A New and Efficient Strategy for the Total Synthesis of Polycyclic Diterpenoids: The Preparation of Gibberellins (±)-GA$_{103}$ and (±)-GA$_{73}$

Geoffrey R. King, Lewis N. Mander,*
Nathaniel J. T. Monck, Jonathan C. Morris, and
Hongbin Zhang

Research School of Chemistry
Australian National University
*Canberra, A.C.T. 0200, Australia*

In a continuing quest for greater efficiency in the synthesis of complex polycyclic natural products,[1] we have recently examined the intramolecular cyclopropanation[2] of the aromatic ring in tetralin diazomethyl ketones, *e.g.*, **1** → **2**.[3] The norcaradiene derivatives that are formed are reasonably stable, and it has been possible to assemble **3** in only seven steps from 1,6-dimethoxynaphthalene with excellent diastereoselectivity and in good overall yield. The C(3) acyl group in **3** may be selectively attacked by methoxide ion,[4] allowing further elaboration to lactone **4** as described previously (Scheme 1).[3]

With the availability of **3** and similar compounds from this type of sequence, we envisage that polycyclic diterpenoids based on kaurane, beyerane, atisane, stemarane, thyrsiflorane, gibberellane, or antheridane skeletons[5] could all be assembled with previously unparalleled efficiencies. As a demonstration of the effectiveness of this new strategy, we now describe the total synthesis of the gibberellins GA$_{103}$ (**5**) and GA$_{73}$ methyl ester (**6**). The 9,15-cyclogibberellin **5** is representative of a new
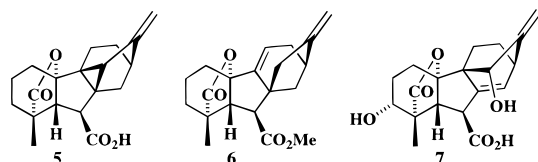

family of hexacyclic gibberellins recently isolated in trace amounts from developing apple seeds[6] and was shown earlier[7] to be a biosynthetic precursor to the major antheridium inducing substance from *Anemia phyllitidis*, antheridic acid (**7**),[8,9] while **6** is an exceptionally potent antheridiogen isolated from several *Lygodium* species.[10] Although **5** and **6** have already been prepared by partial synthesis,[11] a more flexible route was required in order to gain access to isotopically labeled and

Scheme 1
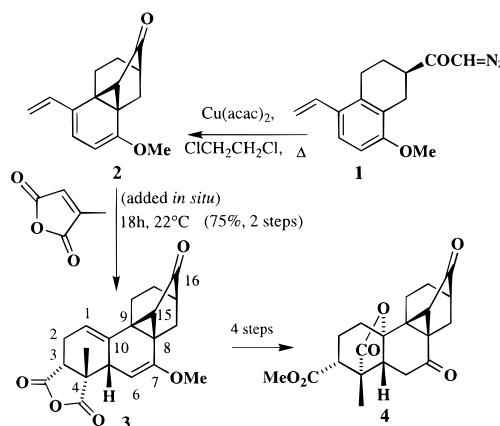
Scheme 2
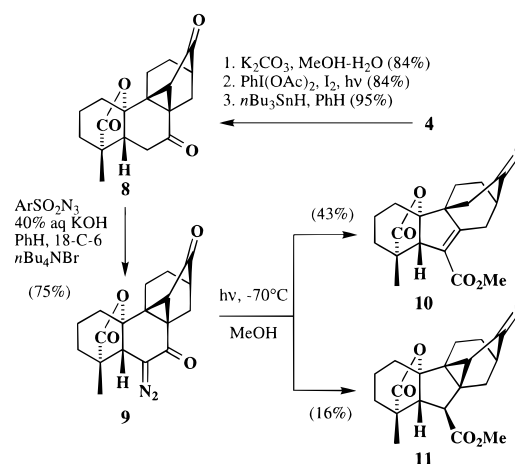
functionalized derivatives required for further structural and biosynthetic studies. Total synthesis was expected to afford the additional flexibility that we required.

