C−H Insertion Approach to the Synthesis of *endo,exo*-Furofuranones: Synthesis of (±)-Asarinin, (±)-Epimagnolin A, and (±)-Fargesin

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A series of novel 5-aryl-4-aryloxymethyl-3-diazotetrahydrofuran-2-ones (**12**, **24**, and **35a/b**) have been prepared and found to undergo regio- and stereoselective C−H insertion reactions to afford 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane-8-ones (**18**, **26**, and **36a/b**) with endo,exo stereochemistry. Subsequent reduction of the lactone ring and cyclization of the resulting diols **27** and **37a/b** permitted the synthesis of three *endo,exo*-furofuran lignans: asarinin (**2**), fargesin (**3**), and epimagnolin A (**4**). En route to the key diazo compounds **24** and **35a/b**, a modified procedure for the Ghosez keteniminium−olefin cyclization was developed, which was required to minimize the decomposition of acid-sensitive functional groups such as electron-rich benzylic ethers that were present in the target compounds **2**−**4**.

Introduction

The furofurans are one of the largest subclass of lignans, and their isolation, characterization, biological activity,[1] biosynthesis, and synthesis have been extensively reviewed.[2,3] The majority of furofuran lignans have their 2,6-diaryl substituents on the exo face of the bicyclic core (e.g., **1**), although many compounds with *endo,exo*-aryl substitution (e.g., **2**−**4**) and some compounds with endo,endo substitution are known (Figure 1). A variety of biological activities have been described within the *endo,exo*-furofuran series, with certain compounds having been isolated during the bioassay-guided fractionation of traditional Asian medicines.[4−8] Asarinin (**2**) has been shown to have several significant biological activities, including the following: anti-tumor promotion,[4] anti-allergic activity,[9] and enhancement of the toxicity of certain insecticides.[10,11] Bioassay-guided fractionation of the Chinese crude drugs *shin-i* and *xinyi*, used to treat nasal congestion and headache, has unveiled the Ca^{2+} and PAF antagonist activity of fargesin (**3**)[6,8] and led to the isolation of a new insecticidal furofuran epimagnolin A (**4**).[7]

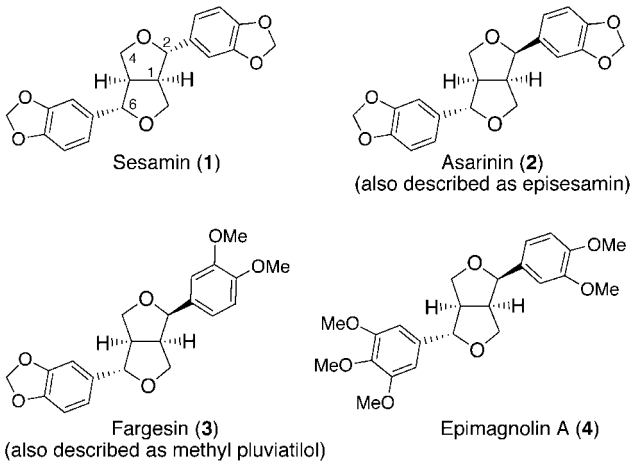

Figure 1. Structures of *exo,exo*- and *endo,exo*-furofuran lignans.

Given the varied biological activities displayed by the furofuran lignans, and interesting structural features there has been substantial interest in their synthesis.[2,3,12−15] The aim of our work was to develop a new strategy for the synthesis of furofuran lignans, which involved the use of an intramolecular C−H insertion reaction to close the C1−C2 σ-bond (Scheme 1).[13,16] Using this approach, we hoped to introduce different aryl groups at the 2- and 6-positions and control the relative

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(1) MacRae, W. D.; Towers, G. H. N. *Phytochemistry* **1984**, *23*, 1207.
(2) For the latest in a series of lignan reviews, see: Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75.
(3) Whiting, D. A. *Nat. Prod. Rep.* **1990**, *7*, 349.
(4) Takasaki, M.; Konoshima, T.; Yasuda, I.; Hamano, T.; Tokuda, H. *Biol. Pharm. Bull.* **1997**, *20*, 776.
(5) Hashimoto, K.; Yanagisawa, T.; Okui, Y.; Ikeya, Y.; Maruno, M.; Fujita, T. *Planta Med.* **1994**, *60*, 124.
(6) Chen, C. C.; Huang, Y. L.; Chen, H. T.; Chen, Y. P.; Hsu, H. Y. *Planta Med.* **1988**, 438.
(7) Miyazawa, M.; Ishikawa, Y.; Kasahara, H.; Yamanaka, J.; Kameoka, H. *Phytochemistry* **1994**, *35*, 611.
(8) Pan, J. X.; Hensens, O. D.; Zink, D. L.; Chang, M. N.; Hwang, S. B. *Phytochemistry* **1987**, *26*, 1377.
(9) Hashimoto, K.; Yanagisawa, T.; Okui, Y.; Ikeya, Y.; Maruno, M.; Fujita, T. *Planta Med.* **1994**, *60*, 124.
(10) Haller, H. L.; McGovran, E. R.; Goodhue, L. D.; Sulivan, W. N. *J. Org. Chem.* **1942**, *7*, 183.
(11) Haller, H. L.; LaForge, F. B.; Sulivan, W. N. *J. Org. Chem.* **1942**, *7*, 185.
(12) Aldous, D. J.; Dutton, W. M.; Steel, P. G. *Synlett* **1999**, 474.
(13) A part of the work described here has been reported in communications: (a) Brown, R. C. D.; Hinks, J. D. *Chem. Commun.* **1998**, 1895. (b) Brown, R. C. D.; Bataille, C. J. R.; Hinks, J. D. *Tetrahedron Lett.* **2001**, *42*, 473.
(14) Hull, H. M.; Jones, R. G.; Knight, D. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1779.
(15) Ohmizu, H.; Ogiku, T.; Iwasaki, T. *Heterocycles* **2000**, *52*, 1399.

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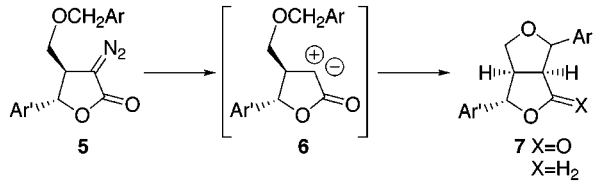
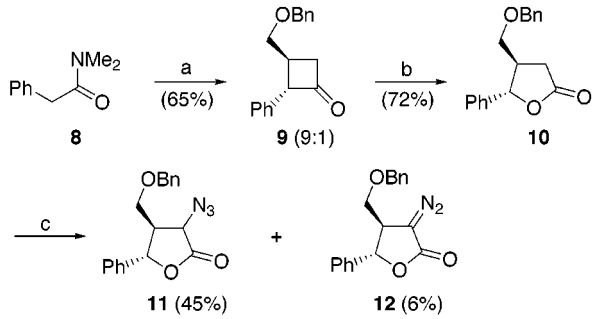
Scheme 1



Scheme 2[a]



[a] Reagents and conditions: (a) Tf_2O, CH_2Cl_2, 2,6-di-*tert*-butylpyridine, allylbenzyl ether; (b) H_2O_2, AcOH; (c) LDA, 4-nitrobenzenesulfonyl azide then pH 7 buffer.

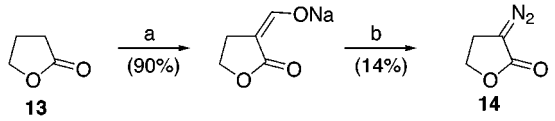
stereochemistry such that either C2-epimer could be produced selectively. At the outset, several issues relating to the key insertion reaction were unclear, not least of all being other potential decomposition pathways of a formal carbene intermediate **6**. Additional uncertainties included the stereoselectivity of the proposed C−H insertion and the synthesis of the pivotal α-diazo-γ-butyrolactone **5**.

To investigate the proposed C−H insertion reaction, we required diazolactone **5**, which would be derived from a diazo-transfer reaction on the corresponding lactone. The desired trans relationship of the lactone substituents would be established in an earlier [2 + 2] keteniminium−olefin cycloaddition reaction.[17,18]

Results and Discussion

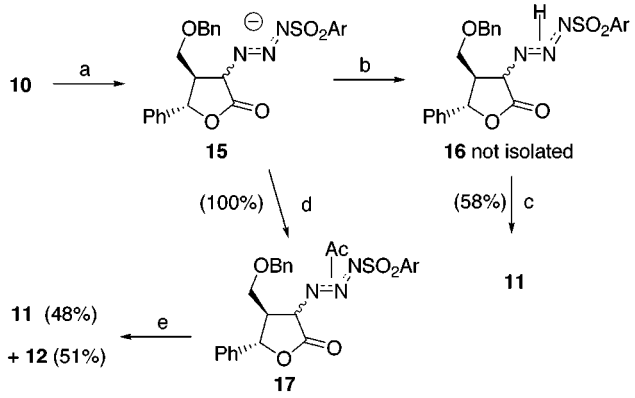
Model Studies. Our investigation began with the synthesis of 3-benzyloxymethyl-2-phenylcyclobutanone (**9**) using the Ghosez [2 + 2] keteniminium−olefin cycloaddition procedure (Scheme 2).[17] The desired cyclic ketone **9** was obtained as a 9:1 mixture of diastereoisomers, which could be separated by preparative normal-phase HPLC (Phenomenex Luna silica column, eluting with ether/hexane 1:9). However, it subsequently became apparent that the benzylic position underwent facile

Scheme 3. Previously Reported Synthesis of an α-diazo-γ-butyrolactone by Schmitz *et al.*[19] [a]



[a] Reagents and conditions: (a) NaOMe, MeO_2CH, Et_2O; (b) TsN_3, CH_3CN.

Scheme 4[a]



[a] Reagents and conditions: (a) LiHMDS, THF, −78 °C, 4-nitrobenzene-sulfonyl azide; (b) AcOH, −78 °C; (c) warm to room temperature; (d) AcCl; (e) DMAP, THF.

epimerisation so separation of the isomers was left until after the next step. Baeyer−Villiger oxidation of **9** to the corresponding lactone **10** was accomplished either with *m*-CPBA or peracetic acid generated in situ, with the latter method returning the lactone in a marginally higher yield. Any of the remaining minor diastereoisomer was removed by column chromatography at this point.

With reasonable quantities of the lactone **10** in hand, we then turned our attention to the diazo-transfer reaction.[16b] Prior to our work, we only knew of one example of an α-diazo-γ-butyrolactone **14**, which had been prepared from γ-butyrolactone (**13**) in low yield using a deformylative method (Scheme 3).[19] Using our substrate **10**, the deformylative diazo-transfer faired no better and gave a mixture of azide **11** and the desired diazo compound **12** in low yield, leading us to consider direct diazo transfer. Results from Evans et al. using imide enolates indicated that it might be possible to prepare the diazolactone **12** by direct diazo transfer to the enolate of **10** using an appropriate sulfonyl azide.[20] However, numerous attempts to effect the diazo-transfer using various metal counterions and workup procedures afforded the azide **11** as the major isolated product (Scheme 2).

In their work, Evans et al. had shown that the intermediate triazine anion, generated upon reaction of a carboximide enolate with a sulfonyl azide, could be protonated at low temperature leading to isolable triazines.[20] Treatment of these triazines with KOAc then led to an azide whereas treatment with pyridine favored the formation of the corresponding diazo compound. Although direct translation of this chemistry to our system failed as the triazine **16** was too unstable to be isolated (Scheme 4), decomposing predominantly to azide **11** upon warming

(16) For a selection of reviews containing examples of cyclisation by metal-catalysed C−H insertion of α-diazocarbonyls: (a) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. (b) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (c) Doyle, M. P.; McKervey, M. A. *J. Chem. Soc., Chem. Commun.* **1997**, 983. (d) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (e) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385. (f) Sulikowski, G. A.; Cha, K. L.; Sulikowski, M. M. *Tetrahedron: Asymmetry* **1998**, *9*, 3145. (g) Taber, D. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, 1045. (h) Taber, D. F. In *Stereoselective Synthesis*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E21a, p 1127. (i) Taber, D. F.; Stiriba, S. E. *Chem. Eur. J.* **1998**, *4*, 990.

