e* (%) 398 (M^+, 12), 329 (3), 248 (31), 223 (100), 222 (49), 176 (21), 73 (33).

4.1.11. 2-{(1*R*,5*S*)-5-Isopropenyl-2-methyl-3-[(dimethyl-*tert*-butylsilyl)oxy]-2-cyclohexen-1-yl}-6-methoxy-3,4-dihydro-1(2H)-naphthalenone (6a and 6b). To a solution of 3.48 g (12 mmol) of dimethyl-*tert*-butylsilylenol ether **3** and 1.5 g (10 mmol) of *R*-carvone in 25 ml CH_2Cl_2 was added 0.24 g (0.4 mmol) of $TrSbCl_6$ at −78°C. After 0.5 h some drops of pyridine were added to destroy the catalyst, the yellow color of the reaction mixture immediately disappeared. The reaction mixture was allowed to warm to room temperature, washed with brine, dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by chromatography on SiO_2 (light petroleum/ethyl acetate/pyridine, 98:1:1). A mixture of two isomers **6a** and **6b** in the ratio of 4:1 was obtained (4.4 g, 100%) as white crystals (mp 72–73°C from pentane).

IR (CCl_4) 2931, 2858, 1678, 1602, 1253 cm^{-1}. ^1H NMR δ: 0.11, 0.14 (s, s, 6H), 0.92, 0.94 (s, s, 9H), 1.42, 1.60 (s, s, 3H), 1.68, 1.72 (s, s, 3H), 1.50–2.40 (m, 7H), 2.74 (dt, J=13.0, 3.8 Hz, 1H), 2.90 (m, 2H), 3.22, 3.32 (br s, br s, 1H), 3.82 (s, 3H), 4.70 (m, 2H), 6.66 (d, J=2.2 Hz, 1H), 6.77 (dd, J=8.7, 2.2 Hz, 1H), 8.00 (d, d, J=8.8 Hz, 1H). ^{13}C NMR (main isomer) δ: −3.66 (2q), 14.25 (q), 18.25 (s), 20.80 (q), 25.44 (t), 25.93 (3q), 29.33 (t), 30.51 (t), 35.22 (t), 36.56 (d), 39.40 (d), 50.56 (d), 55.37 (q), 109.15 (t), 111.20 (s), 112.45 (d), 112.99 (d), 126.97 (s), 129.85 (d), 145.28 (s), 146.56 (s), 148.50 (s), 163.33 (s), 198.51 (s). (Minor isomer): −3.74 (2q), 16.54 (q), 20.98 (q), 22.64 (s), 25.78 (3q), 27.29 (t), 28.83 (t), 29.99 (t), 34.86 (t), 36.34 (d), 38.57 (d), 53.60 (d), 55.24 (q), 110.00 (t), 110.63 (s), 112.28 (d), 113.09 (d), 126.41 (s), 130.13 (d), 144.85 (s), 146.11 (s), 148.68 (s), 158.56 (s), 198.03 (s). HRMS: M^+, found 440.2746. $C_{27}H_{40}O_3Si$ requires 440.2747. MS *m/e* (%) 440 (M^+, 8), 383 (2), 266 (22), 265 (100), 264 (31), 233 (6), 176 (7), 73 (28).

4.1.12. 2-{(1*R*,5*S*)-5-Isopropenyl-2-methyl-3-[(trimethylsilyl)oxy]-2-cyclohexen-1-yl}-6-methoxy-1-vinyl-1,2,3,4-tetrahydro-1-naphthalenol (13a and 13b). To a solution of 3.5 mmol of 1 M vinyl magnesium bromide in THF was added slowly a solution of 0.28 g (0.7 mmol) of the mixture of **5a** and **5b** in 15 ml of THF at 0°C. The reaction mixture was stirred under these conditions for 1 h and at the room temperature for 4–5 h. Then 10 ml of a saturated solution of NH_4Cl was added and the mixture was extracted with ethyl acetate (3×25 ml). The ethyl acetate solution was dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by chromatography on SiO_2 (light petroleum/ethyl acetate, with 1% of pyridine) to give 0.18 g (62%) of a mixture of two isomers **13a** and **13b** in the ratio of 3:2 as a colorless oil.

