Tetrahedron Vol. 49, No. 23, pp. 5039-5046, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Synthesis of Enantiomeric Gibberellin Analogs from Natural Isopimarenes

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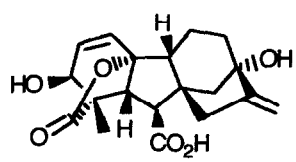
(*Received in USA* 11 *December* 1992; *accepted* 13 *April* 1993)

Key Words: Gibberellane, Gibberellins, Isopimarane, Diterpenes.

Abstract: *The natural isopimarenes* ***2-5****, isolated from Velloziaceae species, with known absolute stereochemistry, were submitted to chemical transformations and afforded the tetracyclic lactones* ***10*** *and* ***11*** *with the gibberellane skeleton of the normal series. The 15-oxa-gibberellanes obtained are enantiomeric analogs of the natural gibberellins and this represents the first synthesis of this type of compounds.*

Introduction

The gibberellins are a class of natural growth hormones; and, since the structure elucidation of gibberellic acid (**1**) in 1959 a series of papers has been published in the literature on this class of diterpenes as well as some on modified gibberellins that were recently synthetized.[2-6] Despite these works on biological activity, isolation, structural determination and synthesis, until now the enantiomeric series of these diterpenes has remained unknown.



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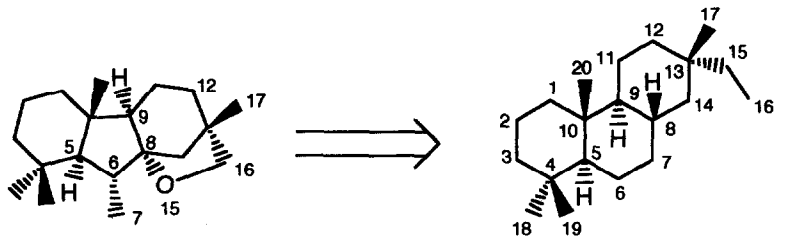
The Velloziaceae species are a rich source of diterpenes, among these isopimarane type is the most abundant.[7-13]

We report here the synthesis of 15-oxa-17(16→13)abeogibberellane diterpenes (Scheme 1),[14] enantiomeric analogs of natural gibberellins, from 7,8-oxygenated isopimarane diterpenes **2-4**, isolated from *Vellozia compacta* Martius ex Schultes f.[7] and *Vellozia patens* L. B. Smith & Ayensu.[9]



15-oxa-17(16→13)abeoGibberellane **Isopimarane**

Scheme 1

Results and Discussion

The starting isopimarenes **2-5** were isolated as described earlier and had the absolute stereochemistry determined by ORD and CD measurements.[7,9]

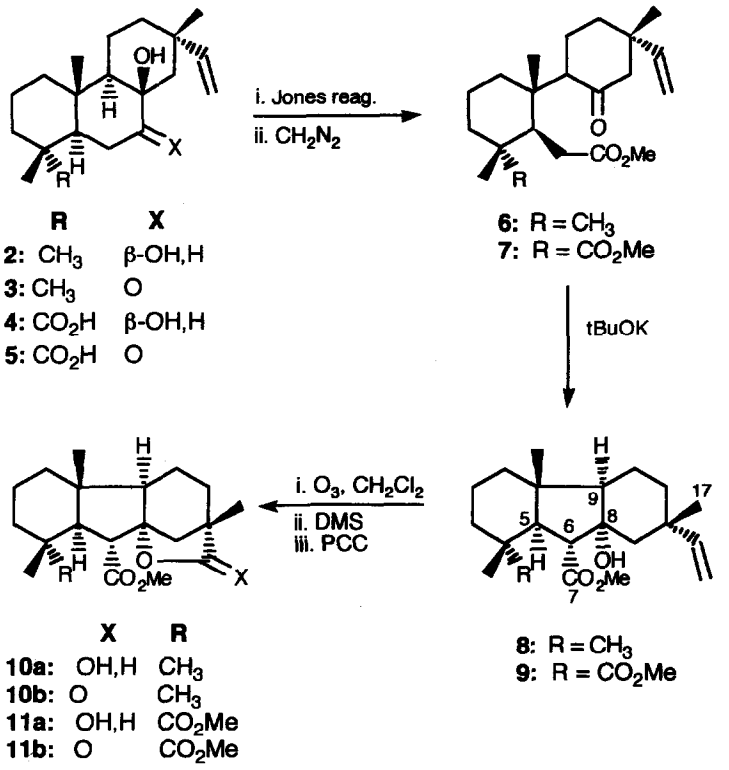
During the studies on synthesis of gibberellins and analogs several approachs have been used to obtain the five membered B ring. Our approach consists of using the oxidative cleavage of **2**, **3** and **4**, **5** with the Jones reagent, a known reaction leading, respectively, to the 7,8-seco-isopimarenes **6** and **7**, in excellent yield,[15] followed by subsequent intramolecular aldol type reaction, which proved to be an excellent method to contract the isopimaranic B ring (Scheme 2).

