

Total Synthesis of Eupomatilones 4 and 6: Structurally Rearranged and Atropisomerically Fluxional Lignan Natural Products

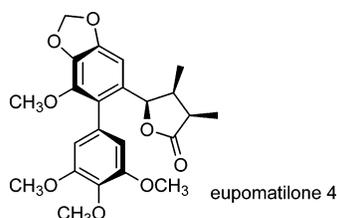
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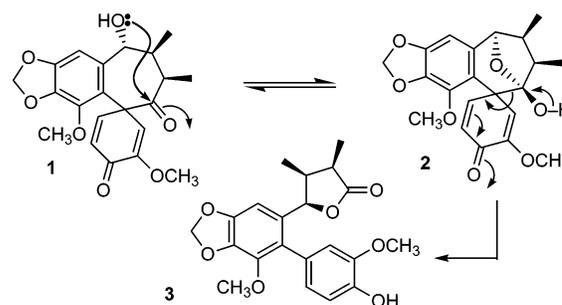
ABSTRACT



A convergent and diastereocontrolled total synthesis of eupomatilones 4 and 6 is reported and was based on a diastereoselective hydroboration/oxidation sequence and a convergent Lipshutz biarylcuprate cross-coupling reaction. The structure of eupomatilone 6 is revised.

The structurally novel lignans eupomatilones 1–7 were isolated in 1991 by Carroll and Taylor from the indigenous Australian shrub *Eupomatia bennettii*, co-occurring with a structurally diverse set of related lignan natural products.¹ The normally dimeric β -cinnamic acid carbon skeleton has undergone an unprecedented rearrangement that involves cleavage of a carbon–aryl bond. As proposed by Carroll and Taylor,² the spirocyclohexadienone skeleton of eupodiene precursor **1** undergoes hemiketal formation to afford **2**, which fragments to lactone **3** (Scheme 1). All six carbons of the side chains of the cinnamic acid precursors end up attached to just one of the aromatic rings. The eupomatilones equilibrate about the biaryl axis, which is stereogenic for eupomatilones 6 and 7. This rotation is slow on the NMR time scale, and two isomers are observed by both ¹H and ¹³C NMR for eupomatilones 6 and 7. The hydrogens on the trimethoxyphenyl ring of eupomatilone 4 are diastereotopic. The atropiastereomers are inseparable, and the coalescence temperature was found to be 97–102 °C.²

Scheme 1



There have been two reports of synthetic approaches to eupomatilone 6.^{3,4} In this paper, we report the total synthesis of eupomatilones 4 and 6 and correct the structure of eupomatilone 6 (Figure 1).

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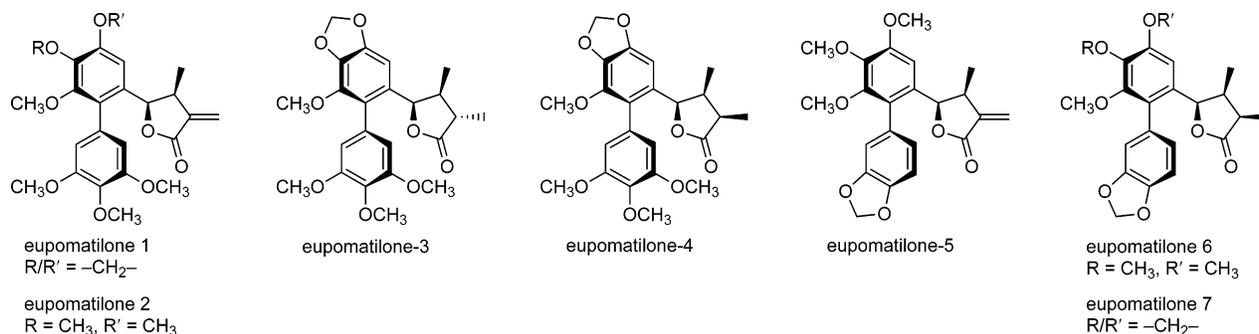
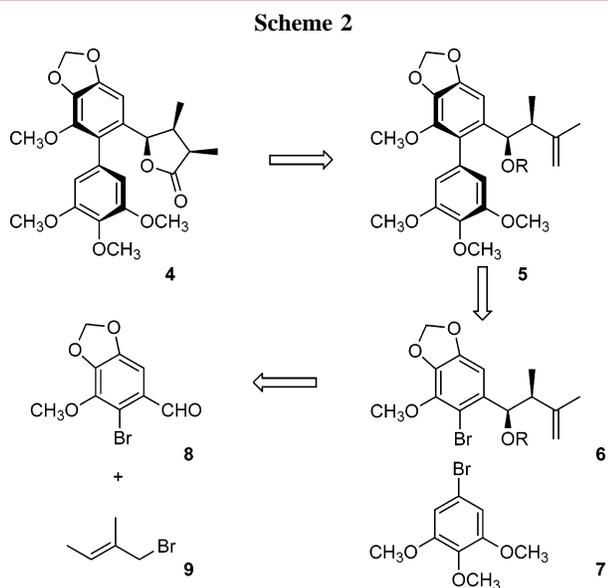


