Displacement of a Bridgehead Methanesulfonate with Lithium Dialkylcuprates: Preparation of 13-Methylgibberellin A_4

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Reaction of lithium dialkylcuprates with the bridgehead 13-methanesulfonate of a gibberellin in the presence of $BF_3{\cdot}Et_2O$ gives the corresponding 13-alkyl derivative in >70% yield; the reaction is used in the synthesis of 13-methylGA_4 **1**.

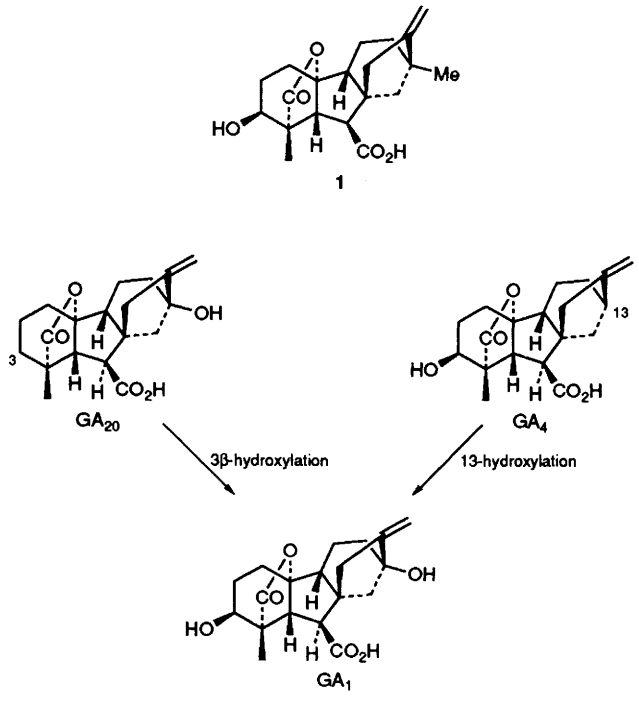
Lithium dialkylcuprates have been used extensively to introduce alkyl groups to molecules *via* nucleophilic attack on α,β-unsaturated carbonyl compounds, epoxides, halides, and primary and secondary sulfonate esters.[1] We now report a further reaction of lithium dialkylcuprates, namely the displacement of a bridgehead methanesulphonate. This new reaction has been used successfully in the synthesis of 13-methylGA_4 **1** which is required to examine structure–bioactivity relationships of gibberellin plant hormones.

It is currently believed that only one of the 90 gibberellins, GA_1, regulates stem elongation in *Pisum sativum* (pea)[2] and *Zea mays* (maize).[3] Other compounds endogenous to pea and maize, *e.g.* GA_{20}, only exhibit biological activity *via* their metabolism to GA_1 (Scheme 1). Recently, GA_4 has been detected in stem tissue of maize where it is metabolised to GA_1[4]. Gibberellin A_4 exhibits biological activity but it is not known if GA_4 is active *per se* or by virtue of its metabolism to GA_1. No mutant of maize which genetically blocks 13-hydroxylation is currently available to probe this activity; therefore analogues of GA_4 are required which are chemically blocked at carbon-13 such that hydroxylation at the bridgehead may not occur. Our target compound was 13-methylGA_4 **1**.

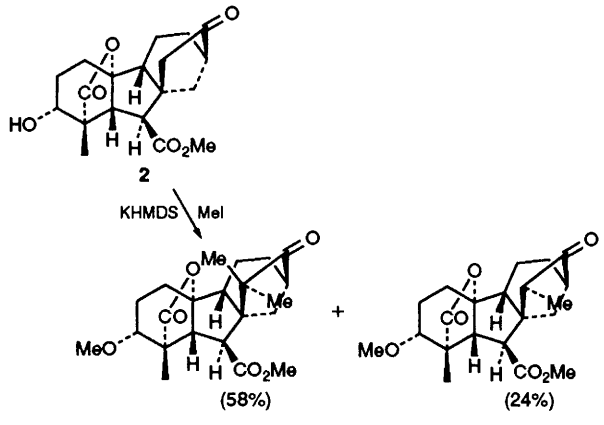
Two strategies were considered for the introduction of the 13-methyl group. The first involved alkylation of the 16-ketone **2**. Although House *et al.*[5] have suggested that bridgehead double bonds may be transiently formed in strained bicyclo[3.2.1]octane systems, reaction of the ketone with potassium hexamethyldisilazide (KHMDS) gave, as expected, the geminal 15-dimethyl derivative with no substitution at C-13 (Scheme 2). During the reaction the 3α-methyl ether was also formed.

The second approach to the synthesis of 13-methylGA_4 **1** involved the displacement of a bridghead methanesulfonate as the key reaction (Scheme 3). The 13-methanesulfonate **3** was prepared in six steps from commercially available GA_3 and treated with lithium dimethylcuprate in the presence of boron trifluoride–diethyl ether at −10 °C. Two products were isolated from the reaction mixture. The less polar compound was 13-methylGA_1 7-methyl ester 3-acetate **5** (40%)† and the more polar product was the hydrolysed derivative, 13-methylGA_1 7-methyl ester **4** (33%).† The reaction was repeated without the addition of boron trifluoride and a lower yield (52%) of the 13-methylgibberellins **4** and **5** was obtained.