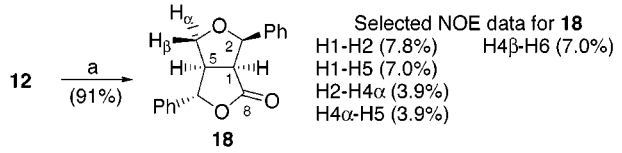
(17) Falmagne, J. B.; Schmit, C.; Escudero, J.; Vanlierde, H.; Ghosez, L. *Org. Synth.* **1990**, *69*, 199.

(18) Ghosez, L.; Marchand-Brynaert, J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 85.

(19) Schmitz, A.; Kraatz, U.; Korte, F. *Chem. Ber.* **1975**, *108*, 1010.

(20) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.

Scheme 5[a]



[a] Reagents and conditions: (a) $Rh_2(OAc)_4$, CH_2Cl_2, rt.

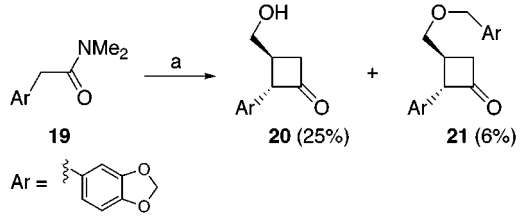
to room temperature, a modification of the method proved more rewarding. It was discovered that the intermediate triazine anion could be trapped by acylation at −78 °C to afford a mixture of isomeric acyl triazines **17**. A study on the decomposition of acyl triazine **17** then revealed that addition of 1 equiv of DMAP in CH_2Cl_2 produced a moderate yield of the desired diazolactone **12**, along with a similar amount of azide **11**, thus permitting further progress toward the furofuranone system. It is worthy to note that the diazolactone **12** was quite robust, surviving chromatography on silica to allow separation of the close-running azide **11** and some 4-nitrophenylsulfonamide byproduct.

The key C−H insertion reaction was then attempted using a catalytic quantity of rhodium(II) acetate dimer, and we were delighted to observe rapid and highly diastereoselective conversion of diazolactone **12** to furofuranone **18** bearing phenyl substituents with the endo,-exo configuration (Scheme 5). The stereochemistry was supported by NOE experiments (see Scheme 5) and by comparison of the spectral data with that reported for analogous furofuranones.[21] More recently, an X-ray structure was obtained for **18**, confirming the proposed relative stereochemistry.[22] The C−H insertion reaction of diazolactone **12** could also be achieved by refluxing **12** in 1,2-dichloroethane (82%), although thermal insertion did not proceed as cleanly as the rhodium-catalyzed reaction and the presence of other minor components was evident from the crude ^{1}H NMR spectrum.

Synthesis of (±)-Asarinin. With the successful synthesis of a model furofuranone **18** having been completed, we embarked upon the synthesis of the *endo,exo*-furofuran lignan (±)-asarinin (**2**) with the expectation that application of the route described above would be fairly straightforward. However, we had underestimated the sensitivity of the electron-rich benzylic ethers to the conditions of the keteniminium−olefin cycloaddition. Attempted formation of the cyclobutanone **21** led to a relatively complex mixture of products, from which the debenzylated cyclobutanone **20** and Friedel−Crafts alkylation products were isolated in modest yield, along with traces of the desired product **21** (Scheme 6). Reasoning that debenzylation might be occurring due to the presence of di-*tert*-butylpyridinium triflate, powdered anhydrous K_2CO_3 was added to the reaction mixture prior to the olefin **22** (Scheme 7). The buffering effect of the K_2CO_3 allowed the desired cycloadduct **21** to be isolated in 56% yield, and this modification may find use in other keteniminium−olefin cycloaddition reactions where acid-sensitive functionalities are present.

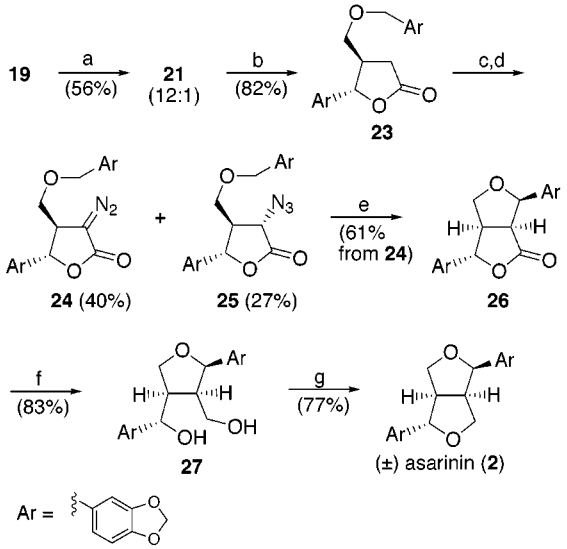
Cyclobutanone **21** was then oxidized to afford the lactone **23**, after removal of the minor diastereoisomer

Scheme 6[a]



[a] Reagents and conditions: (a) (i) Tf_2O, CH_2Cl_2, −25 °C, 2,6-di-*tert*-butylpyridine, CH_2=$CHCH_2OCH_2Ar$ (**22**); (ii) $NaHCO_3$ (aq).

Scheme 7[a]



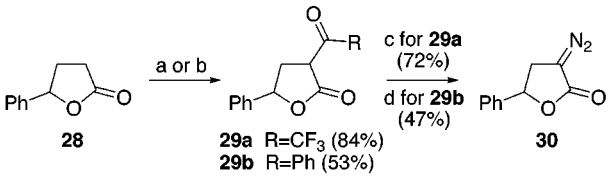
[a] Reagents and conditions: (a) (i) Tf_2O, CH_2Cl_2, −25 °C then K_2CO_3, 2,6-di-*tert*-butylpyridine, **22**; (ii) $NaHCO_3$ (aq); (b) H_2O_2, AcOH; (c) (i) LiHMDS, THF; (ii) 4-nitrobenzenesulfonyl azide, −78 °C; (iii) AcCl; (d) DMAP, THF; (e) $Rh_2(OAc)_4$, CH_2Cl_2; (f) $LiAlH_4$, THF; (g) MsCl, pyr.

by column chromatography, and subsequent diazo-transfer produced the diazolactone **24** in moderate yield. As experienced in the model study, purification of the diazolactone involved a rather tricky chromatographic separation from some recovered parent lactone **23**, azide **25**, and sulfonamide byproducts. C−H insertion of **24** cleanly produced a furofuranone **26** with spectroscopic data in accord with the proposed structure, although the observed melting point (142−143 °C, EtOAc/hexane) was significantly lower than that reported (158-159 °C, EtOAc/hexane).[21] Subsequently, the endo,exo stereochemistry was confirmed by X-ray crystallography.[23]

Various methods for the final transformation of furofuranones to furofurans have been described.[21,24] Reduction of **26** with $LiAlH_4$ followed by acid-promoted cyclization of the resulting diol **27** led to a mixture of diastereoisomeric furofurans and some recovered diol (20%). Asarinin (**2**) was isolated from the mixture in 65% yield, with the major byproduct tentatively assigned as the endo,endo isomer (5%). The diastereoselective conversion of **27** to (±)-asarinin (**2**) was ultimately achieved by exposure of diol **27** to excess methanesulfonyl chloride in pyridine for 17 h.

(21) Stevens, D. R.; Till, C. P.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 185.
(22) Gelbrich, T.; Hursthouse, M. B. *Acta Crystallogr.* **2001**, *E57*, o566.
(23) Coles, S. J.; Hursthouse, M. B. *Acta Crystallogr.* **2001**, *E57*, o544.
(24) Yoshida, S.-i.; Ogiku, T.; Ohmizu, H.; Iwasaki, T. *J. Org. Chem.* **1997**, *62*, 1310.

Scheme 8[a]



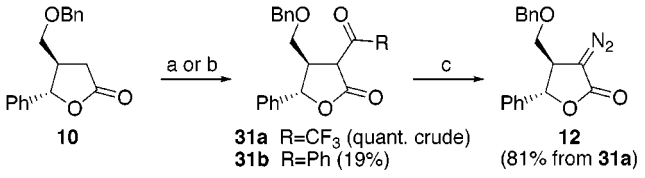
[a] Reagents and conditions: (a) NaH, $F_3CCH_2O_2CCF_3$, DME, MeOH cat.; (b) NaH (4 equiv), $PhCO_2Me$, DME, MeOH cat.; (c) 4-nitrobenzenesulfonyl azide, Et_3N, CH_2Cl_2; (d) 4-nitrobenzenesulfonyl azide, DBU, CH_2Cl_2.

Decarbonylative Diazo-Transfer Strategy. The poor efficiency of the diazo-transfer reactions described above imposed a considerable limitation on the overall approach to furofuran lignans, not just in terms of yield but also introducing a tricky purification of the diazolactones **12** and **24**. To improve the diazo-transfer process, we decided to conduct a survey of more recently introduced decarbonylative diazo-transfer methods using 5-phenyl-γ-butyrolactone (**28**) as a model substrate (Scheme 8).[25,26] Acylation of **28** with either trifluoroacetyl or benzoyl groups was achieved using NaH as the base. The acyl derivatives **29a/b** were then treated with 4-nitrobenzenesulfonyl azide in the presence of base to afford 3-diazo-5-phenylfuran-2-one (**30**) in quite good yields. On the basis of these unoptimized experiments, we settled on the use of Et_3N as base and CH_2Cl_2 as the solvent. The use of excess base, particularly when DBU was employed, was detrimental to the yield of **30**. Control experiments indicated that the base caused decomposition of 4-nitrobenzenesulfonyl azide.

We also examined the use of a supported diazo-transfer reagent to facilitate reaction workup and purification.[27,28] However, sulfonyl azide resin prepared from 20% cross-linked polystyrene following a reported method failed to effect diazo-transfer to the trifluoroacylated lactone **29a** or even to ethyl acetoacetate in our hands.[27] Fortunately sulfonyl azide resin prepared from commercial polystyrenesulfonyl chloride (Argonaut, 1% cross-linked) did function as a diazo-transfer reagent to afford **30** from **29a** in 64% yield, although relatively large amounts of the expensive resin were required and reaction was significantly slower than its homogeneous counterpart. The development of other readily accessible supported diazo-transfer reagents is under investigation in our laboratory and will be reported in due course.[29]

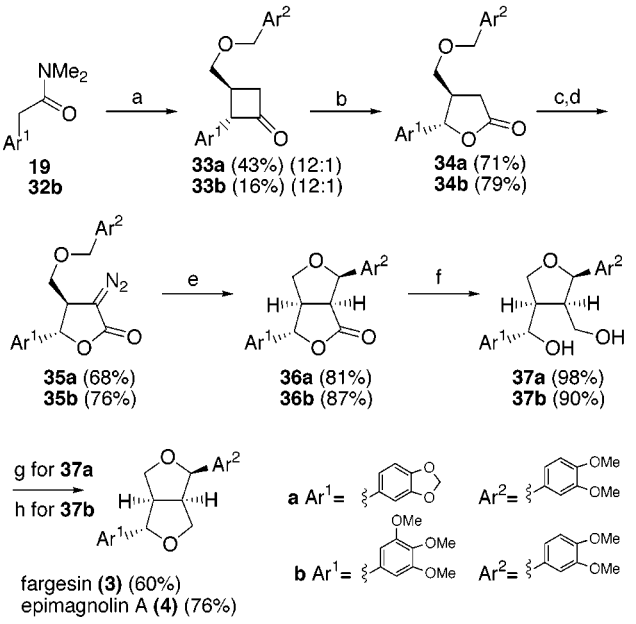
After having established an efficient diazo-transfer protocol for the model lactone **28**, we returned our attention to the 4-benzyloxymethyl substituted lactone **10** (Scheme 9). The acylated lactone **31a** was prepared with quantitative crude mass recovery using NaH or LiHMDS as the base. The trifluoroacyl lactone **31a** was unstable to column chromatography and decomposed fairly rapidly on standing, requiring it to be used directly in diazo-transfer reactions for optimum results. The more stable 3-benzoyl-5-phenylfuran-2-one (**31b**), obtained in modest yield, did not react with the 4-nitrobenzenesulfonyl azide under the conditions developed for the model system, and diazo-transfer reactions with this substrate were not investigated further. The less stable trifluoroacyl derivative **31a** did undergo the desired diazo-transfer efficiently, almost doubling the yield for the conversion of lactone **10** to **12** obtained using our original method. Reaction of **31a** with the sulfonyl azide resin was much slower and was not practically useful for these substrates.