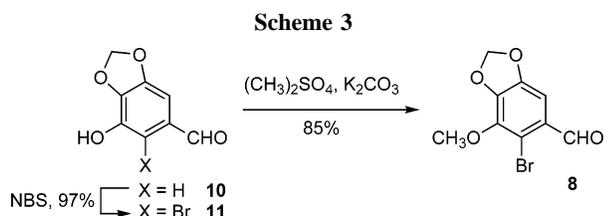
Figure 1. Reported structures of the eupomatilones.

These agents share a fluxional biaryl axis and a γ -lactone bearing two or three stereogenic carbons. A synthetic strategy was developed (Scheme 2) that was based on a Lipshutz



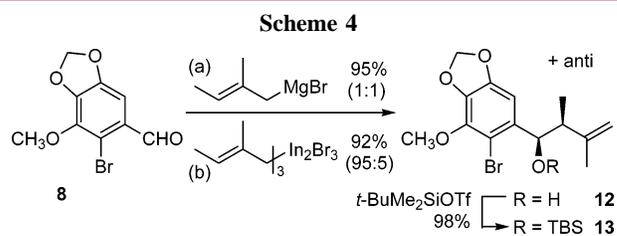
oxidative biarylcuprate cross-coupling of **6** with **7** and a subsequent diastereocontrolled hydroboration/oxidation sequence on the alkene of **5**. Starting from commercially available **7**, readily constructed **8**, and (*E*)-1-bromo-2-methyl-2-butene (**9**), these natural products were synthesized in an efficient and stereocontrolled manner.

Aldehyde **8** was synthesized from 5-hydroxypiperonal (**10**)⁵ (Scheme 3). Bromination (NBS, dioxane, 15 °C)



occurred regioselectively⁶ to afford the *o*-bromoaldehyde **11**, which was methylated (Me₂SO₄, K₂CO₃, acetone, 56 °C) to afford **8**.

Construction of the eupomatilone side chain (Scheme 4) relied on addition of (*E*)-2-methyl-2-buten-1-ylmagnesium bromide to aldehyde **8** (THF, -78 °C, 1.5 h), which provided



a 1:1 mixture of *syn* and *anti* adducts **12** in 95% yield. The undesired *anti* adduct was converted to the desired *syn* adduct by Mitsunobu inversion with *p*-nitrobenzoic acid⁷ (Ph₃P, DIAD, THF, 0–25 °C) and hydrolysis (K₂CO₃, MeOH, 25 °C), which resulted in an overall yield for conversion of **8** to **12** of 73%. Alternatively, **12** could be produced as a 95:5 *syn/anti* mixture in 92% yield⁸ by addition of the analogous indium reagent⁹ to aldehyde **8**. The alcohol of **12** was protected as the *tert*-butyldimethylsilyl ether (*t*-BuMe₂SiOTf, 2,6-lutidine, CH₂Cl₂, -78 °C, 20 min) to afford **13**.

We implemented the methodology of Lipshutz for biaryl coupling,¹⁰ which involves low temperature formation of a mixed biarylcuprate and oxidation of this species to form the carbon–carbon biaryl bond. This reaction is less sensitive to steric or electronic features of the aromatic systems

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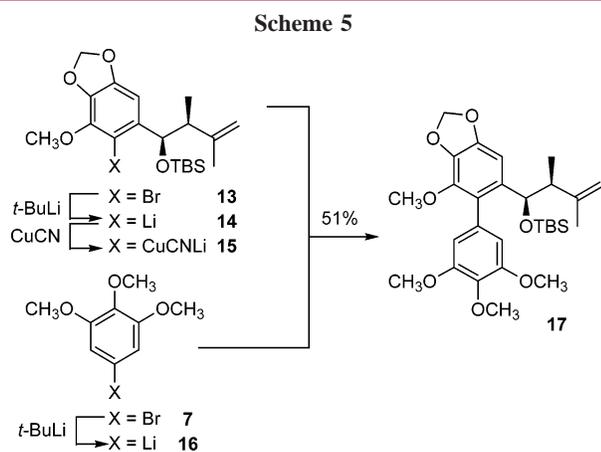
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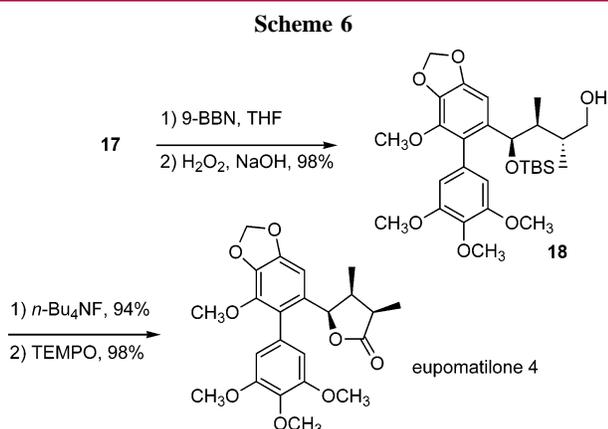
compared to palladium-mediated processes. We have employed this reaction in a stereocontrolled synthesis of the natural products calphostin A and phleichrome.¹¹

