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A Versatile Stereoselective Synthesis of *endo,exo*-Furofuranones: Application to the Enantioselective Synthesis of Furofuran Lignans

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A new stereoselective route to *endo,exo*-2,6-diarylfurofuranones has been developed using Mn(III)-mediated intramolecular cyclopropanation and C−H insertion reactions as key C−C bond-forming steps. Mn(III)-mediated oxidative cyclization of acetoacetate derivative **11** afforded 1-acetyl-4-aryl-3-oxabicyclo[3.1.0]hexan-2-one (**12**) with excellent diastereocontrol (d.r. 22:1). Subsequent Lewis acid-catalyzed opening of the activated cyclopropane ring present in **12** with benzylic alcohols then gave α-acetyl-γ-butyrolactones **16** and **18**−**20**, which reacted efficiently with in situ-generated TfN_3 to secure the key α-diazo-γ-butyrolactones **22**−**25**. Highly stereoselective rhodium-catalyzed C−H insertion reactions of diazolactones **22**−**25** completed the synthesis of *endo,exo*-2,6-diarylfurofuranones **26**−**29** in overall yields ranging from 41 to 48% from 1-phenylallyl alcohol (±)-**10**. The approach developed for the furofuranones **26**−**29** was then applied to the asymmetric syntheses of four furofuran lignans, (+)-xanthoxylol (**1**), (+)-methylxanthoxylol (**2**), (+)-epipinoresinol (**3**), and (+)-epieudesmin (**4**), starting from enantiomerically enriched 1-arylallyl alcohol (*S*)-**31**.

Introduction

Lignans belonging to the furofuran subclass are known to possess broad-ranging biological activities,[1] and many have been isolated as bioactive components of traditional medicines.[2] For example (+)-epipinoresinol (**3**) displays Ca^{2+} antagonist,[3] antitumor,[4] and cAMP phosphodiesterase inhibitory activities,[5] while (+)-methylxanthoxylol (**1**) and (+)-epieudesmin (**4**) have been shown to be low μM PAF antagonists.[2a,b] These biological properties combined with appealing structural features have led to considerable and continued interest in the synthesis of furofurans.[6,7] The broad-ranging pharmacological activities associated with furofurans are currently poorly understood at the molecular level, but one must question whether there is any common basis for these effects. In recent years, increased emphasis has been placed on the importance of so-called privileged structures, due to their repeated occurrence in biologically active molecules.[8] Although there may be many reasons for the diverse biological effects of furofurans, the development of practical stereocontrolled approaches to the furofuran scaffold is an important objective, particularly if it could be readily adapted to allow the synthesis of analogues. We previously reported racemic syntheses of furofuran lignans employing highly diastereoselective C−H insertion reactions of α-diazo-γ-butyrolactones **5** as the key step,

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[†] The University of Southampton.
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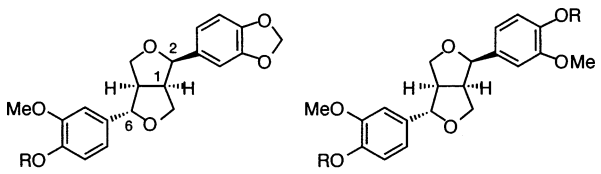
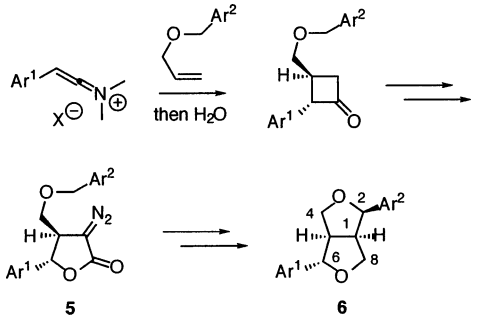


FIGURE 1. Examples of *endo,exo*-furofuran lignans.

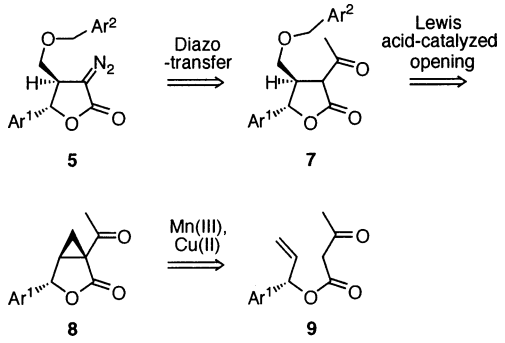
SCHEME 1. Previous Approach to the Synthesis of Furofuran Lignans



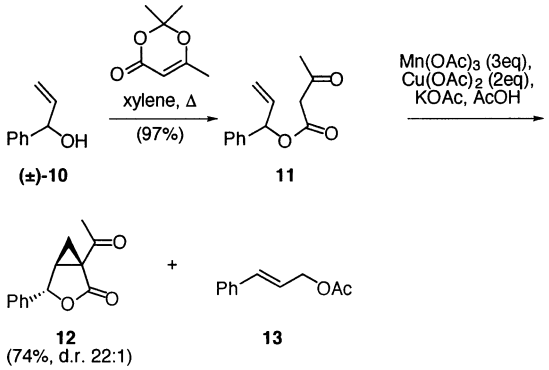
thereby establishing the C2,C6 *endo,exo*-stereochemistry (Scheme 1).[9] The early approach was successful in allowing the total synthesis of several natural products and one simple analogue; however, the initial [2+2] keteniminium cycloaddition used to set up the C5,C6 relative stereochemistry was not directly applicable to the asymmetric synthesis of furofurans.[10]

An important discovery in our original synthesis was the requirement for a deacylative approach to permit efficient access to the key diazolactone intermediate **5**. Reconsideration of the earlier approach, passing through a 3-acylfuran-2-one **7**, suggested that an activated cyclopropane **8** would constitute a suitable precursor to **7** that could be accessed conveniently by Mn(III)/Cu-mediated oxidative cyclization of allyl acetoacetate derivatives (Scheme 2).[11,12] Furthermore, the proposed route should be amenable to asymmetric synthesis of furofurans by simply starting with enantiomerically enriched allylic alcohols. Here we provide a full account of the successful realization of this new route to the furofuranone scaffold and its application to the asymmetric total synthesis of four furofuran lignans.[13]

SCHEME 2. Mn(III)-Mediated Route to Furofurans



SCHEME 3



Results and Discussion

Model Studies and Synthesis of Furofuranone Analogues. The route to furofuranones began with acetoacetylation of racemic 1-phenylallyl alcohol **(±)-10**, which proceeded in excellent yield to afford the desired acetoacetate **11** (Scheme 3).[14] Short reaction times were critical to the success of the reaction, whereas prolonged heating resulted in significant allylic rearrangement. Oxidative cyclization of **11** was ultimately very successful, affording the desired cyclopropanated lactone **12** in high yield and excellent stereoselectivity (d.r. = 22:1 by NMR),[12] although some optimization of the conditions was required to ensure that the desired process occurred at a faster rate than acid-catalyzed allylic displacement to give cinnamyl acetate (**13**).[15] Addition of the allyl acetoacetate **11** to a 3-fold excess of reagents, premixed at 70 °C, gave cyclopropane **12** in 74% yield without any significant formation of the byproduct **13**. The major isomer **12** could be crystallized to diastereomeric purity on a multigram scale, allowing unambiguous determination of its structure by X-ray diffraction.[16]

Attention was then turned to the nucleophilic opening of the activated cyclopropane **12** to introduce C2 of the furofuran scaffold and its pendant group (Scheme 4).[17] Initial efforts to effect the 1,5-addition of methanol to **12** met with little success, although we were encouraged to observe some conversion to the methyl ether **14** after

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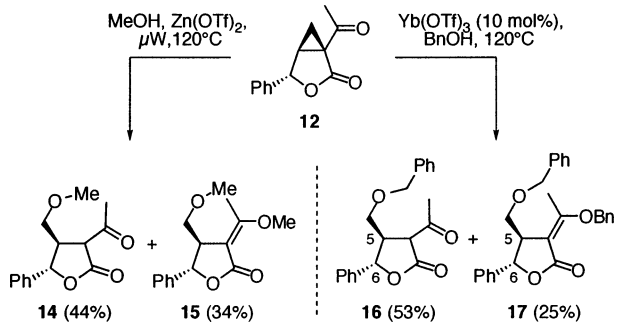
SCHEME 4



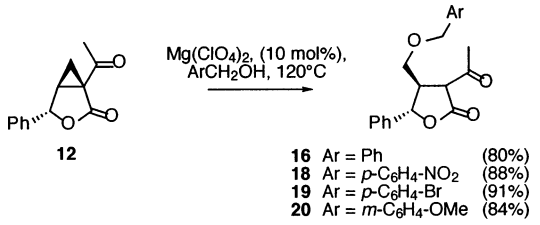
heating at reflux with $Zn(OTf)_2$ (1 equiv) in MeOH for 24 h (ratio of **12** to **14** was estimated to be 5:2 by ^1H NMR). Fortunately, access to a SmithSynthesizer microwave reactor allowed us to investigate a broader range of conditions with the conclusion that cyclopropane **12** could be opened efficiently with methanol at 120 °C.[18] Consumption of **12** was observed after just 30 min at this temperature to provide desired product **14** and the corresponding enol ether **15**.

