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LETTERS

## Diterpenic $\alpha$ - and $\beta$ -hydroxybutanolides with antifeedant activity: semisynthesis and absolute configuration<sup>†</sup>

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### Abstract

Two series of *ent*-halimanolides (15,16-olides and 16,15-olides), analogues of biologically active diterpene lactones, were synthesized starting from *ent*-halimic acid methyl ester. The absolute configuration was determined by CD spectroscopy and corroborated by X-ray analysis. Antifeedant testing has been carried out on these compounds. © 2000 Elsevier Science Ltd. All rights reserved.

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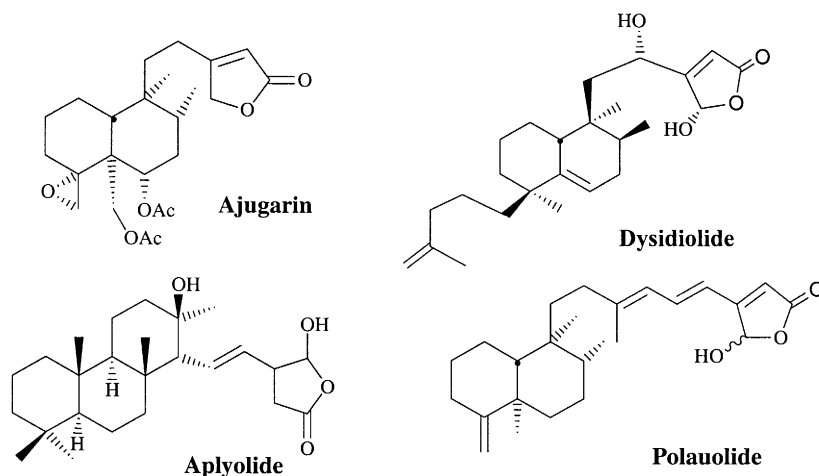
Strong biological activities have been reported for mono- or polycyclic molecules, diterpenes or sesterterpenes, that possess a five-membered oxygenated ring with different functionalities.<sup>1</sup> Ajugarin,<sup>2</sup> a *neo*-clerodane with a butenolide, is an antifeedant, aplyolide<sup>3</sup> has anti-inflammatory activities, dysidiolide<sup>4</sup> is the first naturally derived inhibitor of the cdc25A protein phosphatase and polaulolide<sup>5</sup> (an unsaturated hemiacetal) has antimicrobial properties.

We decided to investigate the synthesis of different chiral  $\alpha$  and  $\beta$ -hydroxybutenolides on the same diterpene skeleton in order to determine the influence of the configuration on the biological activity.

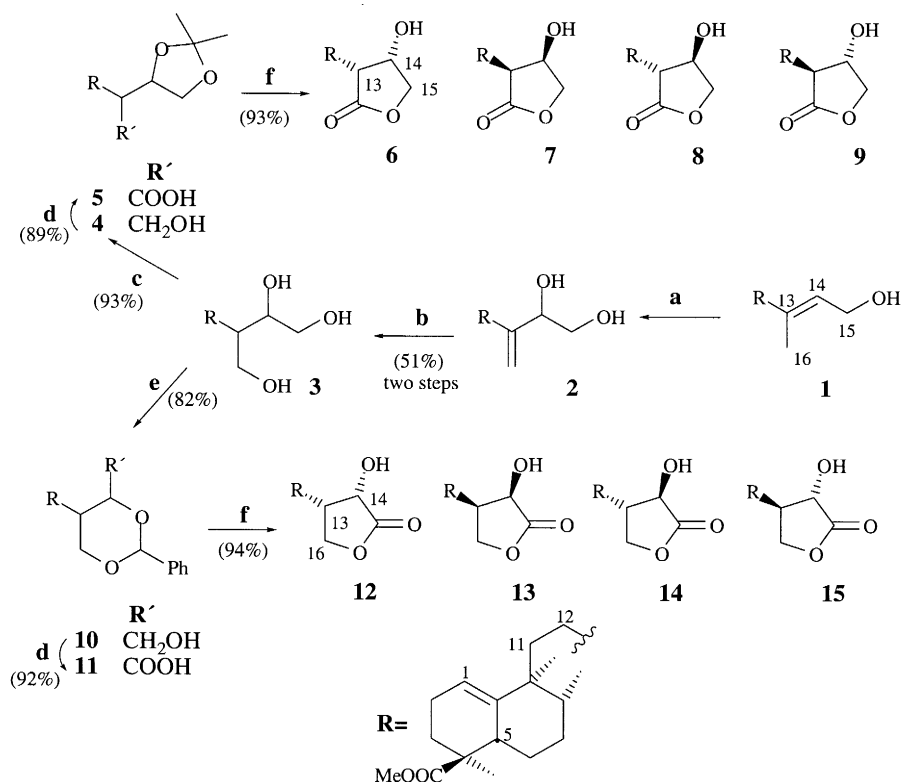
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<sup>†</sup> In respectful memory of the late Professor J. de Pascual Teresa.



