A Regio-, (*E*)-Stereo-, and Chemo-selective Synthesis of Unsymmetrical Divinylmethanols starting from L- and D-Tartrates *via* Organocyanocopper Lewis Acid Mediated 1,3-Chirality Transfer

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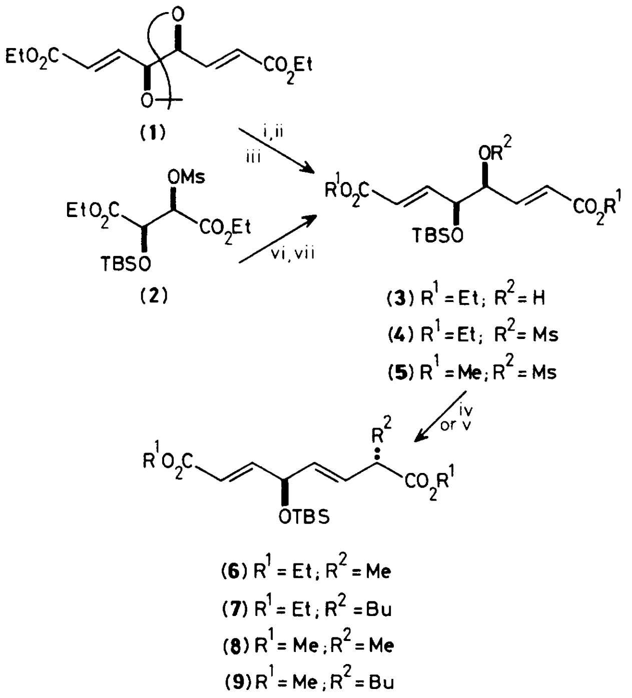
A regio-, (*E*)-stereo-, and chemo-selective synthesis of synthetically useful unsymmetrical divinylmethanol derivatives, compounds that are not easily accessible by other means, *via* an organocyanocopper·BF_3 mediated 1,3-chirality transfer in mixed solvents involving tetrahydrofuran at −78 °C is reported.

Despite recent developments in the preparation and reactions of symmetrical divinylmethanols[1] for the synthesis of chiral natural products *via* the Sharpless epoxidation,[2] efficient and general methods are still sought for the preparation of optically pure divinylmethanols that involve stereochemically well-defined chiral centres. It was for these reasons that we were driven to develop a reliable method for the regio-, stereo-, and chemo-selective preparation of unsymmetrical divinylmethanols from L- or D-tartrate. Based on our previous studies,[3] we anticipated that synthetically useful unsymmetrical divinylmethanol derivatives could be prepared from tartrate derived substrates by the organocopper·BF_3 mediated 1,3-chirality transfer reaction. The commercial availability of both enantiomers makes tartrates an attractive starting material for asymmetric synthesis.

The sequence of reactions in Scheme 1 shows how the L-tartrate was employed in an efficient synthesis of unsymmetrical divinylmethanol. To perform useful, efficient, and selective chemical transformation, it is necessary to protect one of two hydroxy groups as a t-butyldimethylsilyl ether. Thus, the (*E,E*)-dienoate (**4**), derived from (**1**)[4] *via* the hydroxysilyl ether (**3**) in the usual way (steps i—iii; *ca.* 62% overall yield), was treated with MeCu(CN)Li·BF_3(*LiBr*)† and BuCu(CN)Li·BF_3 in either tetrahydrofuran (THF)–Et_2O(*ca.* 10 : 2) or THF–hexane (*ca.* 10 : 2) at −78 °C for 30 min to yield the desired protected divinylmethanols (**6**) [90% isolated yield, 99% diastereoisomeric excess (d.e.)] and (**7**) (90% isolated yield, 99% d.e.), respectively, after flash chromatography over silica gel. The diastereoselectivities were easily



Scheme 1. *Abbreviations;* TBS = t-butyldimethylsilyl; Ms = methanesulphonyl; DMF = dimethylformamide. *Reagents;* i, 5% HCl–EtOH; ii, TBSSiCl–imidazole–DMF–CH_2Cl_2; iii, MsCl–pyridine–CH_2Cl_2; iv, MeCu(CN)Li·BF_3(*LiBr*) in Et_2O–THF (2 : 10) [(**6**) 90% yield, 99% d.e.; (**8**), 93% yield, 96% d.e.]; v, BuCu(CN)Li·BF_3 in n-hexane–THF (2 : 10) [(**7**), 90% yield, 99% d.e.; (**9**), 91% yield, 99% d.e.]; vi, Bu^i_2AlH in CH_2Cl_2, −78 °C, 1 h; vii, $Ph_3P{=}CHCO_2Me$ in CH_2Cl_2.

