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Enantioselective synthesis of 11-substituted 2- or 3-methoxy-17-vinylgona-1,3,5(10)-trien-13-ols

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ABSTRACT

The acylation of the (±)-spiro-γ-lactone **1** lithium enolate (3 equiv) by the *O*-TBDMS methyl (−)-(*S*)-lactate, the *O*-TBDMS methyl (+)-(*S*)-mandelate, or the diacetone-D-glucose carbonate (1 equiv each) occurs with a kinetic resolution. The (*S*,*S*)-enolate is the most reactive with the lactate and it is the (*R*,*R*)-enolate, which selectively reacts with the mandelate or the DAG carbonate. After alkylation of the resulting acyl lactones with 4- or 5-methoxy-1-iodobenzocyclobutene and heating, title compounds were obtained and, after deprotection, the structures of the optically pure new steroids were ascertained by single crystal X-ray analysis.

1. Introduction

Recent trends in pharmaceutical chemistry have triggered a move away from the development of racemates to the development of single enantiomer drugs.[1] In this context, the enantioselective synthesis of steroids is of considerable importance in medical chemistry.[2] The enantioselective total synthesis of steroids has been improved by the preparation of the indenedione of Hajos–Parrish–Eder–Sauer–Wiechert and by its use for the preparation of various steroids.[3] Other specific strategies are less straightforward and often involve molecules from the chiral pool.[2]

The importance of steroids is underlined by the fact that it is estimated that fully one-third of drugs available for prescription either are or contain steroids.[4] Some non-natural steroids possess enhanced activity[5] and, particularly, 19-norsteroids are often more biologically active than the methylated counterpart.[6] As example of steroids that do not exist in Nature, RU-486 is a strong progesterone and glucocorticoid antagonist.[7]

Some years ago, we have reported a convergent 19-norsteroids synthesis based on the A+D→AD→ABCD approach.[8] In continuation, we have recently disclosed a new route for the preparation of optically active steroids by kinetic resolution[9] of (±)-spirolactone **1**, a key intermediate in our synthesis strategy. Excess of racemic spirolactone **1** enolate has been acylated with bornyl carbonate and three optically active unnatural steroids (bearing a 11-bornyloxycarbonyl group) have been obtained, but the purification of these steroids was very laborious (Scheme 1).[10] In order to introduce the pharmacophore lactoyl group in the 11-position of steroids, we have also used the protected methyl (−)-(*S*)-lactate as acylating reagent, but some problems appeared and the synthesis has been unsuccessful. These facts have led us to modify the acylation reaction conditions as well as the following steps and now we present our progress in this area.

2. Results and discussion

2.1. Kinetic resolution from methyl *O*-TBDMS-(−)-(*S*)-lactate

The addition of methyl (−)-(*S*)-lactate protected by the *tert*-butyldimethylsilyl group to 3 equiv of racemic spirolactone **1** lithium enolate gives rise to a mixture of α-ketospirolactone **2** after 20 h at −60 °C (Scheme 2). Unfortunately, the existence of tautomeric equilibrium for each diastereomer (*R*,*R*)-**2** and (*S*,*S*)-**2** did not allow their separation. Alkylation of **2** by 4- or 5-methoxy-1-iodobenzocyclobutene afforded steroid precursor **3a** or **3b**. As demonstrated in previous works, alkylation occurred with a high stereoselectivity: the attack took place at the face of the enolate bearing the vinyl group *anti* to the lactone ring–oxygen linkage.[11] Minor by-product **4a** or **4b** (mixture of isomers) coming from the loss of the protected group was obtained as in the previous work.[10]

Precursor **3a** or **3b** was thermolyzed in trichlorobenzene at reflux providing a mixture of steroids **5a**–**8**, which were

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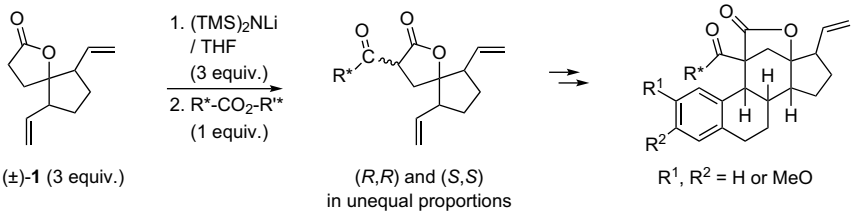


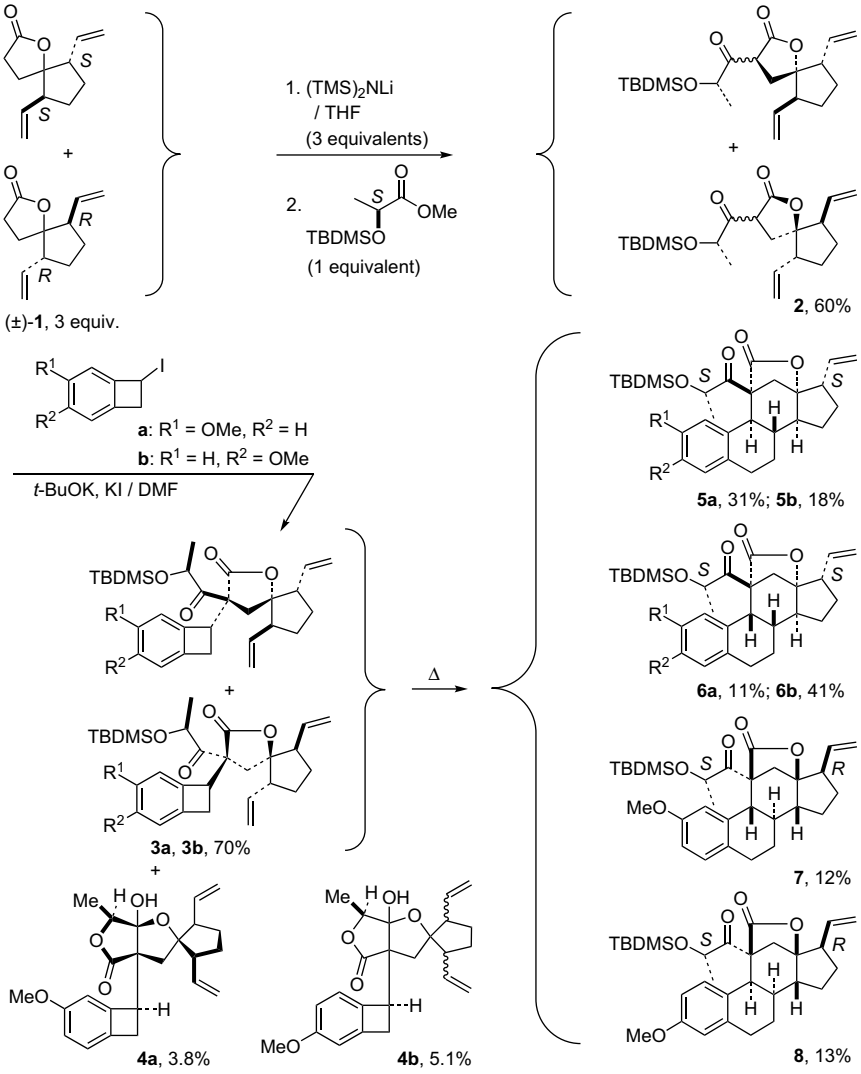
Scheme 1. Lactone kinetic resolution by acylation.

isolated in high purity by chromatography on silica gel but with substantial losses. For the major steroid **5a**, we have checked (as detailed in Section 4) that no racemization occurred in the course of the Claisen condensation.

Steroids **5** and **6** arose from (*S*,*S*)-**1**, whereas steroids **7** and **8** coming from (*R*,*R*)-**1** and the stereoselectivity of the acylation reaction providing **2** was about 4.5:1. Steroids **5a**,**b** or **7** with a trans B/C ring junction resulted from a Diels–Alder reaction involving an *exo* transition state, whereas steroids **6a**,**b** or **8** including a cis B/C ring junction arose from an *endo* transition state. All the steroids were of C/D-cis derivatives. Active steroids as natural cardenolides have a C/D-cis ring junction and it has been said that active components in the *Digitalis* extracts have been 'the most ingested drugs in medicine'.[12,13]

In fact, only two steroids can be obtained from one enantiomer of the spirolactone **1** since the alkylation reaction is stereoselective giving rise to one benzocyclobutene **3a** or **3b**. Then, the cyclization occurred with two transition states *endo* (cis B/C ring junction) or *exo* (trans B/C ring junction). For example, **3a**(*S*,*S*) was the result of the alkylation of **2**(*S*,*S*) and its thermolysis gave only **5a** and **6a**, which are epimers at C(9). In this strategy, five stereogenic centers (8, 11, 13, 14, and 17) are controlled in the course of the synthesis. The proton NMR analysis has shown that for the steroids with a trans B/C ring junction, the proton NMR coupling constant C(9)H–C(8)H was in the range 9–12 Hz [C(9)H, δ=2.90–3.90 ppm].

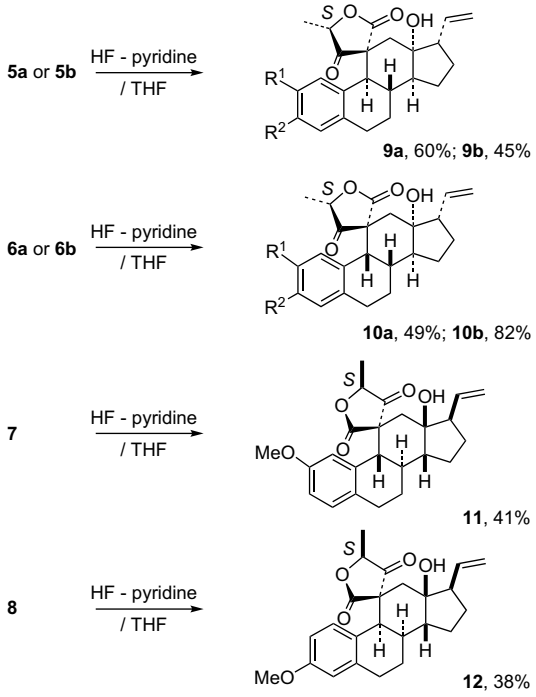
Fluoride-mediated deprotection of steroids **5**–**8** led to different products according to the reagent used. Exposure of **5a** or **5b** to



Scheme 2. Kinetic resolution of the (±)-spirolactone **1** and convergent synthesis of various 11-(*S*)-lactoyl-steroids.

hydrogen fluoride–pyridine [14] gave spirolactones **9a** or 9**b**, respectively, coming from a trans-esterification (Scheme 3). X-ray crystallographic analysis of **9a** (Fig. 1) and **9b** (Fig. 4) confirmed the *trans-anti-cis* fused skeleton of **5a** and **5b**. In the same way, **6a** and **6b** gave rise to **10a** and **10b**, respectively, the *cis–anti–cis* ring configuration of which was unambiguously confirmed by single crystal X-ray analysis (Figs. 2 and 5). Finally, **7** and **8** gave rise to **11** and **12**, respectively. Again, the *trans–anti–cis* configuration of **11** was also confirmed by crystal X-ray analysis (Fig. 3).

In contrast, treatment of **5a** by the tetrabutylammonium fluoride led mainly to an 11β-lactoyl compound **13** resulting from a decarboxylation reaction and a by-product **14** arising from a retro-Claisen process. The β-position of the lactoyl moiety of **13** has been checked by crystal X-ray analysis (Fig. 6). In a same way, **6b** led to 11-(*S*)-lactoyl-steroids **15** (Scheme 4).



Scheme 3. Deprotection of steroids **5**–**8** with HF–pyridine.

Although natural steroids bearing a 17-vinyl group have been isolated from soft coral[15] or gorgonian,[16] we have oxidized **13** to 17-acetyl steroid **16** according to the Wacker process and previously worked out procedure in our laboratory (Scheme 5).[8a,17]

2.2. Kinetic resolution from methyl *O*-TBDMS (+)-(*S*)-mandelate

The acylation of (±)-**1** with *O*-TBDMS methyl (*S*)-(−)-mandelate occurred in the fair yield of 85%. Then, it appears that the alkylation with the 5-methoxy-1-iodobenzocyclobutene presented preferential reaction taking place mainly at the face of the enolate bearing the vinyl group *syn* to the lactone bridge. It is the first example of reverse stereoselectivity in the course of the alkylation of enolates similar to **17**.[8,10,11] The geometrical constraints introduced by the presence of the protected mandeloyl group can explain this reversion of the stereochemistry. The structure of the minor isomer **18a** was ascertained by X-ray crystallographic analysis (Fig. 7). Thermolysis of **18** gave rise to three new steroids, the major, **20** and the very minor, **19**, coming from **1**(*R*,*R*) and for the minor, **21**, from **1**(*S*,*S*) [(*R*,*R*)/(*S*,*S*)≈3.3] (Scheme 6). The configuration has been determined after deprotection by HF–pyridine and the structure of **22** was confirmed by X-ray crystallographic analysis (Fig. 8).

An attempt to induce a deprotection of **18b** by HF–pyridine before the thermolysis led to **24** resulting from a retro-Claisen reaction with the loss of the mandeloyl moiety (Scheme 6).

Wacker-type oxidation of the 17β-vinyl group of **22** afforded the 17β-acetyl-steroid **25** in the fair yield of 57.4% (Scheme 7).

2.3. Kinetic resolution from diacetone-D-glucose carbonate

Finally, as in our previous works,[10] we use an optically active carbonate possessing a C_2-axis of symmetry. Our choice has been the diacetone-D-glucose carbonate **26** (DAG carbonate) obtained by reaction of the cheap and commercially available DAG with phosgene (Scheme 8).[18]

The acylation reaction occurred in the fair yield of 73% after 24 h at −20 °C. Once again, the alkylation by iodobenzocyclobutenes took place at the face of the enolate bearing the vinyl group *anti* to the lactone bridge. Thus, from an enantiomer of the lactone **1**, five stereogenic centers (8, 11, 13, 14, and 17) are controlled in the course of the synthesis. As from *O*-TBDMS methyl (*S*)-(−)-mandelate, major steroids came from the **1**(*R*,*R*) [(*R*,*R*)/(*S*,*S*)≈2.5] (Scheme 9).

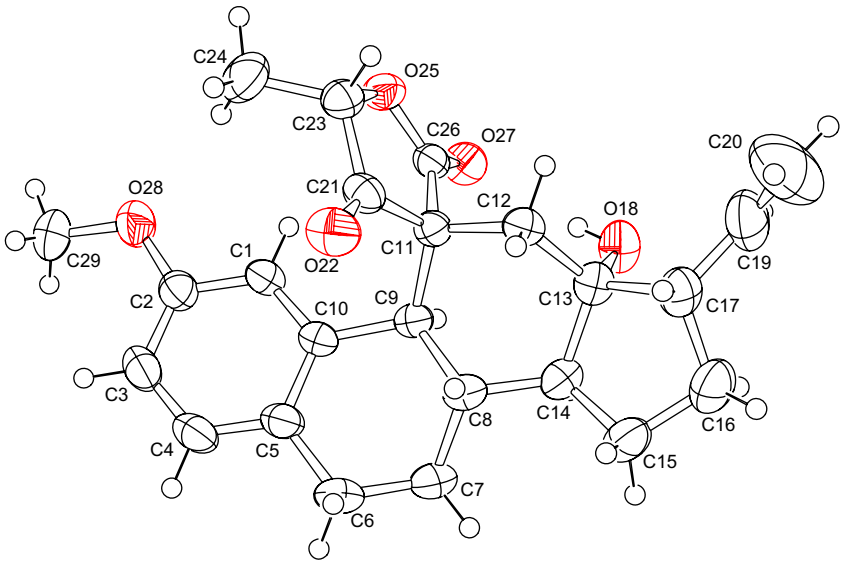


Figure 1. ORTEP diagram of compound **9a**.

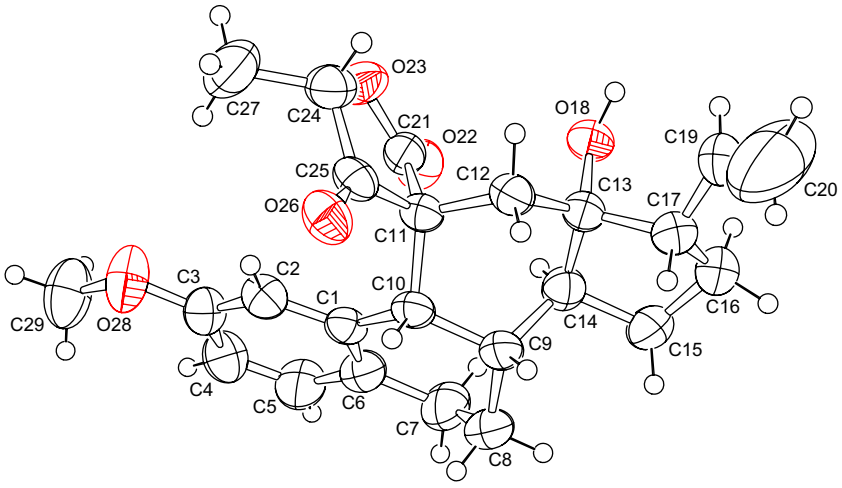


Figure 2. ORTEP diagram of compound **10a**.

Interestingly, the steroid **29b** was synthesized with an overall yield from spirolactone **1** of 24.3% and its isomer **30b** of 9.9%.