The Jones reaction products after esterification with diazomethane were submitted to treatment with a base under different conditions.[14] The reaction of **6** with tBuOK under *n*-hexane under reflux led to a single product in 85% yield, to which was attributed structure **8**.

The configuration of the carbons 6, 8 and 9 were determined through some NMR data (Tables 1 and 2). The (6*S*) configuration was signified by the *trans*-coupling constant (13 Hz) between H-5 and H-6 (Table 1). The *trans*-relationship between C-17 and the hydroxyl group at C-8 followed from the deshielded signal of C-17 in an equatorial position (30 ppm, Table 2).

Ozonolysis of the tricyclic compound **8** afforded a mixture of epimeric lactols **10a** and the lactone **10b**. The PCC oxidation of the mixture gave the tetracyclic lactone **10b** in 90% of total yield. This confirmed the proposed stereochemistry of C-8 (*S*), based on NMR data.

For compound **7** the best aldol results were obtained when the reaction was performed using tBuOK in THF under reflux.[14] The tricyclic compound **9**, obtained in 90% yield, was submitted to the same reactions used for the **8** to **10b** conversion and afforded the lactone **11b** (90 %).



Scheme 2

Also in this case the cyclization was stereospecific leading to a single stereoisomer. Tables 1 and 2 show an excellent correlation for the products. Probably the stereospecificity of the reaction is due to the formation of the more stable product known to be the *trans*-transoid-*cis* isomer.[14,17] This proposal is corroborated by the ^{13}C resonances of the C ring carbon atoms occurring at higher field when compared to *trans*-isomers, as a consequence of the *cis* fused C-ring having adopted a boat conformation[16-19] (Table 2).

This investigation provides the first example of the conversion of isopimarane type diterpenes into enantiomeric gibberellin analogs and, in addition, it also can be useful model for preparation of other compounds in this series.

Table 1 ^{1}H NMR Data of the Diterpenes **8**[a], **9**[b], **10b**[c] and **11b**[c]
δ^1H (m, *J* in Hz)

	8	**9**	**10b**	**11b**
H-5	1.73 (d; 13.3)	2.34 (d; 13.1)	2.01 (d; 13.4)	2.39 (d; 13.4)
H-6	2.48 (d; 13.3)	2.50 (d; 13.1)	2.81 (d; 13.4)	2.89 (d; 13.4)
H-9	d	d	1.76 (dd; 7.4, 10.3)	1.76 (dd; 7.6, 10.6)
H-14	1.97 (d; 15.0)	2.03 (d; 13.1)	2.05 (d, 11.8)	2.11 (s)
	d	d	2.12 (d; 11.8)	2.11 (s)
H-15	6.15 (dd; 12.1, 18.2)	6.17 (dd; 10.8, 17.5)		
H-16	4.88 (d; 12.1)	4.89 (dd; 1.5, 17.5)		
	4.91 (d;18.2)	4.93 (dd; 1.5, 10.8)		
□-CH_3	0.70 (s)	0.83 (s)	0.85 (s)	0.90 (s)
	0.79 (s)	0.99 (s)	0.85 (s)	1.20 (s)
	0.94 (s)	1.22 (s)	0.92 (s)	1.20 (s)
	1.02 (s)		1.20 (s)	
O$\underline{CH_3}$	3.70 (s)	3.56 (s)	3.70 (s)	3.61 (s)
		3.61 (s)		3.66 (s)

a) 200 MHz, $CDCl_3$; b) 300 MHz, $CDCl_3$; c) 500 MHz, $CDCl_3$; d) Not assigned.