IR (CCl_4) 3617, 2936, 1678, 1643, 1607, 1499, 1277, 1175 cm^{-1}. ^1H NMR δ: 0.20 (m, 9H); 1.63, 1.64 (s, s, 3H); 1.70, 1.72 (s, s, 3H); 1.40–2.85 (m, 11H); 3.77 (s, 3H); 4.69 (d, J=5.6 Hz, 2H); 5.35, 5.39 (dd, J=10.3, 2.4 Hz; dd, J=9.8, 2.4 Hz, 1H), 5.62 (dd, J=17.1, 2.4 Hz, 1H); 5.81, 5.84 (dd, J=17.1, 10.3 Hz; dd, J=17.1, 9.8 Hz, 1H); 6.62 (br s, 1H); 6.72 (dd, J=8.6, 2.4 Hz, 1H); 7.29 (m, 1H). ^{13}C NMR (main isomer) δ: 0.89 (3q); 14.56 (q); 20.01 (t); 21.13 (q); 29.09 (t); 31.30 (t); 34.64 (t); 37.67 (d); 38.84 (d); 43.90 (d); 55.24 (q); 76.78 (s); 108.62 (t); 112.50 (d); 113.36 (d); 113.83 (t); 114.36 (s); 129.45 (d); 134.09 (s); 138.16 (s); 143.78 (d); 144.68 (s); 149.03 (s); 158.86 (s). (Minor isomer): 0.81 (3q); 17.37 (q); 20.41 (q); 23.37 (t); 31.35 (t); 35.46 (t); 37.06 (d); 37.86 (t); 38.01 (d); 49.84 (d); 55.25 (q); 75.31 (s); 108.86 (t), 112.63 (d); 113.15 (d); 113.37 (s); 113.48 (t); 130.43 (d); 132.63 (s); 138.45 (s); 143.54 (d); 144.48 (s); 149.47 (s); 158.86 (s). HRMS: M^+, found 426.2590. $C_{26}H_{38}O_3Si$ requires 426.2590. MS *m/e* (%) 426 (M^+, 51), 411 (5), 408 (10), 281 (24), 223 (100), 186 (31), 73 (28).

4.1.13. 2-{(1*R*,5*S*)-5-Isopropenyl-2-methyl-3-[(dimethyl-*tert*-butylsilyl)oxy]-2-cyclohexen-1-yl}-6-methoxy-1-vinyl-1,2,3,4-tetrahydro-1-naphthalenol (14a and 14b). To a solution of 25 mmol of 1 M vinyl magnesium bromide in THF was added slowly a solution of 2.2 g (5 mmol) of a mixture of ketones **6a** and **6b** in 20 ml of THF at 0°C. The reaction mixture was stirred under these conditions for 1 h and at the room temperature for 4–5 h. Then 100 ml of a saturated solution of NH_4Cl was added and the mixture was extracted with ethyl acetate (3×75 ml). The ethyl acetate solution was dried (Na_2SO_4) and the solvent was evaporated. This residue was treated two times again with 15 mmol of 1 M vinyl magnesium bromide as described above and worked up as described above. The residue was purified by chromatography on SiO_2 (light petroleum/ethyl acetate, grad., with 1% of pyridine) to give 1.75 g (75%) of a mixture of **14a** and **14b** in the ratio of 5:1 as a colorless oil.

