Partial Synthesis of 4-*epi*-Trachylobagibberellin A_{12}

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The partial synthesis of 4-*epi*-trachylobagibberellin A_{12}, starting from the natural diterpene trachinodiol (*ent*-7α,18-dihydroxytrachylobane) is reported. The stereospecific ring B contraction was carried out by treatment of a bromohydrin with silver oxide. The structure of a monoester of this gibberellin analogue was determined by *X*-ray analysis.

In previous work[1] we obtained the trachylobagibberellin analogue (**4**) by rearrangement of a chloroenol lactone prepared from trachinodiol (**1**).[2] We also described the microbiological transformation of trachylobane diterpenes into trachylobagibberellins using the fungus *Gibberella fujikuroi*.[3,4] Other authors[5,6] have also obtained trachylobagibberellins by feeding trachyloban-19-oic acid to a mutant of the same fungus.

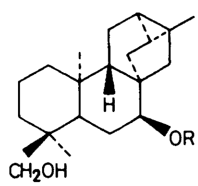
In this work we describe the partial synthesis of 4-*epi*-trachylobagibberellin A_{12} (**5**), an isomer of (**3**)[1] but with the stereochemistry characteristic of the gibberellins at C-5 and C-6.

The keto methyl ester (**7**) was obtained by oxidation of trachinodiol (**1**) with Jones reagent and methylation with diazomethane.[2] Bromination of (**7**) with phenyltrimethylammonium tribromide[7] yielded the bromo ketone (**8**). Its ^1H n.m.r. spectrum showed a coupling constant of 10 Hz between 5-H and 6-H, an indication of equatorial stereochemistry for the bromine at C-6. Reduction of compound (**8**) with sodium borohydride afforded the bromohydrin (**9**) and the alcohol (**10**). The stereochemistry of the hydroxy group in both compounds was given as α-equatorial on the basis of its ^1H n.m.r. spectrum. Moreover, compound (**10**) was different from its 7-epimer (**12**), which was obtained in three steps by chromic oxidation of trachinodiol 7β-monoacetate[8] (**2**), subsequent methylation with diazomethane, and basic hydrolysis of the resulting compound (**11**); the latter was identical with the methyl ester of a trachylobane diterpene isolated from *Xylopia quintasii*.[9]

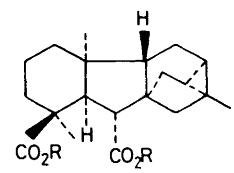
Treatment of the bromohydrin (**9**) with silver oxide[10] gave the aldehyde (**13**), with a M^+ *peak* at m/z 330 and a signal for the aldehyde protons at δ 9.29 (J 5 Hz). The crude aldehyde (**13**) without purification was oxidized with Jones reagent to give the monoacid (**14**) and this with diazomethane afforded the corresponding dimethyl ester. The latter was assigned the structure of 4-*epi*-trachylobagibberellin A_{12} dimethyl ester (**6**) on the basis of its ^1H n.m.r. spectrum. Thus $J_{5,6}$ was 12 Hz and characteristic of 6α-H stereochemistry as reported for C_{20} gibberellins;[11-13] the ^{13}C n.m.r. spectrum is described in Table 1. The stereochemistry was confirmed by *X*-ray analysis of the monoacid (**14**). Finally, compound (**14**) was treated with potassium t-butoxide in dimethyl sulphoxide to give the corresponding diacid (**5**).

Ring contraction of steroid bromohydrins with silver oxide was studied by Nace and Crosby,[10] who found that 6α-bromo-5α-cholestane-3β,7β-diol gave a single aldehyde in a stereospecific manner. Although our results confirmed this, the stereochemistry obtained by us at C-6 is the reverse of that given by the American authors.

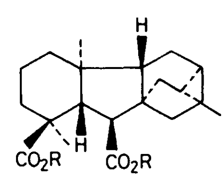
The synthesis of a 4-*epi*-trachylobagibberellin A_{12} (**5**) in this simple way, starting from an abundant natural substrate,[4,7,14] is potentially important with regard to biological applications, since the C_{19} trachylobagibberellins possess biological activity,[5]