Microwave conditions were not required for the opening of **12** using benzyl alcohol due to its higher boiling point, and after briefly screening selected metal triflates, $Yb(OTf)_3$ was identified as a more efficient Lewis acid activator of **12** that provided marginally less of the enol ether byproduct. Reaction of cyclopropane **12** with 5 equiv of benzyl alcohol in the presence of 10 mol % $Yb(OTf)_3$ at 120 °C provided both desired product **16** and corresponding benzyl enol ether **17** in 53% and 25% yields, respectively (Scheme 4). GOESY NMR experiments carried out on **17** confirmed the *trans* relationship between the C5 and C6 substituents (furofuran numbering) and the geometrical isomer of the enol ether.

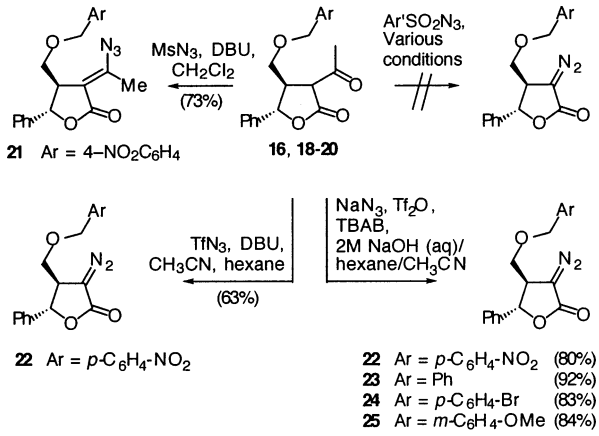
Subsequently, a more in-depth survey into common Lewis acids indicated improved results could be obtained when using $Mg(ClO_4)_2$.[19] Ultimately, optimization of these conditions allowed opening of **12** with 3 equiv of the appropriate alcohol, at 120 °C with 10 mol % of Lewis acid, providing products **16** and various benzylic ether analogues **18**−**20** in excellent yields with little enol ether formation observed (Scheme 5).

Lactone substrates **16** and **18**−**20** proved unreactive to attempted deacetylative diazo-transfer procedures utilizing arylsulfonyl azides, despite the fact that such transformations are well precedented.[20] Therefore, we decided to investigate the more reactive diazo-transfer

SCHEME 5



SCHEME 6



reagent MsN_3.[20c,d−22] Although treatment of **18** with MsN_3 and Hünigs' base provided none of the desired diazo-product, use of DBU provided a surprising result, cleanly converting lactone **18** to vinyl azide **21**. Presumably, the unexpected product arose from *O*-sulfonylation and subsequent conjugate addition−elimination of azide. Having exhausted the repertoire of standard diazo-transfer methods, we turned our attention to TfN_3 as a much more reactive reagent.[23] We were pleased to observe that treatment of acylated lactone **18** with a hexane solution of TfN_3 in the presence of DBU led to rapid formation of the desired α-diazolactone **22** in 63% yield (Scheme 6).

Although no problems were encountered in the handling of TfN_3 solutions, we naturally had some reservations on its frequent use in our diazo-transfer reactions. This led us to devise a facile one-pot method that rapidly transformed acetyl-activated lactones **16** and **18**−**20** into their corresponding diazo-lactones in good to excellent yields following the in situ generation of TfN_3 under phase-transfer conditions (Scheme 6).

In line with our earlier studies,[9,13] the rhodium-catalyzed C−H insertion reactions of α-diazolactones **22**−**25** proceeded with excellent diastereoselectively to provide furofuranones **26**−**29** bearing aryl substituents in

(16) Structures **27**, **28**, **35**, **38b**, and **1** were unambiguously determined by X-ray crystallography. It was also possible to confirm the absolute stereochemistry of **38b** due to the presence of a heavy atom in the structure. Crystallographic data for these structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 219596 (**28**), CCDC 219598 (**35**), CCDC 218116 (**38b**), and CCDC 219597 (**1**). The X-ray structure of **27** has been reported previously: Gelbrich, T.; Hursthouse, M. B. *Acta Crystallogr.* **2001**, *E57*, o566.

(17) For an example of opening of a closely related cyclopropane using thiolate nucleophiles: Lee, C.-S.; Lee, K.-I.; Hamilton, A. D. *Tetrahedron Lett.* **2001**, *42*, 211.

(18) Personal Chemistry is thanked for the donation of the Smith-Synthesizer used in this work.

(19) Although we have not experienced any problem in the handling or heating of these metal perchlorates, care should be taken when manipulating them due to their potentially explosive nature. Sax, N. I. *Dangerous Properties of Industrial Materials*, 5th ed.; Van Nostrand Reinhold Company: New York, 1979.

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(21) MsN_3 was prepared from MsCl and NaN_3 and used in diazo-transfer reactions without further purification: Reagan, M. T.; Nickon, A. *J. Am. Chem. Soc.* **1968**, *90*, 4096.

(22) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.

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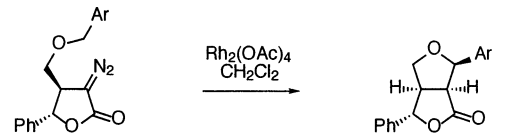
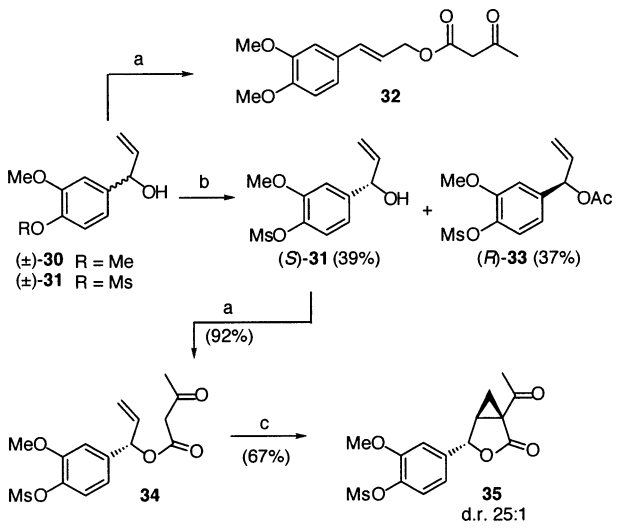
SCHEME 7



22 Ar = *p*-C_6H_4-NO_2
23 Ar = Ph
24 Ar = *p*-C_6H_4-Br
25 Ar = *m*-C_6H_4-OMe

26 Ar = *p*-C_6H_4-NO_2 (78%)
27 Ar = Ph (89%)
28 Ar = *p*-C_6H_4-Br (76%)
29 Ar = *m*-C_6H_4-OMe (82%)

SCHEME 8[a]



[a] Reagents and conditions: (a) 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one, 120 °C open vessel, 10 min; (b) Novozym 435, isopropenyl acetate, and separation of the (*R*)-acetate **33**; (c) $Mn(OAc)_3$, $Cu(OAc)_2$, KOAc, AcOH.

an *endo,exo*-configuration (Scheme 7).[24] Thus the diastereoselective synthesis of the parent furofuranone system **27** (Ar = Ph) had been completed in five steps with 48% overall yield, demonstrating the excellent efficiency of this new approach. Furthermore, the convergent nature of this route provides the opportunity to assemble furofuran lignan-based scaffolds that would be amenable to further elaboration using high-throughput methods.

