

Synthesis of the Spirochroman Core of Dihypoestoxide and Stereochemical Proposal for the Natural Product

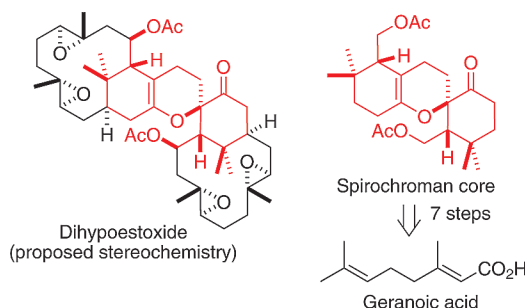
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ABSTRACT



The tricyclic spirochroman core of dihydroestoxide has been synthesized from geranoic acid in seven steps using a hetero-Diels–Alder cycloaddition as a key step, thus providing support for the proposed biosynthesis of the natural product. Furthermore, analysis of the ^{13}C NMR data obtained for all four diastereoisomers of the synthetic spirochroman core has allowed us to propose a full stereochemical assignment for dihydroestoxide.

Hypoestes rosea (Acanthaceae) is an evergreen tropical shrub indigenous to Nigeria, and extracts of the plant have long been used as folk medicines to treat a wide variety of conditions such as skin rashes and fungal infections.¹ This ethnobotanical information has stimulated research efforts to identify the biologically active components of the extract, and the closely related diterpene-derived natural products dihydroestoxide (**1**)² and hypoestoxide (**2**)³ were among the first compounds to be isolated. Although hypoestoxide displays significant biological activity (anti-inflammatory,^{4a} anticancer,^{4b} antimalaria^{4c}), similar studies on dihydroestoxide (**1**) are yet to be reported, but the wide range of therapeutic uses claimed for the plant extracts, coupled with the close structural association of **1** and **2**,

justifies further investigation of the potential biological activity of **1**. The gross structure of dihydroestoxide (**1**) was determined using a combination of NMR spectroscopy and mass spectrometry, and it was proposed that **1** is formed in vivo via a hetero-Diels–Alder dimerization of **2**. The isolation chemists showed that **1** is not an artifact of the isolation of **2**, as a deliberate attempt to dimerize hypoestoxide under the conditions of isolation failed to provide any dihydroestoxide (**1**). Unfortunately, a stereochemical assignment was not achieved at the time of isolation, but if **1** is formed via the hetero-Diels–Alder dimerization of hypoestoxide (**2**) in vivo, then it is sensible

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to propose that **1** shares the same stereochemistry as **2** at all common stereocenters⁵ (Figure 1). If this hypothesis

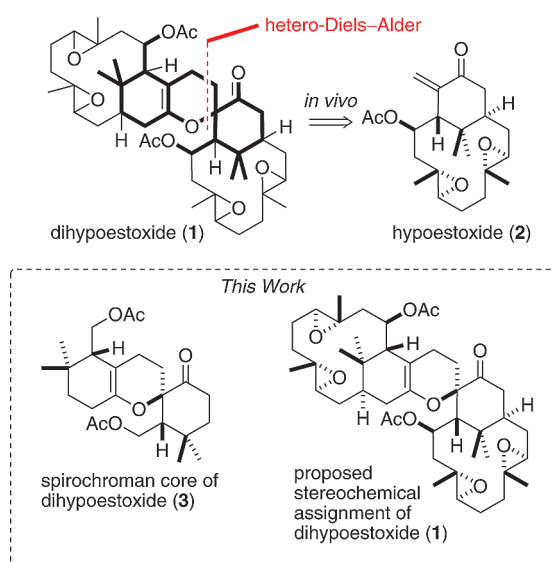


Figure 1. Proposed biosynthesis of dihypoxestoxide (**1**) via hetero-Diels-Alder dimerization of hypoxestoxide (**2**).

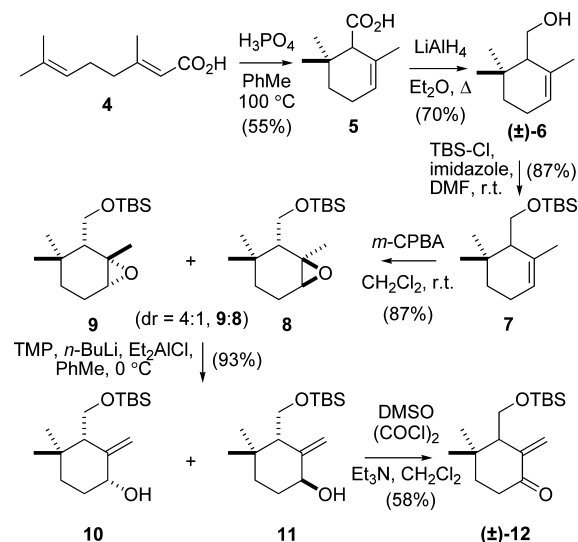
is true, then the only remaining stereocenter to be assigned is that present in the spirochroman ring system formed during the hetero-Diels-Alder dimerization.