Scheme 9[a]



[a] Reagents and conditions: (a) LiHMDS (2 equiv), $F_3CCH_2O_2CCF_3$, THF; (b) NaH (4 equiv), $PhCO_2Me$, DME, MeOH cat.; (c) 4-nitrobenzenesulfonyl azide, Et_3N, CH_2Cl_2.

Scheme 10[a]



[a] Reagents and conditions: (a) Tf_2O, CH_2Cl_2, −25 °C, 2,6-di-*tert*-butylpyridine, K_2CO_3, $CH_2{=}CHCH_2OCH_2Ar^2$ (**38**); (b) H_2O_2, AcOH; (c) LiHMDS (2 equiv), $CF_3CH_2OCOCF_3$, THF; (d) Et_3N, 4-nitrobenzenesulfonyl azide, CH_2Cl_2; (e) $Rh_2(OAc)_4$, CH_2Cl_2; (f) $LiAlH_4$, THF; (g) MsCl, pyr, CH_2Cl_2; (h) MsCl, Et_3N, DMAP, CH_2Cl_2.

Synthesis of Epimagnolin A and Fargesin. To demonstrate the more general utility of the C−H insertion reaction in the synthesis of *endo*,*exo*-furofuran lignans, the syntheses of two unsymmetrically substituted compounds, fargesin (**3**) and epimagnolin A (**4**), were investigated (Scheme 10). The initial [2 + 2] cycloaddition proved to be more problematic for the compounds with the dimethoxyphenyl and trimethoxyphenyl substituents. However, enough of the cyclobutanones **33a/b** were produced to continue with the synthesis. The ring expansion and diazo-transfer proceeded in good yields to provide the C−H insertion precursors **35a/b**, which underwent efficient cyclization upon exposure to 2 mol % of the rhodium(II) catalyst.

(25) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.
(26) Taber, D. F.; You, K.; Song, Y. *J. Org. Chem.* **1995**, *60*, 1093.
(27) Roush, W. R.; Feitler, D.; Rebek, J. *Tetrahedron Lett.* **1974**, 1391.
(28) Durr, H.; Hauck, G.; Bruck, W.; Kober, H. *Z. Naturforsch., B: Chem. Sci.* **1981**, *36*, 1149.
(29) During the course of this work, a paper appeared describing the synthesis and use of an immobilised diazo-transfer reagent, prepared from a commercial sulfonyl chloride resin: Green, G. M.; Peet, N. P.; Metz, W. A. *J. Org. Chem.* **2001**, *66*, 2509.

Confirmation of stereochemistry for **36b** was achieved by X-ray crystallography.[30]

Careful reduction of the lactones **36a/b** afforded the ring-opened diols **37a/b** in excellent yields, prior to reclosure of the lower tetrahydrofuran ring by treatment with excess methanesulfonyl chloride. The syntheses of fargesin (**3**) and epimagnolin A (**4**) were thus completed in 10% and 6% overall yield, respectively.

Summary. A number of novel diazolactones have been prepared and shown to undergo highly efficient and diastereoselective C−H insertion reactions to give *endo,exo*-furofuranones. The scope of the methodology in the context of furofuran lignan synthesis was demonstrated by the synthesis of three lignans: (±)-asarinin, (±)-epimagnolin A, and (±)-fargesin. During the course of this work, we have developed modified conditions for the [2 + 2] keteniminium−olefin cycloaddition to allow the use of acid-sensitive substrates (3,4-methylenedioxybenzyl ethers), although for certain compounds (di- and trimethoxybenzyl ethers) the yields of cycloadducts are still modest. Our future work in this area will focus on the development of an asymmetric synthesis of γ-butyrolactones, and further investigation of the synthesis and reactions of α-diazolactones and lactams.

Experimental Section

General Methods. ^{1}H NMR and ^{13}C NMR were recorded on 300, 360, or 400 MHz spectrometers (300, 360, or 400 MHz, ^{1}H NMR respectively and 75, 90, or 100 MHz, ^{13}C NMR, respectively) in deuteriochloroform ($CDCl_3$) with chloroform (δ 7.26 ppm ^{1}H, δ 77.5 ppm ^{13}C) as the internal standard unless stated otherwise. Infrared (IR) spectra are reported in wavenumbers (cm^{-1}). Melting points were obtained in open capillary tubes and are uncorrected. All nonaqueous reactions were carried out under an inert atmosphere, in oven-dried glassware. The following solvents were distilled before use: THF (from Na/benzophenone) and CH_2Cl_2 (from CaH_2) and where appropriate, other reagents and solvents were purified by standard techniques.[31] *p*-nitrobenezenesulfonyl azide was prepared according to literature procedures.[32,33] TLC was performed on glass-backed plates coated with silica gel 60 with an F_{254} indicator; the chromatograms were visualized under UV light and/or by staining with phosphomolybdic acid (20% solution in ethanol) or $KMnO_4$. Flash column chromatography was performed with 40−63 μm silica gel (Merck) and column dimensions are quoted in cm (width × height).

***N,N*-Dimethyl-2-phenylacetamide (8).** To a solution of phenylacetyl chloride (4.0 mL, 30 mmol) in CH_2Cl_2 (40 mL) at 0 °C (ice/salt bath) was added a solution of dimethylamine hydrochloride (5.87 g, 72 mmol) in aqueous sodium hydroxide solution (3.2 g NaOH in 18 mL of water) by dropwise addition. The reaction mixture was allowed to warm to room temperature and stirred overnight. After dilution with CH_2Cl_2 (40 mL), the reaction mixture was washed sequentially with 2 N HCl (40 mL), saturated $NaHCO_3$ (aq) (40 mL), water (40 mL), and brine (40 mL), dried with $MgSO_4$, and concentrated in vacuo to give the title compound **8** (4.81 g, 29 mmol, 98%) as a viscous colorless oil that solidified on standing to a white solid; spectroscopic details are consistent with those observed in the literature:[34] bp 170−173 °C (0.2 mmHg); mp 37−39 °C (lit.[35] mp 38−40 °C); IR ν_{max} (neat) 1652 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.98 (s, 3H), 3.00 (s, 3H), 3.73 (s, 2H), 7.22−7.36 (m, 5H).

(2*S, 3*S**)-3-[(Benzyloxy)methyl]-2-phenylcyclobutanone (9).** To a solution of *N,N*-dimethyl-2-phenylacetamide **(8)** (1.63 g, 10.0 mmol) in CH_2Cl_2 (20 mL) at −25 °C (internal, CO_2(s)/acetone) was added freshly distilled Tf_2O (2.0 mL, 12 mmol) at such a rate that the temperature did not rise above −20 °C. The colorless homogeneous reaction mixture was stirred at −20 °C for 10 min before addition of a mixture of 2,6-di-*tert*-butylpyridine (2.7 mL, 12 mmol) and allylbenzyl ether[36] (2.3 mL, 15 mmol) in CH_2Cl_2 (15 mL) over a period of 10 min. The reaction was then allowed to warm to room temperature and stirred for 13 h (the formation of the cyclic iminium species was monitored by IR; υ_{max} 1734 cm^{-1}). The mixture was diluted with CH_2Cl_2 (10 mL) and treated with sat. $NaHCO_3$ (aq) (20 mL) with vigorous stirring for 1 h. The organic layer was separated and the aqueous extracted with CH_2Cl_2 (3 × 20 mL), and the combined extracts were washed with water (30 mL) and brine (30 mL), dried with $MgSO_4$, and concentrated in vacuo to yield a orange oil (6.2 g). Purification was accomplished by flash chromatography on silica gel (5 × 10) eluting with Et_2O/hexane (1:9 then 1:4) to give the title compound **9** (1.73 g, 6.5 mmol, 65%) as a colorless oil (9:1 mixture of diastereoisomers). NMR data are given for the major diastereoisomer: IR ν_{max} (neat) 1779 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.81−2.94 (m, 1H), 3.01−3.13 (m, 2H), 3.78 (d, J = 9.0 Hz, 2H), 4.39 (d, J = 7.4 Hz, 1H), 4.62 (s, 2H), 7.21−7.48 (m, 10H); ^{13}C NMR (100 MHz) δ 206.2, 138.2, 136.1, 128.8, 128.7, 128.0, 127.8, 127.3, 127.2, 73.4, 72.1, 66.6, 47.4, 32.5; LRMS (CI, ammonia) *m/z* (relative intensity) 284 (10) [M + NH_4]$^+$, 91 (100) [$PhCH_2$]$^+$, 175 (15) [M − $PhCH_2$]$^+$; HRMS (EI) calcd for $C_{18}H_{18}O_2$ 266.1307, found 266.1303.

(4*R,5*S**)-5-Phenyl-4-[(benzyloxy)methyl]tetrahydro-2-furanone (10).** To a solution of cyclobutanone **9** (1.50 g of an approximately 9:1 mixture of diastereoisomers, 5.6 mmol) in glacial acetic acid (15 mL) at 0 °C (ice bath) was added a 30% aqueous solution of hydrogen peroxide (1.9 mL, 17.2 mmol) dropwise over 5 min and the reaction maintained at 4 °C for 18 h. The reaction mixture was then diluted with Et_2O (40 mL) and quenched with a saturated aqueous solution of sodium bicarbonate (40 mL). The two phases were separated and the organic layer washed with saturated $NaHCO_3$ (aq) (3 × 30 mL) before the combined base washes were extracted with Et_2O (3 × 40 mL). The combined organic layers were then washed with water (50 mL) and brine (50 mL), dried with $MgSO_4$, and concentrated in vacuo to yield a crude yellow oil (1.2 g). Purification and separation from the minor diastereoisomer was accomplished on silica gel (4.5 × 5.5) eluting with Et_2O/hexane (3:7) to yield the title compound **10** (1.08 g, 4.1 mmol, 72%) as a colorless oil: IR ν_{max} (neat) 1779 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.62−2.78 (m, 3H), 3.45−3.61 (m, 2H), 4.53 (d, J = 12.0 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 5.39 (d, J = 5.5 Hz, 1H), 7.12−7.45 (m, 10H); ^{13}C NMR (100 MHz) δ 176.5, 138.9, 137.8, 128.9, 128.7, 128.0, 127.8, 125.8, 82.7, 73.4, 68.3, 44.7, 31.7; LRMS (CI, ammonia) *m/z* (relative intensity) 300 (3) [M + NH_4]$^+$, 91 (100) [$PhCH_2$]$^+$, 191 (25) [M − $PhCH_2$]$^+$; HRMS (EI) calcd for $C_{18}H_{18}O_3$ 282.1256, found 282.1259.

(4*R,5*S**) 3-Diazo-5-phenyl-4-[(benzyloxy)methyl]tetrahydro-2-furanone (12) Following the Original Procedure.** LiHMDS (400 μL of a 0.93M solution in THF, 0.37 mmol) was dissolved in dry THF (2 mL) and cooled to −78 °C under nitrogen. A precooled solution of lactone **10** (100 mg, 0.35 mmol) in THF (2 mL) was added via a cannula and the reaction mixture stirred at −78 °C. After 45 min, a precooled solution of the *p*-nitrobenzenesulfonyl azide (84 mg, 0.37 mmol) in THF (2 mL) was added via cannula and the resulting deep red solution stirred for 10 min. Acetyl chloride (110 mg, 100 mL, 1.4 mmol) was added, and the reaction was allowed to warm slowly to room temperature. The red coloration dissipated within 5 min of adding the acetyl chloride. The reaction mixture was diluted with Et_2O (30 mL) and washed with water and brine (30 mL) each before drying ($MgSO_4$). Removal of

(30) Light, M. E.; Hursthouse, M. B. *Acta Crystallogr.* **2001**, *E57*, o514.
(31) Perin, D. D.; Armarego, W. L. F. *Purification of laboratory chemicals*, 3rd ed.; Butterworth-Heinemann Ltd.: Oxford, 1994.
(32) Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *Synth. Commun.* **1987**, *17*, 1709.
(33) Rector, D. L.; Harman, R. E. *J. Org. Chem.* **1966**, *31*, 2837.
(34) Mårtensson, O.; Nilsson, E. *Acta Chem. Scand.* **1960**, 1129.
(35) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 4327.
(36) Arndt, H. C.; Carroll, S. A. *Synthesis* **1979**, 202.