Synthesis of Furofuran Natural Products. The methodology described above provided the basis for an asymmetric synthesis of furofuran lignans; however, it should be emphasized that it was not directly applicable due to the acid sensitivity of certain intermediates containing electron-rich aromatic rings. This point was illustrated during the attempted acetoacetylation of racemic 1-(3,4-dimethoxy)allyl alcohol (±)-**30**, which instead of the desired product, provided a rearranged acetoacetate derivative **32** (Scheme 8). A simple solution to the problem entailed attenuation of the electron-donating properties of the 3,4-dioxygenated aromatic ring by introducing methanesulfonyl protection at the 4-position,[25] which also provided the opportunity to synthesize furofurans containing free phenolic groups.

Starting from the racemic 1-arylallyl alcohol (±)-**31**, resolution was successfully achieved using a supported lipase (Scheme 8).[26] Subsequently, enantiomerically enriched alcohol (*S*)-**31** (>98% ee)[27] underwent acetoacetylation without detectable racemization or decomposition, to provide the precursor **34** for the intramolecular cyclopropanation. Mn(III)-mediated oxidative cyclization was carried out under the conditions described above to afford the 3-oxabicyclo[3.1.0]hexan-2-one **35** in good yield and excellent diastereoselectivity (d.r. 25:1 by ^{1}H NMR). The minor diastereoisomer could be completely removed by recrystallization.

Opening of the cyclopropane **35** with electron-rich benzylic alcohol **39a** under conditions described above was complicated by a major side-reaction affording the dibenzyl ether. Formation of the byproduct was partially suppressed by addition of 2,6-di-*tert*-butylpyridine to the reaction mixture, and a respectable yield of methylenedioxy adduct **36a** was obtained along with 34% recovered **35** (Scheme 9). The corresponding Lewis acid-catalyzed opening of **35** with the less activated, methanesulfonate-substituted benzylic alcohol **39b** proved to be more efficient, providing the ring-opened adduct **36b** in good yield (72%).

Deacetylative diazo-transfer employing in situ-generated TfN_3 returned the desired diazolactones **37a/b** in excellent yields, and from here, completion of the synthesis proved to be quite straightforward. Rhodium-catalyzed C−H insertion gave the furofuranones **38a/b** as single diastereoisomers that were converted to furofurans **42a/b**, via the diol intermediates **40a/b**, following established procedures.[6b,9a] (+)-Xanthoxylol (**1**) and (+)-epipinoresinol (**3**) were obtained following deprotection of the sulfonate esters by treatment of **42a/b** with NaOH in MeOH/dioxane at 50 °C,[25] thus demonstrating the utility of this protecting group in lignan synthesis (Scheme 10). Synthetic samples of compounds **1** and **3** displayed analytical data consistent with those reported for the natural products.[28,29] The total syntheses of two additional furofuran lignans, (+)-methylxanthoxylol (**2**) and (+)-epieudesmin (**4**), were also completed by methylation of the phenolic hydroxyl groups present in **1** and **3**.[30,31]

In conclusion, we have described a novel and highly efficient stereoselective approach to the *endo,exo*-furofuranone scaffold. A sequence involving intramolecular cyclopropanation followed by Lewis acid-catalyzed cyclo-

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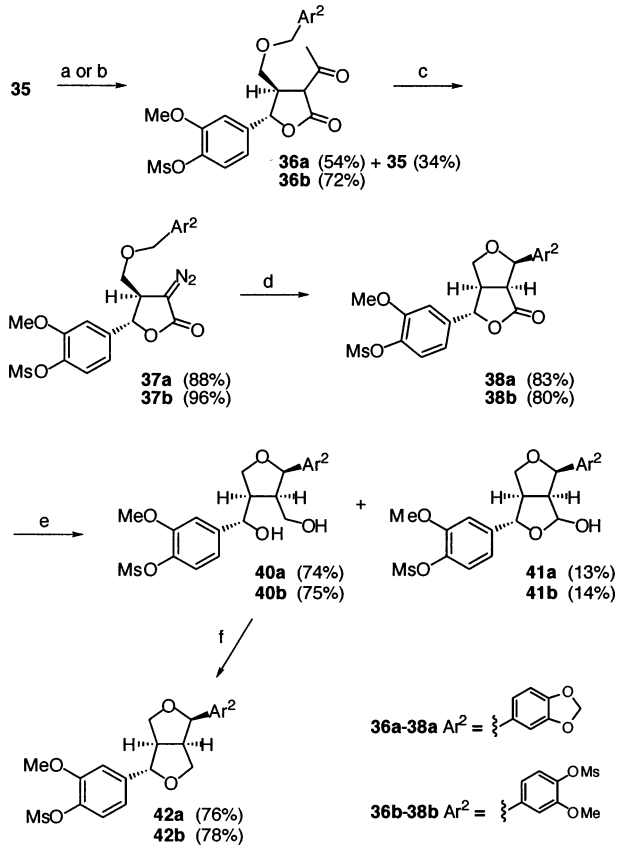
(26) (a) Córdova, A.; Janda, K. D. *J. Org. Chem.* **2001**, *66*, 1906. (b) Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 6129. (c) Morgan, B.; Oehlschlager, A. C.; Stokes, T. M. *J. Org. Chem.* **1992**, *57*, 3231.

(27) Enantiomeric excess of (*S*)-**10** was determined by chiral HPLC on a Chiracel OD-H column, eluting with IPA/hexane (1:9). t_R (*S*)-alcohol = 25.2 min, t_R (*R*)-alcohol = 29.2 min.

(28) Isolation of (+)-xanthoxylol (**1**): (a) Gonzaléz, M. J. T. G.; Pinto, M. M. M.; Kijjoa, A.; Anantachoke, C.; Herz, W. *Phytochemistry* **1993**, *32*, 433. (b) Fang, J. M.; Lee, C. K.; Cheng, Y. S. *Phytochemistry* **1992**, *31*, 3659. Note that in ref 28b the structure of the wrong enantiomer is depicted. The structure of the synthetic sample of **1** prepared in our laboratory was unambiguously confirmed by X-ray crystallography (ref 16).

SCHEME 9[a]



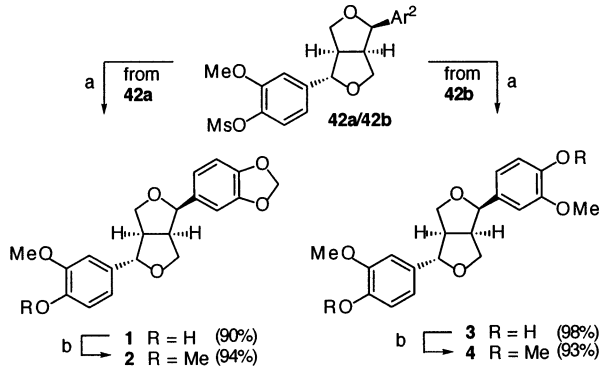
[a] Reagents and conditions: (a) (i) $Mg(ClO_4)_2$, 3,4-methylenedioxybenzyl alcohol (**39a**), 2,6-di-*tert*-butylpyridine; (b) $Mg(ClO_4)_2$, 4-(methanesulfonyloxy)-3-methoxybenzyl alcohol (**39b**), 2,6-di-*tert*-butylpyridine; (c) NaN_3, Bu_4NBr, 2 N NaOH(aq), CH_3CN, hexane, Tf_2O; (d) $Rh_2(OAc)_4$, CH_2Cl_2; (e) $LiAlH_4$, THF; (f) MsCl, Et_3N, DMAP, CH_2Cl_2.

propane ring-opening provides an efficient and highly selective means of establishing relative stereocontrol between the C5 and C6 centers. Following deacylative diazo-transfer, C−H insertion reaction of the resulting α-diazocarbonyl provides the *endo,exo*-furofuranone framework with control of the remaining two stereocenters. The utility of the general approach has been illustrated by the synthesis of several furofuranones and by its application to the enantioselective synthesis of four *endo,exo*-furofuran lignans.

