Lactone Kinetic Resolution by Acylation – Application to the Enantioselective Synthesis of Estrane Derivatives

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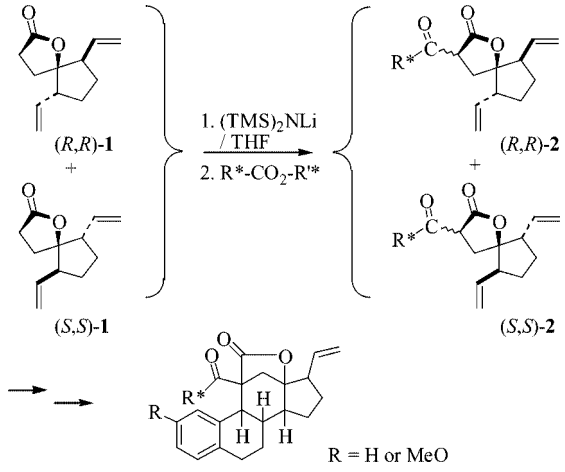
The acylation of an excess of racemic spirolactone **1** (6,9-divinyl-1-oxaspiro[4.4]nonan-2-one) enolate by protected methyl (*S*)-lactate or (–)-bornyl carbonate occurs with a kinetic resolution. The resulting lactones were alkylated with 1-iodobenzocyclobutenes to afford compounds that serve as precursors to nonracemic steroids such as 11α-alkyloxycarbonyl-11β,13β-(γ-carbolactone)-17β-vinylgonatri-1,3,5(10)-enes.

Introduction

In the course of a program directed towards the development of new steroids that might exhibit improved therapeutic action over existing drugs[1] we have reported a convergent steroid synthesis[2] based on the A+D→AD→ABCD approach, involving the use of intramolecular cycloaddition of *o*-xylylenes developed independently by Oppolzer[3] and by Kametani[4] for generation of the BC ring system.

Our strategy was based on the use of spirolactone **1**, arising in 78% yield from the addition of 1,8-bis(trimethylsilyl)-octa-2,6-diene (Bistro) to succinic anhydride. Indeed, compound **1** is an easily available and a very cheap reagent.[1i] With the aim of expanding the scope of this strategy[1i] to the synthesis of optically active steroids, we investigated the possibility of preparing enantiomerically enriched spirolactones by kinetic resolution. In recent years this methodology has proved to be one of the most efficient methods for asymmetric synthesis.[5] Kinetic resolution could indeed be observed in the course of acylation of racemic spirolactone **1** enolate, thus providing an efficient route to various optically active steroids (Scheme 1).



Scheme 1.

Results and Discussions

In a first investigation, the protected methyl (–)-(*S*)-lactate derivative **3** was chosen as acylating agent. The *tert*-butyldimethylsilyl (TBDMS) group was found to be the largest protecting group possible to introduce.[6] When one equivalent of protected methyl lactate **3** was added at –78 °C to a THF solution of three equivalents of racemic lactone **1** enolate, a 4:1 mixture of two products, (*R*,*R*)-**4** and (*S*,*S*)-**4**, was obtained in 73% yield, along with recovered spirolactone **1** in ca. 26% enantiomeric excess. Various conditions – such as the use of pentane as solvent, a lower reaction temperature (–100 °C), the addition of $MgBr_2$ and the use of HMPA or TMEDA as co-solvent – were tested in order to improve the reaction, but without success. Unfortunately, separation of the diastereomers (*R*,*R*)-**4** and (*S*,*S*)-**4** was impossible because of the existence of a tautomeric equilibrium in each case (Scheme 2).

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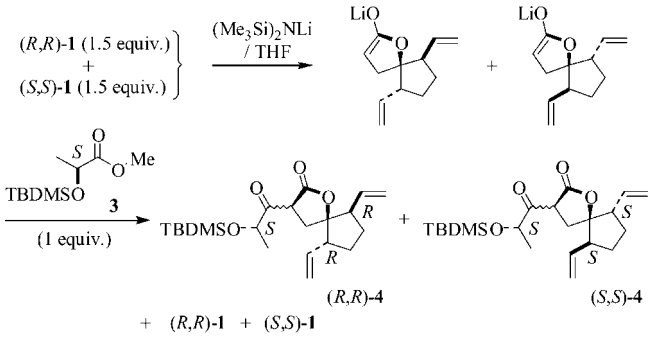
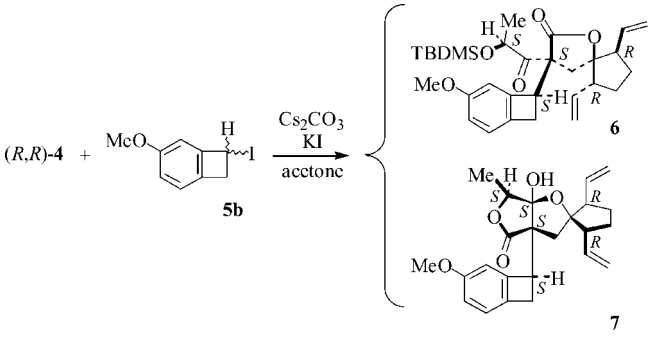


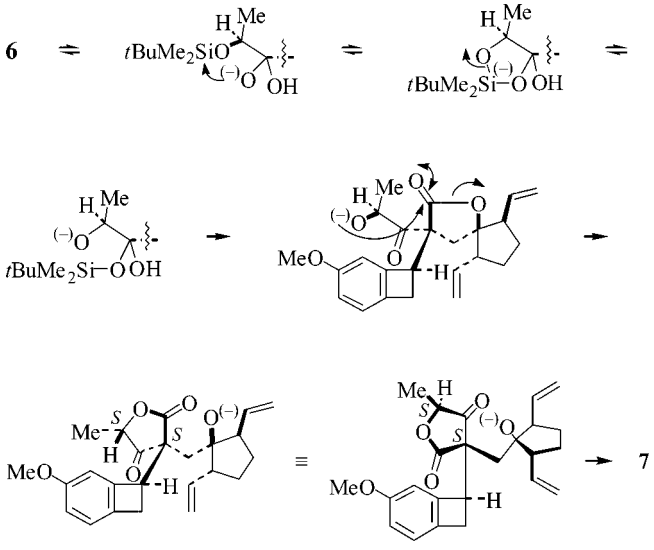
Scheme 2.

The next step of the strategy involved the alkylation of a stabilised enolate of **4** [in the form of a diastereomeric mixture of unseparated (*R*,*R*)-**4** and (*S*,*S*)-**4**] with racemic iodobenzocyclobutene **5b** in the presence of cesium carbonate and potassium iodide according to Claisen's procedure. After chromatography on silica gel, the major polar product **7** was isolated in 57% yield along with the expected steroid precursor **6** in 33% yield. Unfortunately, this latter compound was contaminated with other diastereomers and could not be purified. In contrast, product **7** was obtained in such high purity that it was possible to isolate crystals suitable for X-ray analysis (Scheme 3).



Scheme 3.