As part of our studies directed toward a total synthesis of **1**, we decided to try and assign the stereochemistry at the spirochroman stereocenter by completing a synthesis of all four possible diastereoisomers of a simplified tricyclic spirochroman core structure **3** and then compare the data obtained with that of the natural product **1**. To access **3**, we planned to use the biomimetic hetero-Diels-Alder dimerization of a suitably functionalized α -methylene cyclohexanone precursor as a key step, thus simultaneously testing the validity of the biosynthetic proposal. In this letter, we describe the successful completion of our studies in this area that have resulted in the synthesis of the spirochroman core (**3**) of dihypoxestoxide and have allowed us to propose a complete stereochemical assignment of the natural product **1** (Figure 1).

Our synthetic efforts began by preparing the α -methylene cyclohexanones **12** and **16**, which were to be used in the key hetero-Diels-Alder cycloaddition reaction. The racemic enone **12** was readily prepared from geranoic acid **4** by first treating with H_3PO_4 to provide α -cyclogeranoic acid **5** in reasonable yield⁶ (Scheme 1).

The carboxylic acid **5** was then reduced with lithium aluminum hydride to give cyclogeraniol **6**, and the resulting primary alcohol was protected to give the TBS-ether **7**. Epoxidation with *m*-CPBA gave a 4:1 diastereomeric mixture

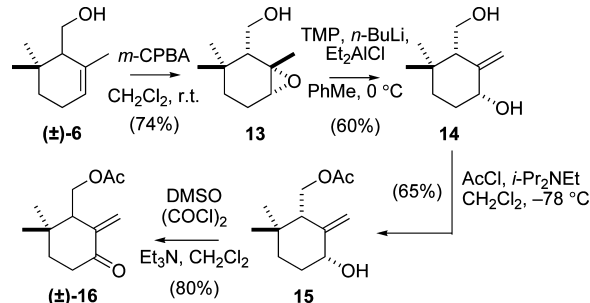
Scheme 1. Preparation of α -Methylene Cyclohexanone ($\pm$)-**12**



of the epoxides **9** and **8**, which were then rearranged using Yamamoto's conditions (TMP, *n*-BuLi, Et_2AlCl)⁷ to afford the corresponding allylic alcohols **10** and **11** in excellent yield. Oxidation of the 4:1 mixture of **10** and **11** under Swern conditions (DMSO, $(\text{COCl})_2$, Et_3N)⁸ finally gave the desired racemic enone **12**.

A similar synthetic sequence was used to access the closely related acetate-protected enone **16** (Scheme 2). Thus, cy-

Scheme 2. Preparation of α -Methylene Cyclohexanone ($\pm$)-**16**



clogeraniol (**6**) was epoxidized with *m*-CPBA to afford the epoxy alcohol **13** as a single diastereoisomer,⁹ and this material was then rearranged to provide the diol **14** using Yamamoto's conditions. Selective acetate protection of the primary alcohol was achieved using acetyl chloride at low temperature,¹⁰ and the secondary alcohol was oxidized under Swern conditions to provide the desired racemic enone **16**.

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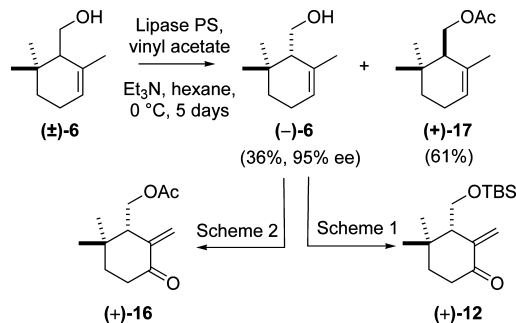
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In addition to preparing the racemic enones **12** and **16**, we also needed access to enantiomerically enriched material to minimize the number of possible diastereomeric outcomes of the hetero-Diels–Alder dimerization. Fortunately, we were able to easily obtain the enantiomerically enriched (>95% ee) enones (+)-**12** and (+)-**16** via enzymatic resolution of racemic cyclogeraniol (**6**) using commercially available lipase PS¹¹ (Scheme 3). Enantiomerically enriched cyclogeraniol