Experimental Section

(±)-1-Phenylallyl Acetoacetate (11).[14b] An open flask containing a rapidly stirring solution of phenylallyl alcohol **10** (705 mg, 5.25 mmol) and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (0.70 mL, 5.36 mmol) in xylenes (1 mL) was immersed in a preheated oil bath (150 °C). The rapid evolution of acetone was observed. After 8 min the flask was removed from the bath and cooled to ambient temperature before concentration in vacuo to remove excess xylenes. Purification was accomplished by flash chromatography on prepacked silica gel (4 × 7) eluting with petrol (200 mL), followed by Et_2O/hexane (1:1) to give the title compound **11** (1075 mg, 4.93 mmol, 94%) as a colorless oil: IR ν_{max} (neat) 1746, 1720, cm^{-1}; ^1H NMR (250 MHz) δ 7.41−7.27 (5H, m), 6.31 (1H, dt, J = 6.0, 1.3 Hz), 6.02 (1H, ddd, J = 16.4, 10.4, 6.0 Hz), 5.37−5.26 (2H, m), 3.50 (2H, s), 2.23 (3H, s); (keto/enol ratio 10:1, enolic acetoacetyl resonances were observed at δ 11.95, 5.09, 1.95); ^{13}C NMR (63 MHz) δ 200.6, 166.5, 138.6, 136.0, 129.0, 129.0, 127.6, 118.0, 77.7, 50.7, 30.5; enolic resonances were observed at δ 176.4, 136.7, 117.3, 90.2, 76.1, 21.6; LRMS (CI, NH_3) m/z (relative intensity) 133 (20) $[M - COCH_2COCH_3]^+$, 117 (100) $[PhCH{=}CHCH_2]^+$, 91 (8) $[PhCH_2]^+$; HRMS (ES +ve) calcd for $C_{13}H_{14}O_3Na$ 241.0835, found 241.0833.

SCHEME 10[a]



[a] Reagents and conditions: (a) 3 N KOH, MeOH, dioxane, 50 °C; (b) MeI, $CsCO_3$, acetone.

(1*R,4*S**,5*S**)-1-Acetyl-4-phenyl-3-oxabicyclo[3.1.0]-hexan-2-one (12).** To a suspension of $Mn(OAc)_3 \cdot 2H_2O$ (72.4 g, 270 mmol), $Cu(OAc)_2$ (24.5 g, 135 mmol), and KOAc (22.1 g, 225 mmol) in AcOH (500 mL) at 70 °C (internal) was added β-ketoester **11** (19.6 g, 90 mmol) in AcOH (50 mL) in one portion. The reaction was maintained at 70 °C for 15 min, whereby the original brown slurry turned to a blue turquoise suspension. The mixture was allowed to cool to room temperature and concentrated in vacuo to remove AcOH. The resulting residue was partitioned between EtOAc (600 mL) and water (500 mL) and the particulate matter removed by filtration through Celite. The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 500 mL), and the combined extracts were washed with water (2 × 500 mL), 10% (w/v) $NaHCO_3$(aq) (2 × 500 mL), and brine (500 mL), dried with $MgSO_4$, and concentrated in vacuo to give a yellow oil (23.1 g). Purification was accomplished by flash chromatography on silica gel (10 × 12) eluting with EtOAc/hexane (1:1) to give the title compound **12** (14.5 g, 67 mmol, 74%) as a pale yellow oil (22:1 mixture of diastereoisomers). A series of triturations with ice-cold Et_2O provided the *trans*-isomer **12** (12.1 g, 56 mmol, 62%) as an off-white solid: mp 78−80 °C; IR ν_{max} (neat) 1774, 1692 cm^{-1}; ^1H NMR (400 MHz) δ 7.44−7.36 (3H, m), 7.31−7.27 (2H, m), 5.31 (1H, s), 2.80 (1H, dd, J = 8.0, 5.5 Hz), 2.60 (3H, s), 2.15 (1H, dd, J = 8.0, 4.3 Hz), 1.59 (1H, dd, J = 5.3, 4.3 Hz); ^{13}C NMR (100 MHz) δ 200.5, 172.8, 139.0, 129.6, 129.6, 125.7, 79.8, 37.4, 37.1, 29.7, 24.6; LRMS (CI, NH_3) m/z (relative intensity) 217 (100) $[M + H]^+$, 234 (65) $[M + NH_4]^+$. Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.21; H, 5.60.

(4*R,5*S**)-3-Acetyl-4-benzyloxymethyl-5-phenyldihydrofuran-2-one (16).** To a solution of cyclopropane **12** (216 mg, 1.0 mmol) in dry benzyl alcohol (0.31 mL, 3.0 mmol) was

(29) Isolation of (+)-epipinoresinol, see ref 2f and: (a) Rahman, M. M. A.; Dewick, P. M.; Jackson, D. E.; Lucas, J. A. *Phytochemistry* **1990**, *29*, 1971. Synthesis of (±)-epipinoresinol: (b) Katayama, T.; Davin, L. B.; Chu, A.; Lewis, N. G. *Phytochemistry* **1993**, *33*, 581−591. (+)-Epipinoresinol from acid-catalyzed isomerization of (+)-pinoresinol: Nishibe, S.; Tsukamoto, H.; Hisada, S. *Chem. Pharm. Bull.* **1984**, *32*, 4653.

(30) Spectroscopic data were consistent with that reported previously for methyl xanthoxylol (**2**): ref 6b and Bytheway, I. R.; Ghisalberti, E. L.; Gotsis, S.; Jefferies, P. R.; Skelton, B. W.; Sugars, K. E.; White, A. H. *Aust. J. Chem.* **1987**, *40*, 1913.

(31) Spectroscopic data were consistent with that reported previously for epieudesmin: (a) Chiba, M.; Hisada, S.; Nishibe, S.; Thieme, H. *Phytochemistry* **1980**, *19*, 335−336. (b) Iida, T.; Nakano, M.; Ito, K. *Phytochemistry* **1982**, *21*, 673. (c) Das, B.; Madhusudhan, P.; Venkataiah, B. *Synth. Commun.* **2000**, *30*, 4001.

added $Mg(ClO_4)_2$ (22 mg, 0.1 mmol) before heating the mixture to 120 °C for 90 min. The reaction was cooled to room temperature before partitioning between CH_2Cl_2 (30 mL) and water (30 mL), the organic layer separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with saturated NH_4Cl(aq) (20 mL) and brine (20 mL), dried with $MgSO_4$, and concentrated in vacuo to give a pale yellow oil (611 mg). The excess benzyl alcohol was removed by distillation under reduced pressure (bp ~120 °C, 0.5 mbar) and the residue purified by flash chromatography on silica gel (2.3 × 8) eluting with EtOAc/hexane (1:9) to EtOAc/hexane (2:3) in 10% increment rises (40 mL each). The title compound **16** (295 mg, 0.80 mmol, 80%) was isolated as a colorless oil along with benzyl enol ether **17** (9 mg, 0.02 mmol, 2%) isolated as a colorless oil. Data for title compound **16**: IR ν_{max} (neat) 1780, 1767, 1720 cm^{-1}; ^1H NMR (400 MHz) δ 7.43−7.20 (10H, m), 5.31 (1H, d, J = 9.5 Hz), 4.56 (1H, d, J = 12.0 Hz), 4.48 (1H, d, J = 12.0 Hz), 4.02 (1H, d, J = 10.5 Hz), 3.50 (1H, dd, J = 3.5, 10.0 Hz), 3.47 (1H, dd, J = 3.5, 10.0 Hz), 3.12 (1H, ddt, J = 10.5, 9.5, 3.5 Hz), 2.49 (3H, s); keto/enol ratio 7:1, enolic resonances were observed at δ 11.28 (1H, s), 5.50 (1H, d, J = 2.5 Hz), 1.94 (3H, s); ^{13}C NMR (100 MHz) δ 200.8, 171.7, 137.9, 137.7, 129.4, 129.2, 129.0, 128.5, 128.4, 126.7, 81.4, 73.7, 65.7, 56.0, 46.7, 30.5; enolic resonances were observed at δ 170.8, 141.0, 128.6, 125.4, 82.8, 72.1, 46.9, 19.5; LRMS (CI, NH_3) m/z (relative intensity) 325 (14) $[M + H]^+$, 342 (5) $[M + NH_4]^+$, 106 (100) $[PhCHO]^+$, 91 (82) $[PhCH_2]^+$; HRMS (ES +ve) calcd for $C_{20}H_{20}O_4Na$ 347.1254, found 347.1250.