In order to obtain a suitable crystallized compound for an X-ray crystallographic analysis, the DAG moieties have been partially hydrolyzed by treatment with acetic acid.[19] Although this reaction was not chemoselective, the new steroids were easily purified (Scheme 10). Only, steroid **37** led to crystals able to give a good X-ray crystallographic analysis (Fig. 9).

Attempts to obtain interesting crystals for an X-ray analysis by esterification (tosylation or 3,5-dinitrobenzoylation) of diols **32**–**39** have failed (Scheme 11).

Finally, Wacker-type oxidation of the 17β-vinyl group of **29b** afforded the 17β-acetyl-steroid **46**. The DAG moiety was partially hydrolyzed and a poor yield of 20% has been observed (Scheme 11).

3. Conclusion

From the absolute configuration of various obtained steroids, we can conclude that with *O*-TBDMS methyl (−)-(*S*)-lactate, the lithium enolate of (*S*,*S*)-**1** was the most reactive [(*S*,*S*)-**1**/(*R*,*R*)-**1**=4.5:1] and for the *O*-TBDMS methyl (+)-(*S*)-mandelate and the DAG-carbonate, it is the contrary (methyl mandelate: (*R*,*R*)-**1**/(*S*,*S*)-**1**=3.3:1; DAG carbonate: (*R*,*R*)-**1**/(*S*,*S*)-**1**=2.5). So, the *O*-TBDMS methyl (−)-(*S*)-lactate and the **1**(*S*,*S*) lithium enolate constitute a 'matched pair' and the combination of *O*-TBDMS methyl (+)-(*S*)-mandelate or DAG-carbonate with the **1**(*R*,*R*) lithium enolate leads to another one. These results should be considered as examples of double asymmetric induction.[20]

4. Experimental part

4.1. General

All reactions were performed under an argon atmosphere in oven-dried glassware. TLC was performed on silica gel 60 F_{254}. Flash chromatography was performed on silica gel (230–400 mesh) obtained from Macherey-Nagel & Co. DMF and DMSO were distilled before use from calcium hydride and THF was distilled from sodium/benzophenone. ^{1}H and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ solutions at 500 or 300, and 75 MHz, respectively, using a Bruker AC300 and Advance DPX 500 spectrometers. Chemical shift are reported in parts per million relative to $CDCl_3$

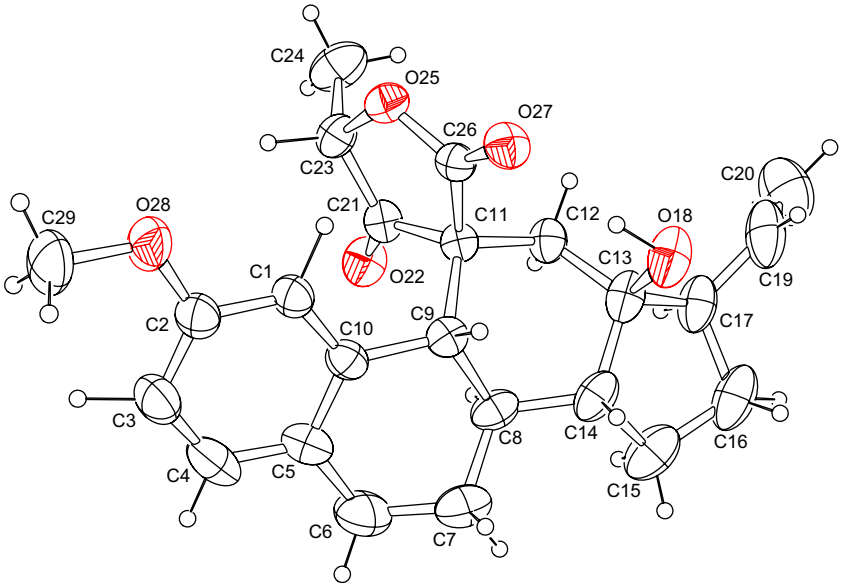


Figure 3. ORTEP diagram of compound **11**.

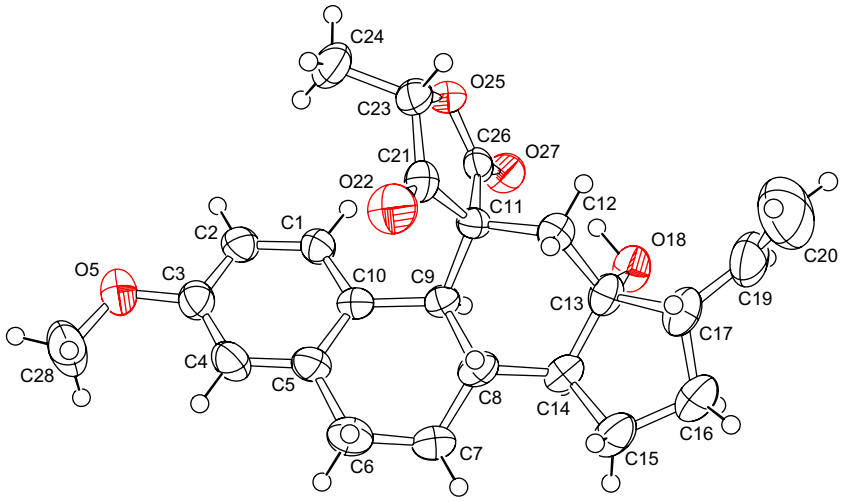


Figure 4. ORTEP diagram of compound **9b**.

(signals for residual $CDCl_3$ in $CDCl_3$: 7.24 for ^1H NMR and 77.16 (central) for ^{13}C NMR). Carbon–proton couplings were determined by DEPT sequence experiments. Spirolactone **1** (CAS number 149252-97-1), 1-iodo-4-methoxybenzocyclobutenes (CAS number 275367-67-4),[8a] 1-iodo-5-methoxybenzocyclobutenes (CAS number 270918-27-9),[8a] *O*-TBDMS methyl (−)-(*S*)-lactate (CAS number 87681-24-1), and *O*-TBDMS methyl (+)-(*S*)-mandelate (CAS number 133187-21-0) were synthesized by the methods previously described.

4.2. 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose carbonate (DAG carbonate) (26)

Phosgene is a hazardous compound and all the operations should be performed under an efficient hood. To a stirred solution of DAG (25 g, 96 mmol) in 250 mL of anhydrous CH_2Cl_2 was added pyridine (12 g, 0.15 mol). The solution was cooled at −20 °C and a phosgene solution in toluene (ca. 20%, 23.5 g, 48 mmol) was slowly added. After 1 h of stirring at −20 °C, the solution was allowed to stand at room temperature for 20 h. The reaction mixture was added to a stirred saturated aqueous $NaHCO_3$ solution. The mixture was then extracted with CH_2Cl_2 and the organic layers were dried on $MgSO_4$. Solvent and pyridine were eliminated under reduced pressure to give white solid of **26** (25 g, 46 mmol, 95%), mp 149 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=5.79 (d, J=3.7 Hz, 1H), 5.11 (d, J=2.3 Hz, 1H), 4.50 (d, J=3.7 Hz, 1H), 4.10–4.14 (m, 2H), 3.98–4.07 (m, 2H), 1.43 (s, 3H), 1.33 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=153.0 (s), 112.4 (s), 109.4 (s), 105.0 (d), 83.2 (d), 79.9 (d), 72.4 (d), 67.3 (t), 26.9 (q), 26.7 (q), 26.2 (q), 25.3 (q) ppm.

4.3. 3-[(*S*)-(2-*tert*-Butyldimethylsilyloxy)propanoyl]-6,9-divinyl-1-oxa-spiro[4,4]nonan-2-one (2)

In a 500 mL three-neck flask equipped with a magnetic stirring bar and a pressure-equalized addition funnel was added LiHMDS (21.8 g, 0.13 mol) in 200 mL of anhydrous THF. The content was stirred until dissolution and then cooled at −20 °C. Racemic lactone **1** (25 g, 0.13 mol) in 43 mL of anhydrous THF was slowly added and stirred for 20 min. The solution was cooled at −80 °C and *O*-TBDMS methyl (−)-(*S*)-lactate (9.4 g, 43 mmol) in 43 mL of anhydrous THF was slowly added. After 1 h of stirring at −80 °C, the solution was stirred at −60 °C for 20 h. The content was added to a chilled saturated solution of NH_4Cl. After extraction with Et_2O, the organic

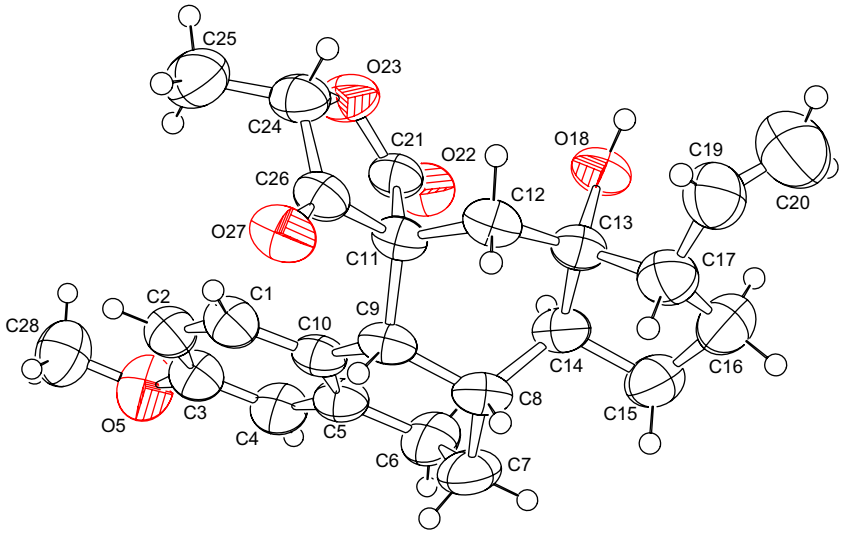


Figure 5. ORTEP diagram of compound **10b**.

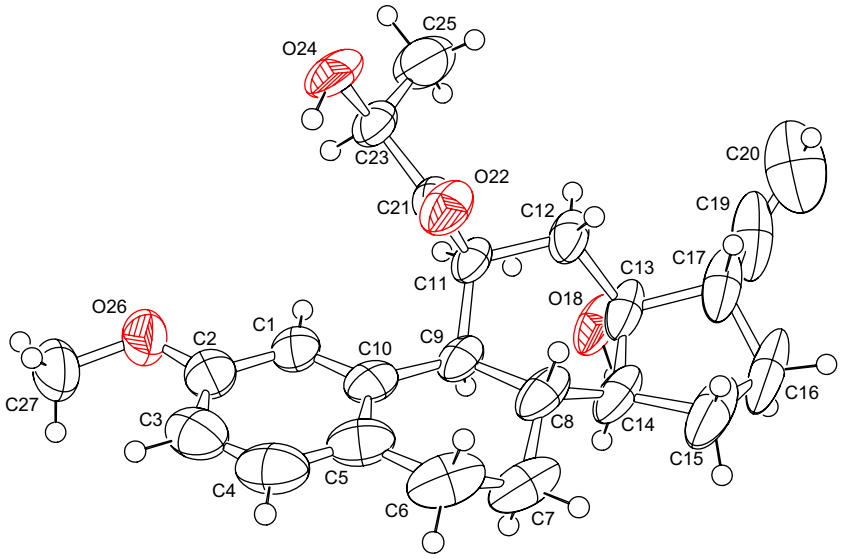
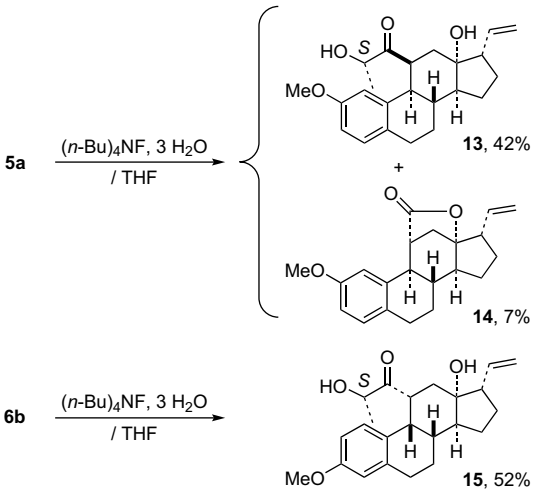
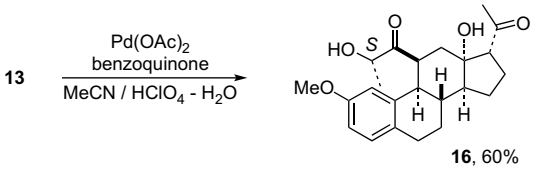


Figure 6. ORTEP diagram of compound **13**.



Scheme 4. Deprotection of steroids **5**–**7** with $(n\text{-Bu})_4$NF.



Scheme 5. Wacker-type oxidation of the vinyl group of **13**.

layers were washed with brine and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was flash chromatographed on silica gel (petroleum ether/Et_2O 97:3) to give **2** (12 g, 31.4 mmol, 73%).[10]

4.4. 3-[(*S*)-(2-*tert*-Butyldimethylsilyloxy)propanoyl]-3-[5-methoxybenzocyclobuten-1-yl]-6,9-divinyl-1-oxa-spiro[4,4]nonan-2-one (3a)

In a 250 mL two-neck flask equipped with a magnetic stirring bar and a pressure-equalized addition funnel was added potassium *tert*-butylate (2.3 g, 20.5 mmol) and KI (3.4 g, 20.5 mmol) in anhydrous DMF (63 mL) at 0 °C. A solution of **2** (6 g, 15.8 mmol) in anhydrous DMF (31.5 mL) and then a solution of 1-iodo-5-methoxybenzocyclobutene (5.34 g, 20.5 mmol) in anhydrous DMF (31.5 mL) was added. The content was stirred for 2 days at room temperature. The mixture was washed with water and the aqueous phases extracted with Et_2O, the organic layers were washed with brine and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was flash chromatographed on silica gel (petroleum ether/Et_2O 95:5 then 80:20) to give **3a** (colorless oil, 5.64 g, 11.0 mmol, 70%)[10] and **4a** (mp 187 °C, 238 mg, 0.6 mmol, 3.8%).[10]

4.5. 3-[(*S*)-(2-*tert*-Butyldimethylsilyloxy)propanoyl]-3-[4-methoxybenzocyclobuten-1-yl]-6,9-divinyl-1-oxa-spiro[4,4]nonan-2-one (3b)

The same procedure with 1-iodo-4-methoxybenzocyclobutene led to **3b** (colorless oil, 5.56 g, 10.9 mmol, 69%) and **4b** (mixture of isomers) (colorless oil, 320 mg, 0.8 mmol, 5.1%). Compound **3b**. ^{13}C NMR (75 MHz, $CDCl_3$) major isomer: δ=203.9 (s), 175.5 (s), 161.0 (s), 144.4 (s), 137.2 (d), 134.8 (d), 134.0 (s), 125.0 (d), 123.8 (d), 119.4 (t), 117.2 (t), 114.7 (d), 114.2 (d), 108.8 (d), 94.4 (s), 70.7 (d), 68.7 (d), 63.4 (q), 55.5 (d), 55.4 (s), 53.0 (d), 52.5 (d), 46.4 (d), 38.2 (t), 31.9 (t), 27.4 (t), 27.0 (t), 25.7 (q), 21.5 (q), 18.1 (s), −4.4 (q) ppm. Compound **4b**. ^{13}C NMR (75 MHz, $CDCl_3$): δ=178.1 (s), 177.6 (s), 160.2 (s), 145.2 (s), 144.3 (s), 139.1 (d), 138.8 (d), 136.6 (s), 135.4 (s), 126.1 (d), 125.3 (d), 117.5 (d), 117.4 (d), 117.1 (d), 117.0 (t), 113.9 (d), 113.7 (d), 109.5 (s), 109.4 (s), 108.1 (d), 108.0 (d), 96.4 (s), 96.0 (s), 83.0 (d), 82.6 (d), 60.4 (s), 58.2 (s), 57.1 (s), 55.3 (d), 55.3 (d), 52.7 (d), 52.6 (d), 51.4 (d), 51.0 (d), 43.1 (d), 42.7 (d), 33.2 (t), 33.0 (t), 32.7 (t), 32.6 (t), 27.7 (t), 27.5 (t), 27.3 (t), 21.0 (q), 17.6 (q), 14.2 (q) ppm. $C_{30}H_{42}O_5Si$ (510.7): C 70.55, H 8.29; found C 70.67, H 8.21.

4.6. General procedure for the thermolysis of 3, 18, and 28

Steroid precursors 1 mmol in 1,2,4-trichlorobenzene (10 mL/mmol) were heated at reflux (214 °C) for 20–24 h (the progress of the reaction was followed by TLC analysis). The solvent was removed under reduced pressure and the residue was flash chromatographed on silica gel.

