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Attempt to Built 13-Hydroxy-9,15-cyclo GA Skeletons

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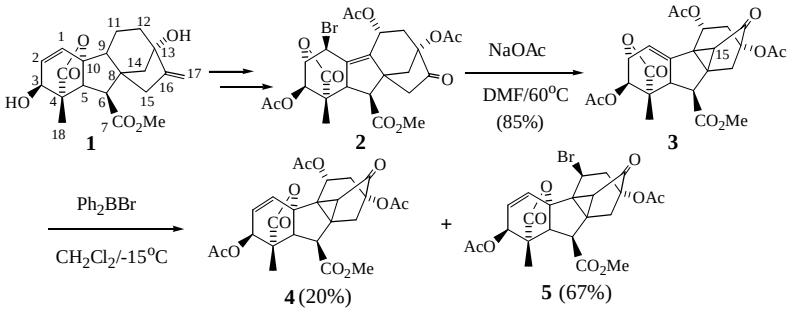
Abstract: An easy and mild way to construct 13-hydroxy-9,15-cyclo GA skeletons was reported and it could be used as a general protocol in the synthesis of GAs with this structure.

Keywords: Gibberellin(GA), cyclopropyl skeleton, cyclo GA structure.

Over 120 different structures of gibberellins (GAs) have been isolated and characterized from natural source. Among them only six 9,15-cyclo GAs were found and there is no report on the natural occurring or synthesis of 13-hydroxy-9,15-cyclo GA yet[1]. In this paper, we report an easy and mild way to synthesize the GA derivatives with cyclopropyl skeleton which could be further transferred to corresponding cyclo GAs for characterizing new compounds from nature or for the bioactivity studies.

According to the literature[2], the 9,15-cyclo ring could be formed only in a stronger base condition (KH in THF and HMPA), but here we found a new way to form the cyclo ring with much mild condition (NaOAc in DMF)[3].

The bromotriacetate **2**, which was prepared from GA_3 methyl ester **1**[4], was used as precursor to form 9,15-cyclo ketone **3**[5], and the iodide **6**[6] could also be converted to **7** by our methodology[7]. The new compounds **4** and **5** with cyclo GA structure were than obtained[8] by treatment of isolactone **3** with diphenylboron bromide[9] at low temperature.



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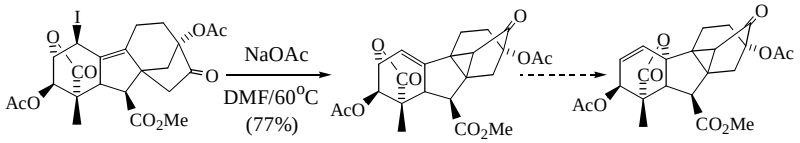

6 **7** **8**

Since the new compounds **4** and **5** were formed with the similar procedure as reported[2], it should be reasonable to transfer compound **7** to **8** with the same conditions, furthermore, to synthesize corresponding 13-hydroxy-9,15-cyclo GAs by introducing 17-methylene group to compounds **4**, **5** and **8**.

Acknowledgment

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References and Notes

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3. The general procedure of the method: The isolactone **2** or **6** (0.04 mmol) and NaOAc (35 mg) in DMF (5 mL) was heated to 60°C and stirred overnight. The reaction mixture was diluted with HCl (1.0 mol/L, 15 mL) and extracted with EtOAc (4×10 mL). Combined organic layer was than washed with brine, dried over Na_2SO_4. Pure product **3** or **7** was obtained by flash chromatography with EtOAc/Hexan (1∶2) as eluting solvents.
4. The papers of synthesis of bromotriacetate **2** will be published elsewhere.
5. The data of compound **3** are : H-NMR δ 1.17 (s, 3H, 4-Me), 2.06, 2.07, 2.10 (s, 3×3H, 3×OAc), 2.15 (dd, 1H, J = 14.8, 1.4 Hz, H12α), 2.27 (ddd, 1H, J = 14.8, 8.4, 2.2 Hz, H12β), 2.44 (s, 1H, H15), 2.52 (d, 1H, J = 11.6 Hz, H14α), 2.99 (dd, 1H, J = 9.8, 2.5 Hz, H5), 3.01 (dd, 1H, J = 11.6, 2.2 Hz, H14β), 3.06 (d, 1H, J = 9.8 Hz, H6), 3.79 (s, 3H, OMe), 4.96 (m, 2H, H2, H3), 5.78 (dd, 1H, J = 6.0, 2.5 Hz, H1), 5.81 (dd, 1H, J = 8.4, 1.4 Hz, H11) ppm. HRMS (High Resolution Mass Spectrum): Found 502.1478; $C_{25}H_{26}O_{11}$ requires 502.1475.
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7. The data of compound **7** are : H-NMR δ 1.16 (s, 3H, 4-Me), 1.81 (m, 1H, H12β), 2.07, 2.10 (s, 2×3H, 2×OAc), 2.44 (s, 1H, H15), 2.97 (br s, 2H, H5, H6), 3.03 (dd, 1H, J = 11.4, 2.6 Hz, H14β), 3.77 (s, 3H, OMe), 4.93 (d, 1H, J = 5.0 Hz, H3), 5.01 (dd, 1H, J = 5.0, 4.8 Hz, H2), 5.77 (br d, 1H, J = 4.0 Hz, H1) ppm. HRMS: Found 444.1422; $C_{23}H_{24}O_9$ requires 444.1420.
8. The GA type A-rings of compounds **4** and **5** were confirmed by their H-NMR spectra as followed: Compound **4**: δ 1.19 (s, 3H, 4-Me), 1.80 (ddd, 1H, J = 14.6, 2.5, 2.0 Hz, H12β), 2.06, 2.08, 2.12 (s, 3×3H, 3×OAc), 2.19 (d, 1H, J = 11.4 Hz, H14α), 2.42 (s, 1H, H15), 2.87 (d, 1H, J = 9.4 Hz, H6), 2.90 (1H, overlap with H6, H12α), 3.04 (d, 1H, J = 9.4 Hz, H5), 3.14 (dd, 1H, J = 11.4, 2.5 Hz, H14β), 3.79 (s, 3H, OMe), 5.37 (d, 1H, J = 3.7 Hz, H3), 5.68 (dd, 1H, J = 8.5, 2.0 Hz, H11), 5.86 (dd, 1H, J = 9.3, 3.7 Hz, H2), 6.58 (d, 1H, J = 9.3 Hz, H1) ppm. Compound **5**: δ 1.18 (s, 3H, 4-Me), 2.09, 2.11 (s, 2×3H, 2×OAc), 2.23 (d, 1H, J = 11.5 Hz, H14α), 2.44 (ddd, 1H, J = 15.0, 2.2, 1.8 Hz, H12β), 2.51 (s, 1H, H15), 2.90 (d, 1H, J = 9.5 Hz, H6), 3.00 (d, 1H, J = 9.5 Hz, H5), 3.14 (m, 2H, H12α, H14β), 3.77 (s, 3H, OMe), 5.03 (dd, 1H, J = 9.3, 1.8 Hz, H11), 5.38 (d, 1H, J = 3.9 Hz, H3), 5.86 (dd, 1H, J = 9.0, 3.9 Hz, H2), 7.17 (d, 1H, J = 9.0 Hz, H1) ppm.
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