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# A Highly Stereocontrolled Formal Synthesis of *rac*-Chokols A and G from a Common *gem*-Borazirconocene Intermediate

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***Summary:*** *The stereoselective synthesis of rac-chokols A and G precursors described herein proceeds from the readily available gem-borazirconocene 2 by conjugate addition to 2-methylcyclopentenone to give the common intermediate 3, which is then transformed in a series of reactions to provide the chokols in overall yields of 16 and 17 % respectively.* Copyright © 1996 Elsevier Science Ltd

Cyclopentanoid natural products have long been attracting wide attention from synthetic as well as biological interest.[2] As part of our continuing efforts to develop borazirconocene 1,1-alkenes as starting point in the synthesis biologically intriguing compounds,[3] we were attracted by a group of fungitoxic sesquiterpenoids, chokols, isolated from the stromata of timothy grass *Phleum pratense* infected by the pathogenic fungus *Epichloe typhina*. Isolated for the first time in 1985,[4] (-)-chokol A, and other chokols B, C, D, and G, have recently received special attention due to their fungitoxic properties.[5] In 1986, Oppolzer and coworkers reported a 12-step synthesis of *rac*-chokol A with an overall yield of 3%.[6] The key step of this synthesis was a stereoselective magnesium-ene reaction. In 1988, Lawler and Simpkins synthesized *rac*-chokol A in six step via a conjugate addition/alkylation reaction in an overall yield of 32%.[7] Unfortunately, the use of toxic and carcinogenic HMPTA could not be avoided. Moreover, the conjugate addition step remains problematic since the yield varies between 30-52%. In 1994, Groth and coworkers reported the synthesis of *rac*-chokol A in an overall yield of 24% by a tandem Michael-addition/Dieckmann cyclization.[8] In 1987, Mash reported the first asymmetric synthesis of (-)-chokol A using diastereoselective cyclopropanation to establish enantioselectivity at the α and β carbon of cyclopentanone.[9] The overall yield was 9% over 13 steps and with an enantiomeric excess of 80%. More recently, Suzuki reported the highly enantioselective synthesis of (-)-chokol A from (R)-2,3-O-isopropylideneglyceraldehyde in 21 steps and with an overall yield of 4%[10a], while Urban reported its synthesis in 6 steps and 22% yield.[10b] *rac*-Chokol G was also synthesized in 1989 in 6 steps form linalool, the key step being the introduction of a hydroxymethyl group into the isoprenyl side chain.[11] In 1993, Trost reported the synthesis of chokol C in 19% overall yield in 7 steps from commercially available materials.[12] The key step was a palladium-catalyzed cycloisomerization of enynes.

Inspection of chokols A and G prompted us to attempt their short and rational synthesis from borazirconocene 1,1-alkenes.[13] It appeared that a concise approach to these chokols would involve reaction of the C-Zr bond with 2-methylcyclopentenone followed by reaction of the C-B bond to provide the functionalized alkyl substituent attached to the double bond. The last formal step in the synthesis would be the known stereoselective addition of a methyl group to a ketone from the less hindered α-side using methylcerium dichloride.[14] The synthetic strategy is outlined in Scheme 1.

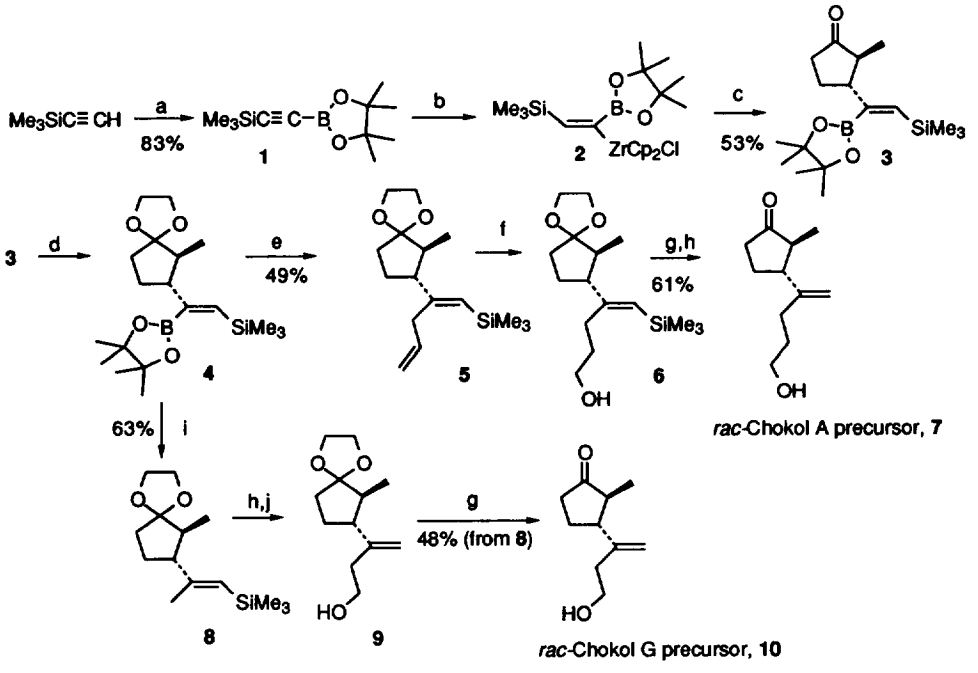
**2** was prepared by hydrozirconation of **1**.[13] The required *trans* stereochemistry in the cyclopentane ring was achieved by copper (10% CuBr.$SMe_2$ ) catalyzed addition[15] of **2** (1.5 equiv) to 2-methylcylopentenone to furnish the desired 1,4-addition product **3** in 53% yield. Some traces of *cis* product were observed but in small amounts (< 5%). On the other hand, the reaction proved somehow capricious, with the amount of hydrolyzed product (where C-Zr is hydrolyzed to C-H), occurring to the extent of 10-20%, probably due to quenching of unreacted bimetallic with aqueous ammonium chloride. However, separation of these two products by column chromatography proved easy. The use of $Ni(acac)_2$ as catalyst gave the same product but in lower yields.