Scheme 3. Lipase PS Resolution of Cyclogeraniol

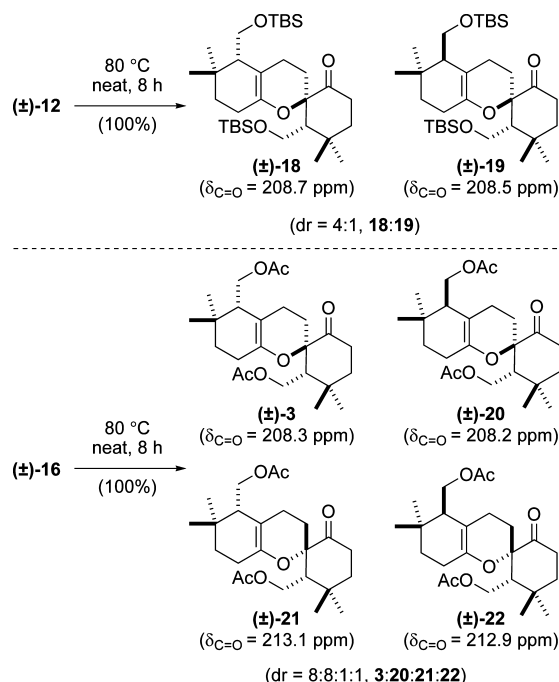


(-)-**6** (36% yield, 95% ee) was readily separated from the acetate **17** via silica gel column chromatography, and this gave access to (+)-**12** and (+)-**16** by following the routes previously used to prepare the equivalent racemic material (Schemes 1 and 2).

With both the racemic and enantiomerically enriched enones **12** and **16** in hand, we were able to begin our studies on the hetero-Diels–Alder dimerization process. Thus, the racemic TBS-protected enone (±)-**12** was heated at 80 °C in the absence of solvent, and the diastereomeric spirochromans (±)-**18** and (±)-**19** (4:1 ratio) were isolated as the only products in quantitative yield (Scheme 4). Similarly, dimerization of (±)-**16** was also achieved under the same conditions to afford all four possible diastereoisomers of the corresponding spirochroman products **3**, **20**, **21**, and **22** (8:1:1:1 ratio) in quantitative yield.

A detailed discussion regarding the stereochemical assignments of all spirochroman products is provided later, but the selective formation of (±)-**18** and (±)-**19**, in preference to the other two possible diastereoisomers, shows that the TBS-protected hydroxymethyl group plays a key role in controlling which face of the “dienophile” is available for cycloaddition. The spirochromans (±)-**18** and (±)-**19** are produced via cycloaddition on the least hindered upper face (as drawn) of the enone (±)-**12**. The 4:1 diastereoselectivity observed during the formation of (±)-**18** and (±)-**19** reflects the facial selectivity expressed by the enone (±)-**12** when acting as the 1-oxa-diene component in the cycloaddition. Once again, the TBS-protected hydroxymethyl group directs cycloaddition to the least hindered face, although its directing influence is weaker in the 1-oxa-diene component than it is

Scheme 4. Hetero-Diels–Alder Dimerizations of Racemic Enones



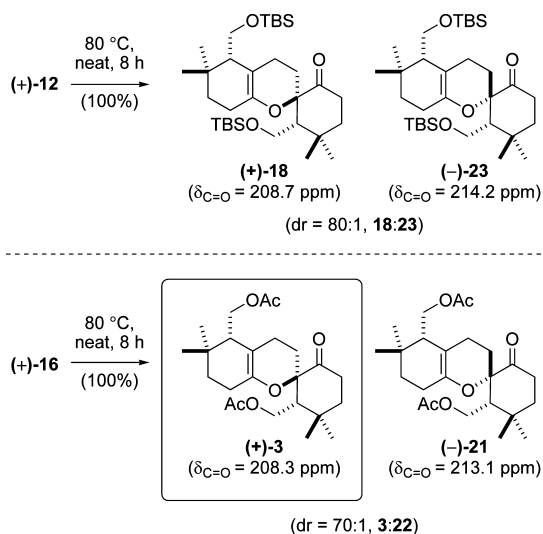
in the dieneophile component. In comparison, the less bulky acetate-protected enone (±)-**16** seems equally likely to undergo cycloaddition from either face when acting as the 1-oxa-diene component in the cycloaddition as (±)-**3** and (±)-**20** are produced in a 1:1 ratio, and (±)-**21** and (±)-**22** are also produced in a 1:1 ratio. However, good levels of diastereoselectivity (8:1) were still observed with respect to the dienophile component, although there is a slight erosion in selectivity when compared to the more hindered TBS example discussed previously.

The analogous dimerization reactions were next performed using the enantiomerically enriched enones (+)-**12** and (+)-**16**. As seen in the racemic series, the spirochroman (+)-**18** was the major product of the dimerization of (+)-**12**, with the previously unseen minor diastereoisomer (-)-**23** being produced in very small quantities (dr = 80:1) (Scheme 5). Similarly, dimerization of (+)-**16** produced the spirochroman (+)-**3** as the major product, with (-)-**21** being produced as a minor product (dr = 70:1).

