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An Approach to the Synthesis of the Eupomatilones†

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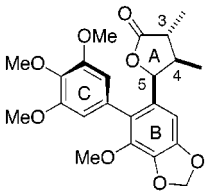
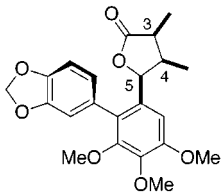
ABSTRACT



Eupomatilone-3 (**1**)



Eupomatilone-6 (**2**)

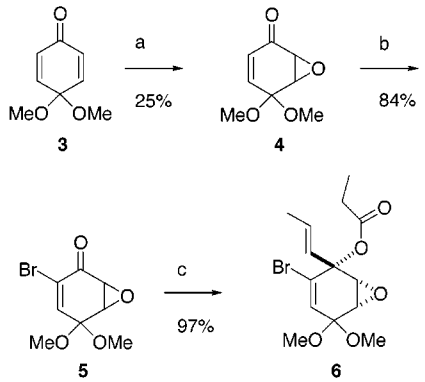
A concise approach to the eupomatilone family of lignans is presented. The strategy employs an intramolecularly competitive Ireland–Claisen rearrangement of a densely functionalized bis-allylic ester. The rearrangement serves both to construct the A-ring and to establish the stereochemistry at C_3 and C_4.

The eupomatilones are a family of lignans isolated from the Australian shrub *Eupomatia bennettii*.[1] The shrub is found in the tropical and subtropical forests of New South Wales and Queensland. The eupomatilones are unusual among the lignan family in that the C_α-phenyl linkage in one of the phenylpropanoid units has been cleaved.[2] They also possess an unusual doubly attached ring system which exhibits hindered rotation about the biaryl bond.[3] Although all members of the family possess the C_4-C_5 *cis* stereochemistry in the butyrolactone ring (A-ring), eupomatilones 3 (**1**) and 6 (**2**) are epimeric at C_3.

Since the A-rings of eupomatilones 3 and 6 consist of stereoisomeric vicinal chiral centers in a 2,3-relationship with respect to the carboxyl group, the Ireland−Claisen rearrangement presented itself as the ideal means of synthesizing either diastereomer.[4−6] We have previously demonstrated that the Ireland−Claisen rearrangement of bis-allylic esters derived from cycloalkenones can be used to generate structurally analogous 2,3-dimethylpentenoic acid derivatives.[6,7] We report herein the application of this strategy in the synthesis of the C_5-epimer of eupomatilone 6.

The synthesis began with epoxidation of commercially available *p*-quinone monoketal **3** to afford epoxy ketone **4** in modest yield (Scheme 1).[8] A bromination−dehydrobro-

Scheme 1. Synthesis of Bis-allylic Ester **6**[a]



[a] (a) H_2O_2, K_2CO_3, THF/H_2O; (b) B r_2, NEt_3, hexane/Et_2O; (c) (*E*)-propenylLi, THF, $(EtCO)_2O$.

† Dedicated to Professor Steven M. Weinreb on the occasion of his 60th birthday.

(1) Carroll, A. R.; Taylor, W. C. *Aust. J. Chem.* **1991**, *44*, 1705−1714.
(2) For a recent review of lignans, see: Ward, R. S. *Nat. Prod. Rep.* **1997**, *14*, 43−74.
(3) Both atropisomers occur naturally and were not chromatographically separable (ref 1).

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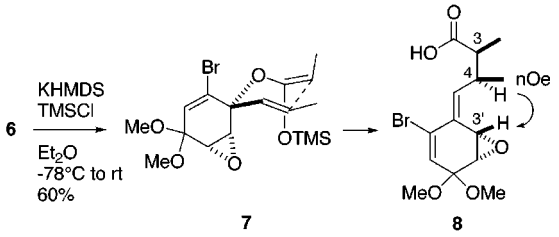
mination sequence gave bromo epoxyketone **5**.[9] Addition of (*E*)-propenyl-Li[10] to ketone **5** and in situ esterification yielded ester **6** as a single stereoisomer.[11]

Treatment of ester **6** with potassium hexamethyldisilylamide (KHMDS) and trimethylsilyl chloride (TMSCl) gave the sensitive vinyl epoxy acid **8** as the (*E*), *anti* stereoisomer on the basis of ^{1}H and ^{13}C NMR analysis of the crude reaction mixture (Scheme 2).[7,12,13] The intermediate (*E*)-silyl