The assignment of the configuration of **7** was made in accordance with the ORTEP diagram (Figure 1). As demonstrated in previous works,[7] the stereoselectivity of the alkylation was such that the attack took place at the face of the enolate bearing the vinyl group *anti* to the lactone ring-oxygen linkage [*Si* face of the enolate of (*R*,*R*)-**4**].[8] The unexpected formation of **7** could be explained by the sequence summarised in Scheme 4. Addition of a hydroxide anion to the ketone function in compound **6** could give the corresponding hydrate anion, which could then add to the silicon atom of the protected group. Opening of the thus formed cyclic siliconate anion would result in the formation of both an alkoxide anion and a monoprotected ketone hydrate.[9] The latter hydrate could eliminate silanolate anion to regenerate the ketone function, whereas alkoxide anion could undergo acylation with the lactone, leaving a new alkoxide anion, which could finally add to the ketone to afford product **7**.[10]



Scheme 4.

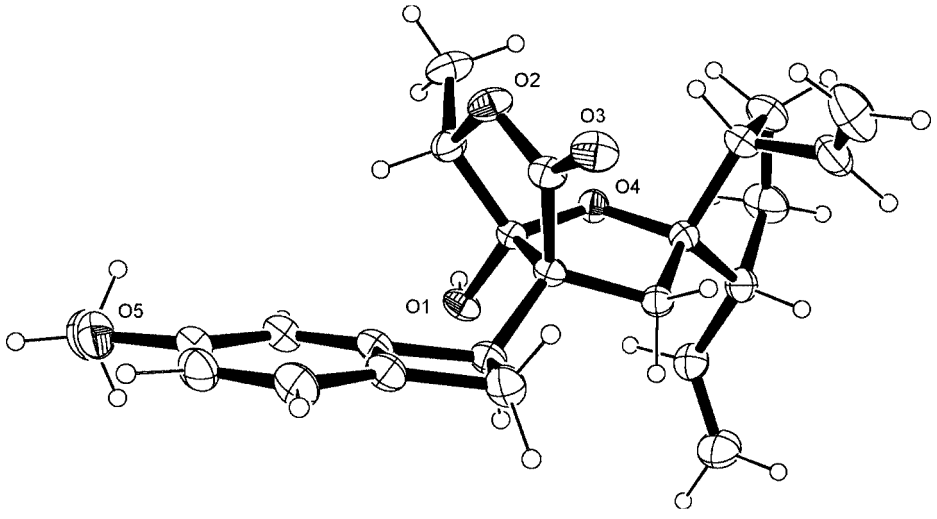
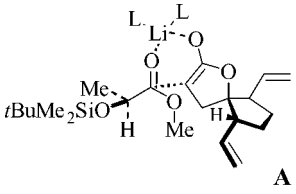


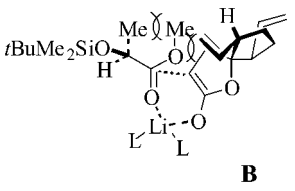
Figure 1. ORTEP diagram of compound **7**.[11]

The fact that one diastereomer was obtained in more than 50% yield was due to iodide-induced racemization of the more slowly reacting enantiomer (*S*)-**5b** to produce the more rapidly reacting enantiomer (*R*)-**5b** in a dynamic kinetic resolution [the racemization of the enantiomer (*S*)-**5b** could be rapid enough with respect to the alkylation reaction].[12] In recent years, dynamic kinetic resolution has been noted as one of the most efficient methods for asymmetric synthesis.[13]



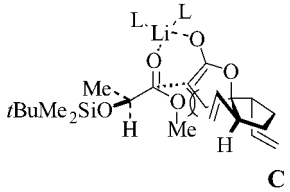
A

Si face of methyl (*S*)-lactate,
Re face of the (*R*,*R*)-enolate



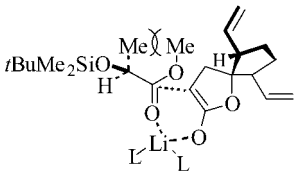
B

Re face of methyl (*S*)-lactate,
Si face of the (*R*,*R*)-enolate



C

Si face of methyl (*S*)-lactate,
Re face of the (*S*,*S*)-enolate



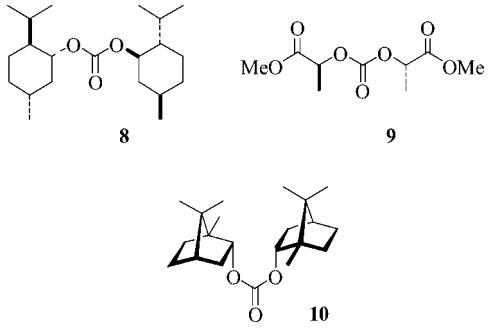
D

Re face of methyl (*S*)-lactate,
Si face of the (*S*,*S*)-enolate

Scheme 5.

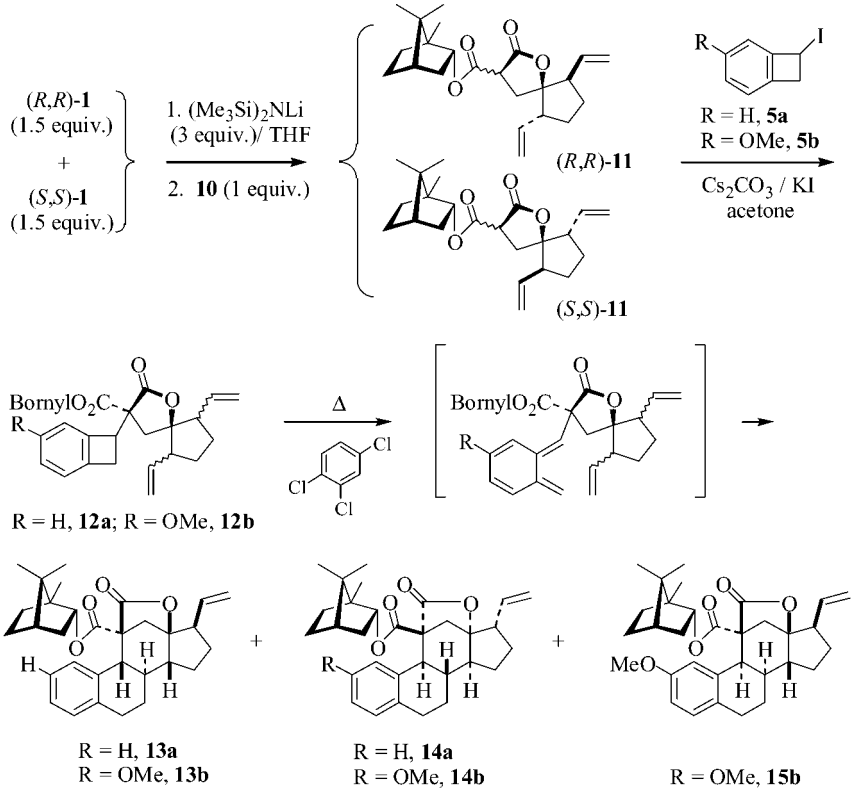
Claisen condensation of the protected methyl (*S*)-lactate with the racemic mixture of spirolactone **1** enolate could occur through eight transition states, as summarised below:
Si-face or *Re*-face of methyl (*S*)-lactate with the *Re*-face of the (*R*,*R*)-**1** enolate,
Si-face or *Re*-face of methyl (*S*)-lactate with the *Si*-face of the (*R*,*R*)-**1** enolate,
Si-face or *Re*-face of methyl (*S*)-lactate with the *Re*-face of the (*S*,*S*)-**1** enolate, or
Si-face or *Re*-face of methyl (*S*)-lactate with the *Si*-face of the (*S*,*S*)-**1** enolate.

