COMMUNICATION

Chemoenzymatic routes to chiral (non-racemic) cyclopropanes. Preparation of a key intermediate for the synthesis of (1*R*)-*cis*-pyrethroids

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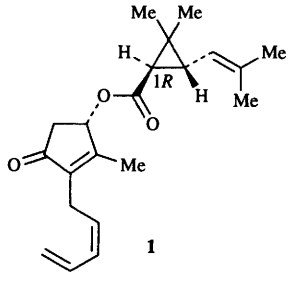
The microbial oxidation product 2 (X = Br) has been converted into the chiral (non-racemic) cyclopropane 11, a synthon for the commercially significant (1*R*)-*cis*-pyrethroid class of insecticides.

Monochiral cyclopropyl compounds continue to attract significant attention, not least because cyclopropane-containing natural products are ubiquitous and the majority of such compounds are enantiopure materials. Especially notable examples include the anti-mitotic agents curacins A–C,[1] the insecticide pyrethrin I **1**[2] and phorbol,[3] ester derivatives of



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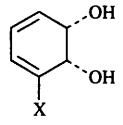
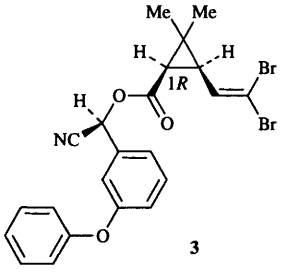


2 (X = Me, Cl, Br, CN *etc*)



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which are powerful tumour promoting agents. Interestingly, two multiply-cyclopropanated and monochiral natural products, *viz.* FR-900848 (a potent anti-fungal agent)[4] and U-106305 (a cholesteryl ester transfer protein inhibitor),[5] have been discovered recently. In the non-natural products arena, there is considerable interest in chiral (non-racemic) aminocyclopropyl carboxylic acids as conformationally restricting entities which can be incorporated into bioactive peptides, thereby causing stabilisation of the peptide towards enzyme cleavage.[6] It is against such a background that various methods for the synthesis of enantiopure cyclopropanes are being pursued. The more traditional approach centres on the diastereofacially selective cyclopropanation of alkenes containing a chiral auxiliary[7] (or related themes[8]). Recently, notable success has also been achieved in the catalytic asymmetric cyclopropanation of prochiral alkenes and allylic alcohols. Such efforts are highlighted by the contributions of, *inter alia*, Charette,[7a] Corey,[9] Davies,[10] Denmark[11] and Doyle.[12]

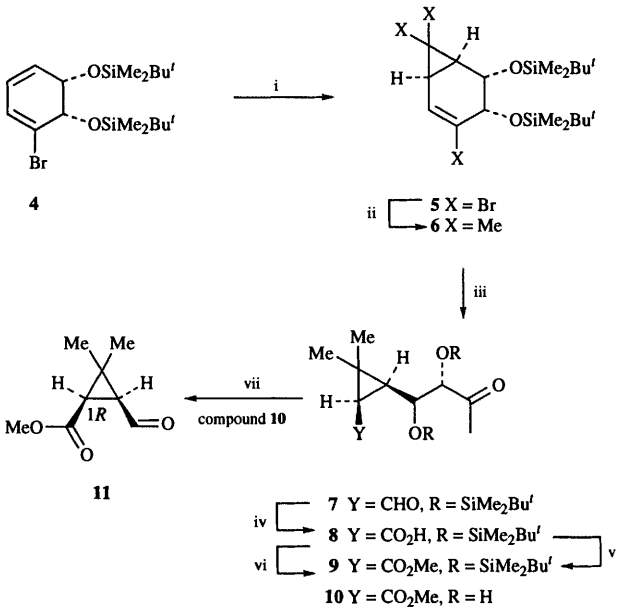
cis-1,2-Dihydrocatechols of the general type **2**, which are produced (generally in high enantiomeric excess) *via* microbial oxidation of the corresponding mono-substituted aromatic compound,[13] offer interesting possibilities as starting materials for the synthesis of enantiopure cyclopropyl compounds. For example, cyclopropanation of either face of a given double bond within such dienes would give two pairs of diastereoisomeric cyclopropanes which, when subjected to oxidative cleavage of the *cis*-diol moiety, should lead to enantiomeric pairs of open-chain cyclopropanes. Alternatively, cyclopropanation of the equivalent face of either double bond in diene **2** followed by removal of the X substituent gives a further set of enantiomeric pairs of cyclopropyl compounds. Other intriguing possibilities include Ullmann-type coupling of *cis*-1,2-dihydrocatechols (where X = Br or I) to give *bis*-dihydrocatechols which, when subjected to exhaustive cyclopropanation and subsequent oxidative cleavage of the *cis*-diol units, might serve as precursors to enantiopure poly(cyclopropane)s related to FR-900848[4] and U-106305.[5]

We now report the first use of microbially-derived *cis*-1,2-dihydrocatechols in the targeted synthesis of chiral (non-racemic) cyclopropanes. Specifically, we describe the application of compound **2** (X = Br) (>98% ee) to the synthesis (in near enantiopure form) of the cyclopropane **11**,[14] a key synthon for the preparation of the highly active and commercially significant (1*R*)-*cis*-class of pyrethroid insecticides, the most notable member of which is deltamethrin **3**.[2]

