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Synthesis of 11-Methoxycarbonyl-13-phenyl-17-vinylgona-1,3,5(10)-trienes

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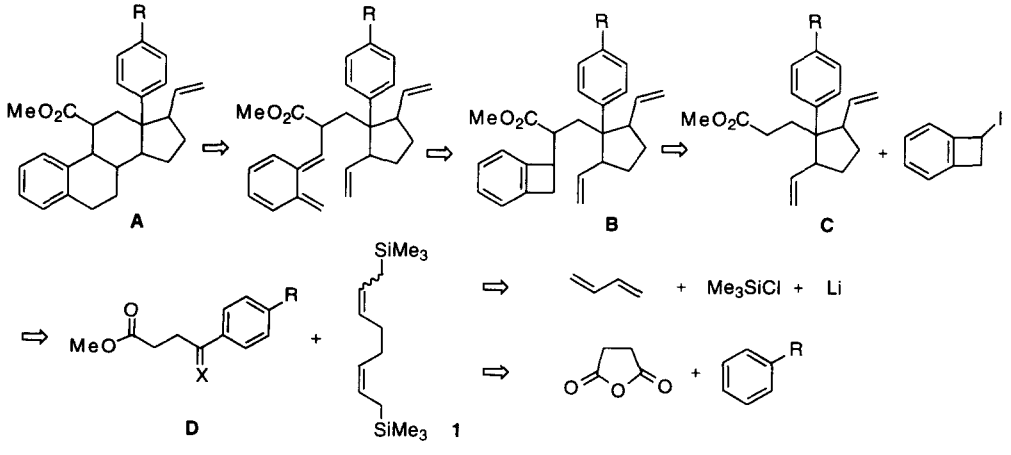
Abstract: Titanium tetrachloride mediated dialkylation of methyl 4-oxo-4-(*p*-bromophenyl)butanoate ethylene ketal by 1,8-bis(trimethylsilyl)-2,6-octadiene (BISTRO) leads to a mixture of methyl *dl* and *meso*-(3-*p*-bromophenyl-2,5-divinylcyclopentan-1-yl)-propanoates. Methoxycarbonylation, alkylation by iodo-benzocyclobutene and then pyrolysis led to the title compounds.

Introduction

Since the first synthesis of equilein and estrone in 1939,[1,2] many steroids have been prepared using several different strategies. Curiously only few 13-arylsteroids have been synthetised.[3] The main step of the syntheses of these 13-arylsteroids is the addition of 2-phenyl-1,3-cyclopentanedione to 1-vinyl-5-methoxytetralol according to the Torgov reaction.[4]

In connection with our interest in steroid synthesis,[5] we reported on a novel strategy for the synthesis of 1,1-disubstituted-2,5-divinylcyclopentanes which involves the addition of 1,8-bis(trimethylsilyl)-2,6-octadiene **1** (BISTRO) to various electrophilic reagents.[6] More recently we have shown with carbonyl compounds that the titanium tetrachloride mediated dialkylation of acetophenones and acetophenone ethylene ketals by BISTRO gives a mixture of *dl* and *meso* 1-alkyl-1-phenyl-2,5-divinylcyclopentanes.[7] These compounds can be used as key intermediates in the synthesis of 13-arylgonatrienes **A** .



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Results and discussion

Initially we studied the dialkylation of alkanophenone derivatives **2**. The best result was obtained with the *p*-bromoalkanophenone ethyleneketal **2e** (Table 1, entry 6) which is in accordance with the previous report concerning the high reactivity of the *p*-bromoacetophenone ethyleneketal.[7] In each case, an inseparable mixture of *dl-meso* **3-4** was obtained in 2.33:1 ratio. We observed that in contrast to the dialkylation of acetophenone ethyleneketal, the presence of nitromethane co-solvent is not necessary. An analogous result has been already observed in the course of the dialkylation of 4-nitro-2-butanone ethylene ketal.[5a]

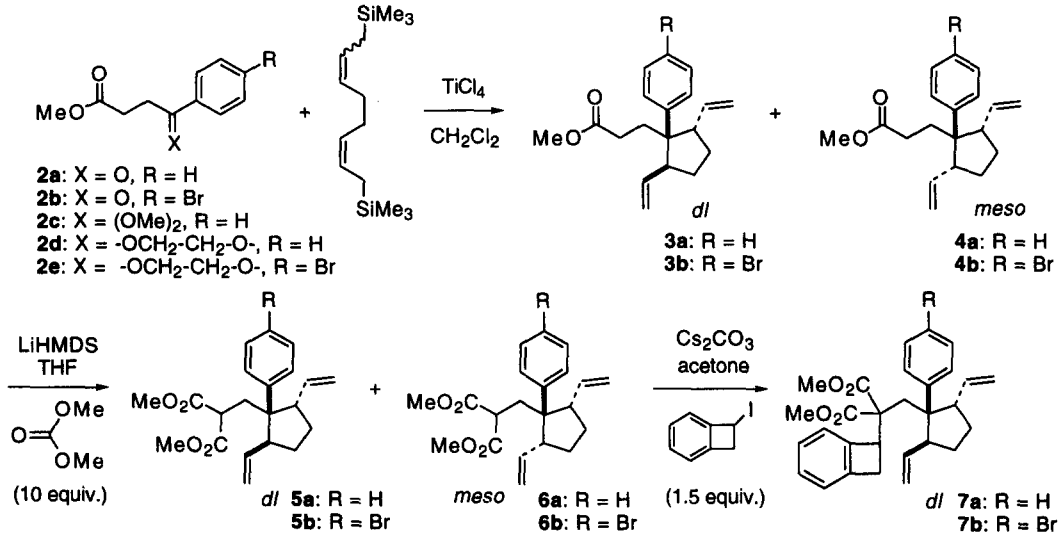
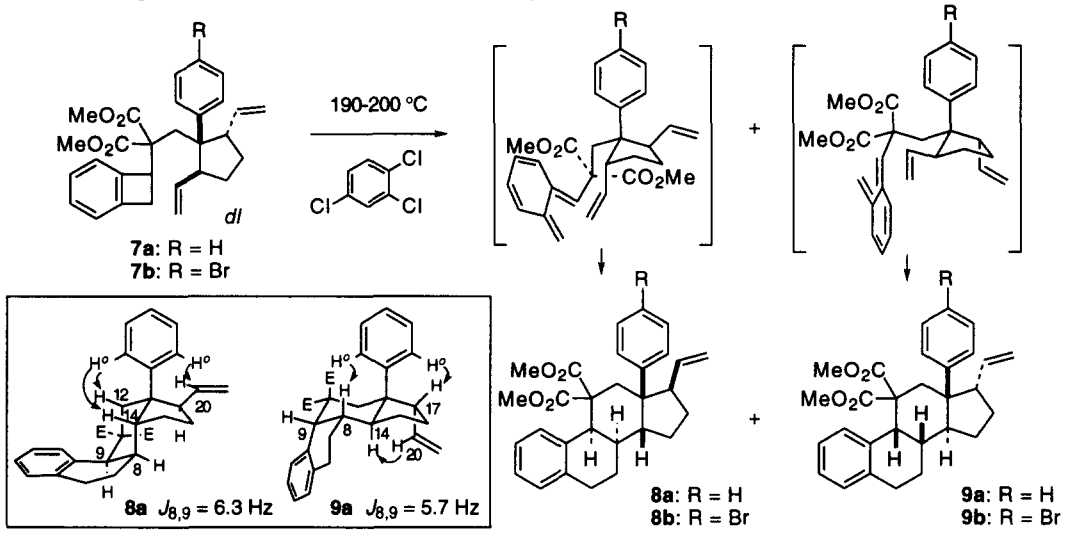