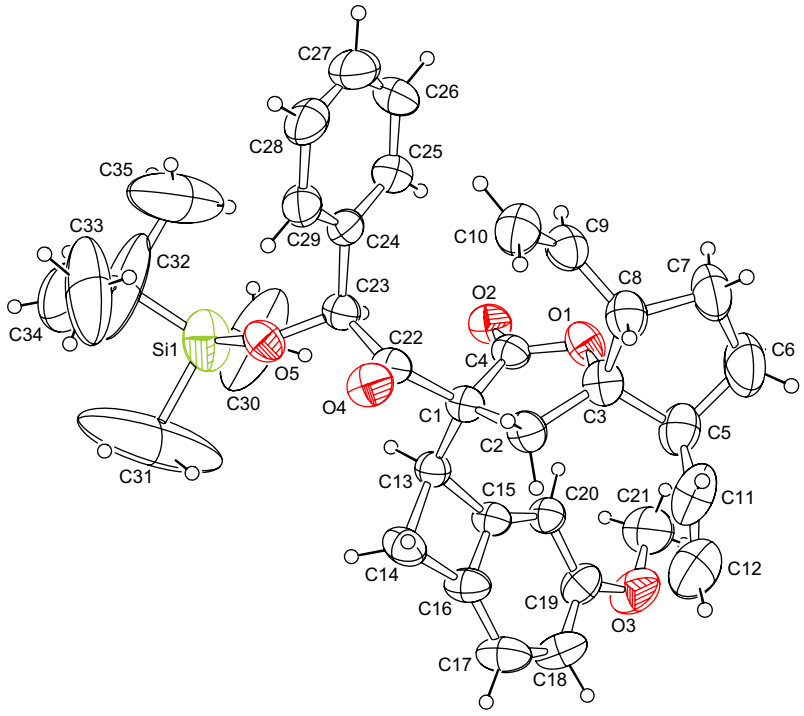
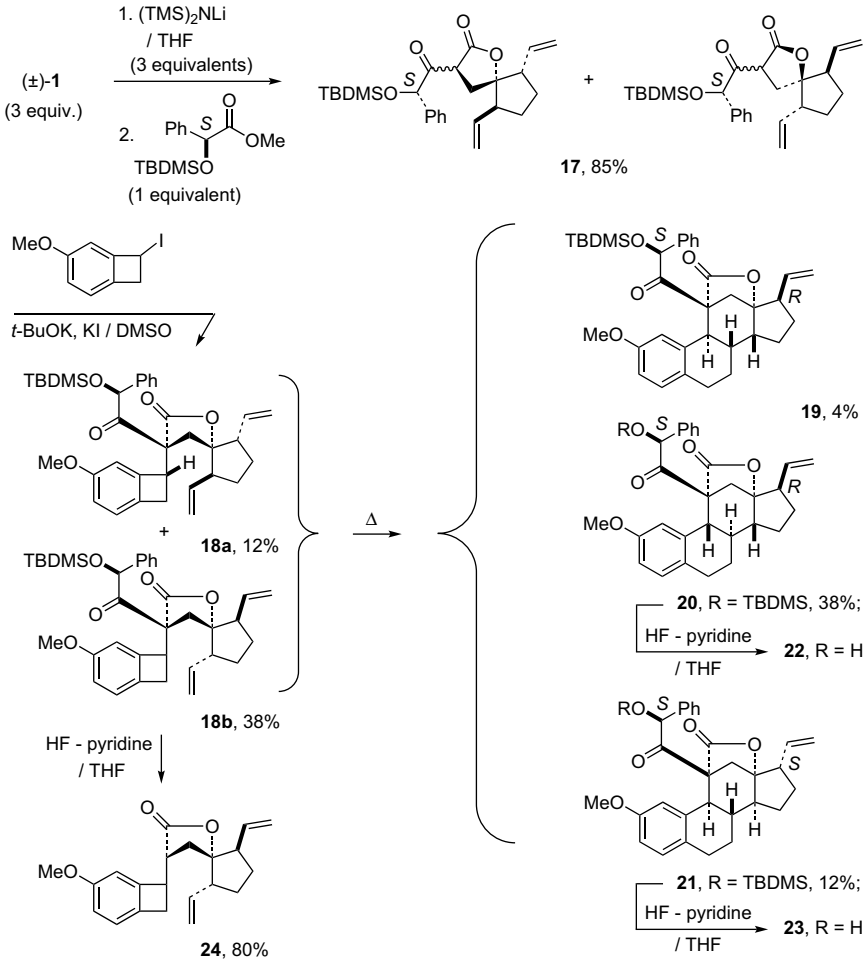


Figure 7. ORTEP diagram of compound **18a**.



Scheme 6. Kinetic resolution of the (±)-spirolactone **1** and convergent synthesis of various 11-(*S*)-mandeloyl steroids.

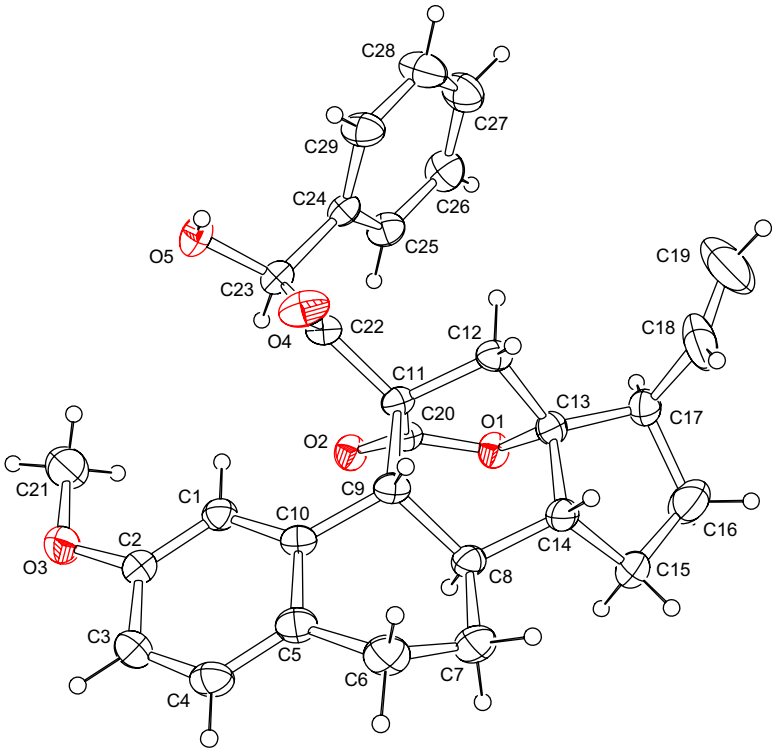
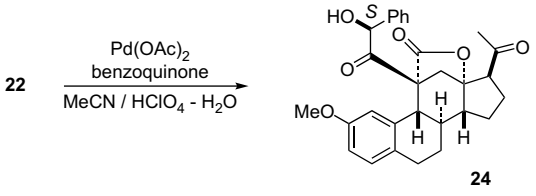
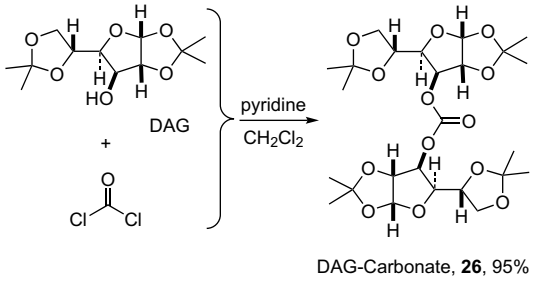


Figure 8. ORTEP diagram of compound **22**.



Scheme 7. Wacker-type oxidation of the vinyl group of **22**.



Scheme 8. Synthesis of diacetone-D-glucose carbonate **26**.

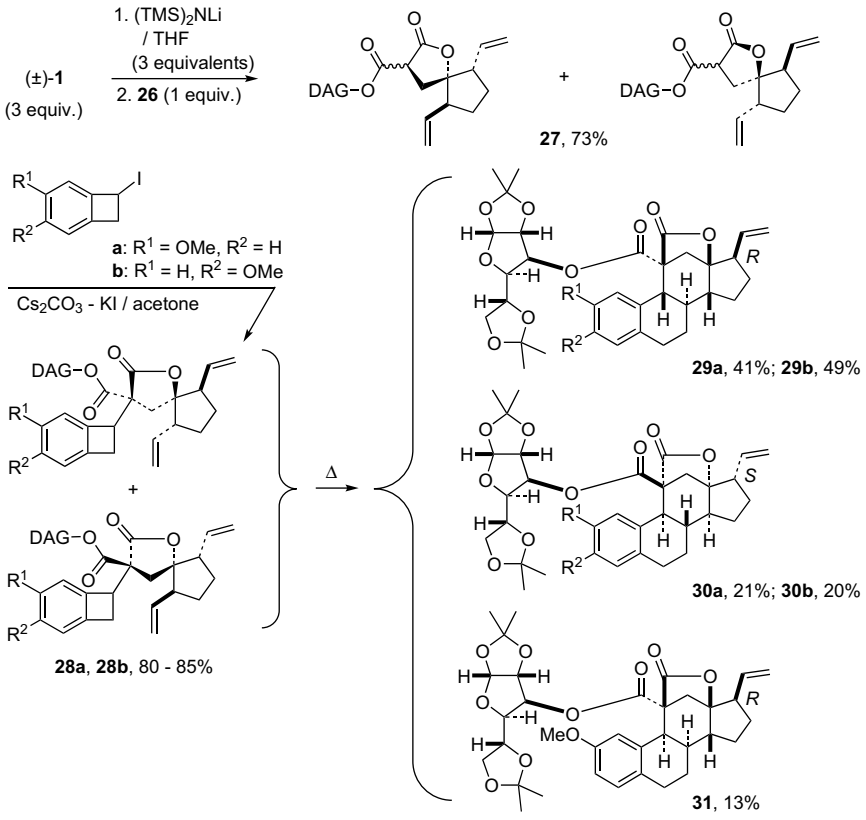
*4.6.1. Thermolysis of **3a***

From **3a** (8 g, 15.7 mmol): **5a** (2.48 g, 4.86 mmol, 31%), **6a** (880 mg, 1.7 mmol, 11%), **7** (936 mg, 1.84 mmol, 12%) after flash chromatography (EP/AcOEt 98:2).

*4.6.1.1. (8β,9α,14α)-11β-[2(S)-(tert-Butyldimethylsilyloxy)propanoyl]-11α,13α-(γ-carbolactone)-2-methoxy-17α-vinylgona-1,3,5(10)-triene (**5a**).* Colorless oil, $[\alpha]_D^{20}$ −65 (*c* 0.2, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ=6.99 (d, *J*=8.2 Hz, 1H), 6.62 (dd, *J*=8.2, 2.4 Hz, 1H), 6.38 (d, *J*=2.2 Hz, 1H), 5.86 (ddd, *J*=17.0, 10.2, 8.3 Hz, 1H), 5.10 (br d, *J*=17.0 Hz, 1H), 5.09 (br d, *J*=10.2 Hz, 1H), 4.70 (q, *J*=6.6 Hz, 1H), 3.68 (s, 3H), 3.35 (d, *J*=11.2 Hz, 1H), 2.80 ($^1/_2$ AB, *J*=12.5 Hz, 1H), 2.74 (q, *J*=8.4 Hz, 1H), 2.68–2.74 (m, 1H), 2.45 (dt, *J*=11.5, 7.4 Hz, 1H), 2.22 ($^1/_2$ AB, *J*=12.4 Hz, 1H), 2.04 (qd, 6.0, 1.0 Hz, 1H), 1.83–1.96 (m, 3H), 1.66 (qd, *J*=12.1, 5.5 Hz, 1H), 1.53 (br qd, *J*=10.9, 3.4 Hz, 1H), 1.39 (d, *J*=6.65 Hz, 3H), 1.27 (dd, *J*=11.3, 7.3 Hz, 1H), 0.96 (qd, *J*=12.0, 5.65 Hz, 1H), 0.71 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=208.9 (s), 175.8 (s), 157.8 (s), 143.5 (s), 135.4 (d), 129.6 (d), 129.2 (s), 117.1 (t), 110.5 (d), 110.2 (d), 93.0 (s), 75.3 (d), 60.7 (s), 55.3 (q), 53.3 (d), 51.2 (d), 44.9 (d), 43.5 (d), 35.9 (t), 31.9 (t), 30.8 (t), 26.7 (t), 26.7 (t), 25.9 (q)(3C), 21.4 (q), 18.1 (s), −4.0 (q), −5.3 (q) ppm. $C_{30}H_{42}O_5Si$ (510.7): C 70.55, H 8.29; found C 70.46, H 8.32.

*4.6.1.2. (8β,9β,14α)-11β-[2(S)-(tert-Butyldimethylsilyloxy)propanoyl]-11α,13α-(γ-carbolactone)-2-methoxy-17α-vinylgona-1,3,5(10)-triene (**6a**).* Colorless oil, $[\alpha]_D^{20}$ −54 (*c* 0.31, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ=6.88 (d, *J*=8.3 Hz, 1H), 6.60 (dd, *J*=8.5, 1.4 Hz, 1H), 6.42 (br s, 1H), 5.87 (br quint, *J*=8.92 Hz, 1H), 5.09 (br d, *J*=17.0 Hz, 1H), 5.05 (br d, *J*=10.4 Hz, 1H), 4.77 (q, *J*=6.9 Hz, 1H), 4.53 (br d, *J*=5.6 Hz), 3.65 (s, 3H), 3.16 (d, *J*=11.6 Hz, 1H), 2.64–2.74 (m, 2H), 3.02 (d, *J*=11.4 Hz, 1H), 2.70 ($^1/_2$ AB, *J*=11.5 Hz, 1H), 2.43–2.51 (m, 3H), 2.24 ($^1/_2$ AB, *J*=11.4 Hz, 1H), 2.12–2.18 (m, 2H), 1.76–1.87 (m, 3H), 1.70 (d, *J*=7.0 Hz, 1H), 1.58 (d, *J*=7.0 Hz, 3H), 0.88 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=209.7 (s), 172.8 (s), 157.1 (s), 136.0 (d), 134.9 (s), 129.9 (d), 129.2 (s), 116.9 (t), 115.6 (d), 112.9 (d), 91.9 (s), 76.2 (d), 61.0 (s), 55.4 (q), 51.8 (d), 46.1 (d), 40.0 (t), 39.1 (d), 35.2 (d), 32.0 (t), 30.5 (t), 26.1 (q)(3C), 25.6 (t), 24.1 (t), 22.7 (q), 18.3 (s), −3.3 (q), −4.7 (q) ppm. $C_{30}H_{42}O_5Si$ (510.7): C 70.55, H 8.29; found C 70.60, H 8.36.

*4.6.1.3. (8α,9β,14β)-11α-[2(S)-(tert-Butyldimethylsilyloxy)propanoyl]-11β,13β-(γ-carbolactone)-2-methoxy-17β-vinylgona-1,3,5(10)-triene (**7**).* Colorless oil, $[\alpha]_D^{20}$ +12 (*c* 0.4, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ=6.98 (d, *J*=8.3 Hz, 1H), 6.60 (dd, *J*=8.3, 2.4 Hz, 1H), 6.21 (d, *J*=2.2 Hz, 1H), 5.90 (ddd, *J*=16.4, 10.7, 8.6 Hz, 1H), 5.105 (d, *J*=16.8 Hz, 1H), 5.10 (d, *J*=10.9 Hz, 1H), 4.81 (q, *J*=6.5 Hz, 1H), 3.67 (s, 3H), 3.17 (d, *J*=10.8 Hz, 1H), 2.82 ($^1/_2$ AB, *J*=12.0 Hz, 1H), 2.72–2.75 (m, 2H), 2.45 (dt, *J*=10.9, 7.6 Hz, 1H), 2.32 ($^1/_2$ AB, *J*=12.0 Hz, 1H), 2.07 (br quint, *J*=6.22 Hz, 1H), 1.84–1.92 (m, 2H), 1.65 (qd, *J*=11.7, 5.5 Hz, 1H), 1.44–



Scheme 9. Kinetic resolution of the (±)-spirolactone **1** and convergent synthesis of various steroids from DAG carbonate.

1.48 (m, 2H), 1.38 (d, *J*=6.6 Hz, 3H), 1.02 (qd, *J*=11.8, 5.7 Hz, 1H), 0.85 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=205.4 (s), 176.3 (s), 157.4 (s), 135.7 (d), 135.7 (s), 129.9 (s), 129.6 (d), 117.1 (t), 112.5 (d), 110.6 (d), 93.2 (s), 74.1 (d), 59.2 (s), 55.4 (q), 52.9 (d), 51.4 (d), 45.6 (d), 42.7 (d), 37.7 (t), 31.9 (t), 30.2 (t), 27.5 (t), 27.2 (t), 26.1 (q)(3C), 20.0 (q), 18.4 (s), −4.4 (q), −4.5 (q) ppm. $C_{30}H_{42}O_5Si$ (510.7): C 70.55, H 8.29; found C 70.44, H 8.26.

*4.6.1.4. Determination of the enantiomeric excess of **5a**.* The enantiomeric excess of **5a** was determined by HPLC analysis [CHIRALPAK-AD, hexane/2-propanol 95:5, 1 mL/min, 254 nm, polarimeter]: (−)-**5a**, 97.6%, (+)-**5a**, 2.4%. This ee was identical of this commercially available *purum* methyl (−)-(*S*)-lactate (Fluka).

