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Gibberellin analogues by reaction of 7-oxo-diterpenes with diacetoxyiodobenzene

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ABSTRACT

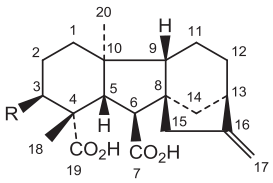
In this work, the reaction of 7-oxo-diterpenes with diacetoxyiodobenzene (DIB) has been proved to be a good method for the preparation of gibberellin analogues, which can be applied to diterpenes with endocyclic or exocyclic double bonds. It has been studied with *ent*-kaur-16-ene, *ent*-trachylobane and *ent*-atis-16-ene diterpenes. Thus, the reaction of 7-oxo-*ent*-kaur-16-en-18-oic acid methyl ester and 7-oxo-*ent*-trachyloban-16-en-18-oic acid methyl ester with this reagent affords 4-*epi*-gibberellin A_{12} dimethyl ester and 4-*epi*-trachylobagibberellin A_{12} dimethyl ester, respectively. In some cases, especially with compounds functionalized at C-19, alternative reactions lead to the introduction in the substrate of a conjugated 5,6-double bond or to the formation of a ketal at the 6-position. Thus, the formation of gibberellin analogues, dehydrogenation products or 6-ketal derivatives depend on the neighbouring group participation of the C-18 (equatorial) and C-19 (axial) substituents at C-4.

1. Introduction

The gibberellins (GAs) are a type of plant hormones formed by a large family of diterpenic acids, biosynthetically derived from *ent*-kaur-16-ene, which have been isolated from plants, fungi and bacteria. In microscopic amounts, they may regulate a variety of biological processes related to plant growth, rendering them an important tool in agriculture. Chemically, these compounds are divided into the C_{20} and C_{19} gibberellins, examples of the former being GA_{12} (**1**) and GA_{14} (**2**) and of the latter GA_3 (**3**) and GA_7 (**4**).[1–4] In recent years we have been interested in the partial synthesis of gibberellins and their analogues using microbiological[5–7] and chemical methods. In these studies the diterpenes employed as starting material were mainly isolated from species of the *Sideritis* genus endemic to the Canary Islands.[8] We have chemically prepared this type of compounds by contraction of ring B of tetra- or pentacyclic diterpenes via different methods: (a) Benzylic acid rearrangement of a 6,7-diketone.[9] (b) Favorskii rearrangement of a 7α-chloro-6-enol-lactone.[10,11] (c) Rearrangement of a 6β,7α-bromohydrin.[12] (d) Solvolysis of a 7α-tosyl-19,6α-lactone.[13]

Hypervalent iodine compounds have contributed significantly to the development of organic synthesis.[14–16] An oxidation with diacetoxyiodobenzene (DIB) and methoxide anion has been used in the α-hydroxylation of oxo groups, via an α-hydroxy-ketal.[17–19] This reaction occurs in simple ketones, such as acetophenones or cycloalkanones. However, in the case of highly substituted systems with steric constraint there are other alternatives for the decomposition of the phenyl iodoso intermediate. Thus, in the reaction of DIB with 3-oxo-steroids,[20,21] or with a 23-oxo sapogenin,[22] ring contractions of the respective cycles were produced by rearrangement.

We have reported on our previous results on the reaction of 7-oxo-*ent*-kaur-16-ene derivatives with diacetoxyiodobenzene in alkaline medium.[23] Now, in this full paper we include the reaction of other *ent*-kaurene derivatives with DIB. Moreover, we have extended these studies to the reaction of this reagent with other 7-oxo-diterpenes possessing *ent*-trachylobane and *ent*-atis-16-ene skeleta, which permitted the synthesis of trachylobagibberellins



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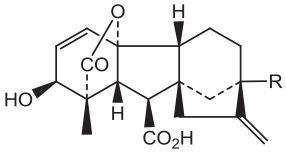
2 R = OH



