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Synthesis of the Putative Structure of Eupomatilone-6

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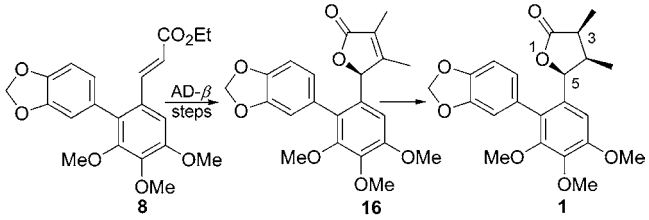
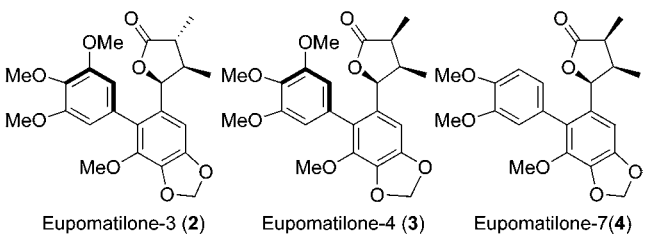
ABSTRACT



The synthesis of eupomatilone-6 (1) has been achieved by using Suzuki coupling, Sharpless asymmetric dihydroxylation, and intramolecular Horner–Wadsworth–Emmons reactions. The spectroscopic studies carried out on synthetic eupomatilone-6 do not agree with those reported for the natural product, and therefore revision of the assigned structure is warranted.

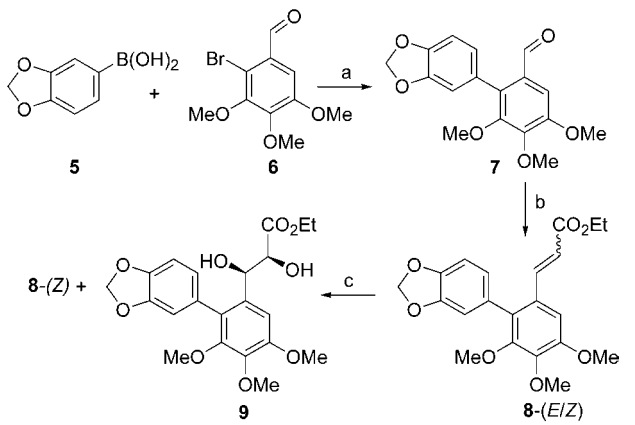
In 1991, Taylor et al. isolated a series of novel lignans eupomatilones **1**−**7** from the shrubs *Eupomatia bennettii* F.Muell., and their relative configurations were elucidated by extensive NMR studies.[1,2] Eupomatilones are characterized by the biaryl system with a substituted γ-lactone ring attached to one of the aryl rings. Although they exist as a mixture of atropisomers, efforts to separate them by HPLC were unsuccessful. Apart from a recent synthesis of (±)-5-epi-eupomatilone-6, no report has yet appeared on the total synthesis of any of these natural products.[3]

As part of our continuing interest in biaryl-containing natural products coupled with the structural peculiarity of eupomatilones, herein we report the total synthesis of eupomatilone-6 (**1**).[4] It is pertinent to mention that the synthetic product did not match spectroscopically with assigned structure of natural eupomatilone-6, and therefore a revision in structure is proposed.



The synthesis began with the Suzuki coupling reaction between **5**[5] and **6**[6] in the presence of Pd(0) to afford the biaryl aldehyde derivative **7**[7] in 79% yield (Scheme 1). Treatment of **7** with ethoxycarbonylmethylenetriphenylphosphorane in CH_2Cl_2 afforded **8** as a mixture of *E*/*Z*-isomers (85:15). In

Scheme 1[a]



[a] Reagents and conditions: (a) $Pd[(PPh_3)]_4$, benezene, ethanol, 2 M Na_2CO_3, reflux, 24 h, 79%; (b) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 3 h; (c) $(DHQD)_2PHAL$, $K_2OsO_4{\cdot}2H_2O$, $MeSO_2NH_2$, K_2CO_3, ^{t}BuOH:H_2O (1:1), 0 °C, 18 h, 80% (for two steps).