The results clearly show that the reaction occurs mainly on the enolate of the enantiomer (*R*,*R*)-**1**. If we assume that the acylation is the result of an attack on the *Re* face of the enantiomer (*R*,*R*)-**1** enolate as the alkylation reaction,[7] we can conclude that the kinetic approach involves the *Si* face of the lactate according to a Felkin–Anh-type approach,[14]



8 **9** **10**

Scheme 6.



Scheme 7.

anti to the silyloxy group. Scheme 5 represents the structures of the four transition states **A**–**D** according to the Zimmerman–Traxler aldol reaction model.[15,16] In the process, the (*R*,*R*)-**1** enolate is relatively free to react through the *Re*-face as depicted in transition state **A**. In contrast, in the case of attack on the *Si*-face, a strong interaction between the vinyl group and the methyl group of the lactate moiety occurs (transition state **B**), whilst a similar interaction occurs in the transition state involving the (*S*,*S*)-**1** enolate (transition state **C**). Moreover, the transition states **B** and **D** also involve attack on the *Re*-face of the lactate, which provokes a strong interaction between the two methyl groups of the lactate moiety.

As the protection of methyl lactate was too labile under the reaction conditions allowing the preparation of steroid precursor **6**, it was decided, in a second investigation, to use optically active carbonates possessing a C_2-axis of symmetry – such as carbonates **8** [from (–)-menthol], **9** [from (–)-methyl lactate] and **10** [from (–)-borneol] (Scheme 6) – as acylating agents.

Interestingly, we found that diastereomeric mixtures of the two expected lactones **11** were obtained in up to 80%

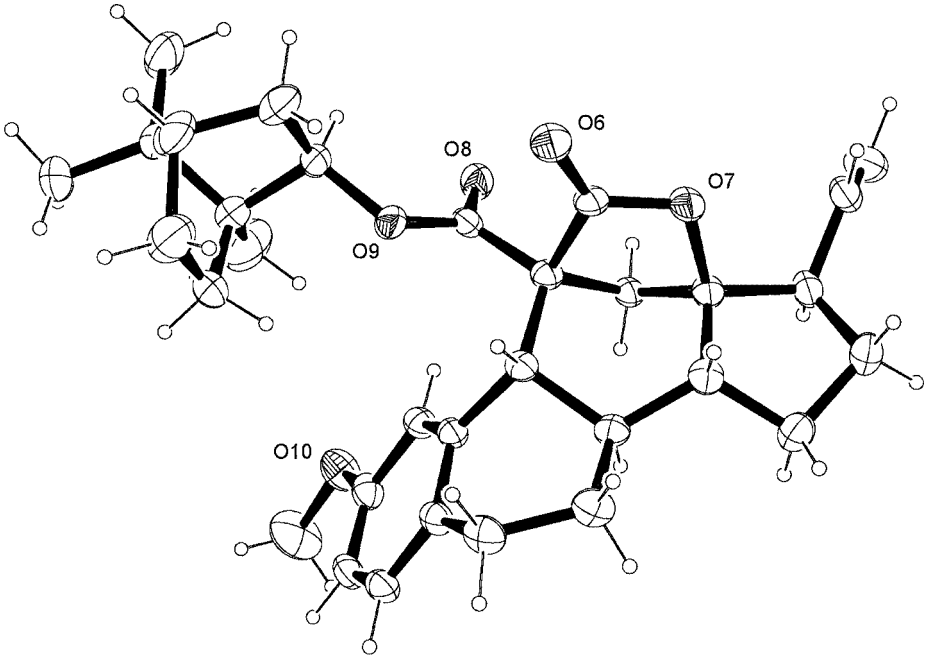


Figure 2. ORTEP diagram of steroid **13b**.[11,18]

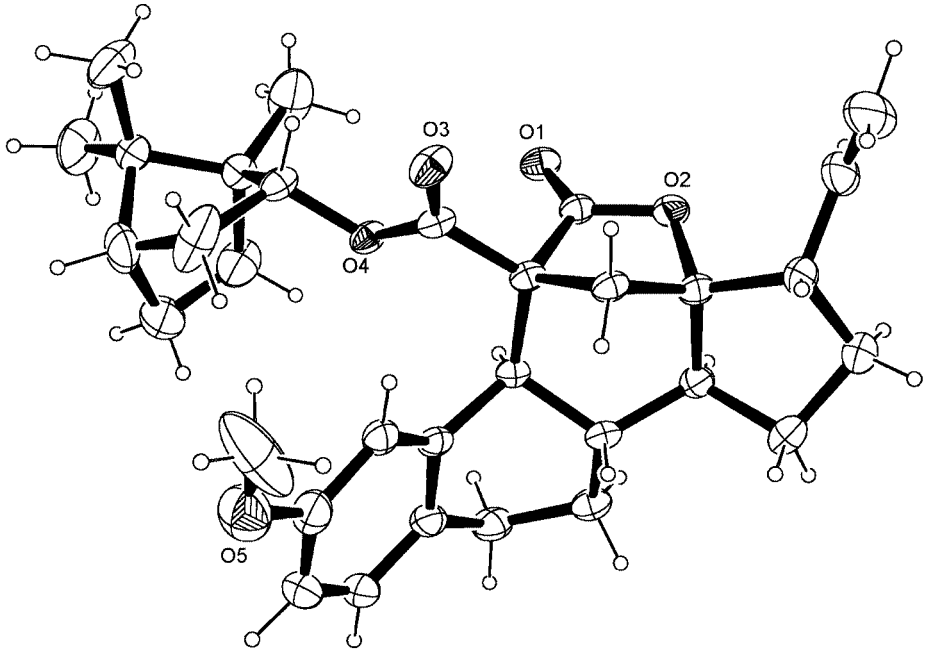


Figure 3. ORTEP diagram of steroid **14b**.[11,18]

yields and with diastereoselectivities ranging from 75:25 to 80:20 when an excess of racemic spirolactone **1** enolate (3 equiv.) was acylated with carbonic acid dibornyl ester **10**. Unfortunately, the use either of menthyl carbonate **8** or of methyl lactate carbonic ester **9** did not give better diastereoselectivities.