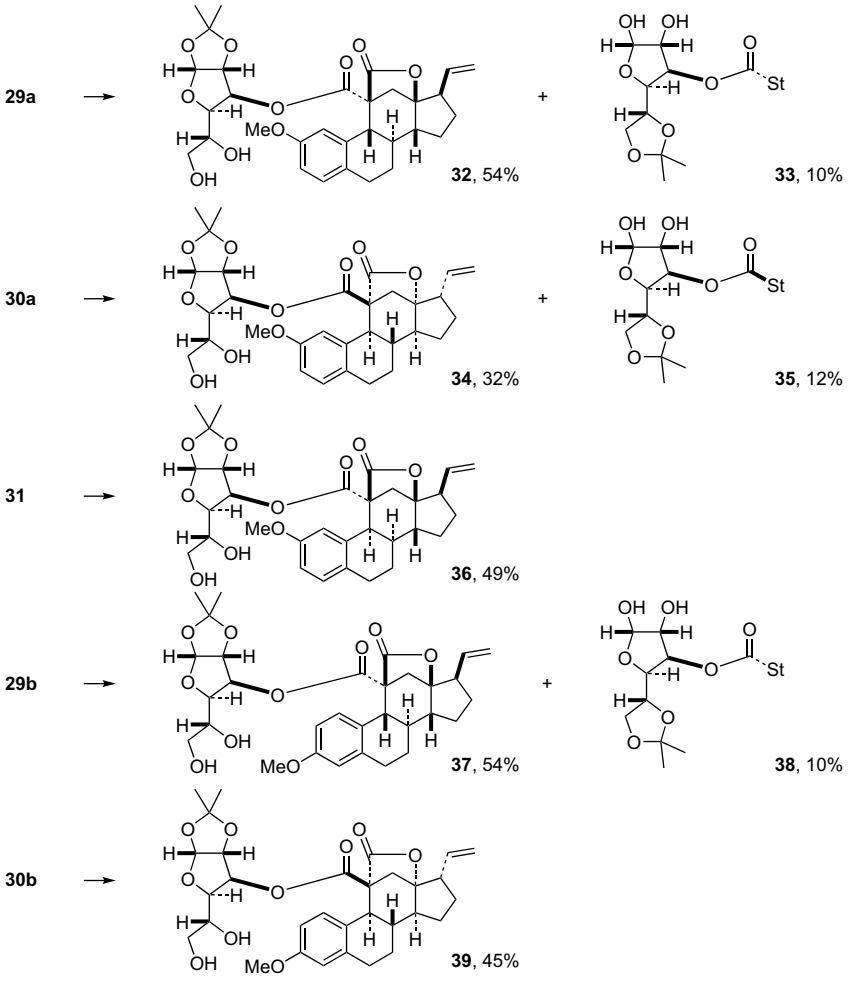
*4.6.2. Thermolysis of **3b***

From **3b** (2 g, 3.9 mmol): **5b** (360 mg, 0.7 mmol, 18%), **6b** (820 mg, 1.6 mmol, 41%), **8** (260 mg, 0.5 mmol, 13%) after flash chromatography (EP/AcOEt 90:10).

*4.6.2.1. (8β,9α,14α)-11β-[2(S)-(tert-Butyldimethylsilyloxy)propanoyl]-11α,13α-(γ-carbolactone)-3-methoxy-17α-vinylgona-1,3,5(10)-triene (**5b**).* Colorless oil, $[\alpha]_D^{20}$ −43 (*c* 0.52,CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.66 (br s, 1H), 6.65 (d, *J*=8.5 Hz, 1H), 6.55 (dd, *J*=8.5, 2.7 Hz, 1H), 5.84 (ddd, *J*=16.6, 10.6, 8.4 Hz, 1H), 5.15 (br d, *J*=17.1 Hz, 1H), 5.10 (br d, *J*=10.2 Hz, 1H), 4.69 (q, *J*=6.7 Hz, 1H), 3.73 (s, 3H), 3.27 (d, *J*=11.1 Hz, 1H), 2.73–2.84 (m, 2H), 2.44 (dt, *J*=11.7, 7.2 Hz, 1H), 2.21 ($^1/_2$ AB, *J*=12.5 Hz, 1H), 2.04 (br quint, *J*=6.4 Hz, 1H), 1.85–1.94 (m, 3H), 1.65 (qd, *J*=11.9, 5.5 Hz, 1H), 1.48–1.56 (m, 2H), 1.35 (d, *J*=6.7 Hz, 3H), 1.28 (dd, *J*=11.3, 7.0 Hz, 1H), 0.97 (qd, *J*=11.7, 5.7 Hz, 1H), 0.84–0.91 (m, 2H), 0.74 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=208.2 (s), 176.2 (s), 157.9 (s), 139.2 (s), 135.5 (d), 134.1 (s), 124.7 (d), 117.1 (t), 114.7 (d), 110.4 (d), 93.1 (s), 75.5 (d), 60.2 (s), 55.4 (q), 53.1 (d), 51.3 (d), 44.6 (d), 43.7 (d), 36.3 (t), 31.9 (t), 30.7 (t), 28.1 (t), 26.6 (t), 25.9 (q)(3C), 21.4 (q), 18.1 (s), −4.1 (q), −5.0 (q) ppm. $C_{30}H_{42}O_5Si$ (510.7): C 70.55, H 8.29; found C 70.46, H 8.22.

*4.6.2.2. (8β,9β,14α)-11β-[2(S)-(tert-Butyldimethylsilyloxy)propanoyl]-11α,13α-(γ-carbolactone)-3-methoxy-17α-vinylgona-1,3,5(10)-triene (**6b**).* Colorless oil, $[\alpha]_D^{20}$ −70.8 (*c* 0.12, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.76 (d, *J*=8.7 Hz, 1H), 6.59 (dd, *J*=8.7, 2.7 Hz, 1H), 6.50 (d, *J*=2.6 Hz, 1H), 5.87 (ddd, *J*=17.2, 10.0, 8.6 Hz, 1H), 5.08 (d, *J*=16.3 Hz, 1H), 5.05 (d, *J*=10.0 Hz, 1H), 4.86 (q, *J*=6.9 Hz, 1H), 4.49 (d, *J*=7.2 Hz, 1H), 3.70 (s, 3H), 2.79 (q, *J*=8.6 Hz, 1H), 2.57 ($^1/_2$ AB, *J*=11.5 Hz, 1H), 2.45–2.51 (m, 2H), 2.26 ($^1/_2$ AB, *J*=11.5 Hz, 1H), 2.07–2.21 (m, 3H), 1.83–1.89 (m, 3H), 1.60–1.69 (m, 2H), 1.53 (d, *J*=6.9 Hz, 3H), 1.05–1.15 (m, 2H), 0.89 (s, 9H), 0.11 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=209.3 (s), 173.3 (s), 157.6 (s), 138.3 (s), 135.9 (d), 131.4 (d), 125.6 (s), 116.9 (t), 113.6 (d), 111.7 (d), 91.9 (s), 75.6 (d), 60.8 (s), 55.2 (q), 51.7 (d), 46.2 (d), 40.0 (t), 39.0 (d), 35.2 (d), 31.9 (t), 30.6 (t), 26.1 (q)(3C), 25.3 (t), 25.2 (t), 22.3 (q), 18.3 (s), −3.6 (q), −4.7 (q) ppm. $C_{30}H_{42}O_5Si$ (510.7): C 70.55, H 8.29; found C 70.52, H 8.26.

*4.6.2.3. (8α,9α,14β)-11α-[2(S)-(tert-Butyldimethylsilyloxy)propanoyl]-11β,13β-(γ-carbolactone)-3-methoxy-17β-vinylgona-1,3,5(10)-triene (**8**).* Colorless oil, $[\alpha]_D^{20}$ 24.7 (*c* 0.15, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.68 (d, *J*=8.2 Hz, 1H), 6.57 (dd, *J*=8.2, 2.6 Hz, 1H), 6.46 (d, *J*=2.6 Hz, 1H), 5.87 (ddd, *J*=17.0, 10.1, 8.6 Hz, 1H), 5.08–5.00 (m, 2H), 4.79 (q, *J*=6.45 Hz, 1H), 4.44 (br d, *J*=5.82 Hz, 1H), 3.70 (s, 3H), 3.19 (d, *J*=11.6 Hz), 3.09 (d, *J*=11.5 Hz), 2.90 ($^1/_2$ AB, *J*=11.5 Hz, 1H), 2.64–2.80 (m, 2H), 2.38–2.50 (m, 2H), 2.26 ($^1/_2$ AB, *J*=11.4 Hz, 1H), 2.0 (m, 2H), 1.80–1.86 (m, 2H), 1.65 (1H, m), 1.54–1.66 (m, 1H), 1.43 (d, *J*=6.5 Hz, 3H), 0.86 (s, 9H), 0.09 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=208.1 (s), 176.1 (s), 157.8 (s), 139.1 (s), 135.4 (d), 134.0 (d), 124.6 (s), 117.0 (t), 114.6 (d), 110.3 (d), 93.1 (s), 75.4 (d), 60.1 (s), 55.3 (q), 53.0 (d), 51.2 (d), 44.5 (d), 43.6 (d), 36.2 (t), 31.8 (t), 30.6 (t), 28.1



Scheme 10. Partial hydrolysis of the DAG moieties of steroids **29**–**31**.

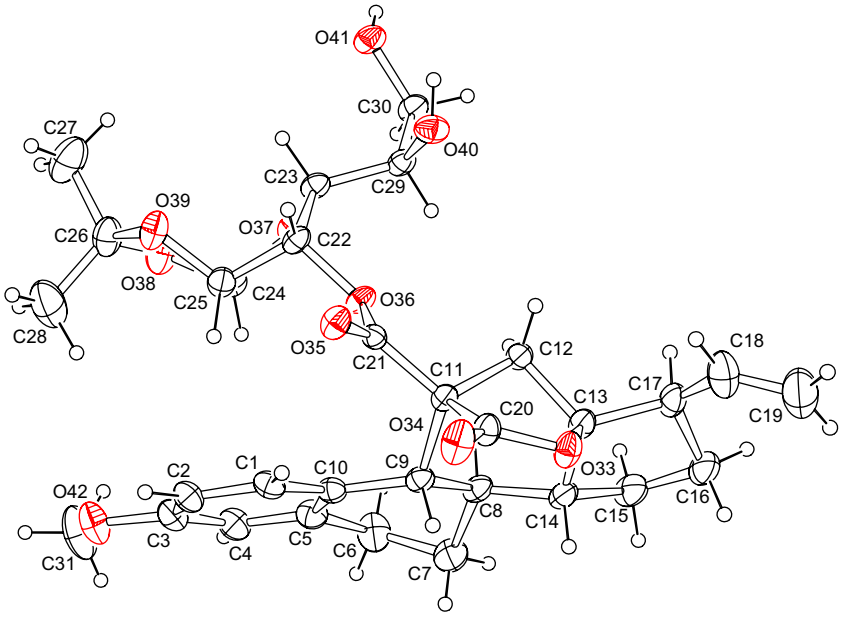
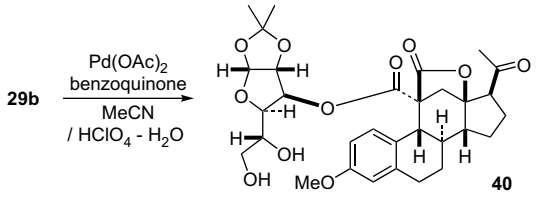


Figure 9. ORTEP diagram of compound **37**.



Scheme 11. Wacker-type oxidation of the vinyl group of **29b**.

(t), 26.5 (t), 25.9 (q)(3C), 21.4 (q), 18.1 (s), −4.1 (q), −5.0 (q) ppm. $C_{30}H_{42}O_5Si$ (510.7): C 70.55, H 8.29; found C 70.48, H 8.21.

4.7. General procedure for the deprotection of alcohols by HF–pyridine

To a stirred solution of 1 mmol of *O*-TBDMS-steroid in THF (15 mL/mmol) at 0 °C was slowly added HF–pyridine solution (1.3 mL/mmol). Then, the solution was stirred at room temperature and the progress of the reaction was followed by TLC analysis. The reaction mixture was quenched with water and diluted with Et_2O. $NaHCO_3$ saturated solution was added to this stirred mixture until neutrality. After extraction with Et_2O, the organic extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was flash chromatographed on silica gel (petroleum ether/AcOEt 80:20).

*4.7.1. (8β,9α,14α)-13α-Hydroxy-[11β-(2(S)-hydroxypropanoyl)-11α-carboxylic acid-γ-lactone]-2-methoxy-17α-vinylgona-1,3,5(10)-triene (**9a**)*

From **5a**: 60% yield after 4.5 days of stirring. White crystals, mp 171 °C, $[\alpha]_D^{20}$ 188 (*c* 0.13, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.95 (d, *J*=8.4 Hz, 1H), 6.60 (dd, *J*=8.4, 2.3 Hz, 1H), 6.41 (d, *J*=1.9 Hz, 1H), 5.87 (ddd, *J*=17.3, 10.2, 8.2, Hz, 1H), 5.08 (br d, *J*=10.3 Hz, 1H), 4.99 (br d, *J*=17.2 Hz, 1H), 4.75 (q, *J*=7.0 Hz, 1H), 3.68 (s, 3H), 3.57 (d, *J*=10.4 Hz, 1H), 2.58–2.80 (m, 2H), 2.12 ($^1/_2$ AB, *J*=14.3 Hz, 1H), 2.0–2.22 (m, 2H), 1.84 ($^1/_2$ AB, *J*=14.6 Hz, 1H), 1.76–1.92 (m, 1H), 1.74 (td, *J*=6.4, 1.2 Hz, 1H), 1.68 ($^1/_2$ AB, d, *J*=11.9, 5.9 Hz, 1H), 1.21 (d, *J*=7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=211.6 (s), 180.2 (s), 157.9 (s), 137.6 (d), 136.2 (s), 131.1 (s), 130.8 (d), 116.3 (t), 112.2 (d), 111.8 (d), 80.4 (d), 79.6 (s), 56.4 (d), 56.3 (d), 55.2 (q), 53.2 (s), 44.5 (d), 41.6 (t), 38.6 (d), 30.4 (t), 30.2 (t), 29.4 (t), 28.1 (t), 14.7 (q) ppm. $C_{24}H_{28}O_5$ (396.5): C 72.70, H 7.12; found C 72.85, H 7.08.

*4.7.2. (8β,9β,14α)-13α-Hydroxy-[11β-(2(S)-hydroxypropanoyl)-11α-carboxylic acid-γ-lactone]-2-methoxy-17α-vinylgona-1,3,5(10)-triene (**10a**)*

From **6a**: 49% yield after 24 h of stirring. White crystals, mp 171 °C, $[\alpha]_D^{20}$ 46 (*c* 0.11, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.99 (d, *J*=8.4 Hz, 1H), 6.61 (dd, *J*=8.4, 2.5 Hz, 1H), 6.04 (d, *J*=2.4 Hz, 1H), 5.89 (ddd, *J*=17.0, 10.6, 8.2 Hz, 1H), 5.00–5.09 (m, 2H), 3.86 (d, *J*=8.2 Hz, 1H), 3.66 (s, 3H), 2.83 (ddd, *J*=15.8, 11.8, 3.8 Hz, 1H), 2.39–2.50 (m, 2H), 2.09–2.19 (m, 3H), 2.06 ($^1/_2$ AB, *J*=14.3 Hz, 1H), 1.80–1.90 (m, 2H), 1.80 ($^1/_2$ AB, *J*=14.4 Hz, 1H), 1.70–1.77 (m, 2H), 1.61 (d, *J*=7.0 Hz, 3H), 1.31–1.45 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=212.7 (s), 176.2 (s), 157.9 (s), 136.9 (d), 135.1 (s), 131.2 (s), 130.5 (d), 116.8 (t), 113.4 (d), 111.1 (d), 84.0 (d), 79.6 (s), 56.0 (d), 55.4 (q), 47.5 (d), 42.4 (d), 40.6 (t), 36.6 (d), 29.8 (t), 29.3 (t), 25.3 (t), 24.3 (t), 16.1 (q) ppm. $C_{24}H_{28}O_5$ (396.5): C 72.70, H 7.12; found C 72.75, H 7.24.

*4.7.3. (8α,9β,14β)-13β-Hydroxy-[11α-(2(S)-hydroxypropanoyl)-11β-carboxylic acid-γ-lactone]-2-methoxy-17β-vinylgona-1,3,5(10)-triene (**11**)*

From **7**: 41% yield after 2.5 days of stirring. White crystals, mp 171 °C, $[\alpha]_D^{20}$ −237 (*c* 0.24, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.96 (d, *J*=8.4 Hz, 1H), 6.64 (dd, *J*=8.4, 2.4 Hz, 1H), 6.56 (d, *J*=2.13 Hz, 1H), 5.93 (ddd, *J*=17.3, 10.2, 8.2 Hz, 1H), 5.07 (dd, *J*=10.2, 1.6 Hz, 1H), 5.0 (d, *J*=17.3 Hz, 1H), 4.28 (q, *J*=7.1 Hz, 1H), 3.69 (s, 3H), 3.60 (d, *J*=10.1 Hz, 1H), 3.32 (s, OH, 1H), 2.58–2.66 (m, 2H), 2.10–2.19 (m, 2H), 1.98–2.03 (m, 1H), 1.99 ($^1/_2$ AB, *J*=14.3 Hz, 1H), 1.87 ($^1/_2$ AB, *J*=14.8 Hz, 1H), 1.82–1.88 (m, 2H), 1.77 (quint, *J*=6.0 Hz, 1H), 1.67 (qd, *J*=12.1, 5.8 Hz, 1H), 1.38 (d, *J*=7.1 Hz, 3H), 1.19–1.24 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=212.0 (s), 181.1 (s), 158.1 (s), 137.9 (d), 135.2 (s), 131.5 (d), 131.03 (s), 116.0 (t), 113.1 (d), 110.7 (d), 82.3 (d), 79.0 (s), 56.8 (d), 56.4 (d), 55.3 (q), 52.4 (s), 46.6 (d), 41.1 (t), 38.2 (d), 30.6 (t)(2C), 29.5 (t), 27.8 (t), 17.0 (q) ppm. $C_{24}H_{28}O_5$ (396.5): C 72.70, H 7.12; found C 72.88, H 7.18.