solvent in vacuo afforded **(4*R**,5*S**)-3-[(*E*)-3-Acetyl-3-[(4-nitrophenyl)sulfonyl]-1-triazenyl]-5-phenyl-4-[(benzyloxy)methyl]tetrahydro-2-furanone (17)**, apparently unstable to silica gel, was isolated as a foam (200 mg, quant.). The compounds inherent instability required its immediate use in the next reaction. Thus, a sample of the material (25 mg, 0.05 mmol) was dissolved in THF (2 mL) and treated with DMAP (7 mg, 0.06 mmol) and the reaction stood at 4°C overnight. The solvent was removed and the crude mixture purified by radial chromatography on silica gel plate (2 mm) eluting with EtOAc/hexane (1:4). The title compound **12** was isolated as a pale yellow solid (8 mg, 0.026 mmol, 51%) along with the azide byproduct **11**, which was also isolated as an oil (8 mg, 0.024 mmol, 48%). Data for diazolactone **12**: mp 57−59 °C (Et_2O/hexane); IR ν_{max} (neat) 2103, 1707 cm^{-1}; ^1H NMR (400 MHz) δ 3.72−3.85 (m, 3H), 4.60 (s, 2H), 5.18 (d, J = 4.0 Hz, 1H), 7.30−7.43 (m, 10H); ^{13}C NMR (100 MHz) δ 169.6, 139.3, 137.6, 129.4, 129.3, 129.0, 128.5, 128.1, 125.8, 80.8, 74.1, 71.1, 45.8. Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.09; H, 5.23. Found: C, 70.01; H, 5.36. Data for **(3*R*,4*R*,5*S*)-3-Azido-5-phenyl-4-[(benzyloxy)methyl]tetrahydro-2-furanone (11)**: IR ν_{max} (CH_2Cl_2) 2116, 1788 cm^{-1}; ^1H NMR (300 MHz) δ 2.36 (ddt, J = 11.2, 10.3, 2.6 Hz, 1H), 3.48 (dd, J = 10.3, 2.6 Hz, 1H), 3.63 (dd, J = 10.3, 2.9 Hz, 1H), 4.54 (d, J = 11.8 Hz, 1H), 4.64 (d J = 12.1 Hz, 1H) superimposed on (d, J = 11.0 Hz, 1H), 5.34 (d, J = 11.9 Hz, 1H), 7.15−7.55 (m, 10H); ^{13}C NMR (75 MHz) δ 172.6, 137.4, 136.5, 129.2, 128.9, 128.7, 128.1, 126.3, 79.6, 73.4, 63.0, 58.8, 51.8; LRMS (EI) *m*/*z* (relative intensity) 323 (10) $[M]^{\bullet+}$, 91 (100) $[PhCH_2]^{\bullet+}$.

(4*R,5*S**)-5-Phenyl-3-diazo-4-[(benzyloxy)methyl]tetrahydro-2-furanone (12) by a Detrifluoroacylative Approach.** To a solution of hexamethyldisilylazane (1.1 mL, 5.02 mmol) in THF (15 mL) at 0 °C (ice/salt bath) was added *n*-BuLi (3.2 mL of a 1.6 M solution in hexanes, 5.16 mmol) dropwise over 5 min. The colorless solution was stirred at 0 °C for 10 min before cooling to −78 °C (CO_2(s)/acetone bath) and adding a solution of lactone **10** (710 mg, 2.51 mmol) in THF (25 mL) dropwise over 10 min. The pale yellow reaction mixture was allowed to stir at −78 °C for 45 min, 2,2,2-trifluoroethyltrifluoroacetate (0.37 mL, 2.76 mmol) was added dropwise over 2 min, and the reaction mixture was warmed to room temperature over 100 min. The reaction mixture was acidified to pH = 4 with an aqueous solution of 1 N HCl and diluted with Et_2O (20 mL) before the organic layer was separated and the aqueous extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried with $MgSO_4$, and concentrated in vacuo to yield **(4R*, 5S*)-5-phenyl-4-[(benzyloxy)methyl]-3-(trifluoroacetyl)tetrahydro-2-furanone (31a)** (950 mg, quantitative) as a crude cream solid − this crude material was used directly in the subsequent diazo-transfer reaction: IR ν_{max} (neat) 1784, 1747 cm^{-1}; ^1H NMR (300 MHz) δ 3.38−3.67 (m, 3H), 4.47−4.66 (m, 3H), 5.38 (d, J = 8.4 Hz, 1H), 7.18−7.45 (m, 10H); ^{13}C NMR (75 MHz) δ 177.5, 137.9, 137.4, 129.4, 129.0, 128.9, 128.8, 128.3, 128.2, 126.9, 125.8, 83.1, 73.6, 65.3, 46.2, 45.5. Thus, to a solution of crude trifluoroacylated lactone **31a** (2.20 mmol thereoretical) in bench grade CH_2Cl_2 (30 mL) at room temperature was added 4-nitrobenzenesulfonyl azide (0.65 g, 2.86 mmol) followed by NEt_3 (0.40 mL, 2.86 mmol) and the yellow reaction mixture was left to stir for 18 h. The mixture was poured onto water (30 mL) and diluted with CH_2Cl_2 (10 mL), the organic layer was separated and the aqueous extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried with $MgSO_4$ and concentrated in vacuo to yield a crude yellow oil (3.2 g). Purification was accomplished by flash chromatography on silica gel (5.5 × 6) eluting with Et_2O/hexane (2:3) to yield the title compound **12** (550 mg, 1.78 mmol, 81% − from lactone **10**) as a pale yellow solid. Spectroscopic data reported above.

(1*S,2*R**,5*R**,6*S**)-2,6-Diphenyl-3,7-dioxabicyclo[3.3.0]-octan-8-one (18).** To a solution of diazo lactone **12** (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 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 on silica gel (1.5 × 7) eluting with Et_2O/hexane (2:3) to yield the title compound **18** (80 mg, 0.29 mmol, 91%) as a white crystalline solid: mp 121−123 °C (Et_2O/hexane); IR ν_{max} (neat) 1773 cm^{-1}; ^1H NMR (400 MHz) δ 3.27 (ddd, J = 9.4, 6.5, 5.5 Hz, 1H), 3.61 (t, J = 8.9 Hz, 1H), 3.96 (dd, J = 9.9, 5.0 Hz, 1H), 4.38 (d, J = 9.4 Hz, 1H), 5.12 (d, J = 8.9 Hz, 1H), 5.33 (d, J = 6.5 Hz, 1H), 7.32−7.45 (m, 10H); ^{13}C NMR (100 MHz) δ 174.7, 140.0, 136.5, 129.4, 129.2, 129.0, 126.7, 125.8, 85.8, 84.4, 72.4, 51.9, 51.6; LRMS (CI, ammonia) *m*/*z* (relative intensity) 281 (65) $[M + H]^+$, 298 (100) $[M + NH_4]^+$, 263 (20) $[M - H_2O]H^+$. Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.27; H, 5.79.

***N*,*N*-Dimethyl-2-(3,4-methylenedioxyphenyl)acetamide (19).** 3,4-Methylenedioxyphenylacetic acid (4.83 g, 26.7 mmol) was suspended in dry CH_2Cl_2 (25 mL) and treated with oxalyl chloride (3.72 g, 2.57 mL, 29.4 mmol) followed by DMF (1 drop). The reaction was stirred until gaseous evolution ceased and the starting acid was fully dissolved. The crude acid chloride (IR ν_{max} 1790 cm^{-1}) was cooled on ice before adding dimethylamine (25% aqueous solution, 10.8 g, 11.5 mL, 60 mmol) by dropwise addition over a period of 20 min. The solution was stirred overnight at room temperature before the reaction mixture was washed with saturated $NaHCO_3$ (aq) (50 mL). Extraction of the aqueous phase with CH_2Cl_2 (3 × 30 mL) was followed by washing of the combined organic layers with brine (20 mL) and drying with $MgSO_4$. The crude product was purified by bulb-to-bulb distillation (2 mmHg, oven temperature >250 °C) to give the title compound **19** as a viscous oil that solidified on standing (4.90 g, 23.7 mmol, 88%): mp 49−52 °C; IR ν_{max} (CH_2Cl_2) 1641 cm^{-1}; ^1H NMR (300 MHz) δ 2.97 (s, 3H), 3.01 (s, 3H), 3.62 (s, 2H), 5.94 (s, 2H), 6.68 (dd, J = 7.7, 1.0 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.77 (bs, 1H); ^{13}C NMR (75 MHz) δ 171.3, 147.9, 146.5, 128.8, 121.9, 109.4, 108.5, 101.1, 40.7, 37.8, 35.8; LRMS (ES +ve) *m*/*z* (relative intensity) 208 (100) $[M + H]^+$, 415 (20) $[2M + H]^+$.

(2*S,3*S**)-2-(3,4-Methylenedioxy)phenyl-3-[[(3,4-methylenedioxybenzyl)oxy]methyl]cyclobutanone (21).** *N*,*N*-Dimethyl-2-(3,4-methylenedioxyphenyl)acetamide (**19**) (517 mg, 2.5 mmol) was dissolved in CH_2Cl_2 (10 mL) under nitrogen. The solution was cooled to −20 °C (internal) and treated with trifluoromethanesulfonic anhydride (0.47 mL, 2.8 mmol) at such a rate that the reaction temperature did not rise above −15 °C. The yellow homogeneous mixture was stirred at −20 °C for 10 min before the addition of anhydrous K_2CO_3 (386 mg, 2.8 mmol) in one portion followed by a mixture of 2,6-di-*tert*-butylpyridine (0.75 mL, 3.3 mmol) and 4-[(allyloxy)-methyl]-1,2-methylenedioxybenzene (**22**) (0.576 g, 3.0 mmol) in CH_2Cl_2 (10 mL) over a period of 10 min. The reaction was stirred at −20 °C for 10 min and allowed to warm to 10 °C. After 1 h at 10 °C, the solution was treated with saturated $NaHCO_3$ (aq) (20 mL) and stirred for a further 1 h at room temperature. The reaction was diluted with CH_2Cl_2 (20 mL) and sequentially washed with water and brine (30 mL each) before drying with $MgSO_4$. After removal of solvent, the crude product was purified by chromatography on silica gel (3 × 6) eluting with EtOAc/hexane (1:4). The title compound **21** was isolated as a colored oil and as a mixture of diastereomers in the ratio of 12 (trans)/1 (cis) (0.497 g, 1.40 mmol, 56%): IR ν_{max} (CH_2Cl_2) 1779 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 2.68−2.84 (m, 1H), 3.04 (d, J = 8.4 Hz, 2H), 3.73 (d, J = 5.5 Hz, 2H), 4.26 (d, J = 7.8 Hz, 1H), 4.51 (s, 2H), 5.86 (s, 2H), 5.88 (s, 2H), 6.67−6.83 (m, 5H), 6.85 (s, 1H); ^{13}C NMR (75 MHz, C_6D_6) δ 206.0, 147.9, 147.2, 147.2, 146.6, 131.9, 129.7, 121.3, 120.3, 108.4, 108.1, 107.8, 101.1, 101.0, 73.1, 71.6, 66.2, 47.0, 32.8; HRMS (EI) calcd for $C_{20}H_{18}O_6$ 354.1103, found 354.1099.

4-[(Allyloxy)methyl]-1,2-methylenedioxybenzene (22). Sodium hydride (60% dispersion in mineral oil, 5.04 g, 87.5 mmol) was washed with dry pentane in oven dried apparatus while under nitrogen. Dry DMF (55 mL) was added to the resulting solid. To this suspension was added 3,4-methylene-

dioxybenzyl alcohol (10.65 g, 70 mmol) by dropwise addition and the mixture stirred at room temperature for 45 min. KI (2.32 g, 14 mmol) was added prior to the addition of a solution of allyl bromide (9.46 g, 6.76 mL, 78 mmol) in DMF (25 mL), which was added over a period of 10 min. The resulting mixture was left to stir for 16 h at room temperature before pouring into an aqueous solution of NaCl (20 g in 250 mL) and extracting with Et_2O (3 × 100 mL). The combined extracts were washed with water and brine (100 mL each) and dried with $MgSO_4$. Purification was effected by vacuum distillation to provide the title compound **22** (12.1 g, 63 mmol, 90%) as a colorless oil: bp 84−88 °C (0.4 mmHg); IR ν_{max} (CH_2Cl_2) 1503, 1490 cm^{-1}; ^1H NMR (300 MHz) δ 4.01 (dt, J = 5.9, 1.1 Hz, 2H), 4.43 (s, 2H), 5.22 (dq, J = 10.3, 1.1 Hz, 1H), 5.31 (dq, J = 16.9, 1.5 Hz, 1H), 5.96 (s, 2H) superimposed on 5.89−6.02 (m, 1H), 6.77−6.83 (m, 2H), 6.87 (bs, 1H); ^{13}C NMR (75 MHz) δ 147.9, 147.2, 134.9, 132.3, 121.5, 117.3, 108.7, 108.2, 101.1, 72.1, 71.0.