Since diastereomers (*R*,*R*)-**11** and (*S*,*S*)-**11** were inseparable due to the presence of an enolisable centre, we decided to alkylate **11** (as the crude mixture) with benzocyclobutene iodides **5a** and **5b**, which yielded **12a** and **12b**, respectively. These latter compounds were then thermolysed in trichlorobenzene at reflux, providing a mixture of steroids **13–15**. In particular, thermolysis of **12a** afforded a mixture of steroids **13a** and **14a** in 88% combined yield (**13a**:**14a** = 70:30). On the other hand, cyclisation of **12b** gave a mixture of **13b** and **14b** in 80% combined yield (**13b**:**14b** = 80:20), along with steroid **15b** isolated in 12% yield (Scheme 7). After extensive recrystallisation and chromatography, steroids **13b** and **14b** were separated. The structures of **13b–15b** were confirmed by X-ray crystallographic analysis (Figure 2, Figure 3 and Figure 4). Steroids **13b** and **15b** arose from (*R*,*R*)-**11**, whereas steroids **14b** arose from (*S*,*S*)-**11**. Consequently, the stereoselectivity of the acylation reaction providing **11** was 76:16 = 4.75, corresponding to a $\Delta G^{\ddagger}$ = 0.78 kcal mol^{-1} (at –20 °C).

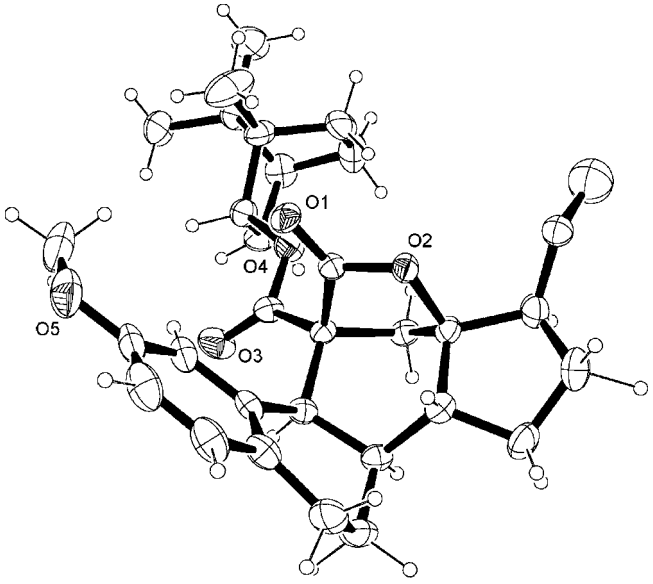
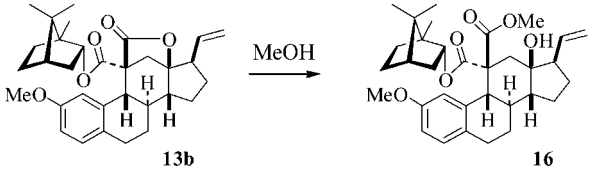


Figure 4. ORTEP diagram of steroid **15b**.[19]

Steroids **13** or **14**, each containing a *trans* B/C ring junction, are the results of a Diels–Alder reaction involving an *exo* transition state, whereas steroid **15b**, with a *cis* B/C ring junction, arises from an *endo* transition state.[17]

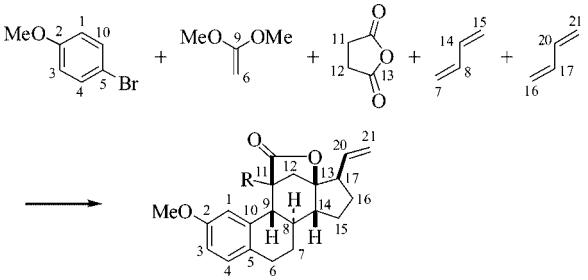


Scheme 8.

The lactone bridge of the main steroid **13b** could be opened cleanly by methanolysis in a neutral medium to give the corresponding compound **16** (Scheme 8).

Conclusions

We have described an expeditious synthesis of the tricyclic core of C-11 functionalised steroids in a few steps (four steps for the preparation of iodobenzocyclobutene **5b**, two steps for the synthesis of **1**, and three steps for the elaboration of steroids) from very cheap reagents (Scheme 9). Moreover, use of a chiral auxiliary such as (–)-borneol allowed nonracemic products to be obtained with fair selectivity by kinetic resolution during the Claisen condensation step.



Scheme 9.

Experimental Section

General: All reactions were run under argon in oven-dried glassware. TLC was performed on silica gel 60 F_{254}. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 400 and 300, and 100 and 75 MHz respectively. Chemical shifts are reported in ppm relative to $CDCl_3$ [signals for residual $CHCl_3$ in the $CDCl_3$: 7.24 for ^{1}H NMR and 77.16 (central) for ^{13}C NMR]. Carbon–proton couplings were determined by DEPT sequence experiments. THF was distilled before use from sodium-benzophenone. For the preparation of spirolactone **1** and iodobenzocyclobutenes **5**, see ref.[1i].

3-[2(*S*)-(*tert*-Butyldimethylsilyloxy)propanoyl]-6,9-divinyl-1-oxaspiro[4.4]nonan-2-one (4): Lactone **1** (25 g, 130 mmol) in THF (20 mL) was added slowly at –90 °C to a solution of lithium hexamethyldisilazide (21.75 g, 130 mmol) in anhydrous THF (200 mL). The solution was stirred for 1 hour, and a solution of protected methyl lactate **3** (9.47 g, 43 mmol) in THF (20 mL) was then slowly added. The solution was stirred for 6 h at –90 °C and the mixture was then allowed to stand at –60 °C for 15 h. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution and the mixture was then extracted with diethyl ether. The organic layer was dried ($MgSO_4$) and the solvents were evaporated. The oil was flash chromatographed on silica gel with elution with petroleum ether/diethyl ether (PE/DE) (97:3) to give **4** (12 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.81–5.53 (m, 2 H), 5.22–5.07 (m, 4 H), 4.54 (q, J = 10.0 Hz, 1 H), 4.34 (d, J = 7.6 Hz, 1 H), 2.42 (m, 2 H), 2.25–1.46 (m, 6 H), 1.31 (d, J = 10.0 Hz, 3 H), 0.89 (s, 9 H), 0.06 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.9 (s), 171.7 (s), 137.3 (d), 135.4 (d), 118.6 (t), 117.2 (t), 95.6 (s), 72.9 (d), 52.9 (t), 52.2 (t), 47.4 (t), 47.4 (d), 29.6 (d), 28.1 (d), 25.5 (q) (3C), 20.9 (q), 17.6 (s), –5.4 (q, 2C) ppm. $C_{21}H_{34}O_4Si$ (378.6): C 66.62, H 9.05; found C 66.69, H 9.09.

(3*S*,6*R*,9*R*)-3-[2(*S*)-(*tert*-Butyldimethylsilyloxy)propanoyl]-3-[(1*S*)-5-methoxybenzocyclobuten-1-yl]-6,9-divinyl-1-oxaspiro[4.4]nonan-2-one (6) and Compound 7: A mixture of spirolactone **4** (11.7 g, 31 mmol), 1-iodobenzocyclobutene **5b** (9.88 g, 38 mmol), cesium carbonate (dried by heating at 100 °C under vacuum; 15.35 g, 47 mmol) and potassium iodide (5 g, 30 mmol) in anhydrous acetone (250 mL) was heated at reflux for 120 h. The mixture was filtered through Celite®, the solid was washed with diethyl ether, and the organic phase was concentrated under reduced pressure. The crude product was flash chromatographed on silica gel with elution with PE/DE [elution order: **6** (mixture) with PE/DE = 97:3 (4.1 g, 33%); **7**, with PE/DE = 87:13; (6.7 g, 57%)].

