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# Total Synthesis of (1S,4S)-7,8-Dihydroxycalamenene via Benzylic Alkylation of $\eta^6$-Arene-$Cr(CO)_3$ Complexes

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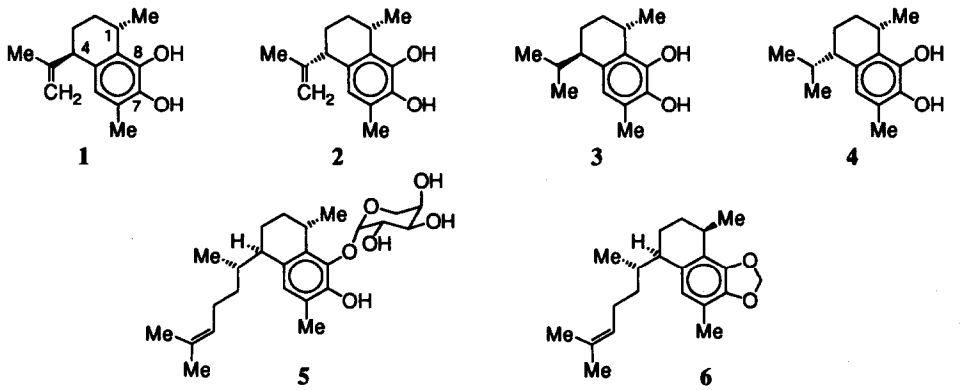
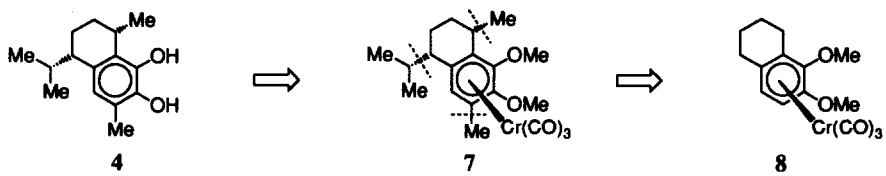
***Abstract:*** The enantioselective total synthesis of the antiinfective sesquiterpene *(1S,4S)*-7,8-dihydroxycalamenene (**4**) is accomplished by a strategy which centrally utilizes the reactivity of arene-$Cr(CO)_3$ complexes. In a sequence involving two successive benzylic deprotonation/alkylation steps, the chiral complex **8** (> 99 % e.e.) is converted completely regio- and diastereoselectively to **7** and further by decomplexation and ether cleavage to the target compound **4** in high overall yield and without loss of enantiomeric purity.

Recently, *Wahyuono* et al. reported the isolation of 7,8-dihydroxycalamenene derivatives **1** and **2** (as a mixture of diastereoisomers) from the plant *Guardiola platyphylla*[1]. These compounds as well as their hydrogenation products **3** and **4** were shown to exhibit potent anti-infective activity against a number of pathogens (*Staphylococcus aureus*, *Bacillus subtillis*, *Klebsiella pneumoniae* and *Candida albicans*). Structurally, the 7,8-dihydroxycalamenenes are related to the aglycones of the antiinflammatory and anti-infective *seco*-pseudopterosins[2] (e.g. **5**) and to the antiviral and cytotoxic helioporins[3] (e.g. **6**).




In this paper we wish to describe a short, efficient and completely stereoselective total synthesis of **4** by an approach which is centrally based on the reactivity of arene-$Cr(CO)_3$ complexes[4], and which should be appropriate also for the total synthesis of other representatives of the above mentioned compounds.

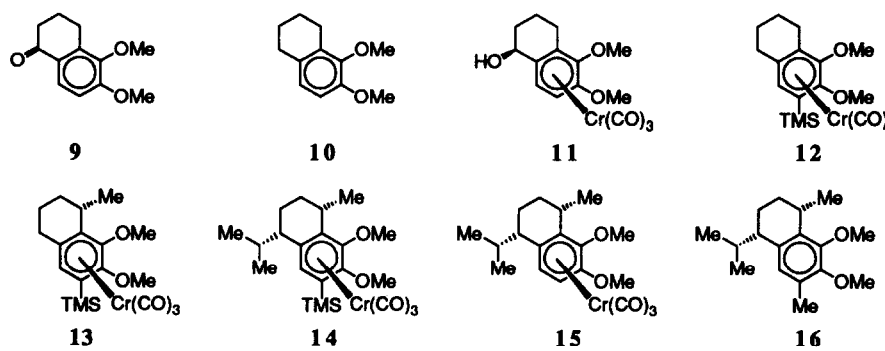
Our strategy is outlined in a retrosynthetic fashion in Scheme 1. The target compound **4** is liberated from **7** by decomplexation and deprotection. This complex now is prepared from the structurally much simpler complex **8** *via* establishing all alkyl substituents at the tetralin-skeleton by successive deprotonation/ alkylation steps. In doing so, the $Cr(CO)_3$ group serves as an activating group by enhancing the acidity at the benzyl (and aryl) positions thus allowing alkylations under mild conditions[5]. Furthermore, the $Cr(CO)_3$ fragment sterically blocks one π-face of the arene ligand (stereochemical controller) forcing all reaction partners to approach diastereoselectively from the opposite face. Therefore, the *cis*-configuration of the benzylic substituents is guaranteed, and the absolute stereochemical information contained in the chiral metal complex substructure of **8** is completely transferred to the newly generated (lasting) chirality centers.