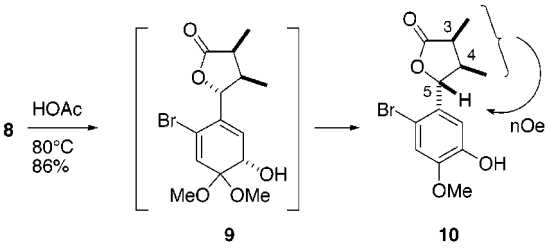
Scheme 2. Ireland−Claisen Rearrangement of Bis-allylic Ester **6**



ketene acetal **7** underwent Ireland−Claisen rearrangement via the *exo* alkene as expected based on extensive model studies.[6,7] The stereochemistry of acid **8** is a consequence of the rearrangement proceeding through a chairlike transition state with the larger allylic carbinol substituent disposed in a pseudoequatorial position.

S_N2' lactonization of epoxy acid **8** to form the A-ring butyrolactone and in situ aromatization of the B-ring was effected by heating the acid in HOAc at 80 °C for 30 min to yield lactone **10** (Scheme 3). The expected C_4−C_5 *trans* stereochemistry was confirmed by NOESY analysis.[14−16]

Scheme 3. Formation of the A-Ring via S_N2' Cyclization



Oxidation of phenol **10** using $PhI(OAc)_2$ gave *o*-quinone monoketal **11** (Scheme 4).[17] The electron-deficient bromoketone smoothly underwent Stille coupling[18,19] with piperonyl tributylstannane[18] to yield tetracycle **12** which possesses all of the carbons of the eupomatilone skeleton.

Regioselective epoxidation of the distal alkene of dienone **12** with dimethyldioxirane (DMDO) gave epoxide **13**.[20,21] Reductive ring opening of the epoxide yielded biaryl **15**, presumably via the intermediacy of keto-alcohol **14**.[22] Biaryl **15** was isolated as an inseparable 1:1 mixture of atropisomers.[1] Atropisomerism was not evident in either dienone **12** or epoxide **13**. Methylation of the phenolic hydroxyl groups gave 5-*epi*-eupomatilone 6 (**16**), also as a 1:1 mixture of atropisomers. Further studies are underway to complete the synthesis of eupomatilone 6 as well as other members of the eupomatilone family.

In summary, an approach to the synthesis of the eupomatilone family has been developed which led to 5-*epi*-eupomatilone 6 (**16**) in 10 steps from commercially available starting material. A novel intramolecularly competitive variant of the Ireland−Claisen rearrangement was used to establish the stereochemistry at the C_3 and C_4 stereocenters and to install the A-ring butyrolactone.

Acknowledgment. We would like to thank Walter Taylor, University of Sydney, for kindly providing copies of the

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(5) For reviews, see: Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 5, pp 827−873. Pereira, S.; Srebnik, M. *Aldrichimica Acta* **1993**, *26*, 17−29. Frauenrath, H. In *Stereoselective Synthesis*, 4th ed.; Helchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E21d, pp 3301−3756.

(6) Zhang, X.; McIntosh, M. C. *Tetrahedron Lett.* **1998**, *39*, 7043−7046. McIntosh, M. C.; Hong, S.-p.; Lindsay, H. A.; Yaramasu, T.; Zhang, X. Submitted for publication.

(7) Hong, S.-P.; McIntosh, M. C. *Tetrahedron* **2001**, *57*, 5055−5060.

(8) The yield was 42% based on recovered starting material. The epoxidation conditions were a result of extensive experimentation. Oxidants examined include H_2O_2, tBuOOH, mCPBA, MMPP, and NaOCl. Overoxidation was likely the principal side reaction: McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *J. Chem. Soc., Chem. Commun.* **1992**, 1589−1591.

(9) Smith, A. B., III; Brancca, S. J.; Pilla, N. N.; Gaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855−1869.

(10) Tsui, H.-C.; Paquette, L. A. *J. Org. Chem.* **1998**, *63*, 9968−9977.

(11) The *anti* addition is based on ample precedent: Taylor, R. J. K.; Alcaraz, L.; Kapfer-Eyer, I.; Macdonald, G.; Wei, X.; Lewis, N. *Synthesis* **1998**, 775−790. Wipf, P.; Coish, P. D. G. *J. Org. Chem.* **1999**, *64*, 5053−5061 and references therein.

(12) (a) The *anti* designation refers to the stereochemistry of the C_3 and C_4 methyl groups in the extended conformation. (b) The β-CH_3 carbons of *anti*-2,3-dimethylpentenoic acids and their derivatives generally appear downfield of 18 ppm (ref 7). The β-CH_3 carbon of epoxy acid **8** appears at 19.3 ppm. (c) The (*E*)-alkene geometry was confirmed by NOESY.

