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CONCISE SYNTHESIS OF 3-HYDROXY-$\Delta^{1.10}$-12,16-CYCLOGIBBERELLIN 12 DIMETHYL ESTER — A TRACHYLOBAGIBBERELLIN ANALOGUE

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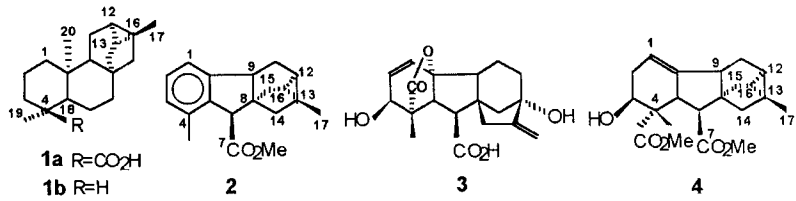
ABSTRACT: Chemical synthesis of a trachylobagibberellin analogue — 3-hydroxy- $\Delta^{1.10}$-12,16-cyclogibberellin dimethyl ester **4** from gibberellin acid GA_3 **3** was described herein. The key step is the decomposition of the tosylhydrazone **11** to construct the novel [3.2.1.$0^{2.7}$] octane system.

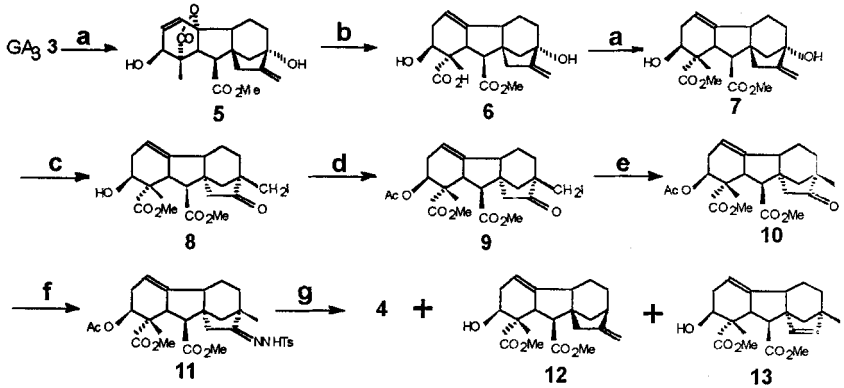
The trachylobane (ent-13R.16-cycloatisane) **1** is an unusual diterpene skeleton compound found in nature. Its novel structural feature belongs to a tricyclo [3.2.1.$0^{2.7}$] octane system.[1] As we know, gibberellins form an important group of plant grouth hormones which have many biological activities.[2] When trachylobanic compounds were first found, scientists began to synthesize a series of compounds containing the structural features of both gibberellins and trachylobanic diterpenes. Up to now, all of the reported works were from trachylobanic compounds which are rare in nature,[3] other than gibberellins as starting materials. We have



Scheme I

reported a successful synthesis of a trachylobagibberellin analogue — methyl 12.16R- cyclogibberate **2** from GA_3.[4] For the limitation of the application of the aromatic A-ring in compound **2,** we herein described the concise synthesis of 3-hydroxy-$\Delta^{1.10}$-cyclogibberellin 12 dimethyl ester **4** which can be converted to trachylobagibberellin A_4 by means of idolactonization of **4** followed by dehalogenation, using GA_3 as starting material. (**Scheme II**). Like the synthesis of trachylobanic compounds,[5] the key step is also to construct the tricyclooctane structral system.

