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PAPER

Stereoselective rearrangement of guaianolides to tricyclic δ-valerolactones†

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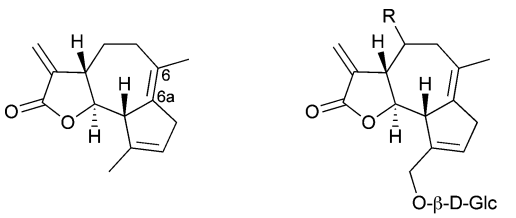
An unprecedented, highly stereoselective rearrangement of guaianolides, bearing a double bond at the C-6/C-6a position, to tricyclic δ-valerolactones is described.

Introduction

The 5,7,5-tricyclic guaianolide framework with a *trans*-annulated γ-butyrolactone moiety is widely occurring in nature.[1] Due to their broad range of biological activities, being mainly manifested in the *exo*-methylene group on the lactone moiety[2] as a potent acceptor for biological nucleophiles, guaianolides have attracted great interest as synthetic targets, and are also available from nature in considerable quantities.[3]

A common structural feature of the guaianolide family is the presence of a C═C double bond between C-6 and C-6a within the seven membered ring. Typical examples include Kauniolide[4] (**1**), Ixerin Y (**2a**) and Ixerin X (**2b**),[5] which were isolated from the aerial parts of *Kaunia arbuscularis* and *Ixeris denticulata f. pinnatipartita* and *Ixeris sonchifolia*, respectively (Fig. 1). During our ongoing studies towards the total synthesis of biologically active guaianolides,[6] we discovered an unprecedented, stereoselective rearrangement of the title compounds, giving access to highly functionalized tricyclic δ-valerolactones that appear to be promising as novel scaffolds in organic synthesis as well as for biological studies.



Kauniolide (**1**)

R = α-OH: Ixerin Y (**2a**)
R = β-OH: Ixerin X (**2b**)

Fig. 1 Representative examples of the guaianolide family.

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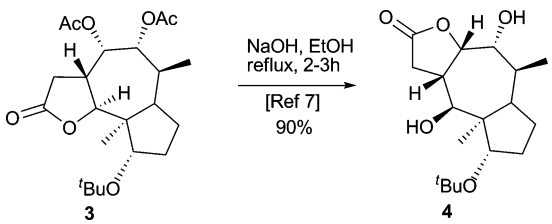
† Electronic supplementary information (ESI) available: Experimental procedures, ^{1}H and ^{13}C NMR spectra. CCDC reference numbers 798357–798361. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00919a

Results and discussion

The *trans*-annulated γ-butyrolactone in the guaianolide framework exhibits considerable ring strain, which causes its facile hydrolysis with concurrent ring opening under hydrolytic conditions (Scheme 1).[7]

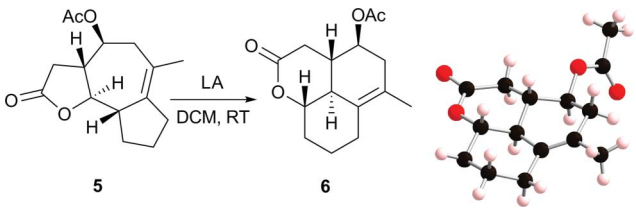


3 **4**

Scheme 1 Hydrolytic lactone opening and lactonisation.

We questioned if the inherent ring strain of the system would also be sufficient to provoke a reaction by catalysis with Lewis acids, which have been proven to initiate a great variety of skeletal transformations[8] in organic synthesis, such as pinacol rearrangements,[9] Claisen rearrangements,[10] zip-like construction of annulated rings[11] and rearrangements of O-glycoside to C-glycosides.[12]

We started our investigation by treating readily available **5**[6] with a variety of Lewis acids. While no reaction was observed with $SnCl_2$, $SbCl_3$ and $MnCl_2$, decomposition of the starting material occurred upon exposure of **5** to $TiCl_4$. Gratifyingly, a number of other Lewis acids resulted in a smooth conversion of **5** to give rise to the tricyclic 6,6,6-valerolactone **6** (Scheme 2, Table 1).



5 **6**

Scheme 2 Lewis acid catalyzed rearrangement of **5** to δ-lactone **6**.