Our initial approach to **5** is outlined in Scheme 2. The C(3) ester function in **4** was hydrolyzed, and the resulting carboxylic acid subjected to iodo-decarboxylation,[12] affording a 3:2 mixture of 3α- and 3β-iodides that were deiodinated to give **8**. Citraconic anhydride was thus established as an *endo*-selective synthetic equivalent for 2-methylacrylic acid in the earlier [4 + 2] cycloaddition, the enhanced reactivity, high yields, and stereochemical control more than compensating for the additional steps required to delete the superfluous carboxy group.[13]

In anticipation of ring-contraction to the desired gibberellin-like structure,[14] diazo-transfer to **8** was effected with trisyl azide under phase transfer conditions.[15] Wolff rearrangement of the resulting diazo ketone **9**, however, was accompanied to a major extent by concomitant fragmentation to the norantheridane skeleton, affording **10** as the predominant product, with only a modest amount of the target ester **11**.[16] During studies of the controlling factors in this reaction, it was observed that prolonged irradiation of **11** for extended periods afforded **10**,

(1) Mander, L. N. *Synlett* **1991**, 134–144.

(2) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091–1160.

(3) Rogers, D. H.; Morris, J. C.; Roden, F. S.; Frey, B.; King, G. R.; Russkamp, F.-W.; Bell, R. A.; Mander, L. N. *Pure Appl. Chem.* **1996**, *68*, 515–522.

(4) Asymmetric anhydrides have been reported to react with nucleophiles at the more substituted acyl group (Kayser, M. M.; Morand, P. *Can. J. Chem.* **1978**, *56*, 1524–1532). For **3**, reaction at the acyl group attached to C-4 was not observed.

(5) Dev, S.; Misra, R. *CRC Handbook of Terpenoids, Diterpenoids Vol IV: Tetracyclic and Pentacyclic Diterpenoids*; CRC Press: Boca Raton, FL, 1986.

(6) Oyama, N.; Yamauchi, Y.; Yamane, H.; Murofushi, N.; Agatsume, M.; Pour M.; Mander, L. N. *Biosci. Biotech. Biochem.* **1996**, *60*, 305–308.

(7) Yamauchi, T.; Oyama, N.; Yamane, H.; Murofushi, N.; Takahashi, N.; Schraudolf, H.; Furber, M.; Mander, L. N.; Patrick, G. L.; Twitchin, B. *Phytochemistry* **1991**, *30*, 3247–3250.

(8) Nakanishi K.; Endo M.; Näf, U.; Johnson L. F. *J. Am. Chem. Soc.* **1971**, *93*, 5579–5581.

(9) Corey, E. J.; Myers, A. G.; Takahashi, N.; Yamane, H.; Schraudolf, H. *Tetrahedron Lett.* **1986**, *27*, 5083–5086.

(10) Furber, M.; Kraft-Klaunzer, P.; Mander, L. N.; Pour, M.; Yamauchi, T.; Murofushi, N.; Yamane, H.; Schraudolf, H. *Aust. J. Chem.* **1995**, *48*, 427–444.

(11) Furber, M.; Mander, L. N.; Patrick, G. L. *J. Org. Chem.* **1990**, *55*, 4860–4870.

(12) Concepcion, J. I.; Francisco, C. G.; Freire, R.; Hernandez, R.; Salazar, J. A.; Suarez, E. *J. Org. Chem.* **1986**, *51*, 402–404.
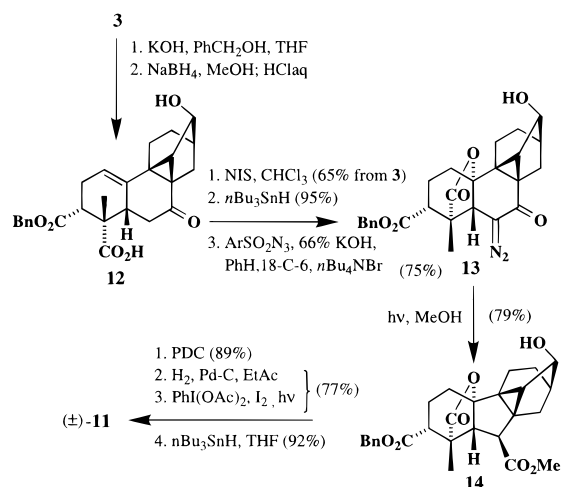
(13) Norcaradiene derivatives such as **2** rearrange rapidly with even the mildest Lewis acids, use of which is therefore not an option for catalyzing the cycloaddition. Without catalysis, methyl methacrylate and its analogues tend to give *endo*/*exo*-mixtures in which the *exo*-isomers predominate (*cf.*, Meek, J. S.; Trapp, W. B. *J. Am. Chem. Soc.* **1957**, *79*, 3909–3912). For other synthetic targets, the 3-carboxy group could be used to introduce A-ring substituents.

