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A NOVEL EXPEDITIOUS ENTRY INTO GIBBERELLINS. THE TOTAL SYNTHESIS OF (±)-GA$_5$

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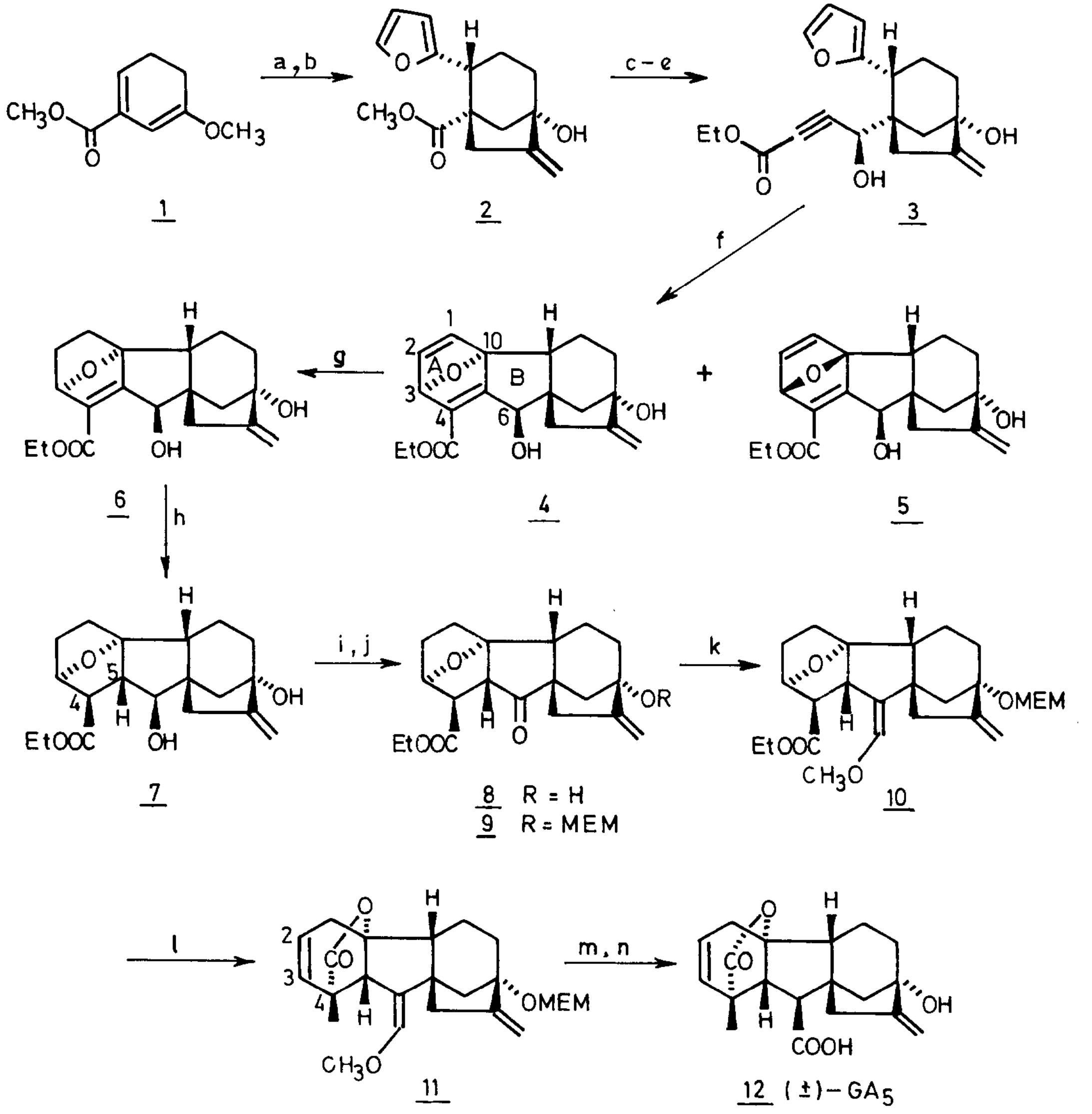
ABSTRACT : A 16-step synthesis of (±)-GA$_5$ (12), starting from m-methoxybenzoic acid, is described. Refunctionalization of the kinetic cycloadduct 4, obtained in 96 % yield from the Diels-Alder reaction of furan 3 in water in the presence of β-cyclodextrin, to ketone 9, followed by Wittig olefination and selective quaternization to 11, leads to the correctly functionalized A-ring for eventual transformation to the title compound.

The considerable efforts that have been devoted to the total synthesis of gibberellin phytohormones have culminated in recent years in the total synthesis of gibberellic acid and several other members of this family[2,3]. The length of the involved sequences (~30 or more steps), however, still leaves room for improvement in terms of synthetic efficiency. In connection with studies aiming at investigating the potential of intramolecular Diels-Alder reactions of furan-dienes in natural product synthesis[4], we wish to report herein on a short entry into gibberellins, which led to the total synthesis of (±)-GA$_5$ (12)[5].