Table 1 Screening of different Lewis acids with **5**[a]

Entry	Lewis acid	Yield (%)[b]
1	$TiCl_4$	Decomposition
2	$SbCl_3$	No reaction
3	$MnCl_2$	No reaction
4	$SnCl_2$	No reaction
5	$ZnBr_2$	37
6	PCl_3	39
7	$AlCl_3$	56
8	$FeCl_3$	66
9	$SnCl_4$	70
10	$Bi(OTf)_3$	80

[a] Lewis acid (0.25 equiv), 48 h, room temp, DCM. [b] Isolated yields.

$Bi(OTf)_3$, which has previously been applied successfully in other rearrangement reactions,[13] was found to be especially suitable to give rise to **6** as a single stereoisomer in 80% yield.

Also, $FeCl_3$ and $SnCl_4$ initiated the rearrangement with good, albeit with slightly lower yields.

To investigate the scope and limitation of this novel rearrangement and to elucidate the reaction mechanism, several other compounds containing the guaianolide framework were investigated (Table 2). Along with the 5,7,6-guaianolide analogue **15**, the structures of **6**, **10**, **14**, and **16** were unambiguously established by X-ray analysis, showing the formation of a 6,6,6- or 6,6,7-tricyclic skeleton in the most stable, all equatorial arrangement on the ring junctions.

As a key structural element for the rearrangement of the guaianolide ring structure, the C=C double bond between C-6 and C-6a[14] was identified (Scheme 4). The corresponding hydrogenated analogues **17a** and **17b** gave no conversion, while the epoxidized analogues **18a** and **18b** resulted in decomposition upon treatment with Lewis acids (Fig. 2). Protection of the C-4 hydroxyl group is advantageous in avoiding translactonisation as a side reaction along the lines reported for the basic hydrolysis of such compounds (*cf.* Scheme 1).[7]

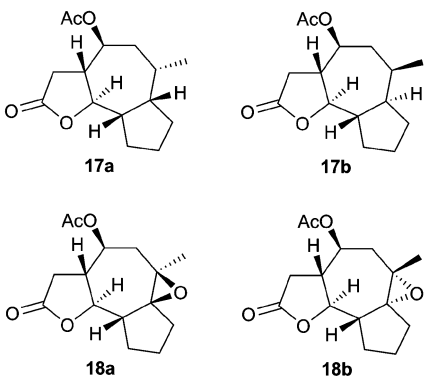
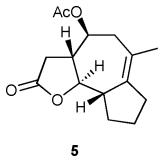
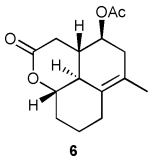
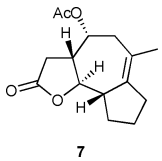
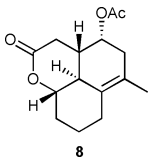
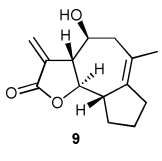
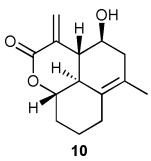
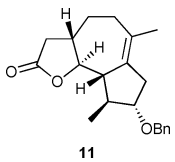
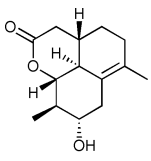
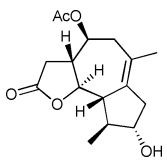
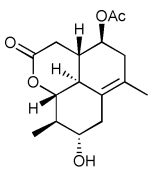
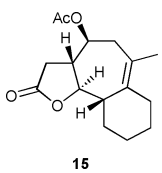
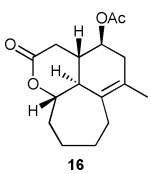


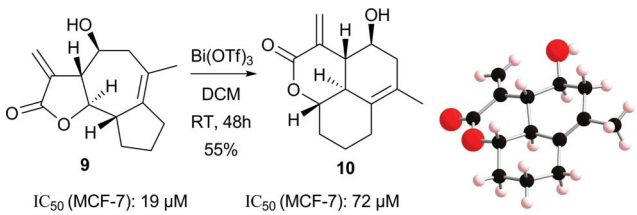
Fig. 2 Guaianolides that do not undergo the title rearrangement.

Remarkably, the highly reactive *exo*-methylene group on the lactone ring, representing a key feature in many guaianolide natural products (*cf.* Fig. 1), is also tolerated during the rearrangement, even with an unprotected hydroxyl group at C-4. Thus, **9** could be converted in the *exo*-methylene substituted δ-lactone **10** with no observable side reactions such as conjugate addition or translactonisation (Scheme 3).