3 R = OH
4 R = H

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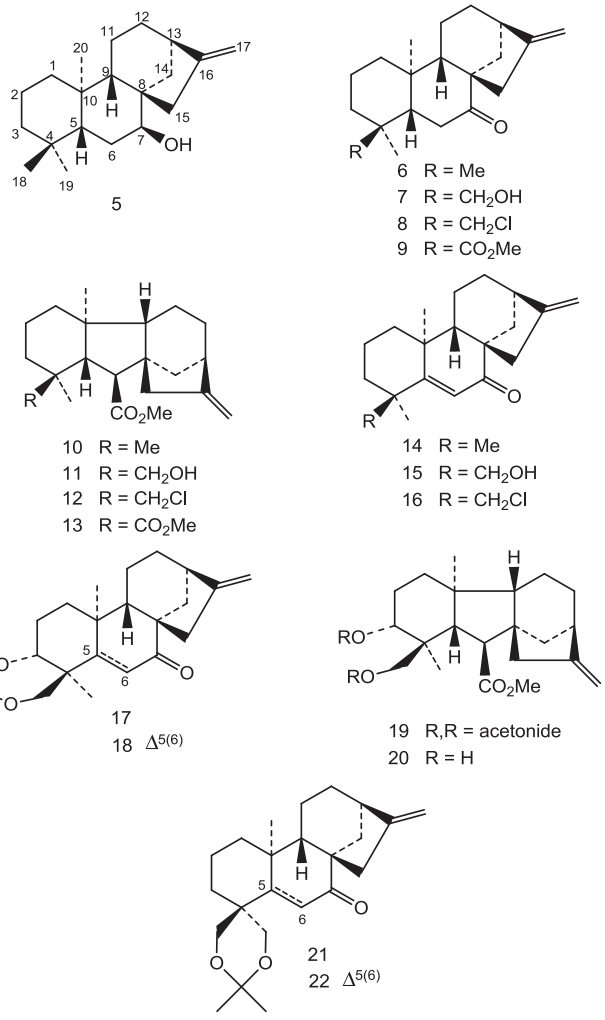
(TGAs) and atisagibberellins (AGAs), respectively. The partial synthesis of the undescribed starting compounds has also been incorporated into this paper.

2. Results and discussion

As starting material we have used diterpenes with *ent*-kaur-16-ene, *ent*-trachylobane and *ent*-atis-16-ene framework, which were conveniently functionalized as 7-oxo derivatives. Oxidation of candol A (**5**), isolated from *Sideritis canariensis*,[24] gave 7-oxo-*ent*-kaur-16-ene[25] (**6**). This compound, by reaction with diacetoxyiodobenzene (DIB) in MeOH/KOH, afforded the gibberellin analogue **10** and the dehydrogenated compound **14** by ring contraction and trans-elimination, respectively (Table 1).



The HRMS of the less polar product **10** was in agreement with the molecular formula $C_{21}H_{32}O_2$. Its ^{1}H NMR spectrum showed a new methoxyl group at δ 3.65 (s) and a pair of doublets of an AB system at δ 1.70 and 2.68 (J=12.6 Hz). These last signals are typical resonances of a trans relationship between H-5 and H-6 in a gibberellin framework. Its structure was confirmed by a 2D NMR study, which permitted the assignment of the ^{13}C NMR spectrum (Table 2). In the HMBC experiment the correlations observed were as follows: H-5 with C-4, C-6, C-7, C-10, C-19 and C-20; H-6 with C-5, C-7, C-8, C-14 and C-15; H-18 with C-3, C-5, C-19; H-19 with C-3, C-5, C-18 and C-20; and H-20 with C-1, C-5, C-9 and C-10. The more polar product **14**, of molecular formula $C_{20}H_{28}O$, proved to be the 6,7-dehydrogented product of **6**. Thus, in the ^{1}H NMR spectrum of **14** an H-6 singlet appears at δ 6.07, which is the typical α-proton resonance of an α,β-unsaturated carbonyl group. The proposed structure was confirmed by a 2D NMR study. In the HMBC spectrum the following correlations were observed: H-6 with C-4, C-8 and C-10; H-18 with C-3, C-4, C-5, C-6 and C-19; H-19 with C-3, C-4, C-5 and C-18; and H-20 with C-5, C-9 and C-10. In the NOESY spectrum a cross-peak was detected between H-6 and H-18. There are no precedents of the formation of dehydrogenated substances using this reagent. This may be due to the fact that previous reactions have been carried out with compounds, such as 3- and 17-oxo-steroids,[17,18] where a trans-elimination is less favourable than in ring B of 7-oxo-diterpenes.