(14) Mander, L. N.; Pyne, S. G. *J. Am. Chem. Soc.* **1979**, *101*, 3373–3375. Nuyttens, F.; Appendino, G.; De Clercq, P. J. *Synlett* **1991**, 526–527.

(15) Lombardo, L.; Mander, L. N. *Synthesis* **1980**, 368–369.

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Scheme 3

Scheme 4

but the rate was such that it could account for only a small amount of this product. Although fission of the C(8)−C(15) bond has been initiated by enolization of the ester function in similar substrates,[11] solvation of the assumed intermediate ketene under the reaction conditions (pH 7−10) would be expected to involve C-protonation,[17] *i.e.*, the enol would be bypassed. Under conditions of low pH (Cl₂CHCO₂H) that would be expected to favor O-protonation and thus enol formation, the reaction could in fact be steered completely in the direction of **10**. No conditions could be found (temperature, solvent, pH, and wavelength) that would lead to an increase in the proportion of **11**, however.[18]
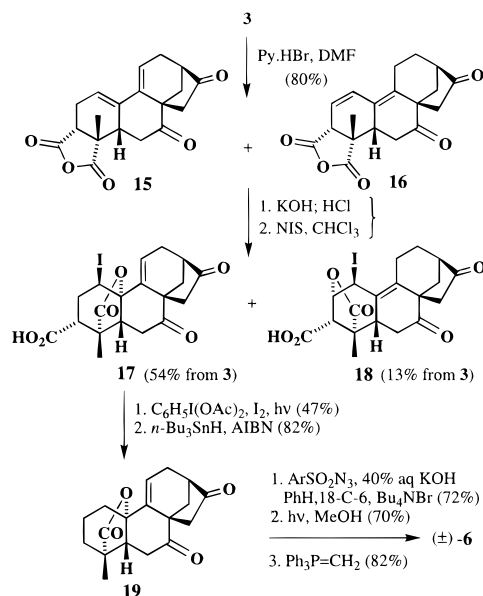
On the presumption that fragmentation was promoted by electron withdrawal by the C(16) carbonyl substituent, the sequence followed in Scheme 2 was modified by replacing this group by hydroxyl, as summarized in Scheme 3. Taking advantage of the initial masking of the 7-keto group as the enol ether function in **3**, the 16-carbonyl group was reduced during a sequence that involved initial solvolysis of the anhydride function, *in situ* reduction with borohydride, and then hydrolysis of the enol ether during the acidic work-up, thereby affording **12**; benzyl alcohol was selected in anticipation of the possible need to liberate the 3-carboxyl under neutral conditions. The remaining steps paralleled the earlier preparation of diazo ketone **9**, except that deletion of the 3-substituent was postponed until after the Wolff rearrangement of the 16-hydroxy analogue **13**. This reaction now proceeded smoothly, furnishing ester **14** in excellent yield. After restoration of the 16-carbonyl group, the 3-carboxyl was liberated by hydrogenolysis and then removed as for **8**. Samples of the (±)-ketone **11**, mp 175−178 °C, obtained from both routes were identical and gave the same NMR and mass spectra as those obtained from the enantiopure material.[11] The carbon skeleton was then completed in 85% yield by the Lombardo modification[19,20] of the Nozaki−Hayashe methylenation, and the ester function demethylated with lithium *n*-propanethiolate[21] to afford (±)-**5**.