Table 2 Lewis acid catalyzed rearrangements of guaianolides[a]

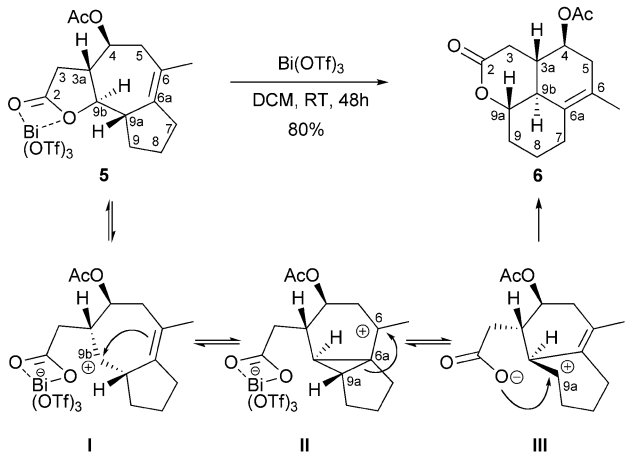
Entry	Substrate	Product	Yield (%)[b]
1	 **5**	 **6**	80
2	 **7**	 **8**	78
3	 **9**	 **10**	55
4	 **11**	 **12**	71[c]
5	 **13**	 **14**	75[d]
6	 **15**	 **16**	57

[a] $Bi(OTf)_3$ (0.25 equiv), 48 h, room temp, DCM. [b] Isolated yields. [c] $FeCl_3$ (5.0 equiv, 24 h, 0 °C, DCM). [d] $Bi(OTf)_3$ (0.3 equiv), 72 h.



Scheme 3 Rearrangement of the *exo*-methylene substituted guaianolide **9** to δ-lactone **10**.

9 exhibits cytotoxicity against human breast cancer cell lines (MCF-7, see ESI†) in the typical range of *exo*-methylene substituted guaianolides (IC_{50}: 19 μM). However, the cytotoxicity of the 6,6,6 membered δ-valerolactone **10** is about four times lower



Scheme 4 Proposed reaction mechanism for the conversion of guaianolides to tricyclic δ-valerolactones.

(IC_{50}: 72 μM), indicating a less pronounced acceptor quality against biological nucleophiles in *exo*-methylene substituted δ-lactones.

Taking all these results into consideration, we propose the following mechanism encompassing two successive homoallyl-cyclopropymethyl carbocation rearrangements[15] (Scheme 4): Lewis acid activation causes ring opening of the lactone. The resulting secondary carbocation **I** undergoes stereoselective attack by the homoallylic double bond to form the highly strained but electronically stabilized tertiary cyclopropyl substituted carbocation **II**.[16] Opening of the cyclopropyl moiety between C-6a and C-9a to **III** followed by stereoselective addition of the lactone oxygen onto C-9a concludes the formation of **6**. It should be noted that the rearrangement occurs with an overall inversion on C-9a and C-9b. Hence, a concerted mechanism rather than postulated discrete intermediates **I–III** would also be in agreement with the products observed.

Conclusions

In conclusion we discovered a rearrangement, converting the naturally occurring 5,7,5 tricyclic guaianolide ring system stereoselectively to a novel tricyclic 6,6,6 δ-valerolactone framework. This reaction can be catalyzed by various Lewis acids, with $Bi(OTf)_3$ being the most favorable.

Experimental

Anhydrous dichloromethane was taken from the MB-SPS solvent purification system. Ethyl acetate and hexanes (40–60 °C) were purified by distillation before use. All reagents were of p.a. quality. Reactions were performed in oven dried and *in vacuo* heated reaction flasks under a predried inert gas (nitrogen or argon) atmosphere. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300, and a Bruker Avance 600 Kryo, with a H/C/P/F QNP gradient probe. The chemical shift δ is given in ppm. Calibration was set on chloroform-d_1 as the internal standard (7.26 ppm for ^1H and 77.00 ppm for ^{13}C). The spectra were evaluated in 1st order and the coupling constants are given in hertz (Hz).[17] Melting points were measured on a Büchi SMP 20 in a silicon oil bath. The melting points are uncorrected. Infrared-spectra were recorded on a Biorad FT-IR Excalibur FTS 3000. Masspectrometry was performed on Varian MAT 311A, Finnigan MAT 95, Thermoquest Finnigan TSQ 7000, Nermag quadrupoles, VG ZAB high-resolution double-focusing and VG Autospec-Q tandem hybrid with EBEqQ configuration. Optical rotation was measured on a 241 MC Perkin–Elmer polarimeter at a wavelength of 589 nm (Na-D) in a 10 cm cell and the $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. X-ray analysis was performed by the crystallography laboratory of the University of Regensburg (STOE-IPDS, Stoe & Cie GmbH).

