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An Ireland−Claisen Approach to Lignans: Synthesis of the Putative Structure of 5-*epi*-Eupomatilone-6

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A novel Ireland−Claisen approach to the putative structure of eupomatilone-6 is described. The rearrangement established the C3 and C4 stereocenters and concomitantly generated a vinyl epoxide. The C5 oxygen was installed by cyclization of the pentenoic acid carboxyl group onto the vinyl epoxide in an S_N2' fashion to afford the C5-epi stereochemistry. The natural C5 stereochemistry was accessed via a substrate directed dihydroxylation.

Introduction

The lignans are a structurally diverse family of phenyl propanoid dimers which are connected via the C2 carbons of the propyl chains (Scheme 1).[1] In many cases, the propyl groups are contained within isolated or annulated hetero- or carbocyclic rings. These include furans, butanolides, naphthalenes and hydronaphthalenes, dibenzocyclooctadienes, and others.[1] In some cases, the two phenyl rings are also connected in a biaryl linkage, as in the dibenzocyclooctadienes such as schisantherin A and the eupomatilones. Many of the lignans contain three or four contiguous stereocenters, of which one is often a benzylic oxygen stereocenter in the form of an ether, alcohol, ester, or lactone. The biological activities of the lignans are diverse and include anticancer, anti-HIV, and antifungal activity, among others.[1]

We felt that an Ireland−Claisen rearrangement approach to the lignans could be used to install multiple stereocenters from readily accessible chiral precursors.[6] Specifically, exocyclic rearrangement of a bis-allylic ester **6** derived from functionalized epoxy cyclohexenone derivative **5** would enable the construction of the bis-propyl moiety in a synthetically flexible fashion (Scheme 2).[7] One propyl unit would be derived from the nucleophile in a carbonyl addition step to epoxy cyclohexenone **5**, while the other would arise from the acyl group in the subsequent acylation step. Ireland−Claisen rearrangement of ester **6** would then connect the two propyl units at the respective C2 carbons to afford vinyl epoxide **7**.[8] The benzylic oxygen substituent would be installed by S_N2' addition of an oxygen nucleophile or its equivalent onto the vinyl epoxide generated in the Ireland−Claisen rearrangement. A variety of pathways could be imagined to further elaborate the resulting lactones to various lignan targets.

We decided to pursue the synthesis of eupomatilone-6 to explore the feasibility of the Ireland−Claisen strategy.[9] The eupomatilones are a small family of so-called "degraded" or secolignans in which one propyl chain has been cleaved from the aromatic ring during biosynthesis. They exist as a readily interconverting 1:1 mixture of atropisomers about the biaryl linkage. No biological studies were reported in the original isolation paper, but the eupomatilones possess some structural features common to known antimitotics such as colchicine.[10]

The originally reported structures of the eupomatilones have recently been called into question by Gurjar and co-workers.[11] The NMR data of the putative structure of eupomatilone-6 did not agree with the published data, but the correct structure has not been identified at this writing.

In the early planning stages of the synthesis, we were concerned that the C6′ oxygen would make the bis-allylic ester precursor to the Ireland−Claisen rearrangement too prone to ionization, so we developed an approach that would allow us to install the C6′ oxygen in the latter part of the synthesis (Scheme 3). The biaryl linkage would be installed via a cross-coupling reaction of an appropriately substituted arylmetal with electron-deficient bromo dienone **9**. The C5 oxygen would be installed in an S_N2' reaction of the vinyl epoxide product **10** of the Ireland−Claisen rearrangement. The bis-allylic ester precursor **11**

(1) Ward, R. S. *Nat. Prod. Rep.* **1997**, *14*, 43−74.
(2) For recent synthetic efforts, see: Roy, S. C.; Rana, K. K.; Guin, C. *J. Org. Chem.* **2002**, *67*, 3242−3248 and references therein.
(3) For recent synthetic efforts, see: Berkowitz, D. B.; Choi, S.; Maeng, J.-H. *J. Org. Chem.* **2000**, *65*, 847−860 and references therein.
(4) For recent synthetic efforts of the related isoschizandrin, see: Molander, G. A.; George, K. M.; Monovich, L. G. *J. Org. Chem.* **2003**, *68*, 9533−9540 and references therein.
(5) Carroll, A. R.; Taylor, W. C. *Aust. J. Chem.* **1991**, *44*, 1705−1714.
(6) Chai, Y.; Hong, S.-P.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905−2928.
(7) Hong, S.-P.; Lindsay, H. A.; Yaramasu, T.; Zhang, X.; McIntosh, M. C. *J. Org. Chem.* **2002**, *67*, 2042−2055.
(8) Knight has employed a ring contraction variant of the Ireland-Claisen rearrangement of oxamacrolides in the synthesis of furan-containing lignans: Hull, H. M.; Jones, E. G.; Knight, D. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1779−1788 and references therein.
(9) Hong, S.-p.; McIntosh, M. C. *Org. Lett.* **2001**, *4*, 19−21.
(10) Hamel, E. *Med. Res. Rev.* **1996**, *16*, 207−231.
(11) Gurjar, M. K.; Cherian, J.; Ramana, C. V. *Org. Lett.* **2004**, *6*, 317.