(4*R,5*S**)-5-(3,4-Methylenedioxy)phenyl-4-[[(3,4-methylenedioxybenzyl)oxy]methyl]tetrahydro-2-furanone (23).** The cyclobutanone **21** (2.06 g of an approximately 12:1 mixture of diastereoisomers, 5.81 mmol) was dissolved in glacial acetic acid (20 mL) and cooled over an ice bath during the addition of 30% hydrogen peroxide solution (1.64 mL, 14 mmol). The reaction was stirred at 0 °C for 4 h before partitioning between 2 M sodium hydroxide (aq) (150 mL) and EtOAc (100 mL). After separation, the aqueous phase was re-extracted with EtOAc (50 mL), and the combined organic phases were washed with sodium metabisulfite (aq), water, and brine (50 mL each) and finally dried with $MgSO_4$. The crude material was purified and separated from the minor diastereoisomer by chromatography on silica gel (6 × 4.5) eluting with EtOAc/hexane (1:4) to provide the title compound **23** (1.76 g, 4.76 mmol, 82%) as a colorless oil: IR ν_{max} (CH_2Cl_2) 1778 cm^{-1}; ^1H NMR (300 MHz) δ 2.56−2.76 (m, 3H), 3.45 (dd, J = 9.6, 4.0 Hz, 1H), 3.51 (dd, J = 9.6, 4.4 Hz, 1H), 4.40 (d, J = 11.8 Hz, 1H), 4.46 (d, J = 11.8 Hz, 1H), 5.23 (d, J = 6.3 Hz, 1H), 5.95 (s, 4H), 6.70−6.82 (m, 6H); ^{13}C NMR (75 MHz) δ 176.1, 148.3, 148.1, 148.0, 147.5, 132.5, 131.6, 121.6, 119.8, 108.6, 108.4, 108.3, 106.4, 101.5, 101.3, 83.2, 73.3, 68.0, 44.8, 32.0; LRMS (EI) *m/z* (relative intensity) 370 (40) $[M]^{\bullet+}$, 135 (100) $[ArCH_2]^{\bullet+}$; HRMS (EI) calcd for $C_{20}H_{18}O_7$ 370.1053, found 370.1035. Anal. Calcd for $C_{20}H_{18}O_7$: C, 64.87; H, 4.89. Found: C, 64.73; H, 4.84.

(4*R,5*S**)-5-(3,4-Methylenedioxy)phenyl-3-diazo-4-[[(3,4-methylenedioxybenzyl)oxy]methyl]tetrahydro-2-furanone (24).** LiHMDS (0.8 mL of a 0.74 M solution in THF, 0.59 mmol) was dissolved in dry THF (3 mL) while under an atmosphere of nitrogen and the solution cooled to −78 °C. To this was added a precooled solution of the lactone **23** (200 mg, 0.54 mmol) in dry THF (3 mL) via a cannula. The yellow solution was stirred at −78 °C for 45 min before treating with a solution of *p*-nitrobenzenesulfonyl azide (135 mg, 0.59 mmol) in dry THF (3 mL) and stirring for a further 10 min. Acetyl chloride (0.153 mL, 2.2 mmol) was added and the reaction allowed to warm to room temperature. The mixture was diluted with Et_2O (25 mL) and water (25 mL) and the organic phase separated and washed with brine (25 mL) before drying with $MgSO_4$. The crude material was partially purified by rapid filtration through silica gel, eluting with EtOAc/hexane (1:1) to give **(4*R**,5*S**)-3-[(*E*)-3-acetyl-3-[(4-nitrophenyl)-sulfonyl]-1-triazenyl]-5-(3,4-methylenedioxy)phenyl-4-[[(3,4-methylenedioxybenzyl)oxy]methyl]tetrahydro-2-furanone** (303 mg, 0.473 mmol, 88%) as a yellow oil: IR ν_{max} (CH_2Cl_2) 1783, 1733, 1609, 1372 cm^{-1}; LRMS (ES +ve) *m/z* (relative intensity) 658 (100) $[M + NH_4]^+$. A portion of the oil (251 mg, 0.39 mmol) was dissolved in THF (5 mL) and treated with DMAP (53 mg, 0.43 mmol) and the reaction stirred at room temperature for 16 h. The solvent was removed, and the crude material was purified by chromatography on silica gel (4.5 × 3) eluting with EtOAc/hexane (1:4) providing the title compound **24** as a colored oil (71 mg, 0.179 mmol, 46% from the triazine) along with the azide **25** (50 mg, 0.122 mmol, 31% from the triazine). Data for diazolactone **24**: IR ν_{max} (CH_2Cl_2) 2102, 1736 cm^{-1}; ^1H NMR (300 MHz) δ 3.62−3.73 (m, 3H), 4.47 (s, 2H), 5.03−5.07 (m, 1H), 5.98 (s, 2H), 5.99 (s, 2H), 6.60−6.80 (m, 6H); ^{13}C NMR (75 MHz) δ 169.2, 148.5, 148.3, 148.1, 147.7, 132.6, 131.1, 121.7, 119.6, 108.5, 108.4, 106.1, 101.6, 101.3, 80.6, 73.6, 70.3, 53.0, 45.4; LRMS (EI) *m/z* (relative intensity) 368 (40) $[M - N_2]^+$; (ES +ve) 414 (80) $[M + NH_4]^+$; 810 (100), $[2M + NH_4]^+$. Data for **(4*R**,5*S**)-5-(3,4-methylenedioxy)phenyl-3-azido-4-[[(3,4-methylenedioxybenzyl)oxy]methyl]tetrahydro-2-furanone (25).** Isolated from the reaction mixture as a 5:1 mixture of diastereoisomers: IR ν_{max} (CH_2Cl_2) 2113, 1784 cm^{-1}; ^1H NMR (300 MHz) δ 2.31 (dt, J = 10.7, 2.9 Hz, 1H), 3.41 (dd, J = 10.3, 2.6 Hz, 1H), 3.57 (dd, J = 10.3, 2.9 Hz, 1H), 4.41 (d, J = 11.8 Hz, 1H), 4.50 (d, J = 11.8 Hz, 1H), 4.56 (d, J = 11.4 Hz, 1H), 5.19 (d, J = 9.9 Hz, 1H), 5.95 (s, 4H), 6.65−6.85 (m, 6H); ^{13}C NMR (75 MHz) 172.4, 148.6, 148.4, 148.2, 147.8, 131.1, 130.0, 122.0, 120.8, 108.8, 108.4, 106.7, 101.6, 101.4, 79.8, 73.4, 62.9, 59.0, 51.6; LRMS (ES +ve) *m/z* (relative intensity) 429 (100) $[M + NH_4]^+$, 840 (95) $[2M + NH_4]^+$.

(1*S,2*R**,5*R**,6*S**)-2-(3,4-Methylenedioxy)phenyl-6-(3,4-methylenedioxy)phenyl-3,7-dioxabicyclo[3.3.0]octan-8-one (26).** The diazo compound **24** (160 mg, 0.404 mmol) was dissolved in CH_2Cl_2 (3 mL) and the solution treated with $Rh_2(OAc)_4$ (5 mg, 0.01 mmol) with stirring at room temperature. After 1 h, the reaction was evaporated to dryness and the resultant residue purified by chromatography on silica gel (3 × 6) eluting with EtOAc/hexane (3:7). The product, initially isolated as a foam, was crystallized from EtOAc/hexane to give the title compound **26** as a white solid (91 mg, 0.247 mmol, 61%): mp 140−141 °C (EtOAc/hexane) (lit.[21] mp 158−159 °C, EtOAc/hexane); IR ν_{max} (CH_2Cl_2) 1774 cm^{-1}; ^1H NMR (300 MHz) δ 3.21 (ddd, J = 9.0, 6.7, 4.5 Hz, 1H), 3.54 (app. t, J = 6.9 Hz, 1H), 3.90 (dd, J = 9.8, 4.6 Hz, 1H), 4.28 (d, J = 9.7 Hz, 1H), 5.02 (d, J = 8.8 Hz, 1H), 5.19 (d, J = 6.6 Hz, 1H), 5.99 (s, 4H), 6.81−6.88 (m, 6H); ^{13}C NMR (75 MHz) δ 174.4, 148.5, 148.2, 148.0, 147.8, 133.3, 130.0, 120.0, 119.6, 108.6, 108.4, 106.8, 106.1,101.5, 101.3, 85.7, 83.9, 71.8, 51.7, 51.3; LRMS (EI) *m/z* (relative intensity) 368 (100) $[M]^{\bullet+}$; HRMS (EI) calcd for $C_{20}H_{16}O_7$ 368.0896, found 368.0886.

(2*R,3*R**,4*S**)-2[(3,4-Methylenedioxy)phenyl]-3-hydroxymethyl-4-[[(3,4-methylenedioxy)phenyl]hydroxy]-methyltetrahydrofuran (27).** $LiAlH_4$ (57 mg, 1.5 mmol) was suspended in THF (2 mL) under nitrogen. A solution of the furofuranone derivative **26** (56 mg, 0.15 mmol) in dry THF (3 mL) was added and the reaction warmed to reflux for 1 h. After cooling, the reaction mixture was treated with wet THF/MeOH followed by 2.0 M HCl (30 mL) before extraction with EtOAc (2 × 30 mL). The combined extracts were washed with brine (30 mL) and dried with $MgSO_4$. The crude material was filtered through silica prior to purification by radial chromatography eluting with EtOAc/hexane (4:6). The title compound **27** was isolated as a white solid (47 mg, 1.26 mmol, 83%): mp 153−155 °C (EtOAc/hexane); IR ν_{max} (CH_2Cl_2) 3604, 3459, 1504 cm^{-1}; ^1H NMR (300 MHz) δ 2.65 (tt, J = 5.9, 2.9 Hz, 1H), 2.97 (qd, J = 9.6, 6.2 Hz, 1H), 3.29 (dd, J = 11.1, 2.9 Hz, 1H), 3.50−3.65 (m, 3H), 4.68 (d, J = 10.3 Hz, 1H), 5.01 (d, J = 5.5 Hz, 1H), 5.96 (s, 2H) 5.97 (s, 2H), 6.70−6.89 (m, 6H); ^{13}C NMR (75 MHz) δ 148.1, 147.9, 147.5, 146.8, 136.6, 132.8, 120.0, 118.7, 108.2, 106.6, 106.2, 101.1, 101.0, 83.5, 73.5, 68.9, 59.4, 51.5, 47.4; LRMS (EI) *m/z* (relative intensity) 372 (40) $[M]^{\bullet+}$, 354 (40) $[M - H_2O]^{\bullet+}$; HRMS (EI) calcd for $C_{20}H_{20}O_7$ 372.1209, found 372.1203.

5-Phenyl-3-(2,2,2,-trifluoroacetyl)tetrahydro-2-furanone (29a). The title compound was prepared according to the method outlined for **29b**, whereby reaction of γ-phenyl-γ-butyrolactone (0.28 mL, 2.0 mmol) with 2,2,2-trifluoroethyl trifluoroacetate (0.40 mL, 3.0 mmol) and workup under the conditions described gave a yellow oil (1.48 g). Purification was accomplished by flash chromatography on silica (3 × 7.5) eluting with Et_2O/hexane (3:7) to yield the product **29a** as a white solid (0.44 g, 1.7 mmol, 84%): mp 72−75 °C (Et_2O/hexane); IR ν_{max} (neat) 1737 cm^{-1}; ^1H NMR (300 MHz) − both diastereoisomers reported δ [2.57 (q, J = 11.4 Hz, 1H) and 2.98−3.13 (m, 1H)] and 2.75−2.87 (m, 2H), 3.23 (dd, J = 12.4, 8.4 Hz, 1H) and 3.51−3.65 (m, 1H), 5.44 (dd, J = 10.9, 6.0 Hz, 1H) and 5.65−5.78 (m, 1H), 7.28−7.48 (m, 2 × 5H); ^{13}C NMR (75 MHz) δ 177.2 and 174.0, 137.5, 129.4, 129.2, 129.1,

128.9, 126.2, 125.6, 124.9, 81.1 and 80.1, 44.2 and 41.6, 33.6 and 32.6.