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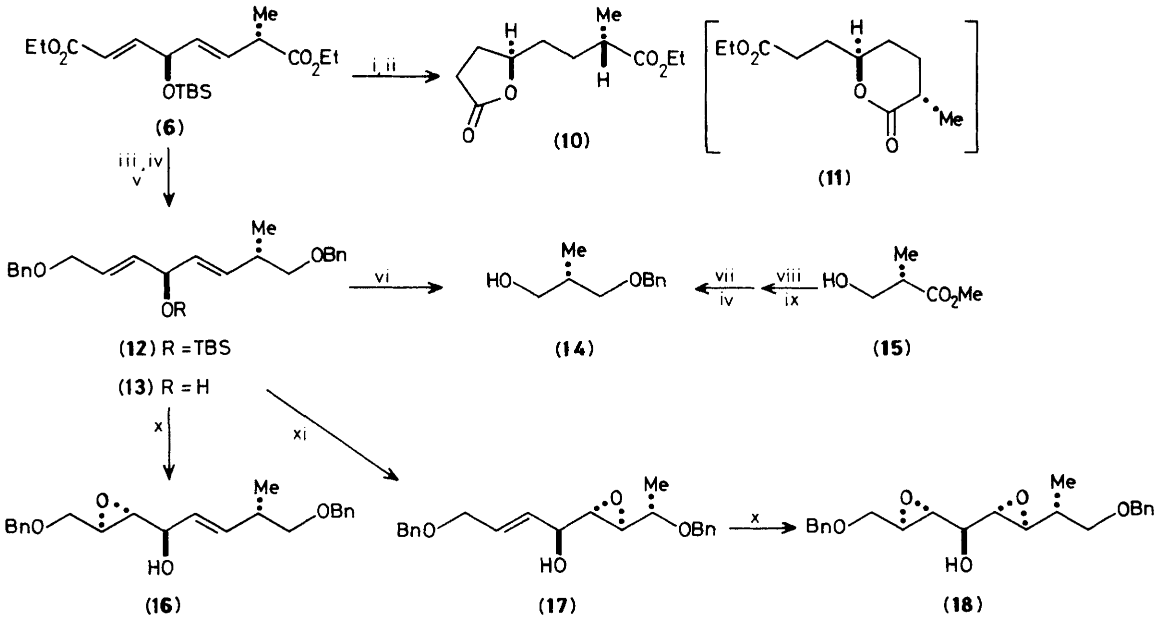
† The expression MeCu(CN)Li·BF_3 (*LiBr*) is intended to indicate that the reagent has been prepared from ethereal MeLi as the LiBr complex, see ref. 3a.



Scheme 2. *Abbreviations*. Bn = benzyl; DIPT = di-isopropyl tartrate. *Reagents*: i, H_2/5% Rh–Al_2O_3 in EtOH; ii, 46% HF–BF_3·Et_2O–MeCN (1:2:10), 0 °C, 3 h; iii, Bu^i_2AlH in CH_2Cl_2, −78 °C; iv, NaH–BnBr–DMF, room temp.; v, Bu^n_4NF in THF; vi, O_3 in n-hexane–CH_2Cl_2 (1:1), −78 °C, then Bu^i_2AlH; vii, Bu^tMe_2SiCl–imidazole in DMF—CH_2Cl_2 (1:1); viii, Bu^i_2AlH in CH_2Cl_2, −78 °C; ix, 46% HF–MeCN (1:50), 0 °C; x, D-(−)-DIPT–Ti(OPr^i)$_4$–Bu^tOOH in CH_2Cl_2, −20 °C; xi, L-(+)-DIPT–Ti(OPr^i)$_4$–Bu^tOOH in CH_2Cl_2, −20 °C.