IR (CCl_4) 3617, 2931, 2859, 1676, 1607, 1558, 1256, 1167 cm^{-1}. ^1H NMR δ: 0.15 (s, 6H), 0.97 (s, 9H), 1.55, 1.58 (s, s, 3H), 1.71, 1.74 (s, s, 3H), 1.80–2.95 (m, 11H), 3.77 (s, 3H), 4.68, 4.72 (d, d, J=6.3 Hz, 2H), 5.35, 5.41 (dd, dd, J=10.2, 2.2 Hz, 1H), 5.63 (dd, J=17.1, 2.2 Hz, 1H), 5.82, 5.85 (dd, dd, J=17.1, 10.2 Hz, 1H), 6.61 (d, J=2.6 Hz, 1H), 6.72 (dd, J=8.6, 2.6 Hz, 1H), 7.27, 7.30 (d, d, J=8.6 Hz, 1H). ^{13}C NMR (main isomer) δ: −3.63 (2q), 14.73 (q), 18.29 (s), 20.05 (t), 21.12 (q), 25.98 (3q), 29.13 (t), 31.31 (t), 34.83 (t), 37.82 (d), 38.92 (d), 43.92 (d), 55.23 (q), 76.78 (s), 108.63 (t), 112.49 (d), 112.91 (s), 113.35 (d), 113.82 (t), 129.50 (d), 134.07 (s), 138.17 (s), 143.83 (d), 144.75 (s), 149.08 (s), 158.85 (s). (Minor isomer): −4.26 (s), 17.19 (q), 17.55 (s), 22.13 (q), 23.40 (t), 25.89 (3q), 27.83 (t), 31.31 (t), 35.60 (t), 37.29 (d), 38.07 (d), 43.62 (d), 55.41 (q), 75.30 (s), 108.87 (t), 111.86 (t), 112.61 (d), 113.16 (d), 130.44 (d), 132.66 (s), 138.45 (s), 143.56 (d), 148.77 (s), 149.48 (s), 155.00 (s). HRMS: M^+, found 468.3066. $C_{29}H_{44}O_3Si$ requires 468.3060. MS *m/e* (%) 468 (M^+, 3), 450 (11), 336 (12), 265 (100), 263 (27), 223 (7), 186 (11), 75 (14), 73 (48).

4.1.14. (3*R*,4a*S*,4b*S*,12a*R*)-3-Isopropenyl-8-methoxy-12a-methyl-3,4,4a,4b,5,6,12,12a-octahydro-1(2H)-chrysenone (9) and (3*R*,4a*S*,4b*R*,12a*R*)-3-isopropenyl-8-methoxy-12a-methyl-3,4,4a,4b,5,6,12,12a-octahydro-1(2H)-chrysenone (15). A suspension 0.3 g (0.7 mmol) of the mixture of adducts **13a** and **13b** and 0.16 g (0.7 mmol) of $ZnBr_2$ in 15 ml of dry CH_2Cl_2 was stirred under nitrogen for 1 h at −78°C. Then the reaction mixture was allowed to warm to room temperature and the solution became clear and green. After 4 h the mixture was poured into 30 ml of saturated sodium bicarbonate solution. The organic solution was separated and the aqueous solution was extracted three times with 30 ml of CH_2Cl_2. The combined organic solution was dried over Na_2SO_4 and the solvent was carefully evaporated. The residue was chromatographed over silica gel (light petroleum/ethyl acetate, 9:1) to give 0.16 g (68%) of a mixture of **9** and **15** in the ratio 1:1.

^1H NMR δ (**9**+**15**): 1.15, 1.35 (s, s, 3H), 1.74, 1.78 (s, s, 3H), 1.68–2.90 (m, 13H), 3.76, 3.78 (s, s, 3H), 4.68, 4.80, 4.88 (s, s, s, 2H), 6.09, 6.17 (m, m, 1H), 6.58 (dd, J=10.0, 2.6 Hz, 1H), 6.69, 6.73 (dd, dd, J=8.6, 2.6 Hz, 1H), 7.48, 7.59 (d, d, J=8.6 Hz, 1H). ^{13}C NMR δ (**15**): 19.64 (q), 22.10 (q), 23.80 (t), 27.44 (t), 31.23 (t), 32.72 (t), 35.29 (d), 39.94 (d), 39.98 (d), 40.63 (t), 47.75 (s), 55.25 (q), 112.46 (t), 112.83 (d), 113.36 (d), 123.17 (d), 124.34 (d), 126.63 (s), 131.95 (s), 138.07 (s), 146.89 (s), 158.45 (s), 215.55 (s). HRMS: M^+, found 336.2083. $C_{23}H_{28}O_2$ requires 336.2089. MS *m/e* (%) 336 (M^+, 100), 239 (18), 225 (30), 224 (19), 187 (33), 186 (57), 171 (16).