*4.7.4. (8β,9α,14α)-13α-Hydroxy-[11β-(2(S)-hydroxypropanoyl)-11-α-carboxylic acid-γ-lactone]-3-methoxy-17α-vinylgona-1,3,5(10)-triene (**9b**)*

From **5b**: 45% yield after 24 h of stirring. White crystals, mp 165 °C, $[\alpha]_D^{20}$ 143.8 (*c* 0.24, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.80 (d, *J*=9.4 Hz, 1H), 6.59 (d, *J*=9.4 Hz, 1H), 6.58 (s, 1H), 5.90 (ddd, *J*=17.3, 10.2, 8.1 Hz, 1H), 5.08 (dd, *J*=10.2, 1.9 Hz, 1H), 4.98 (br dt, *J*=17.3, 0.9 Hz, 1H), 4.73 (q, *J*=7.0 Hz, 1H), 3.72 (s, 3H), 3.56 (d, *J*=10.7 Hz, 1H), 2.86 (s, OH, 1H), 2.66 (dt, *J*=16.1, 2.1 Hz, 1H), 2.70 (dt, *J*=14.3, 2.5 Hz, 2H), 2.12 ($^1/_2$ AB, *J*=14.4 Hz, 1H), 1.98–2.22 (m, 2H), 1.90 (dd, *J*=11.3, 2.7 Hz, 1H), 1.84 ($^1/_2$ AB, *J*=14.4 Hz, 1H), 1.64–1.84 (m, 3H), 1.20–1.30 (m, 2H), 1.19 (d, *J*=7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=211.9 (s), 180.4 (s), 158.0 (s), 140.7 (s), 137.6 (d), 127.6 (d), 127.4 (s), 116.5 (t), 114.4 (d), 112.5 (d), 80.5 (d), 79.6 (s), 56.5 (d), 56.3 (d), 55.3 (q), 53.2 (s), 43.9 (d), 41.6 (t), 38.8 (d), 30.7 (t), 30.4 (t), 30.3 (t), 27.9 (t), 15.0 (q) ppm. $C_{24}H_{28}O_5$ (396.5): C 72.70, H 7.12; found C 72.59, H 7.18.

*4.7.5. (8β,9β,14α)-13α-Hydroxy-[11β-(2(S)-hydroxypropanoyl)-11α-carboxylic acid-γ-lactone]-3-methoxy-17α-vinylgona-1,3,5(10)-triene (**10b**)*

From **6b**: 82% yield after 3 days of stirring. White crystals, mp 175 °C, $[\alpha]_D^{20}$ 46.5 (*c* 1.15, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.59 (d, *J*=2.5 Hz, 1H), 6.55 (dd, *J*=8.5, 2.6 Hz, 1H), 6.42 (d, *J*=8.5 Hz, 1H), 5.89 (ddd, *J*=17.06, 10.5, 8.18 Hz, 1H), 5.07 (br d, *J*=10.4 Hz, 1H), 5.04 (br d, *J*=17.0 Hz, 1H), 4.99 (q, *J*=7.0 Hz, 1H), 3.84 (d, *J*=8.1 Hz), 3.71 (s, 3H), 2.93 (dd, *J*=11.3, 4.1 Hz, 1H), 2.87 (dd, *J*=11.3, 4.1 Hz, 1H), 2.36–2.54 (m, 2H), 2.12–2.23 (m, 3H), 2.05 ($^1/_2$ AB, *J*=14.4 Hz, 1H), 1.84–1.92 (m, 2H), 1.83 ($^1/_2$ AB, *J*=14.3 Hz, 1H), 1.65–1.77 (m, 2H), 1.55 (d, *J*=7.0 Hz, 1H), 1.32–1.39 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=212.9 (s), 176.3 (s), 158.0 (s), 140.6 (s), 137.0 (d), 128.0 (s), 127.6 (d), 116.7 (t), 114.2 (d), 112.4 (d), 79.63 (s or d), 79.58 (s or d), 56.1 (s), 55.8 (d), 55.2 (q), 47.7 (d), 42.2 (d), 39.7 (t), 36.8 (d), 29.7 (t), 29.3 (t), 25.8 (t), 25.2 (t), 16.1 (q) ppm. $C_{24}H_{28}O_5$ (396.5): C 72.70, H 7.12; found C 72.69, H 7.19.

*4.7.6. (8α,9α,14β)-13β-Hydroxy-[11α-(2(S)-hydroxypropanoyl)-11β-carboxylic acid-γ-lactone]-3-methoxy-17β-vinylgona-1,3,5(10)-triene (**12**)*

From **8**: 38% yield after 3 days of stirring. White crystals, mp 168 °C, $[\alpha]_D^{20}$ −13 (*c* 0.05, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.59 (s, 1H), 6.55 (d, *J*=2.6 Hz, 2H), 5.94 (ddd, *J*=16.9, 10.6, 8.3 Hz, 1H), 5.06 (br, *J*=10.0 Hz, 1H), 5.04 (br d, *J*=17.0 Hz, 1H), 4.69 (q, *J*=7.1 Hz, 1H), 3.76 (s, 3H), 3.68 (d, *J*=7.3 Hz, 1H), 3.24 (s, OH, 1H), 2.88 ($^1/_2$ AB, dd, *J*=16.8, 8.5, 5.2 Hz, 1H), 2.53 ($^1/_2$ AB, t, *J*=16.8, 5.8 Hz, 1H), 2.40 (quint, *J*=8.45 Hz, 1H), 2.27 (q, *J*=8.2 Hz, 1H), 2.02–2.10 (m, 1H), 1.91–1.96 (m, 1H), 1.89 (d, *J*=5.2 Hz, 2H), 1.79–1.82 (m, 2H), 1.62–1.69 (m, 2H), 1.40–1.51 (m, 1H), 1.50 (d, *J*=7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=214.5 (s), 177.7 (s), 158.4 (s), 140.4 (s), 137.9 (d), 128.0 (d), 127.0 (s), 115.9 (t), 114.3 (d), 112.5 (d), 81.7 (d), 78.4 (s), 55.5 (d), 55.2 (q), 55.1 (s), 47.6 (d), 42.2 (d), 41.0 (t), 36.5 (d), 28.92 (t), 28.83 (t), 26.7 (t), 25.0 (t), 17.9 (q) ppm. $C_{24}H_{28}O_5$ (396.5): C 72.70, H 7.12; found C 72.79, H 7.22.

4.8. General procedure for the deprotection of alcohols by tetrabutylammonium fluoride trihydrate

To a stirred solution of 1 mmol of *O*-TBDMS-steroid in THF (20 mL/mmol) at 0 °C was slowly added $(n\text{-Bu})_4NF_3\cdot H_2O$ (6 mmol/mmol). Then, the solution was stirred at room temperature and the progress of the reaction was followed by TLC analysis. The reaction mixture was quenched with water and diluted with Et_2O. The organic extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was flash chromatographed on silica gel (petroleum ether/AcOEt 60:40).

*4.8.1. (8β,9α,14α)-13α-Hydroxy-11β-(2(S)-hydroxypropanoyl)-2-methoxy-17α-vinylgona-1,3,5(10)-triene (**13**)*

From **5a**: 42% yield after 20 h of stirring. White crystals, mp 154 °C, $[\alpha]_D^{20}$ −2.6 (*c* 0.11, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.94 (d, *J*=9.0 Hz, 1H), 6.60 (br s, 1H), 6.58 (br d, *J*=9.0 Hz, 1H), 5.82 (dd, *J*=17.5, 10.4, 7.8 Hz, 1H), 5.20 (dd, *J*=10.3, 1.5 Hz, 1H), 5.09 (dd, *J*=17.3, 0.9 Hz), 4.11 (q, *J*=7.1 Hz, 1H), 3.86 (q, *J*=7.4 Hz, 1H), 3.70 (s, 3H), 3.28 (OH), 3.08 (dd, *J*=11.0, 7.4 Hz, 1H), 2.58–2.84 (m, 2H), 2.35 (dt, *J*=11.2, 7.3 Hz, 1H), 1.96–2.20 (m, 4H), 1.83 ($^1/_2$ AB, d, *J*=13.1, 7.9 Hz, 1H), 1.73–1.82 (m, 1H), 1.48–1.70 (m, 2H), 1.36 (d, *J*=7.1 Hz, 3H), 1.08–1.30 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=216.3 (s), 157.9 (s), 138.6 (d), 137.1 (s), 130.5 (d), 130.4 (s), 118.3 (t), 112.0 (d), 111.2 (d), 80.4 (s), 75.2 (d), 55.8 (d), 55.4 (d), 54.1 (q), 42.8 (d), 42.3 (d), 38.8 (d), 37.4 (t), 29.4 (t), 29.4 (t), 29.2 (t), 28.7 (t), 19.1 (q) ppm. $C_{23}H_{30}O_4$ (370.5): C 74.56, H 8.16; found C 74.68, H 8.23.

*4.8.2. (8β,9α,14α)-11α,13α-(γ-lactone)-2-methoxy-17α-vinylgona-1,3,5(10)-triene (**14**)*

From **5a**: 7% yield after 20 h of stirring.[8a]

*4.8.3. (8β,9β,14α)-13α-Hydroxy-11α-(2(S)-hydroxypropanoyl)-3-methoxy-17α-vinylgona-1,3,5(10)-triene (**15**)*

From **6b**: 52% yield after 60 h of stirring. White crystals, mp 159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.68 (d, *J*=8.1 Hz, 1H), 6.57 (br s, 1H), 6.55 (dd, *J*=8.1, 2.7 Hz, 1H), 5.80 (ddd, *J*=17.1, 10.2, 9.1 Hz, 1H), 5.16 (dd, *J*=10.2, 1.7 Hz), 5.08 (ddd, 17.1, 1.7, 0.8 Hz, 1H), 3.71 (s, 3H), 3.47 (q, *J*=7.16 Hz), 3.31 ($^1/_2$ AB, dd, *J*=11.0, 8.3, 2.9 Hz, 1H), 3.18 ($^1/_2$ AB, d, *J*=11.0, 4.4 Hz, 1H), 2.85 ($^1/_2$ AB, dd, *J*=17.2, 6.4, 2.7 Hz, 1H), 2.70 ($^1/_2$ AB, dd, *J*=17.2, 11.0, 6.5 Hz, 1H), 2.28–2.44 (m, 2H), 1.82–2.04 (m, 4H), 1.96 (d, *J*=12.1 Hz, 1H), 1.92 (d, *J*=12.1 Hz, 1H), 1.58–1.68 (m, 3H), 1.48 (br dd, *J*=13.9, 1.7 Hz, 1H), 1.22 (d, *J*=7.2 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=217. 8 (s), 158.2 (s), 139.0 (d), 137.9 (s), 130.5 (d), 129.6 (s), 117.9 (t), 114.2 (d), 111.6 (d), 78.5 (s), 74.5 (d), 55.2 (q), 54.4 (d), 48.6 (d), 44.7 (d), 39.4 (d), 38.4 (t), 36.1 (d), 29.6 (t), 27.4 (t), 26.5 (t), 25.6 (t), 19.0 (q) ppm. $C_{23}H_{30}O_4$ (370.5): C 74.56, H 8.16; found C 74.38, H 8.27.

4.9. Wacker-type oxidation of 13

To a solution of $Pd(OAc)_2$ (18 mg, 0.08 mmol) and benzoquinone (79 mg, 0.73 mmol) in 8.1 mL of acetonitrile were successively added water (1.1 mL) and 70% $HClO_4$ (0.24 mL). After 1 h of stirring, **13** (300 mg, 0.81 mmol) was added and the mixture was stirred until the disappearance of **13** (the progress of the reaction was followed by TLC analysis). The reaction mixture was diluted with Et_2O and a 30% soda solution was slowly added until neutrality. The aqueous layer was extracted with Et_2O and the organic extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was flash chromatographed on silica gel (petroleum ether/AcOEt 50:50) to give **16** (179 mg, 0.46 mmol, 58%).

*4.9.1. (8β,9α,14α)-17α-Acetyl-13α-hydroxy-11β-(2(S)-hydroxypropanoyl)-2-methoxygona-1,3,5(10)-triene (**16**)*

White crystals, mp 45–48 °C, $[\alpha]_D^{20}$ +104 (*c* 0.2, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.96 (d, *J*=8.3 Hz, 1H), 6.64 (br d, *J*=2.4 Hz, 1H), 6.62 (dd, *J*=8.3, 2.45 Hz, 1H), 4.08 (br qd, *J*=7.03, 3.27 Hz, 1H), 3.96 (s, 1H), 3.88 (q, *J*=7.00 Hz, 1H), 3.68–3.75 (m, 1H), 3.73 (s, 3H), 3.25 (br d, *J*=3.77 Hz, 1H), 3.09 (dd, *J*=11.1, 6.7 Hz, 1H), 2.85 (dd, *J*=11.3, 7.6 Hz, 1H), 2.60–2.80 (m, 2H), 2.16–2.25 (m, 2H), 2.25 ($^1/_2$ AB, *J*=16.3, 1H), 2.20 (s, 3H), 2.15 ($^1/_2$ AB, *J*=16.3, 1H), 1.90–2.11 (m, 3H), 1.40–1.48 (m, 1H), 1.35 (d, *J*=7.11 Hz, 3H), 1.1 (qd, *J*=12.3, 4.7 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=216.6 (s), 213.7 (s), 157.9 (s), 138.2 (s), 130.5 (d), 130.3 (s), 111.9 (d), 111.5 (d), 80.3 (s), 75.0 (d), 59.6 (d), 55.4 (d), 55.1 (q), 43.2 (d), 42.5 (t), 38.5 (d), 37.4 (d), 31.1 (q), 29.4 (t), 28.6 (t), 28.4 (t), 27.6 (t), 19.4 (q) ppm. $C_{23}H_{30}O_5$ (386.5): C 71.48, H 7.82; found C 71.36, H 7.92.

4.10. 3-[(*S*)-(2-*tert*-Butyldimethylsilyloxy)-2-phenylacetyl]-6,9-divinyl-1-oxa-spiro[4,4]nonan-2-one (17)

The methodology is similar to that described for the preparation of **2**, but *O*-TBDMS methyl (+)-(*S*)-mandelate (12.0 g, 43 mmol) is used instead of *O*-TBDMS methyl (+)-(*S*)-lactate to give **17** (16.2 g, 36.7 mmol, 85%) as a pink oil. ^{13}C NMR (75 MHz, $CDCl_3$) major isomer: δ=201.7 (s), 172.0 (s), 138.4 (s), 137.5 (d), 135.8 (d), 128.9 (d), 128.6 (d), 127.3 (d), 118.9 (t), 117.7 (t), 96.4 (s), 80.4 (d), 53.3 (d), 53.1 (d), 52.5 (d), 49.3 (d), 29.8 (t), 28.7 (t), 28.4 (t), 25.8 (q), 18.4 (s), −4.7 (q), −4.8 (q) ppm.

4.11. 3-[(*S*)-(2-*tert*-Butyldimethylsilyloxy)-2-phenylacetyl]-3-[5-methoxybenzocyclobuten-1-yl]-6,9-divinyl-1-oxa-spiro[4,4]nonan-2-one (18)

In a 250 mL two-neck flask equipped with a magnetic stirring bar and a pressure-equalized addition funnel was added potassium *tert*-butylate (4.04 g, 36 mmol) and KI (10 g, 60 mmol) in anhydrous DMSO (90 mL). A solution of **17** (13.2 g, 30 mmol) in anhydrous DMSO (60 mL) and then a solution of 1-iodo-5-methoxybenzocyclobutene (15.6 g, 60 mmol) in anhydrous DMSO (60 mL) were added. The content was stirred for 3 days at room temperature. The mixture was washed with water and the aqueous phases extracted with Et_2O, the organic layers were washed with brine and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was flash chromatographed on silica gel (PE/Et_2O 90:10) to give **18** (white solid, 8.6 g, 15 mmol, 50%). Major isomer, mp 132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.48–7.52 (m, 2H), 7.26–7.32 (m, 3H), 6.97 (d, *J*=8.1 Hz, 1H), 6.81 (dd, *J*=8.0, 2.2 Hz, 1H), 6.65 (d, *J*=2.0 Hz, 1H), 6.35 (s, 1H), 4.99–5.16 (m, 2H), 4.50–4.68 (m, 3H), 4.24 (dd, *J*=5.0, 2.2 Hz, 1H), 4.15 (br $^1/_2$ AB, *J*=16.7 Hz, 1H), 4.01 (dd, *J*=9.0, 3.0 Hz, 1H), 3.74 (s, 3H), 3.70 (d, *J*=5.4 Hz, 1H), 3.02 ($^1/_2$ AB, d, *J*=14.6, 5.2 Hz, 1H), 2.61 ($^1/_2$ AB, d, *J*=14.4, 1.9 Hz, 1H), 2.38 ($^1/_2$ AB, *J*=14.4 Hz, 1H), 2.23 (td, *J*=8.6, 3.7 Hz, 1H), 1.91–2.04 (m, 2H), 1.85 ($^1/_2$ AB, *J*=14.4 Hz, 1H), 1.60–1.72 (m, 2H), 1.45–1.56 (m, 1H), 1.30–1.42 (m, 1H), 0.83 (s, 9H), 0.07 (s, 3H), −0.18 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=200.1 (s), 175.0 (s), 160.0 (s), 143.4 (s), 137.9 (s), 137.2 (d), 135.2 (s), 133.5 (d), 129.0 (d)(2C), 128.4 (d), 128.3 (d)(2C), 124.4 (d), 119.0 (t), 117.3 (t), 116.4 (d), 107.9 (d), 94.7 (s), 73.0 (d), 63.8 (s), 55.7 (q), 53.0 (d), 52.5 (d), 46.1 (d), 31.6 (t), 27.7 (t), 27.4 (t), 26.8 (t), 25.8 (q)(3C), 18.2 (s), −4.3 (q), −4.8 (q) ppm.