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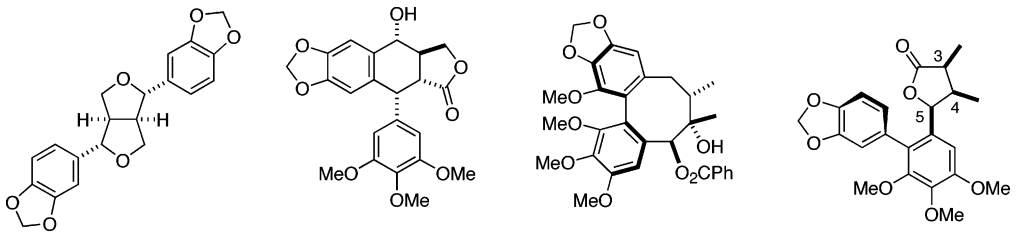
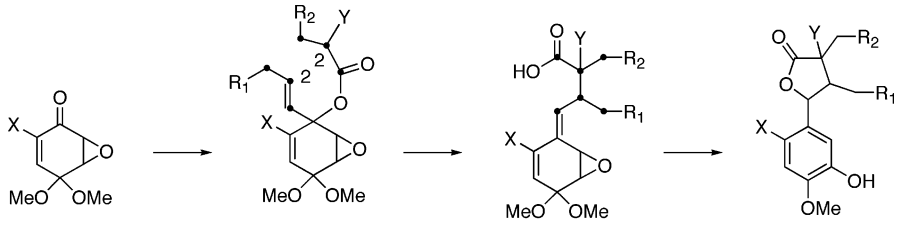
SCHEME 1



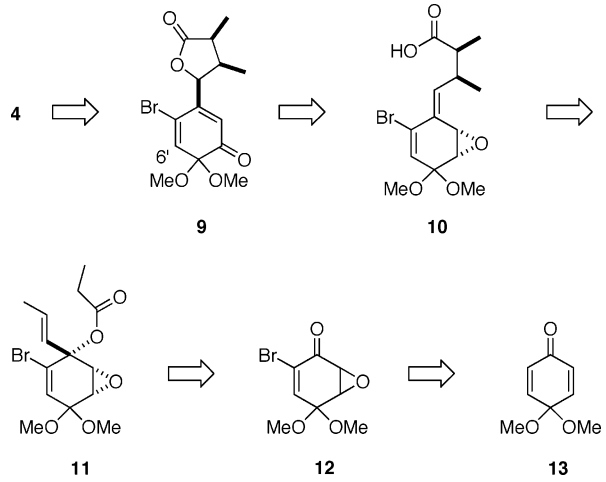
sesamin[2] (**1**) podophyllotoxin[3] (**2**) schisantherin A[4] (**3**) eupomatilone-6[5] (**4**)

SCHEME 2



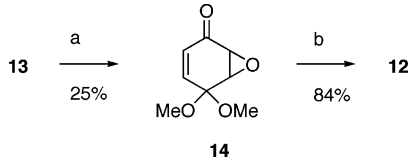
5 **6** (Y=H or OR) **7** **8**

SCHEME 3



9 **10** **11** **12** **13**

SCHEME 4[a]



14

[a] Key: (a) H_2O_2, K_2CO_2, THF/H_2O; (b) Br_2, NEt_3, hexane/Et_2O.

would ultimately be derived from commercially available *p*-quinone monoketal **13**.

Results and Discussion

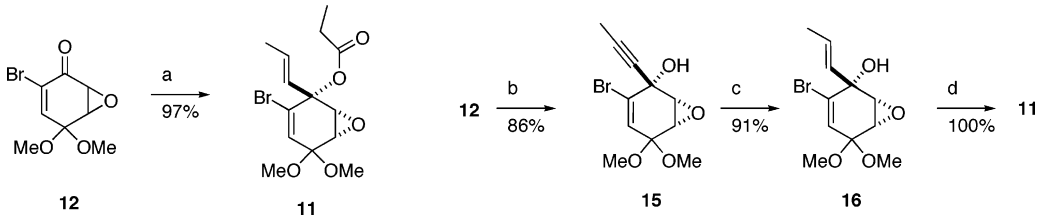
Epoxidation of *p*-quinone monoketal **13** proved to be a troublesome reaction (Scheme 4). Complete consumption of starting material was observed under standard nucleophilic epoxidation conditions (H_2O_2, NaOH, MeOH), but low yields or complex mixtures were obtained. Extensive experimentation with a variety of oxidants (H_2O_2, *t*-BuO_2H, NaOCl, *m*-CPBA), bases (NaOH, K_2CO_3, Cs_2CO_3, DBU, KH), solvents, and solvent mixtures (MeOH, *i*-PrOH, THF, CH_2Cl_2, acetone, hexane, ether, H_2O) failed to afford conditions under which both high conversion and yield were obtained. The optimal conditions proved to be H_2O_2, K_2CO_3, and THF/H_2O, which reproducibly afforded 25% of epoxide **14** (42% based on recovered starting material) accompanied by unreacted starting material. Taylor has reported that nucleophilic epoxidations of quinone monoketals result in facile bis-epoxidation and peroxyhydrate formation.[12] It seems likely that these and other side reactions contributed to the low yield of monoepoxidation products. Bromination of alkene **14** proceeded uneventfully to yield bromo dienone **12**.

Nucleophilic addition of *E*-propenylLi to bromo ketone **12** and in situ acylation afforded the requisite bis-allylic epoxy ester **11** (Scheme 5). The stereochemistry of addition occurred solely anti to the epoxide as expected based on earlier reports by Taylor[13] and Wipf.[14] Because of the cost and uneven availability of *E*-propenyl bromide, we also examined an alternative addition using propynylMgBr to afford propargyl alcohol **15**, also as a single stereoisomer. Reduction of the densely functionalized propargyl alcohol with Red-Al occurred in very good yield to afford the *E*-propenyl alcohol **16**. Acylation then afforded bis-allylic ester **11** in quantitative yield.

