First stereoselective total synthesis of macrocarpal C: structure elucidation of macrocarpal G

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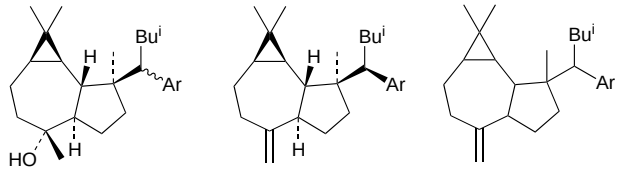
The first stereoselective total synthesis of macrocarpal C is achieved *via* a coupling reaction of a silyl dienol ether with a novel hexasubstituted benzene chromium tricarbonyl complex as an optically active benzyl cation equivalent, thereby clarifying the identity of macrocarpal C and G.

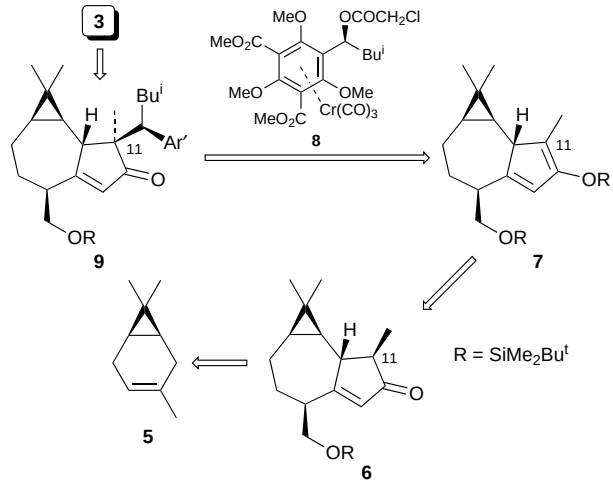
Macrocarpals[1,2] are structurally characterized by fusion of isopentylphloroglucinol dialdehyde to various sesquiterpene skeletons and are known to exhibit various interesting biological activities, such as antibacterial activity,[2a,c,e,g] inhibitory activity of HIV reverse transcriptase,[2b] aldose reductase[2d,e] and glucosyl transferase.[2e,g] Since the original isolation of macrocarpal A **1** from *Eucalyptus macrocarpa* in 1990,[2a] a number of macrocarpals have been isolated from *Eucalyptus* species.[2b–g] Complete structures have been elucidated for macrocarpals A (**1**), B (**2**) and C (**3**) using X-ray diffraction studies and spectral and chemical investigations, and the absolute stereochemistries of **1** and **3** have been determined by a modified Mosher's method.[2b] Macrocarpal G **4**,[2c] however, has been assigned the same planar structure as **3**,† and quite a few macrocarpals have not been designated relative stereochemistries. In this communication, we report the first and highly stereoselective total synthesis of macrocarpal C **3**, thereby clarifying its identity with respect to macrocarpal G **4**.



Macrocarpal A **1** (β-Ar) Macrocarpal C **3** Macrocarpal G **4**
Macrocarpal B **2** (α-Ar)

Ar = 2,4,6-trihydroxy-3,5-diformylphenyl

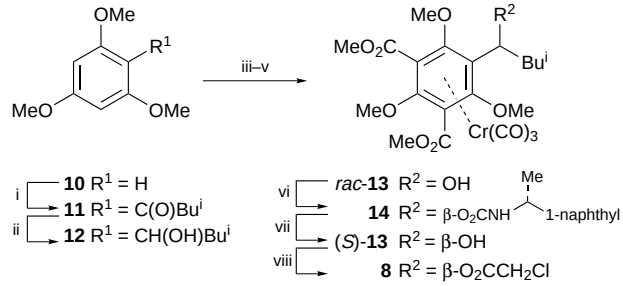
As illustrated in the retrosynthetic analysis of macrocarpal C **3** (Scheme 1), our synthetic approach began from the previously reported tricyclic enone **6**,[3] which we prepared from the commercially available and inexpensive (+)-3-carene **5**. The coupling reaction of the sesquiterpene moiety **6** with the isopentylphloroglucinol dialdehyde part is a crucial step requiring high stereoselectivity at both the benzylic and C11 positions. To this end, we planned the Lewis acid mediated coupling reaction of silyldienol ether **7** with a novel hexasubstituted benzene chromium tricarbonyl complex **8** as an optically active benzyl cation equivalent. Our previous studies suggested that an electrophile would be introduced stereoselectively at the C11 position from the less hindered β-side of **7**.[3] In connection with stereochemical control at the benzylic position, it is known that, with some nucleophiles, S_N1-type carbon–carbon bond formation *via* the $Cr(CO)_3$-stabilized carbonium ion proceeds with stereochemical retention at the benzylic position.[4] Hence, the desired coupling product **9**,



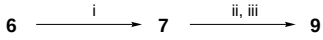
Scheme 1

which possesses the requisite functionalities and desired stereochemistry for the subsequent manipulations toward macrocarpal C **3**, would be obtained selectively after complexation.