(3a*S*,4*S*,9a*S*,9b*S*)-6-methyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydrobenzo[*de*]chromen-4-yl acetate (6)

5 (100 mg, 0.378 mmol, 1 equiv) was dissolved under a nitrogen atmosphere in anhydrous CH_2Cl_2 (5 cm^3) in a flame dried Schlenk flask. Bismuth triflate (62 mg, 0.095 mmol, 0.25 equiv) was added in one portion at room temperature and stirred for 48 h. After completion, the reaction mixture was quenched with aqueous $NaHCO_3$ solution (1 cm^3) and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtrated and the solvent was removed under reduced pressure. Chromatography on flash silica gel (hexanes : ethyl acetate 3 : 1) yielded **6** (80 mg, 80%) as a white solid. **6** gave upon crystallization in a *n*-pentane–CH_2Cl_2 mixture at 5 °C crystals, which were suitable for X-ray analysis.

R_f 0.43 (hexanes : ethyl acetate 2 : 1, Mostain); $[\alpha]_D^{20}$ +227.8 (*c* 1.00 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 1.22–1.40 (1 H, m, 8-H), 1.53 (1 H, ddd, *J* 3.7, 12.7 and 16.0, 9-H), 1.64 (3 H, s, CH_3), 1.69 (1 H, t, *J* 13.6 Hz, 7-H), 1.83–1.89 (1 H, m, 8-H), 1.96–2.02 (1 H, m, 9b-H), 2.02–2.05 (1 H, m, 3a-H), 2.05 (3 H, s, OAc), 2.07–2.12 (1 H, m, 5-H), 2.11–2.17 (1 H, m, 9-H), 2.30 (1 H, dd, *J* 11.8 and 18.3, 3-H), 2.41 (1 H, dd, *J* 5.6 and 16.7, 5-H), 2.66 (1 H, d, *J* 14.9, 7-H), 2.90 (1 H, dd, *J* 5.1 and 18.3, 3-H), 3.91 (1 H, ddd, *J* 4.3, 10.0 and 11.5 Hz, 9a-H), 4.71 (1 H, dt, *J* 5.8, 10.2 and 10.4, 4-H); δ_C (75.5 MHz; $CDCl_3$) 18.87 (+, CH_3), 21.02 (+, $COOCH_3$), 22.73 (–, C-8), 27.06 (–, C-7), 31.73 (–, C-9), 34.51 (–, C-3), 37.39 (–, C-5), 38.97 (+, C-3a), 45.49 (+, C-9b), 72.10 (+, C-4), 83.77 (+, C-9a), 125.49 (C_q, C-6), 126.12 (C_q, C-6a), 169.95 (C_q, C-2), 170.70 (C_q, CH_3COOC-4); ν_{max}(neat)/cm^{-1} 2970, 2922, 2862, 1723, 1452, 1363, 1240, 1033; *m*/*z* (EI) 205.1 (15%) [M^+ – H_3CO], 204.1 (100) [M^+ – HAc], 162.1 (66), 132.1 (77), 118.1 (74); *m*/*z* (LSIMS): 265.1435 [MH^+ $C_{15}H_{21}O_4$ requires 265.1440].