4.1.15. (3*R*,4a*S*,4b*S*,12a*R*)-3-Isopropenyl-8-methoxy-12a-methyl-3,4,4a,4b,5,6,12,12a-octahydro-1(2H)-chrysenone (9) and (3*R*,4a*S*,4b*R*,12a*R*)-3-isopropenyl-8-methoxy-12a-methyl-3,4,4a,4b,5,6,12,12a-octahydro-1(2H)-chrysenone (15). A suspension 0.35 g (0.75 mmol) of a 4:1 mixture of adducts **14a** and **14b** and 0.17 g (0.75 mmol) of $ZnBr_2$ in 50 ml of dry CH_2Cl_2 was stirred under nitrogen for 1 h at −78°C. Then the reaction mixture was allowed to warm to room temperature and the solution became clear and green. After 1 h the mixture was poured into 15 ml of saturated sodium bicarbonate solution. The organic solution was separated and the aqueous solution was washed three times with 50 ml of CH_2Cl_2. The combined organic solution was dried over Na_2SO_4 and the solvent was carefully evaporated. The residue was chromatographed over silica gel (light petroleum/ethyl acetate, 9:1) to give 0.18 g (72%) of a mixture of **9** and **15** in the ratio 5:3.

4.1.16. (3*R*,4a*S*,12a*R*)-3-Isopropenyl-8-methoxy-12a-methyl-3,4,4a,5,6,11,12,12a-octahydro-1(2H)-chrysenone (11). A mixture (5:3 or 1:1) of compounds **9** and **15** (0.13 g, 0.38 mmol) was stirred in 30 ml of 5:1 MeOH/10N HCl for 1 h. The MeOH was removed and the remaining aqueous suspension was diluted with 30 ml NaH_2PO_4 buffer (pH 4) and extracted three times with 30 ml of ethyl acetate. The combined extract was dried over Na_2SO_4, and the solvent was evaporated to give 0.13 g (100%) of **11** as a colorless oil.

4.1.17. (1*R*)-6-Methoxy-2-{2-methyl-3-[(triethylsilyl)-oxy]-2cyclopenten-1-yl}-3,4-dihydro-1(2H)-naphthalenone (16). To a solution of 2.03 g (7 mmol) of triethylsilylenol ether **4** and 0.5 g (5.25 mmol) methyl cyclopentenone in 30 ml CH_2Cl_2 was added 0.03 g (0.07 mmol) of $TrSbCl_6$ at −78°C. After 1 h some drops of pyridine were added to destroy the catalyst, and the yellow color of the reaction mixture immediately disappeared. The reaction mixture was allowed to warm to room temperature, washed with brine, dried (Na_2SO_4), and the solvent was evaporated. A mixture of two diastereomers **16a** and **16b** in the ratio of 3:2 was obtained (2.02 g, 100%) as a colorless oil.