**4** **7** **8**

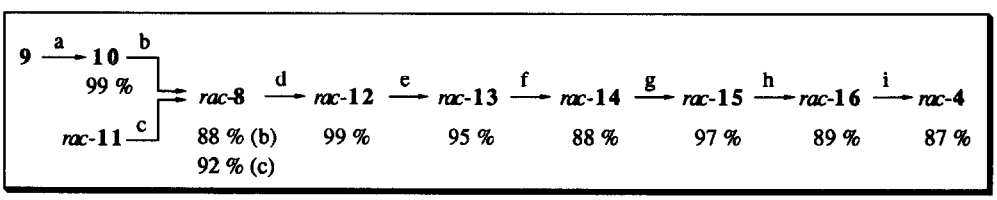
**Scheme 1**

The synthesis was at first elaborated employing racemic compounds[6] (Scheme 2): Complex *rac*-**8** was prepared from 5,6-dimethoxy-1-tetralone (**9**)[7] *via* benzylic deoxygenation to **10** and complexation with 1.1 eq. $Cr(CO)_6$ under standard conditions[8]. Alternatively *rac*-**8** was obtained by ionic hydrogenation[9] of the *endo*-tetralol complex *rac*-**11**[10].




**9** **10** **11** **12**

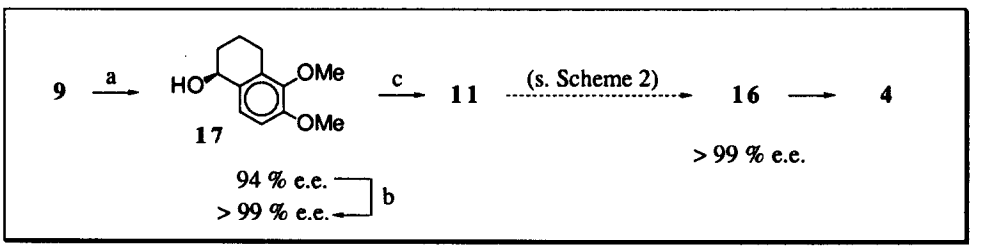
**13** **14** **15** **16**




**Scheme 2:** a) $H_2$, Pd-C, EtOH; b) $Cr(CO)_6$, $Bu_2O$/THF (10:1), reflux, 48 h; c) $HSiEt_3$, TFA, $CH_2Cl_2$, rt., 2 h; d) *n*-BuLi, THF, -50°C, 0.5 h, then TMSCl, 0°C, 1 h; e) *n*-BuLi, THF, HMPA, -60 → 0°C, 2 h, then MeI, 0°C, 1 h; f) *s*-BuLi, THF, -55 → -30°C, 1 h, then HMPA, *i*-PrI, -25°C, 1 h; g) TBAF, THF, rt., 1h; h) *n*-BuLi, THF, -30°C, 1 h, then MeI, then $I_2/Et_2O$; i) $BBr_3$, $CH_2Cl_2$, -40 → rt., 1h.

To prepare for the benzylic alkylations, the acidic *ortho*-methoxy aryl position of *rac*-**8** was first protected by silylation (*n*-BuLi/TMSCl). Deprotonation of *rac*-**12** with *n*-BuLi in THF/HMPA followed by addition of methyl iodide then furnished *rac*-**13** as a single regio- and diastereoisomer[11]. The second benzylic alkylation step was accomplished in a similar way, except that *s*-BuLi in THF was used to deprotonate *rac*-**13**. Subsequent addition of HMPA and isopropyl iodide cleanly afforded the desired product *rac*-**14**, again as a single diastereomer[12]. The concluding steps of the synthesis were performed as follows: Fluoride-induced desilylation, *ortho*-methylation (*n*-BuLi/MeI) and oxidative decomplexation with iodine furnished *rac*-**16** (*via rac*-**7**), which was finally converted to *rac*-**4** by $BBr_3$-cleavage[13] of the methyl ether groups. The transformation of *rac*-**8** to *rac*-**4** was thus achieved in only six steps with 62 % overall yield[14].

