Studies towards the Synthesis of FR-900848: Stereoselective Preparation of *anti*-Bicyclopropane Derivatives

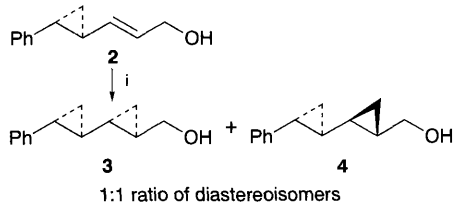
Anthony G. M. Barrett* and Gary J. Tustin

Department of Chemistry, Imperial College of Science, Technology & Medicine, London, UK SW7 2AY

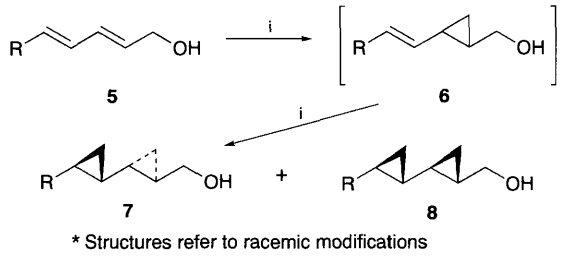
Double Simmons–Smith cyclopropanation of 2,4-dien-1-ols stereoselectively gives the corresponding *anti*-bicyclopropane derivatives.

FR-900848 **1** is a pentacyclopropane antibiotic extracted from the fermentation broth of *Streptoverticullium fervens* HP-891.[1] In our studies towards the synthesis of this structurally remarkable molecule we have been investigating methodology to produce serial cyclopropanes. Recently, we reported[2] the stereoselective preparation of bicyclopropane derivatives using tartrate esters as chiral auxillaries[3] and a stereospecific method to elaborate (*E*)-1,2-*bis*-[(1*S*,2*S*)-2-methylcyclopropyl]ethene.[4] As part of these studies, we observed that Simmons–Smith cyclopropanation of the enantiomerically pure allylic alcohol **2** gave both *syn*- and *anti*- bicyclopropanes **3** and **4** as a 1 : 1 mixture of diastereoisomers (Scheme 1). This result indicated that the first cyclopropane entity had no influence on the stereochemistry of the second cyclopropanation reaction. However in the cyclopropanation of allylic alcohol **2**, the ratio of bicyclopropanes **3** and **4** was controlled by using tartrate ester additives.[5] We now report that the double cyclopropanation of a 2,4-dienol selectively provides the *anti*-bicyclopropanemethanol diastereoisomer.

A series of 2,4-dienols **5**† were prepared from reaction of the corresponding (*E*)-α,β-unsaturated aldehydes (RCH=CHCHO)[6] with ethyl(diethoxyphosphono)acetate[7] in the presence of sodium hydride and subsequent DIBAL-H reduction.[8] 5-Phenylpenta-2,4-dien-1-ol (**5**, R = Ph) was allowed to react with diethylzinc and diiodomethane in 1,2-dichloroethane at −20 °C to generate the corresponding



Scheme 1 *Reagents and conditions*: i, Et_2Zn, CH_2I_2, $ClCH_2CH_2Cl$, −20 °C, 16 h, 80%



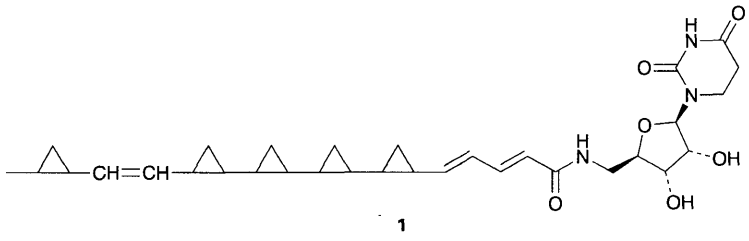
Scheme 2 *Reagents and conditions*: i, Et_2Zn, CH_2I_2, $ClCH_2CH_2Cl$, −20 °C 16 h

bicyclopropane derivatives **7** and **8** (Scheme 2). Much to our delight the reaction was shown to proceed in high yield (80%) and with good diastereoselectivity favouring the racemic *anti*-bicyclopropane derivative **7**. The selectivity of the reaction was determined by ^{13}C NMR spectroscopy[9] and this was consistent with an *anti*-**7** (R = Ph) : *syn*-**8** (R = Ph) isomer ratio of 5 : 1. The relative stereochemistry of each cyclopropane **7** (R = Ph) and **8** (R = Ph) as determined by comparison with authentic materials that were previously synthesised and authenticated by a single crystal X-ray structure analysis.[2] This comparison unequivocally established that the major isomer **7** (R = Ph) formed in the reaction had the *anti* configuration.