3-Benzoyl-5-phenyltetrahydro-2-furanone (29b). The title compound was prepared according to the general procedure described by Taber et al.[26] NaH (1.53 g of a 60% dispersion in mineral oil, 40.0 mmol) was washed twice with dry hexanes (2 × 10 mL) and then suspended in DME (freshly distilled over CaH_2, 25 mL). To this suspension at 0 °C (ice/salt) was added γ-phenyl-γ-butyrolactone (1.40 mL, 10.0 mmol) in DME (8 mL). After 10 min at 0 °C, methyl benzoate (1.87 mL, 15.0 mmol) in DME (8 mL) was added dropwise. After four drops of methanol were added, the mixture was allowed to warm to room temperature and allowed to stir for 4 h. The reaction mixture was acidified to pH = 4 with an aqueous solution of 1 N HCl and diluted with Et_2O (20 mL). The yellow organic layer was separated and the aqueous extracted with Et_2O (3 × 40 mL), dried with $MgSO_4$, and concentrated in vacuo to give a yellow oil that crystallized on standing. This crude product was treated with ice-cold Et_2O and filtered to yield the product as a white solid (0.87 g, 3.3 mmol, 33%). The filtrate was concentrated in vacuo and purified by flash chromatography on silica (3 × 9) eluting with Et_2O/hexane (3:2) to provide the title compound (0.53 g, 2.1 mmol, 21%) as an off-white solid (1:1 mixture of diastereoisomers) − overall yield of **29b** (1.40 g, 5.3 mmol, 53%): mp 95−97 °C (Et_2O/hexane); IR ν_{max} (neat) 1765, 1686 cm^{-1}; ^1H NMR (300 MHz) − both distereoisomers reported δ 2.48 (dt, J = 12.9, 8.4 Hz, 1H) and 3.03 (dt, J = 13.4, 8.0 Hz, 1H), 2.82 (ddd, J = 13.4, 8.9, 6.5 Hz, 1H) and 3.21 (ddd, J = 10.4, 6.9, 3.5 Hz, 1H), 4.75 (dd, J = 8.9, 3.0 Hz, 1H) and 4.83 (dd, J = 10.9, 8.9 Hz, 1H), 5.57 (dd, J = 10.4, 6.5 Hz, 1H) and 5.80 (dd, J = 8.5, 7.0 Hz, 1H), 7.32−7.45 (m, 2 × 5H), 7.48 − 7.57 (m, 2 × 2H), 7.59−7.70 (m, 2 × 1H), 8.08 (dd, J = 7.4, 1.5 Hz, 2H) and 8.15 (dd, J = 7.4, 1.5 Hz, 2H); ^{13}C NMR (75 MHz) δ 193.0 and 192.9, 172.3 and 172.2, 139.1 and 138.5, 136.0 and 135.1, 134.4 and 134.2, 129.8 and 129.6, 129.0 and 128.8, 126.1 and 125.6, 81.2 and 80.3, 49.9 and 49.4, 35.0 and 34.2; LRMS (AP +ve) m/z (relative intensity) 267 (100) $[M + H]^+$. Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.67; H, 5.29.

3-Diazo-5-phenyltetrahydro-2-furanone (30). To a solution of trifluoroacylated lactone **29a** (30 mg, 0.11 mmol) in bench-grade CH_2Cl_2 (2 mL) was added NEt_3 (20 μL, 0.14 mmol) and the mixture stirred at room temperature for 10 min before *p*-nitrobenzenesulfonyl azide (33 mg, 0.14 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 13 h, diluted with CH_2Cl_2 (5 mL), and quenched with water (5 mL). The organic phase was separated and the aqueous extracted with CH_2Cl_2 (3 × 8 mL), washed with brine (10 mL), dried with $MgSO_4$ and concentrated in vacuo to yield a yellow oil (25 mg). Purification was accomplished by column chromatography on silica (3 × 3) eluting with Et_2O/hexane (3:2) to yield the title compound **30** (15 mg, 0.08 mmol, 72%) as a yellow oil: IR ν_{max} (neat) 2095, 1729 cm^{-1}; ^1H NMR (300 MHz) δ 3.28 (dd, J = 12.9, 6.9 Hz, 1H), 3.75 (dd, J = 12.9, 8.9 Hz, 1H), 5.56 (dd, J = 8.4, 6.9 Hz, 1H), 7.33−7.46 (m, 5H); ^{13}C NMR (75 MHz) δ 173.9, 139.4, 129.1, 129.0, 125.5, 78.1, 31.7.

(4*R,5*S**)-3-Benzoyl-4-[(benzyloxy)methyl]-5-phenyltetrahydro-2-furanone (31b).** The title compound was prepared according to the method outlined for **29b**, whereby reaction of lactone **10** (0.29 g, 1.0 mmol) with methyl benzoate (0.19 mL, 1.5 mmol) and workup under the conditions described gave a colorless oil (0.68 g). Purification was accomplished by column chromatography on silica (3 × 6.5) eluting with Et_2O/hexane (3:7) to yield the title compound **31b** (3 mg, 0.19 mmol, 19%) as a colorless oil: IR ν_{max} (neat) 1770, 1681 cm^{-1}; ^1H NMR (300 MHz) − major diastereoisomer reported δ 3.32−3.43 (m, 1H), 3.44−3.57 (m, 2H), 4.47 (d, J = 12.4 Hz, 1H), 4.56 (d, J = 12.4 Hz, 1H), 5.00 (d, J = 10.9 Hz, 1H), 5.44 (d, J = 9.4 Hz, 1H), 7.18−7.47 (m, 10H), 7.54 (dd, J = 7.9, 7.4 Hz, 2H), 7.64 (dd, J = 7.4, 1.5 Hz, 1H), 8.08 (d, J = 7.4 Hz, 2H); ^{13}C NMR (75 MHz) δ 193.1, 171.7, 137.4, 136.3, 134.2, 129.7, 129.2, 128.9, 128.7, 128.2, 128.1, 126.7, 81.5, 73.4, 65.0, 51.0, 48.6.

***N*,*N*-Dimethyl-2-(3,4,5-trimethoxyphenyl)acetamide (32b).** To a suspension of 3,4,5-trimethoxyphenyl acetic acid (7.92 g, 35 mmol) in CH_2Cl_2 (35 mL), at room temperature, was added oxalyl chloride (3.4 mL, 38.5 mmol) followed by two drops of DMF. The reaction was stirred for 6 h where upon gaseous evolution had ceased and full conversion of acid was observed (monitoring by IR $-C{=}O_{(COOH)}$ 1699 cm^{-1} and $-C{=}O_{(COCl)}$ 1793 cm^{-1}). The crude acid chloride was immediately converted to the amide according to the method outlined for **19**. Purification was accomplished by distillation under reduced pressure to give the title compound **32b** (8.45 g, 33 mmol, 95%) as a viscous colorless oil that solidified on standing to a white solid: bp 136−139 °C (0.5 mbar); mp 53−55 °C; IR ν_{max} (neat) 1652 cm^{-1}; ^1H NMR (400 MHz) δ 3.01 (s, 3H), 3.05 (s, 3H), 3.68 (s, 2H), 3.85 (s, 3H), 3.87 (s, 6H), 6.51 (s, 2H); ^{13}C NMR (100 MHz) δ 171.3, 153.7, 137.3, 131.1, 106.3, 61.2, 56.5, 41.5, 38.1, 36.1. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.58; H, 7.65; N, 5.45.

(2*S,3*S**)-2-(3,4-Methylenedioxy)phenyl-3-[[(3,4-dimethoxybenzyl)oxy]methyl]cyclobutanone (33a).** To a solution of *N*,*N*-dimethyl(3,4-methylenedioxy)phenylacetamide (**19**) (207 mg, 1.0 mmol) in CH_2Cl_2 (3.5 mL) at −25 °C (internal, CO_2(s)/acetone) was added Tf_2O (0.18 mL, 1.05 mmol) at such a rate that the temperature did not rise above −20 °C. The colorless homogeneous reaction mixture was stirred at −25 °C for 2 min before addition of anhydrous potassium carbonate (152 mg, 1.1 mmol) followed by a mixture of 2,6-di-*tert*-butylpyridine (0.25 mL, 1.1 mmol) and 4-[(allyloxy)methyl]-1,2-dimethoxybenzene (**38**)[37] (310 mg, 1.5 mmol) in CH_2Cl_2 (0.5 mL) over a period of 2 min. The reaction was then allowed to warm to room temperature and stirred for 18 h (the formation of the cyclic iminium species was monitored by IR; υ_{max} 1733 cm^{-1}). The mixture was diluted with CH_2Cl_2 (10 mL) and treated with saturated $NaHCO_3$ (aq) (10 mL) with vigorous stirring for 1 h. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL), and the combined extracts were washed with water (20 mL) and brine (20 mL), dried with $MgSO_4$, and concentrated in vacuo to yield a yellow oil (740 mg). Purification was accomplished by flash chromatography on silica gel (3 × 8.5) eluting with EtOAc/hexane (3:7) to give the title compound **33a** as a 12:1 mixture of diastereoisomers (158 mg, 0.43 mmol, 43%) as a colorless oil. NMR data is reported for the major diastereoisomer: IR ν_{max} (neat) 1778 cm^{-1}; ^1H NMR (400 MHz) δ 2.70−2.79 (m, 1H), 3.02 (d, J = 9.0 Hz, 2H), 3.69−3.77 (m, 2H), 3.84 (s, 3H), 3.87 (s, 3H), 4.24 (d, J = 8.0 Hz, 1H), 4.52 (s, 2H), 5.91 (s, 2H), 6.69−6.76 (m, 3H), 6.81−6.87 (m, 3H); ^{13}C NMR (100 MHz) δ 206.3, 149.6, 149.2, 148.3, 147.0, 131.0, 130.1, 120.6, 111.4, 108.8, 108.2, 101.4, 73.5, 72.2, 66.8, 56.4, 56.2, 47.5, 33.1; LRMS (CI, ammonia) m/z (relative intensity) 388 (10) $[M + NH_4]^+$, 235 (70) $[M - ArCH_2]^{\bullet+}$, 151 (100) $[ArCH_2]^+$; HRMS (EI) calcd for $C_{21}H_{22}O_6$ 370.1416, found 370.1426.

(2*S,3*S**)-3-[[3,4-Dimethoxybenzyl)oxy]methyl]-2-(3,4,5-trimethoxyphenyl)cyclobutanone (33b).** The title compound was prepared according to the method outlined for **33a**, whereby *N*,*N*-dimethyl(3,4,5-trimethoxy)phenylacetamide **32b** (2.78 g, 11.0 mmol) and 4-[(allyloxy)methyl]-1,2-dimethoxybenzene (**38**)[37] (3.44 g, 16.5 mmol) were reacted under the conditions described (except reaction quenched at +5 °C after 150 min). Purification was accomplished by flash chromatography on silica gel (5 × 10) eluting with EtOAc/hexane (1:9) followed by EtOAc/hexane (1:1) to yield the title compound **33b** as a 12:1 mixture of diastereoisomers (720 mg, 1.73 mmol, 16%) as a very pale yellow oil. NMR data is reported for the major diastereoisomer: IR ν_{max} (neat) 1777 cm^{-1}; ^1H NMR (400 MHz) δ 2.77−2.86 (m, 1H), 3.04 (dd, J = 4.5, 1.5 Hz, 1H), 3.05 (dd, J = 5.5, 1.5 Hz, 1H), 3.71−3.78 (m, 2H), 3.79 (s, 6H), 3.80 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 4.28 (d, J = 8.0 Hz, 1H), 4.54 (s, 2H), 6.52 (s, 2H), 6.81−6.85 (m, 1H), 6.84−6.89 (m, 2H); ^{13}C NMR (100 MHz) δ 206.2, 153.7, 149.3, 149.2, 137.5, 132.0, 131.0, 120.8, 111.6, 111.4, 104.6, 73.6, 72.5, 67.3, 61.2, 56.5, 56.4, 56.3, 47.4, 33.0; LRMS (EI) m/z (relative intensity) 416 (20) $[M]^{\bullet+}$, 265 (15) $[M - ArCH_2]^{\bullet+}$, 151 (100) $[ArCH_2]^{\bullet+}$; HRMS (EI) calcd for $C_{23}H_{28}O_7$ 416.1835, found 416.1837.

(37) Denmark, S. E.; Herbert, B. *J. Org. Chem.* **2000**, *65*, 2887.