The synthetic route elaborated in the racemic series was then applied to the preparation of the optically active compounds. For this purpose, the non-racemic *endo*-alcohol complex **11** was prepared from the ketone **9** *via* enantioselective, oxazaborolidin-catalyzed borane reduction[15,10] followed by diastereoselective complexation[10] (Scheme 3). While the enantioselectivity of the reduction step was not complete, a single recrystallization of **17** provided an almost enantiomerically pure material (≥ 99 % e.e.)[16]. The conversion of **11** to the target compound **4** (using the conditions given in Scheme 2) proceeded without loss of enantiomeric purity as it was proven at the stage of **16**[17,18].




**Scheme 3:** a) CBS-reduction[10,15]: 0.2 eq. D-proline derived oxazaborolidine, addition of 0.6 eq. $BH_3 \cdot Me_2S$ over 5 h, THF, 25 °C, (93 %); b) recryst. (EtOAc/hexane) (70 %); c) 1.1.eq. $Cr(CO)_6$, cat. THF, $Bu_2O$/heptane (1:1), reflux, 27 h (74%);

Having thus demonstrated the usefulness of complex **8** as a chiral synthetic building block, we are now going to synthesize other target compounds by a related approach[19].

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11. For *rac*-**13**: Fp. 155-156 °C; IR(KBr): ν [$cm^{-1}$] = 1947, 1862; $^1$H-NMR (270 MHz, $CDCl_3$): δ = 0.35 (s, 9 H), 1.31 (d, 3 H, J = 7.0 Hz), 1.62-1.76 (m, 3 H), 1.90-2.03 (m, 1 H), 2.49 (m, 2 H), 3.18 (m, 1 H), 3.76 (s, 3H), 3.85 (s, 3 H), 5.25 (s, 1 H); The constitution of *rac*-**13** was further proven by NOE measurements: Irradiation in d at 1.31 ppm: 1.3 % NOE at 3.18 ppm and 0.3 % NOE at 3.8 ppm; irradiation in m at 2.49 ppm: 1.7 % NOE at 5.25 ppm; irradiation in s at 5.25 ppm: 3.3 % NOE at 2.49 ppm and 4.3 % NOE at 0.35 ppm.
12. For *rac*-**14**: Fp. 104-106 °C; IR(KBr): ν [$cm^{-1}$] = 1951, 1875, 1872; $^1$H-NMR (270 MHz, $CDCl_3$): δ = 0.35 (s, 9 H), 0.73 (d, 3 H, J = 6.8 Hz), 0.99 (d, 3 H, J = 6.8 Hz), 1.27 (d, 3 H, J = 7.1 Hz), 1.49-1.72 (m, 3 H), 1.99 (m, 1 H), 2.12 (m, 1 H), 2.51 (m, 1 H), 3.14 (m, 1 H), 3.78 (s, 3H), 3.85 (s, 3 H), 5.39 (s, 1 H).
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14. The $^1$H-NMR data of *rac*-**16** and *rac*-**4** were identical to those given in lit.[1].
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16. The enantiomeric purity of **17** was determined by HPLC on a *Daicel Chiralcel OJ* column (hexane/ isopropanol = 5 + 1); retention times of the enantiomers: 9.86 min (R) and 10.94 min (S).
17. The enantiomeric purity of **16** was determined by GLC on a *Macherey-Nagel FS-Hydrodex β-PM* capillary column (150 °C, $H_2$ as carrier gas).
18. Selected data of nonracemic compounds; **14**: Fp. 75 °C, $[\alpha]_D^{20}$ = -43.9° (c = 0.30 in $CHCl_3$); **15**: Fp. 141-144 °C, $[\alpha]_D^{20}$ = +180.2° (c = 0.43 in $CHCl_3$); **7**: Fp. 137-139 °C, $[\alpha]_D^{20}$ = -38° (c = 0.35 in $CHCl_3$); **16**: (oil), $[\alpha]_D^{20}$ = -43.9° (c = 0.30 in $CHCl_3$); $^{13}$C-NMR (63 MHz, $CDCl_3$, additional DEPT): δ = 15.9 ($CH_3$), 16.3 ($CH_3$), 17.2 ($CH_2$), 21.0 ($CH_3$), 21.7 ($CH_3$), 27.2 (CH), 29.0 ($CH_2$), 30.9 (CH), 42.9 (CH), 59.7 ($CH_3$), 60.2 ($CH_3$), 124.4 (CH), 129.8, 135.2, 135.5, 148.5, 150.3; **4**: Fp. 84-86 °C, $[\alpha]_D^{20}$ = -68.9° (c = 1.06 in $CHCl_3$).
19. A completely different strategy for the synthesis of (racemic) monohydroxy-calamenenes also using arene-$Cr(CO)_3$ complexes to control benzylic stereochemistry was described earlier: a) Uemura, M.; Isobe, K.; Take, K.; Hayashi, Y. *J. Org. Chem.* **1983**, *48*, 3855-3858; b) Uemura, M.; Isobe, K.; Hayashi, Y. *Chem. Lett.* **1985**, 91-94.


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