Formal reaction of GA_3 **3** with CH_2N_2 in methanol at 0°C gave the GA_3 methyl ester **5** in quantitative yield. Following the published method,[6] the $\Delta^{1.10}$-olefinic acid **6** was prepared by nickel boride selectively reductive cleavage of the A-ring allylic lactone in GA_3 methyl ester in 95% yield using $NaBH_4$, $NiCl_2{\cdot}6H_2O$ in methanol. Esterification of **6** with CH_2N_2 in methanol followed by iodination with saturated aqueous sodium hydrogen carbonate and iodine in a mixture of THF and CH_2Cl_2 (1:2) afforded the Wagner-Meerwein rearrangement product **8** in 95%.[7] Acetylation of the hydroxyl group of **8** [8] gave the 3-acetate compound **9**. Then dehalogenation of **9** with TBTH and cat. AIBN in toluene [7] under



Reagents and Condition: a. CH_2N_2, CH_3OH, 0°c. b. $NiCl_2 \cdot 6H_2O$, $NaBH_4$, CH_3OH, rt. c. I_2, $NaHCO_3$, THF-CH_2Cl_2. d. Ac_2O, DMAP, pyridine. e. TBTH, AIBN, toluene, reflux. f. $TsNHNH_2$, pure EtOH, reflux. g. 10% EG in DEC, NaOMe, reflux.

Scheme II

reflux yielded **10** in 80%. Treatment of the solution of **10** in pure ethanol with tosylhydrazine gave stoichiometric amount of tosylhydrazone **11**.[9]

Previously, we had reported that decomposition of the tosylhydrazone of methyl gibberate with 6.0 equiv. NaOMe in a mixture of ethylene glycol and diethylcarbitol at 180-190°C mainly gave the cyclopropane-containing structure **2**.[4] However, in the reaction of **11** with 6.0 equiv. of sodium methoxide, none of the diterpene skeleton compounds was detected. According to the synthesis of trachylobanic compounds,[9] decomposition of the tosylhydrazone **11** with 10% ethylene glycol in diethylcarbitol containing 1.0 equiv. of sodium methoxide afforded a mixture of esters in 55% yield, including the cyclopropane-containing structure **4** (50% of the ester mixture), and the two olefinic esters **12** (25% of the ester mixture), **13** (25% of the ester mixture). Rechromatography over SiO_2-$AgNO_3$ afforded pure **4** in 28% yield.

In conclusion, the trachylobagibberellin type analogue **4** was synthesized via basicdecomposition of corresponding tosylhydrazone **11**.

EXPERIMENTAL

Melting points are uncorrected. For chromatography, 200-300 mesh or H silica gel were used. IR spectra were recorded on a Nicolet FT-170SX spectrophotometer as liquid films or KBr discs. ^{1}H-NMR spectra were measured on a Bruker Ac-80 or a Bruker AM-400 spectrometer using $CDCl_3$ or CD_3OD solution with TMS as internal standard. ^{13}C-NMR spectrum was recorded on a Bruker AM-400 spectrometer. Mass spectra were determined on a V.G.ZAB-HS spectrometer (EI, 70ev or 30ev).

Methyl 4α-carboxy-3β.13α-dihydroxy-4β-methyl-16-methylenegibb-1-ene-6β-carboxylate (6)

To a solution of GA_3 methyl ester **5** (180 mg) and $NiCl_2.6H_2O$ (20 mg) in MeOH (5 ml), $NaBH_4$ (180 mg) was added with stirring at room temperature for 1 h. When the reaction was completed (checked with TLC), the solvent was evaporated off, the residue was added into water (5 ml), cooled to 0°C and acidified with 10% HCl to PH=6. The product was extracted with ethyl acetate and n-butanol (1:1), and dried over anhydrous $MgSO_4$. Chromatography on silica gel gave **6** which was recrystallized from ethyl acetate as prism 172 mg (95%). m.p. 236-238°C (decomp.) (Lit.[10] 236-238°C). IR: ν=3500-3000 (-COOH, -OH), 1749 (C=O), 1668 (C=C) cm^{-1}. ^{1}H-NMR: δ=10.9 (br,1H, -COOH), 5.20 (t, J=3.2Hz, 1H, 1-H), 5.07,4.97 (each brs, each 1H, 17- H), 4.10 (brs, 1H, 3-H), 3.73, 3.65 (each s, each 3H, 2XCO_2Me), 1.31 (s, 3H, -CH_3). MS: m/z (%)= 362

(M^+, 10), 344 (M^+-H_2O, 40), 326 (10), 241(100). Anal. Calcd. for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.19; H, 7.22.