Table 1. Reaction of BISTRO (1) with Acetophenone Derivatives 2.

Entry	Reag.	Reaction conditions	Yield 3 + 4 (%)	*dl* : *meso* 3 : 4
1	**2a**	**1**, 1.2 eq.; $TiCl_4$, 1.2 eq.; CH_3NO_2, 4 eq.; 20 °C, 24 h	30	2.03 : 1
2	**2b**[8]	**1**, 5 eq.; $TiCl_4$, 3 eq.; CH_3NO_2, 4 eq.; 20 °C, 19 h	18	2.33 : 1
3	**2c**[9]	**1**, 2.5 eq.; $TiCl_4$, 2.2 eq.; CH_3NO_2, 4 eq.; –90 °C, 1h; –55 °C, 1 h	46	2.33 : 1
4	**2d**[10]	**1**, 2.5 eq.; $TiCl_4$, 2.2 eq.; CH_3NO_2, 4 eq.; –90 °C, 1h; –55 °C, 2 h	44	2.33 : 1
5	**2e**	**1**, 2.5 eq.; $TiCl_4$, 3 eq.; CH_3NO_2, 4 eq.; –55 °C, 14 h	49	2.33 : 1
6	**2e**	**1**, 2.5 eq.; $TiCl_4$, 3 eq.; –90 °C, 1 h; –55 °C, 10 h	85	2.33 : 1

The following step of our strategy is the alkylation of the enolate of **3** by iodobenzocyclobutene.[11] The first attempts required the use of 10 mol equivalents of benzocyclobutenyl iodide for an effective alkylation of **3** which made the preparation of the steroid precursor extremely inefficient. With the aim of enhancing the nucleophilic character of the enolate, the ester **3** was previously acylated with dimethyl carbonate to provide the inseparable *dl-meso* mixture of dimethyl malonates **5** and **6** (72% yield).[12] Thus the alkylation of the diesters **5**, **6** was carried out at reflux in acetone in the presence of anhydrous cesium carbonate and only 1.5 mol equivalent of iodobenzocyclobutene using the very simple Claisen's procedure.[13] Interestingly, the alkylation of the *dl*-isomer **5** occurs with a higher rate than that of the *meso*-isomer **6** which allowed a kinetic separation. Consequently, the alkylation of the diesters **5**, **6** afforded exclusively the *dl*-isomer **7**, the *meso*-isomer **6** was

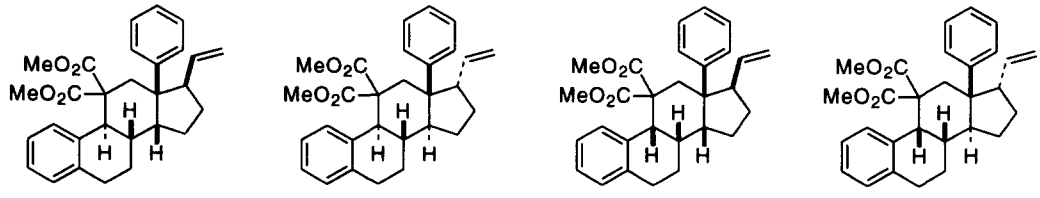
mainly recovered (67% yield in **7**, 96% yield from **5** and 28 % yield in pure **6**). This result confirms our recent work concerning the diastereofacial selectivity of the alkylation of ester enolates.[14]



Thermolysis of the benzocyclobutenic intermediate **7a** (or **7b**) affords the steroids **8a** (or **8b**) and **9a** (or **9b**) in 40 % and 42% yield respectively.

The relative stereochemistry of the steroids **8** and **9** has been determined by a series of 1D, COSY and NOESY experiments (400 MHz). A phase mode NOESY experiment showed the vicinal relationship between the *ortho* protons of the phenyl group and the vinylic proton $H^{(20)}$, the axial protons $H^{(14)}$ and $H^{(12)}$ of the tetracycle **8**. In contrast, no cross peak has been observed between $H^{(8)}$ and $H^{(14)}$. On the other hand, the *cis* relationship between $H^{(9)}$ and $H^{(8)}$ was confirmed by the vicinal coupling constant (J = 6.3 Hz). In the case of **9**, the proximal position of the *ortho* protons of the phenyl group and the protons $H^{(17)}$ and $H^{(8)}$ was indicated by the existence of cross peaks. A similar interaction proved the syn relationship $H^{(14)}$ and $H^{(20)}$. In contrast, no cross peaks have been observed between the *ortho* protons of the phenyl group and the protons $H^{(14)}$, $H^{(20)}$. Finally, the doublet signal of $H^{(9)}$ corresponds to a *cis* relationship with $H^{(8)}$ (J = 5.7 Hz).