Table 2 δ^{13}C (m)[a] NMR Data of the Diterpenes **6**[b], **7**[b], **8**[b], **9**[c], **10b**[b] and **11b**[b]

carbon	**6**	**7**	**8**[d]	**9**	**10b**	**11b**
1	31.3 (t)	31.8 (t)	39.4 (t)	38.9 (t)	38.6 (t)	38.0 (t)
2	18.2 (t)	17.6 (t)	19.1 (t)	18.3 (t)	19.1 (t)	18.2 (t)
3	41.6 (t)	34.5 (t)	41.9 (t)	36.1 (t)	41.6 (t)	34.9 (t)
4	34.9 (s)	49.9 (s)	33.4 (s)	44.7 (s)	34.4 (s)	44.9 (s)
5	45.6 (d)	40.8 (d)	57.1 (d)	50.9 (d)	56.6 (d)	51.9 (d)
6	36.7 (t)	36.7 (t)	54.5 (d)	53.7 (d)	50.4 (d)	50.1 (d)
7	175.2 (s)	174.0 (s)	179.1 (s)	173.6 (s)	170.9 (s)	169.3 (s)
8	211.5 (s)	210.5 (s)	80.0 (s)	78.9 (s)	89.5 (s)	89.1 (s)
9	58.0 (d)	56.1 (d)	59.4 (d)	59.5 (d)	54.7 (d)	54.6 (d)
10	39.1 (s)	38.6 (s)	43.2 (s)	42.6 (s)	42.9 (s)	42.9 (s)
11	23.7 (t)	23.9 (t)	17.3 (t)	17.6 (t)	15.2 (t)	15.8 (t)
12	32.2 (t)	32.2 (t)	32.8 (t)	33.2 (t)	30.0 (t)	29.9 (t)
13	42.5 (s)	42.3 (s)	35.4 (s)	35.3 (s)	41.4 (s)	41.3 (s)
14	54.9 (t)	54.7 (t)	49.4 (t)	49.2 (t)	40.9 (t)	40.6 (t)
15	147.5 (d)	147.4 (d)	148.5 (d)	149.2 (d)	181.2 (s)	180.9 (s)
16	110.1 (t)	110.1 (t)	110.0 (t)	109.5 (t)		
17	22.9 (q)*	22.6 (q)	30.0 (q)	29.3 (q)	21.9 (q)	21.3 (q)
18	33.5 (q)	178.3 (s)	33.4 (q)	177.8 (s)	33.3 (q)	177.2 (s)
19	22.3 (q)*	20.0 (q)	21.3 (q)	16.9 (q)	21.3 (q)	16.9 (q)
20	19.0 (q)	20.0 (q)	16.7 (q)	17.0 (q)	16.9 (q)	17.9 (q)
OCH_3-21	51.6 (q)	51.6 (q)*		51.7 (q)*	51.7 (q)	51.8 (q)*
OCH_3-22		51.9 (q)*		51.3 (q)*		51.3 (q)*

a) Assigned by DEPT sequence; b) 75 MHz, $CDCl_3$; c) 125 MHz; $CDCl_3$; d) Data of the 7-carboxylic acid derivative of **8**.
* Starred values in the same column can be interchanged.

Experimental Section

The isolation and purification of the starting isopimarenes are described in previous papers. The natural known compounds were identified by comparison of their spectral data with those of authentic samples.[7,9]

The reaction products were also analysed by HRGC on a SE-54 glass capillary column (25 m x 0.30 mm, df = 0.25mm) using hydrogen as carrier and temperature progamming from 100 to 290 °C at 8°C/min. Same chromatographic conditions were used for the HRGC-MS-C analysis on a HP 5987 A, using linear scanning (50-500 DA, 1.87 s/decade) and electron impact (70 eV) ionization. The products were considered pure when the chromatographic analysis revealed relative concentrations more then 99 %. The yields reported are relating to isolated and purified compounds.

The Jones reagent is a solution of 8N of chromic acid in diluted sulfuric acid.10 ml of this reagent was prepared by adding CrO_3 (2.672 g) to H_2SO_4 (2.3 ml), then diluting with H_2O to complete the volume.

*Methyl 8-oxo-7,8-secoisopimar-15-en-7-oate (**6**):*

The Jones reagent was added to an 0.1 M acetone solution of the substrate (**2** or **3**) to the point of a persistent brown colour. After work-up the pure product (**6**) was obtained in 90-97% yield.[15]
Colourless crystals in *n*-hexane mp 70-71°C. EIMS 70 eV *m/z* (rel. int.):334 $[M]^+$ (3.8), 303 (0.8), 302 (0.6), 301 (0.4), 287 (0.1), 285 (0.8), 274 (0.4), 259 (0.8), 249 (1.4), 231 (4.8), 200 (1.8), 205 (2.0), 197 (54), 181 (32), 165 (30), 138 (70), 123 (100), 109 (30), 95 (64) and 81 (40). ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (3 H,s), 0.96 (3 H, s), 1.01 (3 H, s), 1.08 (3 H, s), 1.95 (1 H, t, J = 5.0 Hz), 2.07 (1 H, d, J =11.9 Hz), 2.41 (1 H, d, J = 11.9 Hz), 3.72 (3 H, s), 4.95 (1 H, d, J = 10.2 Hz), 4.97 (1 H, d, J = 17.7 Hz) and 5.87 (1 H, dd, J = 17.7 and 10.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): Table 2.

