Enantioselective Route to (−)-Chokol A

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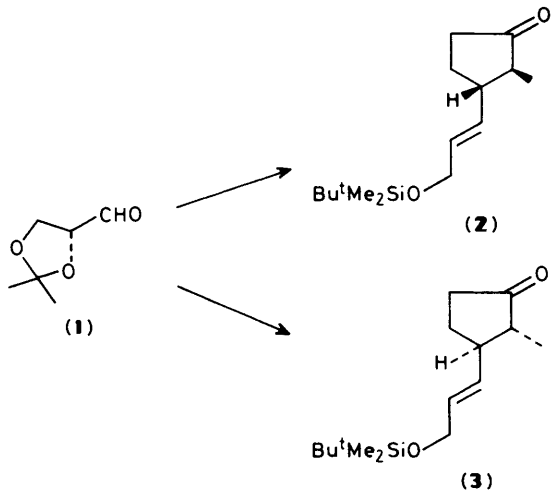
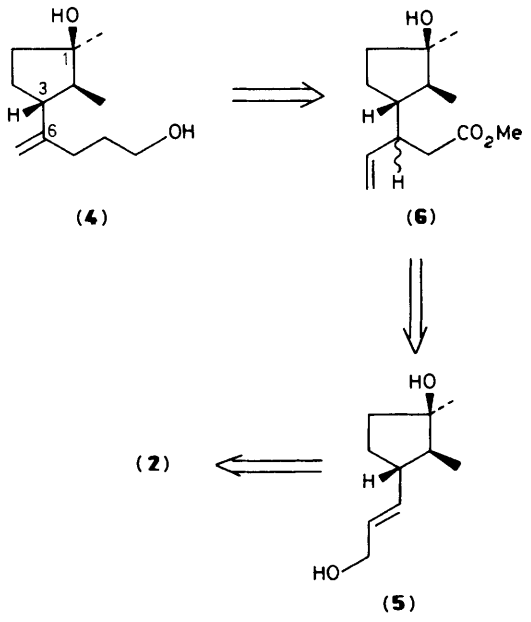
Stereoselective introduction of a methyl group to (3*R*)-2-methylcyclopentanone (**2**), followed by orthoester Claisen rearrangement provided the methyl ester (**6**) leading to (−)-chokol A (**4**).

Chokol A, a fungitoxic modified sesquiterpene isolated from stroma of the timothy *Phleum pratense* infected by the fungus *Epichloe typhina*,[1] has been shown, initially by spectral evidence and confirmed by syntheses of both racemic and optically active forms,[2,3] to possess the structure and absolute stereochemistry of (**4**).

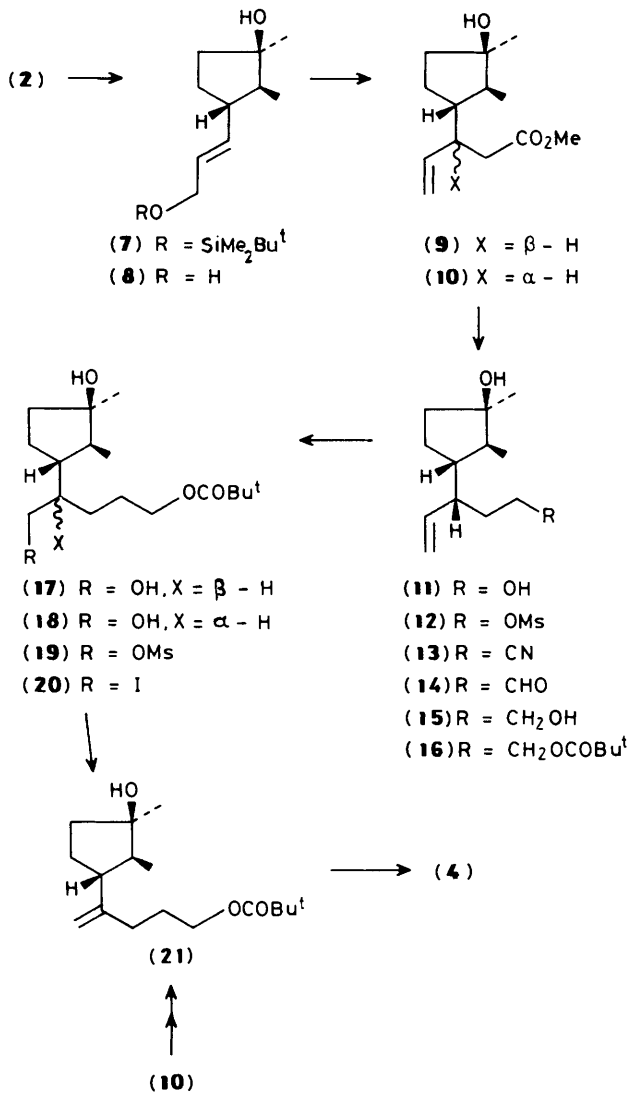
As part of our program aimed at the synthesis of biologically active natural products using simple chiral templates, we recently reported that (3*R*)- and (*S*)-methylcyclopentanones (**2**) and (**3**), efficiently derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**1**) (Scheme 1), could be potential intermediates for steroids[4] and vitamin D_3.[5] In this context,



Scheme 1



Scheme 2



Scheme 3

we report here an enantioselective synthesis of (−)-chokol A from (3*R*)-methylcylopentanone (**2**).