Scheme 2 outlines the synthesis of the chiral chromium complex **8** starting from commercially available 1,3,5-trimethoxybenzene **10**. Friedel–Crafts acylation of **10** with isovaleryl chloride, followed by LAH reduction led to alcohol **12** *via* ketone **11**. After complexation of **12** with $Cr(CO)_6$, stepwise introduction of two methoxycarbonyl groups *via* direct nuclear lithiation[5] to the aromatic ring furnished diester *rac*-**13**. The resolution of this racemic benzyl alcohol was then examined. Diastereomeric carbamates derived from the CuCl assisted[6]



Scheme 2 *Reagents and conditions*: i, isovaleryl chloride, $AlCl_3$, CH_2Cl_2, 0 °C, 81%; ii, LAH, Et_2O, 0 °C, 91%; iii, $Cr(CO)_6$, Bu^n_2O–1,4-dioxane–*n*-heptane (5 : 5 : 1), 120 °C, 43% (92% based on conversion); iv, Bu^nLi, TMEDA, THF, −78 °C, then CO_2, −78 °C, then $TMSCHN_2$, C_6H_6–MeOH (4 : 1); v, LDA, TMEDA, THF, −50 °C, then CO_2, −78 °C, then $TMSCHN_2$, C_6H_6–MeOH (4 : 1), 75% overall; vi, (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate, CuCl, DMF, 99%, then separation; vii, $BF_3{\cdot}Et_2O$, wet MeCN, 0 °C, 81%; viii, $(ClCH_2CO)_2O$, pyridine, CH_2Cl_2, 0 °C, 92%

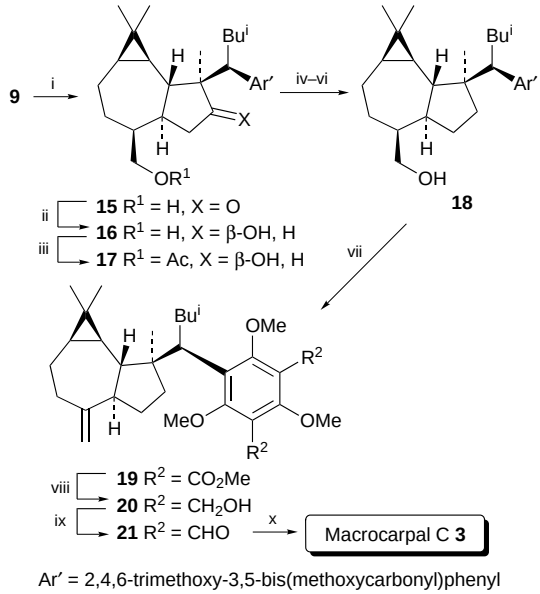


Scheme 3 *Reagents and conditions*: i, Bu^{t}Me$_2$SiOTf, Et$_3$N, Et$_2$O–CH$_2$Cl$_2$ (1 : 1), 98%; ii, **8**, ZnCl$_2$, CH$_2$Cl$_2$; iii, CAN, MeOH, 0 °C, 61% from **8**

reaction of *rac*-**13** with (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate[7] were separated by simple chromatography on silica gel. Hydrolysis of the polar carbamate **14** was achieved by treatment with BF_3·Et_2O in hydrous MeCN to provide the alcohol (*S*)-**13**, $[\alpha]_D^{26}$ −21.9 (> 98% ee) without racemization.‡ Finally, (*S*)-**13** was converted to the chloroacetate **8**, which was expected to have the required reactivity.[8]

With the desired chiral complex **8** as an aromatic side-chain unit in hand, we subjected **8** to the coupling reaction (Scheme 3). For this purpose, the enone **6** was converted to the *tert*-butyldimethylsilyl dienol ether **7**. A 1.5-fold excess of this intermediate was then coupled with the chiral complex **8** in the presence of $ZnCl_2$[9] to afford **9** stereoselectively§ after decomplexation with ceric ammonium nitrate (CAN).