The preparation of (±)-GA₇₃ methyl ester (**6**) was undertaken next, as outlined in Scheme 4. It was expected that the Δ^1(10) alkene should provide activation for cleavage of the C(9)−C(15) bond of the cyclopropyl ring in **3**, and fragmentation was induced with pyridinium hydrobromide to afford an inseparable 3:2 mixture of the dienes **15** and **16**. Hydrolysis of the anhydride mixture followed by *in situ* iodo lactonization then gave rise to a mixture of **17** and **18** from which the major isomer **17** was readily separated. Deletion of the superfluous functionality afforded dione **19** from which (±)-**6** was smoothly prepared by ring contraction as for **11** followed by Wittig methylenation.

The three sequences, each one involving fewer than 20 steps, were completed with essentially complete stereocontrol and are competitive in efficiency and brevity with the earlier partial syntheses beginning with fungal gibberellins;[10,11] they are also significantly more direct than most earlier total syntheses of gibberellins.[22] The benefits of utilizing benzenoid synthons with appropriate dearomatization processes for the preparation of polycyclic targets[1] are thus well demonstrated. Extension of the general strategy to the preparation of further polycyclic diterpenes based on the full C₂₀ skeleton, as foreshadowed in the introduction, is well advanced,[23] and although the present study has been conducted with racemates, good methodology for the enantioselective synthesis of tetralin carboxylic acids as starting materials is available.[24]

Supporting Information Available: Experimental plus ¹H and ¹³C NMR spectra for compounds **3**−**4** and **8**−**19** and all synthetic intermediates (69 pages). See any current masthead page for ordering and Internet access instructions.

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(16) Only the formation of the 6β-epimer was observed in this and later ring contraction steps.

(17) Blake, P. In *The Chemistry of Ketenes, Allenes and Related Compounds*; Patai, S., Ed.; Wiley: New York, 1980; pp 310−357.

(18) It appears plausible, therefore, that fission occurs at the (presumed) intermediate carbene stage: the filled orbital on C(6) would be expected to take up the 6α-axial conformation (*cf.*, Scott, A. P.; Nobes, R. H.; Schaefer, H. F.; Radom, L. *J. Am. Chem. Soc.* **1994**, *116*, 10159−10164) and is then better oriented to interact with the σ*-orbital of C(8)−C(15) than to form the new π-bond of the incipient ketene. As C(8) migrates to C(6), it would be possible for π-bond formation to take place between these two carbons with fission of C(8)−C(15) and delocalization of the electrons into the 16-carbonyl group; solvation of the developing C(7) acylium ion could be concerted with these processes. Clearly, the ring contraction/cyclopropyl fragmentation in a 3-substituted substrate would allow an expeditious synthesis of antheridic acid (**7**). See: Corey, E. J.; Myers, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5574−5576. Shimano, M.; Nagaoka, H.; Yamada, Y. *Tetrahedron Lett.* **1996**, *37*, 7553−7556.

(19) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293−4296.

(20) The Wittig method affords a very poor yield with this kind of substrate (*cf.*, Furber, M.; Mander, L. N. *J. Am. Chem. Soc.* **1987**, *109*, 6389−6396).

(21) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1970**, 4459−4462.

(22) Mander, L. N. *Chem. Rev.* **1992**, *92*, 573−612.

(23) Reliable methodology for the stereocontrolled introduction of C-10 substituents is available (Dawe, R. D.; Mander, L. N.; Turner, J. V.; Pan, X. *Tetrahedron Lett.* **1985**, *26*, 5725−5728; Mander, L. N.; Owen, D. J. *Tetrahedron Lett.* **1996**, *37*, 723−726).

(24) Buisson, D.; Cecchi, R.; Laffitte, J.-A.; Guzzi, U.; Azerad, R. *Tetrahedron Lett.* **1994**, *35*, 3091−3094. Genêt, J. P.; Pfister, X.; Ratovelomanana-Vidal, V.; Pinel, C.; Laffitte, J. A. *Tetrahedron Lett.* **1994**, *35*, 4559−4562.