Treatment of ester **11** with KHMDS and TMSCl then afforded epoxy pentadienoic acid as a single alkene stereoisomer and with >10:1 ds based on ^{1}H NMR analysis favoring the expected anti isomer **10** (Scheme 6). The rearrangement presumably proceeded via transition state **a** in which the larger C1′ carbon occupied a pseudoequatorial position. Even though both of the carbons flanking the carbinol carbon are substituted, the epoxide is oriented approximately orthogonal to the mean plane of the cyclohexene ring. Thus, the C3′ carbon presents only a proton toward the pseudoaxial substit-

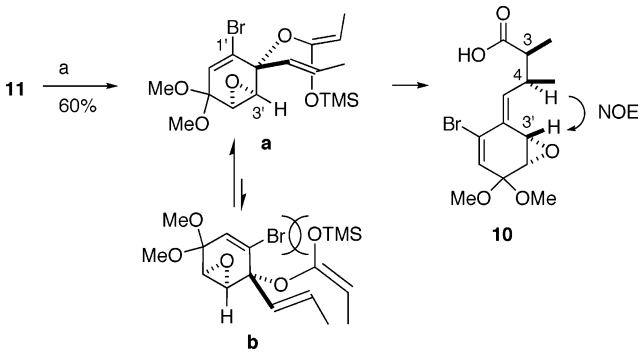
(12) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *J. Chem. Soc., Chem. Commun.* **1992**, 1589−1591.
(13) Alcaraz, L.; Macdonald, G.; Ragot, J.; Lewis, N. J.; Taylor, R. J. K. *Tetrahedron* **1999**, *55*, 3707−3716.
(14) Wipf, P.; Coish, P. D. G. *J. Org. Chem.* **1999**, *64*, 5053−5061.

SCHEME 5[a]



[a] Key: (a) (i) (*E*)-propenylLi, THF; (ii) $(EtCO)_2O$; (b) propynylMgBr, ether, 0 °C; (c) Red-Al, THF, −10 °C to rt; (d) (i) ^{n}BuLi, ether, −78 °C, (ii) $(EtCO)_2O$.

SCHEME 6[a]



[a] Key: (a) KHMDS, TMSCl, Et_2O, −78 °C to rt.

uents of the chairlike transition state, whereas the Br substituent on the C1′ carbon results in substantial 1,3-diaxial-like interactions in transition state **b**. The alkene geometry of diene **10** was confirmed by NOESY analysis.

We have previously reported that the relative stereochemistry of *syn*- and *anti*-2,3-dialkylpentenoic acids and related compounds can be determined by inspection of the ^{13}C NMR spectra.[15] The C3 and C4 methyl carbons resonate downfield for the anti isomer relative to the syn isomer. In the absence of both isomers, the stereochemistry can still be determined by examination of the chemical shift of the C4 carbon. In anti isomers, it lies downfield of 18 ppm, whereas in syn isomers it lies upfield of 18 ppm. The C4 methyl carbon of pentenoic acid **10** resonates at 19.3 ppm, confirming the anti stereochemistry (the C3/C4 stereochemistry is anti in the extended conformation of the pentenoic acid moiety). The sensitive acid was purified over Florisil to suppress cyclization to the butyrolactone (vide infra).

The next step was to install the C5 oxygen. The 1,2-alkene migration inherent in the Ireland−Claisen rearrangement resulted in the formation of a vinyl epoxide group that we hoped would undergo an S_N2' reaction with an oxygen nucleophile or equivalent (Scheme 7).[16] Direct cyclization of the carboxyl group would likely give the C5-epi stereochemistry (vide infra). We therefore considered three different strategies that would enable us to indirectly access the natural C5 stereochemistry: (i) syn S_N2' displacement of vinyl epoxide **10** by a halogen or oxygen nucleophile followed by S_N2 cyclization to the 4,5-syn isomer **17**; (ii) anti S_N2' displacement of the vinyl epoxide by an oxygen (or oxygen equivalent) nucleophile, followed by lactonization to **17**; (iii) anti S_N2' cyclization to 5-*epi*-**17** and subsequent epimerization to **17**.

Treatment of epoxy acid **10** in HOAc at 80 °C smoothly afforded lactone 5-*epi*-**17**, the product of syn S_N2' cyclization and subsequent aromatization, in high yield (Scheme 8). The stereochemistry was confirmed by NOESY. The stereochemistry of cyclization was almost certainly directed by the allylic C4 methyl group.[17] Cyclization in a syn S_N2' fashion via conformer **10a** avoids the allylic strain that would be encountered in conformer **10b** leading to the anti pathway.[18,19] Base-mediated cyclizations (pyridine, $NaHCO_3$, K_2CO_3, CuO) gave similar results.

To obtain the requisite C5 stereochemistry, we initially pursued a double-displacement strategy in which a halide would initially displace the vinyl epoxide in a syn S_N2' sense (cf. strategy i, Scheme 7).[20] The carboxyl group would then undergo an S_N2 reaction with the alkyl halide to afford a net anti substitution. Unfortunately, all experimental variations on this approach using a variety of halide sources (LiBr, NaBr, NaI, $MgBr_2$, Et_4NI) and using either the carboxylic acid or the corresponding TIPS ester gave only 5-*epi*-**17**, complex mixtures or recovered starting material.