We have previously disclosed the synthesis of Diels-Alder precursor 3 from diene 1 (readily available from m-methoxybenzoic acid via Birch reduction[6], followed by esterification), and its cycloaddition reaction in refluxing benzene to a mixture of 4 and 5 (24 h; 70 % yield; 3:1 ratio of 4:5)[7]. The observed change in ratio of both adducts upon prolonged heating revealed 4 as being the kinetically preferred adduct (120 h; 70 % yield; 1:1 ratio of 4:5). Combined lowering of the reaction temperature and shortening of the reaction time led to the expected gain in selectivity but at the expense of the yield (benzene, 65°C, 6 h; 25 % yield; >95:5 ratio of 4:5). An important rate enhancement resulted when working under the same conditions, but in water[8] as the solvent (56 % yield; >95:5 ratio of 4:5)[9]. Finally, optimal reaction conditions were realized when working in the presence of β-cyclodextrin[8,9a] which afforded the desired 4 in 96 % isolated yield. Its structure has been defined unambiguously by X-ray diffraction analysis[7c].

The conversion of adduct 4 into a C_{19}-gibberelin[10] further requires : (1) the stereoselective introduction of a quaternary methyl group at C-4; (2) the transformation of the 6-hydroxyl group into a carboxylic acid; (3) adequate refunctionalization of the A-ring, especially with regard to obtaining the required *trans*-fused AB-ring system. This has now been accomplished as follows. After selective hydrogenation of the $\Delta^{1,2}$-bond with Pd-$BaSO_4$ as a catalyst (quantitative), sodium borohydride reduction of the unsaturated ester 6[11] led to the exclusive 1,4-introduction of the hydride from the β-face, giving ester 7[11] in 86 % yield. Diastereomer 7 is the more stable product arising from in situ equilioration of the kinetically favored epimer at C-4; the latter can be isolated after immediate work-up. In accord with the proposed structures H-4 exhibits (^{1}H NMR) a broad triplet in 7 (2.98 ppm; J ~5.0 Hz) and a doublet in 4-epi-7 (2.99 ppm; J = 9.25 Hz). After Swern oxidation to 8[11] (77 % yield), the tertiary alcohol was protected as the methoxyethoxymethyl ether 9[11] (89 % yield)[12]. Subsequent reaction with methoxymethylenetriphenylphosphorane (obtained from the corresponding phosphonium chloride and potassium *tert*-amylate in benzene) gave the *E*-olefin 10[11] in 40 % yield, next to 50 % of a cyclopentenone derivative arising from base induced oxygen bridge opening in 9. The *E*-derivative is obtained with high selectivity; less than 10 % of the corresponding *Z*-isomer is detected by ^{1}H NMR[13]. Treatment of ester 10 with 6 equiv of lithium isopropylcyclohexylamide (-78°C, then r.t.), followed by the addition of methyl iodide, resulted in the direct formation of lactone 11[11] in 52 % yield via a one-pot sequence which involves : (1) enolate formation, followed by bridge opening to the $\Delta^{3,4}$-unsaturated ester; (2) subsequent deprotonation, followed by regio- and stereoselective methylation of the resulting $\Delta^{2,3}$-dienolate; (3) in situ lactone formation by internal transesterification of the syn-diaxial oriented alkoxide and ester groups.

Eventually, acid hydrolysis to the corresponding hydroxy aldehyde (56 % yield), followed by sodium chlorite oxidation[14] (90 % yield), gave (±)-GA_5 (decomp. 209°C)[11], whose spectral properties (360 ^{1}H NMR) and TLC behavior were identical with those of an authentic sample[15]. Although the yields of several steps still need to be improved upon, the present sequence represents the shortest entry yet known in this field (16 steps from m-methoxybenzoic acid) and should provide for enough flexibility for the synthesis of related gibberellins. Also the problem of adapting the sequence for the synthesis of the chiral natural forms will be addressed in the future[16].



MEM = $CH_2OCH_2CH_2OCH_3$. (a) C_4H_3OMgI (1.4 equiv), ether, 2 h at −20°C; $BrCH_2C(Br)=CH_2$ (2.6 equiv), HMPT, −20°C, then 2 h at −20°C; 2 N HCl-THF, 3 h at rt. (b) *n*-Bu_2CuLi (10 equiv), THF, 30 min at −50°C. (c) LAH, THF, 30 min at 0°C. (d) $(COCl)_2$, DMSO, CH_2Cl_2, 45 min at −60°C; then Et_3N, 14 min at −60°C; then 2 h at rt. (e) LiC≡CCOOEt (2.4 equiv), THF, 1 h at −90°C; HOAc at −90°C, then rt. (f) ß-cyclodextrin (1 equiv), H_2O, 6 h at 65°C. (g) H_2, Pd-$CaCO_3$ (5 %), EtOAc, till uptake of 1 equiv. (h) $NaBH_4$, EtOH, 3 h at rt; with separate isomerization with NaOEt if 4-epi-*7* is still present (scale-dependent; TLC). (i) see (d). (j) MEMCl and *i*-Pr_2NEt (3 equiv), CH_2Cl_2, 20 h at rt. (k) $CH_3OCH=PØ_3$ (5 equiv; from $CH_3OCH_2PØ_3Cl$, *t*-AmOK, benzene), benzene, 20 h at rt. (l) *i*-$PrC_6H_{11}NLi$ (6 equiv), −78°C to rt over 2 h, then 1 h at rt; MeI (20 equiv), HMPT, −78°C, then 20 h at rt. (m) C_6H_5NHOTs (10 equiv), *t*-BuOH, 80°C, 16 h. (n) $CH_3C(CH_3)=CHCH_3$, $NaClO_2$, NaH_2PO_4 buffer, *t*-BuOH, 1 h at rt.