In the present case (Scheme 5), aryl bromide **13** was converted to the aryllithium reagent **14** (*t*-BuLi, MeTHF, -78



°C), and subsequently to the lower order cyanocuprate **15** (CuCN, MeTHF, -40 °C). Aryl bromide **7** was similarly converted to aryllithium **16** (*t*-BuLi, MeTHF, -78 °C), which was added to cyanocuprate **15** (-125 °C, 30 min) to form a biarylcuprate species. Treatment with oxygen (-125 °C, 3 h) affected conversion to the biaryl system **17** in modest yield.

Hydroboration of **17** (9-BBN, THF, 0–25 °C, 12 h) followed by oxidation (NaOH, H₂O₂, 0–25 °C, 3 h) afforded primary alcohol **18** in essentially quantitative yield, with complete control of diastereoselectivity (Scheme 6). Depro-

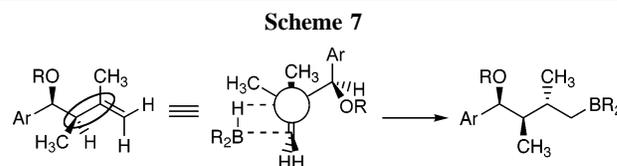


tection of the silyl ether of **18** (*n*-Bu₄NF, THF, 25 °C, 3 h) and oxidation of the primary alcohol (TEMPO, NCS, *n*-Bu₄NI, CH₂Cl₂/1:1 0.05 M K₂CO₃/0.5 M NaHCO₃, 25 °C, 1 h)¹² was accompanied by lactonization and afforded eupo-

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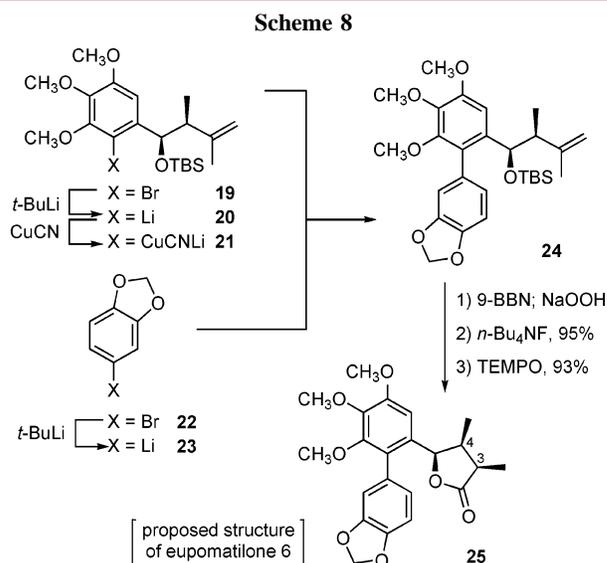
matilone **4** in 92% yield for the two-step sequence. Eupomatilone **4** was synthesized in eight steps from known **7** and **10** in 33% overall yield. The ¹H NMR spectrum of synthetic eupomatilone **4** was identical with that reported for the natural product.²

The origin of the diastereoselection in the hydroboration of **17** is detailed in Scheme 7. In the lowest energy



conformation (MM3) about the sp²–sp³ bond, the allylic hydrogen is eclipsed with the alkene in order to minimize A^{1,3} strain. The least sterically congested approach by 9-BBN is from the side of the allylic methyl group, giving a new stereogenic center wherein the methyl groups are *anti*. This model has precedent in several related contexts.¹³

Total synthesis of eupomatilone **6** proceeded from aryl bromides **19**¹⁴ and commercially available **22** (Scheme 8).