(3a*S*,4*R*,9a*S*,9b*S*)-6-methyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydrobenzo[*de*]chromen-4-yl acetate (8)

R_f 0.32 (hexanes : ethyl acetate 2 : 1, Mostain); δ_H (300 MHz; $CDCl_3$) 1.20–1.37 (1 H, m, 8-H), 1.50–1.61 (1 H, m, 9-H), 1.63 (3 H, s, CH_3), 1.68–1.83 (1 H, m, 7-H), 1.83–1.94 (1 H, m, 8-H), 1.95–2.10 (2 H, m, 9b-H and 2a-H), 2.04 (3 H, s, CH_3), 2.10–2.16 (1 H, m, 5-H), 2.16–2.21 (1 H, m, 9-H), 2.40 (1 H, dd, *J* 3.2 and 18.9, 5-H), 2.46 (1 H, dd, *J* 11.9 and 18.3, 3-H), 2.62–2.74 (1 H, m, 7-H), 2.67 (1 H, dd, *J* 5.4 and 18.3, 3-H), 3.91 (1 H, ddd, *J* 4.3, 10.0 and 11.5, 9a-H), 4.97 (1 H, dt, *J* 1.7 and 4.0, 4-H); δ_C (75.5 MHz; $CDCl_3$) 18.92 (+, CH_3), 21.12 (+, $COOCH_3$), 22.84 (–, C-8), 27.06 (–, C-7), 31.78 (–, C-9), 33.63 (–, C-3), 36.84 (–, C-5), 36.99 (+, C-3a), 40.47 (+, C-9b), 67.85 (+, C-4), 84.08 (+, C-9a), 124.32 (C_q, C-6), 126.08 (C_q, C-6a), 170.25 (C_q, C-2), 170.94 (C_q, CH_3COOC-4).

(3a*R*,4*S*,9a*S*,9b*S*)-4-hydroxy-6-methyl-3-methylidene-3a,4,5,7,8,9,9a,9b-octahydrobenzo[*de*]chromen-2(3*H*)-one (10)

R_f 0.65 (ethyl acetate, Mostain); $[\alpha]_D^{20}$ +333.0 (*c* 1.00 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 1.20–1.36 (1 H, m, 8-H), 1.49 (1 H, ddd, *J* 3.6, 12.7 and 15.9, 9-H), 1.64 (3 H, s, CH_3), 1.68 (1 H, bs, OH), 1.78–1.88 (1 H, m, 7-H), 1.90–2.09 (2 H, m, 8-H and 9b-H), 2.11–2.24 (2 H, m, 9-H and 5-H), 2.33–2.46 (2 H, m, 5-H and 3a-H), 2.65 (1H, d, *J* 14.7, 7-H), 3.96–4.05 (1 H, m, 4-H), 3.91 (1 H, ddd, *J* 4.3, 10.0 and 11.5, 9a-H), 6.38 (1 H, m, =C-H), 6.49 (1 H, m, =C-H); δ_C (75.5 MHz; $CDCl_3$) 18.79 (+, CH_3), 22.68 (–, C-8), 27.13 (–, C-7), 32.10 (–, C-9), 42.19 (–, C-5), 46.13 (+, C-3a), 46.54 (+, C-9b), 68.03 (+, C-4), 83.46 (+, C-9a), 125.92 (C_q, C-6), 126.09 (C_q, C-6a), 127.46 (–, $=CH_2$), 137.40 (C_q, C-3), 165.94 (C_q, C-2); ν_{max}(neat)/cm^{-1} 3407, 2912, 2864, 2833, 1692, 1612, 1447, 1372, 1275, 1241, 1189, 1147, 1026, 973, 814, 653, 599, 571, 445, 362; *m*/*z* (EI) 234.12537 (M^+ $C_{14}H_{18}O_3$ requires 234.1256), 234.1 (M^+, 100%), 216.1 (61, $M^+ - H_2O$), 201.1 (4, $M^+ - CH_3$), 190.1 (76, $M^+ - CO_2$), 134.1 (59).

(3a*S*,8*S*,9*R*,9a*R*,9b*S*)-8-hydroxy-6,9-dimethyl-3a,4,5,7,8,9,9a,9b-octahydrobenzo[*de*]chromen-2(3*H*)-one (12)

Compound **11** (60 mg, 0.18 mmol, 1 equiv) was dissolved under a nitrogen atmosphere in anhydrous CH_2Cl_2 (5 cm^3) in a flame dried Schlenk flask. Anhydrous $FeCl_3$ (29 mg, 0.18 mmol, 1.0 equiv) was added in one portion. After 14 and 18 h reaction time, more portions of $FeCl_3$ were added (1.0 and 3.0 equiv). After 24 h hours total reaction time H_2O (1 cm^3) and CH_2Cl_2 (10 cm^3) were poured into the reaction mixture and the layers were separated. The aqueous layer was extracted again with CH_2Cl_2 (1 × 4 cm^3 mmol^{-1}). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography on silica gel (hexanes : ethylacetate 1 : 1) afforded **12** (31 mg, 71%).[18]