The second critical point was the introduction of the hydroxylated side chain. For *rac*-chokol A, this proved problematic. We first tried a Suzuki coupling[16] of the alkenylboronate with hydroxy-protected 1-iodo-3-propanol. However, and not surprisingly, the reaction provided only homocoupled product. Then, we considered 1,4-addition of the alkenylboronate[17,18] with acrolein to provide the corresponding aldehyde that could be reduced in the alcohol. Unfortunately, polymerization of acrolein seemed to be the predominant reaction. Finally, we considered coupling of the alkenylboronate with allyl bromide to provide an unsaturated side chain that could be hydroborated and oxidized to provide the desired hydroxylated side chain. This proved to be the successful approach.

Coupling of **4** (ethylene glycol, $Me_3SiCl$, 25 °C, 4h) with allyl bromide in the presence of NaOH occurred smoothly and provided **5** in 49% yield. The tandem hydroboration/oxidation sequence provided the desired alcohol **6** which was not isolated. Hydrolysis of **6** (aqueous HCl, THF, 25 °C, 20h) followed by desilylation (KF, MeOH, 25 °C, 6h) gave *rac*-chokol A precursor, **7**, in 61% yield.[19]

Using the common intermediate **4**, we also synthesized *rac*-chokol G. Thus, Suzuki coupling with MeI (1 equiv MeI, 10 mol % $Pd(PPh_3)_4$, 2 equiv $K_3CO_4$, dioxane) provided **8** in 63 % yield. The crucial step in this synthesis was the introduction of a hydroxymethyl group into the isoprenyl side chain. This was successfully

**Scheme 1. Synthesis of *rac*-Chokols A and G Precursors**




(a) n-BuLi. i-PrO-B ; HCl/$Et_2O$. (b) $HZrCp_2Cl$, THF, 30 min. (c) 2-methylcyclopentenone, CuBr·$SMe_2$ (10 mol%), 24 h. (d) Ethylene glycol, $Me_3SiCl$ (4 equiv), $CH_2Cl_2$. (e) Allyl bromide, $Pd(PPh_3)_4$ (10 mol%), NaOH (2 equiv). (f) 9-BBN; $^-OH/H_2O$. (g) 5% HCl/THF, 25 °C, 20 h. (h) KF, $CH_3OH$, 25 °C, 6h. (i) MeI, $Pd(PPh_3)_4$ (10 mol%), $K_3PO_4$ (2 equiv). (j) $(CH_2O)_n$, $Me_2AlCl$, $CH_2Cl_2$, 0 °C; 25 °C, 1.5 h.

carried out using a Lewis acid-catalyzed intermolecular ene-reaction on the desilylated **8** (KF, MeOH, 25 °C, 6h) to give **9**.[11,20] Hydrolysis of **9** (aqueous HCl, THF, 25 °C, 20h) provided *rac*-chokol G precursor, **10**[19], in 48% yield from **8**.

In conclusion complete stereocontrol in the synthesis of two cyclopentanoid natural products has been demonstrated using borazirconocene chemistry.[21] The control is possible due to the selective reactivity of the C-Zr and C-B bonds, with the former always reacting first in a predictable manner. Other cyclopentanoids should also be accessible by this approach, especially novel prostaglandins.

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