IR (CCl_4) 2957, 2877, 1679, 1601, 1250 cm^{-1}. ^1H NMR δ: 0.62 (m, 6H), 0.94 (m, 9H), 1.29, 1.51 (s, s, 3H), 1.30–2.35 (m, 6H), 2.53–2.65 (m, 1H), 2.86–2.92 (m, 2H), 3.43–3.70 (m, 1H), 3.81 (s, 3H), 6.65 (d, J=2.2 Hz, 1H), 6.77 (dd, J=8.8, 2.2 Hz, 1H), 7.98 (dd, J=8.8, 2.2 Hz, 1H). ^{13}C NMR (main isomer) δ: 5.39 (3t), 6.68 (3q), 10.02 (q), 22.36 (t), 22.91 (t), 29.92 (t), 33.19 (t), 43.90 (d), 49.68 (d), 55.34 (q), 112.31 (d), 112.81 (s), 112.93 (d), 127.05 (s), 129.62 (d), 146.78 (s), 148.07 (s), 163.31 (s), 198.96 (s). (Minor isomer): 5.36 (3t), 6.68 (3q), 11.68 (q), 23.62 (t), 25.02 (t), 29.79 (t), 32.98 (t), 43.26 (d), 52.15 (d), 55.34 (q), 112.36 (d), 113.01 (d), 113.87 (s), 126.55 (s), 129.94 (d), 146.48 (s), 148.26 (s), 163.26 (s), 197.79 (s). HRMS: M^+, found 386.2273. $C_{23}H_{34}O_3Si$ requires 386.2277. MS *m/e* (%) 386 (M^+, 8), 290 (10), 270 (12), 211 (100), 176 (27), 87 (15).

4.1.18. (1*R*)-6-Methoxy-2-{(1*R*)-2-methyl-3-[(triethylsilyl)oxy]-2-cyclopenten-1-yl}-1-vinyl-1,2,3,4-tetrahydro-1-naphthalenol (17). To a solution of 15 mmol of 1 M vinyl magnesium bromide in THF was added slowly a solution of 1.16 g (3 mmol) of the diastereomeric mixture of **16** in 15 ml of THF at 0°C. The reaction mixture was stirred under these conditions for 1 h and at the room temperature for 4–5 h. Then 25 ml of a saturated solution of NH_4Cl was added and the mixture was extracted with ethyl acetate (3×75 ml). The ethyl acetate solution was dried (Na_2SO_4) and the solvent was evaporated. This residue was treated again with 10 mmol of 1 M vinyl magnesium bromide as described above and worked up as described above (this procedure was repeated once more). The residue was purified by chromatography on SiO_2 (light petroleum/ethyl acetate, grad.) to give 0.93 g (75%) of a diastereomeric mixture of **17** in the ratio of 10:1 as a colorless oil.

IR (CCl_4) 3617, 2956, 2876, 1609, 1498, 1240 cm^{-1}. ^1H NMR (main isomer) δ: 0.68 (q, J=7.9 Hz, 6H), 1.00 (t, J=7.9 Hz, 9H), 1.47 (s, 3H), 1.50–1.91 (m, 4H), 2.21–2.26 (m, 2H), 2.7–2.95 (m, 4H), 3.76 (s, 3H), 5.35 (dd, J=10.4, 2.2 Hz, 1H), 5.58 (dd, J=17.1, 2.2 Hz, 1H), 5.80 (dd, J=17.1, 10.4 Hz, 1H), 6.60 (d, J=2.2 Hz, 1H), 6.71 (dd, J=8.6, 2.2 Hz, 1H), 7.28 (d, J=8.6 Hz, 1H). ^{13}C NMR δ: 5.42 (3t), 6.71 (3q), 10.14 (q), 18.06 (t), 22.64 (t), 31.01 (t), 33.71 (t), 44.04 (d), 44.07 (d), 55.17 (q), 76.44 (s), 112.47 (d), 113.22 (d), 113.38 (t), 114.40 (s), 130.09 (d), 133.30 (s), 138.61 (s), 144.37 (d), 147.73 (s), 158.73 (s). ^1H NMR (minor isomer) δ: 0.65 (q, J=7.9 Hz, 6H), 0.99 (t, J=8.0 Hz, 9H), 1.63 (s, 3H), 1.40–2.9 (m, 10H), 3.77 (s, 3H), 5.30 (dd, J=10.4, 1.8 Hz, 1H), 5.50 (dd, J=17.1, 10.4 Hz, 1H), 5.84 (dd, J=17.1, 10.4 Hz, 1H), 6.60 (d, J=2.6 Hz, 1H), 6.71 (dd, J=8.6, 2.6 Hz, 1H), 7.30 (d, J=8.6 Hz, 1H). ^{13}C NMR δ: 6.32 (3t), 7.11 (3q), 13.12 (q), 21.48 (t), 25.33 (t), 31.11 (t), 32.51 (t), 43.95 (d), 50.39 (d), 55.21 (q), 75.42 (s), 111.58 (d), 112.56 (d), 113.05 (t), 115.54 (s), 130.16 (d), 133.04 (s), 138.40 (s), 144.72 (d), 149.00 (s), 158.68 (s). HRMS: M^+, found 414.2590. $C_{25}H_{38}O_3Si$ requires 414.2590. MS *m/e* (%) 414 (M^+, 8), 385 (7), 300 (8), 227 (11), 211 (16), 186 (100), 176 (11), 171 (6).