R_f 0.31 (hexanes : ethyl acetate 1 : 1, Mostain); $[\alpha]_D^{20}$ + 98.5 (*c* 0.540 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 1.20 (3 H, d, *J* 6.4, 9-C*H*$_3$), 1.66 (3 H, s, 6-C*H*$_3$), 1.68–1.78 (2 H, m), 1.79–1.90 (2 H, m), 1.91–2.17 (4 H, m), 2.20 (1 H, dd, *J* 18.3 and 12.2, 7-H$_b$), 2.73 (1 H, dd, *J* 18.3 and 5.2, 7-H$_a$), 2.92 (1 H, *J* 14.0 and 4.7, 3-H$_a$), 3.11 (1 H, ddd, *J* 10.8, 10.4 and 4.6, 8-H), 3.42 (1 H, dd, *J* 10.4 and 10.4 Hz, 9a-H); δ_C (75.5 MHz; $CDCl_3$) 13.5 (+, 9-*C*H_3), 19.2 (+, 6-*C*H_3), 27.6 (–), 31.6 (–), 34.9 (+), 36.9 (–), 37.8 (–), 44.7 (+), 44.9 (+), 72.5 (+, 8-C), 86.6 (+, 9a-C), 122.0 (C_q, 6-C), 130.7 (C_q, 6a-C) and 170.9 (C_q, 2-C); ν_{max}(KBr)/cm^{-1} 3408, 3323, 2925, 1732, 1690, 1233, 1055, 799, 645; *m*/*z*(EI) 236.1408 (M^+ $C_{14}H_{20}O_3$ requires 236.1412).

(3a*S*,4*S*,8*S*,9*R*,9a*R*,9b*S*)-8-hydroxy-6,9-dimethyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydrobenzo[*de*]chromen-4-yl acetate (14)

In a flame dried Schlenk flask under a nitrogen atmosphere **13** (8 mg, 0.027 mmol, 1 equiv) was dissolved in anhydrous CH_2Cl_2 (2.5 cm^3) and the solution was cooled down to 0 °C. Anhydrous bismuth triflate was added in one portion and the solution was warmed up to room temperature and stirred for 72 h. After complete conversion of the starting material, water (1 cm^3) was added and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtrated and the solvent removed under reduced pressure. Purification by column chromatography on flash silica gel (CH_2Cl_2 : MeOH 100 : 1) yielded **14** (6 mg, 75%) as a white solid. **14** could be crystallized from CH_2Cl_2–hexanes (bp. 60–80 °C) at 5 °C to give crystals which were suitable for X-ray analysis.

R_f 0.36 (hexanes : ethyl acetate 1 : 2, phosphomolybdic acid); mp 179–180 °C (decomp., from CH_2Cl_2–hexanes); $[\alpha]_D^{20}$ +97.4 (*c* 0.195 in $CHCl_3$); δ_H (600 MHz; $CDCl_3$) 1.23 (3 H, d, *J* 6.9, 9-CH_3), 1.64–1.71 (4 H, m, 9-H, 6-CH_3), 1.72 (1 H, d, *J* 4.8, OH), 1.78–1.89 (1 H, m, 7-H$_a$), 1.98 (1 H, ddd, *J* 5.2, 11.1 and 22.8, 3a-H), 2.07 (3 H, s, OAc), 2.03–2.16 (2 H, m, 5-H$_a$, 9b-H), 2.31 (1 H, dd, *J* 12.2 and 18.3, 3-H$_a$), 2.41–2.48 (1 H, m, 5-H$_b$), 2.91 (1 H, dd, *J* 5.3 and 18.3, 3-H$_b$), 2.98 (1 H, dd, *J* 4.7 and 14.1, 7-H$_b$), 3.15–3.23 (1 H, m, 8-H), 3.53 (1 H, t, *J* 10.4, 9a-H), 4.74 (1 H, dt, *J* 5.8 and 10.4, 4-H); δ_C (150 MHz; $CDCl_3$) 13.28 (+, 9-CH_3), 18.88 (+, 6-CH_3), 20.95 (+, O_2C-*C*H_3), 34.06 (–, 3-C), 36.56 (–, 7-C), 37.37 (–, 5-C), 38.89 (+, 3a-C), 44.35 (+, 9b-C), 44.81 (+, 9-C), 71.95 (+, 4-C), 72.24 (+, 8-C), 85.66 (+, 9a-C), 122.08 (C_q, C=C), 128.34 (C_q, C=C), 169.51 (C_q, 2-C), 170.63 (C_q, CH_3*C*OOC-4); ν_{max}(neat)/cm^{-1} 3460, 2971, 2839, 1730, 1438, 1377, 1235, 1190, 1070, 1039, 1015, 916; *m*/*z* (LSIMS) 295.1545 (MH^+ $C_{16}H_{23}O_5$ requires 295.1552).

