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SYNTHESIS OF A 19→10-THIOLO ANALOG OF THE PHYTOHORMONE GIBBERELLIN A_1[1]

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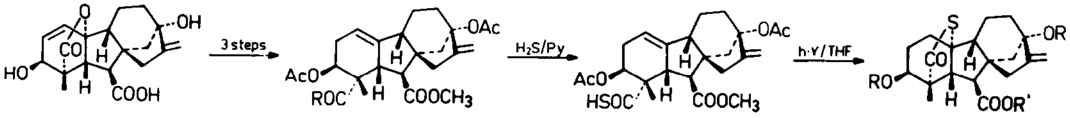
Summary: The 19→10-thiololactone analog 7 of the phytohormone gibberellin A_1 was synthesized via the $\Delta^{1(10)}$-unsaturated carboxylic acid 2, its transformation to the 19-thiocarboxylic acid 4 and intramolecular photochemical thiolactone ring closure.

Recently, we reported the preparation of 7-thiologibberellins and their photochemical ring closure to 7→15α-thiolactones.[2] In continuation of our efforts directed toward further gibberellin phytohormone analogs for biological studies this note describes a synthetic pathway to 19→10-thiologibberellin A_1 (7) from GA_3 (1). The strategy for the chosen reaction sequence envolved the use of the diacetylated $\Delta^{1(10)}$-19-carboxylic acid 2 as key compound for its transformation to the corresponding 19-thiolocarboxylic acid 4 followed by intramolecular photochemical thiololactone ring closure.
The preparation of 2 from GA_3 (1) via catalytic hydrogenation of GA_3 methylester and acetylation has been described earlier.[3,4] Compound 2 (2.5 mmol) was transformed with excess $SOCl_2$ in 7 ml benzene (1 h, r.t.) to the crude chloride 3 which was directly sulfhydrolysed with excess H_2S in 60 ml abs. pyridine (2h, r.t.). Repeated SiO_2 chromatography gave 47 % 19-thiolocarboxylic acid 4 with m.p. 198 °C dec. (aceton/n-hexane) and $[\alpha]_D^{24}$ $-$ 9.8° (c 0.3, EtOH) as the main product. MS: M^+ m/z 462.1732 (calc. for $C_{24}H_{30}O_7S$ 462.1712) IR (nujol): ν_{max} 890 ($>C=CH_2$), 1710 (COSH), 1720, 1735 cm^{-1} (ester C=O). UV (MeOH): λ_{max} (ε) 245 nm (2020) ORD (MeOH): $[M]_{310}$ + 240°, $[M]_{262}$ $-$ 4000° (a + 42).[5] 200 MHz ^1H NMR: $\delta^{acetone-d_6}_{TMS}$ 1.40 (s, 18-H_3), 1.96 and 2.06 (s, acetyl-H_3), 3.69 (s, methylester-H_3), 4.95 (m, 17-H_2 and 3α-H), 5.25 (m, 17-H_2), 5.48 ppm (1-H). Upon irradiation of 4 (0.15 mmol) in 20 ml abs. THF (Hanovia photoreactor, 254 nm, 2h, r.t., argon) regio- and stereoselective intramolecular photoaddition of the COSH-function to the $\Delta^{1(10)}$ double bond took place leading after SiO_2 chromatography to 72 % 5 with m.p. 183 °C dec. and $[\alpha]_D^{25}$ + 69.9°. MS: M^+ m/z 462.1742 (calc. for $C_{24}H_{30}O_7S$ 462.1712). IR: ν_{max} 890 ($>C=CH_2$), 1702 (thiololactone C=O), 1730, 1745 cm^{-1} (ester C=O). UV λ_{max} (ε) 242 nm (3030). ORD: $[M]_{304}$ $-$ 1440°, $[M]_{256}$ 22300° (a $-$ 237). ^1H NMR: δ 0.88 (s, 18-H_3), 1.97, 2.09 (s, acetyl-H_3), 2.99 (d, J = 11 Hz, 6-H), 3.18 (d, J = 11 Hz, 5-H), 3.70 (s, methylester-H_3), 4.76 (3α-H), 4.92,



1

2: R=OH
3: R=Cl

4

5: R=Ac; R'=CH₃
6: R=H; R'=CH₃
7: R=R'=H

5.13 ppm (m, 17-H_2). Especially the doublet character of the 5-H signal as well as the absence of a $-S-\overset{|}{\underset{|}{C}}-\underline{H}$ resonance indicated the formed 19→10-thiololactone function, arising via Markovnikov addition of the COSH function to the $\Delta^{1(10)}$ double bond, and excluded an alternative 19→1-ring structure.[6] Treatment of 5 with 2 equivalents $NaOCH_3$ in abs. methanol (4h, r.t.) yielded the dihydroxy thiololactone 6 (69 %, m.p. 233 °C dec., $[\alpha]_D^{24}$ + 16.0°) which was demethylated with lithium-n-propylmercaptide in HMPT[7] (3h, r.t.) to give 76 % of the desired 19→10-thiologibberellin A_1 7 with m.p. 165 °C dec. (ethylacetate/n-hexane) and $[\alpha]_D^{24}$ + 18.4°. MS: M^+ m/z 364.1320 (calc. for $C_{19}H_{24}O_5S$ 364.1345). IR: ν_{max} 1690 (thiololactone), 1710 (COOH), 3400 cm^{-1} (OH). ^1H NMR: δ 1.06 (18-H_3), 2.52 (d, J = 11 Hz, 6-H), 2.98 (d, J = 11 Hz, 5-H), 3.59 (t, J = 5 Hz, 3α-H), 4.80, 5.16 ppm (m, 17-H_2).

In preliminary biotests in comparison to GA_1 its thioanalog 7 showed the same activity in the dwarf maize assay and about 10 % GA_1 activity in the dwarf pea assay.[8]

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