As a starting material the *ent*-halimic acid methyl ester<sup>6</sup> **1** was used. By selective photooxygenation and hydroboration it was transformed into the triol **3**. The selective protection of the hydroxy groups on C-14 and C-15 or C-14 and C-16 as 1,3-dioxolane or 1,3-dioxane gave **4** and **10**, respectively. These compounds were oxidized to the corresponding acids **5** and **11**, respectively, by treatment with PDC in DMF. Finally, deprotection with TsOH in MeOH allowed the access to  $\beta$ -hydroxybutanolides, in a ratio (27:33:20:20) **6–9** or  $\alpha$ -hydroxybutanolides, ratio (22:22:28:28) **12–15**, as indicated in Scheme 1.



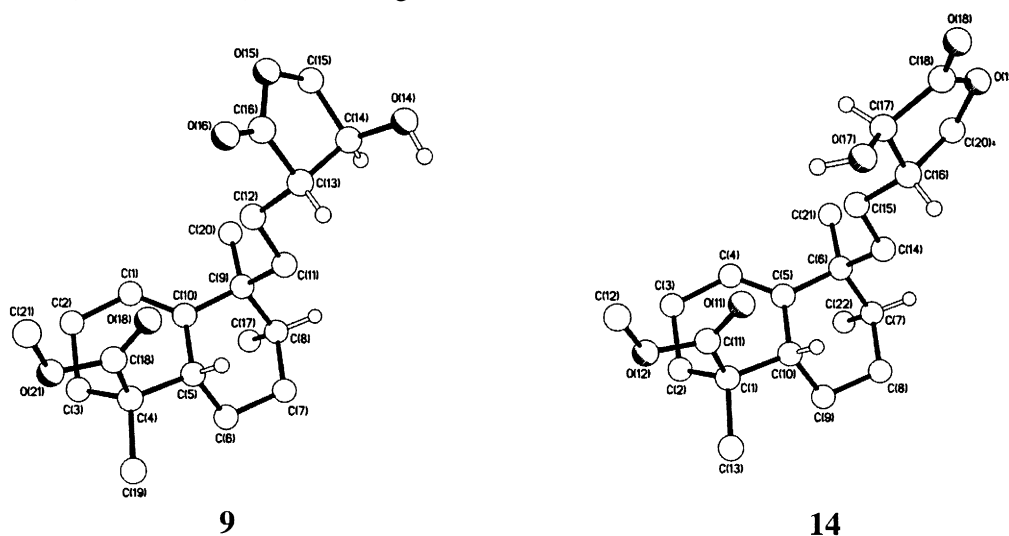
Scheme 1. (a) Rose Bengal, hv, O<sub>2</sub>, then NaBH<sub>4</sub>; (b) BH<sub>3</sub>, THF, then H<sub>2</sub>O<sub>2</sub>/NaOH; (c) 2,2 DMP, CSA; (d) PDC, DMF; (e) PhCHO, CSA; (f) TsOH, MeOH

The relative configuration of R, and of the hydroxy group on the lactone ring for **6** to **9**, was established by  $^1\text{H}$  NMR spectroscopy (Table 1). Taking account of the coupling constants of H-C14 and H-C15 it was deduced that the more polar lactones **8** and **9** have a *trans* stereochemistry whilst the less polar lactones **6** and **7** are *cis*.