A strategically similar approach involved a syn Pd(0)-catalyzed addition of an external oxygen nucleophile that could be converted into a leaving group for a subsequent S_N2 cyclization.[21] The reactions employed $Pd_2(dba)_3$−$CHCl_3$ in combination with PPh_3, P(*o*-Tol)$_3$, PBu_3 or $P(OEt)_3$ and an oxygen nucleophile (Ph_3SiOH, NaOAc, TMSOAc, Bu_3SnOAc, Bu_4NOAc). As before, however, all attempts resulted only in formation of 5-*epi*-**17**, complex mixtures or recovered starting material using either the free acid or the corresponding TIPS ester.

Still another related approach involved the addition of an oxygen equivalent that would add in an anti S_N2' fashion to directly yield the requisite stereochemistry at C5 (cf. strategy ii, Scheme 7). Clive has reported Cu-mediated anti S_N2' additions of silyl nucleophiles to vinyl

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

(16) For an earlier example of the generation of a vinyl epoxide via a Claisen rearrangement, see: Eshelby, J. J.; Parsons, P. J.; Sillars, N. C.; Crowley, P. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1497−1498.

(17) For an illustration of the importance of allylic strain in S_N2' cyclizations, see: Chouteau, F.; Addi, K.; Bénéchie, M.; Prangé, T.; Huuong-Huu, F. *Tetrahedron* **2001**, *57*, 6229−6238.

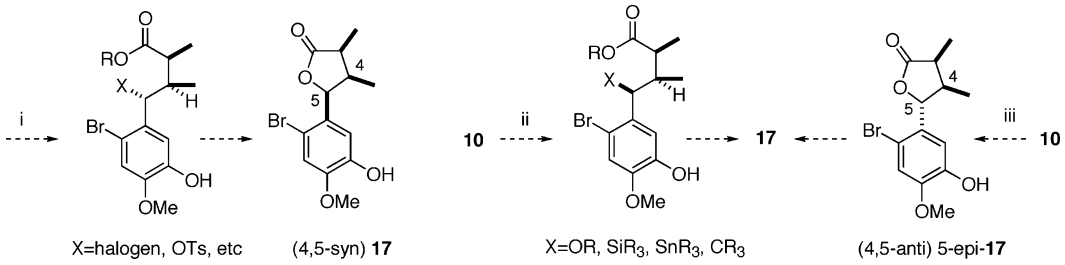
(18) Paquette, L. A.; Stirling, C. J. M. *Tetrahedron* **1992**, *48*, 7383−7423. Magid, R. M. *Tetrahedron* **1980**, *36*, 1901−1930.

(19) For reviews of allylic strain directed reactions, see: Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860. Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

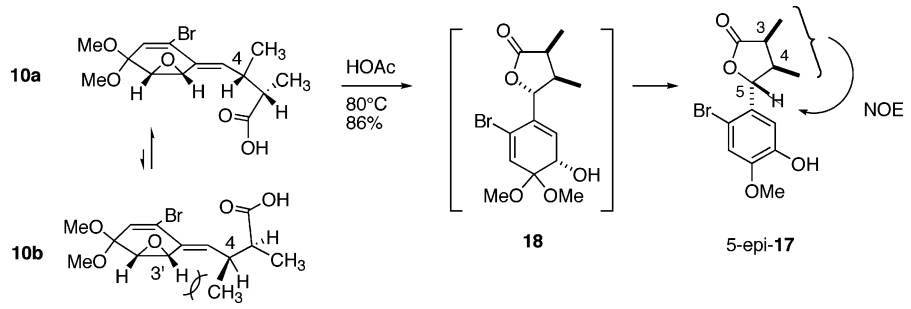
(20) Sutherland, J. K.; Watkins, W. J.; Bailey, J. P.; Chapman, A. K.; Davies, G. M. *Chem. Commun.* **1989**, 1386−1387. Myers, A. G.; Siu, M. *Tetrahedron* **2002**, *58*, 6397−6404. Hecht, S.; Amslinger, S.; Jauch, J.; Kis, K.; Trentinaglia, V.; Adam, P.; Eisenreich, W.; Bacher, A.; Rohdich, F. *Tetrahedron Lett.* **2002**, *43*, 8929−8933.

(21) Trost, B. M.; Ito, N.; Greenspan, P. D. *Tetrahedron Lett.* **1993**, *34*, 1421−1424. Trost, B. M.; Organ, M. *J. Am. Chem. Soc.* **1994**, *116*, 10320−10321.

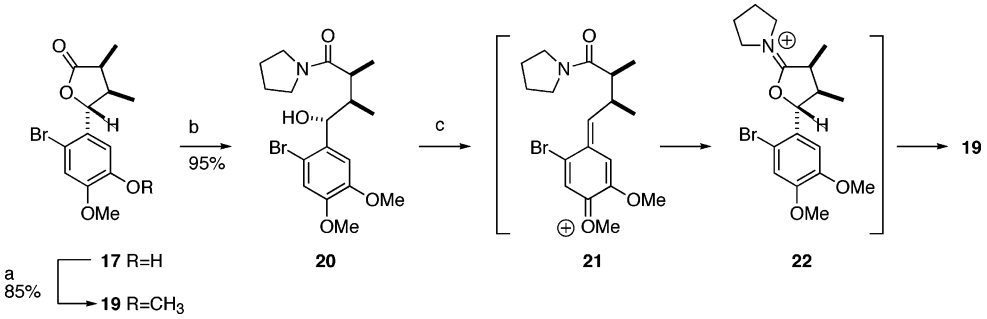
SCHEME 7



SCHEME 8



SCHEME 9[a]



[a] Key: (a) CH_3I, K_2CO_3, acetone, reflux; (b) pyrrolidine, PhH, rt; (c) PPh_3, DEAD, RCO_2H or TsCl, NEt_3.

epoxides.[22] Similarly, Cu-mediated additions of carbon nucleophiles to vinyl epoxides of similar structure have been reported, although in those case the exocyclic alkene was unsubstituted.[23,24] In the event, addition of Si, Sn, or carbon nucleophiles ($Me_2PhSiLi$, Bu_3SnLi, vinylMgBr, MeLi, MeMgCl) to the free acid, TIPS ester, or methyl ester in the presence of catalytic or stoichiometric amounts of various Cu(I) salts (CuCN, CuI, CuBr−SMe_2) gave only 5-*epi*-**17**, complex mixtures, or recovered starting material.

