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Conversion of a Gibberellin Aldehyde into a 20-Norkaurenoid Lactone

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Abstract: The Lewis acid-catalysed rearrangement of a 6β-hydroxy-gibberellin-7α-carboxaldehyde results in ring-expansion of the 5-membered B-ring of the gibberellin molecule to afford access to highly functionalised 20-norkaurenoids.
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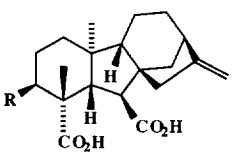
Considerable effort has been invested in transforming kaurene derivatives into gibberellins ("GAs"), either by incubation with the fungus, *Gibberella fujikuroi*,[1] or chemically,[2] the latter studies affording GA_{12} (**1**),[3] GA_{14} (**2**),[4] GA_{15} (**3**)[5-7] and GA_{37} (**4**).[7] Indeed, the most effective means of gaining access to gram quantities of **1**, is via an efficient five-step sequence beginning with the 7β-hydroxy-kaurenolide **5**.[3]



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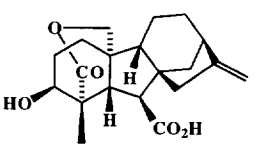
2 R = OH



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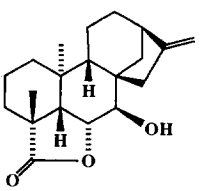

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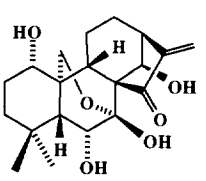
Most kaurenoids, however, are not as easily obtained as the more common GAs, especially gibberellic acid (GA_3) (**9**), which is readily available at modest cost. We have accordingly commenced a study on the conversion of GAs into kaurene derivatives, the preliminary results of which are disclosed in this Letter. A particularly attractive aspect of such a conversion is the opportunity to draw on the wealth of experience gained from the transformation of GA_3 (**9**) into an extensive range of other GAs.[2] The densely functionalised nature of this substrate was also expected to facilitate the preparation of the more complex kaurenoids that characteristically show greater therapeutic potential.[8] Of special interest is the *Rabdosia* family of diterpenes, many of which have antibacterial and antineoplastic properties, *e.g.* oridonin (**6**),[9] shikodonin (**7**)[10] and enmein (**8**).[11]



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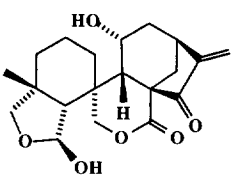

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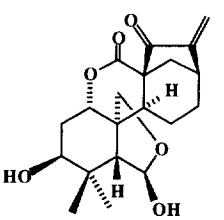

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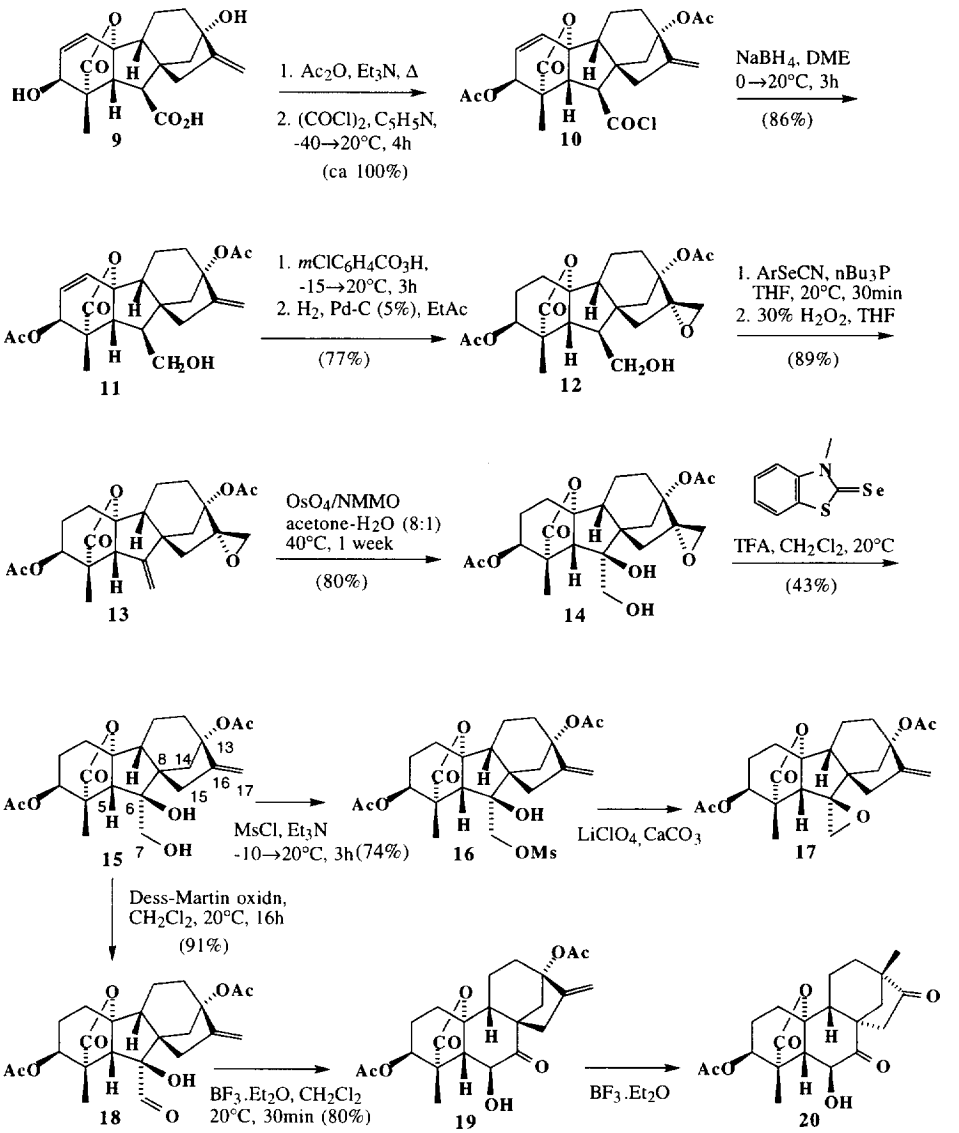

Scheme 1. Conversion of a gibberellin into a 20-norkaurenoid lactone.