(4*R,5*S**)-5-(3,4-Methylenedioxy)phenyl-4-[[(3,4-dimethoxybenzyl)oxy]methyl]tetrahydro-2-furanone (34a).** The title compound was prepared according to the method outlined for **23**, whereby reaction of cyclobutanone **33a** (1.50 g, 4.05 mmol) with hydrogen peroxide and workup under the conditions described led to a crude yellow oil (1.9 g). Purification and separation from the minor diastereoisomer was accomplished on silica gel (5 × 7) eluting with EtOAc/hexane (2:3) to yield the title compound **34a** (1.11 g, 2.87 mmol, 71%) as a colorless oil: IR ν_{max} (neat) 1777 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.57−2.75 (m, 3H), 3.45−3.53 (m, 2H), 3.88 (s, 6H), 4.44 (d, J = 11.5 Hz, 1H), 4.49 (d, J = 11.5 Hz, 1H), 5.23 (d, J = 6.5 Hz, 1H), 5.95 (s, 2H), 6.69−6.77 (m, 3H), 6.84 (s, 3H); ^{13}C NMR (100 MHz) δ 176.4, 149.6, 149.3, 148.6, 148.3, 132.9, 130.6, 120.8, 119.9, 111.5, 111.4, 108.7, 106.6, 101.7, 83.4, 73.6, 68.6, 56.4, 56.3, 45.0, 32.2; LRMS (EI) *m*/*z* (relative intensity) 386 (30) $[M]^{\bullet+}$, 235 (70) $[M - ArCH_2]^{\bullet+}$, 151 (100) $[ArCH_2]^{\bullet+}$; HRMS (EI) calcd for $C_{21}H_{22}O_7$ 386.1366, found 386.1372.

(4*R,5*S**)-4-[[(3,4-Dimethoxybenzyl)oxy]methyl]-5-(3,4,5-trimethoxyphenyl)tetrahydro-2-furanone (34b).** The title compound was prepared according to the method outlined for **23**, whereby reaction of cyclobutanone **33b** (650 mg, 1.56 mmol) with hydrogen peroxide and workup under the conditions described led to a crude yellow oil (3.5 g). Purification and separation from the minor diastereoisomer was accomplished by flash chromatography on silica gel (4 × 8) eluting with EtOAc/hexane (3:2) to yield the title compound **34b** (535 mg, 1.24 mmol, 79%) as a colorless oil: IR ν_{max} (neat) 1778 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.59−2.77 (m, 3H), 3.52 (d, J = 4.5 Hz, 2H), 3.79 (s, 6H), 3.82 (s, 3H), 3.87 (s, 3H), 3.87 (s, 3H), 4.44 (d, J = 11.5 Hz, 1H), 4.53 (d, J = 11.5 Hz, 1H), 5.27 (d, J = 6.0 Hz, 1H), 6.45 (s, 2H), 6.81−6.87 (m, 3H); ^{13}C NMR (100 MHz) δ 176.3, 153.8, 149.4, 149.2, 138.3, 134.8, 130.4, 120.7, 111.4, 111.2, 102.8, 83.3, 73.5, 68.6, 61.1, 56.4, 56.2, 44.8, 31.9; LRMS (EI) *m*/*z* (relative intensity) 432 (30) $[M]^{\bullet+}$, 281 (35) $[M - ArCH_2]^{\bullet+}$; 151 (100) $[ArCH_2]^{\bullet+}$; HRMS (EI) calcd for $C_{23}H_{28}O_8$ 432.1784, found 432.1790.

(4*R,5*S**)-5-(3,4-Methylenedioxy)phenyl-3-diazo-4-[[(3,4-dimethoxybenzyl)oxy]methyl]tetrahydro-2-furanone (35a).** To a solution of hexamethyldisilylazane (1.1 mL, 5.2 mmol) in THF (15 mL) at 0 °C (ice/salt bath) was added *n*-butyllithium (3.8 mL, 5.3 mmol) dropwise over 5 min. The colorless solution was stirred at 0 °C for 10 min before cooling to −78 °C (CO_2(s)/acetone) and adding a solution of lactone **34a** (1.0 g, 2.6 mmol) in THF (20 mL) dropwise over 10 min. The pale yellow reaction mixture was left stirring at −78 °C for 60 min and 2,2,2-trifluoroethyltrifluoroacetate (0.38 mL, 2.86 mmol) was added dropwise over 2 min. and the reaction was warmed to room temperature over 100 min. The reaction mixture was acidified to pH = 4 with an aqueous solution of 1 N HCl and diluted with Et_2O (20 mL) before the organic layer was separated and the aqueous extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried with $MgSO_4$ and concentrated in vacuo to afford crude **(4*R**,5*S**)-5-(3,4-methylenedioxy)phenyl-4-[[(3,4-dimethoxybenzyl)oxy]methyl]-3-(trifluoroacetyl)-tetrahydro-2-furanone** (1.39 g, quantitative) as a pale orange foam. This crude material was used directly in the subsequent diazo-transfer reaction, which was conducted following the procedure described for **12**, whereby reaction of crude trifluoroacylated lactone (2.6 mmol theoretical) with 4-nitrobenzenesulfonyl azide (0.77 g, 3.4 mmol) and workup under the conditions described gave a crude yellow oil (3.2 g). Purification was accomplished by flash chromatography on silica gel (5 × 7) eluting with EtOAc/hexane (2:3) to yield the title compound **35a** (730 mg, 1.77 mmol, 68% − from lactone **34a**) as a bright yellow oil: IR ν_{max} (neat) 2101, 1733 cm^{-1}; ^{1}H NMR (400 MHz) δ 3.65−3.76 (m, 3H), 3.87 (s, 3H), 3.87 (s, 3H), 4.49 (s, 2H), 5.02 (d, J = 5.0 Hz, 1H), 5.96 (s, 2H), 6.72−6.79 (m, 3H), 6.80−6.85 (m, 3H); ^{13}C NMR (100 MHz) δ 171.9, 152.1, 151.8, 151.2, 151.0, 135.4, 132.6, 123.3, 122.3, 113.9, 113.9, 111.3, 108.8, 104.3, 83.4, 76.2, 73.2, 58.9, 58.8, 55.7, 48.2.

(4*R,5*S**)-3-Diazo-4-[[(3,4-dimethoxybenzyl)oxy]methyl]-5-(3,4,5-trimethoxyphenyl)tetrahydro-2-furanone (35b).** The title compound was prepared according to the method outlined for **35a**, whereby reaction of lactone **34b** (450 mg, 1.04 mmol) with lithium hexamethyldisilyl azide and 2,2,2-trifluoroethyltrifluoroacetate (0.15 mL, 1.14 mmol) under the conditions described gave crude **(4*R**,5*S**)-4-[[(3,4-dimethoxybenzyl)oxy]methyl]-3-(trifluoroacetyl)-5-(3,4,5-trimethoxyphenyl)tetrahydro-2-furanone** (600 mg, quantitative) as a foam. This crude material was used directly in the subsequent diazo-transfer reaction, which was conducted following the procedure described for **12**, whereby reaction of crude the trifluoroacylated lactone (1.04 mmol theoretical) with 4-nitrobenzenesulfonyl azide (310 mg, 1.35 mmol) and workup under the conditions described gave a crude yellow oil (1.2 g). Trituration with Et_2O/EtOAc and filtration gave the title compound **35b** (294 mg, 0.64 mmol, 62%) as a pale yellow solid. Further purification of the filtrate was accomplished by flash chromatography on silica gel (3 × 7) eluting with EtOAc/hexane (3:2) to yield **35b** (66 mg, 0.14 mmol, 14%) as a pale yellow powdery solid—overall yield of **35b** (360 mg, 0.79 mmol, 76%—from lactone **34b**): mp 131−132 °C; IR ν_{max} (neat) 2110, 1730 cm^{-1}; ^{1}H NMR (400 MHz) δ 3.71−3.81 (m, 3H), 3.82 (s, 6H), 3.83 (s, 3H), 3.88 (s, 3H), 3.88 (s, 3H), 4.51 (d, J = 11.5 Hz, 1H), 4.54 (d, J = 11.5 Hz, 1H), 5.09 (d, J = 4.0 Hz, 1H), 6.49 (s, 2H), 6.84 (s, 3H); ^{13}C NMR (100 MHz) δ 169.5, 154.1, 149.7, 149.5, 138.8, 134.8, 130.1, 120.9, 111.5, 111.4, 102.8, 81.0, 74.0, 70.7, 61.3, 56.7, 56.4, 56.3, 53.2, 45.7. Anal. Calcd for $C_{23}H_{26}N_2O_8$: C, 60.26; H, 5.72; N, 6.11. Found: C, 60.21; H, 5.78; N, 6.21.

(1*S,2*R**,5*R**,6*S**)-2-(3,4-Dimethoxy)phenyl-6-(3,4-methylenedioxy)phenyl-3,7-dioxabicyclo[3.3.0]octan-8-one (36a).** The title compound was prepared according to the method outlined for **26**, whereby reaction of diazo-lactone **35a** (0.48 g, 1.16 mmol) with dirhodium(II) tetraacetate (10 mg, 0.02 mmol) and workup under the conditions described gave crude furofuranone as a yellow oil (0.48 g). Purification was accomplished on silica gel (4.5 × 10) eluting with EtOAc/hexane (2:3) to yield the title compound **36a** (0.36 g, 0.94 mmol, 81%) as a white crystalline solid: mp 125−127 °C; IR ν_{max} (neat) 1761 cm^{-1}; ^{1}H NMR (400 MHz) δ 3.21 (ddd, J = 9.0, 6.5, 4.5 Hz, 1H), 3.54 (t, J = 8.5 Hz, 1H), 3.87 (s, 3H), 3.89 (s, 3H), 3.90 (dd, J = 10.0, 5.0 Hz, 1H), 4.29 (d, J = 9.5 Hz, 1H), 5.03 (d, J = 8.5 Hz, 1H), 5.20 (d, J = 6.5 Hz, 1H), 5.97 (s, 2H), 6.81 (s, 3H), 6.86−6.89 (m, 2H), 6.95 (dd, J = 8.0, 2.0 Hz, 1H); ^{13}C NMR (100 MHz) δ 174.7, 149.5, 149.4, 148.8, 148.5, 133.7, 128.9, 119.8, 119.3, 111.5, 109.9, 108.9, 106.3, 101.8, 85.9, 84.3, 72.1, 56.3, 56.2, 51.9, 51.7. Anal. Calcd for $C_{21}H_{20}O_7$: C, 65.62; H, 5.24. Found: C, 65.23; H, 5.02.

(1*S,2*R**,5*R**,6*S**)-2-(3,4-Dimethoxy)phenyl-6-(3,4,5-trimethoxy)phenyl-3,7-dioxabicyclo[3.3.0]octan-8-one (36b).** The title compound was prepared according to the method outlined for **26**, whereby reaction of diazo lactone **35b** (320 mg, 0.70 mmol) with $Rh_2(OAc)_4$ (6 mg, 0.01 mmol) and workup under the conditions described gave the crude furofuranone as an off-white powdery solid (285 mg). Purification was accomplished on silica gel (2.5 × 4) eluting with EtOAc/hexane (3:2) to give the title compound **36b** (261 mg, 0.60 mmol, 87%) as a white powdery solid: mp 175−176 °C; IR ν_{max} (neat) 1763 cm^{-1}; ^{1}H NMR (400 MHz) δ 3.24 (ddd, J = 9.0, 6.5, 4.5 Hz, 1H), 3.55 (t, J = 9.0 Hz, 1H), 3.85 (s, 3H), 3.88 (s, 6H), 3.88 (s, 3H), 3.90 (s, 3H), 3.94 (dd, J = 9.5, 4.5 Hz, 1H), 4.34 (d, J = 9.5 Hz, 1H), 5.05 (d, J = 8.5 Hz, 1H), 5.24 (d, J = 6.5 Hz, 1H), 6.54 (s, 2H), 6.87−7.00 (m, 3H); ^{13}C NMR (100 MHz) δ 174.8, 154.2, 149.6, 149.5, 138.8, 135.5, 128.8, 119.3, 111.5, 110.0, 102.8, 85.9, 84.3, 72.2, 56.7, 56.3, 56.2, 51.9, 51.8. Anal. Calcd for $C_{23}H_{26}O_8$: C, 64.18; H, 6.09. Found: C, 63.87; H, 5.89.