The retrosynthetic plan is outlined in Scheme 2. Stereoselective introduction of a methyl group to (**2**), followed by orthoester Claisen rearrangement of the allyl alcohol (**5**) provides the methyl ester (**6**) possessing the requisite functional groups for further elaboration of the side chain at C_3 in chokol A (**4**).

Stereoselective introduction of a methyl group into (3*R*)-methylcyclopentanone (**2**) (Scheme 3) with methyl cerium dichloride[6] [1.8 equiv., tetrahydrofuran (THF), −78 °C, 2 h] gave the desired alcohol (**7**) {$[\alpha]_D^{26}$ −41.9° (*c* 0.139, $CHCl_3$)} in 76.6% yield. Deprotection of the silyl group (cat. *p*-TsOH, MeOH, room temp., 3 h) followed by orthoester Claisen rearrangement [$(MeO)_3CMe$ (5 equiv.), propionic acid (0.1 equiv.), xylene, 145—150 °C, 1.5 h] of the resultant allyl alcohol (**8**) {$[\alpha]_D^{25}$ −31.3° (*c* 1.40, $CHCl_3$)} afforded the separable methyl esters (**9**) {$[\alpha]_D^{25}$ −23.6° (*c* 0.77, $CHCl_3$)} (51.1% yield) and (**10**) {$[\alpha]_D^{25}$ −37.0° (*c* 0.27, $CHCl_3$)} (18.9%) along with the starting material (5.0%), respectively. Reduction [$LiAlH_4$ (3 equiv.), THF, room temp., 2 h] of (**9**) and subsequent selective mesylation [$MeSO_2Cl$ (1.2 equiv.), 4-*N*,*N*-dimethylaminopyridine (DMAP) (1.5 equiv.), CH_2Cl_2, 0 °C, 1 h] of the primary alcohol in (**11**) {$[\alpha]_D^{25}$ −41.9° (*c* 0.63, $CHCl_3$)} provided in 90.1% overall yield, the monomesylate (**12**) {$[\alpha]_D^{22}$ −37.3° (*c* 0.57, $CHCl_3$)}, which on treatment with potassium cyanide (4 equiv., DMSO, 60 °C, 1.5 h) gave the nitrile (**13**) {$[\alpha]_D^{24}$ −10.5° (*c* 0.19, $CHCl_3$)}. Partial reduction of (**13**) with an excess of di-isobutylaluminium hydride (6 equiv., toluene, −78 °C, 4 h, followed by acid work-up) followed by a brief treatment of the resulting aldehyde (**14**) with an excess of sodium borohydride (MeOH, 0 °C, 10 min) afforded the diol (**15**) }$[\alpha]_D^{25}$ −38.7° (*c* 0.31, $CHCl_3$)} in 77.9% overall yield. Selective protection of the primary hydroxy group in (**15**) [pivaloyl chloride (1.0 equiv.), DMAP (1.2 equiv.), CH_2Cl_2, 0 °C, 5.5 h] followed by sequential treatment of the resulting ester (**16**) {$[\alpha]_D^{25}$ −17.0° (*c* 0.27, $CHCl_3$)} with osmium tetraoxide (0.1 equiv.), sodium periodate (2.5 equiv.), and sodium borohydride (MeOH, 0 °C, 5 min) provided the separable alcohol (**17**) {$[\alpha]_D^{24}$ −33.9° (*c* 0.2, $CHCl_3$)} (71.5%) and its C-6 epimer (**18**) {$[\alpha]_D^{24}$ −33.6° (*c* 0.05, $CHCl_3$)} in 19.6% overall yield. Selective mesylation

[$MeSO_2Cl$ (1.2 equiv.), DMAP (1.3 equiv.), CH_2Cl_2, 0 °C, 2 h) of the primary hydroxy group in (**17**), followed by treatment of the resulting (**19**) {$[\alpha]_D^{25}$ −34.2° (*c* 0.16, $CHCl_3$)}, with sodium iodide (4 equiv., acetone, 70 °C, 5 h) gave the iodide (**20**) which on treatment without purification with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (4.5 equiv., benzene, 75 °C, 8 h) afforded the protected chokol A (**21**) {$[\alpha]_D^{25}$ −32.0° (*c* 0.05, $CHCl_3$)} in 68.5% overall yield. Finally, mild hydrolysis of pivaloyl ester (**21**) with potasssium carbonate (MeOH, room temp., 4 h) furnished in almost quantitative yield (−)-chokol A (**4**) {$[\alpha]_D^{26}$ −55.0° (*c* 0.16, EtOH); lit.[3] $[\alpha]_D^{23}$ −46.3° (*c* 1.07, EtOH)},† identified by comparison of the i.r. and ^1H n.m.r. spectra and t.l.c. behaviour of the synthetic material with those of the natural material. Chokol A (**4**) was also synthesised *via* (**18**) from the methyl ester (**10**) using the same sequence described above.

† Professor E. A. Mash postulates that the actual optical rotation for natural (−)-chokol A is approximately −58° by careful examination of the 500 MHz ^1H n.m.r. spectrum of a sample provided by Professor T. Yoshihara, and concluded the enantiomeric excess of his synthetic material to be 80%.

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