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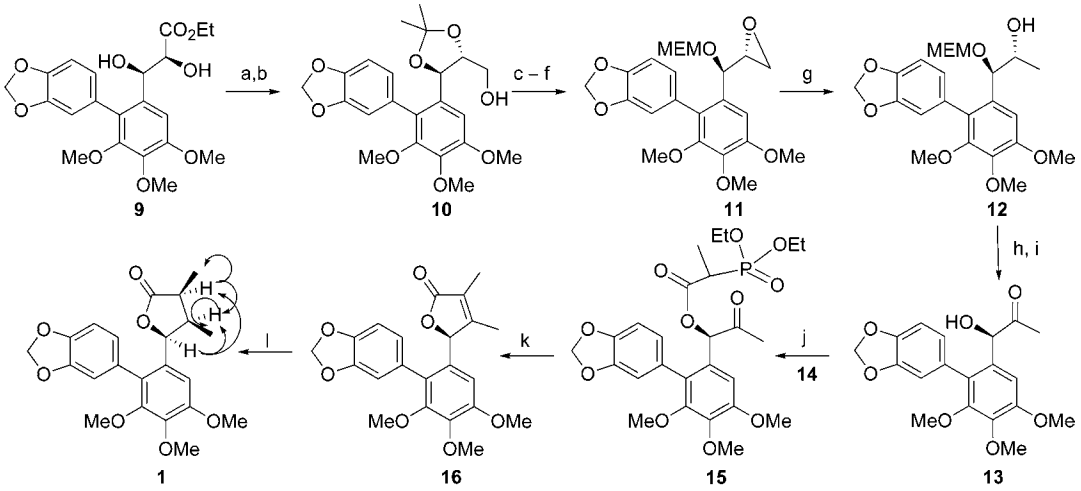
Scheme 2[a]



[a] Reagents and conditions: (a) DMP, CH_2Cl_2, *p*-TSA, rt, 94%; (b) $LiAlH_4$, THF, 0 °C, 2 h, 78%; (c) TsCl, Et_3N, CH_2Cl_2, 0 °C, 6 h, 90%; (d) MeOH, HCl, rt, 1 h, 88%; (e) K_2CO_3, MeOH, 30 min, rt, 75%; (f) MEMCl, DIPEA, CH_2Cl_2, rt, 8 h, 83%; (g) $LiAlH_4$, THF, 0 °C, 3 h, 94%; (h) PDC, CH_2Cl_2, 4 Å molecular sieves, 4 h, 67%; (i) PPTS, ^{t}BuOH, 80 °C, 12 h, 75%; (j) $(EtO)_2P(O)-CH(Me)-COCl$ (**14**), DIPEA, CH_2Cl_2, 0 °C, 3 h 70%; (k) NaH, THF, 0 °C, 30 min., 87%; (l) Rh/Al_2O_3, H_2, 60 psi, 20 h, 60%.

the ^{1}H NMR spectrum of **8**, the olefinic protons of the *E*-isomer appeared at δ 6.26 and 7.48 as doublets (J = 16.2 Hz), whereas the *Z*-isomer revealed olefinic protons at δ 5.80 and 6.61 as doublets (J = 12.2 Hz). Asymmetric dihydroxylation of **8***E* using $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, and $K_2OsO_4 \cdot 2H_2O$ in ^{t}BuOH:H_2O (1:1) at 0 °C for 18 h gave the dihydroxy derivative **9** in 80% yield.[8]

The presence of two atropisomers of the dihydroxyl derivative **9** was indicated by the ^{1}H NMR spectrum in which H-3 proton revealed two signals at δ 4.84 (J = 7.3 Hz) and δ 4.86 (J = 7.3 Hz). Attempted separation of these atropisomers at this stage using chiral HPLC was not successful. The chromatogram showed only a single peak with various chiral columns (Chiralcel OD, Chiralpak AD-H, Cyclobond, Chiralcel OJ columns) used in this protocol. This study did suggest that compound **9** had been obtained with excellent ee. Protection of **9** as an isopropylidene derivative (Scheme 2) followed by reduction of the COOEt group with $LiAlH_4$ gave the alcohol **10**. Following a sequence of reactions such as (a) tosylation of primary hydroxyl group, (b) deprotection of isopropylidene group, (c) cyclization to the epoxide derivative, and (d) protection of free hydroxyl group as the MEM ether, **10** was converted into **11** in 49% overall yield. Reductive ring opening of the epoxide ring present in **11** with $LiAlH_4$ in THF at 0 °C formed **12**.

Oxidation of **12** with PDC gave the keto derivative, which was treated with PPTS in ^{t}BuOH at 80 °C to cleave the MEM group and afford the α-hydroxyketone derivative **13**. Compound **13** was reacted with the acid chloride **14** in the presence of DIPEA−CH_2Cl_2 to afford the phosphonate **15** (Scheme 2). The intramolecular Horner−Wadsworth−Emmons reaction of **15** was carried out by using NaH in DME at 0 °C.[9−11] The resulting unsaturated-γ-lactone **16** (80% 5*S*, 20% 5*R*) was hydrogenated in the presence of Rh/Al_2O_3 in EtOAc at 60 psi to give **1** and its (3*R*,4*S*,5*R*)-isomer.[12] To obtain analytical data, a small portion of this mixture was chromatographed on chiral HPLC (for **1**, t_R = 14.75, and for (3*R*,4*S*,5*R*)-isomer, t_R = 17.99; Chiralcel-OD 4.6 × 25, λ = 254 nm, hexane/2-propanol 78/12, 0.5 mL/min) and pure **1** was isolated.