The steroid **8** which exhibits *cis-anti-cis* ring fusion stereochemistry comes from a cycloaddition process involving the vinyl group *syn* to the benzocyclobutene moiety. According to molecular model studies, **8** could result from an *endo* approach of the *E o*-xylylene intermediate.[15] In contrast, the formation of the *cis-anti-trans* tetracycle **9** which results also from an *endo* approach of the *E o*-xylylene involves the vinyl group *anti* to the chain bearing the benzocyclobutene. The cycloadducts **8** and **9** are kinetic products since molecular mechanic calculations order the stability of the eight theorically possible isomers resulting from the cyclization of *dl*-isomer **7a** as follows:

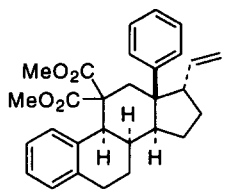


trans-syn-cis
E = 39.38 kcal/mol

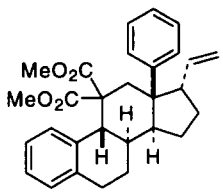
trans-anti-trans
E = 41.12 kcal/mol

cis-syn-cis
E = 44.10 kcal/mol

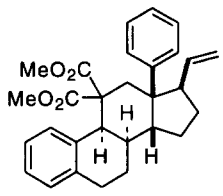
9a, *cis-anti-trans*
E = 44.80 kcal/mol



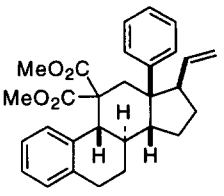
cis-syn-trans
E = 47.46 kcal/mol



trans-syn-trans
E = 47.65 kcal/mol

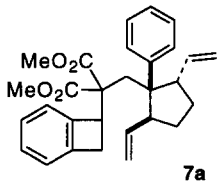


8a, *cis-anti-cis*
E = 51.00 kcal/mol



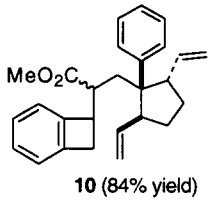
trans-anti-cis
E = 52.58 kcal/mol

The major strain dictated the transition state results from the 1,3-diaxial interaction between the methoxycarbonyl groups and the phenyl group. With the aim to reduce this interaction, we first performed a decarbomethoxylation according to the Krapcho procedure.[16] Heating the new benzocyclobutene intermediate **10** led to a mixture of three inseparable cycloadducts **11** in 85% yield. Reduction of the methoxycarbonyl group to a hydroxymethyl afforded the three isomers **12**, **13** and **14** which were relatively difficult to isolate by flash chromatography. Interestingly, the main product **12** matches the *trans-anti-trans* ring fusion stereochemistry of the natural products.



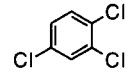
7a

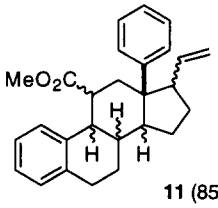
NaCN
DMSO



10 (84% yield)

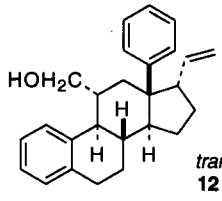
190-200 °C





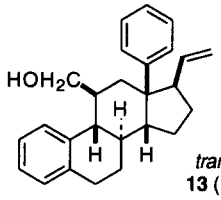
11 (85% yield)

$LiAlH_4$
THF



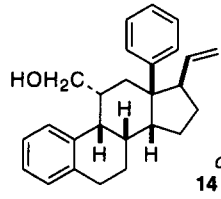
trans-anti-trans
12 (34% yield)

+



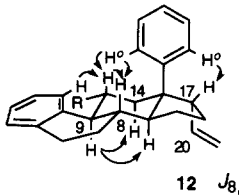
trans-anti-cis
13 (18% yield)

+

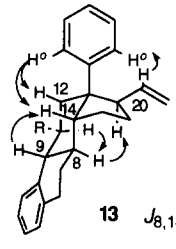


cis-syn-cis
14 (28% yield)

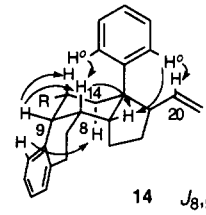
As for the steroids **8** and **9**, the relative stereochemistry of alcohols **12-14** was determined by a series of 1D, COSY and NOESY experiments.



12 $J_{8,9}$ = 9.1 Hz



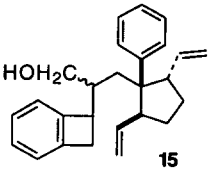
13 $J_{8,14}$ = 10.0 Hz



14 $J_{8,9}$ = 5.0 Hz

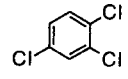
Thermolysis of the reduced benzocyclobutene intermediate **15** gave similar results.

10 $\xrightarrow[THF]{LiAlH_4}$



15

190-200 °C



12 (32% yield) + **13** (18% yield) + **14** (26% yield)

Conclusion: We have described a short and efficient synthesis of 13β-phenyl-17-vinylgonatrienes from 1,3-butadiene and benzocyclobutenol. The possibility to change the nature of the substituent of the phenyl group as well as the opportunity to transfom the vinyl group by a Wacker-type oxidation enhances the synthetic versatility of our methodology.

Experimental section

General. All reactions were run under argon in oven-dried glassware. ^{1}H (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Bruker AC 200 spectrometer in $CDCl_3$ solutions. Chemical shift (δ) are reported in ppm with tetramethylsilane as internal standard. IR spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. Flash chromatography was performed on silica gel (Merk 60 GF_{254} 230-400 mesh) and TLC on silica gel (Merck 60 F_{254}). The *dl-meso* ratio was determined by ^{1}H NMR for compounds **3** and **4**. The structures of the steroids were more precisely established by a series of 1D, NOESY, NOE and decoupling experiments. The ^{1}H NMR coupling constants were determined on 1D-COSY spectra with semiselective excitation unit on a 400 MHz spectrometer.

Material. All solvents were distilled before used, CH_2Cl_2 and $CHCl_3$ from P_2O_5, MeOH under $Mg(OMe)_2$, THF over sodium/benzophenone. **1,8-bis(trimethylsilyl)-2,6-octadiene (BISTRO) 1** was prepared according to the previously described procedure.[17] **Ethylene Ketal 2d** was prepared in 75 % overall yield from the commercially available 3-benzoylpropionic acid by esterification and acetalization. **Ethylene Ketal 2e** was obtained in 60% overall yield from bromobenzene and succinic anhydride by acylation followed by esterification, then ketalization. **Iodobenzocyclobutene** is generated through a six-step sequence. According to literature procedure,[11] anthranilic acid is easily converted into benzocyclobutenone which was quantitatively reduced by $LiAlH_4$ in THF. The alcohol is then transformed into the corresponding mesylate ($ClSO_2Me$, NEt_3, CH_2Cl_2). The crude mixture is directly treated by NaI (in refluxed acetone) to give expected iodobenzocyclobutene.[18] The overall yield of the sequence is 29% from anthranilic acid.