(2*R,3*R**,4*S**)-2[(3,4-Dimethoxy)phenyl]-3-hydroxymethyl-4-[[(3,4-methylenedioxy)phenyl]hydroxy]-methyltetrahydrofuran (37a).** To a suspension of $LiAlH_4$ (35 mg, 0.93 mmol) in THF (5 mL) at 0 °C (ice/salt) was added furofuranone **36a** (120 mg, 0.31 mmol) in THF (10 mL), and the gray suspension warmed to room temperature over 20 min. Water (0.04 mL), 15% NaOH (aq) (0.04 mL) and water (0.12 mL) were sequentially added dropwise, producing a pale gray/white granular precipitate that was filtered and washed with THF (5 mL) and Et_2O (10 mL). The filtrate was poured onto brine (15 mL), the organic phase separated, and the aqueous

extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried with $MgSO_4$, and concentrated in vacuo to yield crude diol as a white solid (125 mg). Purification was accomplished on silica gel (3 × 2.5) eluting with EtOAc/hexane (1:1) to yield the title compound **37a** (118 mg, 0.30 mmol, 98%) as a white powdery solid: mp 66−68 °C; IR ν_{max} (neat) 1254, 1237 cm^{-1}; ^1H NMR (400 MHz) δ 2.30 (br s, 1H), 2.70−2.77 (m, 1H), 3.04 (dq, J = 6.0, 9.5 Hz, 1H), 3.41 (dd, J = 11.0, 2.5 Hz, 1H), 3.49 (br s, 1H), 3.60−3.70 (m, 3H), 3.88 (s, 3H), 3.88 (s, 3H), 4.78 (d, J = 10.5 Hz, 1H), 5.09 (d, J = 5.0 Hz, 1H), 5.97 (s, 2H), 6.77−6.87 (m, 5H), 6.93 (d, J = 1.5 Hz, 1H); ^{13}C NMR (100 MHz) δ 149.4, 148.6, 148.5, 147.8, 137.0, 131.8, 120.2, 118.2, 111.6, 109.2, 108.7, 107.0, 101.5, 83.7, 74.0, 74.0, 69.2, 60.2, 56.4, 56.3, 51.9, 47.8; LRMS (EI) *m*/*z* (relative intensity) 388 (75) $[M]^{\bullet+}$, 370 (100) $[M - H_2O]^{\bullet+}$; HRMS (EI) calcd for $C_{21}H_{24}O_7$ 388.1522, found 388.1518.

(2*R,3*R**,4*S**)-2[(3,4-Dimethoxy)phenyl]-3-hydroxymethyl-4-[[(3,4,5-trimethoxy)phenyl]hydroxy]methyltetrahydrofuran (37b).** The title compound was prepared according to the method outlined for **37a**, whereby reaction of furofuranone **36b** (165 mg, 0.38 mmol) with $LiAlH_4$ (43 mg, 1.14 mmol) and workup under the conditions described gave crude diol as a white solid (166 mg). Purification was accomplished on silica gel (10 × 2.3) eluting with EtOAc/hexane (7:3) to yield the title compound **37b** (149 mg, 0.34 mmol, 90%) as a powdery white solid: mp 141−143 °C; IR ν_{max} (neat) 1241 cm^{-1}; ^1H NMR (400 MHz) δ 2.55 (br s, 1H), 2.69−2.76 (m, 1H), 3.05 (dq, J = 6.5, 9.5 Hz, 1H), 3.39 (d, J = 11.0 Hz, 1H), 3.61−3.69 (m, 2H), 3.72 (q, J = 9.0 Hz, 1H), 3.84 (s, 3H), 3.87 (s, 6H), 3.87 (s, 6H), 4.76 (d, J = 10.5 Hz, 1H), 5.08 (d, J = 5.0 Hz, 1H), 6.61 (s, 2H), 6.79−6.86 (m, 3H); ^{13}C NMR (100 MHz) δ 153.8, 149.4, 148.6, 138.7, 138.1, 131.8, 118.2, 111.6, 109.2, 103.6, 83.7, 74.3, 69.2, 61.2, 60.1, 56.6, 56.4, 56.3, 51.9, 47.8. Anal. Calcd for $C_{23}H_{30}O_8$: C, 63.58; H, 6.96. Found: C, 63.31; H, 6.99.

(1*R,2*R**,5*R**,6*S**)-2,6-Di[(3,4-methylenedioxy)phenyl]-3,7-dioxabicyclo[3.3.0]octane ((±)-Asarinin) (2).** The diol **27** (42 mg, 0.11 mmol) was dissolved in THF (5 mL) and treated with 2.0 M HCl (5 mL). The reaction was stirred at room temperature for 3 days. Although still not complete, the reaction mixture was diluted with Et_2O (10 mL) and washed with saturated $NaHCO_3$ (aq), water, and brine (10 mL of each) before drying with $MgSO_4$. The crude material was subjected to radial chromatography eluting with EtOAc/hexane (1:4). (±)-Asarinin (**2**) was isolated as a crystalline solid (27 mg, 0.07 mmol, 65%) along with recovered starting material **27** (8 mg, 20%): mp 130−131°C (CH_2Cl_2/hexane) (lit.[21] mp 132−133 °C); spectroscopic data were in accord with those described in the literature;[38] IR ν_{max} (CH_2Cl_2) 1504, 1490 cm^{-1}; ^1H NMR (360 MHz) δ 2.85 (q with fine coupling, J = 7.3, 0.9 Hz, 1H), 3.27−3.33 (m, 2H), 3.83 (dd, J = 9.4, 6.2 Hz, 1H) superimposed on 3.83−3.87 (m, 1H), 4.10 (d, J = 9.2 Hz, 1H), 4.39 (d, J = 7.2 Hz, 1H), 4.83 (d, J = 5.4 Hz, 1H), 5.95 (s, 2H), 5.97 (s, 2H), 6.77−6.87 (m, 6H); ^{13}C NMR (90 MHz) δ 148.1, 147.8, 147.3, 146.7, 135.2, 132.3, 119.7, 118.8, 108.2, 106.6, 106.5, 101.2, 101.1, 87.8, 82.1, 71.0, 69.8, 54.8, 50.3.

Improved Procedure for the Preparation of (±)-Asarinin (2) from Diol 27. The diol **27** (80 mg, 0.22 mmol) was dissolved in dry CH_2Cl_2, and the solution was cooled on ice. Pyridine (180 μL, 2.2 mmol) was added rapidly followed by freshly distilled MsCl (25 μL, 0.33 mmol). The reaction was allowed to warm to room temperature and stirred for 5 h. A further aliquot of MsCl (50 μL, 0.06 mmol) was added and stirring continued for an additional 12 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed sequentially with 1.0M HCl (aq), sat. $NaHCO_3$ (aq) then brine (20 mL of each) before drying ($MgSO_4$) and removal of solvent in vacuo. The crude product was purified by chromatography on silica gel (3 × 3) loading in CH_2Cl_2 and eluting with EtOAc/hexane (1:1) to afford the title compound **2** as a white solid (60 mg, 0.17 mmol, 77%).

(38) Pelter, A.; Ward, R. S. *Tetrahedron* **1976**, *32*, 2783.

(1*R,2*R**,5*R**,6*S**)-2-(3,4-Dimethoxy)phenyl-6-(3,4-methylenedioxy)phenyl-3,7-dioxabicyclo[3.3.0]octane ((±)-Fargesin) (3).** To a solution of diol **37a** (40 mg, 0.103 mmol) in CH_2Cl_2 (0.4 mL) and pyridine (0.1 mL) at 0 °C (ice/salt) was added MsCl (40 μL, 0.515 mmol) and the reaction warmed to room temperature and stirred for 4 days. The mixture was pipetted onto 1 N HCl (aq) (5 mL) and diluted with CH_2Cl_2 (8 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with 1 N HCl (aq) (10 mL) and brine (15 mL), dried with $MgSO_4$, and concentrated in vacuo to yield a crude orange oil (51 mg). Purification was accomplished on silica gel (2.3 × 2.5) eluting with EtOAc/hexane (2:3) to yield (±)-fargesin (**3**) (23 mg, 0.062 mmol, 60%) as a white solid: spectroscopic data were consistent with those reported previously;[24,38,39] mp 138−141 °C (lit.[24] mp 138−141 °C, lit.[39] mp 145 °C, lit.[40] mp 138−139 °C); IR ν_{max} (neat) 1239, 1033 cm^{-1}; ^1H NMR (400 MHz) δ 2.84−2.91 (m, 1H), 3.28−3.37 (m, 2H), 3.81−3.88 (m, 2H), 3.88 (s, 3H), 3.91 (s, 3H), 4.12 (d, J = 9.5 Hz, 1H), 4.42 (d, J = 7.0 Hz, 1H), 4.87 (d, J = 5.0 Hz, 1H), 5.95 (s, 2H), 6.76−6.87 (m, 5H), 6.93 (s, 1H); ^{13}C NMR (100 MHz) δ 149.3, 148.5, 148.4, 147.6, 135.6, 131.4, 119.9, 118.1, 111.5, 109.4, 108.6, 106.9, 101.4, 88.1, 82.4, 71.4, 70.2, 56.3, 56.3, 55.0, 50.6; MS (EI) *m*/*z* (relative intensity) 370 (45) $[M]^{\bullet+}$, 339 (6) $[M - OMe]^{\bullet+}$, 149 (100), 165 (50) $[ArCO]^{\bullet+}$.

(1*R,2*R**,5*R**,6*S**)-2-(3,4-Dimethoxy)phenyl-6-(3,4,5-trimethoxy)phenyl-3,7-dioxabicyclo[3.3.0]octane ((±)-Epimagnolin A) (4).** To a solution of diol **37b** (40 mg, 0.092 mmol) in CH_2Cl_2 (1 mL) at 0 °C (ice/salt) was added Et_3N (38 μL, 0.276 mmol) and DMAP (1 mg, cat.) followed by MsCl (9 μL, 0.11 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 6 h before additional MsCl (4 μL, 0.046 mmol) was added and the reaction stirred for a further 12 h. TLC analysis still showed starting diol **37b** so NEt_3 (38 μL, 0.276 mmol) and MsCl (18 μL, 0.221 mmol) were again added and the reaction stirred for 15 min before pipetting onto water (5 mL) and diluting with CH_2Cl_2 (8 mL). The organic layer was separated and the aqueous extr acted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with 1N HCl (aq) (15 mL) and brine (15 mL), dried with $MgSO_4$ and concentrated in vacuo to yield an orange oil (58 mg). Purification was accomplished on silica gel (2.3 × 2) eluting with EtOAc/hexane (3:2) to yield epimagnolin A (**4**) (29 mg, 0.070 mmol, 76%) as a glassy solid/viscous oil: spectroscopic data were consistent with those reported previously;[7] IR ν_{max} (neat) 1234, 1127 cm^{-1}; ^1H NMR (400 MHz) δ 2.90−2.97 (m, 1H), 3.31−3.39 (m, 2H), 3.84 (s, 3H), 3.86−3.91 (m, 2H), 3.88 (s, 6H), 3.89 (s, 3H), 3.92 (s, 3H), 4.17 (d, J = 9.0 Hz, 1H), 4.45 (d, J = 7.0 Hz, 1H), 4.89 (d, J = 5.5 Hz, 1H), 6.60 (s, 2H), 6.87 (s, 2H), 6.95 (s, 1H); ^{13}C NMR (100 MHz) δ 153.8, 149.3, 148.5, 138.0, 137.3, 131.3, 118.1, 111.5, 109.4, 103.4, 88.2, 82.4, 71.5, 70.2, 61.2, 56.6, 56.4, 56.3, 55.0, 50.5; MS (EI) *m*/*z* (relative intensity) 416 (100) $[M]^{\bullet+}$, 385 (10) $[M - OMe]^{\bullet+}$.

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Supporting Information Available: Copies of ^1H or ^{13}C NMR spectra for compounds **2**−**4**, **9**, **10**, **19**, **21**, **22**, **24**−**27**, **29a**, **30**, **31a**, **33a/b**, **34a/b**, **35a**, and **37a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(39) Kakisawa, H.; Chen, Y. P.; Hsü, H. Y. *Phytochem.* **1972**, *11*, 2289.

(40) Ogiku, T.; Yoshida, S. I.; Ohmizu, H.; Iwasaki, T. *J. Org. Chem.* **1995**, *60*, 1148.

(41) The United Kingdom Database Service. Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746.