Table 1

	<b>6</b>	<b>7</b>	<b>8</b>	<b>9</b>
H-13	2.36, ddd, J=2.9,4.7 and 11.1	2.53,m	2.41, q J= 7.0	2.61, m
H-14	4.62,m	4.60, dt J= 1.5 and 3.5	4.33, dddd J= 3.2,6.7,6.7 and 7.0	4.65, dddd J= 4.1, 7.3, 7.3 and 7.9
H-15A	4.34, d J= 9.9	4.31, dd J= 3.5 and 10.2	4.47, dd J= 6.7 and 9.4	4.47, dd J= 7.3 and 9.1
H-15B	4.26, dd J= 3.5 and 9.9	4.27, dd J= 1.5 and 10.2	3.98, dd J= 6.7 and 9.4	3.94, dd J= 7.9 and 9.1

The absolute configuration was established by CD spectroscopy by applying the chirality rule of the lactone ring established by Wolf, Legrand and Beecham.<sup>7</sup> The more stable conformation for **9** is the one with R and OH equatorial. The dihedral angle is negative and the Cotton effect is positive ( $\Delta\epsilon_{218}=+0.810$ ) so the configuration of **9** is 13*S*,14*S*. In the same manner, **8** ( $\Delta\epsilon_{233}=-0.020$ ) will be 13*R*,14*R*. The structure for **9** was corroborated by single crystal X-ray analysis.<sup>8</sup> The absolute configuration for the isomers **6** and **7** with the hydroxy group pseudo axial and the side chain pseudo equatorial was deduced by the sign of the Cotton effect: negative for **6** ( $\Delta\epsilon_{227}=-0.582$ ) so the configuration is 13*R*,14*S*, and positive for **7** ( $\Delta\epsilon_{222}=+1.221$ ) so the configuration is 13*S*,14*R*.



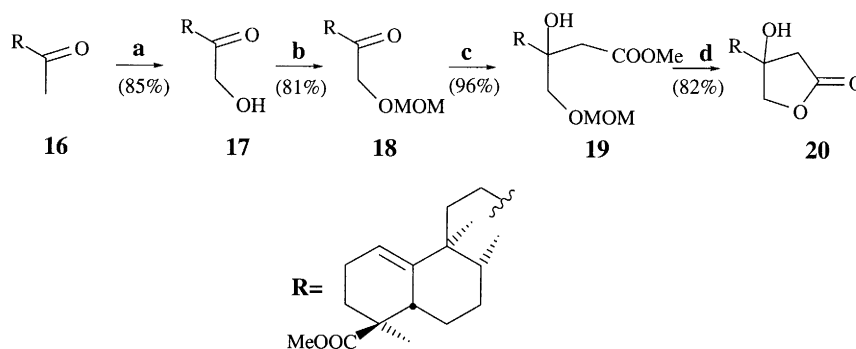
The relative configurations for the  $\alpha$ -hydroxybutanolides **12**–**15** were established on the basis of the coupling constants in the  $^1\text{H}$  NMR (Table 2) for H-C14 and H-C16, being *cis* for the side chain and the hydroxy group on the lactone ring for **12** and **13** and *trans* for **14** and **15**. The structure of **14** was corroborated by a single crystal X-ray analysis.<sup>9</sup> Their absolute configurations were again established by CD: **12** ( $\Delta\epsilon_{219}=+2.162$ ), 13*S*,14*S*; **13** ( $\Delta\epsilon_{224}=-0.841$ ), 13*R*,14*R*; **14** ( $\Delta\epsilon_{223}=-1.717$ ), 13*S*,14*R* and, hence, **15**, 13*R*,14*S*.

In order to check for antifeedant activity, lactone **20** was synthesized starting from **16** (Scheme 2).<sup>9</sup> The treatment with LDA/TMSCl and ulterior oxidation with *m*CPBA gave **17** that was protected as its

Table 2

	<b>12</b>	<b>13</b>	<b>14</b>	<b>15</b>
H-14	4.53, d J=6.8	4.45, d J= 6.8	4.16, d J= 10.7	4.18, d J= 10.7
H-16A	4.30, dd J= 6.4 and 9.8	4.35, dd J= 5.9 and 9.3	4.42, dd J= 7.8 and 9.3	4.43, dd J= 7.8 and 9.3
H-16B	4.12, dd J= 3.5 and 9.8	4.23, dd J= 3.4 and 9.3	3.79, dd J= 9.3 and 10.7	3.99, dd J= 9.3 and 10.7

MOM derivative **18**. A Reformatsky<sup>10</sup> reaction of ethyl bromoacetate and **18** gave the mixture (1:1) of hydroxyesters, **19**, which, after deprotection, led to the required hydroxylactones **20**.



