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SYNTHESIS OF (±)-DIHYDROXYSERRULATIC ACID VIA (ARENE)CHROMIUM COMPLEXES

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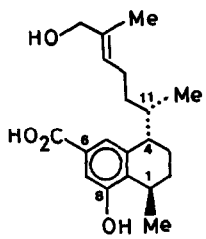
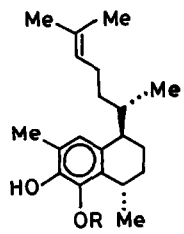
Summary; The title compound has been synthesized with high selectivity by utilizing some characteristic properties of (arene)chromium complexes.

Serrulatane class diterpenoids, dihydroxyserrulatic acid **(1)**, seco-pseudopterosins[2] A-D, pseudopterosins[3] A-D and related compounds,[4] have been isolated from the leaves of *Eremophila serrulate*, a viscid shrub and marine sea whip *Pseudopterogorgia elisabethae*. Some of these natural products possess the potent anti-inflammatory and analgesic properties.[5] For a stereo- and regioselective synthesis of these terpenoids from tetraline derivatives, the following three tactical problems are required to be solved: (1) stereocontrol at C-4 and C-11 positions, (2) trans arrangement of two benzylic substituents (at C-1 and C-4) and (3) introduction of C-1 unit at 6-position. We report herein highly selective synthesis of (±)-**1** via (tetraline)chromium complexes in order to overcome the above problems.



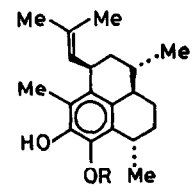
1

Dihydroxyserrulatic acid



2

Seco-pseudopterosin A; R= arabinose

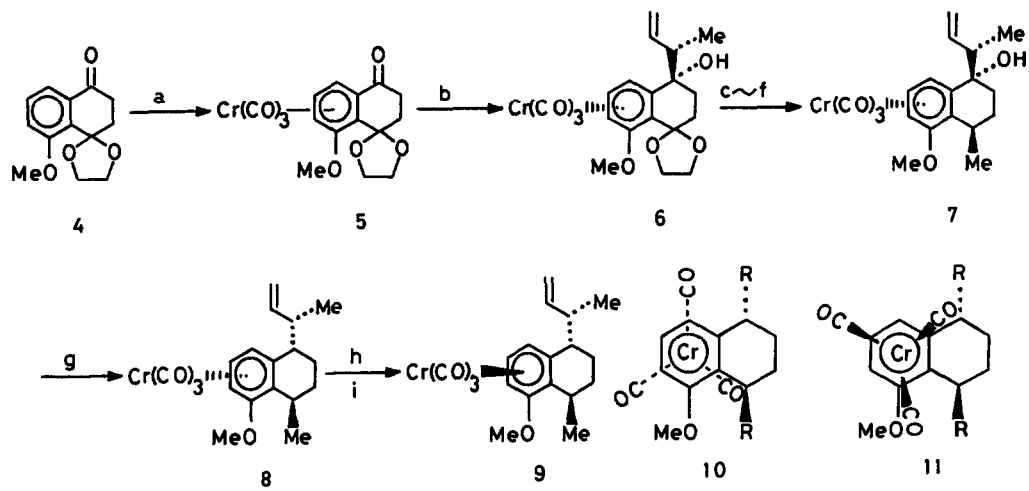


3

Pseudopterosin A ; R = β-xylose

Mono ethyleneacetal of dihydro-1,4-naphthoquinone **4**[6] was converted to the corresponding (arene)chromium complex **5** by thermal conditions. The complex **5** was treated with crotylaluminum "ate" complex[7] to afford a stereochemically desirable adduct **6** (in C-4/C-11 relationship) and a C-11 stereoisomeric compound (ratio 85-90:15-10) via a six-membered chair like transition state. Stereoselective conversion of the acetal group to exo methyl derivative **7** was achieved in 61% overall yield in four steps as shown in the Scheme.[8] An ionic hydrogenolysis[8] of the benzylic hydroxyl

of the complex **7** produced C-4 endo-substituted complex **8** in 56% yield, along with a dehydration product at C-3/C-4 position (18% yield). The stereochemical outcome at the benzylic positions resulted in an exo face attack of the reagents. The relative configuration at C-1, C-4 and C-11 in the complex **8** is contented with that of dihydroxyserrulatic acid **(1)**, and next requirement for the synthesis of 1 is an introduction of carboxyl equivalent at C-6 position. Nucleophilic addition to (arene)chromium complexes with strong donor substituents such as methoxyl is well known to occur at meta position of the donor groups with high selectivity.[9] However, reaction of the complex **8** with 2-lithio-1,3-dithiane and subsequent oxidative demetallation gave an undesirable mixture of ortho- and meta-substituted compounds (ratio, 3:1) in less than 10% yield. This low yield and unexpected formation of ortho isomer as major product may be contributed to a conformation of three carbonyl ligands to the arene ring. In the (anisole)$Cr(CO)_3$, carbonyl ligands prefer to take a syn-eclipsed conformation with OMe, and, therefore, nucleophiles attack