Methyl 3β.13α-dihydroxy-4β-methyl-16-methylenegibb-1-ene-4α.6β-dicarboxylate (7)

The $\Delta^{1.10}$-olefinic acid **6** (500 mg) was dissolved in MeOH (20 ml), diazomethane was added with stirring at 0°C. When the reaction was completed (the color of the solution became constant pale yellow), the solvent was evaporated off and the product was recrystallized from ethyl acetate as prism 520 mg (100%). m.p. 178-180°C (Lit.[10] 180-182°C). IR: ν=3431 (OH), 2930, 1729 (C=O), 1660 (C=C), 1456, 1164, 893 cm^{-1}. ^{1}H-NMR: δ=5.24 (brs, 1H, 17-H), 5.10 (t, J=3.2Hz, 1H, 1-H), 4.96 (brs, 1H, 17-H), 4.01 (brs, 1H, 3-H), 3.70,3.62 (each s, each 3H, 2XCO_2Me), 3.49 (d, J=7.0Hz, 1H, 6-H), 3.04 (m, 1H, 9-H), 2.90 (d, J=6.9Hz, 1H, 5-H), 1.30 (s, 3H, -CH_3). MS: m/z (%)= 376 (M^+, 15), 358 (M^+-H_2O, 30), 340 (5), 239(100). Anal. Calcd. for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50. Found: C, 67.15; H, 7.53.

Methyl 3β-hydroxy-4β-methyl-13-iodomethyl-16-oxogibb-1-ene-4α.6β-dicarboxylate (8)

A solution of methyl gibberellate **7** (500 mg) in a mixture of THF (17 ml) and methylene dichloride (34 ml) was vigorously stirred with saturated aqueous sodium hydrogen carbonate (25.5 ml) and iodine (2.04 g) for 10h. The organic layer was seperated, washed with aqueous sodium thiosulphate and dried over anhydrous $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel to give ketone **8** as needles 600 mg (95%). m.p. 200-202°C. IR: ν=3442 (OH), 2934, 1728 (C=O), 1658 (C=C), 1436, 1165, 892 cm^{-1}. ^{1}H-NMR: δ=5.14 (t, J=3.2Hz, 1H, 1-H), 4.02 (brs, 1H, 3-H), 3.77,3.62 (each s,

each 3H, 2XCO_2Me), 3.47 (d, J=7.2Hz, 1H, 6-H), 3.13 (m, 1H, 9-H), 3.01(d, J=6.9Hz, 1H, 5-H), 1.25 (s, 3H, -CH_3). MS: m/z (%)= 502 (M^+, 5), 484 (M^+-H_2O, 10), 424 (42), 365 (50), 195 (100). Anal. Calcd. for $C_{21}H_{27}IO_6$: C, 50.21; H, 5.42. Found: C, 50.03; H, 5.40.

Methyl 3β-acetyl-4β-methyl-13-iodomethyl-16-oxogibb-1-ene-4α.6β-dicarboxylate (9)

Employing the literature method, compound **9** (250 mg) was prepared with Ac_2O and cat. DMAP in pyridine and crystallized from ethyl acetate as needles 270 mg (98%). m.p. 190-192°C. IR: ν=2950 , 1736 (C=O), 1670 (C=C), 1452, 1165, 870 cm^{-1}. ^{1}H-NMR: δ=5.34 (t, J=3.3Hz, 1H, 3-H), 5.15 (t, J=3.2Hz, 1H, 1-H), 3.80,3.65 (each s, each 3H, 2XCO_2Me), 3.35 (d, J=7.0Hz, 1H, 6-H), 3.22 (m, 1H, 9-H), 2.93 (d, J=7.1Hz, 1H, 5-H), 2.11 (s, 3H, OAc), 1.21 (s, 3H, -CH_3). MS: m/z (%) = 544 (M^+, 20), 484 (M^+-OAc, 50), 424 (60), 365 (60), 195 (100). Anal. Calcd. for $C_{23}H_{29}IO_7$: C, 50.75; H, 5.37. Found: C, 50.63; H, 5.36.