Scheme 2. (a) LDA/TMSCl, then *m*CPBA; (b) (MeO)<sub>2</sub>CH<sub>2</sub>/P<sub>2</sub>O<sub>5</sub>; (c) Zn–Cu/I<sub>2</sub>/BrCH<sub>2</sub>COOMe; (d) HCl, MeOH

Finally, compounds **6–9**, **12–15** and **20** were tested for their antifeedant activity against larvae of *Spodoptera littoralis*. The results of these bioassays are shown in Table 3.

Table 3  
Effect of some *neo*-clerodane on the feeding behaviour of larvae of *Spodoptera littoralis*, antifeedant index\*

Compound	Antifeedant Index* at 100ppm(#)	AI <sub>50</sub>
<b>6</b>	-8 (4.7)	>5000
<b>7</b>	20 (15.8)	>5000
<b>8</b>	-2 (8.4)	>5000
<b>9</b>	-44 (4.1)	>5000
<b>12 and 13</b>	5 (6.7)	>5000
<b>14 and 15</b>	48 (11.2)	200
<b>20</b>	50 (9.04)	58

\*Antifeedant Index: [(C–T)/(C+T)]x100; C =Weight of control disc eaten, T=weight of treatment disc eaten.

This index identifies both phagoestimulants (- ve values) and antifeedants (+ ve values).

# (In parenthesis mortality)

As can be deduced from Table 3, none of the β-hydroxybutanolides are antifeedants, α-hydroxybutanolides **14** and **15** are weakly active and **20** is moderately so. Studies to increase the activities are in progress.

In this paper, we have established, via CD spectroscopy, the absolute configurations of some butanolides not anchored to rigid systems.

## Acknowledgements

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8. Crystal data for **9**: C<sub>21</sub>H<sub>32</sub>O<sub>5</sub>, *M*=364.5, monoclinic, space group *P*2<sub>1</sub> (no. 4), *a*=6.737(1), *b*=9.083(2), *c*=16.227(4) Å,  $\beta$ =94.23(1)°, *V*=990.2(3) Å<sup>3</sup>, *Z*=2, *D*<sub>c</sub>=1.222 g cm<sup>-3</sup>,  $\mu$ (Cu-K $\alpha$ )=6.93 cm<sup>-1</sup>, *F*(000)=396. For **14**·H<sub>2</sub>O C<sub>21</sub>H<sub>34</sub>O<sub>7</sub>, *M*=382.5, orthorhombic, space group *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> (no. 19), *a*=6.869(3), *b*=9.203(5), *c*=33.377(15) Å, *V*=2110(2) Å<sup>3</sup>, *Z*=4, *D*<sub>c</sub>=1.204 g cm<sup>-3</sup>,  $\mu$ (Cu-K $\alpha$ )=7.08 cm<sup>-1</sup>, *F*(000)=832. Data for both compounds (for **9**, 1645 independent reflections,  $2\theta < 124^\circ$ , and for **14**·H<sub>2</sub>O, 1975 independent reflections,  $2\theta < 125^\circ$ ) were measured on a Siemens P4 rotating anode diffractometer with Cu-K $\alpha$  radiation (graphite monochromator) using  $\omega$ -scans. The structures were solved by direct methods and the non-hydrogen atoms were refined anisotropically by full-matrix least squares based on *F*<sup>2</sup> to give, for **9**, *R*<sub>1</sub>=0.087 and *wR*<sub>2</sub>=0.222 for 1158 independent observed reflections [ $|F_o| > 4\sigma(|F_o|)$ ], and for **14**·H<sub>2</sub>O, *R*<sub>1</sub>=0.043 and *wR*<sub>2</sub>=0.106 for 1635 independent observed reflections [ $|F_o| > 4\sigma(|F_o|)$ ]. The absolute chiralities of both structures were determined by internal reference. Further details of the crystal structure investigations are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ (UK), on quoting the full literature citation.
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