Our efforts directed towards the desired B-ring expansion are outlined in Scheme 1. They were initially focussed on the pinacolic rearrangement of diol (**15**)[12] and to prepare this compound, GA_3 (**9**) was protected as its 3,13-diacetate, which was reduced to carbinol (**11**)[13] *via* acyl chloride (**10**).[14] After "protection" of the 16-methylene function as the 16,17-epoxide and reduction of the A-ring double bond, formation of the alkene (**13**) was effected by means of the Grieco procedure[15] and the 6,7-diol (**14**) prepared by reaction with osmium tetraoxide using *N*-methylmorpholine *N*-oxide as a co-oxidant.[16] The Δ^{16}-alkene function was then reconstituted by deoxygenation[17] of the epoxide function to afford diol (**15**). The stereochemistry of this product was established as the 6β-hydroxy epimer by a NOESY NMR spectrum which clearly indicated interaction between the 7-methylene and the H14 protons, but not with either H5 or the H15 protons. The

approach of the reagent to the β-face of the substrate is consistent with the reported protonation of a GA 6-enolate to afford a 6-*epi*-GA.[14]

In spite of a number of encouraging precedents,[12,18] the derived mesylate (**16**) failed to undergo rearrangement, furnishing instead the corresponding 6,7-epoxide (**17**). An attempt was made to prepare the triflate[19] corresponding to (**16**), but this derivative proved to be too unstable. We turned, therefore, to the acyloin rearrangement of the hydroxy aldehyde (**18**). Several precedents exist in the steroid literature,[20] the ring expansions being attributed to the reduction of ring strain.[21] The relief of additional strain in the GA skeleton was expected to favour the desired outcome even more strongly. In the event, oxidation of diol (**15**) by the Dess-Martin procedure[22] followed by treatment with boron trifluoride etherate furnished an excellent yield of ketol (**19**). The structure of this product was apparent initially from ^{1}H NMR spectra that, *inter alia*, displayed signals from H5 and H6 in the expected chemical shift range as a pair of doublets with a vicinal coupling constant of 10 Hz. The provisional assignment of structure was then confirmed by single crystal X-ray diffraction which showed (Figure 1) a C-7 carbonyl group and a 6β-hydroxyl. It was also of some interest to see that the C-ring, normally a quasi-boat in gibberellins,[23] had adopted a chair conformation. This conformational change should also contribute to the relieved of strain in the GA system.

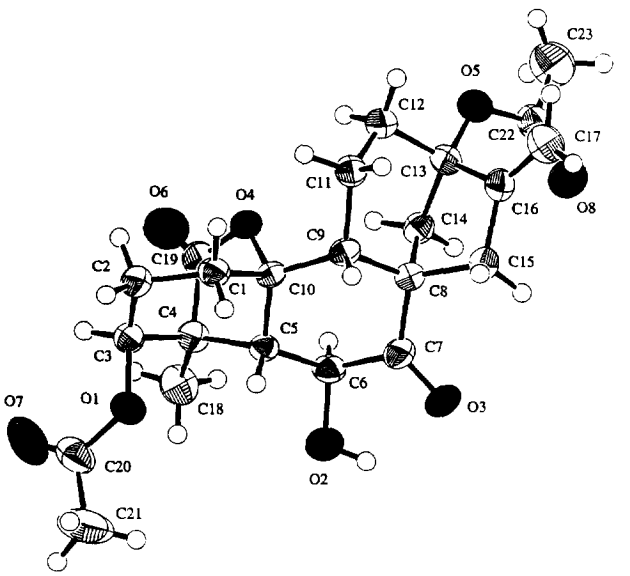

Figure 1. Structure of Norkaurenoid Lactone (19)

Assuming that (**19**) is a kinetic product, its formation may be rationalised in terms of the 1,2-shift of the C5-C6 bond to afford a chair-like transition state in preference to the alternative migration of the C8-C6 bond (leading to a boat conformation for the B-ring).[24] Interestingly, the ring expansion may be achieved in the presence of the labile D-ring functionality which would be expected to undergo rearrangement on exposure to Lewis acids. Indeed, prolonged exposure of (**19**) to boron trifluoride etherate afforded the beyerane analogue (**20**) as would be expected from similar rearrangements observed for 13-hydroxy gibberellins[25] and steviol.[26]

The yields throughout the sequence are excellent, apart from the deoxygenation of epoxide (**14**), a procedure that could be avoided, either through an alternative preparation of the hydroxy aldehyde (**18**), or by choosing a different procedure for masking the 16-ene function. Current efforts are being directed towards such aspects with a view to exploring the biological properties of the 20-norkaurenoid lactones accessible from

(**18**) and its analogues. The main focus of future work, however, will be the application of the methodology to C_{20}-GAs with a view to preparing the full kaurene skeleton, thereby allowing access to some of the more complex kaurenoids as foreshadowed in the introduction.

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