*Methyl 8-oxo-7,8-seco-isopimar-15-ene-7,18-dioate (**7**):*

Using the same as that procedure described for **6**, the diterpenes **4** and **5** were transformed into **7** in quantitative yields.[15]
Colourless oil. EIMS 70eV *m/z* (rel. int.): 378 $[M]^+$ (3), 361 (2) 347 (2), 328 (2), 319 (2), 304 (3), 273 (2), 241 (30), 209 (20), 195 (14), 181 (100), 165 (25), 149 (33), 121 (43), 107 (62) and 44 (60). ^1H NMR (300 MHz, $CDCl_3$): δ 0.97 (3 H, s), 1.09 (3 H, s), 1.22 (3 H, s), 2.05 (1 H, d, J = 12.0 Hz), 2.85 (1 H, bt), 3.64 (3 H, s), 3.68 (3 H, s), 4.92 (1 H, d, J = 10.0 Hz), 4.94 (1 H, d, J = 18.0 Hz) e 5.80 (1 H, dd, J = 10.0 and 18.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): Table 2.

*Methyl 8α-hydroxy-8(7→6βH)abeoisopimar-15-en-7-oate (**8**):*

A solution of **6** (20 mg, 0.06 mmoles) in *n*-hexane (5.0 ml) and freshly prepared tBuOK (30 mg, 0.27 mmoles) was heated for 4 h under reflux. A saturated solution of NH_4Cl was added and the mixture

was extracted with CH_2Cl_2 (3x, 10 ml). After the evaporation of the solvent the residue was purified on a column of silica gel in a Pasteur pipette using hexane as the eluant to give 16 mg (85%) of **8**.

Colourless crystals in hexane, mp 73-74 °C. IR ν_{max}^{KBr} cm^{-1}: 3507, 2931, 1724, 1640, 1464, 1437, 1389, 1371, 1268, 1187, 1165, 1052 and 904. EIMS 70eV *m/z* (rel. int.): 334 $[M]^{+\cdot}$ (8), 316 (5), 303 (2), 302 (12), 301 (50), 275 (4), 257 (10), 256 (10), 241 (40), 233 (10), 231 (6), 219 (12), 205 (8), 196 (20), 187 (18), 177 (20), 173 (22), 165 (100), 166 (40), 159 (25), 149 (26), 138 (32), 137 (40), 123 (64), 109 (70), 95 (98) and 81 (96). ^1H NMR (200 MHz, $CDCl_3$): Table 1.

Hydrolysis of **8** gave the pure *8α-hydroxy-8(7→6βH)abeoisopimar-15-en-7-oic acid:*
^1H NMR (300 MHz, $CDCl_3$): δ 0.86 (6 H, s), 0.93 (3 H, s), 1.02 (s), 2.10 (1 H, d, J = 13.2 Hz), 2.18 (2 H, s), 2.55 (1 H, d, J = 13.3 Hz), 4.94 (1 H, d, J = 17.0 Hz), 4.98 (1 H, d, J = 10.6 Hz) and 6.16 (1 H, dd, J = 10.6 and 17.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): Table 2.

*Methyl 8α-hydroxy-8(7→6βH)abeoisopimar-15-en-7,18-dioate (**9**):*

To a solution of 30 mg of **7** (0.08 mmol) in THF (5.0 ml) 40 mg of tBuOK was added. After 4 h under reflux the THF was evaporated and the residue submitted to the same work-up used for **8** affording 27 mg of **9** (90%).

Colourless oil. EIMS 70 eV *m/z* (rel. int.): 378 $[M]^{+\cdot}$, 363 (2), 360 (4), 346 (12), 328 (12), 318 (18), 300 (40), 285 (100), 274 (18), 259 (10), 241 (30), 225 (10), 200 (20), 180 (20), 165 (20) and 121 (25). IR (liquid film, $CHCl_3$) ν_{max} cm^{-1}: 3505, 3429, 2950, 1728, 1650, 1450, 1150, 1010 and 906. ^1H NMR (300 MHz, $CDCl_3$): Table 1. ^{13}C NMR (125 MHz, $CDCl_3$): Table 2.