Compound 6: Major isomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.2–6.88 (m, 2 H), 6.79 (d, J = 1.7 Hz, 1 H), 5.57–5.48 (m, 2 H), 5.36 (q, J = 6.5 Hz, 1 H), 5.18–4.98 (m, 4 H), 4.67 (d, J = 10.2 Hz, 1 H), 4.16–4.02 (m, 1 H), 3.73–3.68 (m, 1 H), 3.71 (s, 3 H), 2.96 (dd, J = 14.4, 5.2 Hz, 1 H), 2.78–2.70 (m, 1 H), 2.68–2.53 (m, 1 H), 2.50 (½AB, J = 14.4 Hz,1 H), 2.40–2.20 (m, 2 H), 2.15–2.0 (m, 1 H), 1.93 (½AB, J = 14.4 Hz, 1 H), 1.90–1.55 (m, 2 H), 1.22 (d, J = 6.5 Hz, 3 H), 0.87 (s, 9 H), 0.09 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.8 (s), 175.6 (s), 160.0 (s), 143.3 (s), 137.2 (s), 135.1 (d), 134.9 (d), 124.4 (d), 119.6 (t), 117.5 (t), 116.5 (d), 107.9 (d), 94.8 (s), 68.7 (d), 63.3 (s), 55.8 (q), 53.2 (d), 53.1 (d), 52.7 (d), 46.5 (q), 31.7 (t), 29.5 (t), 27.6 (t), 27.2 (t), 25.9 (q) (3C), 21.7 (s), –4.4 (q, 2C) ppm.

Compound 7: White crystals, m.p. 187 °C. $[\alpha]_D^{20}$ = 2.0 (CH_2Cl_2, c = 0.01). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.93 (d, J = 8.1 Hz, 1 H), 6.79 (d, J = 2.1, 1 H), 6.77 (dd, J = 8.1, 2.1 Hz, 1 H), 5.84 (ddd, J = 17.4, 10.2, 8.1 Hz, 1 H), 5.53 (ddd, J = 18.6 13.9, 8.9 Hz, 1 H), 5.26 (dd, J = 10.4, 1.8 Hz, 1 H), 5.15 (dd, J = 17.4, 1.3 Hz, 1 H), 5.05 (m, 2 H), 4.55 (q, J = 6.5 Hz, 1 H), 3.75 (s, 3 H), 3.64 (dd, J = 5.2, 2.7 Hz, 1 H), 3.29 (½ABX, J = 13.8, 2.8 Hz,1 H), 3.18 (½ABX, J = 13.8, 5.2 Hz, 1 H), 2.57 (½AB, J = 13.8 Hz, 1 H), 2.52–2.30 (m, 3 H), 2.15–1.90 (2H), 1.87 (½AB, J = 13.8 Hz, 1 H), 1.39 (d, J = 6.5 Hz, 3 H), 0.87 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.8 (s), 159.5 (s), 144.7 (s), 138.9 (d), 138.4 (d), 135.4 (s), 123.9 (d), 118.2 (t), 117.3 (t), 115.2 (d), 109.4 (d), 109.2 (s), 97.0 (s), 79.0 (d), 58.8 (s), 55.6 (q), 53.2 (d), 50.7 (d), 42.8 (d), 34.4 (t), 31.6 (t), 28.0 (t), 27.6 (t), 12.8 (q) ppm. $C_{24}H_{28}O_5$ (396.5): C 72.70, H 7.12; found C 72.76, H 7.15.

General Procedure for the Formation of Carbonate Esters 8–10: Phosgene is a hazardous compound and all the operations should be performed under an efficient hood. The alcohol (0.30 mol) in CH_2Cl_2 (50 mL) and molecular sieves (60 g) were added to a phosgene solution in toluene (ca. 20%, 200 mL, 0.20 mol). The solution was stirred at room temperature for 48 h (monitored by TLC). The reaction mixture was filtered and the solution was stirred for 30 min. with saturated aqueous $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and the solvents were evaporated. The yellow oil was flash chromatographed on silica gel with elution with a PE/DE (10:1) to affording dialkyl carbonate.

Bis[(1*R*)-menthyl] Carbonate (8):[20] This compound was synthesized from (–)-menthol (56.8 g) to give **8** [43.1 g (85%)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.71 (td, J = 10.9, 4.5 Hz, 2 H), 2.11 (dq, J = 11.7, 1.6 Hz, 2 H), 1.92 (sept.d, J = 7.0, 2.7 Hz, 2 H), 1.67 (m, 4 H), 1.45 (m, 8 H), 1.12 (m, 2 H), 0.92 (d, J = 7.0 Hz, 6 H), 0.89 (d, J = 7.0 Hz, 6 H), 0.78 (d, J = 7.0 Hz, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 157.1 (s), 74.9 (d), 47.3 (d), 41.3 (d), 34.3 (d), 31.3 (t), 26.3 (t), 23.5 (t), 22.0 (q), 20.7 (q), 16.5 (q) ppm.

Dimethyl *O*,*O*'-Carbonylbis[(*S*)-lactate] (9):[21] This compound was synthesized from (–)-methyl L-lactate (31.2 g) to give **9** [29.8 g (85%)]. $[\alpha]_D^{20}$ = –42.7 (CH_2Cl_2, c = 0.01). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.07 (q, J = 7.2 Hz, 1 H), 3.69 (s, 3 H), 1.49 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.0 (s), 150.3 (s), 75.1 (d), 52.7 (t), 16.6 (q) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 1792, 1758 cm^{-1}.

Bis[(1*S*)-bornyl] Carbonate (10):[22] This compound was synthesized from (–)-borneol (46.2 g) to give **10** [42.6 g (85%)]. $[\alpha]_D^{20}$ = –27.8 (CH_2Cl_2, c = 0.01). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.77 (ddd, J = 9.9, 3.4, 1.9 Hz, 2 H), 2.32 (m, 2 H), 1.96 (m, 2 H), 1.80–1.70 (m, 2 H), 1.68–1.64 (m, 2 H), 1.33–1.21 (m, 4 H), 1.06 (dd, J = 13.8, 3.4 Hz, 2 H), 0.88 (s, 6 H), 0.86 (s, 6 H), 0.85 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.2 (s), 83.6 (d), 49.0 (s), 48.1 (s), 44.9 (d), 36.6 (t), 28.1 (t), 27.0 (t), 19.9 (q), 19.0 (q), 13.7 (q) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 1772, 1728, 1162 cm^{-1}.