The complete lack of success in addition of an external nucleophile to the C5 position prompted us to examine the final strategy of epimerization of the C5 stereocenter. Ring opening of lactone **19** with pyrrolidine gave amide **20** in excellent yield (Scheme 9).[25] Attempts at activation of alcohol **20** under Mitsunobu[26] or sulfonylation conditions led to isolation of the undesired 5-*epi* lactone **19**. It seems likely that the activated alcohol underwent ionization to *p*-methoxybenzyl cation **21**. Allylic strain directed cyclization of the amide and subsequent hydrolysis would then afford 5-*epi* lactone **19**.[27]

In an attempt to suppress the ionization, we sought to oxidize the aromatic ring to the *o*-quinone monoketal prior to activation of the C5 oxygen. Oxidation of phenol **17** to quinone monoketal **23** occurred smoothly in high yield (Scheme 10).[28] However, addition of pyrrolidine to lactone **23** resulted in addition of pyrrolidine to the quinone ring to give a product tentatively identified as bis-pyrrolidine **24**. The bis-addition presumably occurred by initial conjugate addition at C6′ followed by a S_N2 displacement of the resulting allylic bromide at C1′. An alternative route involving oxidation of hydroxy amide **25** yielded only complex mixtures.

In a final attempt at the epimerization strategy, lactone **17** was reduced and selectively protected to silyl ether **27** (Scheme 11). A variety of attempts at oxidation of phenol **27** to dienone **28** afforded only complex mixtures.

(22) Clive, D. L. J.; Zhang, C. *J. Org. Chem.* **1995**, *60*, 1413−1427. Clive, D. L. J.; Zhang, C.; Zhou, Y.; Tao, Y. *J. Organomet. Chem.* **1995**, *489*, C35−C37.

(23) Marino, J. P.; Abe, H. *Synthesis* **1980**, 872−874.

(24) For a review, see: Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135−631.

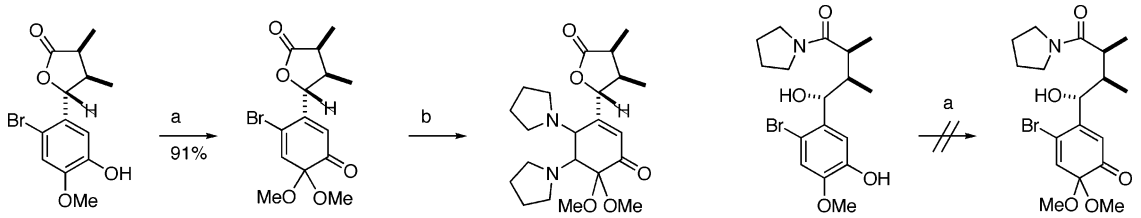
(25) Mandai, T.; Moriyama, T.; Tsujimoto, K.; Kawada, M.; Otera, J. *Tetrahedron Lett.* **1986**, *27*, 603−606.

(26) For a review, see: Hughes, D. L. *Org. Prep. Proceed. Int.* **1996**, *28*, 127−164.

(27) Satoh, M.; Washida, S.; Takeuchi, K. *Heterocycles* **2000**, *52*, 227−236.

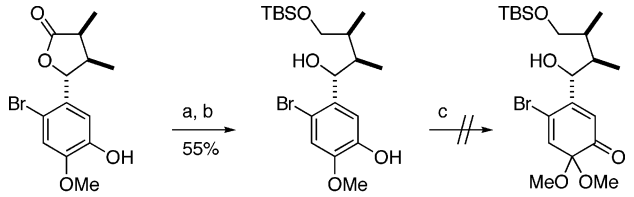
(28) For a review, see: Yamamura, S. In *The Chemistry of Phenols*; John Wiley & Sons: West Sussex, England, 2003; Vol. 2, pp 1153−1346.

SCHEME 10[a]



[a] Key: (a) $PhI(OAc)_2$, MeOH; (b) pyrrolidine, PhH, rt.

SCHEME 11[a]



[a] Key: (a) $LiAlH_4$, THF, 38 °C; (b) TBDMSCl, imidazole, DMAP, DMF; (c) $PhI(OAc)_2$, MeOH.

At this point, we elected to continue the synthesis of the target as the C5-epimer and pursue the installation of the natural stereochemistry at a later point. Thus, Stille cross-coupling of dienone **23** with piperonyl tributylstannane gave tetracycle **29** in 67% yield (Scheme 12).[29] The stage was now set for addition of the C6′ oxygen. Although oxygen nucleophiles do not readily participate in conjugate additions to enones,[30] we reasoned that the electron-deficient nature of dienone **29** might allow for such a reaction. This proved not to be the case, however, with no reaction occurring in attempts to add alcohols or carboxylic acids under either acidic or basic conditions to dienone **29**. Attempts at Cu-mediated additions of boron-,[31] silicon-, or carbon-based nucleophiles returned only complex mixtures.