Data for (4*R,5*S**)-3-(1-Benzyloxyethylidene)-4-benzyloxymethyl-5-phenyldihydrofuran-2-one (17):** IR ν_{max} (neat) 1702, 1693, 1642 cm^{-1}; ^1H NMR (400 MHz) δ 7.40−7.20 (15H, m), 5.57 (1H, d, J = 5.0 Hz), 5.17 (1H, d, J = 12.7 Hz), 5.10 (1H, d, J = 12.7 Hz), 4.57 (1H, d, J = 12.1 Hz), 4.51 (1H, d, J = 12.1 Hz), 3.82 (1H, dd, J = 9.3, 3.5 Hz), 3.58 (1H, t, J = 8.5 Hz), 3.48−3.42 (1H, m), 2.34 (3H, s); ^{13}C NMR (100 MHz) δ 170.6, 165.9, 142.0, 138.9, 137.0, 129.1, 129.0, 128.9, 128.5, 128.5, 128.4, 128.1, 125.7, 102.0, 87.1, 73.4, 71.6, 65.8, 52.1, 15.0; LRMS (CI, NH_3) m/z (relative intensity) 415 (10) $[M + H]^+$, 307 (18) $[M + H(-BnOH)]^+$, 106 (70) $[PhCHO]^+$, 91 (100) $[PhCH_2]^+$; HRMS (EI) calcd for $C_{27}H_{26}O_4$ 414.1831, found 414.1826.

(4*R,5*S**)-3-(1-Azidoethylidene)-4-benzyloxymethyl-5-phenyldihydrofuran-2-one (21).** To a solution of lactone **18** (60 mg, 0.16 mmol) in MeCN (1 mL) at room temperature was added DBU (24 μL, 0.16 mmol). After 5 min a solution of MsN_3 (58 mg, 0.48 mmol) in MeCN (0.6 mL) was added and the reaction stirred at room temperature for 18 h. The mixture was then diluted with CH_2Cl_2 (20 mL) and water (20 mL), the organic layer separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, and concentrated in vacuo to yield a yellow oil (132 mg). Purification was accomplished by flash chromatography on silica gel (2.2 × 7) eluting with EtOAc/hexane (1:1) to give the title compound **21** (46 mg, 0.12 mmol, 73%) as a pale yellow oil: IR ν_{max} (neat) 2110, 1765, 1737, 1643 cm^{-1}; ^1H NMR (400 MHz) δ 8.23 (2H, dt, J = 8.8, 1.8 Hz), 7.51 (2H, d, J = 8.8 Hz), 7.39−7.24 (5H, m), 5.51 (1H, d, J = 2.3 Hz), 4.72 (1H, d, J = 13.1 Hz), 4.68 (1H, d, J = 13.1 Hz), 3.82 (1H, dd, J = 9.0, 4.0 Hz), 3.62 (1H, t, J = 8.8 Hz), 3.41−3.37 (1H, m), 2.57 (3H, s); ^{13}C NMR (100 MHz) δ 170.3, 149.4, 147.9, 145.8, 141.0, 129.2, 128.6, 128.0, 125.4, 124.1, 110.2, 80.5, 72.4, 71.2, 48.5, 14.5; LRMS (ES +ve) m/z (relative intensity) 811 (100) $[2M + Na]^+$; HRMS (ES +ve) calcd for $C_{40}H_{36}O_{10}N_8Na$ (dimer) 811.2447, found 811.2472.

(4*R,5*S**)-5-Phenyl-3-diazo-4-([benzyloxy]methyl)tetrahydro-2-furanone (23).** To a solution of NaN_3 (364 mg, 5.60 mmol) and Bu_4NBr (2 mg, 1 mol %) in 2 N NaOH(aq) (12 mL) and hexane (6 mL) at 0 °C (ice/salt bath) was added Tf_2O (0.47 mL, 2.80 mmol) dropwise over 2 min. The clear colorless reaction mixture was to left stir for 10 min before the rapid addition of a solution of lactone **16** (227 mg, 0.70 mmol) in MeCN (6 mL) with vigorous stirring. The resulting bright yellow solution was allowed to stir at 0 °C for a further 30 min before dilution with EtOAc (30 mL) and water (20 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 30 mL), and the organic extracts were combined, washed with brine (30 mL), dried with Na_2SO_4, and concentrated in vacuo to yield a yellow foam (380 mg). Purification was accomplished by flash chromatography on silica gel (2.1 × 2.5) eluting with EtOAc/hexane (1:9) to EtOAc/hexane (1:1) in 5% increment rises (30 mL each) to give the title compound **23** (199 mg, 0.65 mmol, 92%) as a powdery yellow solid. Analytical data were identical to that reported previously.[9a]

(1*S,2*R**,5*R**,6*S**) 2,6-Diphenyl-3,7-dioxabicyclo[3.3.0]-octan-8-one (27).** To a solution of diazolactone **23** (100 mg, 0.32 mmol) in CH_2Cl_2 (4 mL) at room temperature was added $Rh_2(OAc)_4$ (3 mg, 0.006 mmol), and the resulting pale green, effervescing (N_2) reaction mixture was stirred under nitrogen for 3 h. The mixture was diluted with CH_2Cl_2 (10 mL) and poured onto water (10 mL), the organic layer separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$-(aq) (10 mL) and brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo to yield a white solid (105 mg). Purification was accomplished by flash chromatography on silica gel (1.5 × 7) eluting with Et_2O/hexane (2:3) to yield the title compound **27** (80 mg, 0.29 mmol, 89%) as a white crystalline solid. Analytical data were identical to that reported previously.[9a]

1-(4-Methanesulfonyloxy-3-methoxyphenyl)prop-2-en-1-ol ((±)-31). To a suspension of 4-methanesulfonyloxy-3-methoxybenzaldehyde[32] (23.02 g, 0.100 mol) in THF (200 mL) at −60 °C (internal, CO_2(s)/acetone) was added vinylmagnesium bromide (105 mL of a 1 M solution in THF, 0.105 mol) via dropping funnel at such a rate that the temperature did not rise above −55 °C (90 min). The resulting yellow homogeneous solution was warmed to −10 °C, diluted with EtOAc (200 mL), and treated with saturated NH_4Cl(aq) (300 mL) with vigorous stirring. The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 300 mL). The combined organic layers were washed with brine (400 mL), dried with Na_2SO_4, and concentrated in vacuo to yield the title compound (±)-**31** (27.1 g, quantitative) as a pale yellow oil; this crude material was used directly in the subsequent enzymatic resolution. See compound (+)-**31** for analytical data.

(1*S*)-(4-Methanesulfonyloxy-3-methoxyphenyl)prop-2-en-1-ol ((+)-31). To a solution of crude alcohol (±)-**31** (0.10 mol, theoretical) in isopropenyl acetate (110 mL, 1.00 mol) was added Novozym 435 (12.90 g, 50 wt %), and the mixture was gently stirred and warmed to 40 °C for 17 h (reaction monitored by chiral HPLC, column: Chiracel OD-H, until 50% completion). The enzyme was filtered and washed with EtOAc (200 mL) and the filtrate concentrated in vacuo to yield a crude yellow oil (33.1 g). Purification was accomplished by flash chromatography on silica gel (9 × 30) eluting with EtOAc/hexane (3:7 then 2:3 then 1:1). The title compound (+)-**31** (10.11 g, 0.039 mol, 39%) was isolated as a pale yellow oil along with acetate (*R*)-**33** (11.08 g, 0.037 mol, 37%), which was also isolated as a pale yellow oil.

Data for (*S*)-31: $[\alpha]_D$ +16.7 (*c* 0.50, $CHCl_3$); IR (neat) ν_{max} 3521, 1600 cm^{-1}; ^1H NMR (400 MHz) δ 7.25 (1H, d, J = 8.3 Hz), 7.06 (1H, d, J = 1.8 Hz), 6.93 (1H, dd, J = 8.3, 1.8 Hz), 6.00 (1H, ddd, J = 17.1, 10.3, 6.3 Hz), 5.36 (1H, dt, J = 17.1, 1.3 Hz), 5.22 (1H, dt, J = 10.3, 1.3 Hz), 5.18 (1H, br d, J = 6.0 Hz), 3.89 (3H, s), 3.16 (3H, s); ^{13}C NMR (100 MHz) δ 151.9, 143.5, 140.2, 138.0, 124.8, 119.3, 116.3, 111.2, 75.2, 56.5, 38.7; LRMS (CI, NH_3) m/z (relative intensity) 276 (15) $[M + NH_4]^+$, 241 (40) $[M + H(-H_2O)]^+$, 79 (100) $[CH_3SO_2]^+$; HRMS (ES +ve) calcd for $C_{22}H_{28}S_2O_{10}Na$ (dimer) 539.1016, found 539.1034.