3-[*endo*-(1*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yloxycarbonyl]-6,9-divinyl-1-oxaspiro[4,4]nonan-2-one (11): Lactone **1** (36.5 g, 190 mmol) in THF (150 mL) was slowly added at –20 °C to a solution of lithium hexamethyldisilazide (43 g, 257 mmol) in anhydrous THF (400 mL). The solution was stirred for 1 hour, and a solution of bornyl carbonate **10** (28.4 g, 85 mmol) in THF (250 mL) was then slowly added. The solution was stirred for 12 h at –20 °C and the mixture was then allowed to stand at –20 °C for 5 days. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution and the mixture was then extracted with diethyl ether. The organic layer was dried ($MgSO_4$) and the solvents were evaporated. The oil was flash chromatographed on silica gel, with elution with petroleum ether/diethyl ether (PE/DE) (elution order: borneol with PE/DE = 99:1; **11**, with PE/DE = 97:3; **1**, with PE/DE = 97:3).

Compound 11: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.83–5.53 (m, 2 H), 5.22–5.08 (m, 4 H), 4.97–4.88 (m, 1 H), 3.62 (t, J = 9.6 Hz, 1 H) (major isomer), 3.59 (td, J = 11.3, 1.7 Hz, 1 H) (minor isomer), 2.83–2.65 (m, 2 H), 2.54–2.24 (m, 3 H), 2.22–2.15 (m, 2 H), 2.0–1.85 (m, 1 H), 1.83–1.76 (m, 1 H), 1.66–1.64 (m, 1 H), 1.58 (d, J = 1.7 Hz, 3 H), 1.33–1.17 (m, 1 H), 1.06–0.96 (m, 1 H), 0.87 (s, 3 H), 0.85 (s, 3 H), 0.81 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) (major/minor): δ = 171.4/171.2 (s), 168.3/167.8 (s), 137.5/138.1 (d), 135.4/135.3 (d), 119.0/118.6 (t), 117.6/117.4 (t), 96.0/95.4 (s), 81.6/81.8 (d), 53.5/53.2 (d), 53.0/52.4 (d), 49.1/48.9 (s), 47.9 (s), 47.7/47.6 (d), 44.8 (d), 36.4/36.6 (t), 30.9–30.8 (t), 28.9/29.0 (t), 28.4/28.6 (t), 27.95/27.9 (t), 27.05/27.0 (t), 19.7 (q), 18.8 (q), 13.42 (q) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3078, 1766, 1675, 1639 cm^{-1}. $C_{23}H_{32}O_4$ (372.5): C 74.16, H 8.66; found C 74.26, H 8.59.

3-[*endo*-(1*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yloxycarbonyl]-3-(benzocyclobuten-1-yl)-6,9-divinyl-1-oxaspiro[4,4]nonan-2-one (12a) or 3-[*endo*-(1*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yloxycarbonyl]-3-(5-methoxybenzocyclobuten-1-yl)-6,9-divinyl-1-oxaspiro[4,4]nonan-2-one (12b): A mixture of spirolactone **11** (7.57 g, 20 mmol), 1-iodobenzocyclobutene **5a** (6.00, 26 mmol) or **5b** (6.76 g, 26 mmol), cesium carbonate (dried by heating at 100 °C under vacuum, 9.8 g, 30 mmol) and potassium iodide (2.72 g, 16 mmol) in anhydrous acetone (250 mL) was heated at reflux for 120 h. The mixture was filtered, the solid was washed with diethyl ether, and the organic phase was concentrated under reduced pressure. The crude product was flash chromatographed on silica gel with elution with pentane/diethyl ether (95:5), affording **12a** (6.92 g, 14.6 mmol, 73%) or **12b** (9.07 g, 18 mmol, 90%).

Compound 12a: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17 (m, 2 H), 7.02 (m, 2 H), 5.67 (m, 2 H), 5.05 (m, 4 H), 4.66 (dd, J = 10.2, 1.6 Hz, 1 H), 4.15 (dd, J = 4.7, 2.3 Hz, 1 H), 3.21 (m, 1 H), 2.96 (m, 1 H), 2.27 (m, 3 H), 1.99 (m, 4 H), 1.80–1.10 (m, 8 H), 0.84 (s, 3 H), 0.82 (s, 3 H), 0.80 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9 (s), 169.7 (s), 143.7 (s), 142.8 (s), 137.2 (d), 134.8 (d),

128.5 (d), 127.1 (d), 123.0 (d), 122.6 (d), 118.5 (t), 117.3 (t), 93.5 (s), 81.7 (d), 57.3 (d), 53.3 (d), 52.8 (d), 52.4 (t), 48.7 (s), 47.6 (s), 47.0 (s), 44.5 (d), 36.1 (t), 33.1 (t), 27.7 (t), 26.9 (t), 26.8 (t), 26.6 (t), 19.3 (q), 18.5 (q), 13.3 (q) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 1775, 1569, 1264, 1094, 1033, 812, 739 cm^{-1}.

Compound 12b: ^1H NMR (300 MHz, $CDCl_3$): δ = 6.94–6.86 (m, 1 H), 6.79–6.71 (m, 1 H), 6.59–6.51 (m, 1 H), 5.76–5.30 (m, 2 H), 5.26–5.03 (m, 4 H), 4.92–4.61 (t, 4 H), 4.25 (d, J = 7.0 Hz, 1 H), 4.09 (br. s, 1 H), 3.69 (s, 3 H), 3.27–3.13 (m, 1 H), 2.95–2.81 (m, 1 H), 2.39–2.28 (m, 3 H), 2.16–1.63 (m, 5 H), 1.29–1.13 (m, 2 H), 0.87 (s, 3 H), 0.85 (s, 3 H), 0.81 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5 (s), 170.0 (s), 159.8 (s), 143.7 (s), 137.3 (d), 135.3 (s), 135.2 (d), 124.1 (d), 118.84 (t), 117.4 (t), 116.3 (d), 107.9 (d), 93.8 (s), 81.9 (d), 57.7 (s), 55.5(q), 53.2 (d), 52.8 (d), 49.1 (s), 48.0 (s), 46.4 (d), 44.9 (d), 37.0 (t), 36.5 (t), 32.4 (t), 30.1 (t), 28.0 (t), 27.7 (t), 27.2 (t), 19.7 (q), 18.9 (q), 13.7 (q) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 1776, 1566, 1262, 1096, 813, 736 cm^{-1}.

General Procedure for the Thermolysis of 12: Compound **12a** (8.54 g, 18 mmol) or **12b** (9.1 g, 18 mmol) in anhydrous 1,2,4-trichlorobenzene (150 mL) was heated at 215 °C for 36 h (the progress of the reaction was followed by TLC analysis). The solvent was removed under reduced pressure and the residue was flash chromatographed (PE/DE 93:7) to give steroid analogues. From **12a**: **13a** + **14a**, crystallised from petroleum ether, 7.5 g (88%), white crystals, m.p. 153 °C (**13a**:**14a** = 70:30). From **12b**: **13b** + **14b**, 7.27 g (14.4 mmol, 80%, 80:20 mixture), crystallised from petroleum ether, white crystal, m.p. 170 °C; **15b**, 1.28 g, 2.5 mmol, 12%.