determined by 200 or 400 MHz ^1H n.m.r. spectroscopy using Eu(hfc)$_3$ (hfc = heptafluoropropylhydroxymethylene). In the reaction of (**4**) with MeCu(CN)Li·BF_3(*LiBr*), a reductive elimination product, diethyl (4*R*)-t-butyldimethylsiloxy-(2*E*,5*E*)-octadienoate was also isolated as a by-product in 0.38% yield. Thus, the organocyanocopper·BF_3 reagent[5] reacts only with the mesyloxy functionality in an S_N2' manner, but does not undergo conjugate addition. Alternatively, the siloxy-mesylate (**5**), derived from the diester (**2**) by successive treatment with Bu^i_2AlH and Ph_3P=$CHCO_2Me$, yielded the 1,3-chirality transfer products (**8**) (93% yield, 96% d.e.) and (**9**) (91% yield, 99% d.e.). The enantiomer of (**4**) was similarly available starting from diethyl D-tartrate and reacts similarly with organocyanocopper·BF_3 reagents. All the highly selective 1,3-chirality transfer reactions described above are generally complete in a few minutes at −78 °C although we usually stir the reaction mixture for 30 min. It is of particular interest that these chirality transfers exhibit both high levels of chemoselectivity and an impressive degree of diastereoselectivity (> 98 : 2—99 : 1). An important aspect of the reaction is the high degree of desired stereoselectivity for the (*E*)-stereochemistry of the β,γ-double bond in the products.

As shown in Scheme 2, the absolute configuration of the alkylated carbon centre could not be determined by lactonization[6] (steps i and ii) since only the γ-lactone (**10**) [i.r. ($CHCl_3$) ν 1768 and 1727 cm^{-1}] was obtained in 77% overall yield from (**6**) [(**10**) : (**11**) = 100 : 0]. However the absolute configuration of the alkyl-bearing carbon centre, although clear from the reaction course of the *anti* S_N2' attack of organocopper reagents,[7] could be firmly established by chemical degradation. For example, ozonolysis of dibenzyl ether (**12**), derived from (**6**) by a two-step process (steps iii and iv; 69% overall yield), followed by reduction with Bu^i_2AlH, yielded the known benzyloxy alcohol (**14**) {$[\alpha]_D$ − 17.9 °C ($CHCl_3$)}[8] which was identified with an authentic sample of (**14**) obtained from the commercially available methyl (*S*)-3-hydroxy-2-methylpropionate (**15**).

Finally, the benzyl ether (**12**) could easily be converted to the divinylmethanol (**13**) by treatment with Bu^n_4NF in THF at 0 °C in 94% yield. The Sharpless epoxidation of (**13**) using Bu^tOOH, Ti(OPr^i)$_4$ and D-(−)-di-isopropyl tartrate in the presence of 4Å molecular sieves at −20 °C in CH_2Cl_2 gave the epoxide (**16**) as the sole product (85% isolated yield; >97% d.e. by ^{13}C n.m.r. analysis). In a similar manner, the isomeric epoxy alcohol (**17**) was obtained by using L-(+)-di-isopropyl tartrate instead of D-(−)-isomer (83% isolated yield; >97% d.e.). Furthermore, treatment of (**17**) with Bu^tOOH, Ti(OPr^i)$_4$, and D-(−)-di-isopropyl tartrate as described above gave the diepoxy alcohol (**18**) (97% isolated yield; >97% d.e.). The position of the epoxide ring in (**16**) or (**17**) was easily determined by the spin–spin decoupling in their ^1H n.m.r. spectra. The stereochemistry of the epoxides (**16**), (**17**), and (**18**) shown in Scheme 2 was assigned on the basis of the well known mechanism of the Sharpless asymmetric epoxidation with titanium-tartrate catalysts.[2]

In summary, we have demonstrated that reactions of (E)-γ-mesyloxy-α,β-enoates, derived from tartrates, with organocyanocopper·BF_3 reagents provide a highly efficient route to synthetically useful divinylmethanol derivatives. THF or mixed solvents containing THF along with proportions of ether and/or n-hexane are highly preferred solvents over those rich in Et_2O as clean reactions occur in these media at −78 °C within a short period of time. The 1,3-chirality transfer products thus obtained provide easy access to divinylmethanols that have great promise as intermediates for the synthesis of natural products.

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