Methyl 3β-acetyl-4β.13β-dimethyl-16-oxogibb-1-ene-4α.6β-dicarboxylate (10)

The iodination compound **9** (229 mg) was dissolved in toluene (12 ml) and THF (1 ml). The solution was treated with TBTH (1.8 ml) and AIBN (286 mg) under reflux for 5h. The solvent was evaporated off, the residue was extracted with acetonitrile and then the solution was washed with petroleum (60-90°C). The acetonitrile was evaporated off and the residue was chromatographed on silica gel to give **10** as neddles 140 mg (80%). m.p. 172-174°C. IR: ν=2953 , 1737 (C=O), 1670 (C=C), 1457, 1165, 866 cm^{-1}. ^{1}H-NMR: δ=5.36 (t, J=3.4Hz, 1H, 3-H), 5.15 (t, J=3.2Hz, 1H, 1-H), 3.80, 3.65 (each s, each 3H, 2XCO_2Me), 3.35 (d, J=7.0Hz, 1H, 6-H), 3.20 (m, 1H, 9-H), 2.98 (d, J=7.2Hz, 1H, 5-H), 2.11

(s, 3H, OAc), 1.22, 1.06 (each s, each 3H, 2XCH_3). MS: m/z (%)= 418 (M^+, 5), 358 (M^+-OAc, 40), 298 (80), 239 (100). Anal. Calcd. for $C_{23}H_{30}O_7$: C, 66.01; H, 7.22. Found: C, 66.10; H, 7.25.

Methyl 3β-acetyl-4β.13β-dimethyl-16-tosylhydrazongibb-1-ene-4α.6β -dicarboxylate (11)

The deiodination compound **10** (170 mg) was dissolved in pure ethanol (10 ml), and p-TsNHNH_2 (76 mg) was added under reflux for 8h. The solvent was eaporated off and the residue was chromatographed on silica gel to give tosylhydrazone **11** as needles 202 mg (85%). m.p. 98-100°C. IR: ν=3461 (NH), 3207 (bezene), 2953 , 1781,1736 (C=O), 1669 (C=C), 1598,1494,1457, 1166, 868 cm^{-1}. ^{1}H-NMR: δ=7.89, 7.35 (each d, J=8.2Hz, each 2H, p-Tol-H), 5.33 (t, J=3.3Hz, 1H, 3-H), 5.05 (t, J=3.2Hz, 1H, 1-H), 3.70,3.68 (each s, each 3H, 2XCO_2Me), 3.46 (d, J=7.0Hz, 1H, 6-H), 3.16 (m, 1H, 9-H), 3.04 (d, J=6.8Hz, 1H, 5-H), 2.43 (s, 3H, p-Tol-CH_3), 2.09 (s, 3H, OAc), 1.17, 1.09 (each s, each 3H, 2XCH_3). MS: m/z (%)= 586 (M^+, 15), 526 (M^+-OAc, 10), 467 (40), 282 (70), 223 (100). Anal. Calcd. for $C_{30}H_{38}N_2O_8S$: C, 61.42; H, 6.35. Found: C, 61.28; H, 6.30.

Methyl 3β-hydroxy-4β.13β-dimethyl-12.16-cyclogibb-1-ene-4α.6β-dicarboxylate (4)

Methyl 3β-hydroxy-4β-methyl-16-methylenegibb-1-ene-4α.6β-dicarboxylate (12)

Methyl 3β-hydroxy-4β.13β-dimethylgibb-1.15-diene-4α.6β-dicarboxylate (13)

The tosylhydrazone **11** (100 mg) was allowed to react with sodium methoxide (1.0 equiv.) in methanol (3 ml) for 30 min.. The methanol was

removed by gentle heating under a light stream of dry nitrogen. Then added 10% ethylene glycol in diethylcarbitol (5 ml), and the bath temperature was quickly brought to 180-190°C. After 3h at reflux temperature, the solution was cooled and the product was extracted with ethyl acetate (dried with anhydrous K_2CO_3). The crude product was chromatographed on silica gel to give a more polar fraction (34 mg, 55%).