(8α,9β,14β)-11α-[*endo*-(1*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yloxycarbonyl]-11β,13β-(γ-carbolactone)-17β-vinylgonatri-1,3,5(10)-ene (13a): ^1H NMR (400 MHz, $CDCl_3$): δ = 7.11 (m, 3 H), 6.92 (d, J = 6.4 Hz, 1 H), 5.88 (ddd, J = 17.0, 10.1, 8.3 Hz, 1 H), 5.12 (br. d, J = 17.0 Hz, 1 H), 5.10 (br. d, J = 10.1 Hz, 1 H), 4.74 (dt, J = 9.0, 2.2 Hz, 1 H), 3.10 (d, J = 11.0 Hz, 1 H), 2.90–2.82 (m, 2 H), 2.80–2.75 (m, 2 H), 2.71 (½AB, J = 12.1 Hz, 1 H), 2.47 (td, J = 7.2, 11.7 Hz, 1 H), 2.23 (m, 2 H), 2.21 (½AB, J = 12.3 Hz, 1 H), 2.03 (dt, J = 11.7, 6.1 Hz, 1 H), 1.98–1.82 (m, 4 H), 1.75–1.48 (m, 6 H), 1.23 (m, 1 H), 1.07 (m, 1 H), 0.81 (s, 3 H), 0.75 (s, 3 H), 0.29 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.7 (s), 170.2 (s), 142.2 (s), 137.6 (s), 135.2 (d), 128.5 (d), 126.0 (d), 125.8 (d), 121.7 (d), 117.1 (t), 93.0 (s), 82.2 (d), 55.2 (s), 53.5 (d), 50.8 (d), 48.6 (s), 47.7 (s), 44.9 (d), 43.2 (d), 42.8 (d), 35.9 (t), 35.5 (t), 31.9 (t), 30.7 (t), 27.6 (t), 27.4 (t), 27.2 (t), 26.1 (t), 19.6 (q), 18.9 (q), 12.9 (q) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 1610, 1582, 1271, 745 cm^{-1}. $C_{31}H_{38}O_4$ (474.6): C 78.45, H 8.07; found C 78.40, H 8.09.

(8α,9β,14β)-2-Methoxy-11α-[*endo*-(1*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxycarbonyl]-11β,13β-(γ-carbolactone)-17β-vinylgonatri-1,3,5(10)-ene (13b): ^1H NMR (300 MHz, $CDCl_3$): δ = 7.01 (d, J = 8.2 Hz, 1 H), 6.62 (dd, J = 8.2, 2.5 Hz, 1 H), 6.50 (d, J = 2.5 Hz, 1 H), 5.87 (ddd, J = 17.0, 10.2, 8.1 Hz, 1 H), 5.11 (d, J = 17.0 Hz, 1 H), 5.09 (d, J = 10.1 Hz, 1 H), 4.76 (dt, J = 8.7, 2.6 Hz, 1 H), 3.68 (s, 3 H), 3.07 (d, J = 11.2 Hz, 1 H), 2.85–2.72 (m, 1 H), 2.68 (½AB, J = 12.2 Hz, 1 H), 2.46 (dt, J = 11.8, 7.3 Hz, 1 H), 2.22 (½AB, J = 12.1 Hz, 1 H), 2.03 (quint., J = 6.0 Hz, 1 H), 1.88 (m, 4 H), 1.71–1.45 (m, 6 H), 1.27–1.19 (m, 2 H), 1.07 (m, 1 H), 0.82 (s, 3 H), 0.75 (s, 3 H), 0.33 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.4 (s), 170.0 (s), 157.8 (s), 143.0 (s), 135.1 (d), 129.4 (s), 129.1 (d), 117.0 (t), 110.9 (d), 108.5 (d), 92.8 (s), 82.0 (d), 55.2 (q), 55.2 (s), 53.4 (d), 50.8 (d), 48.5 (s), 47.6 (s), 44.8 (d), 43.1 (d), 43.0 (d), 35.8 (t), 35.6 (t), 31.8 (t), 30.6 (t), 27.5 (t), 27.2 (t), 26.4 (t), 22.6 (t), 19.5 (q), 18.8 (q), 12.8 (q) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3051, 1774, 1716, 1263, 895, 727 cm^{-1}. $C_{32}H_{40}O_5$ (504.7): C 76.16, H 7.99; found C 76.28, H 8.03.

(8β,9α,14α)-11β-[*endo*-(1*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yloxycarbonyl]-11α,13α-(γ-carbolactone)-17α-vinylgonatri-1,3,5(10)-ene (14a): ^1H NMR (400 MHz, $CDCl_3$): δ = as **13a**, except for the following signals: 5.73 (ddd, J = 17.0, 10.1, 8.3 Hz, 1 H), 4.89 (dt, J = 9.0, 2.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.7 (s), 170.1 (s), 142.2 (s), 137.7 (s), 135.2 (d), 128.5 (d), 126.1 (d), 125.6 (d), 121.8 (d), 117.1 (t), 93.2 (s), 82.0 (d), 55.4 (s), 53.5 (d), 50.8 (d), 49.1 (s), 47.6 (s), 44.8 (d), 43.4 (d), 42.7 (d), 35.5 (t), 35.0 (t), 31.9 (t), 30.8 (t), 27.5 (t), 27.3 (t), 27.1 (t), 26.1 (t), 19.6 (q), 18.9 (q), 13.2 (q) ppm.

(8β,9α,14α)-2-Methoxy-11β-[*endo*-(1*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxycarbonyl]-11α,13α-(γ-carbolactone)-17α-vinylgonatri-1,3,5(10)-ene (14b): ^1H NMR (300 MHz, $CDCl_3$): δ = 7.02 (d, J = 8.1 Hz, 1 H), 6.61 (dd, J = 8.2, 2.5 Hz, 1 H), 6.51 (d, J = 2.5 Hz, 1 H), 5.87 (ddd, J = 17.0, 10.2, 8.1 Hz, 1 H), 5.11 (d, J = 17.0 Hz, 1 H), 5.09 (d, J = 10.1 Hz, 1 H), 4.88 (dt, J = 8.7, 2.6 Hz, 1 H), 3.67 (s, 3 H), 3.07 (d, J = 11.2 Hz, 1 H), 2.85–2.72 (m, 1 H), 2.68 (½AB, J = 12.2 Hz, 1 H), 2.46 (dt, J = 11.8, 7.3 Hz, 1 H), 2.22 (½AB, J = 12.1 Hz, 1 H), 2.03 (quint., J = 6.0 Hz, 1 H), 1.88 (m, 4 H), 1.71–1.45 (m, 6 H), 1.27–1.19 (m, 2 H), 1.07 (m, 1 H), 0.83 (s, 3 H), 0.75 (s, 3 H), 0.33 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.5 (s), 169.8 (s), 157.6 (s), 143.2 (s), 135.1 (d), 129.4 (s), 129.1 (d), 117.0 (t), 110.4 (d), 108.9 (d), 92.9 (s), 81.8 (d), 55.2 (q), 55.2 (s), 53.4 (d), 50.8 (d), 48.9 (s), 47.6 (s), 44.8 (d), 43.2 (d), 35.8 (t), 35.0 (t), 31.6 (t), 30.6 (t), 27.5 (t), 27.1 (t), 26.3 (t), 22.6 (t) 19.4 (q), 18.7 (q), 13.0 (q) ppm.