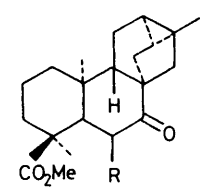
(**1**) R = H
(**2**) R = Ac



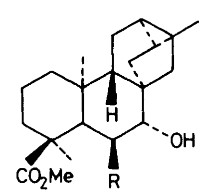
(**3**) R = H
(**4**) R = Me



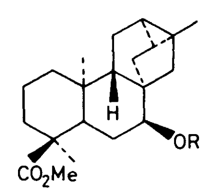
(**5**) R = H
(**6**) R = Me



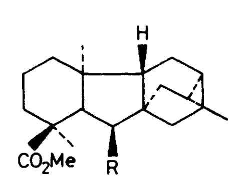
(**7**) R = H
(**8**) R = Br



(**9**) R = Br
(**10**) R = H



(**11**) R = Ac
(**12**) R = H



(**13**) R = CHO
(**14**) R = CO_2H

and other tetracyclic analogues can be obtained by opening of the cyclopropane ring of (**5**).

Table 2 gives the atomic co-ordinates of the absolute molecular structure of (**14**), which also represents the absolute stereochemistry. This was not determined because the absolute configuration of the starting material, trachinodiol (**1**), is known. Essentially, the geometry of the molecule, in terms of

Table 1. ^{13}C N.m.r. spectral data ($CDCl_3$, 50.32 MHz)

C	1	6	12
1	38.71	35.03	38.27
2	17.63	18.17	17.21
3	35.16	37.94	36.92
4	37.19	43.21	45.51
5	39.04	48.65	41.75
6	27.11	54.17	30.52
7	76.11	174.20	75.47
8	45.44	47.37	46.81
9	47.56	57.02	47.65
10	38.27	44.75	37.80
11	19.45	18.79	19.06
12	20.75	18.79	20.49
13	24.16	21.30	23.95
14	32.84	35.03	32.57
15	45.44	46.24	45.19
16	23.09	25.14	22.91
17	20.62	20.77	20.31
18	70.61	177.48	178.87
19	17.93	17.24	16.41
20	15.04	15.67	14.82

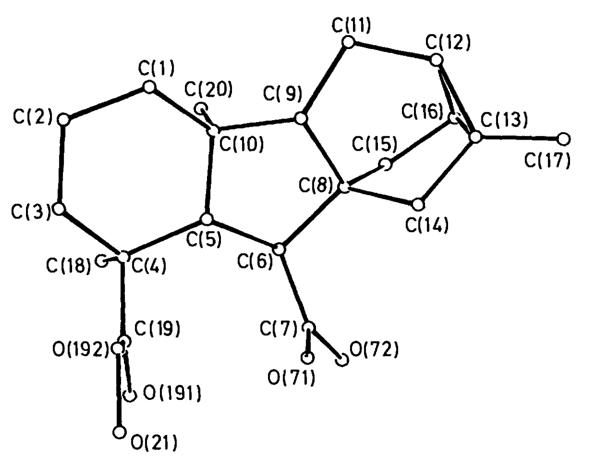


Figure 1. Perspective view of the molecule (**14**). The atom numbering for this *X*-ray Figure is different from the chemical nomenclature of (**14**)

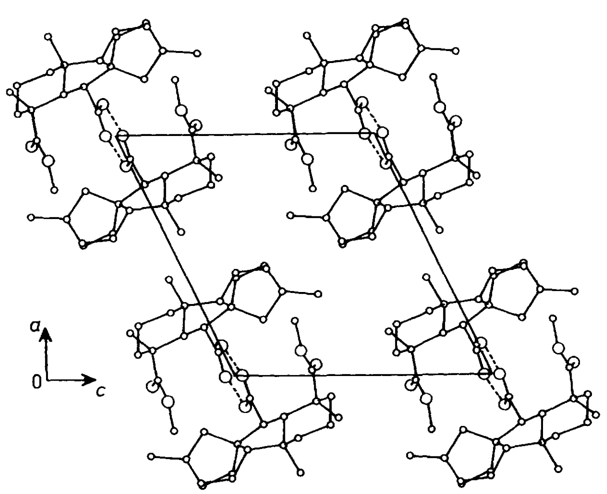


Figure 2. The molecular packing viewed down the *b* axis

Table 2. Atomic co-ordinates (× 10) and equivalent isotropic thermal parameters (A × 10) with e.s.d.s in parentheses