Cuprate coupling of the corresponding aryllithium reagents **20** and **23** under previously described conditions afforded biphenyl **24**. Following reaction conditions used in the total

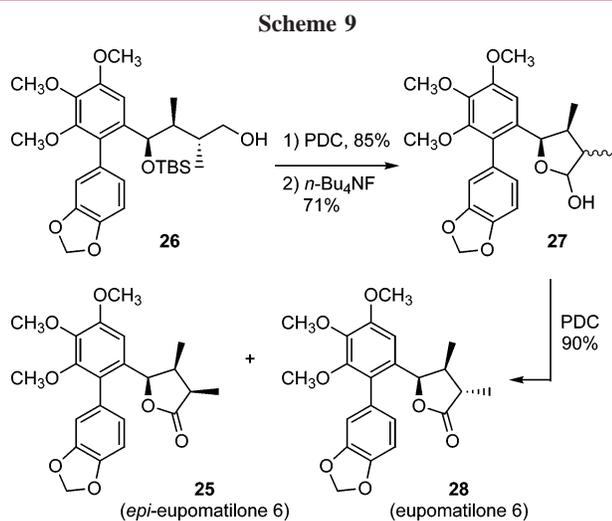
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(14) Prepared from 2-bromo-3,4,5-trimethoxybenzaldehyde (cf. Molander, G. A.; George, K. M.; Monovich, L. G. *J. Org. Chem.* **2003**, *68*, 9533) as described for the preparation of **13**.

synthesis of eupomatilone 4, hydroboration/oxidation of the alkene of **24** afforded the corresponding primary alcohol (42% for two steps). Fluoride-mediated desilylation and selective oxidation of the primary alcohol afforded γ -lactone **25**, supposedly eupomatilone 6. However, the ^1H NMR spectrum of synthetic **25** did not match the data published for eupomatilone 6,² differing slightly in the chemical shifts of and coupling constants between C3-H and C4-H. Our spectral data matched that obtained by Gurjar and co-workers⁴ in their synthesis of this putative structure of eupomatilone 6.

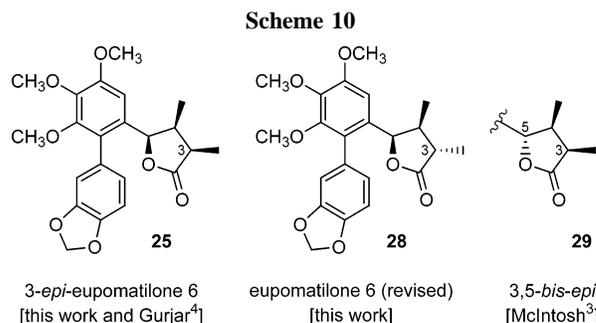
We had inadvertently synthesized the correct structure of eupomatilone 6 during studies on the oxidation/lactone formation sequence (Scheme 9). Oxidation of alcohol **26** with



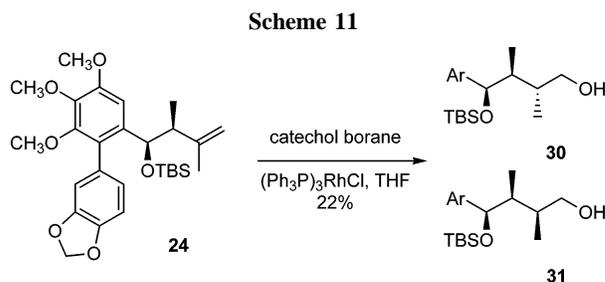
pyridinium dichromate (CH_2Cl_2 , 25 °C, 3 h, 85%) afforded the corresponding aldehyde, which cyclized to lactol **27** after fluoride-mediated deprotection of the silyl ether (THF, 25 °C, 6 h). Compound **27** was produced as a mixture of diastereomers, presumably from epimerization of the intermediate aldehyde under basic reaction conditions. Lactol to lactone oxidation (CH_2Cl_2 , 25 °C, 2 h, 90%) afforded a 1:3 mixture of **25** and its epimer **28**, which could be separated—with difficulty—by preparative TLC. The ^1H NMR spectrum of pure **28** proved identical with that published for eupomatilone 6.²

Our synthesis of **25** (Scheme 8) produced 3-*epi*-eupomatilone 6, whereas the structure of the natural product must possess a *trans* relationship of the C3 and C4 methyl groups, as in **28** (Scheme 10). This result changes the work of

McIntosh and co-workers,³ whose reported synthesis of 5-*epi*-eupomatilone 6 should now be regarded as a synthesis of 3,5-bis-*epi*-eupomatilone 6 (**29**).



Attempts to alter the diastereoselectivity of the hydroboration of **24** using rhodium catalysis¹⁵ were unproductive, producing a 4:3 mixture of diastereomers **30** and **31** (Scheme 11). Although a stereocontrolled route from **24** to **31**, and



thence to eupomatilones 3 and 6, has not been achieved, this is beyond the intended scope of this work. The total synthesis of eupomatilone 6 has been achieved by a serendipitous route involving base-induced epimerization.

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Supporting Information Available: Experimental procedures and spectral characterization of intermediates and products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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