4.1.19. 3-Methoxyestra-1(10),2,4,9(11)-tetraen-17-one (18). A suspension 0.36 g (0.9 mmol) of the mixture of adducts **17** and 0.2 g (0.9 mmol) of $ZnBr_2$ in 15 ml of dry CH_2Cl_2 was stirred under nitrogen for 1 h at −78°C. Then the reaction mixture was allowed to warm to room temperature and the solution became clear and green. After 2 h the mixture was poured into 25 ml of saturated sodium bicarbonate solution. The organic solution was separated and the aqueous solution was extracted three times with 30 ml of CH_2Cl_2. The combined organic solution was dried over Na_2SO_4 and the solvent was carefully evaporated. The residue was chromatographed over silica gel (light petroleum/ethyl acetate, 9:1) to give 0.1 g (40%) of a diastereomeric mixture of **18** in the ratio of 4:1 as white crystals (mp 94–95°C from ethyl acetate/pentane).

IR (CCl_4) 2961, 2934, 2836, 1742, 1608, 1499, 1252 cm^{-1}. ^1H NMR δ: 1.09 (s, 3H), 1.4–2.4 (m, 10H), 2.84 (m, 2H), 3.77, 3.79 (s, s, 3H), 6.06, 6.11 (m, m, 1H), 6.60 (d, J=2.1 Hz, 1H), 6.70 (dd, J=8.6, 2.7 Hz, 1H), 7.45, 7.55 (d, d, J=8.6 Hz, 1H). ^{13}C NMR δ: 23.05 (q), 25.12 (t), 29.72 (t), 29.85 (t), 30.63 (t), 34.70 (t), 37.97 (d), 47.17 (s), 47.88 (d), 55.24 (q), 112.61 (d), 113.12 (d), 115.53 (d), 124.96 (d), 128.16 (s), 135.17 (s), 137.47 (s), 158.58 (s), 221.69 (s). HRMS: M^+, found 282.1618. $C_{19}H_{22}O_2$ requires 282.1620. MS *m/e* (%) 282 (M^+, 100), 267 (16), 225 (24), 186 (51).

4.1.20. 3-Methoxyestra-1(10),2,4,8-tetraen-17-one (19).[21] The diastereomeric mixture of compounds **18** (0.07 g, 0.25 mmol) was stirred at the room temperature in 12 ml of 5:1 MeOH/10N HCl for 1 h. The MeOH was evaporated and the remaining aqueous suspension was diluted with 15 ml NaH_2PO_4 buffer (pH 4) and extracted three times with 30 ml of ethyl acetate. The combined extracts were dried over Na_2SO_4, the solvent was evaporated to give 0.07 g (100%) of the enantiomeric mixture of **19** as white crystals, mp 85–87°C (from ethyl acetate/pentane), lit.[21] mp 88–90°C (from ether/hexane).