The mechanism of the displacement of the bridgehead methanesulfonate with lithium dimethylcuprate is, as yet, unknown. We have found that a variety of cuprate reagents may be used to introduce alkyl groups at C-13. For example when the reaction was repeated using lithium di-n-butylcuprate in the presence of boron trifluoride–diethyl ether, the 13-n-butyl derivative **6** was isolated as the sole product in 75% yield (Scheme 4). In contrast reaction of a 13-methanesulfonate with either a Grignard reagent (MeMgI in the presence or absence of copper) or with trimethylaluminium, which is known[6] to displace tertiary halides, simply returned the bridgehead methanesulfonate.



Scheme 1 Biosynthesis of gibberellin A_1 in maize



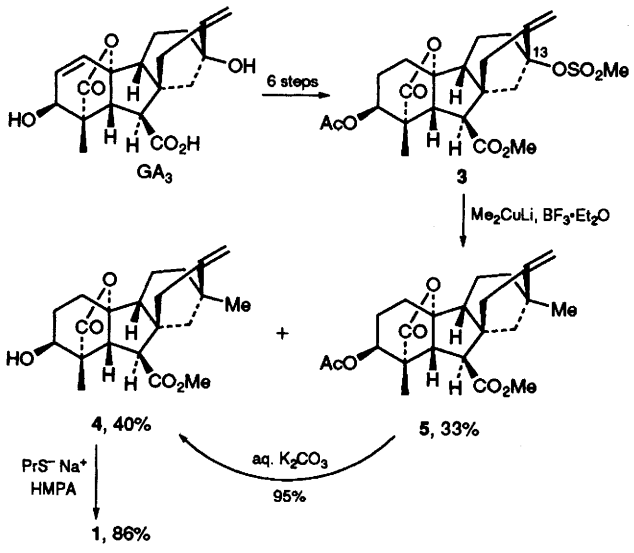
Scheme 2

† *Spectroscopic data*: compound **1**: m.p. 192–193 °C; δ($CDCl_3$) 1.13 and 1.19 (2s, 18-H_3 and 13-CH_3), 2.68 (d, *J* 10 Hz, 6-H), 3.13 (d, *J* 10 Hz, 5-H), 3.86 (s, 3-H), 4.85 and 4.90 (2 br s, 17-H_2); *m/z* 346 (M^+, 14%), 310 (9), 328 (32), 300 (36), 284 (100), 105 (20) and 77 (15).

Compound **4**: δ($CDCl_3$) 1.13 and 1.15 (2s, 18-H_3 and 13-CH_3), 2.67 (d, *J* 10.5 Hz, 6-H), 3.20 (d, *J* 10.5 Hz, 5-H), 3.71 (s, OCH_3), 3.84 (br s, 3-H), 4.84 and 4.89 (2s, 17-H_2); *m/z* 360 (M^+, 7%), 342 (9), 328 (100), 300 (68), 298 (44) and 238 (29).

Compound **5**: δ($CDCl_3$) 1.06 and 1.14 (2s, 18-H_3 and 13-CH_3), 2.14 (s, 3-OAc), 2.66 (d, *J* 10.5 Hz, 6-H), 3.17 (d, *J* 10.5 Hz, 5-H), 3.72 (s, OCH_3), 4.85 and 4.89 (2 br s, 17-H_2) and 4.97 (br s, 3-H); *m/z* 402 (M^+, 1%), 370 (8), 342 (14), 325 (5), 310 (7), 298 (100) and 238 (57).

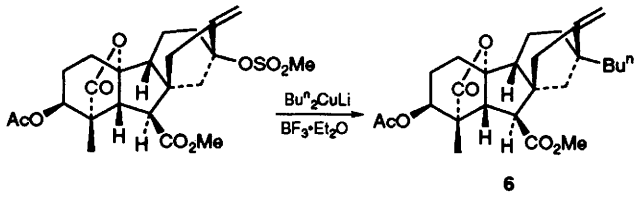
Satisfactory elemental analyses were obtained for **1** and satisfactory high resolution mass spectral data were obtained for **4** and **5**.



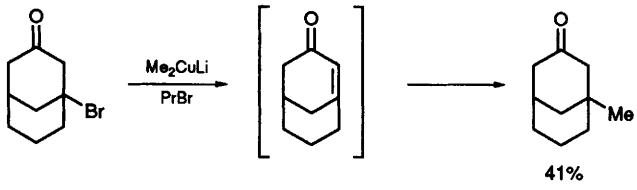
Scheme 3 Preparation of 13-methyl GA_4

Interestingly Kraus and Kirihara[7] have reported recently that the displacement of the bridgehead bromide of a [3.3.1]bicyclic ketone occurs with lithium dimethylcuprate in the presence of propyl bromide (Scheme 5). However, they indicated that this reaction proceeds *via* conjugate addition to an enone even though no alkylation of the resultant enolate was observed. We are currently exploring further the scope and mechanisms of the reactions leading to the displacement of bridgehead sulfonate esters and halides with lithium dialkylcuprates.

To complete the synthesis of the target compound 13-methylGA$_4$ (Scheme 3), 13-methylGA$_4$ 3-acetate **5** was carefully hydrolysed with aqueous potassium carbonate to give the 3β-alcohol **4**. Under more vigorous hydrolysis conditions, epimerisation to the more stable 3α-alcohol occurs.[8] Finally deprotection of the 7-methyl ester with sodium propane thiolate in hexamethylphosphoric triamide



Scheme 4 Displacement of the methanesulfonate with lithium di-*n*-butylcuprate



Scheme 5 Displacement of a bridgehead bromide with lithium dimethylcuprate[7]

(HMPA) gave 13-methylGA$_4$ **1**† in 60% overall yield from the methanesulfonate **3**. The bioactivity of 13-methylGA$_4$ is currently being assessed in maize.

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