(8α,9α,14β)-2-Methoxy-11α-[*endo*-(1*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxycarbonyl]-11β,13β-(γ-carbolactone)-17β-vinylgonatri-1,3,5(10)-ene (15b): $[\alpha]_D^{20}$ = 24.5 (CH_2Cl_2, c = 0.01). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.89 (d, J = 8.5 Hz, 1 H), 6.82 (d, J = 2.3 Hz, 1 H), 6.64 (dd, J = 8.5, 2.3 Hz, 1 H), 5.86 (ddd, J = 17.6, 9.6, 8.1 Hz, 1 H), 5.09 (d, J = 17.4 Hz, 1 H), 5.08 (d, J = 10.1 Hz, 1 H), 4.31 (br. d, J = 6.4 Hz, 1 H), 3.71 (s, 3 H), 2.72 (q, J = 8.1 Hz, 1 H), 2.56–2.34 (m, 5 H), 2.51 (d, J = 8.3 Hz, 1 H), 2.19–2.09 (m, 3 H), 1.94–1.86 (m, 4 H), 1.77–1.58 (m, 3 H), 1.34–1.17 (m, 3 H), 1.02 (dd, J = 13.8, 3.4 Hz, 1 H), 0.93 (s, 3 H), 0.91 (s, 3 H), 0.87 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0 (s, 2C), 157.3 (s), 135.6 (d), 134.2 (s), 129.8 (d), 128.7 (s), 116.8 (t), 115.3 (d) 113.9 (d), 91.3 (s), 82.0 (d), 57.5 (s), 55.4 (q), 51.7 (d), 49.4 (s), 48.2 (s), 45.9 (d), 45.0 (d), 41.3 (t), 40.0 (d), 36.8 (t), 35.2 (d), 31.6 (t), 30.4 (t), 28.2 (t), 27.2 (t), 25.2 (t), 24.0 (t), 19.8 (q), 19.1 (q), 13.6 (q) ppm.

(8α,9β,14β)-2-Methoxy-11α-[*endo*-(1*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxycarbonyl]-11β-methoxycarbonyl-17β-vinylgonatri-1,3,5(10)-en-13β-ol (16): Compound **13b** (1 g, 2 mmol) was heated at reflux in anhydrous methanol (20 mL) for 36 h (the progress of the reaction was followed by TLC analysis). The solvent was removed under reduced pressure and the residue was flash chromatographed (PE/DE 93:7) to give **13b** and then **16**.

Compound 16: White crystals, m.p. 137 °C. $[\alpha]_D^{20}$ = –29.0 (CH_2Cl_2, c = 0.046). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.01 (s, 1 H), 6.84 (d, J = 8.3 Hz, 1 H), 6.55 (dd, J = 8.3, 2.5 Hz, 1 H), 5.75 (ddd, J = 17.4, 10.4, 7.5 Hz, 1 H), 5.14 (br. s, J = 10.4 Hz, 1 H), 5.10 (d, J = 17.4 Hz, 1 H), 4.44 (dt, J = 9.1, 2.5 Hz, 1 H), 3.79 (s, 3 H), 3.61 (s, 3 H), 2.77 (½ AB, J = 14.0 Hz, 1 H), 2.67 (m, 3 H), 2.19–1.96 (m, 4 H), 2.05 (½ AB, J = 14.0 Hz, 1 H), 1.80–1.63 (m, 3 H), 1.62–1.50 (m, 4 H), 1.45 (m, 2 H), 1.30–1.15 (m, 4 H), 0.7 (s, 3 H), 0.67 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.7 (s), 172.2 (s), 157.6 (s), 138.2 (s), 136.4 (d), 129.9 (s), 129.6 (d), 118.2 (t), 113.8 (d), 112.8 (d), 81.3 (d), 79.2 (s), 59.8 (s), 55.9 (q), 55.1 (q), 52.8 (d), 48.4 (s), 47.4 (s), 44.6 (d), 44.4 (d), 42.2 (t), 40.6 (d), 34.5 (t), 31.0 (t), 30.3 (d), 29.9 (t), 29.4 (t), 28.6 (t), 27.6 (t), 27.3 (t),

Table 1. Crystal data and structure refinement for **7**, **13b** + **14b** and **15b**.

	7	**13b** + **14b**	**15b**
Empirical formula	$C_{24}H_{28}O_5$	$C_{128}H_{160}O_{20}$	$C_{32}H_{40}O_5$
Formula mass	396.46	2018.56	504.64
Crystal colour	colourless	colourless	colourless
Crystal size [mm]^3	0.4×0.4×0.3	0.5×0.3×0.3	0.4×0.15×0.15
Crystal system	monoclinic	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1$	$P2_1$
a [Å]	9.0960(2)	11.3903(1)	10.7630(8)
b [Å]	12.8020(6)	23.5785(3)	11.5830(4)
c [Å]	18.4210(9)	21.8713(3)	11.5950(8)
β [°]	97.924(3)	104.7571(5)	99.541(3)
V [A^3]	2124.59(15)	5680.03(12)	1425.53(15)
Z	4	2	2
D_c [g·cm^{-3}]	1.239	1.18	1.176
M (Mo-K_α) [mm^{-1}]	0.086	0.078	0.078
No. of unique data	3884	16154	2786
No. parameters refined	262	1333	332
No. refl. in refinement	3889 [$F^2 > 4\sigma F^2$]	10716 [$F^2 > 4\sigma F^2$]	2414 [$F^2 > 4\sigma F^2$]
R	0.0481	0.0852	0.0556
wR [all reflections]	0.1389[a]	0.2031[b]	0.1251[c]
Goodness of fit	1.188	1.091	1.072
Residual Fourier [e·Å^{-3}]	–0.233; 0.238	–0.214; 0.315	–0.206; 0.217

[a] $w = 1/[\sigma^2(F_o^2) + (0.0692\,P)^2 + 0.5517\,P]$ where $P = (F_o^2 + 2F_c^2)/3$. [b] $w = 1/[\sigma^2(F_o^2) + (0.0943\,P)^2 + 1.92366\,P]$ where $P = (F_o^2 + 2F_c^2)/3$. [c] $w = 1/[\sigma^2(F_o^2) + (0.0545\,P)^2 + 0.5135\,P]$ where $P = (F_o^2 + 2F_c^2)/3$.

19.5 (q), 18.6 (q), 13.6 (q) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 1738, 1719, 1264, 910 cm^{-1}. $C_{33}H_{44}O_6$ (536.7): C 73.85, H 8.26; found C 73.95, H 8.19.

X-ray Crystallography: CCDC-273092 (for **7**), CCDC-273093 (for **13b+14b**) and CCDC-273094 (for **15b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

A summary of the crystal data, data collection, and refinements is given in Table 1.

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