*Methyl 13ξ-ol-15-oxa-17(16→13)abeogibberell-7-oate (**10a**):*

A solution of 14.1 mg of **8** in CH_2Cl_2 at -78°C was submitted to an ozone flux (0.01 mmol/min) during 4.2 min. Addition of dimethylsulfide and evaporation of the solvent yielded the mixture of lactols **10a.**

Colourless oil. EIMS 70 eV *m/z* (rel. int.): 303 $[M-33]^+$ (16), 290 (10), 276 (18), 275 (100), 274 (4), 273 (20), 259 (18), 245 (2), 230 (95), 229 (40), 213 (15), 161 (22), 147 (28) and 123 (35). IR (liquid film, $CHCl_3$) ν_{max} cm^{-1}: 3420, 1733 and 1133. ^1H NMR (200 MHz, $CDCl_3$): δ 0.73 (s), 0.77 (*s*), 0.78 (s), 0.82 (s), 0.85 (s), 1.00 (s), 1.35 (s), 1.26-2.49 (m), 3.53-3.67 (m), 3.65 (s) and 3.67 (s).

*Methyl 13ξ-ol-15-oxa-17(16→13)abeogibberell-7,18-dioate (**11a**):*

A solution of 34.1 mg of **9** in CH_2Cl_2 at -78°C was submitted to an ozone flux (0.01 mmol/min) during 9.02 min. Addition of dimethylsulfide and evaporation of the solvent yielded the mixture of lactols **11a.**

Colourless oil. EIMS 70 eV *m/z* (rel. int.): 302 $[M-78]^+$ (60), 287 (20), 274 (42), 259 (38), 243 (65), 215 (40), 213 (20), 199 (35), 159 (30), 157 (25), 142 (20), 134 (15), 130 (18), 129 (30), 121 (60) and 94 (100). IR (liquid film, $CHCl_3$) ν_{max} cm^{-1}: 3497, 3018, 2938, 1746, 1720, 1438, 1252, 1197, 1175 and 1110. ^1H NMR (200 MHz, $CDCl_3$): δ 0.84 (s), 1.14 (s), 1.99 (s), 2.32 (d, J = 13.2 Hz), 2.83 (d, J = 13.2 Hz), 3.50-3.58 (m), 3.54 (s) and 3.58 (s).

*Methyl 13-oxo-15-oxa-17(13→12)abeogiberel-7-oate (**10b**):*

The mixture **10a** obtained was redissolved with CH_2Cl_2 and treated with 15 mg (0.069 mmol) of PCC.[20] After 2 h the usual work-up afforded 12.6 mg (0.038 mmol, 90% from **8**) of **10b**.
Colourless oil. EIMS 70 eV *m/z* (rel. int.): 275 [M-$C_2H_3O_2$] (42), 231 (12), 230 (74), 215 (34), 213 (12), 207 (12), 175 (10), 161 (24), 160 (24), 147 (32), 121 (62), 94 (94) and 55 (100). HREIMS obs. 275.2002, $C_{18}H_{27}O_2$, calc. 275.2011. IR (liquid film, $CHCl_3$) ν_{max} cm^{-1}: 2923, 2855, 1770, 1743, 1456, 1394, 1283, 1265, 1157, 1124, 1082 and 1030 .^{1}H NMR (500 MHz, $CDCl_3$): Table 1. ^{13}C NMR (75 MHz, $CDCl_3$): Table 2.

*Methyl 13-oxo-15-oxa-17(13→12)abeogiberel-7,18-oato (**11b**):*

To a solution of **11a** in CH_2Cl_2 was added 30 mg (0.139 mmol) of PCC.[20] After 2 h the usual work-up afforded 30.7 mg (0.081 mmol, 90% from **9**) of **11b**.
Colourless oil. EIMS 70 eV *m/z* (rel. int.): 319 [M-$C_2H_3O_2$]$^+$ (6), 302 (6), 275 (16), 274 (80), 273 (48), 259 (100), 231 (6), 215 (32), 213 (24), 199 (14), 159 (22), 145 (28) and 121 (14). HREIMS obs. 319.1901, $C_{19}H_{27}O_4$, calc. 319.1909. IR (liquid film, $CHCl_3$) ν_{max} cm^{-1}: 2929, 1766, 1727, 1458, 1257, 1238, 1212, 1169, 1150 and 1131. ^{1}H NMR (500 MHz, $CDCl_3$): Table 1. ^{13}C NMR (75 MHz, $CDCl_3$): Table 2.

Acknowledgements

This work was supported by CNPq (Brazil) grant. The authors are grateful to the ICMIB-NMR Service Staff, particularly, to Dr. A. Madaio for 500 MHz NMR analysis of some compounds and to Dr. Vitor Rumjanek (IQ-UFRuRJ) for the 200 MHz NMR analysis. Special thanks are extended to Prof. W. B. Kover (IQ-UFRJ) for reading the manuscript.

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