We next turned to epoxidative methods. Both Ph_3-COOH/KHMDS and buffered *m*-CPBA gave products resulting from nucleophilic addition to the enone β-carbon (C2′) rather than δ-carbon (C6′). While Ph_3COOH gave C2′-C3′ epoxide **30**, buffered *m*-CPBA gave a product identified as ortho ester **31**, apparently resulting from nucleophilic addition of the peroxide at C2′ followed by Bayer−Villiger oxidation (see the Supporting Information). We were finally rewarded with the desired C1′−C6′ epoxide upon treatment of dienone **29** with dimethyldioxirane (DMDO) to give epoxide **32** in synthetically useful yield.

Reductive cleavage of epoxide **32** with Mg afforded biaryl **34** upon extended heating in HOAc (Scheme 13).[32] When the reduction was carried out at room temperature, hydroxy ketone **33** could be isolated and purified by flash chromatography on silica gel without aromatization (see the Supporting Information). Methylation of the phenolic hydroxyl groups then afforded the structure originally assigned as 5-*epi*-eupomatilone-6 (**35**). Biaryls **34** and **35** both exhibited atropisomerism in ^1H and ^{13}C NMR spectra as was observed for all of the eupomatilones.[5]

With the failure of the earlier attempts at epimerization of the C5 stereocenter, we next sought to take advantage of the inherent facial bias induced by the C4 stereocenter. We reasoned that dihydroxylation of the exocyclic alkene would occur syn to the smaller C4 substituent (i.e. the methyl group), since allylic strain should cause the C4−C5 bond to orient itself such that the C4 proton is approximately eclipsed with the C3′ carbon (cf. Scheme 8). Gratifyingly, dihydroxylation of diene **36** with OsO_4, NMO, and pyridine gave diol **37** as a single stereoisomer, albeit in only 31% yield (Scheme 14). Very high OsO_4 loading (24 mol %) was necessary to obtain even this modest yield. Use of $K_3Fe(CN)_6$ as reoxidant allowed for a significant increase in yield to 66% at essentially the same OsO_4 loading (25 mol %). Interestingly, the best yield and lowest OsO_4 loading was obtained by use of a pseudoracemic mixture of $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ to afford 71% yield of dihydroxylation product using 15 mol % OsO_4.[33] The pseudoracemic mixture was employed to avoid kinetic resolution of the racemic vinyl epoxides. The isolated product was neither diol **37** nor the corresponding lactone, but Payne rearrangement product **38**.[34] The selective formation of epoxy alcohol isomer **38** is consistent with the well precedented stabilizing effect of unsaturation adjacent to the epoxide in the thermodynamically favored Payne rearrangement isomer.[34]

Formation of rearranged epoxy ketone **38** simplified the subsequent deoxygenation process. Swern oxidation of alcohol **38** gave epoxy enone **39** in quantitative yield (Scheme 15). Deoxygenation with SmI_2 in MeOH/THF afforded a 60% yield of the desired all syn dienone **9**.[35]

Conclusion

Although at this point we could have presumably completed the synthesis via a route analogous to that used for the 5-epi series, the route had become too long to be attractive for the synthesis of the eupomatilones. Furthermore, the utility of the Ireland−Claisen strategy

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(31) Takahashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, 982−983.
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(33) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.
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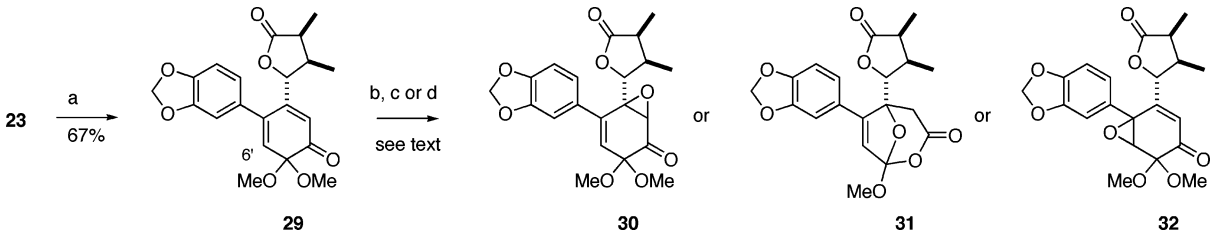
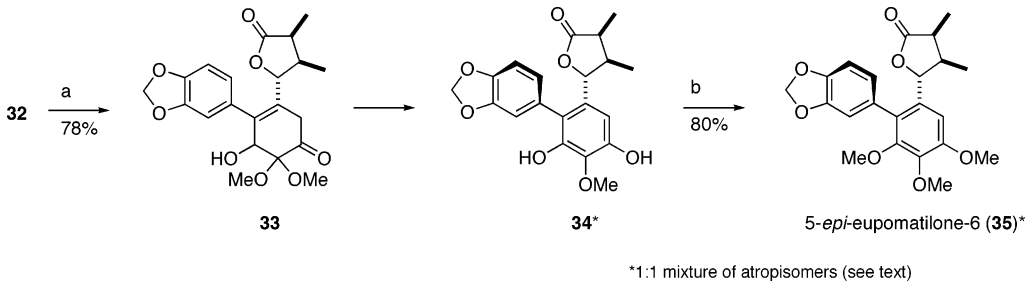
SCHEME 12[a]



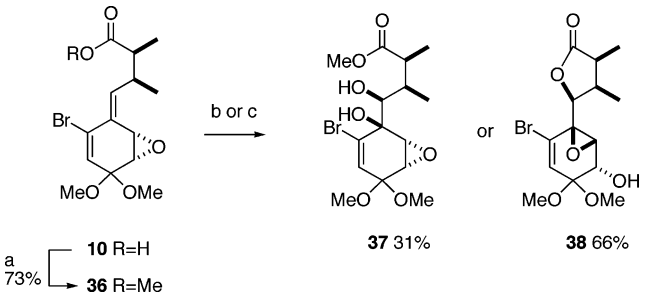
[a] Key: (a) $Pd_2dba_3{-}CHCl_3$, PPh_3, CuI, THF, piperonyl tributylstannane, 80 °C; (b) Ph_3COOH, KHMDS, THF; (c) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; (d) DMDO, acetone, CH_2Cl_2, rt.

