

The Unified Synthesis of Eudesmanolides, Combining Biomimetic Strategies with Homogeneous Catalysis and Free-Radical Chemistry.

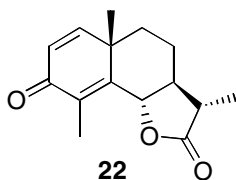
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Titanocene-catalyzed cyclization of epoxygermacrolide **7** (a model experimental procedure).

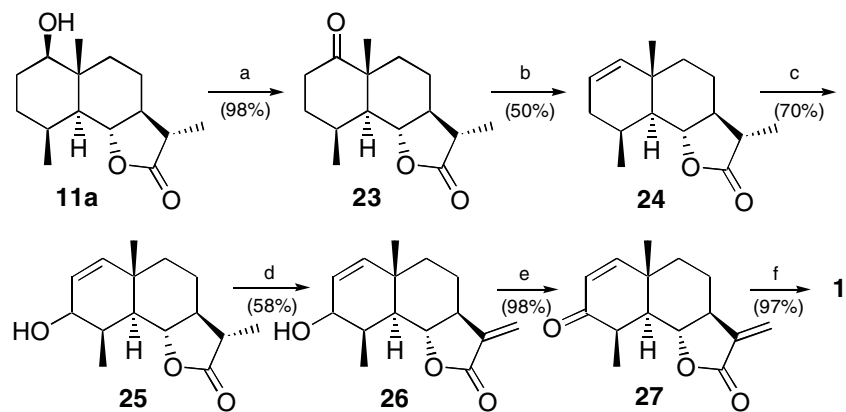
Strictly deoxygenated THF (15 mL) was added to a mixture of commercially available Cp_2TiCl_2 (11 mg, 0.044 mmol) and Mn dust (95 mg) in an Schlenk-type flask under an Ar atmosphere, and the suspension was stirred at 25 °C until it turned lime green (after about 15 min). Then a mixture of **7** (55 mg, 0.22 mmol), H_2O (20 μL , 1.1 mmol) and 2,4,6-collidine (0.13 mL, 1.1 mmol) in THF (5 mL) and, subsequently, 2,4,6-collidine hydrochloride (**15**) (158 mg, 1.0 mmol) were added to the green suspension, giving a deep-blue mixture which was stirred at 25 °C for 7 h. The solvent was then removed from the mixture, *t*-BuOMe (30 mL) was added to the residue and the ethereal solution was washed with 2N HCl and brine. The organic layer was dried over anhyd. Na_2SO_4 and the ether was removed. Flash chromatography (hexane/*t*-BuOMe, 1/9) of the residue afforded eudesmanolides **11a** (40 mg, 72% yield) and **12** (8 mg, 14%). Spectroscopic data for **11a** and **12** in refs. 4b and 10 respectively.

Following a similar procedure but excluding water and employing a freshly prepared mixture of Me_3SiCl plus collidine in THF instead of **15**, a mixture of **11a**, **12**, and **13** in relative proportions about 2:9:1 respectively (determined by ^1H NMR) was obtained. Spectroscopic data for **13** in ref. 14.

Chemical structure of (-)- α -santonin (**22**).



Synthesis of (+)-tuberiferine (**1**) from **11a**.



Scheme 5. a) Dess-Martin periodinane (DMP); b) i: TsNHNH₂, ii: NaH; c) SeO₂; d) i: (Me₃Si)₂NK, PhSeCl; ii: H₂O₂, Py; e) DMP; f) DBU