Data for (1*R*)-(4-Methanesulfonyloxy-3-methoxyphenyl)allyl acetate ((*R*)-33): $[\alpha]_D$ +38.6 (*c* 0.47, $CHCl_3$); IR (neat)

(32) Battersby, A. R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1056.

ν_{max} 1736, 1504 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.27 (1H, d, J = 8.5 Hz), 6.99−6.94 (2H, m), 6.23 (1H, d, J = 6.0 Hz), 5.97 (1H, ddd, J = 17.1, 10.3, 5.8 Hz), 5.31 (1H, dt, J = 17.1, 1.3 Hz), 5.27 (1H, dt, J = 10.3, 1.3 Hz), 3.89 (3H, s), 3.17 (3H, s), 2.12 (3H, s); ^{13}C NMR (100 MHz) δ 170.3, 151.9, 139.8, 138.5, 136.1, 125.0, 120.3, 117.9, 112.4, 76.0, 56.5, 38.8, 21.6; LRMS (CI, NH_3) m/z (relative intensity) 241 (60) [M + H(−CH_3CO_2H)]$^+$, 260 (100); HRMS (ES +ve) calcd for $C_{13}H_{16}SO_6Na$ 323.0560, found 323.0564.

(1*S*)-(4-Methanesulfonyloxy-3-methoxyphenyl)allyl Acetoacetate (34). The title compound was prepared according to the method outlined for **11** whereby (1*S*)-(4-methanesulfonyloxy-3-methoxyphenyl)prop-2-en-1-ol ((*S*)-**31**) (5.94 g, 23 mmol) and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (3.0 mL, 23.2 mmol) were reacted under the conditions described (except reaction for 15 min). Purification was accomplished by flash chromatography on silica gel (8 × 7) eluting with petrol (800 mL), followed by EtOAc/hexane (1:1) to give the title compound **34** (7.25 g, 21.2 mmol, 92%) as a pale yellow oil: $[\alpha]_D$ −38.2 (*c* 0.34, $CHCl_3$); IR ν_{max} (neat) 1737, 1714, 1504 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.28 (1H, d, J = 8.3 Hz), 7.02 (1H, d, J = 2.0 Hz), 6.95 (1H, ddd, J = 8.3, 2.0, 0.5 Hz), 6.28 (1H, d, J = 6.0 Hz), 5.97 (1H, ddd, J = 17.1, 10.5, 6.0 Hz), 5.36 (1H, dt, J = 17.3, 1.3 Hz), 5.31 (1H, dt, J = 10.3, 1.3 Hz), 3.91 (3H, s), 3.53 (2H, s), 3.17 (3H, s), 2.25 (3H, s); keto/enol ratio 6:1, enolic acetoacetyl resonances were observed at δ 11.90 (1H, d, J = 0.8 Hz), 5.08 (1H, d, J = 0.8 Hz), 3.89 (3H, s), 1.97 (3H, s); ^{13}C NMR (100 MHz) δ 200.6, 166.4, 152.0, 139.2, 138.5, 135.5, 125.0, 120.1, 118.7, 112.2, 77.0, 56.6, 50.6, 38.8, 30.7; enolic acetoacetyl resonances were observed at δ 177.0, 139.8, 136.2, 117.9, 112.1, 90.0, 75.4, 21.7; LRMS (ES +ve) m/z (relative intensity) 365 (100) [M + Na]$^+$, 707 (30) [2M + Na]$^+$; HRMS (ES +ve) calcd for $C_{15}H_{18}SO_7Na$ 365.0665, found 365.0675.

(1*R*,4*S*,5*S*)-1-Acetyl-4-(4-methanesulfonyloxy-3-methoxyphenyl)-3-oxabicyclo[3.1.0]hexan-2-one (35). The title compound was prepared according to the method outlined above for the preparation of **12**, whereby β-ketoester **34** (6.85 g, 20.0 mmol), $Mn(OAc)_3$·$2H_2O$ (16.1 g, 60.0 mmol), $Cu(OAc)_2$ (5.45 g, 30.0 mmol), and KOAc (22.1 g, 225 mmol) were reacted and worked up under the conditions described to yield a crude yellow oil (7.38 g). Purification was accomplished by flash chromatography on silica gel (5 × 12) eluting with EtOAc/hexane (2:3) to give the title compound **35** (4.59 g, 13.5 mmol, 67%) as a pale yellow oil (25:1 mixture of diastereoisomers). A series of triturations with ice-cold Et_2O/hexane provided the *trans*-isomer as an off-white solid: mp 113−115 °C (EtOAc/hexane); $[\alpha]_D$ +96.6 (*c* 0.38, $CHCl_3$); IR ν_{max} (neat) 1770, 1695, 1599 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.33 (1H, d, J = 8.8 Hz), 6.93−6.89 (2H, m), 5.30 (1H, s), 3.90 (3H, s), 3.19 (3H, s), 2.82 (1H, dd, J = 8.0, 6.0 Hz), 2.58 (3H, s), 2.15 (1H, dd, J = 8.0, 4.3), 1.61 (1H, m); ^{13}C NMR (100 MHz) δ 200.1, 172.5, 152.5, 139.4, 139.1, 125.7, 118.0, 110.3, 78.9, 56.6, 39.0, 37.2, 36.7, 29.7, 24.7; LRMS (ES +ve) m/z (relative intensity) 703 (100) [2M + Na]$^+$. CHN Anal. Calcd for $C_{15}H_{16}SO_7$: C, 52.94; H, 4.74. Found: C, 52.93; H, 4.78.

(4*R*,5*S*)-5-(4-Methanesulfonyloxy-3-methoxy)phenyl-4-{[(4-methanesulfonyloxy-3-methoxybenzyl)oxy]methyl}-3-acetyltetrahydro-2-furanone (36b). To a mixture of cyclopropane **35** (204 mg, 0.60 mmol), 4-methanesulfonyloxy-3-methoxybenzyl alcohol (**39b**) (418 mg, 1.80 mmol), and 2,6-di-*tert*-butylpyridine (13 μL, 0.06 mmol) was added $Mg(ClO_4)_2$ (13 mg, 0.06 mmol) and the mixture heated to 120 °C for 2.5 h. The reaction mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 (30 mL), and treated with saturated NH_4Cl(aq) (25 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried with Na_2SO_4, and concentrated in vacuo to yield a crude yellow oil (730 mg). To a solution of this crude material in isopropenyl acetate (3 mL) was added Novozym 435 (140 mg, 50 wt % based on 1.2 mmol of excess alcohol 40 remaining) and the gently stirred mixture warmed to 40 °C for 12 h. The enzyme was then filtered, washed with EtOAc (30 mL), and the filtrate concentrated in vacuo to yield a colorless oil (790 mg). Purification was accomplished by flash chromatography on silica gel (3.2 × 14) eluting with EtOAc/hexane (1:1 then 2:1 then 3:1) to give the title compound **36b** (247 mg, 0.43 mmol, 72%) as a white foamy solid: mp 57−59 °C; $[\alpha]_D$ +31.2 (*c* 0.38, $CHCl_3$); IR ν_{max} (neat) 1771, 1718 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.30−7.25 (2H, m), 6.94−6.91 (2H, m), 6.89 (1H, dd, J = 8.3, 1.8 Hz), 6.76 (1H, dd, J = 8.3, 1.8 Hz), 5.26 (1H, d, J = 9.0 Hz), 4.53 (1H, d, J = 12.3 Hz), 4.44 (1H, d, J = 12.3 Hz), 3.96 (1H, d, J = 10.0 Hz), 3.89 (3H, s), 3.85 (3H, s), 3.55 (2H, d, J = 3.8 Hz), 3.20 (3H, s), 3.18 (3H, s), 3.13 (1H, ddt, J = 10.0, 9.0, 3.8 Hz), 2.50 (3H, s); keto/enol ratio 12:1, enolic resonances were observed at δ 11.24 (1H, s), 5.49 (1H, d, J = 2.5 Hz), 4.58 (1H, d, J = 10.0 Hz), 1.96 (3H, s); ^{13}C NMR (100 MHz) δ 200.4, 171.3, 152.5, 152.1, 139.1, 138.3, 138.3, 125.2, 125.1, 120.6, 119.4, 112.7, 110.7, 81.0, 73.2, 67.0, 56.7, 56.6, 56.3, 46.3, 39.0, 38.9, 30.5; enolic resonances were observed at δ 141.4, 117.8, 19.8; LRMS (ES +ve) m/z (relative intensity) 595 (100) [M + Na]$^+$. Anal. Calcd for $C_{24}H_{28}S_2O_{12}$: C, 50.34; H, 4.93. Found: C, 50.19; H, 5.01.