*4.11.1. Thermolysis of **18***

From **18** (2.86 g, 5 mmol): **19** (138 mg, 0.24 mmol, 4.2%) and an inseparable mixture of **20**+**21** (1.5 g, 0.21 mmol, 52.4%), after flash chromatography (EP/AcOEt 98:2).

*4.11.1.1. (8β,9α,14β)-11β-[2(S)-2-(tert-Butyldimethylsilyloxy)-2-phenylacetyl]-11α,13α-(γ-lactone)-2-methoxy-17β-vinylgona-1,3,5(10)-triene (**19**).* Mp 75 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.44 (d, *J*=7.95 Hz, 1H), 7.27–7.32 (m, 3H), 6.98 (d, *J*=8.3 Hz, 1H), 6.65 (dd,

J=8.3, 2.2 Hz, 1H), 6.34 (d, J=1.6 Hz, 1H), 5.43 (dt, J=17.0, 9.7 Hz, 1H), 5.05 (d, J=16.9 Hz, 1H), 4.98 (dd, J=10.1, 0.75 Hz, 1H), 3.99 (d, J=5.52 Hz, 1H), 3.58 (s, 3H), 2.98 (dd, J=12.1, 1.0 Hz, 1H), 2.83 (td, J=8.7, 4.3 Hz, 1H), 2.59–2.71 (m, 2H), 2.15–2.22 (m, 1H), 1.94 ($^1/_2$ AB, J=12.1 Hz, 1H), 1.83–1.90 (m, 1H), 1.39–1.64 (m, 3H), 0.82–0.94 (m, 2H), 0.78 (9H, s), 0.04 (3H, s), −0.30 (3H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=204.1 (s), 173.7 (s), 157.8 (s), 138.7 (s), 137.6 (s), 135.3 (d), 130.9 (s), 129.6 (d), 128.6 (d), 128.4 (d)(2C), 128.2 (t), 128.1 (d)(2C), 116.8 (d), 114.5 (d), 111.7 (d), 96.1 (s), 78.4 (d), 64.8 (s), 55.2 (q), 49.1 (d), 45.7 (d), 40.7 (t), 36.6 (t), 36.4 (t), 29.8 (t), 27.1 (t), 25.9 (q)(3C), 25.7 (q), 18.1 (s), −4.3 (q), −4.9 (q) ppm. $C_{35}H_{44}O_5Si$ (572.8): C 73.39, H 7.74; found C 73.28, H 7.82.

*4.11.1.2. (8α,9β,14β)-11β-[2(S)-2-(tert-Butyldiméthylsilyloxy)-2-phenylacetyl]-11α,13α-(γ-lactone)-2-methoxy-17β-vinylgona-1,3,5(10)-triene (**20**).* In mixture with **21**. ^{1}H NMR (300 MHz, $CDCl_3$) (partial): δ=6.99 (d, J=8.2 Hz, 1H), 6.61 (dd, J=2.3 Hz, 1H), 6.32 (d, J=2.3 Hz, 1H), 5.27 (s, 1H), 5.05 (d, J=11.2 Hz, 1H), 5.00 (d, J=18.0 Hz, 1H), 3.53 (s, 3H), 3.32 (d, J=10.7 Hz, 1H), 2.20 ($^1/_2$ AB, J=12.4 Hz, 1H), 0.76 (9H, s), 0.09 (3H, s), −0.23 (3H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=204.7 (s), 176.2 (s), 157.6 (s), 141.2 (s), 138.5 (s), 135.4 (d), 129.5 (d), 128.9 (d), 128.7 (d), 128.3 (d), 116.8 (t), 112.7 (d), 110.3 (d), 92.6 (s), 80.9 (d), 59.9 (s), 55.0 (q), 52.8 (d), 51.1 (d), 46.1 (d), 42.9 (d), 37.3 (t), 31.6 (t), 30.2 (t), 27.5 (t), 27.2 (t), 25.9 (q)(3C), 18.2 (s), −4.7 (q), −4.8 (q) ppm.

4.12. Deprotection of alcohols 21 + 22 by HF–pyridine

The methodology is similar to that described for the deprotection of **5**–**8**.

4.13. (8α,9β,14β)-11β-[2(*S*)-2-Hydroxy-2-phenylacetyl]-11α,13α-(γ-lactone)-2-methoxy-17β-vinylgona-1,3,5(10)-triene (22)

White crystals in 54% yield, mp 104 °C, $[\alpha]_D^{20}$ 163 (c 0.17, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.25–7.42 (m, 5H), 7.01 (d, J=8.0 Hz, 1H), 6.69 (d, J=8.0 Hz, 1H), 6.68 (s, 1H), 5.85 (ddd, J=17.5, 10.4, 7.7 Hz, 1H), 5.20 (s, 1H), 5.01 (br dd, J=10.4, 1.6 Hz, 1H), 4.87 (br d, J=17.5 Hz, 1H), 4.87 (br d, J=17.5 Hz, 1H), 3.72 (s, 3H), 3.66 (br d, J=10.5 Hz, 1H), 2.67 (s, OH, 1H), 1.97 ($^1/_2$ AB, J=14.8 Hz, 1H), 1.76 ($^1/_2$ AB, J=14.7 Hz, 1H), 1.60–2.20 (m, 7H), 1.17 ($^1/_2$ AB, J=14.9 Hz, 1H), 1.12–1.32 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=208.3 (s), 180.8 (s), 158.3 (s), 137.5 (d), 135.4 (s), 132.6 (s), 131.5 (d), 131.2 (s), 129.2 (s), 129.1 (d)(2C), 125.2 (d)(2C), 116.3 (t), 113.3 (d), 110.5 (d), 85.8 (d), 79.1 (s), 56.2 (d), 56.1 (d), 55.3 (q), 52.2 (s), 46.6 (d), 41.2 (t), 38.3 (d), 30.3 (d), 29.5 (t), 28.0 (t) ppm. $C_{29}H_{30}O_5$ (458.5): C 75.96, H 6.59; found C 76.03, H 6.51.

4.14. (8β,9α,14α)-11β-[2(*S*)-2-Hydroxy-2-phenylacetyl]-11α,13α-(γ-lactone)-2-methoxy-17α-vinylgona-1,3,5(10)-triene (23)

White crystals in 21% yield, mp 166 °C, $[\alpha]_D^{20}$ +69 (c 0.2, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.21–7.35 (m, 5H), 6.87 (d, J=8.5 Hz, 1H), 6.41 (dd, J=8.4, 2.2 Hz, 1H), 6.36 (d, J=2.1 Hz, 1H), 5.70 (s, 1H), 5.93 (m, 1H), 4.94–5.14 (m, 4H), 3.65 (d, J=9.3 Hz, 1H), 2.63 (tt, J=12.4, 2.3 Hz, 2H), 3.39 (s, 3H), 2.77 (ddd, J=17, 5.4, 2.1 Hz, 1H), 2.29 ($^1/_2$ AB, J=13.6 Hz, 1H), 2.16–2.19 (m, 2H), 1.97 ($^1/_2$ AB, J=13.5 Hz, 1H), 1.95–2.00 (m, 1H), 1.76–1.90 (m, 3H), 1.14–1.27 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=208.3 (s), 179.7 (s), 157.9 (s), 137.6 (d), 135.7 (s), 131.0 (s), 130.8 (d), 130.6 (s), 128.8 (d), 128.5 (d)(2C), 126.5 (d)(2C), 116.7 (t), 112.4 (d), 111.5 (d), 83.7 (d), 79.9 (s), 56.7 (d), 56.4 (d), 54.8 (q), 53.6 (s), 44.4 (d), 42.5 (t), 38.8 (d), 30.5 (t), 30.3 (t), 29.5 (t), 28.2 (t) ppm. $C_{29}H_{30}O_5$ (458.5): C 75.96, H 6.59; found C 75.86, H 6.63.

4.15. 3-[5-Methoxybenzocyclobuten-1-yl]-6,9-divinyl-1-oxa-spiro[4,4]nonan-2-one (24)

The deprotection by HF–pyridine of **18b** led to **24** in 80% yield. Compound **24**: white wax. ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.97 (d, J=2.0 Hz, 1H), 6.87 (d, J=8.1 Hz, 1H), 6.77 (dd, J=8.1, 2.0 Hz, 1H), 5.92 (ddd, J=17.4, 10.2, 8.5 Hz, 1H), 5.56–5.46 (m, 2H), 5.20 (dd, J=10.2, 1.9 Hz, 1H), 5.04–5.14 (m, 4H), 3.78 (s, 3H), 3.52–3.55 (m, 1H), 3.01 ($^1/_2$ AB, d, J=14.4, 2.6 Hz, 1H), 2.91 ($^1/_2$ AB, d, J=14.5, 5.2 Hz, 1H), 2.58–2.67 (m, 2H), 2.34–2.46 (m, 3H), 2.04–2.15 (m, 2H), 1.88 (d, J=13.9 Hz, 1H), 1.64–1.77 (m, 3H), 1.48–1.65 (m, 2H), 1.15–1.26 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=178.3 (s), 159.6 (s), 145.5 (s), 139.1 (d), 138.3 (d), 135.5 (s), 135.1 (s), 128.5 (d), 126.2 (d), 123.4 (d), 123.4 (d), 117.9 (t), 117.4 (t), 115.8 (d), 109.6 (d), 96.5 (s), 86.4 (d), 56.7 (s), 55.7 (d), 53.1 (d), 51.7 (d), 42.6 (d), 33.3 (t), 32.3 (t), 28.1 (t), 27.9 (t) ppm. $C_{21}H_{24}O_3$ (324.4): C 77.75, H 7.46; found C 77.86, H 7.53.

4.16. Wacker-type oxidation of 22

The methodology is similar to that described for the oxidation of **13**.

4.17. (8α,9β,14β)-17β-Acetyl-11β-[2(*S*)-2-hydroxy-2-phenylacetyl]-11α,13α-(γ-lactone)-2-methoxygona-1,3,5(10)-triene (25)

Yield 57.4%, mp 110 °C, $[\alpha]_D^{20}$ +115 (c0.10, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.27–7.38 (m, 5H), 7.00 (d, J=8.3 Hz, 1H), 6.70 (d, J=2.5 Hz, 1H), 6.66 (br s, 1H), 5.21 (s, 1H), 3.72 (s, 3H), 3.60 (d, J=10.3 Hz, 1H), 2.65–2.70 (m, 2H), 2.50 (dd, J=11.5, 7.4 Hz, 1H), 2.30 ($^1/_2$ AB, J=14.7 Hz, 1H), 2.18–2.25 (m, 2H), 2.03 (s, 3H), 1.89 ($^1/_2$ AB, J=15.0 Hz, 1H), 1.84–2.00 (m, 2H), 1.16 ($^1/_2$ AB, J=15.0 Hz, 1H), 1.15–1.30 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=210.4 (s), 208.5 (s), 180.2 (s), 158.3 (s), 135.3 (s), 132.6 (s), 131.4 (s), 131.2 (d), 129.3 (d), 129.2 (d)(2C), 125.2 (d)(2C), 113.4 (d), 110.6 (d), 85.7 (d), 79.7 (s), 61.7 (d), 55.3 (q), 55.1 (d), 52.2 (s), 46.2 (d), 41.2 (t), 38.1 (d), 30.8 (q), 29.7 (t), 29.5 (t), 28.1 (t), 27.0 (t) ppm. $C_{29}H_{30}O_6$ (474.5): C 73.40, H 6.37; found C 73.49, H 6.41.

4.18. 3-Carboxy-6,9-divinyl-1-oxa-spiro[4,4]nonan-2-one (1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl) ester (27)

The methodology is similar to that described for the preparation of **2**, but DAG carbonate (**26**) (20.5 g, 43 mmol) is used instead of *O*-TBDMS methyl (+)-(*S*)-lactate and the reaction mixture was stirred at −20 °C for 24 h to give **27** (14.6 g, 30.5 mmol, 71%) as a white wax. ^{13}C NMR (75 MHz, $CDCl_3$) major isomer: δ=170.3 (s), 166.2 (s), 137.2 (d), 134.8 (d), 118.8 (t), 117.4 (t), 112.1 (s), 109.1 (s), 104.9 (d), 95.4 (s), 82.9 (d), 79.4 (d), 77.1 (d), 71.9 (d), 67.1 (t), 52.8 (d), 52.1 (d), 47.4 (d), 30.6 (t), 28.8 (t), 28.4 (t), 26.7 (q), 26.5 (q), 26.0 (q), 24.9 (q) ppm.

4.19. 3-Carboxy-3-(5-methoxybenzocyclobuten-1-yl)-6,9-divinyl-1-oxa-spiro[4,4]nonan-2-one (1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl) ester (28a)

In a 250 mL two-neck flask equipped with a magnetic stirring bar and a pressure-equalized addition funnel was added **27** (2.5 g, 5.2 mmol) in anhydrous acetone (31 mL), KI (1.12 g, 6.8 mmol), and cesium carbonate (2.2 g, 6.8 mmol). A solution of 1-iodo-5-methoxybenzocyclobutene (1.76 g, 6.8 mmol) in anhydrous acetone (34 mL) was added. The content was stirred at reflux for 2 days. The mixture was cooled, filtered (washing with Et_2O), and concentrated under reduced pressure. The crude

product was flash chromatographed on silica gel (PE/Et_2O 80:20) to give **28a** (white powder, 2.4 g, 3.9 mmol, 76%). ^{13}C NMR (75 MHz, $CDCl_3$) major isomer: δ=172.9 (s), 168.4 (s), 159.9 (s), 143.4 (s), 137.1 (d), 135.0 (d), 124.2 (d), 118.9 (t), 117.6 (t), 116.3 (d), 112.4 (s), 109.5 (s), 108.0 (d), 105.3 (d), 94.0 (s), 83.2 (d), 80.3 (d), 77.6 (d), 72.4 (d), 67.9 (t), 57.7 (s), 55.7 (d), 53.2 (d), 52.8 (d), 46.1 (d), 32.4 (t), 30.1 (t), 28.0 (t), 27.8 (t), 27.0 (q), 26.8 (q), 26.3 (q), 25.4 (q) ppm.

4.20. 3-Carboxy-3-(4-methoxybenzocyclobuten-1-yl)-6,9-divinyl-1-oxa-spiro[4,4]nonan-2-one (1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl) ester (28b)

The same procedure with 1-iodo-4-methoxybenzocyclobutene led to **28b** (white powder, 2.66 g, 4.35 mmol, 84%). ^{13}C NMR (75 MHz, $CDCl_3$) major isomer: δ=172.8 (s), 168.5 (s), 160.8 (s), 144.6 (s), 137.3 (d), 135.2 (d), 134.3 (d), 124.0 (d), 118.9 (t), 117.5 (t), 114.1 (d), 112.4 (s), 109.5 (s), 108.3 (d), 105.3 (d), 94.0 (s), 83.2 (d), 80.3 (d), 77.6 (d), 72.4 (d), 67.8 (t), 57.8 (s), 55.6 (d), 53.1 (d), 52.8 (d), 46.1 (d), 32.8 (t), 30.1 (t), 28.0 (t), 27.8 (t), 27.0 (q), 26.8 (q), 26.2 (q), 25.4 (q) ppm.

*4.20.1. Thermolysis of **28a***

From **28a** (2.4 g, 3.9 mmol): **29a** (984 mg, 1.61 mmol, 41.3%), **30a** (509 mg, 0.83 mmol, 21.2%), but in mixture with remaining **28a**, and **31** (312 mg, 0.51 mmol, 13.4%) after flash chromatography (EP/AcOEt 80:20).

*4.20.1.1. (8α,9β,14β)-11α-Carboxy-11β,13β-(γ-lactone)-2-methoxy-17β-vinylgona-1,3,5(10)-triene (1,2:5,6-di-O-isopropylidene-α-D-glucofuranos-3-yl) ester (**29a**).* White powder, mp=90 °C, $[\alpha]_D^{20}$ +34.4 (*c* 0.16, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ=7.01 (d, *J*=8.2 Hz, 1H), 6.63 (dd, *J*=8.2, 2.4 Hz, 1H), 6.50 (d, *J*=2.1 Hz, 1H), 5.85 (ddd, *J*=17.7, 9.6, 8.1 Hz, 1H), 5.79 (d, *J*=2.9 Hz, 1H), 5.21 (d, *J*=2.9 Hz, 1H), 5.12 (d, *J*=15.8 Hz, 1H), 5.11 (d, *J*=10.8 Hz, 1H), 4.38 (d, *J*=3.3 Hz, 1H), 4.10 (dd, *J*=7.1, 2.9 Hz, 1H), 3.85 (dd, *J*=8.3, 4.1 Hz, 1H), 3.70 (s, 3H), 3.48–3.55 (m, 2H), 3.04 ($^1/_2$ AB, *J*=11.0 Hz, 1H), 2.66–2.80 (m, 3H), 2.46 (dt, *J*=11.2, 7.6 Hz, 1H), 2.26 ($^1/_2$ AB, *J*=12.2 Hz, 1H), 2.05 (quint, *J*=6.02 Hz, 1H), 1.82–1.92 (m, 3H), 1.66 (qd, *J*=12.3, 5.5 Hz, 1H), 1.46 (s, 3H), 1.30 (s, 3H), 1.25 (s, 3H), 0.99 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=175.1 (s), 169.4 (s), 158.0 (s), 134.9 (d), 129.5 (d), 129.3 (s), 117.4 (t), 112.3 (s), 112.3 (d), 109.1 (s), 105.2 (d), 93.2 (s), 82.3 (d), 79.4 (d), 77.6 (d), 72.0 (d), 66.4 (t), 55.5 (s), 55.1 (q), 53.2 (d), 50.9 (d), 43.2 (d), 42.9 (d), 35.5 (t), 31.8 (t), 30.7 (t), 26.75 (q), 26.72 (q), 26.5 (t), 26.4 (t), 26.2 (q), 24.3 (q) ppm. $C_{34}H_{42}O_{10}$ (610.7): C 66.87, H 6.93; found C 66.95, H 7.03.