Methyl (*dl, meso*)-3-(1-phenyl-2,5-divinylcyclopentan-1-yl)-propanoates (3a, 4a). To a stirred solution of 3.5 ml of $TiCl_4$ (2.2 eq., 31.6 mmol) and 3.1 ml of CH_3NO_2 (4 eq., 57.4 mmol) in 45 ml of anhydrous CH_2Cl_2 under argon was added slowly, at -60 °C, 3.4 g of ethylene ketal **2d** (14.4 mmol) in 14 ml of anhydrous CH_2Cl_2. The resulting solution was cooled at - 90 °C and 9.2 g of BISTRO **1** (2.5 eq., 36 mmol) in 36 ml of anhydrous CH_2Cl_2 were added. After stirring 1 hour at -90 °C, the resulting solution was allowed to warm to -50 °C. After stirring 2 hours at -50 °C, the reaction was quenched by adding an excess of a saturated NH_4Cl aqueous solution. The mixture was decanted and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with a saturated $NaHCO_3$ aqueous solution and water, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient of petroleum ether/ether) to give 1.80 g (44%) of an inseparable mixture of **3a** and **4a** in 2.33 : 1 ratio. IR (neat) 1738, 1634, 1171, 913, 703 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ **3a**: 7.38-7.12 (5H, m), 6.05-5.84 (1H, m), 5.32 (1H, ddd J = 18.0, 9.5, 8.1 Hz), 5.08-4.88 (4H, m), 3.56 (3H, s), 3.08 (1H, dt, J = 9.0, 4.7 Hz), 2.58 (1H, br q, J = 8.1 Hz), 2.36-1.56 (8H, m); **4a** (in part): 3.57 (3H, s), 2.98-2.79 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ **3a**: 174.4 (s), 142.2 (s), 140.9 (d), 139.7 (d), 128.2 (d), 127.8 (d), 127.5 (d), 115.4 (t), 114.5 (t), 54.8 (s), 54.6 (d), 51.4 (q), 49.9 (d), 30.7 (t), 29.6 (t), 27.4 (t), 24.8 (t); **4a** (in part): 174.6 (s), 144.5 (s), 138.9 (d), 126.9 (d), 126.0 (d), 115.8 (t), 53.6 (d), 30.1 (t), 28.9 (t).

Methyl (*dl, meso*)-3-(1-*p*-bromophenyl-2,5-divinylcyclopentan-1-yl)-propanoates (3b, 4b). Reaction of methyl 3-(2-*p*-bromophenyl-1.3-dioxolan-2-yl)-propanoate **2e** following the previous

procedure without nitromethane (12.5 ml of $TiCl_4$ (3 eq.; 113.5 mmol) in 113 ml of CH_2Cl_2, 12 g of ethylene ketal **2e** (37.8 mmol) in 38 ml of CH_2Cl_2, 24.1 g of BISTRO **1** (2.5 eq., 94.5 mmol) in 95 ml of CH_2Cl_2, 1 hour at -90 °C then -90 °C to -50 °C) gave 11.7 g (85%) of an inseparable mixture of **3b** and **4b** in 2.33 : 1 ratio. IR (neat) 1736, 1636, 1171, 1006, 915, 737 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ **3b**: 7.45-7.36 (2H, m), 7.22-7.08 (2H, m), 6.01-5.79 (1H, m), 5.29 (1H, ddd, J = 18.4, 9.9, 8.1 Hz), 5.08-4.90 (4H, m), 3.56 (3H, s), 2.99 (1H, dt, J = 9.0, 4.8 Hz), 2.56 (1H, br q, J = 7.8 Hz), 2.31-1.58 (8H, m); **4b** (in part): 3.57 (3H, s), 2.92-2.71 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ **3b**: 173.9 (s), 141.3 (s), 140.3 (d), 139.1 (d), 130.7 (d), 129.9 (d), 119.9 (s), 115.7 (t), 114.7 (t), 54.5 (s), 54.1 (d), 51.3 (q), 49.8 (d), 30.4 (t), 29.9 (t), 29.3 (t) 28.7 (t); **4b** (in part): 174.1 (s), 143.3 (s), 138.2 (d), 131.1 (d), 128.5 (d), 116.2 (t), 53.6 (d), 30.4 (t), 27.1 (t), 24.2.

Methyl (*dl*, *meso*)-2-methoxycarbonyl-3-(1-phenyl-2,5-divinylcyclopentan-1-yl)-propanoates (5a, 6a). To a stirred solution of 28 ml (2.2 eq., 27.9 mmol) of a 1M solution of LiHMDS in THF under argon was added slowly at -65 °C, 3.6 g (12.7 mmol) of the mixture **3a**, **4a** in 14 ml of anhydrous THF. After stirring at -65 °C for 30 minutes, 16 ml (15 eq., 190.0 mmol) of dimethylcarbonate in 20 ml of anhydrous THF were added. After stirring 1 hour at -65 °C, the resulting solution was allowed to warm to 20 °C. After stirring 1 hour at room temperature, the reaction was quenched by adding an excess of a saturated NH_4Cl aqueous solution. The mixture was decanted and the aqueous layer was extracted twice with ether. The combined organic layers were washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. The yellow residue was purified by flash chromatography on silica gel (gradient of petroleum ether/ether) to give 2.85 g (66%) of an inseparable mixture of **5a** and **6a**. IR (neat) 1755, 1738, 1253, 1200, 1151, 914, 704 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ **5a**: 7.38-7.12 (5H, m), 6.09-5.94 (1H, m), 5.41 (1H, ddd, J = 17.2, 10.0, 8.2 Hz), 5.21-4.88 (4H, m), 3.59 (3H, s), 3.24 (3H, s), 3.25-3.07 (1H, m), 2.72-2.30 (4H, m), 2.24-1.49 (4H, m); **6a** *vide infra*; ^{13}C NMR (50 MHz, $CDCl_3$) δ **5a**: 170.3 (s), 170.2 (s), 141.3 (s), 140.6 (d), 139.7 (d), 128.7 (d), 127.4 (d), 126.0 (d), 115.2 (t), 115.1 (t), 54.9 (s), 53.7 (d), 52.4 (q), 52.3 (q), 49.3 (d), 48.9 (d), 34.9 (t), 29.6 (t), 27.7 (t); **6a** *vide infra*.