(4*R*,5*S*)-5-(4-Methanesulfonyloxy-3-methoxy)phenyl-3-diazo-4-{[(4-methanesulfonyloxy-3-methoxybenzyl)oxy]methyl}tetrahydro-2-furanone (37b). The title compound was prepared according to the method outlined for **23**, whereby reaction of lactone **36b** (160 mg, 0.28 mmol) with Tf_2O (0.19 mL, 1.12 mmol) and NaN_3 (146 mg, 2.24 mmol) and workup under the conditions described gave a crude yellow oil (226 mg). Purification was accomplished by flash chromatography on silica gel (2.2 × 9) eluting with EtOAc/hexane (3:1) to give the title compound **37b** (150 mg, 0.27 mmol, 96%) as a viscous bright yellow foam: $[\alpha]_D$ +42.3 (*c* 0.41, $CHCl_3$); IR ν_{max} (neat) 2101, 1731, 1603 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.30 (1H, d, J = 8.3 Hz), 7.27 (1H, d, J = 8.3 Hz), 6.97 (1H, d, J = 2.0 Hz), 6.96 (1H, d, J = 2.0 Hz), 6.89 (1H, d, J = 1.8 Hz), 6.87 (1H, d, J = 1.8 Hz), 5.18 (1H, d, J = 4.8 Hz), 4.58 (2H, s), 3.88 (3H, s), 3.87 (3H, s), 3.85−3.71 (3H, m), 3.19 (3H, s), 3.19 (3H, s); ^{13}C NMR (100 MHz) δ 169.2, 152.5, 152.2, 139.7, 138.9, 138.4, 138.1, 125.5, 125.0, 120.4, 118.2, 112.3, 110.2, 80.1, 73.5, 71.3, 56.7, 56.5, 53.0, 45.7, 39.0, 38.9.

(1*S*,2*R*,5*R*,6*S*)-2-(4-Methanesulfonyloxy-3-methoxy)-phenyl-6-(4-methanesulfonyloxy-3-methoxy)phenyl-3,7-dioxabicyclo[3.3.0]octan-8-one (38b). The title compound was prepared according to the method outlined for **27**, whereby reaction of diazolactone **37b** (128 mg, 0.23 mmol) with $Rh_2(OAc)_4$ (2 mg, cat.) and workup under the conditions described gave crude furofuranone as a white foam (118 mg). Purification was accomplished by flash chromatography on silica gel (2.2 × 7) eluting with EtOAc/hexane (4:1) then EtOAc to give the title compound **38b** (97 mg, 0.18 mmol, 80%) as a white powdery solid: mp 135−137 °C (EtOAc/hexane); $[\alpha]_D$ +81.8 (*c* 0.38, $CHCl_3$); IR (neat) ν_{max} 1779, 1602 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.32 (2H, d, J = 8.3 Hz), 7.04 (1H, d, J = 1.2 Hz), 7.01 (1H, dd, J = 8.3, 1.5 Hz), 6.97 (1H, d, J = 1.2 Hz), 6.91 (1H, dd, J = 8.3, 1.5 Hz), 5.27 (1H, d, J = 6.3 Hz), 5.08 (1H, d, J = 8.3 Hz), 4.37 (1H, d, J = 9.8 Hz), 3.98 (1H, dd, J = 9.8, 4.8 Hz), 3.90 (3H, s), 3.90 (3H, s), 3.60 (1H, t, J = 8.8 Hz), 3.26 (1H, ddd, J = 8.8, 6.3, 4.8 Hz), 3.20 (3H, s), 3.14 (3H, s); ^{13}C NMR (100 MHz) δ 174.2, 152.5, 152.0, 140.4, 138.8, 138.7, 136.8, 125.5, 124.9, 119.5, 118.1, 111.4, 110.2, 85.0, 83.6, 72.7, 56.7, 56.6, 51.6, 51.3, 39.0, 38.5; LRMS (ES +ve) m/z (relative intensity) 1079 (100) [2M + Na]$^+$. Anal. Calcd for $C_{22}H_{24}S_2O_{11}$: C, 49.99; H, 4.58. Found: C, 49.81; H, 4.59.

(2*R*,3*R*,4*S*)-2[(4-Methanesulfonyloxy-3-methoxy)phenyl]-3-hydroxymethyl-4-{[(4-methanesulfonyloxy-3-methoxy)phenyl]hydroxy}methyltetrahydrofuran (40b). To a suspension of $LiAlH_4$ (84 mg, 2.21 mmol) in THF (17 mL) at 0 °C (ice bath) was added a solution of furofuranone **38b** (390 mg, 0.74 mmol) in THF (25 mL) dropwise over 10 min and the gray suspension stirred for a further 10 min. Water (0.12 mL), 15% NaOH(aq) (0.12 mL), and water (0.36 mL) were sequentially added dropwise to the reaction mixture at 0 °C,

producing a pale gray/white granular precipitate that was filtered through Celite and washed with THF (20 mL) and EtOAc (30 mL). The filtrate was poured onto brine (60 mL), the organic phase separated, and the aqueous layer extracted with EtOAc (2 × 60 mL). The combined organic layers were washed with brine (60 mL), dried with Na_2SO_4, and concentrated in vacuo to yield an off-white foam (385 mg). Purification was accomplished by flash chromatography on silica gel (3.2 × 9) eluting with EtOAc/hexane (4:1) to give the title compound **40b** (295 mg, 0.55 mmol, 75%) as a white powdery solid along with lactol **41b** (55 mg, 0.10 mmol, 14%) as a white foam. Data for **40b**: mp 162−164 °C; $[\alpha]_D$ +77.3 (*c* 0.43, $CHCl_3$); IR (neat) ν_{max} 3384 br, 1602, 1503 cm^{-1}; ^1H NMR (400 MHz) δ 7.26 (1H, d, J = 3.5 Hz), 7.24 (1H, d, J = 3.5 Hz), 7.08 (1H, s), 6.95 (1H, s), 6.90 (1H, d, J = 8.3 Hz), 6.83 (1H, d, J = 8.3 Hz), 5.07 (1H, d, J = 4.8 Hz), 4.77 (1H, d, J = 10.0 Hz), 3.90 (3H, s), 3.87 (3H, s), 3.74 (1H, t, J = 9.3 Hz), 3.65−3.56 (2H, m), 3.27 (1H, d, J = 9.5 Hz), 3.18 (3H, s), 3.17 (3H, s), 3.06−2.96 (1H, m), 2.80−2.71 (1H, m); ^{13}C NMR (100 MHz) δ 152.2, 151.9, 143.5, 139.9, 138.3, 137.6, 124.9, 124.8, 119.2, 118.6, 111.1, 110.6, 83.2, 73.5, 69.0, 59.7, 56.5 (×2), 52.3, 47.5, 38.8, 38.8; LRMS (ES +ve) *m/z* (relative intensity) 555 (100) $[M + Na]^+$. Anal. Calcd for $C_{22}H_{28}S_2O_{11}$: C, 49.62; H, 5.30. Found: C, 49.90; H, 5.40.