*4.20.1.2. (8α,9α,14β)-11α-Carboxy-11β,13β-(γ-lactone)-2-methoxy-17β-vinylgona-1,3,5(10)-triene (1,2:5,6-di-O-isopropylidene-α-D-glucofuranos-3-yl) ester (**31**).* White powder, mp=88 °C, $[\alpha]_D^{20}$ 50 (*c* 0.105, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ=6.9 (d, *J*=8.4 Hz, 1H), 6.76 (d, *J*=2.3 Hz, 1H), 6.62 (dd, *J*=8.4, 2.5 Hz, 1H), 5.86 (d, *J*=3.6 Hz, 1H), 5.77–5.85 (m, 1H), 5.47 (d, *J*=2.7 Hz, 1H), 5.03–5.08 (m, 2H), 4.49 (d, *J*=3.6 Hz, 1H), 4.23 (td, *J*=8.0, 2.7 Hz, 1H), 4.05 (dd, *J*=8.5, 5.8 Hz, 1H), 3.94 (dd, *J*=8.5, 4.5 Hz, 1H), 3.70 (s, 3H), 2.64–2.78 (m, 2H), 2.54 ($^1/_2$ AB, *J*=11.5 Hz, 1H), 2.39–2.55 (m, 2H), 2.38 ($^1/_2$ AB, *J*=11.5 Hz, 1H), 2.10–2.16 (m, 3H), 1.83–1.92 (m, 4H), 1.51 (s, 3H), 1.40 (s, 3H,), 1.30 (s, 3H), 1.29 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.2 (s), 170.4 (s), 157.2 (s), 135.2 (d), 133.6 (s), 129.8 (d), 128.6 (s), 117.0 (t), 115.4 (d), 113.1 (d), 112.5 (s), 109.4 (s), 105.0 (d), 91.3 (s), 83.2 (d), 80.2 (d), 77.6 (d), 71.9 (d), 67.2 (t), 57.2 (s), 55.1 (q), 51.5 (d), 45.9 (d), 41.2 (t), 40.1 (d), 34.9 (d), 31.5 (t), 30.3 (t), 26.9 (q), 26.7 (q), 26.2 (q), 25.1 (t), 24.9 (q), 23.8 (t) ppm. $C_{34}H_{42}O_{10}$ (610.7): C 66.87, H 6.93; found C 66.77, H 6.86.

*4.20.2. Thermolysis of **28b***

From **28b** (3.2 g, 5.4 mmol): **29b** (1.58 g, 2.59 mmol, 49.4%), and **30b** (620 mg, 1.04 mmol, 20%) after flash chromatography (EP/AcOEt 70:30).

*4.20.2.1. (8α,9β,14β)-11α-Carboxy-11β,13β-(γ-lactone)-3-methoxy-17β-vinylgona-1,3,5(10)-triene (1,2:5,6-di-O-isopropylidene-α-D-glucofuranos-3-yl) ester (**29b**).* White powder, mp=95 °C, $[\alpha]_D^{20}$ +11.6 (*c* 0.19, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ=6.86 (d, *J*=8.5 Hz, 1H), 6.69 (d, *J*=2.5 Hz, 1H), 6.62 (dd, *J*=8.5, 2.6 Hz, 1H), 5.87 (d, J=3.5 Hz, 1H), 5.85 (ddd, *J*=17.7, 9.5, 8.2 Hz, 1H), 5.77 (d, *J*=3.4 Hz, 1H), 5.20 (d, *J*=3.0 Hz, 1H), 5.08–5.152 (m, 2H), 4.29 (d, *J*=3.2 Hz, 1H), 4.13 (dd, *J*=6.6, 3.0 Hz, 1H), 3.83 (dd, *J*=8.3, 4.7 Hz, 1H), 3.71 (s, 3H), 3.54 (q, *J*=5.9 Hz, 1H), 3.47 (dd, *J*=8.1, 6.6 Hz, 1H), 2.99 (d, *J*=11.0 Hz, 1H), 2.70–2.78 (m, 2H), 2.65 ($^1/_2$ AB, *J*=12.2 Hz, 1H), 2.45 (dt, *J*=10.8, 7.3 Hz, 1H), 2.26 ($^1/_2$ AB, *J*=12.3 Hz, 1H), 2.01–2.07 (m, 2H), 1.84–1.94 (m, 4H), 1.66 (qd, *J*=12.2, 6.3 Hz, 1H), 1.45 (s, 3H), 1.30 (s, 3H), 1.23 (s, 3H), 0.99 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=175.2 (s), 169.3 (s), 158.1 (s), 139.2 (s), 135.0 (d), 117.4 (t), 114.7 (d), 112.3 (s), 111.1 (d), 109.0 (s), 105.2 (d), 93.2 (s), 82.4 (d), 79.5 (d), 77.7 (d), 72.3 (d), 66.3 (t), 60.4 (s), 55.5 (q), 55.2 (s), 53.2 (d), 51.0 (d), 43.4 (d), 42.3 (d), 35.7 (t), 31.8 (t), 30.5 (t), 28.0 (t), 26.8 (q), 26.7 (t), 27.0 (q), 26.2 (q), 26.1 (t), 24.6 (q) ppm. $C_{34}H_{42}O_{10}$ (610.7): C 66.87, H 6.93; found C 66.91, H 6.88.

*4.20.2.2. (8β,9α,14α)-11β-Carboxy-11α,13α-(γ-lactone)-3-methoxy-17α-vinylgona-1,3,5(10)-triene (1,2:5,6-di-O-isopropylidene-α-D-glucofuranos-3-yl) ester (**30b**).* White powder, mp=93 °C, $[\alpha]_D^{20}$ +12 (*c* 0.1, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ=7.13 (d, *J*=8.8 Hz, 1H), 6.62 (dd, *J*=8.8, 2.6 Hz, 1H), 6.51 (d, *J*=2.7 Hz, 1H), 5.87 (d, *J*=3.7 Hz, 1H), 5.77–5.86 (m, 1H), 5.57 (d, *J*=2.9 Hz, 1H), 5.05–5.13 (m, 3H), 4.47 (d, *J*=3.7 Hz, 1H), 4.34–4.41 (m, 2H), 4.27 (br d, *J*=7.4 Hz, 1H), 4.24 (dd, *J*=8.3, 3.05 Hz, 1H), 4.08 ($^1/_2$ AB, d *J*=8.6, 6.1 Hz, 1H), 3.97 ($^1/_2$ AB, d *J*=8.7, 4.5 Hz, 1H), 3.70 (s, 3H), 2.79 (quint, *J*=8.04 Hz, 2H), 2.54 ($^1/_2$ AB, *J*=11.6 Hz, 1H), 2.40–2.46 (m, 2H), 2.37 ($^1/_2$ AB, *J*=11.7 Hz, 1H), 2.09–2.24 (m, 2H), 1.84–1.90 (m, 3H), 1.64 (qd, *J*=11.9, 5.3 Hz, 1H), 1.52 (s, 3H), 1.44 (s, 3H), 1.37 (s, 3H), 1.30 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.4 (s), 170.1 (s), 157.7 (s), 137.9 (s), 135.3 (d), 131.8 (d), 124.7 (s), 117.0 (t), 113.4 (d), 112.5 (d), 112.1 (s), 109.4 (s), 105.2 (d), 91.3 (s), 83.4 (d), 80.4 (d), 77.3 (d), 72.2 (d), 67.4 (t), 57.1 (s), 55.1 (q), 51.6 (d), 45.8 (d), 41.1 (t), 39.5 (d), 35.1 (d), 31.6 (t), 30.3 (t), 27.1 (q), 26.8 (q), 26.4 (q), 25.4 (q), 25.0 (t), 24.7 (t) ppm. $C_{34}H_{42}O_{10}$ (610.7): C 66.87, H 6.93; found C 66.85, H 6.87.

4.21. Partial deprotection of steroids 29 and 30

Steroid (1 mmol) in 70% acetic acid (20 mL/mmol) was stirred at room temperature for 20 h. After concentration under reduced pressure, the crude product was flash chromatographed on silica gel (EP/AcOEt 50:50).

4.22. (8α,9β,14β)-11α-Carboxy-11β,13β-(γ-lactone)-2-methoxy-17β-vinylgona-1,3,5(10)-triene (1,2-*O*-isopropylidene-α-D-glucofuranos-3-yl) ester (32)

From **29a**: 54% yield. White powder, mp=99 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=7.11 (d, *J*=8.2 Hz, 1H), 6.71 (dd, *J*=8.2, 2.0 Hz, 1H), 6.55 (d, *J*=1.5 Hz, 1H), 5.88 (d, *J*=3.6 Hz, 1H), 5.80–5.92 (m, 1H), 5.34 (d, *J*=2.4 Hz, 1H), 5.15 (d, *J*=16.5 Hz, 1H), 5.13 (d, *J*=11.0 Hz, 1H), 4.49 (d, *J*=3.4 Hz, 1H), 4.12 (dd, *J*=7.9, 2.5 Hz, 1H), 3.73 (s, 3H), 3.34–3.52 (m, 4H), 3.05 (d, *J*=10.8 Hz, 1H), 3.03–3.06 (m, 1H), 2.78 ($^1/_2$ AB, *J*=12.0 Hz, 1H), 2.69–2.86 (m, 2H), 2.48 (dt, *J*=11.7, 7.3 Hz, 1H), 2.23 ($^1/_2$ AB, *J*=12.1 Hz, 1H), 2.00–2.10 (m, 2H), 1.80–1.96 (m, 4H), 1.68 (dd, *J*=12.5, 5.2 Hz, 1H), 1.49–1.65 (m, 3H), 1.45 (s, 3H), 1.26 (s, 3H), 1.15–1.25 (m, 2H), 0.94 (qd, *J*=12.0, 5.5 Hz,

1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=175.0 (s), 169.2 (s), 158.2 (s), 139.7 (s), 134.8 (d), 133.0 (s), 122.6 (d), 117.1 (t), 115.2 (d), 112.1 (s)(2C), 110.2 (d), 104.9 (d), 93.1 (s), 81.9 (d), 78.6 (d), 77.4 (d), 68.4 (d), 63.9 (t), 55.2 (q), 52.9 (d), 50.6 (d), 42.9 (d), 42.2 (d), 35.5 (t), 31.6 (t), 30.2 (t), 27.9 (t), 26.5 (q), 26.0 (q), 25.8 (t) ppm. $C_{31}H_{38}O_{10}$ (570.6): C 65.25, H 6.71; found C 65.16, H 6.75.

4.23. (8α,9β,14β)-11α-Carboxy-11β,13β-(γ-lactone)-2-methoxy-17β-vinylgona-1,3,5(10)-triene (5,6-*O*-isopropylidene-α-D-glucofuranos-3-yl) ester (33)

From **29a**: 10% yield. White powder, mp=99 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.05 (d, *J*=8.3 Hz, 1H), 6.72 (dd, *J*=8.3, 2.0 Hz, 1H), 6.41 (d, *J*=1.9 Hz, 1H), 5.67 (d, *J*=3.6 Hz, 1H), 5.49 (d, *J*=2.8 Hz, 1H), 5.42 (dt, *J*=17.4, 9.1 Hz, 1H), 5.08 (d, *J*=17.0 Hz, 1H), 5.01 (d, *J*=10.0 Hz, 1H), 4.98–5.09 (m, 2H), 4.59 (d, *J*=3.68 Hz, 1H), 4.31 (dd, *J*=9.0, 2.8 Hz, 1H), 4.14 (br d, *J*=4.5 Hz, 1H), 3.94–4.02 (m, 1H), 3.84 (br dd, *J*=11.2, 2.0 Hz, 1H), 3.70 (s, 3H), 3.61–3.67 (m, 2H), 2.87 (td, *J*=8.5, 4.2 Hz, 1H), 2.80 ($^1/_2$ AB, *J*=12.2 Hz, 1H), 2.66–2.70 (m, 2H), 2.08–2.23 (m, 4H), 1.87 ($^1/_2$ AB, *J*=12.2 Hz, 1H), 1.84–1.90 (m, 1H), 1.71 (dd, *J*=13.4, 4.7 Hz, 1H), 1.53–1.60 (m, 2H), 1.49 (s, 3H), 1.27 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=174.9, 169.0, 158.1, 136.8, 134.6, 130.7, 130.6, 117.4, 112.9, 112.5, 111.4, 105.3, 97.7, 82.4, 79.3, 78.6, 69.0, 64.9, 60.8, 55.4, 48.9, 44.5, 40.7, 36.3, 36.1, 31.7, 29.5, 27.1, 26.8, 26.1, 25.4, 25.0 ppm.

4.24. (8β,9α,14α)-11β-Carboxy-11α,13α-(γ-lactone)-2-methoxy-17α-vinylgona-1,3,5(10)-triene (1,2-*O*-isopropylidene-α-D-glucofuranos-3-yl) ester (34)

From **30a**: 32% yield. White powder, mp=97 °C, $[\alpha]_D^{20}$ −107 (*c* 0.2, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.06 (d, *J*=8.3 Hz, 1H), 6.63 (dd, *J*=8.3, 2.1 Hz, 1H), 6.43 (d, *J*=1.9 Hz, 1H), 5.81 (ddd, *J*=17.2, 10.0, 8.2 Hz, 1H), 5.24 (t, *J*=1.4 Hz, 1H), 5.11 (br d, *J*=17.2 Hz, 1H), 5.09 (br d, *J*=10.0 Hz, 1H), 4.93 (d, *J*=3.4 Hz, 1H), 4.62 (d, *J*=3.5 Hz, 1H), 4.18 (dd, *J*=9.0, 2.9 Hz, 2H), 3.74–3.84 (m, 1H), 3.69 (s, 3H), 3.66–3.71 (m, 1H), 3.50 (dd, *J*=11.5, 6.6 Hz, 1H), 2.91 (d, *J*=11.0 Hz, 1H), 2.78 ($^1/_2$ AB, *J*=11.7 Hz, 1H), 2.65–2.82 (m, 3H), 2.48 (dt, *J*=11.8, 7.4 Hz, 1H), 2.22 ($^1/_2$ AB, *J*=12.3 Hz, 1H), 1.92–2.02 (m, 2H), 1.80–1.94 (m, 4H), 1.63 (qd, *J*=12.3, 5.3 Hz, 1H), 1.45–1.60 (m, 2H), 1.41 (s, 3H), 1.22 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=177.2 (s), 168.9 (s), 157.2 (s), 143.1 (s), 134.5 (d), 130.0 (d), 129.5 (s), 117.6 (t), 112.1 (s), 109.1 (d), 108.5 (d), 104.9 (d), 94.8 (s), 81.1 (d), 78.9 (d), 78.4 (d), 69.2 (d), 64.4 (t), 56.0 (q), 55.2 (s), 53.3 (d), 50.6 (d), 43.1 (d), 41.9 (d), 34.7 (t), 31.7 (t), 30.8 (t), 26.5 (q), 26.1 (t), 25.8 (t), 25.6 (q) ppm. $C_{31}H_{38}O_{10}$ (570.6): C 65.25, H 6.71; found C 65.33, H 6.71.

4.25. (8β,9α,14α)-11β-Carboxy-11α,13α-(γ-lactone)-2-methoxy-17α-vinylgona-1,3,5(10)-triene (5,6-*O*-isopropylidene-α-D-glucofuranos-3-yl) ester (35)

From **30a**: 12% yield. White powder, mp=98 °C, $[\alpha]_D^{20}$ 11.4 (*c* 0.72, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.01 (d, *J*=8.3 Hz, 1H), 6.93 (d, *J*=2.3 Hz, 1H), 6.67 (dd, *J*=8.1, 2.4 Hz, 1H), 5.92 (d, *J*=3.7 Hz, 1H), 5.58 (dt, *J*=17.0, 9.6 Hz, 1H), 5.34 (d, *J*=2.6 Hz, 1H), 5.13 (br d, *J*=17.0 Hz, 1H), 5.09 (br d, *J*=9.0 Hz, H), 4.57 (d, *J*=3.6 Hz, 1H), 4.14 (dd, *J*=9.1, 2.6 Hz, 1H), 4.08 (q, *J*=7.3 Hz, 1H), 3.72 (s, 3H), 3.59–3.60 (m, 1H), 3.50 (dd, *J*=11.0, 5.3 Hz, 1H), 3.31–3.33 (m, 1H), 3.08 ($^1/_2$ AB, *J*=11.7 Hz, 1H), 2.86 (td, *J*=8.6, 3.9 Hz, 1H), 2.68–2.74 (m, 2H), 2.65 ($^1/_2$ AB, *J*=11.7 Hz, 1H), 2.16–2.28 (m, 2H), 2.09 (d, *J*=11.5 Hz, 1H), 1.84–2.04 (m, 3H), 1.52–1.80 (m, 4H), 1.47 (s, 3H), 1.28 (s, 3H), 1.20–1.26 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=169.9 (s), 169.7 (s), 157.5 (s), 138.7 (s), 137.0 (d), 130.2 (s), 128.9 (d), 117.4 (t), 112.5 (s), 111.4 (d), 105.0 (d), 93.5 (s), 82.7 (d), 78.9 (d), 77.7 (d), 68.4 (d), 64.2 (t), 55.7 (s), 55.4 (q), 50.9 (d), 48.9 (d), 45.2 (d), 44.8 (t), 40.2 (d), 29.7 (t), 27.7 (t), 26.7 (t), 26.6 (q), 26.2 (q), 26.16 (t) ppm.

