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METHODOLOGY FOR TRANSLOCATING THE CARBOXY GROUP IN GIBBERELLINS: THE PARTIAL SYNTHESIS OF 7(6→15βH)ABEO-GA_4

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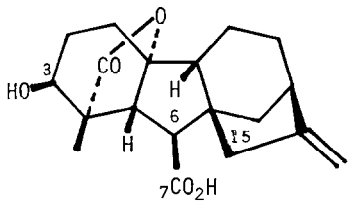
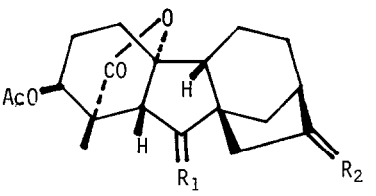
Summary: The carboxylic acid group has been excised from phytohormone gibberellin A_4 and relocated on the D-ring, thereby generating a new class of gibberellin derivatives related structurally to helminthosporic acid.

In a continuation of our investigations into the molecular basis for the phytohormonal activity of gibberellins,[1] we have now developed mild and efficient procedures for excising the biologically important B-ring carboxylic acid group and relocating it on the D-ring. The present work complements other reports which describe the chemical modification[2] and configurational inversion[3] of this group, and encompasses the preparation of a new class of gibberellin derivatives related structurally to helminthosporins.[4] The methodology is illustrated by the following conversion of gibberellin A_4 [GA_4 (1)] into 7(6→15βH)abeo-GA_4 (10).[5]

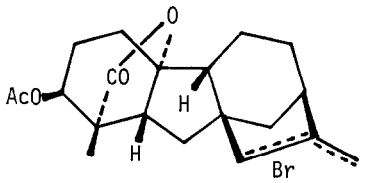
GA_4 (1) was first acetylated (Ac_2O, Py, 4 eq, 0°, 6 h; H_2O, 0.75 h) and then converted by ozonolysis (EtOH, -5°; Zn-AcOH) into the amorphous 17-nor-keto acetate (2).[8] Iododecarboxylation promoted by lead tetra-acetate (3.1 eq during 3.5 h, $ClCH_2CH_2Cl$, reflux), iodine (2.5 eq during 3.5 h), and light (300 W tungsten lamp)[9,10] gave the iodide [(3), 82% overall from GA_4],[8] which was dehalogenated using chromous acetate (3.1 eq, Me_2SO-propanethiol, 25°, 7.5 h)[11] to yield 7,17-dinor-GA_4 acetate [(4), 72%].[8] A careful Wittig methylenation ($Ph_3P^+CH_3Br^-$, KO t Bu, t BuOH-THF, 1.04 eq, 20°, 1 h)[12] gave 7-nor-GA_4 acetate [(5), 92%][8] which reacted with N-bromosuccinimide (1.1 eq, CCl_4, reflux, 0.6 h) to afford a mixture of primary and secondary bromides (6)[8] that was sufficiently pure for immediate use. Treatment with pyrrolidinyl-1-acetonitrile (PAN) (1.2 eq, Me_2SO, 70°, 24 h) gave the expected primary allylic ammonium salt (7)[8,13] which underwent a base-induced [2,3]-sigmatropic rearrangement in situ after dilution with THF, cooling (-20°), then careful addition of KO t Bu in t BuOH (1M, 1 eq, 15 min).[14] The pyrrolydinyl nitrile (8)[8,15] thus formed was immediately hydrolysed (30% oxalic acid aqu-THF, 1:1, reflux 8 min)



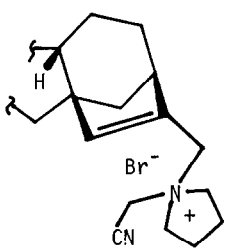
(1)



	R_1	R_2
(2)	βCO_2H, αH	O
(3)	βI, αH	O
(4)	βH, αH	O
(5)	βH, αH	CH_2



(6)