Atom	*x*	*y*	*z*
C(71)	8 719(2)	1 560(0)	−135(2)
C(72)	10 015(2)	3 801(4)	327(2)
C(191)	11 036(2)	5 843(4)	3 038(3)
C(192)	10 444(3)	3 214(5)	3 367(3)
C(1)	7 379(3)	8 697(5)	1 250(3)
C(2)	7 916(3)	8 499(6)	2 765(3)
C(3)	9 087(3)	7 379(6)	3 303(3)
C(4)	8 924(3)	5 534(5)	2 678(3)
C(5)	8 304(2)	5 804(4)	1 150(2)
C(6)	7 972(2)	4 226(4)	223(2)
C(7)	9 030(2)	3 209(4)	176(2)
C(8)	7 144(2)	5 012(4)	−1 172(2)
C(9)	6 906(2)	6 923(4)	−878(3)
C(10)	7 093(2)	6 921(4)	570(3)
C(11)	5 733(3)	7 641(5)	−2 026(3)
C(12)	5 542(3)	6 734(5)	−3 307(3)
C(13)	6 517(3)	5 605(5)	−3 460(3)
C(14)	7 674(2)	5 146(4)	−2 203(2)
C(15)	5 927(2)	3 983(5)	−1 960(3)
C(16)	5 433(3)	4 766(5)	−3 328(3)
C(17)	6 630(3)	5 601(6)	−4 754(3)
C(18)	10 205(3)	4 716(5)	3 081(3)
C(19)	8 203(4)	4 314(6)	3 177(3)
C(20)	5 969(3)	6 104(5)	694(3)
C(21)	12 264(3)	5 148(7)	3 393(5)

bond lengths and angles, shows normal values. The mean values of C–C bond lengths and C–C–C angles for saturated A, B, and C rings are 1.53(1) Å, and 111.3(4)°, although the individual values vary to some extent: C(5)–C(10) = 1.56(1) Å, and 1.51(1)Å for C(6)–C(7), 122.7(4)° for C(10)–C(9)–C(11), and 96.7(3)° for C(5)–C(10)–C(9). Figure 2 shows the molecular packing in the unit cell. This packing is due to hydrogen bonds between O(72) ··· O(71) atoms: $(2 - x, y - \frac{1}{2}, -z), (2 - x, y + \frac{1}{2}, -z)$ [O(72) ··· O(71) = 2.638(13) Å, HO(72) ··· O(71) = 1.74(1) Å, O(72) ··· HO(72) = 0.96(7) Å, O(72) ··· HO(72) ··· O(71) = 155.2(2)°]. Each molecule is linked to another by a two-fold screw axis parallel to the *b* axis.

Experimental

M.p.s are determined with a Kofler hot-plate apparatus and are uncorrected. ^{1}H and ^{13}C N.m.r. spectra were taken for solutions in $CDCl_3$. Silica gel Merck (0.05—0.2 mm) was used for column chromatography.

Bromination of Compound (**7**).—A solution of phenyltrimethylammonium tribromide (130 mg) in dry tetrahydrofuran (3 ml) was added dropwise to a stirred solution of the ketone (**7**) (90 mg) in the same solvent (3 ml) until the mixture turned yellow. This was stirred at room temperature for a further 5 min. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with ethyl ether. Evaporation of the extract afforded the bromo derivative (**8**) as an oil (Found: M^+, 408.1308. $C_{21}H_{29}{}^{79}BrO_3$ requires *M*, 408.1298); $\nu_{max}(CS_2)$ 3 020, 1 730, and 1 708 cm^{-1}; δ_H(200 MHz) 0.94, 1.20, and 1.29 (each 3 H, s), 2.58 and 4.47 (each 1 H, d, *J* 10 Hz, 5-H and 6-H), and 3.67 (3 H, s); *m/z* 410 (1), 408 (1), 229 (20), 311 (1), 297 (2), 269 (26), 221 (11), 213 (11), 199 (8), 161 (24), and 147 (30).