Interestingly, the ^{1}H NMR spectrum of synthetic **1** did not match that of either the natural product[1] or the 5-*epi*-eupomatilone-6[3] isomer. The observed NOEs between the H-3, H-4, and H-5 in the NOESY spectrum of **1** clearly

(1) Taylor, W. C.; Carroll, A. R. *Aust. J. Chem.* **1991**, *44*, 1615−1626.
(2) (a) Ward, R. S. *Nat. Prod. Rep.* **1997**, *14*, 43−74. (b) Macrae, W. D.; Towers, G. H. N. *Phytochemistry* **1984**, *23*, 1207−1220.
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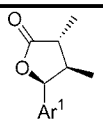
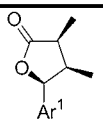
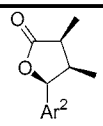
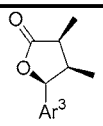
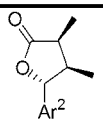
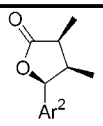
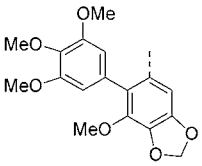
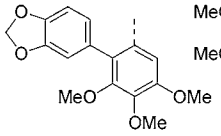
(7) Ni(0) catalyst-mediated Negishi coupling had been used for the preparation of **7**: Larson, E. R.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1982**, 521−525.
(8) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.
(9) For a review of butenolide synthesis, see: Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625−694.
(10) (a) Katsumura, S.; Kimura, A.; Isoe, S. *Tetrahedron* **1989**, *45*, 1337−1346. (b) Nangia, A.; Prasuna, G. *Tetrahedron* **1996**, *52*, 3435−3450. (c) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfield, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183−2186.
(11) We have noticed that the epimerization happens mainly during the conversion of **13** to **15**. For analytical purposes, we have synthesized (±)-**16** from 8*E* by following the same sequence of reactions but with an achiral dihydroxylation step and showed it to be a 1:1 racemic mixture by performing HPLC analysis on a Chiralcel-OD column using 5% 2-propanol in hexane.
(12) Matsubara, J.; Nakao, K.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1992**, *33*, 4187−4190.

Table 1.

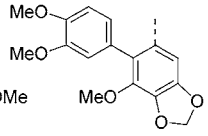
	 eup-3[1]	 eup-4[1]	 eup-6[1]	 eup-7[1]	 synthetic (McIntosh's)[3]	 synthetic (Gurjar's)
H-3	2.39 quintet J = 7.4	2.71 quintet J = 7.4	2.36, 2.37 multiplet J = 7.0, 5.2	2.64, 2.67 multiplet J =7.6	2.75 multiplet	2.74 quinet J = 7.2
H-4	2.04 sexet J = 7.4	2.17 multiplet J = 7.4, 5.2	2.02, 1.97 multiplet J = 7.0, 5.2	2.05, 2.16 multiplet J = 7.6, 5.4	2.36 multiplet	2.20 multiplet
H-5	5.50 doublet J = 7.4	5.28 dd J = 5.2, 0.5	5.54, 5.65 doublet J = 7.0	5.31, 5.20 dd J = 5.4, 0.5	5.0, 5.10 doublet J = 4.4	5.32, 5.41 doublet J = 5.0
3-Me	1.18 doublet J = 7.4	1.10 doublet J = 7.4	1.20, 1.19 doublet J = 7.0	1.08, 1.09 doublet J = 7.6	1.06, 1.07 doublet J = 7.5	1.13 doublet J = 7.2
4-Me	0.78 doublet J = 7.4	0.59 doublet J = 7.4	0.70, 0.73 doublet J = 7.0	0.55, 0.58 doublet J = 7.6	0.65, 0.67 doublet J = 6.8	0.54, 0.56 doublet J = 7.2



Ar[1]



Ar[2]



Ar[3]

indicated a cis relationship between these protons. Additionally, the presence of NOE between 3-Me and 4-Me and the absence of NOE between H-5 and any Me group substantiated this assignment. A careful examination (Table 1) of the chemical shifts and coupling constants of the aliphatic protons of six eupomatilones indicated that the data of synthetic **1**, eupomatilone-4 (**3**), and eupomatilone-7 (**4**) were similar, whereas the data of natural eupomatilone-6 were close to that of eupomatilone-3 (**2**) except the $J_{3,4}$ value. This clearly indicates that the assigned relative stereochemistry of three aliphatic protons of eupomatilone-6 deserve revision and suggests either a 3α,4β,5β-configuration (like in eupomatilone-3) or a 3α,4β,5α-configuration.

In summary, the previously assigned structure of eupomatilone-6 has been synthesized and warrants revision. Efforts to synthesize eupomatilone-6 and other eupomatilones are in progress.

Acknowledgment. We thank Dr. S. R. Bhide for HPLC analyses, and J.C. thanks CSIR (New Delhi) for financial assistance in the form of a research fellowship.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **1** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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