4.26. (8α,9α,14β)-11α-Carboxy-11β,13β-(γ-lactone)-2-methoxy-17β-vinylgona-1,3,5(10)-triene (1,2-*O*-isopropylidene-α-D-glucofuranos-3-yl) ester (36)

From **31**: 49% yield. White powder, mp=97 °C, $[\alpha]_D^{20}$ 74 (*c* 0.53, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.87 (d, *J*=8.5 Hz, 1H), 6.66 (d, *J*=2.3 Hz, 1H), 6.59 (dd, *J*=8.5, 2.3 Hz, 1H), 5.88 (d, *J*=3.7 Hz, 1H), 5.77 (ddd, *J*=17.6, 9.5, 8.3 Hz, 1H), 5.55 (d, *J*=3.2 Hz, 1H), 5.52 (d, *J*=3.4 Hz, 1H), 5.06 (d, *J*=17.6 Hz, 1H), 5.05 (d, *J*=9.5 Hz, 1H), 4.49 (d, *J*=3.7 Hz, 1H), 4.32 (d, *J*=6.5 Hz, 1H), 3.84–3.92 (m, 1H), 3.76 (dd, *J*=11.2, 2.0 Hz, 1H), 3.65 (s, 3H), 3.64 (dd, *J*=11.2, 5.1 Hz, 1H), 2.62–2.74 (m, 1H), 2.54 ($^1/_2$ AB, *J*=11.7 Hz, 1H), 2.38–2.50 (m, 3H), 2.34 ($^1/_2$ AB, *J*=11.7 Hz, 1H), 2.02–2.20 (m, 4H), 1.80–1.90 (m, 3H), 1.65 (qd, *J*=11.9, 4.6 Hz, 1H), 1.47 (s, 3H), 1.26 (s, 3H), 1.17 (q, *J*=7.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.1 (s), 170.8 (s), 156.8 (s), 134.9 (d), 133.5 (s), 129.9 (d), 128.8 (s), 117.1 (t), 115.4 (d), 112.4 (d), 112.2 (s), 105.0 (d), 92.2 (s), 83.2 (d), 78.8 (d), 78.6 (d), 68.3 (d), 64.5 (t), 57.1 (s), 55.1 (q), 51.1 (d), 45.5 (d), 40.8 (t), 40.0 (d), 34.4 (d), 31.4 (t), 30.1 (t), 26.6 (q), 26.2 (q), 24.8 (t), 23.5 (t) ppm. $C_{31}H_{38}O_{10}$ (570.6): C 65.25, H 6.71; found C 65.32, H 6.81.

4.27. (8α,9β,14β)-11α-Carboxy-11β,13β-(γ-lactone)-3-methoxy-17β-vinylgona-1,3,5(10)-triene (1,2-*O*-isopropylidene-α-D-glucofuranos-3-yl) ester (37)

From **29b**: 54% yield. White powder, mp=103 °C, $[\alpha]_D^{20}$ 68 (*c* 0.11, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.83 (d, *J*=8.4 Hz, 1H), 6.69 (d, *J*=2.0 Hz, 1H), 6.61 (dd, *J*=8.5, 2.3 Hz, 1H), 5.80 (ddd, *J*=17.1, 10.1, 8.3 Hz, 1H), 5.70 (d, *J*=3.3 Hz, 1H), 5.15 (d, *J*=2.4 Hz, 1H), 5.07 (br d, *J*=18.0 Hz, 1H), 5.06 (br d, *J*=9.7 Hz, 1H), 4.16 (br d, *J*=2.3 Hz, 1H), 4.03 (dd, *J*=7.2, 1.1 Hz, 1H), 3.67 (s, 3H), 3.31–3.47 (m, 2H), 3.04–3.10 (m, 1H), 3.0 (d, *J*=11.0 Hz, 1H), 2.71–2.82 (m, 2H), 2.61 ($^1/_2$ AB, *J*=12.2 Hz, 1H), 2.42 (dt, *J*=11.1, 7.3 Hz, 1H), 2.23 ($^1/_2$ AB, *J*=12.2 Hz, 1H), 2.01 (q, *J*=5.6 Hz, 1H), 1.80–1.90 (m, 2H), 1.61 (qd, *J*=11.9, 5.3 Hz, 1H), 1.37 (s, 3H), 1.17 (s, 3H), 0.94 (qd, *J*=11.7, 5.4 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=175.0 (s), 169.2 (s), 158.2 (s), 139.7 (s), 134.8 (d), 133.1 (s), 122.5 (d), 117.2 (t), 115.2 (d), 112.1 (s)(2C), 110.2 (d), 105.0 (d), 93.2 (s), 81.9 (d), 78.6 (d), 77.5 (d), 68.4 (d), 63.9 (t), 55.2 (q), 52.9 (d), 50.6 (d), 43.0 (d), 42.2 (d), 35.5 (t), 31.6 (t), 30.2 (t), 27.9 (t), 26.5 (q), 26.0 (q), 25.8 (t) ppm. $C_{31}H_{38}O_{10}$ (570.6): C 65.25, H 6.71; found C 65.28, H 6.61.

4.28. (8α,9β,14β)-11α-Carboxy-11β,13β-(γ-lactone)-3-methoxy-17β-vinylgona-1,3,5(10)-triene (5,6-*O*-isopropylidene-α-D-glucofuranos-3-yl) ester (38)

From **29b**: 10% yield. White powder, mp=100 °C, $[\alpha]_D^{20}$ −98 (*c* 0.7, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.77 (d, *J*=8.4 Hz, 1H), 6.74 (d, *J*=2.5 Hz, 1H), 6.58 (dd, *J*=8.4, 2.6 Hz, 1H), 5.83 (ddd, *J*=17.0, 10.3, 8.2 Hz, 1H), 5.26 (d, *J*=3.2 Hz, 1H), 5.13 (br d, *J*=17.4 Hz, 1H), 5.12 (br d, *J*=9.5 Hz, 1H), 5.06 (d, *J*=3.6 Hz, 1H), 4.52 (d, *J*=3.6 Hz, 1H), 4.19 (dd, *J*=9.1, 3.2 Hz, 2H), 3.72 (s, 3H), 3.54 (dd, *J*=11.4, 6.5 Hz, 1H), 2.93 (d, *J*=10.7 Hz, 1H), 2.79 ($^1/_2$ AB, *J*=12.5 Hz, 1H), 2.68–2.78 (m, 2H), 2.48 (dt, *J*=12.1, 7.2 Hz, 1H), 2.21 ($^1/_2$ AB, *J*=12.2 Hz, 1H), 1.96–2.08 (m, 2H), 1.81–1.93 (m, 4H), 1.65 (qd, *J*=12.4, 5.3 Hz, 1H), 1.51–1.60 (m, 1H), 1.43 (s, 3H), 1.23 (s, 3H), 0.91 (qd, *J*=11.9, 5.3 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=177.4 (s), 169.4 (s), 158.3 (s), 139.7 (s), 134.6 (s), 134.5 (d), 120.9 (d), 117.8 (t), 115.0 (d), 112.4 (s), 109.8 (d), 105.1 (d), 95.0 (s), 81.5 (d), 79.2 (d), 78.7 (d), 69.0 (d), 64.6 (t), 56.3 (s), 55.4 (q), 53.3 (d), 50.7 (d), 44.1 (d), 41.6 (d), 34.9 (t), 31.9 (t), 30.9 (t), 27.3 (t), 26.8 (q), 26.3 (q), 25.7 (t) ppm.

Table 1
Crystal data and structure refinement for **9a**, **10a**, **11**, **9b**, **10b**, **13**, **18a**, **22**, and **37**

Compound	**9a**	**10a**	**11**	**9b**	**10b**	**13**	**18a**	**22**	**37**
Formula	$C_{24}H_{28}O_5$	$C_{48}H_{56}O_{10}$	$C_{48}H_{56}O_{10}$	$C_{24}H_{28}O_5$	$C_{24}H_{28}O_5$	$C_{46}H_{62}O_9$	$C_{35}H_{44}O_5Si$	$C_{58}H_{60}O_{10}$	$C_{32}H_{39}Cl_3O_{10}$
M_w	396.4	792.93	792.93	396.46	396.46	757.9	572.79	917.06	689.98
Crystal color	Colorless	Colorless	Colorless	Colorless	Colorless	Colorless	Colorless	Colorless	Colorless
Crystal size/mm^3	0.4×0.2×0.1	0.3×0.15×0.1	0.4×0.3×0.15	0.3×0.15×0.15	0.3×0.3×0.2	0.4×0.5×0.2	0.3×0.1×0.1	0.5×0.3×0.15	0.3×0.3×0.2
Crystal system	Orthorhombic	Monoclinic	Monoclinic	Monoclinic	Orthorhombic	Monoclinic	Orthorhombic	Monoclinic	Monoclinic
Space group	$P2_12_12_1$	$P2_1$	$P2_1$	$P2_1$	$P2_12_12_1$	$C2$	$P2_12_12_1$	$P2_1$	$P2_1$
a/Å	7.7442(1)	9.2413(2)	10.0027(2)	11.525(1)	9.3657(1)	9.4900(2)	7.815(1)	9.7235(1)	11.1904(2)
b/Å	13.1467(2)	18.2436(4)	17.7986(5)	7.7099(4)	11.9569(2)	19.0420(5)	15.934(1)	12.9429(2)	10.8096(2)
c/Å	20.5181(4)	12.7072(4)	12.4305(4)	11.905(1)	18.4932(4)	11.7460(4)	27.327(1)	19.4645(3)	14.3389(3)
β/°		96.918(1)	104.660(1)	102.137(5)		99.1130(1)		99.8867(6)	108.2357(6)
V/Å^3	2088.95(6)	2126.77(9)	2140.9(1)	1034.2(1)	2070.96(6)	2095.81(1)	3402.9(5)	2413.23(6)	1647.38(5)
Z	4	2	2	2	4	2	4	2	2
D_c/g cm^{-3}	1.261	1.238	1.23	1.273	1.272	1.199	1.118	1.26	1.391
μ(Mo Kα)/cm^{-1}	0.87	0.86	8.5	0.88	0.88	0.82	1.06	0.85	3.34
No. of unique data	2279	4051	4086	2090	2136	4408	4522	6484	3145
No. of param. refined	263	523	527	265	262	250	371	617	411
R [$I>2\sigma(I)$]	0.046 [2099]	0.069 [3557]	0.049 [3383]	0.052 [1678]	0.040 [1994]	0.066 [3941]	0.084 [2816]	0.060 [4535]	0.040 [3005]
wR [unique]	0.164[a]	0.188[b]	0.1279[c]	0.120[d]	0.115[e]	0.159[f]	0.222[g]	0.198[h]	0.132[i]
Goodness of fit	1.211	1.107	1.082	1.080	1.075	1.075	1.035	1.124	1.186
Min; max $\Delta\rho$/e Å^{-3}	−0.265; 0.258	−0.296; 0.048	−0.148; 0.026	−0.157; 0.038	−0.150; 0.024	−0.134; 0.026	−0.326; 0.292	−0.607;0.491	−0.387; 0.101

$w=1/[\sigma^2(F_o^2)+(AP)^2+BP]$ where $P=(F_o^2+2F_c^2)/3$.
[a] A=0.1053; B=0.2277.
[b] A=0.1001; B=0.9663.
[c] A=0.0555; B=0.4268.
[d] A=0.0378; B=0.4773.
[e] A=0.0741; B=0.1601.
[f] A=0.0629; B=0.9709.
[g] A=0.0925; B=1.1158.
[h] A=0.1261; B=0.0.
[i] A=0.0819; B=0.3179.

4.29. (8β,9α,14α)-11β-Carboxy-11α,13α-(γ-lactone)-3-methoxy-17α-vinylgona-1,3,5(10)-triene (1,2-*O*-isopropylidene-α-D-glucofuranos-3-yl) ester (39)

From **30b**: 45% yield. White powder, mp=104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.96 (d, J=8.8 Hz, 1H), 6.61 (dd, J=8.8, 2.6 Hz, 1H), 6.51 (d, J=2.6 Hz, 1H), 5.91 (d, J=3.6 Hz, 1H), 5.81 (ddd, J=17.2, 9.5, 8.4 Hz, 1H), 5.48 (d, J=3.5 Hz), 5.10 (br d, J=10.0 Hz, 1H), 5.09 (br d, J=16.4, 1H), 4.52 (d, J=3.6 Hz, 1H), 4.38 (dd, J=8.7, 3.5 Hz, 1H), 4.34 (d, J=6.9 Hz, 1H), 3.76–3.79 (m, 1H), 3.72 (d, J=2.8 Hz, 1H), 3.70 (s, 3H), 2.70–2.84 (m, 3H), 2.56 ($^1/_2$ AB, J=11.5 Hz, 1H), 2.44–2.50 (m, 2H), 2.38 ($^1/_2$ AB, J=11.5 Hz, 1H), 2.08–2.24 (m, 3H), 1.82–1.94 (m, 3H), 1.64 (qd, J=11.6, 4.7 Hz, 1H), 1.50 (s, 3H), 1.29 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=174.0 (s), 171.1 (s), 157.9 (s), 138.1 (s), 134.9 (d), 131.2 (d), 124.6 (s), 117.4 (t), 113.9 (d), 112.5 (s), 112.0 (d), 105.3 (d), 92.7 (s), 83.5 (d), 79.4 (d), 79.0 (d), 68.8 (d), 64.6 (t), 57.7 (s), 55.2 (q), 51.5 (d), 45.6 (d), 40.9 (t), 39.3 (d), 34.9 (d), 31.6 (t), 30.3 (t), 26.8 (q), 26.5 (q), 24.9 (t), 24.7 (t) ppm. $C_{31}H_{38}O_{10}$ (570.6): C 65.25, H 6.71; found C 65.18, H 6.68.

4.30. Wacker-type oxidation of 29b

The methodology is similar to that described for the oxidation of **13**.

4.31. (8α,9β,14β)-17β-Acetyl-11α-carboxy-11β,13β-(γ-lactone)-3-methoxygona-1,3,5(10)-triene (1,2-*O*-isopropylidene-α-D-glucofuranos-3-yl) ester (40)

Yield 20%. ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.88 (d, J=8.4 Hz, 1H), 6.76 (d, J=2.5 Hz, 1H), 6.67 (dd, J=8.4, 2.7 Hz, 1H), 5.80 (d, J=3.6 Hz, 1H), 5.28 (s, 2H), 5.20 (d, J=2.8 Hz, 1H), 4.23 (d, J=3.1 Hz, 1H), 4.11 (dd, J=8.67, 2.83 Hz, 1H), 3.74 (s, 3H), 3.52 ($^1/_2$ AB, J=11.5, 3.5 Hz, 1H), 3.42 ($^1/_2$ AB, J=11.5, 5.9 Hz, 1H), 3.13 (tt, J=5.3, 3.7 Hz, 1H), 3.07 (d, J=11.2 Hz, 1H), 2.93 (d, J=7.6 Hz, 1H), 2.70–2.80 (m, 2H), 2.48 (d, J=12.3 Hz, 1H), 2.25 (s, 3H), 2.13–2.20 (m, 2H), 1.98 (td, J=11.2, 6.8 Hz, 1H), 1.84–1.92 (m, 2H), 1.48–1.59 (m, 2H), 1.45 (s, 3H), 1.24 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=203.3 (s), 173.1 (s), 168.2 (s), 157.7 (s), 152.5 (s), 139.0 (s), 114.6 (d), 111.5 (s), 109.4 (d), 104.2 (d), 91.2 (s), 81.2 (d), 78.1 (d), 77.0 (d), 67.6 (d), 63.3 (t), 56.8 (d), 54.6 (q), 54.5 (d), 52.6 (s), 51.6 (d), 42.4 (d), 41.1 (d), 35.8 (t), 29.9 (q), 29.0 (t), 27.1 (t), 26.1 (t), 25.8 (q), 25.2 (q), 25.1 (t) ppm. $C_{31}H_{38}O_{11}$ (586.6): C 63.47, H 6.53; found C 63.38, H 6.58.

4.32. X-ray crystallography

CCDC-686694 (for **9a**), CCDC-686695 (for **10a**), CCDC-686692 (for **11**), CCDC-686693 (for **9b**), CCDC-686696 (for **10b**), CCDC-686689 (for **13**), CCDC-686690 (for **18a**), CCDC-686691 (for **22**), and CCDC-686697 (for **37**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk]. A summary of the crystal data, data collection, and refinements is given in Table 1.

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