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TOTAL SYNTHESIS OF GIBBERELLIN A_4

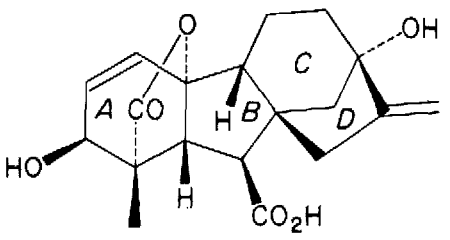
Ailsa L. Cossey, Luciano Lombardo and Lewis N. Mander*

Research School of Chemistry, Australian National University

P.O. Box 4, Canberra, A.C.T. 2600, AUSTRALIA

ABSTRACT: A general approach to the preparation of 13-deoxy C_{19} gibberellins has been established with the total synthesis of (±) gibberellin A_4 (3).

The C_{19} gibberellin phytohormones may be conveniently classified into two groups: those with a 13-hydroxyl function, e.g. A_3, gibberellic acid, (1) and A_1 (2), and those without, e.g. A_4 (3). Although the 13-hydroxyl group usually enhances growth promotion, it may suppress activity, as in the Curcubitaceae.[1] Consequently, in designing a strategy for gibberellin synthesis, we were concerned that it should be suitable for the preparation of both classes of compounds. We have recently described the preparation of gibberellins A_3 (1) and (±) A_1 (2),[2] and now report the total synthesis of (±) A_4 (3)[3] through application of the same methodology.



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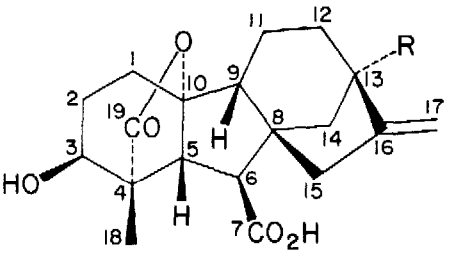
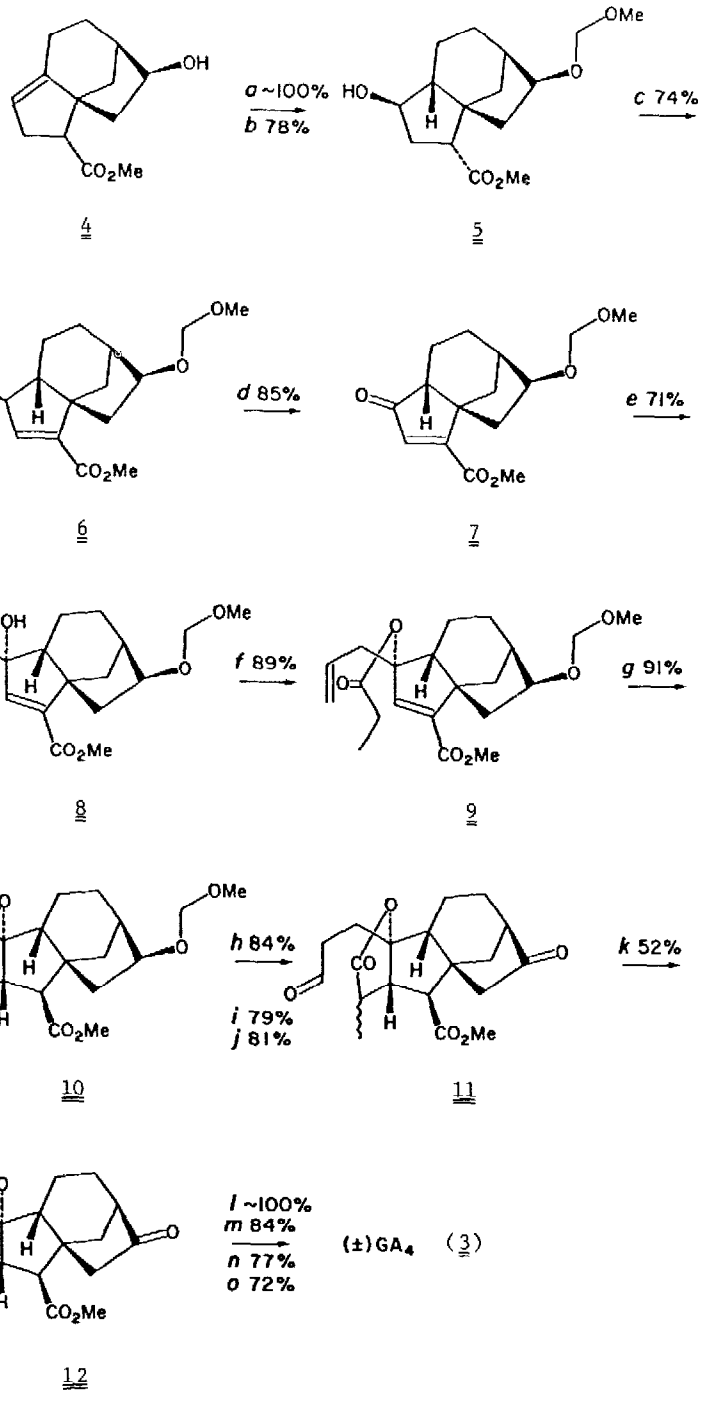