The more polar fraction was rechromatographed on 10% silver nitrate-silica gel to give three components.The least polar component (the cyclopropane **4**) was a colorless oil 17 mg (50%). IR: ν=3485 (OH), 2918 , 1732 (C=O), 1657 (C=C), 1456, 1162, 858 cm^{-1}. ^{1}H-NMR (CD_3OD): δ=5.17 (t, J=3.2Hz, 1H, 1-H), 3.94 (t, J=3.3Hz, 1H, 3-H), 3.67,3.58 (each s, each 3H, $2XCO_2Me$), 3.34 (d, J=6.6Hz, 1H, 6-H), 3.03 (m, 1H, 9-H), 2.93 (d, J=6.7Hz, 1H, 5-H), 2.03 (dd, J=13.8Hz, 4.0Hz, 1H, 15-H), 1.78 (dd, J=13.5Hz, 8.7Hz, 1H, 15-H), 1.19,1.17 (each s, each 3H, $2XCH_3$), 0.89 (brdd, J=8.6Hz, 3.5Hz, 1H, 16-H), 0.60 (brdd, J=8.4Hz, 4.2Hz, 1H, 12-H). ^{13}C-NMR (CD_3OD): δ=179.29, 178.84, 144.59, 111.56, 71.35, 52.01, 51.84, 51.24, 47.22, 47.05, 43.15, 36.00, 30.78, 25.57, 24.06, 21.60, 21.13, 21.02, 20.39. MS: m/z (%)= 360 (M^+, 30), 342 (M^+-H_2O, 25), 329 (30), 223 (100). Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 69.82; H, 7.80.

The second and third conponents (the olefinic esters **12**, **13**) were colorless oil. **12** : 8.0 mg (25%). IR: ν=3485 (OH), 2932 , 1730 (C=O), 1657 (C=C), 1434, 1165, 880 cm^{-1}. ^{1}H-NMR: δ=5.19 (t, J=3.2Hz, 1H, 1-H), 5.02,4.88 (each br, each 1H, 17-H), 3.99 (t, J=3.4Hz, 1H, 3-H), 3.65,3.59 (each s, each 3H, $2XCO_2Me$), 3.38 (d, J=6.3Hz, 1H, 6-H), 3.06 (m, 1H, 9-H), 3.01 (d, J=6.2Hz, 1H, 5-H), 1.25 (s, 3H, $-CH_3$) MS: m/z (%)= 360 (M^+, 25), 342 (M^+-H_2O, 20), 329 (10), 223 (100). Anal.

Calcd. for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 69.90; H, 7.81. **13** : 9.0 mg (25%). IR: ν=3453 (OH), 2922 , 1732 (C=O), 1660 (C=C), 1455, 1160, 890 cm^{-1}. ^{1}H-NMR: δ=5.62 (d, J=5.5Hz, 1H, 15-H), 5.53 (d, J=5.3Hz, 1H, 16-H), 5.02 (t, J=3.3Hz, 1H, 1-H), 4.00 (t, J=3.4Hz,1H, 3-H), 3.71,3.65 (each s, each 3H, $2XCO_2Me$), 3.50 (d, J=6.6Hz, 1H, 6-H), 3.16 (m, 1H, 9-H), 3.02 (d, J=6.7Hz, 1H, 5-H), 1.32,1.08 (each s, each 3H, $2XCH_3$) MS: m/z (%)= 360 (M^+, 15), 342 (M^+-H_2O, 10), 329 (10), 223 (100). Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 69.99; H, 7.85.

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