SCHEME 13[a]



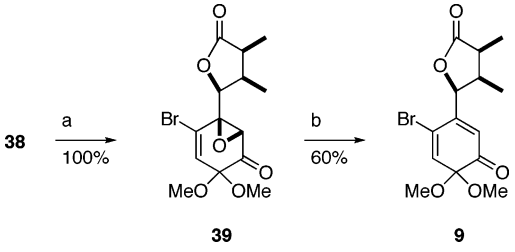
[a] Key: (a). Mg, HOAc, rt to 80 °C; (b) K_2CO_2, MeI, acetone.

SCHEME 14[a]



[a] Key: (a) CH_2N_2, ether; (b) OsO_4, NMO, $MeSO_2NH_2$, acetone, H_2O; (c) OsO_4; $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*-BuOH, H_2O.

SCHEME 15[a]



[a] Key: (a) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C; (b) SmI_2, THF, MeOH, 0 °C to rt.

to the lignans had been satisfactorily illustrated by the five-step assembly of lactone 5-*epi*-**17** (cf. Scheme 8) containing three contiguous stereocenters common to many lignans. This strategy could presumably be applied to the synthesis of a variety of ligans of biomedical interest (cf. Scheme 1).

Experimental Section

Acid 10. KHMDS (5.8 mL, 0.5 M in toluene, 2.9 mmol) was added to a solution of ester **11** (0.5 g, 1.4 mmol) in ether (50 mL) at −78 °C, followed after 5 min by TMSCl (0.55 mL, 4.3 mmol). The mixture was allowed to warm to rt and stirred for 2 h. After extractive workup with ether, the residue was purified by flash chromatography on Florisil with 20/80 ethyl acetate/hexane, followed by 1/99 AcOH/ether to give acid **8** as yellow oil (0.30 g, crude 60%): IR (film) 3368 (m), 2968 (m), 1772 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 1.12 (d, J = 6.53 Hz, 3H), 1.16 (d, J = 7.13 Hz, 3H), 2.41 (m, 1H), 3.00 (m, 1H), 3.30 (s, 3H), 3.45 (s, 3H), 3.61 (dd, J = 3.96, 2.38 Hz, 1H), 4.01 (d, J = 4.35 Hz, 1H), 6.10 (d, J = 2.18 Hz, 1H), 6.22 (d, J = 10.89 Hz, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) 15.5, 19.3, 35.5, 45.6, 49.3, 49.6, 49.6, 54.2, 97.3, 124.3, 127.0, 128.1, 145.2, 181.4.

Lactone 5-*epi*-17. A solution of acid **10** (0.375 g, 1.08 mmol) in AcOH (10 mL) was heated 80 °C for 30 min. The solution was allowed to cool to rt and concentrated in vacuo. After extractive workup with ether, the residue was purified by flash chromatography on silica gel with 20/80 ethyl acetate/hexane to give lactone 5-*epi*-**17** as yellow oil (0.293 g, 86%): IR (film) 3416 (br), 2972 (m), 1774 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 1.15 (d, J = 7.51 Hz, 3H), 1.18 (d, J = 7.13 Hz, 3H), 2.52 (pd, J = 7.32, 3.17 Hz, 1H), 2.75 (p, J = 7.51 Hz, 1H), 3.87 (d, 3H), 5.26 (d, J = 3.17 Hz, 1H), 5.69 (s, 1H), 6.86 (s, 1H), 7.01 (s, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) 9.8, 14.1, 36.7, 41.4, 56.4, 84.2, 110.3, 112.4, 115.4, 131.0, 145.4, 146.9, 149.8, 179.8; MS *m*/*z* 314, 230, 56, 41, 29.

***o*-Quinone Monoketal 23.** $PhI(OAc)_2$ (0.204 g, 0.63 mmol) was added to a solution of lactone **17** (0.200 g, 0.63 mmol) in MeOH (50 mL). After 30 min, the mixture was concentrated in vacuo and the residue purified by flash chromatography on silica gel with 20/80 ethyl acetate/hexane to give *o*-quinone monoketal **23** as yellow oil (0.200 g, 91%): IR (film) 2977 (m), 1787, 1684 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 1.14 (d, J = 6.93 Hz, 3H), 1.21 (d, J = 6.93 Hz, 3H), 2.65 (m, 2H), 3.35 (s, 6H), 4.91 (s, 1H), 5.96 (d, J = 1.78 Hz, 1H), 6.79 (s, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) 9.4, 14.8, 35.3, 38.9, 50.3, 50.4, 82.5, 92.7, 118.8, 121.3, 138.1, 148.7, 178.2, 191.9; MS *m*/*z* 344, 315, 265, 237, 181, 79, 55, 41, 29.