Reduction of the Bromo Ketone (**8**).—The bromo derivative (**8**) (125 mg) in diethyl ether (5 ml) was treated with sodium borohydride (3 mg) in absolute ethanol (1.5 ml). The reaction mixture was stirred for 5 min after which it was diluted with water and extracted with diethyl ether. Evaporation of the extract and chromatography of the residue, eluting with light petroleum–ethyl acetate (4:1), gave the *bromohydrin* (**9**) (105 mg), m.p. 152–153 °C [Found: $(M - H_2O)^+$, 394.1328. $C_{21}H_{29}{}^{81}BrO_2$ requires $M - H_2O$, 394.1330]; δ_H(80 MHz) 0.67 and 0.83 (each 1 H, m, 12-H and 13-H), 1.04, 1.15, and 1.32 (each 3 H, s), 2.40 (1 H, d, *J* 12 Hz, 5-H), 3.62 (1 H, d, *J* 10 Hz, 7-H), 4.34 (1 H, dd, *J* 12 and 10 Hz, 6-H), and 3.65 (3 H, s); *m/z* 412 (M^+, 0.5%), 410 (0.5), 394 (43), 392 (43), 353 (4), 351 (4), 330 (16), 313 (100), 271 (62), 254 (100), 211 (39), 197 (61), 183 (37), 171 (50), and 157 (59). Further elution afforded the alcohol (**10**) (11 mg) (Found: M^+, 332.2349. $C_{21}H_{32}O_3$ requires *M*, 332.2352); δ_H 0.67 and 0.83 (each 1 H, t, 12-H and 13-H), 0.97 (3 H, s), 1.13 (6 H, s), 3.65 (3 H, s), and 3.67 (1 H, br signal, 7-H); *m/z* 332 (M^+, 0.3%), 314 (48), 299 (9), 275 (16), 255 (28), 239 (15), 196 (8), 185 (32), 183 (19), 157 (55), and 131 (32).

Reaction of Compound (**9**) *with Silver Oxide*.—The bromohydrin (**9**) (100 mg) in hexane (25 ml) was treated with freshly prepared silver oxide (500 mg) at reflux under argon for 1 h, after which the mixture was cooled to room temperature and filtered. The flask and the silver salts were washed several times with diethyl ether. The filtrate and washings were combined and evaporated to give a crude residue of the aldehyde (**13**) (69 mg) that was not purified; δ_H(80 MHz) 3.50 (3 H, s) and 9.29 (1 H, d, *J* 5 Hz); *m/z* 330 (M^+).

Oxidation of the Aldehyde (**13**).—The crude aldehyde (60 mg), obtained in the above reaction, in acetone (3 ml) was oxidized with Jones reagent (0.25 ml) at 0 °C for 1 h. The excess of chromic acid was destroyed with methanol, after which the solvent was partially evaporated, and the residue diluted with water and extracted with ethyl acetate. Work-up and subsequent chromatography of the residue with light petroleum–ethyl acetate (4:1) as eluant gave 4-epi-*trachylobagibberellin* A_{12} 18-*methyl ester* (**14**) (28 mg), m.p. 186—189 °C (from light petroleum–ethyl acetate) (Found: *m/z* 346.2103. $C_{21}H_{30}O_4$ requires *M*, 346.2142); δ_H(200 MHz) 0.60 and 0.80 (each 1 H, dd, 12-H and 13-H), 0.91, 1.12, and 1.18 (each 3 H, s), 1.85 and 2.66 (each 1 H, d, *J* 12.4, 5-H and 6-H), and 3.54 (3 H, s); *m/z* 346 (M^+, 7%), 328 (3), 314 (5), 300 (12), 286 (47), 271 (31), 241 (19), 225 (11), and 185 (11). The *dimethyl ester* (**6**), obtained by methylation with diazomethane, had m.p. 90—95 °C (from methanol) (Found: M^+, 360.2277. $C_{22}H_{32}O_4$ requires *M*, 360.2301); δ_H(200 MHz) 0.58 and 0.80 (each 1 H, dd, 12-H and 13-H), 0.89, 1.12, and 1.15 (each 3 H, s), 1.93 and 2.62 (each 1 H, d, *J* 12 Hz), 5-H and 6-H), and 3.51 and 3.62 (each 3 H, s); *m/z* 360 (M^+, 5%), 328 (7), 300 (65), 285 (40), 241 (33), and 225 (18).

ent-*Trachylobagibberellane-7,18-dioic Acid* (4-epi-*Trachylobagibberellin* A_{12}) (**15**).—The monomethyl ester (**14**) (24 mg) dissolved in dimethyl sulphoxide (4 ml) was treated with potassium t-butoxide (50 mg) and stirred under nitrogen at 80 °C for 2 h. The reaction mixture was poured into water, acidified with dilute hydrochloric acid (3%), and extracted with ethyl acetate; work-up of the extract gave the acid (**5**) (13 mg), m.p. 256—259 °C (Found: M^+, 332.2024. $C_{20}H_{28}O_4$ requires *M*, 332.1986); δ_H(200 MHz) 0.71 and 0.79 (each 1 H, m, 12-H and 13-H), 0.91, 1.15, and 1.23 (each 3 H, s), and 2.07 and 2.61 (each 2 H, d, *J* 12 Hz, 5-H and 6-H); *m/z* 332 (6), 314 (6), 286 (100), 271 (95), 258 (5), 241 (15), 258, 241, 332, 286, and 271.