The cyclopropanation reaction was extended to four further 2,4-dienols **5** (Scheme 2). In each case double cyclopropanation of the 2,4-dienols **5** gave the corresponding racemic bicyclopropanemethanols **7** and **8** in good yields (68–78%). Additionally in each case, the reaction led to the predominant formation of the *anti*-diastereoisomer **7** (**7**:**8** = 5 : 1 to >95 : 5). Diastereoselectivity of reaction was determined by ^{13}C NMR spectroscopy[9]‡ and the results are summarised in Table 1. In all four cases structural assignment of the major isomer **7** rests by analogy with bicyclopropane **7** (R = Ph). However, in one case **7** (R = $Bu^tPh_2SiOCH_2$), the assignment of *anti*-stereochemistry was further substantiated by an alternative synthesis and chiroptical analysis (Scheme 3). Thus the monocyclopropane derivative **10** ($[\alpha]_D$ −12.0; 50% e.e.) was prepared from diethyl muconate[10] *via* DIBAL-H reduction to (*E*,*E*)-hexa-2,4-diene-1,6-diol, mono-protection[11] (44%) and asymmetric monocyclopropanation in the presence of L-(+)-diethyl tartrate (77%).[5] Subsequent cyclopropanation of **10** gave the corresponding bicyclopropyl alcohol derivative **11** (79%; $[\alpha]_D$ −9.2). In this experiment, the major non-racemic product **11** was spectroscopically identical with the product derived from the direct double cyclopropanation of dienol **5** (R = $Bu^tPh_2SiOCH_2$). Finally, *tert*-butyldiphenylsilylation of the alcohol **11** gave the corresponding disilyl ether **12** (86%; $[\alpha]_D$ −0.4). The low optical rotation of this *meso*-substance is fully in agreement with an assignment of *anti*-stereochemistry.

Table 1 Double cyclopropanation of dienols **5**

R	Yield (%)	Diastereoisomeric Ratio **7**:**8**
Ph	80	5:1
Me	68	5:1
Pr^i	72	6:1
C_6H_{11}	78	7:1
$Bu^tPh_2SiOCH_2$	72	>95:5



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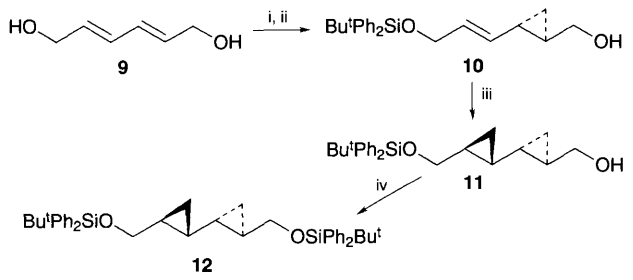
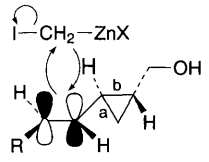


Scheme 3 *Reagents and conditions*: i, Bu^{t}Ph$_2$SiCl, imidazole, DMF, 16 h, 44%; ii, Et_2Zn, CH_2I_2, $ClCH_2CH_2Cl$, L-(+)-diethyl tartrate, −20 °C, 16 h, 77%; iii, Et_2Zn, CH_2I_2, $ClCH_2CH_2Cl$, −20 °C, 16 h, 79%; iv, Bu^{t}Ph$_2$SiCl, imidazole, DMF, 16 h, 86%



It is necessary to briefly comment on the origin of stereocontrol of the double cyclopropanation reactions in Scheme 2. It is known that cyclopropanation of allylic alcohols proceeds much faster than those of isolated alkenes due to precoordination of the zinc carbenoid to the hydroxyl group prior to methylene transfer.[12] On this basis, it is reasonable to propose that the conversion of the 2,4-dienols **5** into adducts **7** and **8** proceeded *via* the intermediacy of the racemic monocyclopropane **6** only. Indeed in several cases the monocyclopropane **6** (R = Ph) was observed in the ^1H and ^{13}C NMR spectra of incomplete double cyclopropanation reaction mixtures. Secondly, the monocyclopropanation of the unsaturated allylic ether **10** is fully consistent with the results obtained on the double cyclopropanation of 2,4-dienols **5** (R = Bu^{t}Ph$_2$SiOCH$_2$ further supporting the intermediacy of alkene **6** (R = Bu^{t}Ph$_2$SiOCH$_2$). It is reasonable to speculate that the alkenes **6** are subject to both steric and stereoelectronic control of the second cyclopropanation step (see diagram of **13**). In this analysis, overlap of the most electron rich cyclopropane σ- bond (bond a not bond b) with the alkene π-system should enhance its nucleophilicity and favour *anti*-delivery of the zinc carbenoid electrophile. Additionally, the cyclopropane ring in **13** should shield one face of the π-system thereby biasing the direction of methylene transfer. Fortunately, both these effects are complimentary. This analysis is also consistent with the enhanced *anti*-stereoselectivity seen with alkene **6** (R = Bu^{t}Ph$_2$SiOCH$_2$). In this case, the electron withdrawing ether group should deactivate the alkene thereby emphasising $\sigma \rightarrow \pi^*$ delocalisation. Finally, it should be noted that stereoelectronic control of double cyclopropanation reactions (Scheme 1)[2] is overwhelmed if the second ring is introduced next to polar Lewis basic functionality.

It is clear from these results that the presence of a cyclopropane ring system has a significant effect upon adjacent cyclopropanation reactions. Further aspects of this stereocontrol and studies on the total synthesis of FR-900848 **1** will be reported in due course.

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Footnotes

† All new compounds were fully characterized by spectral data and microanalyses or HRMS.

‡ In the case of diene **5** (R = Pr^i) the ratio of bicyclopropanes **7** and **8** was confirmed by conversion into the derived carbamates with phenyl isocyanate and HPLC analysis.

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