(3a*S*,4*S*,10a*S*,10b*S*)-6-methyl-2-oxo-3,3a,4,5,7,8,9,10,10a,10b-decahydro-2*H*-cyclohepta[*ij*]isochromen-4-yl acetate (16)

R_f 0.40 (hexanes : ethyl acetate 2 : 1, Mostain); $[\alpha]_D^{20}$ +184.0 (*c* 1.00 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 1.35–1.55 (2 H, m, 8-H, 9-H), 1.63 (3 H, s, CH_3), 1.75–2.04 (4 H, m, 10-H, 7-H, 8-H, 9-H), 2.05 (3 H, s, CH_3), 1.07–2.32 (5 H, m, 10b-H, 3a-H, 5-H, 10-H, 3-H), 2.35–2.47 (2 H, m, 5-H, 7-H), 2.83 (1 H, dd, *J* 3.5 and 17.1, 3-H), 4.15 (1 H, ddd, *J* 2.5, 10.5 and 10.7, 10a-H), 4.70 (1 H, dt, *J* 5.8, 9.9 and 10.0, 4-H); δ_C (75.5 MHz; $CDCl_3$) 19.66 (+, CH_3), 21.04 (+, COO*C*H_3), 24.44 (–, C-9), 24.44 (–, C-8), 29.60 (–, C-7), 33.58 (–, C-10), 36.40 (–, C-3), 37.76 (–, C-5), 39.34 (+, C-3a), 47.95 (+, C-10b), 72.21 (+, C-4), 86.29 (+, C-10a), 127.43 (C_q, C-6), 127.59 (C_q, C-6a), 170.15 (C_q, C-2), 170.69 (C_q, CH_3*C*OOC-4); ν_{max}(neat)/cm^{-1} 2926, 2858, 1725, 1448, 1367, 1326, 1234, 1203, 1134, 1013, 972, 908, 823, 801, 766, 691, 659, 613, 573, 520, 498; *m*/*z* (EI) 279.1597 (MH^+ $C_{16}H_{23}O_4$ requires 279.1596), 279.1 (MH^+, 2%), 218.1 (92) [M^+ – HAc], 204.1 (100), 190.1 (60), 172.1 (50), 158.1 (45), 143.1 (49), 119.0 (70), 105.0 (100), 91.0 (42), 42.9 (66).

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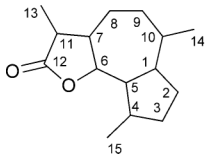
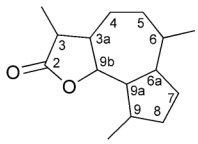
14 The guainolide framework is commonly numbered in the way shown below (left). We opted to use the systematic numbering (right) to keep consistent with the systematic numbering of the products .





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16 For the stability of cyclopropylmethyl cations see G. A. Olah, G. K. S. Prakash, Á. Molnár, J. Sommer, in *Superacid Chemistry*, Wiley, Hoboken, New Jersey, 2nd edn, 2009, ch. 3, pp. 120, and references cited therein.

17 The following abbreviations for the spin multiplicity were used: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dt = doublet of a triplet, dd = double doublet, ddd = doublet of a double doublet. The multiplicity of the signals were detected by DEPT 135 and 90 and are given as: + = primary and tertiary C-atom (positive DEPT 135 signal; tertiary C-atom: DEPT 90 signal), − = secondary C-atom (negative DEPT 135 signal), C_q = quaternary C-atom (zero DEPT signal intensity).

18 A further product resulting from water addition to the double bond could also be isolated (see the ESI†).