Similarly, the reaction of 18-hydroxy-7-oxo-*ent*-kaur-16-ene[25] (**7**) with DIB afforded the ring contraction product **11** and the dehydrogenated product **15**, the ^{1}H NMR spectrum of the former showed signals of H-5 and H-6 as two doublets at δ 1.85 and 2.75 (J=13.0 Hz), while that in the latter the resonance of a singlet at δ 5.99 was observed. However, the reaction of its 4-epimer, 19-hydroxy-7-oxo-*ent*-kaur-16-ene (**24**), with DIB led to the 6-ketal **27**. This was the first time that a ketal, in α-position to the oxo-group, was formed using this reagent.

The structure of **27** was determined considering its molecular formula $C_{21}H_{30}O_3$, indicating that a new carbon had been introduced in the molecule during the reaction. This should be part of a methoxy group, because a singlet at δ 3.20 (3H) was observed in the ^{1}H NMR spectrum. Moreover, the signal of H-5 resonates as a singlet at δ 1.90 and the two H-19 appear at lower field and with a different coupling constant, δ 3.86 and 3.89 (J=8.3 Hz), in comparison with those of the starting compound **24**, δ 3.52 and 3.75 (J=11 Hz). This coupling value of the two H-19 in **27** is characteristic of products with a 6,19-ether group.[26] In the ^{13}C NMR spectrum C-6 appears at δ 105.2, a typical resonance of a ketalic carbon, whilst C-19 does at 82.2, with a $\Delta\delta$=+17.0 with respect to the same signal in **24** (Table 3). In the HMBC experiment, correlations of C-6 with H-5, H-19 and the methoxy group were observed.

A possible mechanism of the formation of **27**, involving two steps and 2 equiv of DIB, is indicated in Scheme 1. The formation of a cyclic ether, analogous to the intermediate **24i**, had been observed by Turuta et al.[27] These authors had obtained a 17-spiro-oxetan-20-one in the treatment of a 17β-acetyl-17α-hydroxysteroid with DIB, but in this case the reaction did not continue in a second step to form a ketal analogous to **27**. The substrate **24** was prepared in the following way: 7β-angeloxy-*ent*-kaur-16-en-19-oic acid[28] (**28**), isolated by us from an extract of *Margotia gummifera*, was reduced with lithium aluminium hydride affording the diol (**31**), which was partially acetylated to give the diacetate **32** and the 19-monoacetate **33**. The latter was oxidized to the 7-oxo-19-acetoxy derivative **23**, which by hydrolysis led to the alcohol **24**.

For a better comparison of the effect produced by oxygenated compounds at C-18 and C-19, we decided to carry out the reaction with DIB of the 3,18- and 18,19-acetonides **17** and **21**, respectively. Moreover, in the second case we could avoid the attack of the 19-hydroxyl group on C-6 to form the 6-ketal (see above). In the reaction with the 3,18-acetonide[25] **17**, the ring contraction compound **19** and the 5,6-dehydrogenation product **18** were obtained. We observed that **19** was partially hydrolyzed in the NMR tube over time. Accordingly, treatment of the tube content with hydrogen chloride gas yielded pure 4-decarboxy-4β-hydroxymethyl-3-*epi*-GA_{14} methyl ester (**20**). In this acid medium, epimerization at C-6 was not observed. When the reaction with DIB was performed with the 18,19-acetonide **21**, prepared from the corresponding diol,[25] only the 5,6-dehydrogenated product **22** was formed.

We have also studied the reaction of DIB with 18- and 19-chloro derivatives. Treatment of 7-oxo-18-hydroxy-*ent*-kaur-16-ene[25] (**7**) with triphenylphosphine in CCl_4 led to the 18-chloro derivative **8**, which by reaction with DIB afforded the ring B contraction product