(13) Eshelby, J. J.; Parsons, P. J.; Sillars, N. C.; Crowley, P. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1497−1498.

(14) The stereochemistry of the lactonization is likely a result of allylic strain-directed cyclization rather than an intrinsic stereoelectronic preference for a *syn* S_N2'pathway: Chouteau, F.; Addi, K.; Bénéchie, M.; Prangé, T.; Huuong-Huu, F. *Tetrahedron* **2001**, *57*, 6229−6238.

(15) (a) For reviews of allylic strain directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370. Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860. (b) For reviews of the S_N2' reaction, see: Magid, R. M. *Tetrahedron* **1980**, *36*, 1901−1930. Paquette, L. A.; Stirling, C. J. M. *Tetrahedron* **1992**, *48*, 7383−7423.

(16) The C_3 and C_4 methyl groups overlap in the ^{1}H NMR spectrum, so the NOESY cross-peaks with the C_5 proton might arise from nOe interactions with either or both methyl groups.

(17) Churcher, I.; Hallett, D.; Magnus, P. *J. Am. Chem. Soc.* **1998**, *120*, 10350−10358.

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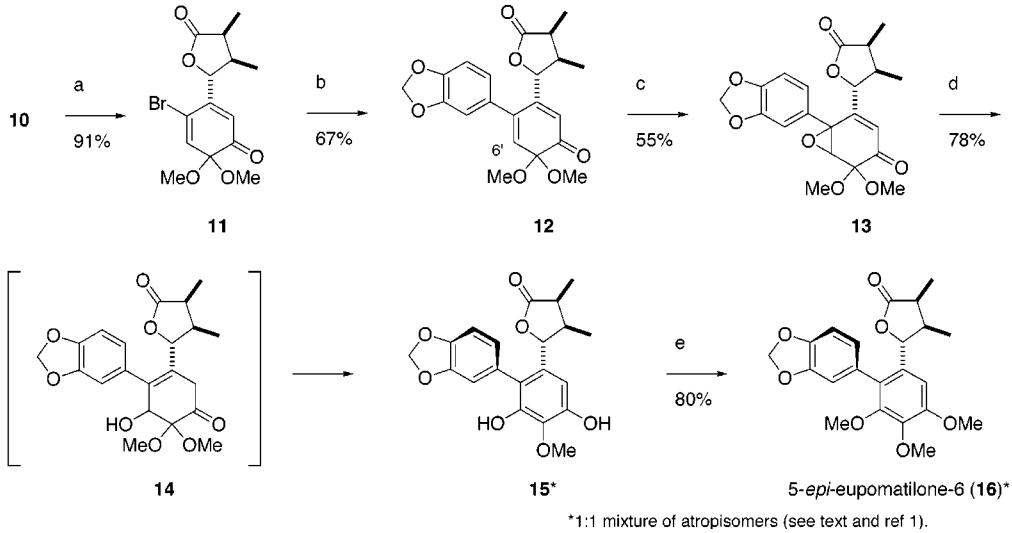
(19) For a review, see: Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1996**, *50*, 1−652.

(20) (a) Ley, S. V.; Cox, L. R.; Meek, G.; Metten, K.-H.; Pique, C.; Worrall, J. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3299−3313. (b) Treatment of dienone **12** with Ph_3COOK resulted in epoxidation only of the proximal alkene; cf. Corey, E. J.; Wu, L. I. *J. Am. Chem. Soc.* **1993**, *115*, 9327−9328.

(21) Although the epoxide is presumably a 1:1 mixture of diastereomers, only one set of signals were evident in the ^{1}H and ^{13}C NMR spectra.

(22) Pak, C. S.; Lee, E.; Lee, G. H. *J. Org. Chem.* **1993**, *58*, 1523−1530.

Scheme 4[a]



[a] (a) $PhI(AcO)_2$, MeOH; (b) $Pd_2dba_3-CHCl_3$, PPh_3, CuI, THF, 80 °C, piperonyl tributylstannane; (c) DMDO, acetone, CH_2Cl_2, rt; (d) Mg, HOAc, rt to 80 °C; (e) K_2CO_3, MeI, acetone.

spectra of the eupomatilones and Yian Shi, Colorado State University, for helpful discussions. This work was supported by the NIH (GM59406).

Supporting Information Available: Characterization data for compounds **4**−**6**, **8**, **10**, **11**−**13**, **15**, and **16** and experimental procedures for the preparation of compounds **10** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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