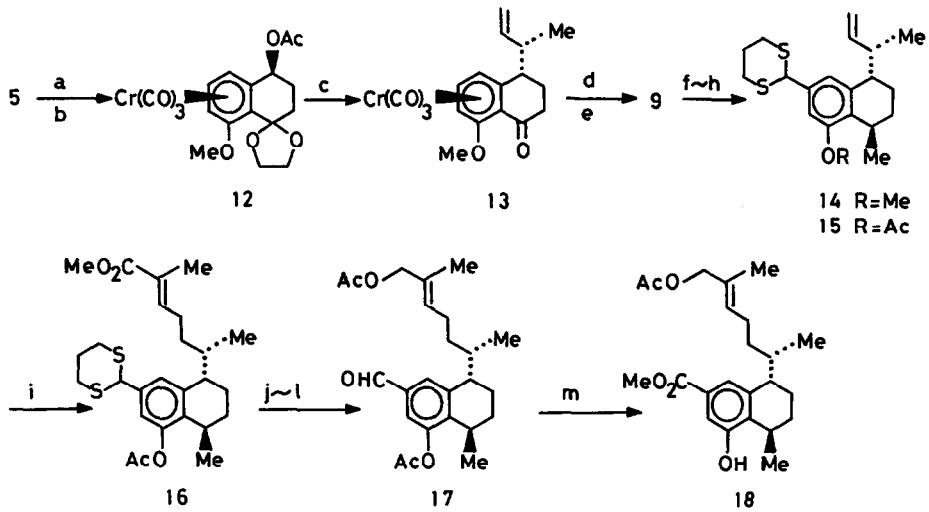


a) $Cr(CO)_6$ (80%), b) $MeCH{=}CHCH_2MgCl/Et_3Al$ (81%), c) 1N-HCl (90%), d) $NaBH_4$ (95%), e) Ac_2O/pyr (95%), f) Me_3Al (75%), g) $Et_3SiH/BF_3{\cdot}OEt_2$ (56%) h) hv-O_2 (95%), i) $Cr(CO)_6$ (60%)

at the meta position, also eclipsed with CO, owing to the balance of charge control and frontier orbital control.[10,11] However, carbonyl ligands in the complex **8** would avoid a severe steric interaction with the endo-oriented butenyl group at C-4 and adopt an anti-eclipsed conformation **10**, which results in the major attack of the nucleophile at C-7 position.[12] In this context, the exo-orientation of the large butenyl group seems to be essential for meta-introduction of the nucleophile. Therefore, we next attempted to invert the face of the chromium complexation from **8** to **9**; the later complex would adopt syn-eclipsed structure **11** because of free

from the steric interaction between the butenyl group and CO ligands. On oxidative demetallation and subsequent re-complexation with $Cr(CO)_6$, **8** gave the inverted 4-exo-substituted complex **9** in 60% yield, but still accompanied by the diastereoisomer **8** in 20% yield. And in this route, $Cr(CO)_6$ have to use in two times. Therefore, we turned our efforts to an alternative method for the synthesis of the key intermediate **9**.

Endo acetate complex **12** obtained from the chromium complex **5** was reacted with (E)-crotyl trimethylsilane[13] in the presence of boron trifluoride etherate to afford a stereochemically desirable exo-substituted tetalone chromium complex **13** in 72% yield, accompanied by C-11 stereoisomer (24%). Stereoselective introduction of endo-methyl group at C-1 position was straightfoward. Treatment of the complex **13** with MeLi followed by hydrogenolysis of the resulting carbinol produced 1-endo-4-exo-substituted tetraline complex **9** in 45% overall yield.



a) $LiAlH_4$ (95%), b) Ac_2O/pyr (98%), c) (E)-MeCH=$CHCH_2SiMe_3$/BF_3·OEt_2 (72%), d) MeLi (60%), e) Et_3SiH/CF_3CO_2H (75%), f) 2-lithio-1,3-dithiane/THF, then I_2 (50%), g) EtSH/NaH/DMF (95%), h) Ac_2O/pyr (96%), i) 9-BBN, then (E)-methyl-β-bromomethacrylate/$PdCl_2$(dppf)/K_2CO_3/H_2O (77%), j) Dibal-H (90%), k) Ac_2O/pyr (98%), l) HgO/BF_3·OEt_2/H_2O (69%), m) NaCN/MnO_2/MeOH/AcOH (85%)

Nucleophilic addition of dithianyl carbanion to the complex **9** followed by oxidative demetallation gave 6-dithianylated tetraline **14**, as expectedly, in 50% yield without detectable amount of regioisomers. The acetate compound **15**, derived from **14** by de-methylation and acetylation, was converted to coupling product **16** by the reaction with methyl β-bromomethacrylate in the presence of Pd(0) after a hydroboration.[14] Reduction of ester group in **16** followed by acetylation and subsequent

hydrolysis of 1,3-dithianyl group produced an aldehyde **17**. The compound **17** was oxidized[15] to a phenolic methylester **18**, which was succcessfully converted to (±)-dihydroxyserrulatic acid by basic hydrolysis.

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