Preparation of Compound (**11**).—The 7β-monoacetate of trachinodiol (**2**) (600 mg) in acetone (20 ml) was oxidized with Jones reagent at room temperature for 5 h. The acetone solution was filtered and the chromic salts were washed with acetone. The combined acetone solutions were concentrated under reduced pressure and then poured into cold water and extracted with ethyl ether. The extract was worked up and the residue was methylated with diazomethane. Chromatography of the product with light petroleum–ethyl acetate (6:1) as eluant, afforded ent-7α-*acetoxytrachyloban*-18-*oic methyl ester* (**11**), m.p. 155—156 °C [lit.,[9] m.p. 154—157 °C (from light petroleum–ethyl acetate)] [Found $(M - AcOH)^+$ 314.2268. $C_{21}H_{30}O_2$ requires M − AcOH, 314.2246]; δ_H(200 MHz) 0.61 and 0.88 (each 1 H, m, 12-H and 13-H), 0.98, 1.11, and 1.13 (each 3 H, s), 2.07 (3 H, s), 3.68 (3 H, s), and 4.58 (1 H, t, *J* 3 Hz, 7-H); *m/z* 374 (M^+, 1%), 314 (100), 299 (19), 255 (34), 254 (27), 239 (23), 199 (11), 185 (28), and 157 (34).

Hydrolysis of Compound (**11**).—Compound (**11**) (140 mg) in methanolic potassium hydroxide (5%) (15 ml) was left at room temperature for 72 h. Work-up afforded compound (**12**), m.p. 146—148 °C (from methanol) (Found: M^+, 332.2336. $C_{21}H_{32}O_3$ requires *M*, 332.2349); δ_H(60 MHz) 0.96 (3 H, s), 1.13 (6 H, s), 3.50 (1 H, t, $W_{\frac{1}{2}}$ 6 Hz, 7-H), and 3.64 (3 H, s); *m/z* 332 (M^+, 3%), 314 (100), 299 (16), 255 (51), 254 (23), 239 (25), 199 (15), 185 (39), and 157 (53).

Crystallographic Data for Compound (**14**).—The crystal data are given in Table 3. Bond distances and angles and the thermal

Table 3. Crystal analysis parameters

Crystal data	
Formula	$C_{21}H_{26}O_4$
Crystal habit	Transparent colourless needles
Symmetry	Monoclinic, *P*21
Unit cell determination	Least-squares fit from 48 reflexions (θ < 45°)
Size of the crystal	0.22 × 0.25 × 0.18 mm
Unit cell dimensions	*a* = 11.969(1), *b* = 7.665(0), *c* = 11.233(1) Å, β = 115.961(1)
D_c(g cm^{-3}), *M*	1.0074, 281.056
F(000), *Z*, μ (cm^{-1})	1 064, 2, 3.856
Experimental data	Four-circle diffractometer PW 1100 Philips. Graphite oriented monochromated Cu-K_α *w*/2θ scans, scan width 1.5, detector aperture 1 × 1, up θ max. 65°, 1 min/reflex.
Number of reflexions	
Independent	1 678
Observed	1 648 [2σ(*I*) criterion], 2 reflex. every 90 min. Variation: no
Solution and refinement	
Solution	Direct methods
Refinement	L.S. on $F_{obs.}$ with 1 block
Parameters	
Number of variables	226
Degrees of freedom	1 422
Ratio of freedom	7.292
H atoms	Difference synthesis for all atoms, all of them were considered as fixed isotropic contributors
Final shift error	0.03
w-scheme	Empirical as to give no trends ⟨wΔ*F*⟩ *vs.* ⟨$F_{obs.}$⟩ and ⟨sin θ/λ⟩
Max. thermal value	$U_{33}(C_{21})$ = 0.085 58 Å^2
Final *R* and R_w values	3.9 and 4.3
Computer and programs	VAX 11/750, DIRDIF[15] X-RAY 76[16]
Scattering factors	International Tables for X-Ray Crystallography[17]

parameters are available on request from the Cambridge Crystallographic Data Centre.*

Acknowledgements

We thank the CAICYT (Madrid) for financial support. R. G. thanks the Spanish Research Council (CSIC) and Ministry of Education and Science for a fellowship.

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* See Instructions for Authors *J. Chem. Soc., Perkin Trans 1*, 1988, Issue 1.

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Received 5*th June* 1987; *Paper* 7/984