References and notes

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9. (a) For an example where the hydrophobic effect actually slows down an intramolecular Diels-Alder reaction with furan-diene (IMDAF), see : D.D. Sternbach and D.M. Rossana, J. Am. Chem. Soc., 104, 5853 (1982); (b) for an impressive rate enhancement of an IMDAF reaction in water, see ref. 5b.
10. C_{19}-gibberellins lack an angular carbon atom at C-10 (gibberellin numbering).
11. Satisfactory spectral data were obtained for all compounds. Relevant ^{1}H NMR data (360 MHz, ∂ downfield from Me_4Si, $CDCl_3$: **6** (d_6-acetone) : 5.12 (1H, d, 5.0 Hz), 5.09 (1H, m), 4.93 (1 H, m), 4.52 (1H, s), 4.44 (1H, bs), 3.79 (1H, bs), 4.16 (2H, m), 1.25 (3H, t, 7.3 Hz) ppm; **7** : 5.17 (1H, bt, 2.0 Hz), 5.03 (1H, bs), 4.69 (1H, bt, 4.5 Hz), 4.18 (2H, q, 7.0 Hz), 3.65 (1H, d, 2.3 Hz), 2.98 (1H, bt, 5.0 Hz), 1.28 (3H, t, 7.0 Hz) ppm; **8** : 5.22 (1H, t, 2.5 Hz), 4.93 (1H, bs); 4.74 (1H, bt, 4.5 Hz), 4.18 (2H, q, 7.0 Hz), 3.25 (1H, bt, 4.5 Hz), 2.98 (1H, d, 4.5 Hz), 1.28 (3H, t, 7.0 Hz) ppm; **9** : 5.10 (1H, m), 5.00 (1H, m), 4.84 (1H, d, 7.3 Hz), 4.69 (1H, d, 7.3 Hz), 4.74 (1H, t, 4.5 Hz), 4.18 (2H, m), 3.77 (1H, m), 3.62 (1H, m), 3.53 (2H, m), 3.38 (3H, s), 3.25 (1H, t, 4.5 Hz), 2.97 (1H, d, 4.0 Hz), 1.28 (3H, t, 7.0 Hz) ppm; **E-10** : 5.88 (1H, d, 2.5 Hz), 5.06 (1H, m), 5.03 (1H, bs), 4.91 (1H, d, 7.5 Hz), 4.69 (1H, d, 7.5 Hz), 4.67 (1H, m), 4.18 (2H, m), 3.82 (1H, m), 3.49 (3H, s), 3.39 (3H, s), 3.11 (1H, dd, 5.5, 2.5 Hz), 2.95 (1H, bt, 5.5 Hz), 1.27 (3H, t, 7.0 Hz) ppm; **11**: 6.06 (1H, d, 2.5 Hz), 5.77 (2H, m), 5.07 (2H, bs), 4.92 (1H, d, 7.5 Hz), 4.68 (1H, d, 7.5 Hz), 3.83 (1H, m), 3.56 (3H, s), 3.38 (3H, s), 3.01 (1H, d, 2.5 Hz), 1.35 (3H, s) ppm; **12** (d_5-pyridine) : 5.73 (2H, m), 5.61 (1H, bs), 5.05 (1H, bs), 3.14 (1H, AB d, 9.5 Hz), 3.08 (1H, AB d, 9.5 Hz), 1.46 (3H, s) ppm.
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13. The *E/Z* assignments rest on 2D NOESY experiments (200 MHz) which show an effect between $COOCH_2CH_3$ (4.18 ppm) and $=CHOCH_3$ (3.49 ppm) in *E*-10, and between $COOCH_2CH_3$ (1.28 ppm) and $=CHOCH_3$ (5.80 ppm) in *Z*-10. We thank Prof. J. Gelan (Limburgs Universitair Centrum, Diepenbeek) for recording these spectra.
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15. We are grateful to Prof. MacMillan (The University of Bristol, UK) for kindly sending an authentic sample of methyl ester GA$_5$ 13-acetate, which was converted to (-)-GA$_5$ via saponification following : M.H. Beale, P. Gaskin, P.S. Kirkwood, and J. MacMillan, J. Chem. Soc., Perkin I, 885 (1980).
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