Data for (1*S*,2*R*,5*R*,6*S*)-2-(4-Methanesulfonyloxy-3-methoxy)phenyl-6-(4-methanesulfonyloxy-3-methoxy)-phenyl-3,7-dioxabicyclo[3.3.0]octan-8-ol (41b): $[\alpha]_D$ +74.3 (*c* 0.38, $CHCl_3$); IR (neat) ν_{max} 3488 br, 1737, 1504, 1360, 1173, 1150, 1114 cm^{-1}; ^1H NMR (400 MHz) δ 7.26 (2H, t, J = 8.5 Hz), 7.19 (1H, s), 7.09 (1H, s), 6.97 (2 × 1H, t, J = 8.3 Hz), 4.95 (1H, d, J = 7.0 Hz), 4.87 (1H, br s), 4.79 (1H, d, J = 5.8 Hz), 4.15 (1H, d, J = 9.3 Hz), 3.90 (3H, s), 3.88 (3H, s), 3.90−3.85 (1H, m), 3.18 (3H, s), 3.17 (3H, s), 3.17−3.08 (2H, m); ^{13}C NMR (100 MHz) δ 152.0, 151.8, 143.2, 138.9, 138.1, 137.8, 124.8, 124.7, 119.2, 119.0, 111.3, 111.3, 101.3, 87.2, 81.9, 72.2, 57.2, 56.5, 56.5, 53.5, 38.8, 38.7; LRMS (ES +ve) *m/z* (relative intensity) 553 (50) $[M + Na]^+$, 594 (95) $[M + Na + MeCN]^+$, 1083 (100) $[2M + Na]^+$; HRMS (ES +ve) calcd for $C_{44}H_{52}S_4O_{22}$-Na (dimer) 1083.1725, found 1083.1756.

(1*R*,2*R*,5*R*,6*S*)-2-(4-Methanesulfonyloxy-3-methoxy)-phenyl-6-(4-methanesulfonyloxy-3-methoxy)phenyl-3,7-dioxabicyclo[3.3.0]octane (42b). To an ice-cooled solution of diol **40b** (122 mg, 0.23 mmol), DMAP (2 mg, 0.016 mmol), and Et_3N (39 μL, 0.28 mmol) in CH_2Cl_2 (10 mL) was added Ms_2O (60 mg, 0.35 mmol). After 8 h the reaction had not reached completion, so further Et_3N (64 μL, 0.46 mmol), DMAP (7 mg, 0.057 mmol), and MsCl (80 mg, 46 mmol) were added. After 48 h the reaction was then cooled to 0 °C (ice bath), diluted with CH_2Cl_2 (10 mL), and treated with 1 N HCl(aq) (40 mL). The mixture was allowed to warm to room temperature, the organic phase separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine (40 mL), dried with Na_2SO_4, and concentrated in vacuo to yield crude furofuran as a pale orange oil (204 mg). Purification was accomplished by flash chromatography on silica gel (2.2 × 8) eluting with EtOAc/hexane (2:1) to give the title compound **42b** (93 mg, 0.18 mmol, 78%) as a white powdery solid: mp 137−139 °C (EtOAc/hexane); $[\alpha]_D$ +114.0 (*c* 0.40, $CHCl_3$); IR (neat) ν_{max} 1602, 1504 cm^{-1}; ^1H NMR (400 MHz) δ 7.29 (1H, d, J = 8.3 Hz), 7.28 (1H, d, J = 8.3 Hz), 7.12 (1H, d, J = 1.8 Hz), 7.05 (1H, d, J = 1.8 Hz), 6.92 (1H, dd, J = 8.3, 2.0 Hz), 6.88 (1H, dd, J = 8.3, 1.8 Hz), 4.90 (1H, d, J = 5.8 Hz), 4.51 (1H, d, J = 6.9 Hz), 4.18 (1H, d, J = 9.5 Hz), 3.93 (3H, s), 3.91 (3H, s), 3.93−3.85 (2H, m), 3.43−3.34 (1H, m), 3.28 (1H, t, J = 8.3 Hz), 3.19 (3H, s), 3.18 (3H, s), 2.96−2.89 (1H, m); ^{13}C NMR (100 MHz) δ 152.1, 151.9, 142.2, 139.4, 138.2, 137.7, 125.0, 124.9, 118.9, 118.6, 110.9, 110.8, 87.5, 82.1, 71.6, 70.3, 56.6, 56.6, 55.1, 50.4, 38.8 (×2). Anal. Calcd for $C_{22}H_{26}S_2O_{10}$: C, 51.35; H, 5.09. Found: C, 51.50; H, 5.16.

(+)-Epipinoresinol (3). To a solution of furofuran **42b** (80 mg, 0.16 mmol) in dioxane/MeOH (8 mL, 1:1) was added 3 N KOH(aq) (8 mL). The cloudy mixture was stirred at 50 °C for 40 h and the resulting clear yellow solution diluted with EtOAc (30 mL) and acidified with 2 N HCl(aq) (30 mL). The organic layer was separated, the aqueous layer was extracted with EtOAc (3 × 30 mL), and the combined extracts were washed with brine (30 mL), dried with Na_2SO_4, and concentrated in vacuo to yield a yellow oil (68 mg). Purification was accomplished by flash chromatography on silica gel (3.2 × 4) eluting with EtOAc/hexane (2:3) to give the title compound **3** (56 mg, 0.16 mmol, 98%) as a white powdery solid. Spectroscopic details were consistent with those previously reported:[2f,29] mp 135−137 °C (lit.[29a] 138−139 °C); $[\alpha]_D$ +115.7 (*c* 0.38, $CHCl_3$) (lit.[29c] +118.4, $CHCl_3$; lit.[29a] +110, MeOH); IR (neat) ν_{max} 3474 br, 1628, 1494, 1452, 1395, 1130 cm^{-1}; ^1H NMR (400 MHz) δ 6.97−6.76 (6H, m), 5.65 (1H, s), 5.63 (1H, s), 4.86 (1H, d, J = 5.0 Hz), 4.44 (1H, d, J = 7.0 Hz), 4.12 (1H, d, J = 9.3 Hz), 3.91 (3H, s), 3.89 (3H, s), 3.89−3.80 (2H, m), 3.37−3.28 (2H, m), 2.94−2.87 (1H, m); ^{13}C NMR (100 MHz) δ 147.2, 146.9, 145.8, 145.1, 133.5, 130.8, 119.6, 118.9, 114.7, 109.0, 108.9, 88.2, 82.6, 71.5, 70.2, 56.5, 56.4, 55.0, 50.6; LRMS (ES +ve) *m/z* (relative intensity) 717 (100) $[2M + H]^+$.

(+)-Epieudesmin (4). To a solution of furofuran **3** (26 mg, 0.073 mmol) in AnalaR acetone (5 mL) was added cesium carbonate (35 mg, 0.11 mmol) followed by MeI (44 μL, 0.71 mmol) in one portion. The cloudy mixture was stirred at reflux for 18 h and the resulting clear colorless solution diluted with EtOAc (20 mL) and 1 N HCl(aq) (15 mL). The organic layer was separated, the aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined extracts were washed with brine (20 mL), dried with Na_2SO_4, and concentrated in vacuo to yield a yellow oil (35 mg). Purification was accomplished by flash chromatography on silica gel (2.2 × 3) eluting with EtOAc/hexane (2:3) to give the title compound **4** (26 mg, 0.068 mmol, 93%) as a white powdery solid. Spectroscopic details were consistent with those previously reported:[31] mp 126−127 °C (lit.[31c] 124−125 °C; lit.[31b] 122−125 °C); $[\alpha]_D$ +118.2 (*c* 0.17, $CHCl_3$) (lit.[31b] +113.3 − $CHCl_3$); IR (neat) ν_{max} 2841, 1513, 1446, 1265, 1235, 1141, 1019 cm^{-1}; ^1H NMR (400 MHz) δ 6.95−6.82 (6H, m), 4.88 (1H, d, J = 5.3 Hz), 4.45 (1H, d, J = 7.0 Hz), 4.14 (1H, d, J = 9.5 Hz), 3.91 (3H, s), 3.90 (3H, s), 3.89 (3H, s), 3.88 (3H, s), 3.90−3.83 (2H, m), 3.40−3.29 (2H, m), 2.95−2.89 (1H, m); ^{13}C NMR (100 MHz) δ 149.8, 149.4, 149.2, 148.5, 134.2, 131.5, 119.0, 118.2, 111.6, 111.6, 109.7, 109.5, 88.1, 82.6, 71.5, 70.2, 56.5, 56.4, 56.4, 55.0, 50.7.

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Supporting Information Available: Experimental procedures and characterization data for compounds **1**, **2**, **14**, **15**, **18**−**20**, **22**, **24**−**26**, **28**−**30**, **36a**, **37a**, **38a**, **40a**, **41a**, and **42a**. Copies of the ^1H spectra for compounds **1**−**4**, **11**, **14**−**17**, **20**−**22**, **24**, **25**, **31**, **33**−**35**, **36a/b**−**38a/b**, **41a/b**, and **42a/b**. ^{13}C NMR spectra for compounds **1**−**4** and X-ray data for **1**, **28**, **35**, and **38b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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