Methyl (*dl*, *meso*)-2-methoxycarbonyl-3-(1-*p*-bromophenyl-2,5-divinylcyclopentan-1-yl)-propanoates (5b, 6b). Reaction of methyl (*dl*, *meso*)-3-(1-*p*-bromophenyl-2,5-divinylcyclopentan-1-yl)-propanoates **3b**, **4b** following the previous procedure (0.52 g (2.2 eq., 3.1 mmol) of LiHMDS salt in 5 ml of THF, 0.50 g (1.4 mmol) of the mixture **3b**, **4b** in 3 ml of THF, 3.9 ml (15 eq., 45.8 mmol) of dimethylcarbonate in 8 ml of THF, 1 hour at -65 °C, 2.5 hours at room temperature) gave 0.30 g (72%) of an inseparable mixture of **5b** and **6b**. 0.11 g (21%) of starting material was recovered. IR (neat) 1752, 1736, 1637, 1210, 1151, 704 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ **5b**: 7.41-7.12 (4H, m), 6.05-5.86 (1H, m), 5.38 (1H, ddd, J = 17.3, 10.0, 8.2 Hz), 5.16-4.89 (4H, m), 3.59 (3H, s), 3.28 (3H, s), 3.25-3.05 (1H, m), 2.85-2.29 (4H, m), 2.17-1.43 (4H, m); **6b** *vide infra*; ^{13}C NMR (50 MHz, $CDCl_3$) δ **5b**: 170.1 (s), 169.6 (s), 140.6 (s), 140.1 (d), 139.3 (d), 130.7 (d), 130.6 (d), 130.4 (d), 130.3 (d), 120.1 (s), 115.7 (t), 115.5 (t), 54.6 (s), 54.2 (q), 53.8 (q), 52.2 (d), 52.1 (d), 48.7 (d), 34.9 (t), 29.5 (t), 28.2 (t); **6b** *vide infra*.

Methyl (*dl*)-2-benzocyclobutenyl-2-methoxycarbonyl-3-(1-phenyl-2,5-divinyl-cyclopentan-1-yl)-propanoates (7a). To a stirred solution of 1.06 g (3.1 mmol) of the mixture **5a**, **6a** in 25 ml of analytical acetone under argon was added successively 1.31 g (1.3 eq., 4.0 mmol) of Cs_2CO_3 and 1.07 g (1.5 eq., 4.6 mmol) of iodobenzocyclobutene. The mixture was stirred 39 hours at reflux then cooled to room temperature, filtered under celite and concentrated under *vacuo*. The residue was purified by flash chromatography on silica gel (gradient of petroleum ether/ether) to give 0.85 g (62%, 88% from **5a**) of diester

7a as a mixture of two diastereoisomers. 0.29 g (27%) of pure *meso* diastereoisomer **6a** was recovered. **7a**: IR (neat) 1729, 1635, 1246, 1200, 913, 762, 706 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.44-6.87 (9H, m), 6.30-6.06 (1H, m), 5.68-5.44 (1H, m), 5.14-4.94 (4H, m), 4.18-4.14 and 3.89-3.85 (Σ1H, m), 3.56, 3.14, 3.13, 3.09 (Σ6H, s), 3.21-2.42 (4H, m), 2.22-1.15 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.7, 170.8, 170.7, 145.9, 145.7, 143.3, 143.1, 142.8, 142.2, 141.4, 141.2, 141.1, 140.8, 129.3, 129.1, 127.5, 127.4, 127.1, 126.4, 126.3, 125.9, 123.8, 123.7, 122.2, 122.1, 115.6, 115.4, 115.3, 115.1, 58.5, 58.4, 55.2, 54.9, 53.3, 52.2, 51.8, 51.7, 51.5, 51.4, 51.3, 50.9, 48.2, 47.8, 38.6, 38.4, 32.8, 32.7, 30.0, 29.8, 29.2, 28.9.

Methyl (*meso*)-2-methoxycarbonyl-3-(1-phenyl-2,5-divinylcyclopentan-1-yl)-propanoate (6a). IR (neat) 1755, 1738, 1253, 1200, 1151, 914, 704 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.37-7.16 (5H, m), 5.98 (2H, ddd, J = 16.8, 10.5, 7.9 Hz), 5.08-4.95 (4H, m), 3.45 (6H, s), 3.25-3.15 (1H, m), 3.02-2.81 (2H, m), 2.45 (2H, d, J = 5.2 Hz), 1.98-1.70 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.0 (s), 144.0 (s), 138.4 (d), 127.6 (d), 127.1 (d), 125.8 (d), 116.1 (t), 54.5 (s), 53.5 (d), 52.1 (q), 49.1 (d), 29.1 (t), 27.5 (t). Anal. calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.57; H, 7.71.

Methyl (*dl*)-2-benzocyclobutenyl-2-methoxycarbonyl-3-(1-*p*-bromophenyl-2,5-divinyl-cyclopentan-1-yl)-propanoate (7b). Reaction of methyl (*dl*, *meso*)-2-methoxycarbonyl-3-(1-*p*-bromophenyl-2,5-divinylcyclopentan-1-yl)-propanoates **5b, 6b** following the previous procedure (0.55 g of the mixture **5b, 6b**, 0.6 g (1.3 eq., 1.7 mmol) of Cs_2CO_3, 0.46 g (1.5 eq, 2.0 mmol) of iodobenzocyclobutene, 15 ml of analytical acetone, 27 hours at reflux) gave 0.46 g (67%, 96% from **5b**) of diester **7b** as a mixture of two diastereoisomers. 0.14 g (26%) of pure *meso* diastereoisomer **6b** was recovered. **7b**: IR (neat) 1731, 1630, 1246, 1195 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40-6.91 (8H, m), 6.25-6.02 (1H, m), 5.62-5.41 (1H, m), 5.12-4.94 (4H, m), 4.20-4.12 and 3.90-3.87 (Σ1H, m), 3.54, 3.18, 3.14, 3.11 (Σ6H, s), 3.15-2.43 (4H, m), 2.23-1.41 (6H, m).