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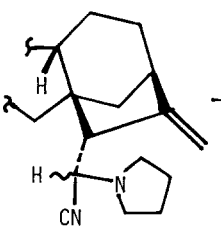
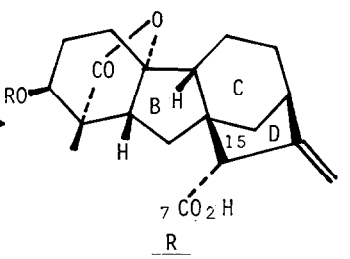


(8)



	R
(9)	Ac
(10)	H

and the resulting β,γ-unsaturated aldehyde[8] oxidized (titration CrO_3-H_2O, acetone, 0°)[16,17] to furnish the abeo-GA_4 acetate (9) in ∿65% overall yield from the olefin (5).

With due regard for the potential hazards of epimerization at C3 and conjugation of the β,γ-olefinic bond, the 3β-acetate was cleaved by mild methanolysis (MeOH-H_2O-10%K_2CO_3, 1:1:1, 20°, 6 h)[18] to produce in this final step the target, 7(6→15βH)abeo-GA_4 (10).

Preliminary bioassays indicate that the activity of abeo-GA_4 is very much less than that of GA_4. This is particularly interesting, because a recent X-ray

crystallographic comparison of gibberellic acid with a helminthosporin related to the B/C/D portion of abeo-GA_4,[19] shows that the hydroxy groups of carboxylic acid functions at C6 or C15 can occupy similar positions in space; furthermore, the configuration of the carboxy group does not seem to be a critical factor in the gibberellin-like activity of helminthosporins.[20] Possible reasons for the lower potency of abeo-GA_4 relative to GA_4 are currently being investigated.

