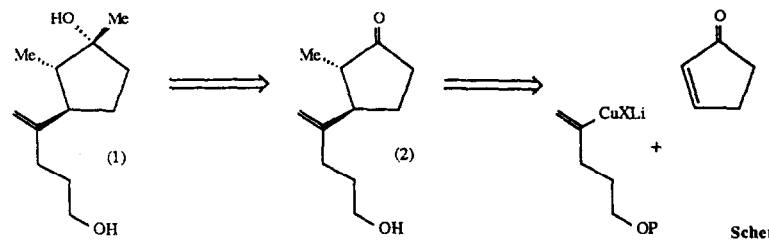
Tetrahedron Letters,Vol.29,No.10,pp 1207-1208,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

A CONCISE SYNTHESIS OF (±)CHOKOL A

David M. Lawler and Nigel S. Simpkins*
Department of Chemistry, Queen Mary College, Mile End Road, London, E1 4NS

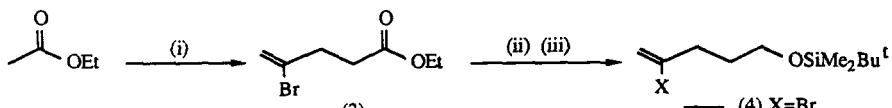
ABSTRACT: The fungitoxic sesquiterpene chokol A was synthesized via a six step sequence which used the addition reaction of a functionalised cuprate reagent to cyclopentenone as the key step.

In connection with some other studies, which involved the reaction of unsaturated organocuprates with various cyclic enones, we were attracted to the possibility of using these reagents in a synthesis of the recently isolated fungitoxic compound chokol A (1).[1] It appeared to us that the most concise approach to this compound would involve reaction of a suitably functionalised organocopper reagent with cyclopentenone as outlined in Scheme 1.[2]



Scheme 1

Our strategy required that the initial addition-alkylation product (2) have the desired trans stereochemistry, and that subsequent addition of a methyl group would then occur trans to the existing methyl group to give the final product.
The side chain required for the conjugate addition was readily prepared by alkylation of ethyl acetate with 2,3-dibromopropene at low temperature,[3] followed by treatment of the product ester (3) with excess $LiAlH_4$, and lastly, protection of the resulting primary alcohol as its TBDMS ether, Scheme 2.[4]

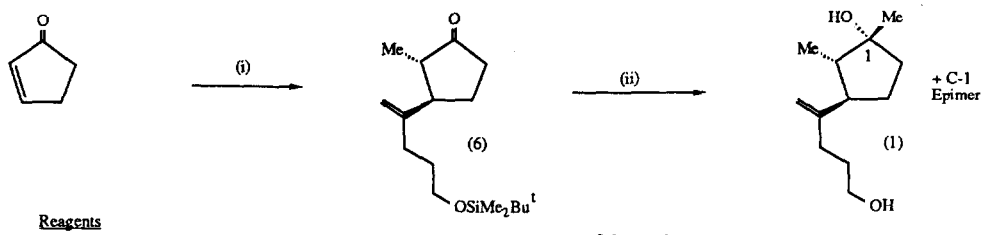


Reagents
(i) LDA, THF, CuI, -110°C, then Br, 75%
(ii) $LiAlH_4$, Et_2O, 74%
(iii) Bu^tMe_2SiCl, CH_2Cl_2, Imidazole, 85%. (iv) Bu^tLi (2 eq.), Et_2O, -78°C

Scheme 2

We found that metallation of the vinyl bromide (4) to give the corresponding vinyllithium (5) could be cleanly accomplished by use of 2 eq. of Bu^tLi in ether at -78°C, as evidenced by quenching of the anion with water. The key conjugate addition-alkylation step proved to be problematic, and poor results were obtained with many different cuprate reagents, and under a wide variety of conditions.[5] Particularly disappointing was the failure of heterocuprates and Lewis-acid assisted species of various

types to react with either cyclopentenone or 2-methylcyclopentenone, which would have enabled more efficient use of the vinyl bromide side chain.
Best results were obtained by reacting the homocuprate derived from 2 eq. of vinyllithium (5) and 1 eq. of $CuBr{\cdot}SMe_2$ in degassed THF/ether, with cyclopentenone, followed by quenching the resulting enolate with MeI/HMPA. Even under these conditions the reaction proved somewhat capricious, with yields of ketone (6) in the range 30-52%. However, we were pleased to find that the alkylated product was a single isomer, and our subsequent conversion of this material through to chokol A indicates that this product has the trans-configuration, Scheme 3.[6]



Reagents
(i) R_2CuLi (from 2eq. (5) and $CuBr{\cdot}SMe_2$), then MeI, HMPA, 52%.

(ii)MeMgBr, Et_2O, 0°C; then Bu_4NF, THF, 62% overall.

Scheme 3

Completion of the synthesis required only the addition of a methyl group to the ketone (6). This was achieved in a stereoselective fashion by addition of excess MeMgI to a solution of (6) in ether at 0°C, to give a mixture of chokol A and its C-1 epimer in a *ca* 2:1 ratio, after desilylative work-up and chromatography. Attempts to improve the stereoselection in this last step, by conducting the Grignard reaction at lower temperatures, or by using a titanium modified reagent,[7] proved unsuccessful.[8] Our synthetic chokol A exhibited spectral characteristics fully in accord with the published data for the natural product, whereas the C-1 epimer showed distinctly different features in both its ^1H- and ^{13}C-nmr spectra.
The synthesis of chokol A described here proceeds in only 6 steps, compared with 13 steps for the previous racemic synthesis, furthermore, with the advent of methods for asymmetric cuprate conjugate addition this route clearly becomes attractive for the preparation of members of this family of modified sesquiterpenes in optically active form.[9]

Acknowledgements
We thank the SERC, and May and Baker Ltd, Dagenham, for a CASE studentship to DML.

References
1 T. Yoshihara, S. Togiya, H. Koshino, S. Sakamura, T. Shimanuki, T. Sato, and A. Tajima, Tetrahedron Lett., 1985, 26, 5551.
2 For previous synthesis of racemic chokol A see W. Oppolzer and A. F. Cunningham, Tetrahedron Lett., 1986, 27, 5467.
3 I. Kuwajima and R. Doi, Tetrahedron Lett., 1972, 1163.
4 Both the ester (3) and the corresponding primary alcohol have been synthesized previously, see J. Ficini and A. M. Touzin, Tetrahedron Lett., 1977, 1081.
5 For a similar conjugate addition to a five-membered ring enone see P. Magnus and D. Quagliato, J. Org. Chem., 1985, 50, 1621.
6 We were able to prepare mixtures of diastereomers of the ketone (6), in which the cis-compound predominated, by reacting the same cuprate with 2-methylcyclopentenone.
7 M. T. Reetz, S. H. Kyung, and M. Hullmann, Tetrahedron, 1986, 42, 2931.
8 This problem has now been solved in a chiral synthesis of chokol A, by making use of methyl cerium dichloride, see E. A. Mash, J. Org. Chem., 1987, 52, 4142.
9 E. J. Corey, R. Naef, and F. J. Hannon, J. Am. Chem. Soc., 1986, 108, 7114.

(Received in UK 9 January 1988)