Methyl (*meso*)-2-methoxycarbonyl-3-(1-*p*-bromophenyl-2,5-divinylcyclopentan-1-yl)-propanoate (6b). IR (neat) 1752, 1736, 1637, 1210, 1151, 704 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.37 (2H, d, J = 8.8 Hz), 7.23 (2H, d, J = 8.8 Hz), 5.98 (2H, ddd, J = 10.4, 8.0, 7.0 Hz), 5.09-4.95 (4H, m), 3.48 (6H, s), 3.15 (1H, dd, J = 10.3, 5.2 Hz), 2.98-2.79 (2H, m), 2.42 (2H, d, J = 5.2 Hz), 1.98-1.76 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.3 (s), 143.5 (s), 138.3 (d), 130.8 (d), 129.3 (d), 120.1 (s), 116.8 (t), 54.4 (s), 53.9 (q), 52.5 (d), 49.2 (d), 29.2 (t), 27.8 (t).

General procedure for the thermolysis of steroid precursors. The benzocyclobutenic intermediate was dissolved in 1,2,4-trichlorobenzene (1 ml/0.1 mmol). The resulting solution was stirred at 180-190 °C under argon for an indicated time, then concentrated under *vacuo*. The residue was purified by flash chromatography on silica gel (gradient of petroleum ether/ether).

(8α, 9α, 14β)-11,11-dimethoxycarbonyl-13β-phenyl-17β-vinylgona-1,3,5(10)-triene (8a) and (8β, 9β, 14α)-11,11-dimethoxycarbonyl-13β-phenyl-17α-vinylgona-1,3,5(10)-triene (9a). Reaction of 334 mg of methyl (*dl*,)-2-benzocyclobutenyl-2-methoxycarbonyl-3-(1-phenyl-2,5-divinyl-cyclopentan-1-yl)-propanoate **7a** following the general procedure gave, after 17 hours at 180-190 °C, 132 mg (40%) of steroid **8a** (mp : 175-176 °C) and 142 mg (42%) of steroid **9a** (mp : 178-179 °C). **8a**: IR (CCl_4) 1733, 1637, 1246, 1074, 911 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (2H, d, J = 8.6 Hz, Ph), 7.15-7.05 (7H, m, H1-H4, Ph), 5.02 (1H, ddd, J = 17.1, 10.2, 8.7 Hz, H20), 4.65 (1H, d, J = 16.9 Hz, H21), 4.55 (1H, d, J = 11.0 Hz, H21), 3.69 (1H, d, J = 6.3 Hz, H9), 3.40 (3H, s), 3.16-3.03 (1H, m, H8), 2.99 (1H, d, J = 14.7 Hz, H12), 2.88 (3H, s), 2.66 (1H, d, J = 14.7 Hz, H12), 2.74-2.60 (3H, m, 2H6, H17), 2.38-2.28 (1H, m, H7), 1.83-1.73 (1H, m, H16), 1.60-1.39 (3H, m, H7, H14, H15), 1.30-1.23 (1H, m, H16), 0.99-

0.85 (1H, m, H15); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.9, 171.1, 142.6, 140.7 (Ar), 140.4 (C20), 139.3, 127.6 (Ar), 127.5 (4C, Ar), 126.0, 125.8, 125.7, 113.6 (C21), 57.9 (C17), 56.1 (C11), 52.7, 52.1, 51.7 (C13), 42.3 (C14), 39.1 (C8, C9), 35.4 (C12), 29.8 (C6), 29.2, 27.7, 24.8 (C15). Anal. calcd. for $C_{29}H_{32}O_4$: C, 78.34; H, 7.23. Found: C, 78.26; H, 7.33. **9a**: IR (CCl_4) 1733, 1637, 1246, 1074, 911 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (2H, dd, *J* = 8.6, 1.2 Hz, Ph), 7.23 (1H, t, *J* = 7.8 Hz, Ph), 7.14-7.08 (6H, m, H1-H4, Ph), 5.64-5.55 (1H, m, H20), 5.01-4.97 (2H, m, H21), 3.68 (1H, d, *J* = 5.7 Hz, H9), 3.57 (1H, ddt, *J* = 13.0, 9.7, 5.8 Hz, H8), 3.49 (3H, s), 3.07 (1H, dd, *J* = 14.4, 1.0 Hz, H12), 2.82 (3H, s), 2.74-2.60 (3H, m, 2H6, H17), 2.54 (1H, d, *J* = 14.4 Hz, H12), 2.38 (1H, dddd, *J* = 13.1, 9.8, 5.2, 3.0 Hz, H7), 1.81 (1H, dq, *J* = 12.3, 4.5 Hz, H15), 1.70-1.61 (1H, m, H15), 1.51-1.37 (2H, m, H14, H16), 1.24 (1H, tt, *J* = 9.4, 4.8 Hz, H16), 1.12 (1H, tt, *J* = 12.9, 5.7 Hz, H7); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.0, 171.0, 145.3, 141.9 (Ar), 139.7 (C20), 137.8, 129.5 (2C, Ar), 127.3 (2C, Ar), 127.0 (Ar), 126.0, 125.6, 125.5, 124.6, 115.8 (C21), 59.1 (C17), 56.5 (C11), 52.9, 52.4, 52.0 (C13), 46.9 (C14), 41.9 (C9), 37.2 (C12), 31.0 (C8), 28.6 (C6), 27.0, 26.9, 24.2 (C15). Anal. calcd. for $C_{29}H_{32}O_4$: C, 78.34; H, 7.23. Found: C, 78.42; H, 7.25.