References and Notes

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2. M. Lischewski and G. Adam, Tetrahedron, 36, 1237 (1980).
3. M. Lischewski and G. Adam, Tetrahedron Letters, 21, 1627 (1980).
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5. The prefix 7(6→15βH)abeo is applied to the ent-gibberellane skeleton[6] and follows the IUPAC-IUB Rules for Steroid Nomenclature, J. Org. Chem., 34, 1517 (1969).
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8. Selected data as follows: (2): $[\alpha]_D^{20}$ +68° (1.0 $CHCl_3$): ^1H NMR ($CDCl_3$) δ 1.12 (s, 3H), 2.16 (s, 3H), 2.76 (d, J=10Hz, 1H), 3.16 (d, J=10Hz, 1H), 5.02 (m, H3), 6.64 (e, 1H, OH). (3): m.p. 151-152° (dec); $[\alpha]_D^{20}$ -33°(1.0 $CHCl_3$): ^1H NMR ($CDCl_3$) δ 1.38 (s, 3H), 2.10 (s, 3H), 3.05 (d, J=10Hz, H5), 3.90 (d, J=10Hz, H6), 4.96 (m, H3); IR (Nujol) 1775, 1735, 1225 cm^{-1}. Anal. $C_{19}H_{23}O_5I$ (C,H). (4): m.p. 157-160°; $[\alpha]_D$ +100° (1.0 $CHCl_3$); ^1H NMR ($CDCl_3$) 1.07 (s, 3H), 2.04 (s, 3H), 4.82 (m, H3); IR (Nujol) 1755, 1730, 1220 cm^{-1} M.s. m/z 332 (M^+, 13%), 291 (21), 228 (100), 185 (50); Anal. $C_{19}H_{24}O_5$(C,H). (5): m.p. 146-148°; $[\alpha]_D$ +32° (1.0 $CHCl_3$): ^1H NMR ($CDCl_3$) δ 1.04 (s, 3H), 2.05 (s, 3H), 2.60 (m, 2H), 4.78 (m, H3), 4.90 (br s, C=CH_2); IR (Nujol) 1770, 1740, 1660 (w), 1220 cm^{-1}; M.s. m/z 330 (M^+, 10%), 226 (100). Anal. $C_{20}H_{26}O_4$ (C,H). (6): ^1H NMR ($CDCl_3$) δ 1.08 (s, 3H), 2.14 (s, 3H), 2.92 (t, J_{AB} = 5Hz, $BrCH_2$, 0.5H), 4.70 (m, H3, 1.0H), 4.90 (br s, methylene H + HCBr, 1.75H), 5.22 (br s, methylene H), 5.64 (br s, HC=C, 0.25H), thus 2°:1° bromide ∿3:1; IR (film) 1770, 1735, 1230 cm^{-1}; M.s. high resolution M^+, 408.0928: $C_{20}H_{25}O_4$ ^{79}Br calc. M^+ 408.0936. (7): ^1H NMR (d6-Me_2SO) δ 1.0 (s, 3H), 2.06 (s, 3H), 4.24 (br s, $\overset{+}{N}CH_2CN$), 4.70 (m, H3), 4.80 (br s, $\overset{+}{N}$-CH_2C=C), 6.4 (s, HC=C). (8): m.p. 145-151° (diastereomers); ^1H NMR ($CDCl_3$) δ1.14 (br s, 3H), 2.05 (s, 3H), 2.6 (m, $N(CH_2)_2$), 4.0 (m, HCCN, epimeric), 4.92 (m, H3), 5.24 (m, 2H); IR (Nujol) 1770, 1740, 1245, 920, 900 cm^{-1}; M.s. high resolution M^+. 438.2516: $C_{26}H_{34}N_2O_4$ calc. M^+ 438.2518; M.s m/z 438 (M^+, 43%), 411 (M^+ – HCN, 100). (8, 7-aldehyde): ^1H NMR ($CDCl_3$) δ 2.10 (s, 3H), 4.90 (m, H3 + methylene H), 5.20 (m, methylene H), 9.24 (d, J=4Hz, 0.7H), 9.84 (br s, 0.3H), thus unconj. :conj. aldehyde ∿7 : 3: IR (Nujol) 2720, 1770, 1740, 1720 (shoulder), 1650 (m, conj. CHO), 1230, 890 cm^{-1}. (9): m.p. 190-193°, $[\alpha]_D^{21}$ + 39° (1.0 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.06 (s, 3H),

2.05 (s, 3H), 2.70 (m, H5 + H13), 3.13 (br s, $\underline{H}CO_2H$), 4.90 (m, H3), 5.08 + 5.16 (2 br s, $C{=}CH_2$), 9.0 (br e, OH); IR (Nujol) 3000-2600 (OH), 1760 (lactone), 1745 (acetate), 1700 (acid), 1650 (w, C=C), 1230, 885 cm^{-1}; M.s. m/z 374 (M^+, 5%), 270 (100); Anal. $C_{21}H_{26}O_6$ (C,H). (10): m.p. 207-209° dec., $[\alpha]_D^{24}$ -1° (0.5 $CHCl_3$); δ 1.2 (s, 3H), 2.72 (m, H5 + H13), 3.13 (br s, $\underline{H}CO_2H$), 3.82 (m, H3), 5.08 + 5.16 (2 br s, $C{=}CH_2$), 6.1 (br e, 2 OH); IR (Nujol) 3500-2400 (OH), 1750 (lactone), 1700 (acid), 1650 (w, C=C), 1200 (br), 895 cm^{-1}; M.s. m/z 332 (M^+, 11%), 314 (20), 288 (M^+-CO_2, 44), 270 (100); Anal. $C_{19}H_{24}O_5$ (C,H).

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13. The allylic secondary bromide reacted in an $Sn2'$ mode.[4]

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15. Diastereomeric at C7; 15βH stereochemistry follows from the expectation that rearrangement has taken place on the less hindered exo-face[14], as with analogous examples.[1,4,19]

16. The α,β-unsaturated isomer in the mixture is not oxidized under the reaction conditions.

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