SYNTHESIS OF GIBBERELLINS A_8 AND A_56 FROM GIBBERELLIN A_3


A mixture of gibberellin A_3 derivatives with 1(10)-ene-2β,3β-diol and 1(10)-ene-2α,3β-diol (2:5) groups, readily obtained from gibberellin A_3, has been used for a new and simple synthesis of gibberellin A_8 and its esters. The hydrolysis of GA_8 and the iodolactonization of a mixture of the 2-epimers was carried out in aqueous solution in a single flask, as also was a synthesis of GA_56 from GA_3 by a method that we have modified. The mixture of 18-iodides of GA_8 and GA_56 was separated by chromatography on SiO_2 in the form of methyl or p-bromophenacyl esters which were then deiodinated and the methyl or p-bromophenacyl ester of GA_8 was isolated. Free GA_8 was obtained by the dephenylation of the latter ester. By two-dimensional NMR spectroscopy we succeeded in assigning all the signals in the 13C and 1H NMR spectra of the methyl esters of GA_8 and GA_56. In an attempt to obtain GA_8 methyl ester by the action of trimethylchlorosilane/sodium iodide on the 2α,3β-diol system in GA_56 methyl ester, the 8,13-epimer of the latter was formed, the structure of its molecule being established from the results of X-ray structural analysis.

At the present time, 86 gibberellin phytohormones are known [1], of which only one is readily available — gibberellin A_3 (GA_3) (1), which explains its use as the starting material for the synthesis of other, less accessible, gibberellins. We have reported a simple synthesis of the new diacid (2) from GA_3 (1) [2]. This diacid (2) contains in ring A the 2β,3β-diol grouping that is characteristic for GA_8 (3) isolated from plants and another 11 gibberellins. We have investigated the possibility of synthesizing GA_8 (3) from the diacid (2), which is complicated by the fact that (2) is formed in a mixture with the main diacid (4) in a ratio of 2:5, respectively.
GA₈ (3) has previously been obtained by only one method — by treating GA₅ (5) with osmium tetroxide [3]. Product (3) was isolated from the four-component reaction mixture with a yield of 27%. A three-stage synthesis of GA₅ (5) with a yield of 18% has been described [4], and the overall yield in the synthesis of GA₈ (3) and GA₃ (1) will not exceed 4.9%.

We assumed that it would be possible to use the diacid (2) for the synthesis of GA₈ (3) just as was done in the three-stage synthesis of GA₅₆ (6) from GA₃ (1) via the diacid (4) [5]. The method of synthesizing GA₅₆(6) that has been described included the alkaline hydrolysis of GA₃ (1) to (4), its isolation and purification, iodolactonation with the production of compound (7), and deiodination of the latter to GA₅₆ (6).

We have found that it is possible to eliminate the laborious stages of extracting and purifying the diacid (4) in the synthesis of GA₅₆ (6) and to obtain the iodolactone (7) without the isolation of the diacid (4) and the use of THF and CH₂Cl₂ (see [6]), which is important in preparative syntheses. For this, we performed a total alkaline hydrolysis of GA₃ (1) in an aqueous solution of KOH in the cold, acidified the solution with hydrochloric acid to pH 3-4, and then added an excess of sodium bicarbonate to the solution, followed by an aqueous solution of iodine and potassium iodide and obtained a quantitative yield of 1β-iodogibberellin A₅₆ (7).

It is known that 1β-iodogibberellin A₄ (8) is smoothly deiodinated under the action of NaBH₄ in DMSO [7] but Japanese chemists did not succeed in obtaining the reduction product of lα-iodoGA₅₆ (7) under these conditions. On investigating the reaction mixture by the HPLC method, we found that in this case, as well, the iodination takes place completely with the formation of GA₅₆ (6) but it is impossible to isolate the GA₅₆ from aqueous DMSO by extraction. It was found that the reduction of the iodide (7) in DMSO not subjected to absolutization is accompanied by the side reaction of the formation of the epoxide (9), for which better conditions of formation have been found [8]. * For the deiodination of (7) we used tri-n-butylstannane, and not di-n-butylstannane [5], and obtained a quantitative yield of the crystalline stannyl ester of A₅₆ (10), from which the acid (6) was obtained by treatment with glacial acetic acid [9]. The formation of a stannyl ester of the type of (10) was suggested in the 13-deoxygenation of GA₃ (1) [10] but it could not be purified, and the free acid was isolated from the ester during chromatography on silica gel.

It is interesting to note that the synthesis of GA₅₆ (6) and GA₃ (1) could be simplified and performed in aqueous solution in three stages in one flask if in the last stage the new water-soluble tri(methoxyethoxypropyl)stannane, working in weakly alkaline aqueous solutions [11], was used for the reduction of the iodide (7).

We used the two-stage method of synthesizing the iodide (7) from (1) in one flask described above for the synthesis of GA₈ (3). For this purpose, we boiled GA₃ (1) in aqueous Na₂CO₃, and the resulting mixture of the diacids (2) and (4) was relactonized, giving quantitatively a mixture of the iodides (7) and (11) in a ratio of 2:5, respectively. The mixture of acids (7) and (11) was methylated with diazomethane, the mixture of methyl esters (12) and (13) was separated by chromatography on SiO₂, and the pure iodides (12) and (13) were reduced with tri-n-butylstannane in a mixture of THF and benzene, giving the esters (14) and (15). The yield of GA₈ methyl ester (14) was 97% on the diacid (2) and 26% on the (1).

The GA₅₆ Me ester (15) was readily hydrolyzed in 0.2 M aqueous methanolic alkali, while the hydrolysis of GA₈ Me ester (14) was accompanied by the formation of a complex mixture. In this connection, we have performed the synthesis of free GA₈ (3) by the procedure described above, replacing the methylation stage by a phenacylation stage, for which the mixture of acids (7) and (11) was treated with triethylamine and p-bromophenacyl bromide in acetone [12]. The phenacyl esters (16) and (17) were separated by chromatography on SiO₂ and were deiodinated to (18) and (19), after which the phenacyl group in (18) was eliminated under conditions that we had modified, giving GA₈ (3) with a yield of 64% on the diacid (2) and 17% on the initial GA₃ (1).

The conversion of the cis-diols into alkenes under the action of Me₃SiCl and NaI in acetonitrile has been described [13]. We attempted to use this reaction for the conversion of GA₅₆ (6) into GA₅ (5), and from GA₅₆ Me ester (15) we obtained a well-crystallizing product having, according to XSA, the structure of the ketone (20). The cis-diol system proved to be resistant to the action of Me₃SiCl/NaI, and compound (20) was formed by a rearrangement known for 13-hydroxygibberellins under the action of the acid [1] liberated on the silylation of the hydroxy group of ring A in (15). The molecular structure of

*In a paper by N. A. Pankrushina et al., "1α,2α-Epoxygibberellin A₅: Partial synthesis, NMR spectra, biological activity, and crystal structure of its methyl ester," published in this Journal (No. 4, 549 (1993)), in Table 1 the chemical shifts for H-1 and H-2 (2.56 and 2.62) should be replaced by 3.57 and 3.64, respectively.