(8α, 9α, 14β)-11,11-dimethoxycarbonyl-13β-*p*-bromophenyl-17β-vinylgona-1,3,5(10)-triene (8b) and (8β, 9β, 14α)-11,11-dimethoxycarbonyl-13β-*p*-bromophenyl-17α-vinylgona-1,3,5(10)-triene (9b). Reaction of 533 mg of methyl (*dl*)-2-benzocyclobutenyl-2-methoxycarbonyl-3-(1-*p*-bromophenyl-2,5-divinyl-cyclopentan-1-yl)-propanoate **7b** following the general procedure gave, after 15 hours at 180-190 °C, 213 mg (40%) of steroid **8b** and 192 mg (36%) of steroid **9b**. **8b**: IR (CCl_4) 1736, 1635, 1246, 789 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (2H, d, *J* = 8.6 Hz, Ph), 7.21-7.02 (6H, m, H1-H4, Ph), 5.04-4.92 (1H, m, H20), 4.64 (1H, d, *J* = 17.8 Hz, H21), 4.56 (1H, d, *J* = 11.2 Hz, H21), 3.66 (1H, d, *J* = 5.4 Hz, H9), 3.40 (3H, s), 3.15-2.87 (2H, m, H8, H12), 2.93 (3H, s), 2.73-2.50 (4H, m, 2H6, H12, H17), 2.41-2.19 (1H, m, H7), 1.81-1.63 (1H, m, H16), 1.50-1.34 (3H, m, H7, H14, H15), 1.30-1.17 (1H, m, H16), 1.17-0.95 (1H, m, H15); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 170.8, 144.3, 141.7 (Ar), 139.2 (C20), 137.4, 130.6 (2C, Ar), 130.2 (2C, Ar), 127.5, 125.9, 125.6, 119.4 (Ar), 114.0 (C21), 57.8 (C17), 56.4 (C11), 52.8, 52.0, 51.4 (C13), 42.3 (C14), 38.9 (C8, C9), 36.8 (C12), 27.6 (C6), 26.9, 26.7, 24.0 (C15). Anal. calcd. for $C_{29}H_{31}O_4Br$: C, 66.53; H, 5.98. Found: C, 66.54; H, 6.01. **9b**: IR (CCl_4) 1736, 1635, 1246, 789 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.32 (2H, m, Ph), 7.37 (1H, d, *J* = 7.7 Hz, H1), 7.16-7.03 (5H, m, H2-H4, Ph), 5.61-5.49 (1H, m, H20), 5.04-4.90 (2H, m, H21), 3.66 (1H, d, *J* = 5.5 Hz, H9), 3.48 (3H, s), 3.46-3.41 (1H, m, H8), 2.99 (1H, d, *J* = 14.4 Hz, H12), 2.90 (3H, s), 2.73-2.58 (3H, m, 2H6, H17), 2.52 (1H, d, *J* = 14.4 Hz, H12), 2.43-2.25 (1H, m, H7), 1.78-1.58 (2H, m, 2H15), 1.48-1.33 (2H, m, H14, H16), 1.30-1.18 (1H, m, H16), 1.08 (1H, tt, *J* = 12.9, 5.7 Hz, H7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 170.8, 144.3, 141.8 (Ar), 139.9 (C20), 137.4, 131.2 (2C, Ar), 130.4 (2C, Ar), 125.9, 125.7, 124.5, 119.6 (Ar), 116.0 (C21), 57.8 (C17), 56.4 (C11), 52.6, 52.2, 52.0 (C13), 46.6 (C14), 41.7 (C9), 37.0 (C12), 30.9 (C8), 28.5 (C6), 26.9, 26.7, 24.0 (C14). Anal. calcd. for $C_{29}H_{31}O_4Br$: C, 66.53; H, 5.98. Found: C, 66.63; H, 6.05.

Methyl (*dl*)-2-benzocyclobutenyl-3-(1-phenyl-2,5-divinylcyclopentan-1-yl)-propanoate (10). To a stirred solution of 480 mg (1.08 mmol) of diester **7a** in 4 ml of wet dimethylsulfoxide was added 158 mg (3 eq., 3.23 mmol) of sodium cyanide (NaCN). The resulting solution was stirred 22 hours at 90 °C then cooled to room temperature and poured in a large excess of water. The mixture was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient of petroleum ether/ether) to

give 350 mg (84%) of the monoester **10** as an inseparable mixture of four diastereoisomers. IR (neat) 1733, 1635, 1161, 913, 750, 706 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.48-6.78 (9H, m), 6.25-6.08, 6.12-5.80, 5.79-5.40 (2H, m), 5.22-4.78 (4H, m), 3.60-3.42 (2H, m), 3.40, 3.26, 3.13, 3.07 (3H, s), 3.30-1.60 (10H, m).

11-dimethoxycarbonyl-13β-phenyl-17-vinylgona-1,3,5(10)-trienes (11). Reaction of 380 mg of **10** following the general procedure gave, after 17 hours at 180-190 °C, 321 mg (85%) of **11** as an inseparable mixture of three steroids. ^1H NMR (200 MHz, $CDCl_3$) δ 7.43-6.73 (9H, m, H1-H4, Ph), 5.95 (1H, ddd, J = 16.3, 8.7, 10.9 Hz) and 5.32-5.15 (1H, m, H21), 5.11-4.93, 4.71-4.55 (2H, m, H22), 3.75, 3.69, 3.60 (3H, s), 3.37 (1H, dd, J = 10.7, 5.4 Hz, H11), 2.96-1.35 (14H, m, H6-H9, H12, H14-H17).