Since the stereoselective route to the promising precursor of macrocarpal C **9** had already been developed, we further pursued the total synthesis (Scheme 4). Catalytic hydrogenation of the enone **9** afforded desilylated ketone **15** with the desired stereochemistry.[3] $NaBH_4$ reduction of **15** followed by acetylation of the primary hydroxy group led to monoacetate **17**¶ *via* diol **16**. The application of modified Grieco's protocol[10] allowed dehydration of the C10 secondary hydroxy group of **17**. Deacetylation of the resulting product followed by catalytic hydrogenation afforded alcohol **18**, which was subjected to dehydration again, furnishing *exo*-olefin **19**. DIBAL-H reduction of diester **19** followed by oxidation afforded trimethyl macrocarpal C **21** *via* diol **20**. Finally, the cleavage of all three methyl ethers was fully achieved by our original method (10 equiv. of 4-MeC$_6$H$_4$SLi, 50 equiv. of HMPA, toluene, reflux)‖ to furnish macrocarpal C **3**, which was identical to a natural authentic sample (^{1}H and ^{13}C NMR).** Moreover, the synthetic sample was found to be identical to natural macrocarpal G **4**.††



Scheme 4 *Reagents and conditions*: i, H_2 (5 atm), 10% Pd–C, MeOH, 88%; ii, $NaBH_4$, MeOH, 96%; iii, Ac_2O, DMAP, CH_2Cl_2, 100%; iv, 2-$NO_2C_6H_4$-SeCN, Bu$^n_3$P, THF, sealed tube, 75 °C, then 30% aq. H_2O_2 0 °C; v, NaOMe, MeOH, 64% from **17**; vi, H_2 (5 atm), 10% Pd–C, MeOH, 100%; vii, 2-$NO_2C_6H_4$SeCN, Bu$^n_3$P, THF, 50 °C, then 30% aq. H_2O_2, 0 °C, 77%; viii, DIBAL-H, toluene, −78 °C, 100%; ix, Pr$^n_4$NRuO$_4$, 4-methylmorpholine *N*-oxide, molecular sieves 4 Å, MeCN, 87%; x, 4-MeC$_6$H$_4$SLi, HMPA, toluene, reflux, 58%

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Footnotes and References

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† The ^{1}H and ^{13}C NMR spectra of macrocarpals C **3** and G **4** were measured in different solvents, which made comparison difficult. In ref. 1, however, it has been considered that these were diastereomers due to the difference between their physicochemical properties.

‡ Enantiomeric purity was determined by ^{1}H NMR analysis of Mosher ester derivatives.[11] Absolute stereochemistry was assigned by Mosher's method.[12]

§ A small amount (2%) of the benzylic epimer of **9** was obtained, but neither the C11 epimer nor the regioisomer was isolated.

¶ The structural assignment of **17** was confirmed by X-ray crystallographic analysis of its C10 carbonylimidazolide derivative **22**. *Crystal data* for **22**: $C_{39}H_{54}N_2O_{11}$, M = 726.86, orthorhombic, space group $P2_12_12_1$, a = 16.723(2), b = 19.979(2), c = 11.547(2) Å, V = 3858.0(9) Å^3, Z = 4, D_c = 1.251 g cm^{-3}, μ(Cu-Kα) = 7.13 cm^{-1}, F(000) = 1560, T = 293 K. The structure was solved by direct methods and refined by full-matrix least-squares to R = 0.052 and R_w = 0.067 using 2185 reflections with F_o > 3σ(F_o). CCDC 182/601.

‖ A preliminary study suggested that only bis-demethylation would occur by the use of sodium salt (4-MeC$_6$H$_4$SNa), as previously reported.[13]

** Synthetic **3** displayed ^{1}H and ^{13}C NMR spectra that were indistinguishable from those of the natural isolate and showed the following optical properties: $[\alpha]_D^{25}$ −22.1 (*c* 0.150, EtOH). A small rotation, $[\alpha]_D^{24}$ −3.0 (*c* 0.92, EtOH), was originally reported for **3** that had been isolated from *E. globulus*.[2b] This rotation, however, is believed to be erroneous due to contamination of the natural sample (M. Nishizawa, personal communication, April 15, 1997).

†† Synthetic **3** exhibited spectroscopic data (^{1}H, ^{13}C, IR) identical to those for natural macrocarpal G **4**. The rotation for synthetic **3**, $[\alpha]_D^{25}$ −24.7 (*c* 0.135, MeOH), corresponded closely to the rotation reported for **4**, $[\alpha]_D$ −27.1 (*c* 0.59, MeOH).[2c]

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