As none of the spirochroman products (**3**, **18–23**) were crystalline, stereochemical assignment proved to be an interesting challenge and was only possible because we had access to both the racemic and enantiomerically enriched enones **12** and **16**. Since we knew that all four possible diastereoisomers (8:8:1:1 ratio) were produced during the hetero-Diels–Alder dimerization of (±)-**16** and that only two products ((+)-**3** and (-)-**21**) could possibly be (and indeed were) produced during the dimerization of the single enantiomer (+)-**16**, we could immediately identify compounds **3** and **21** within the four products produced from (±)-**16**. As this type of hetero-Diels–Alder cycloaddition prefers an *endo*-pathway,¹² we could confidently assign the major

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Scheme 5. Hetero-Diels–Alder Dimerizations of Enantiomerically Enriched Enones



product (+)-**3** as having the stereochemistry shown in Scheme 5. This means that (–)-**21** is the minor *exo*-product and must have the opposite stereochemistry at the spiro stereocenter (Scheme 5). Therefore, the remaining two compounds were obviously **20** and **22**, but at this stage we did not know which was which. Further confirmation of the stereochemical assignment of **3** and **21** comes from analysis of the ^{13}C NMR data for the carbonyl present in the spirochroman ring system, with compound (+)-**3** having a $\delta_{\text{C=O}} = 208.3$ ppm and (–)-**21** having a $\delta_{\text{C=O}} = 213.1$ ppm. These values are in accord with those observed in similar spirochromans present in the dimer of 5-oxotaxinine ($\delta_{\text{C=O}} = 206.4$ ppm)¹³ and tagalsin I ($\delta_{\text{C=O}} = 213.4$ ppm),¹⁴ respectively, whose structures have been solved by X-ray crystallography. Inspection of the published X-ray structures reveals that the ethereal C–O bond of the dihydropyran fragment of the dimer of 5-oxotaxinine is in an equatorial position on the cyclohexanone fragment, and the equivalent ethereal C–O bond of the dihydropyran fragment of tagalsin I is in an axial position on the cyclohexanone fragment of the corresponding spirochroman ring system. Applying this knowledge to our data, we can see that spirochromans **3**,

18, **19**, and **20** possess the stereochemistry represented by structure **A** (Figure 2) as they all have $\delta_{\text{C=O}} = 208 \pm 1$ ppm,

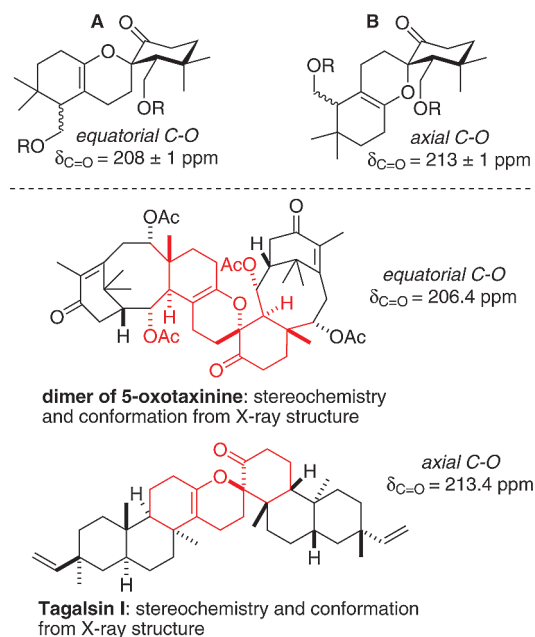


Figure 2. Correlation of spirochroman configuration with ^{13}C data.

and spirochromans **21**, **22**, and **23** possess the stereochemistry represented by structure **B** as they all have $\delta_{\text{C=O}} = 213 \pm 1$ ppm. The ability to assign configuration at the spirochroman spirocenter (relative to the protected hydroxymethyl substituent on the cyclohexanone ring) using ^{13}C NMR allows us to propose the stereochemistry shown in Figure 1 for dihypoxestoxide, as the natural product has $\delta_{\text{C=O}} = 207.5$ ppm, which fits extremely well with our data for the core structure **3**.

In conclusion, we have shown that hetero-Diels–Alder cycloaddition/dimerization could account for the formation of dihypoxestoxide from hypoxestoxide, although the conditions required to accomplish this transformation *in vivo* are yet to be established. Furthermore, we have been able to propose a complete stereochemical assignment of dihypoxestoxide based upon analysis of its ^{13}C NMR data.

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Supporting Information Available: Copies of the ^1H and ^{13}C NMR spectra and detailed experimental procedures for the preparation of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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