Aryl Ketal 29. Piperonyl tributylstannane (155 mg, 0.38 mmol) was added to a solution of *o*-quinone monoketal **23** (130 mg, 0.38 mmol), $Pd(dba)_3{\cdot}CHCl_3$ (10 mg), Ph_3P (10 mg), and CuI (10 mg) in THF (20 mL) and the mixture heated under reflux for 16 h. After extractive workup with ethyl acetate,

the residue was purified by flash chromatography on silica gel with 20/80 ethyl acetate/hexane to give aryl ketal **29** as yellow oil (100 mg, 67%): IR (film) 2940 (m), 1783, 1680 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 0.45 (d, J = 7.18 Hz, 3H), 1.00 (d, J = 7.42 Hz, 3H), 2.15 (m, 1H), 2.60 (m, 1H), 3.33 (s, 6H), 4.77 (s, 1H), 5.98 (s, 3H), 6.19 (s, 1H), 6.70 (m, 2H), 6.82 (d, J = 7.67, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) 9.3, 14.5, 35.3, 38.5, 50.1, 50.1, 81.3, 91.4, 101.6, 108.6, 109.2, 119.7, 122.4, 130.3, 134.9, 137.6, 147.9, 148.1, 151.3, 178.5, 193.6.

Aryl Epoxyenone 32. DMDO (10 mL, ca. 0.1 M in acetone) was added to a solution of aryl ketal **29** (300 mg, 0.78 mmol) in CH_2Cl_2 (15 mL). After 16 h, the mixture was concentrated in vacuo and the residue purified by flash chromatography on silica gel with 20/80 ethyl acetate/hexane to give arylepoxy enone **30** as yellow oil (170 mg, 55%): IR (film) 2982 (m), 1783, 1692 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 0.52 (d, J = 7.13 Hz, 3H), 1.06 (d, J = 7.34 Hz, 3H), 2.27 (m, 1H), 2.63 (pentet, J = 7.62 Hz, 1H), 3.31 (s, 3H), 3.52 (s, 3H), 4.66 (dd, J = 1.78, 1.58 Hz, 1H), 6.01 (s, 2H), 6.04 (d, J = 1.58 Hz, 1H), 6.85 (d, J = 8.31 Hz, 1H), 6.98 (m, 2H); ^{13}C NMR (67 MHz, $CDCl_3$) 9.6, 14.4, 35.5, 38.3, 50.3, 50.9, 59.1, 61.1, 82.3, 93.8, 101.7, 108.6, 109.0, 122.5, 124.8, 127.5, 148.0, 148.4, 156.3, 178.0, 187.9.

Phenol 34. Mg (100 mg, 4.1 mmol) was added to a solution of epoxyenone **32** (100 mg, 0.25 mmol) in AcOH (10 mL) in water. The mixture was stirred for 30 min at rt and then heated to 80 °C for 3 h. After cooling to rt, the mixture was slowly quenched with saturated $NaHCO_3$ solution. After extractive workup with CH_2Cl_2, the residue was purified by flash chromatography on silica gel with 20/80 ethyl acetate/hexane to give phenol **34** as colorless oil (78 mg, 78%): ^1H NMR (270 MHz, $CDCl_3$) 0.67 (d, J = 7.13 Hz, 3H), 1.06 (d, J = 7.52 Hz, 3H), 2.36 (m, 1H), 2.77 (m, 1H), 3.94 (s, 3H), (d × 2 [atropisomers], J = 3.76 Hz, 1H), 5.12 (bs, 1H), 5.67 (bs, 1H), 6.04 (m, 2H), 6.54 (s, 1H), 6.77 (m, 2H), 6.92 (m, 1H).

Lactone 35 (Structure Originally Assigned as 5-*epi*-Eupomatilone-6). A mixture of phenol **34** (128 mg, 0.34 mmol), K_2CO_3 (500 mg, 3.6 mmol), and MeI (0.145 mL, 2.3 mmol) in acetone (20 mL) was heated under reflux for 16 h. After cooling to rt, the mixture was filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel with 20/80 ethyl acetate/hexane to give 5-*epi*-eupomatilone-6 (**35**) (110 mg, 80%): ^1H NMR (270 MHz, $CDCl_3$, two atropisomers) 0.65 (d, J = 6.93 Hz, 3H), 0.67 (d, J = 6.73 Hz, 3H), 1.06 (d, J = 7.51 Hz, 3H), 1.07 (d, J = 7.53 Hz, 3H), 2.36 (m, 2H), 2.75 (m, 2H), 3.62 (s, 3H), 3.63 (s, 3H), 3.87 (s, 6H), 3.88 (s, 6H), 5.00 (d, J = 4.35 Hz, 1H), 5.10 (d, J = 4.35 Hz, 1H), 6.01 (m, 4H), 6.64 (m, 6H), 6.86 (d, J = 7.91 Hz, 2H); ^{13}C NMR (67 MHz, $CDCl_3$) 180.0, 153.1, 151.8, 147.8, 147.0, 146.9, 142.0, 132.9, 132.8, 129.0, 128.9, 124.2, 123.0, 111.8, 110.2, 108.5, 108.3, 103.7, 101.2, 82.9, 61.2, 61.1, 60.9, 56.3, 41.7, 41.6, 37.2, 13.4, 9.9.

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Supporting Information Available: Experimental procedures for the preparation of compounds **9**, **11**, **12**, **14**−**16**, and **36**−**39**; ^1H and ^{13}C NMR spectra for compounds **9**−**12**, **14**−**17**, **23**, **29**, **32**, and **34**−**39**. This material is available free of charge via the Internet at http://pubs.acs.org.

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