2 R = OH
3 R = H

The sequence leading to 3, which is outlined in the Scheme, is based on the stereo-controlled addition of the A-ring to ester 4, m.p. 78-80°,[4] which was available from earlier studies.[5] The olefinic bond in 4 is equally exposed on both faces, except for the 6α-ester substituent. Reagent approach to the β-face is therefore favoured, and hydroboration afforded 5 (parent diol m.p. 138-140°) which was converted into enone 7, m.p. 77-78°, UV (MeOH) 244 nm (log ε 3.94), IR (Nujol) 1723, 1705, 1592 cm^{-1}, δ 6.70 (s, C=CH), by α-selenenylation of the ester function,[6] selenoxide elimination to 6 and then oxidation by a modified Collins procedure.[7] Addition of triallyl alane[8] to 7 furnished an 11:2 mixture of 8 with its C(10) epimer (stereochemistry based on the expected approach of reagent along the equatorial vector) and the derived propionate 9[9] transformed to the A-seco-gibberellin



4 5 6 7 8 9 10 11 12

Reagents: a *$MeOCH_2Cl$, $(i\text{-}Pr)_2NEt$, 24°, 2 days.* b *B_2H_6, THF, 0°, 5 h; Na_2HPO_4, H_2O_2, 65°, 2 h* c *KH, $(PhSe)_2$, THF, 0°, 1 h; 30% H_2O_2, Py, CH_2Cl_2, 0°, 0.5 h.* d *$CrO_3 \cdot 2Py$, CH_2Cl_2, 0°, 5 min.* e *$(CH_2{=}CHCH_2)_3Al$, THF, -78°, 5 min.* f *$(EtCO)_2O$, NEt_3, 4-dimethylamino-pyridine, 2°, 5½ days.* g *KH, DMF, -20°, 0.5 h.* h *BBr_3, CH_2Cl_2, -78°, 5 min;*

$NaHCO_3$, H_2O, THF, 24°, 16 h. i *$(i\text{-}Am)_2BH$, Et_2O, 1 h; Na_2HPO_4, H_2O_2, 35°, 2 h.* j *$CrO_3 \cdot 2Py$, CH_2Cl_2, 24°, 1 h.* k *2% K_2CO_3, MeOH-H_2O (4:1), 24°, 2.5 h.* l *PhCOCl, Py, 24°, 16 h.* m *$Ph_3\overset{+}{P}CH_3\bar{B}r$, KOtBu, THF, tBuOH, 24°, 3 min.* n *n-PrSLi, HMPA, 24°, 1 h.* o *As for k, 3 h.*

mixture 10 by a novel intramolecular Michael reaction. The prognosis for this crucial reaction seemed to be poor, since it appeared, from an examination of molecular models, that considerable torsional strain would be incurred during the transition state, in order to maintain optimal orbital overlap between the donor and acceptor π-bonds. Indeed, most reagents and solvents failed to induce the desired conjugate addition. The combination of potassium hydride with a dipolar aprotic solvent appears to be crucial for success.

It was possible for four diastereomers to be formed in the Michael reaction, but when the reaction mixture was quenched at -40° by triethylammonium acetate a 2:1 mixture of 4α,6β- and 4β,6β-isomers, respectively, was formed. The observation of a ^{13}C-NMR resonance at δ 11.7 for the former, and at δ 17.4 for the latter indicated that the methyl group of the major epimer was in the sterically more congested environment, ie, endo. The absence of resonances in the δ 30-37 range of the spectrum was consistent with the 6β-configuration, since the shielding effect of a 6α-ester group would be expected[5] to produce a chemical shift of δ ∿ 33 for C(14) (cf. δ 33.5 in 5). The combined isomers were elaborated to aldehyde mixture 11, as indicated, and then transformed by an intramolecular aldol reaction into a 3:1 mixture of the norgibberellin 12 with its 3α-epimer.[10] Although 3β-hydroxygibberellins are rapidly isomerized to the thermodynamically preferred 3α-isomers by strong bases,[11] the aldol reaction proceeded readily at pH 10 ($T_{½}$ ∿ 1.3 h), and under these conditions the C(3) inversion was relatively slow ($T_{½}$ ∿ 16 h). (±)-Hydroxyketone 12, m.p. 209-211°, furnished IR, NMR, and mass spectra which were indistinguishable from those of the (+)-enantiomer, m.p. 212-213°, derived from A_4.[3c]

Completion of the sequence was straightforward, but carried out with due regard for the possibility of isomerization at C(3). Accordingly, 12 was converted to its benzoate, m.p. 180-181°, subjected to Wittig methylenation[12] and then demethylated[13] to give (±)-gibberellin A_4 3-benzoate, m.p. 273-276°. Finally, hydrolysis at pH 10 furnished (±)-A_4 (3), m.p. 220-222°. IR, NMR, and mass spectra were indistinguishable from those of the (-)-enantiomer, m.p. 215° or 255°.[3d]

Earlier gibberellin syntheses have depended on relays[14] and have been characterized by long and arduous sequences.[15] The brevity and simplicity of the present approach provide a sharp contrast to those earlier studies. Further applications to C_{19} gibberellin derivatives and adaptation of the strategy to the construction of C_{20} gibberellins will be reported shortly.

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References and Footnotes

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