IR (CCl_4) 2935, 2835, 1740, 1608, 1500, 1251 cm^{-1}. ^1H NMR δ: 1.07 (s, 3H), 1.51 (m, 1H), 1.77 (m, 2H), 2.05–2.39 (m, 8H), 2.71 (t, J=8.2 Hz, 2H), 3.79 (s, 3H), 6.69 (s, 1H), 6.71 (d, J=7.4 Hz, 1H), 7.10 (d, J=7.4 Hz, 1H). ^{13}C NMR

δ: 20.63 (q), 21.98 (t), 25.47 (t), 26.88 (t), 27.48 (t), 28.86 (t), 36.79 (t), 47.22 (s), 48.64 (d), 55.29 (q), 110.92 (d), 113.49 (d), 123.08 (d), 126.40 (s), 129.04 (s), 131.84 (s), 137.08 (s), 158.13 (s), 223.40 (s). HRMS: M^+, found 282.1620. $C_{19}H_{22}O_2$ requires 282.1620. MS *m/e* (%) 282 (M^+, 100), 254 (7), 226 (25), 225 (20), 211 (9).

Acknowledgements

The authors gratefully acknowledge financial support from the Dutch Technology Foundation (Grant CW/STW-project 790.35.215) and from Organon International. The authors thank A. van Veldhuizen for NMR and IR spectroscopic data, and M. A. Posthumus for mass spectroscopic measurements.

References

1. Nazarov, I. N.; Torgov, I. V.; Verkholetova, G. N. *Dokl. Akad. Nauk. SSSR* **1957**, *112*, 1067.
2. Ananchenko, S. N.; Limanov, V. Y.; Leonov, V. N.; Rzheznikov, V. N.; Torgov, I. V. *Tetrahedron* **1962**, *18*, 1355.
3. Ananchenko, S. N.; Torgov, I. V. *Tetrahedron Lett.* **1963**, *5*, 1553.
4. Gaidamovich, N. N.; Torgov, I. V. *Steroids* **1964**, *4*, 729.
5. Zakharychev, A. V.; Ananchenko, S. N.; Torgov, I. V. *Steroids* **1964**, *4*, 31.
6. Kuo, C. H.; Taub, D.; Wendler, N. L. *J. Org. Chem.* **1968**, *33*, 3126.
7. Makk, N.; Toth, G.; Tomorkeny, E. *Steroids* **1975**, *25*, 611.
8. Garland, R. B.; Palmer, J. R.; Pappo, R. *J. Org. Chem.* **1976**, *41*, 531.
9. Magriotis, P. A.; Johnson, F. *J. Org. Chem.* **1984**, *49*, 1460.
10. Groen, M. B.; Zeelen, F. J. *Recl. Trav. Chim.* **1986**, *105*, 465, and references cited therein.
11. Gauthier, V.; Cazes, B.; Goré, J. *Tetrahedron Lett.* **1991**, *32*, 915.
12. Gauthier, V.; Cazes, B.; Goré, J. *Bull. Soc. Chim. Fr.* **1996**, *133*, 563.
13. Gilchrist, T. L.; Stanford, J. E. *J. Chem. Soc., Perkin Trans. 1* **1987**, 225.
14. Gilchrist, T. L.; Summersell, R. J. *Tetrahedron Lett.* **1987**, *28*, 1469.
15. Gilchrist, T. L.; Summersell, R. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2203.
16. Gilchrist, T. L.; Summersell, R. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2595.
17. Posner, G. H.; Mallamo, J. P.; Black, A. Y. *Tetrahedron* **1981**, *37*, 3921.
18. Grieco, P. A.; May, S. A.; Kaufman, M. D. *Tetrahedron Lett.* **1998**, *39*, 7047.
19. Steroid numbering is used throughout the discussion.
20. Djuric, S.; Sarkar, T.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 6886.
21. Quinkert, G.; Del Grosso, M.; Bucher, A.; Bauch, M.; Doering, W.; Bats, J. W.; Duerner, G. *Tetrahedron Lett.* **1992**, *33*, 3617.
22. Kooijman, H.; Spek, A. L. *Acta Crystallogr. Sect. E* **2003**, *59*, 121.
23. Quinkert, G.; Del Grosso, M.; Doring, A.; Doering, W.; Schenkel, R. I.; Bauch, M.; Dambacher, G. T.; Bats, J. W.; Zimmermann, G.; Duerner, G. *Helv. Chim. Acta* **1995**, *78*, 1345.
24. Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2075.