(8β, 9α, 14α)-11α-hydroxymethyl-13β-phenyl-17α-vinylgona-1,3,5(10)-trienes (12), (8α, 9β, 14β)-11β-hydroxymethyl-13β-phenyl-17β-vinylgona-1,3,5(10)-trienes (13) and (8β, 9β, 14β)-11α-hydroxymethyl-13β-phenyl-17β-vinylgona-1,3,5(10)-triene (14). To a stirred suspension of 61 mg of $LiAlH_4$ (1.16 mmol) in anhydrous THF (3 ml) under argon was added at 0 °C, 321 mg (0.83 mmol) of steroids **11** in 2 ml of anhydrous THF. After stirring 4 hours at 20 °C, 5 ml of wet ether and celite were added. Then, the mixture was stirred for 30 mn before filtration. After evaporation under reduced pressure, the residue was purified by flash chromatography on silica gel (gradient of petroleum ether/ether) to give 109 mg (34%) of **12**, 58 mg (18%) of **13** and 90 mg (28%) of **14**. **12**: IR (CCl_4) 3628, 3422, 1634,1262, 1035, 1008, 910 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.33 (2H, br dd, J = 8.6, 1.2 Hz, Ph), 7.07-6.89 (6H, m, H2-H4, Ph), 6.78 (1H, d, J = 7.7 Hz, H1), 5.93 (1H, ddd, J = 16.9, 10.3, 8.6 Hz, H20), 5.10 (1H, dd, J = 10.2, 2.3 Hz, H21), 5.07 (1H, dd, J = 16.9, 2.3 Hz, H21), 3.73 (1H, dd, J = 10.5, 2.2 Hz, CH_2OH), 3.27 (1H, dd, J = 10.5, 6.4 Hz, CH_2OH), 2.79 (1H, dd, J = 13.2, 3.1 Hz, H12), 2.68 (1H, t, J = 7.4 Hz, H17), 2.64-2.55 (2H, m, 2H6), 1.96 (1H, br q, J = 9.1 Hz, H8), 1.90-1.65 (7H, m, H9, H11, H14, H15, 2H16), 1.62-1.50 (2H, m, H12, H15), 1.42-1.34 (1H, m, H7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7 (Ar), 140.3 (C20), 147.3, 139.5, 128.1 (2C, Ar), 128.0 (2C, Ar), 127.5 (Ar), 125.6, 125.5, 125.2, 122.9, 114.8 (C21), 67.0, 56.2 (C17), 52.8 (C13), 52.3 (C11), 42.5 (C14), 40.4 (C12), 38.1, 36.6, 27.3, 27.1, 26.9, 26.0. Anal. calcd. for $C_{26}H_{30}O$: C, 87.09; H, 8.45. Found: C, 87.13; H, 8.50. **13**: IR (CCl_4) 3628, 3422, 1634,1262, 1035, 1008, 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.29 (4H, m, Ph), 7.33-7.07 (5H, m, H1-H4, Ph), 5.20 (1H, br ddd, J = 18.2, 8.7, 7.4 Hz, H20), 4.96 (1H, br dd, J = 17.2, 2.2 Hz, H21), 4.91 (1H, br dd, J = 10.0, 2.2 Hz, H21), 3.52 (1H, dd, J = 11.1, 5.0 Hz, CH_2OH), 3.03 (1H, br t, J = 10.2 Hz, CH_2OH), 2.88 (2H, dd, J = 7.9, 7.7 Hz, 2H6), 2.55 (1H, dd, J = 15.0, 4.2 Hz, H12), 2.45-2.38 (2H, m, H11, H17), 2.27 (1H, td, J = 10.0, 4.5 Hz, H14), 2.25-2.12 (2H, m, H7, H14, H15), 2.01-1.95 (1H, m, H9), 1.96 (1H, dd, J = 15.0, 5.3 Hz, H12), 1.68-1.51 (3H, m, H8, H15, H16), 1.44-1.23 (2H, m, H7, H16); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3 (Ar), 139.6 (C20), 145.6, 137.8, 128.7 (Ar), 127.8 (2C, Ar), 127.6 (2C, Ar), 126.1, 126.0, 125.9, 125.7, 115.0 (C21), 66.8, 51.6 (C13), 56.5, 49.4, 43.4 (C14), 41.6, 40.9, 34.0 (C12), 30.1, 29.6, 29.4, 28.3. Anal. calcd. for $C_{26}H_{30}O$: C, 87.09; H, 8.45. Found: C, 87.01; H, 8.54. **14**: IR (CCl_4) 3628, 3422, 1634,1262, 1035, 1008, 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16-6.99 (5H, m, H1-H4, Ph), 5.27 (1H, ddd, J = 17.1, 10.1, 8.5 Hz, H20), 4.67 (1H, dd, J = 17.1, 1.8 Hz, H21), 4.60 (1H, dd, J = 10.2, 1.8 Hz, H21), 3.74 (1H, dd, J = 10.6, 3.0 Hz, CH_2OH), 3.60 (1H, dd, J = 10.6, 5.0 Hz, CH_2OH), 2.43 (1H, dd, J = 5.0, 9.4 Hz, H9), 2.80-2.75 (1H, m, H15), 2.67-2.63 (2H, m, 2H6), 2.57 (1H, d, J = 11.7 Hz, H12), 2.43 (1H, q, J = 7.5 Hz, H17), 2.19-2.14 (1H, m, H8), 2.12-1.93 (2H, m, H15, H16), 1.81-1.75 (2H, m, H11, H12), 1.69-1.54 (3H, m, H7, H14, H16), 1.47-1.38 (1H, m, H7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6 (C20), 138.6 (Ar), 144.3, 137.4, 127.9 (2C, Ar), 127.5 (2C, Ar),

130.0, 129.0, 126.0, 125.5, 125.0, 112.7 (C21), 66.4 , 51.7 (C13), 58.5, 47.7, 39.4, 38.2, 37.8, 37.4 (C12), 30.2, 30.1, 29.4, 27.2. Anal. calcd. for $C_{26}H_{30}O$: C, 87.09; H, 8.45. Found: C, 87.04; H, 8.51.

(*dl*)-2-benzocyclobutenyl-3-(1-phenyl-2,5-divinylcyclopentan-1-yl)-propan-1-ol (15). To a stirred solution of 0.12 mg (3.26 mmol) of $AlLiH_4$ in 8 ml of anhydrous THF under argon was added slowly in an ice bath, 0.9 mg (2.33 mmol) of the esters **10** in 8 ml of anhydrous THF. After stirring at room temperature for 4.5 hours, the reaction was quenched by adding successively 3.9 g of celite, 3.9 g of $Na_2SO_4.10H_20$ and 0.8 ml of water. After stirring an additional 30 minutes, the mixture was filtered and concentrated under reduced pressure to give 0.79 g (95%) of the alcohols **15** as an inseparable mixture of four diastereoisomers. IR (neat) 3445, 1640, 1265, 896 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.58-7.02 (9H, m), 6.38-6.08, 6.02-5.82, 5.78-5.42 (2H, m), 5.28-4.95 (4H, m), 3.50-3.10 (3H, m), 2.90-2.60 (2H, m), 2.40-1.58 (8H, m).

Reaction of 123 mg of (*dl*)-2-benzocyclobutenyl-3-(1-phenyl-2,5-divinylcyclopentan-1-yl)-propan-1-ol **15** following the general procedure gave, after 8 hours at 180-190 °C, 40 mg (32%) of steroid **12**, 23 mg (18%) of steroid **13** and 33 mg (26%) of steroid **14**.

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