The synthetic sequence (Scheme 1) starts with the bis(*tert*-butyldimethylsilyl) ether **4** (94%) {$[\alpha]_D$ +30.5 (*c* 4.2, 20 °C)†}‡ which is obtained by standard methods from compound **2** (X = Br). Treatment of diene **4** with dibromocarbene, generated under phase transfer conditions from bromoform and aqueous sodium hydroxide, afforded the adduct **5** (70% at 70% conversion) {$[\alpha]_D$ −64.2 (*c* 3.8, 20 °C)} as the only isolable product of reaction. This latter compound was subjected to reaction, at −78 °C, with 15 mol. equiv. of the higher order cuprate $Me_2Cu(CN)Li_2$[15] which resulted in formation of the trimethylated compound **6** (68%) {$[\alpha]_D$ −1.3 (*c* 3.8, 20 °C)}. Ozonolytic cleavage of the double bond within the Δ^4-carene **6** then afforded the keto aldehyde **7** (78%) {$[\alpha]_D$ −24.5 (*c* 3.8, 20 °C)} which was oxidised to the corresponding acid **8** using Pinnick's sodium chlorite ($NaClO_2$) procedure.[16] This latter compound

† All new compounds had spectroscopic data (IR, NMR and mass spectra) consistent with the assigned structure. Satisfactory combustion and/or high resolution mass spectral analytical data were obtained for all new substances and/or suitable derivatives.

‡ Compound **4** was chosen as the starting material because of the high levels of regio- and diastereo-selection observed on its reaction with dibromocarbene. In contrast, when various appropriately protected derivatives of *cis*-1,2-dihydrocatechol **2** (X = Me) react with dihalogenocarbenes, mixtures of regioisomeric adducts are observed (see, for example, M. G. Banwell and M. P. Collis, *J. Chem. Soc., Chem. Commun.*, 1991, 1343).



Scheme 1 *Reagents and conditions:* i, $CHBr_3$ (5 mol. equiv.), 50% w/v aq. NaOH, $PhCH_2NEt_3Cl$, C_6H_6, 5–18 °C, 16 h; ii, $Me_2Cu(CN)Li_2$ (15 mol. equiv.), MeI (40 mol. equiv.), THF–Et_2O, −78 to 0 °C, 0.5 h; iii, O_3 (excess), CH_2Cl_2, −78 °C, 5 min, then Me_2S (excess), −78 to 18 °C, 16 h; iv, $NaClO_2$ (3 mol. equiv.), NaH_2PO_4 (1 mol. equiv.), 2-methylbut-2-ene (4 mol. equiv.), Bu^{t}OH–THF–H_2O, 18 °C, 3 h; v, CH_2N_2 (excess), Et_2O–CH_2Cl_2, 18 °C, 2 h; vi, TBAF·H_2O (3 mol. equiv.), THF, 18 °C, 3 h; vii, $Pb(OAc)_4$ (2 mol. equiv.), $CaCO_3$ (12 mol. equiv.), CH_2Cl_2, 0 °C, 0.75 h

was immediately converted (using diazomethane) into the corresponding methyl ester **9** (86% from **7**) {$[\alpha]_D$ −20.7 (*c* 2.3, 20 °C)} which could be disilylated with tetrabutylammonium fluoride (TBAF) monohydrate to give compound **10** (60%) {$[\alpha]_D$ +29.7 (*c* 1.9, 20 °C)}. Finally, lead tetraacetate-promoted cleavage of diol **10** afforded the target cyclopropane **11** (71%) {$[\alpha]_D$ −55 (*c* 1.3, 20 °C, $CHCl_3$); lit.,[14] $[\alpha]_D$ −76.9 (*c* 17.1, 20 °C, acetone)}.

The present work provides a first generation synthesis of compound **11** from **2** (X = Br) and highlights the potential utility of microbially-derived *cis*-1,2-dihydrocatechols in the preparation of monochiral cyclopropanes. Current efforts are being directed towards, *inter alia*, a more atom-economical pyrethroid synthesis wherein the alkenyl bromide moiety contained within compound **2** (X = Br) is exploited in the formation of the vinylic *gem*-dibromide unit associated with deltamethrin **3**.

Experimental

Methyl (1*R*,3*S*)-3-formyl-2,2-dimethylcyclopropane-1-carboxylate 11

A solution of lead tetraacetate (208 mg, 0.47 mmol) in CH_2Cl_2 (4 ml) was added dropwise to a magnetically stirred mixture of compound **10** (50 mg, 0.22 mmol) and calcium carbonate (266 mg, 2.66 mmol) in CH_2Cl_2 (4 ml) maintained at 0 °C. After 45 min Et_2O (20 ml) was added to the reaction mixture, which was then filtered through a Celite pad. The filtrate was concentrated under reduced pressure and the residue subjected to flash chromatography (silica 1 : 1 hexane–Et_2O elution) to give, after concentration of the appropriate fractions (R_f 0.6), compound **11**[14] (24 mg, 71%) as a clear colourless oil, $[\alpha]_D$ −55 (*c* 1.3, 20 °C, $CHCl_3$) [Found: $(M - CH_3^{\cdot})^+$, 141.0553, $C_8H_{12}O_3$ requires $(M - CH_3^{\cdot})^+$, 141.0552]; ν_{max}(NaCl)/cm^{-1} 1729 and 1701; δ_H(300 MHz, $CDCl_3$) 9.75 (d, *J* 6.5 Hz, 1 H), 3.71 (s, 3 H), 2.13 (d, *J* 8.7 Hz, 1 H), 1.85 (dd, *J* 6.5 and 8.7 Hz, 1 H), 1.55 (s, 3 H), 1.27 (s, 3 H); δ_C(75 MHz, $CDCl_3$) 200.8, 170.7, 52.5, 41.1, 36.3, 30.2, 28.5, 15.2; *m/z* (70 eV) 141 (35%, $M - CH_3^{\cdot}$), 97 (100, $M - H_3CO_2C^{\cdot}$).

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