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Stereoselective Synthesis of Lignans of Three Structural Types from a Common Intermediate, Enantioselective Synthesis of (+)-Yangambin

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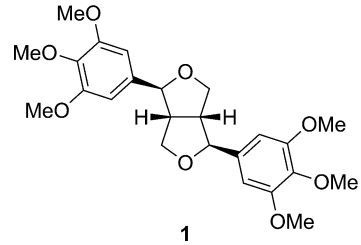
Keywords: Total synthesis / Asymmetric synthesis / Natural products / Lignans / Sulfoxides

Enantioselective total synthesis of (+)-yangambin was achieved. The key transformation is one-pot conjugate addition/aldol reaction that involves an enantioenriched benzyl *tert*-butyl sulfoxide, an enone, and gaseous formaldehyde to construct the bis(phenylpropanoid) backbone with excellent stereoselectivity and in good yield. Reduction of the ketone with diisobutylaluminium hydride and acid-catalysed cyclisation in EtOH furnished (+)-yangambin in good yield. The resulting synthesis is short, efficient and highly selective. Formation of 2,5-diaryltetrahydrofuran lignans was observed as a side reaction in the final step of yangambin synthesis. Acid-catalysed cyclisation of the aldol intermediate gave a completely different outcome. Dehydration to give an enone was followed by two electrophilic aromatic substitution reactions to furnish a derivative of the lignan lirionol.

Introduction

Many furofuran and tetrahydrofuran lignans have been isolated as bioactive plant constituents and they have shown a wide range of biological effects,[1–4] Because of this biological activity there is sustained interest in the development of efficient methods for their synthesis.[1,5–9] We became interested in the synthesis of furofuran lignans, and chose to focus on yangambin **1**, which was isolated from *Ocotea duckei* Vattimo (Lauraceae),[10]and possesses a broad range of biological activities, including platelet-activating factor receptor antagonist activity,[11] antileishmanial activity,[12] apoptosis induction activity,[13] prevention of cardiovascular collapse during anaphylactic shocks,[14] depressant activity on the central nervous system,[15] and anti-inflammatory activity.[16] A synthesis of racemic yangambin was accomplished in 1995,[17] and syntheses of (+)-yangambin **1** were subsequently achieved through asymmetric dimerisation of cinnamic acid derivatives,[18] and dianion aldol condensation.[19] Both of these asymmetric approaches were efficient, but they are restricted to the formation of lignans in which the two aryl substituents are identical. Earlier, we showed the potential of a sulfoxide-based methodology for lignan synthesis in a very short formal total synthesis of (±)-podophyllotoxin.[20] We subsequently developed an enantioselective synthesis of the benzyl *tert*-butyl sulfoxides needed as precursors for enantioselective synthesis of lignans.[21] We now report an enantioselective total synthesis of yangambin by using the sulfoxide-based strategy, which should be applicable both to symmetrical and unsymmetrical furofuran lignans. In the course of this work representative members of other families of lignans (**2** and **3**) were also prepared, which emphasises the versatility of this emerging strategy.



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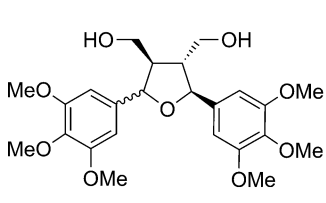

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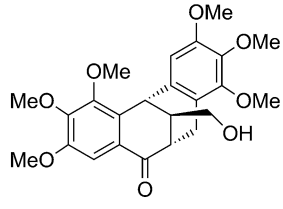

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The key feature in the proposed synthesis of yangambin was a one-pot reaction that involving conjugate addition of sulfoxide **5** to enone **6** and trapping of the enolate with formaldehyde to assemble intermediate **4** with the full bis(phenylpropanoid) lignan backbone. It was envisaged that reduction of the ketone and acid-catalysed cyclisation would then complete the synthesis of yangambin **1** (Scheme 1).

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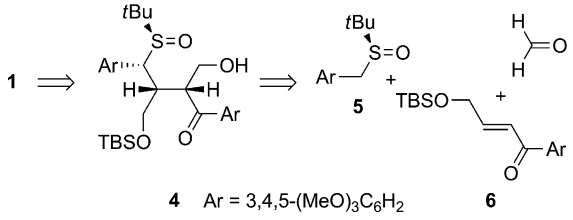
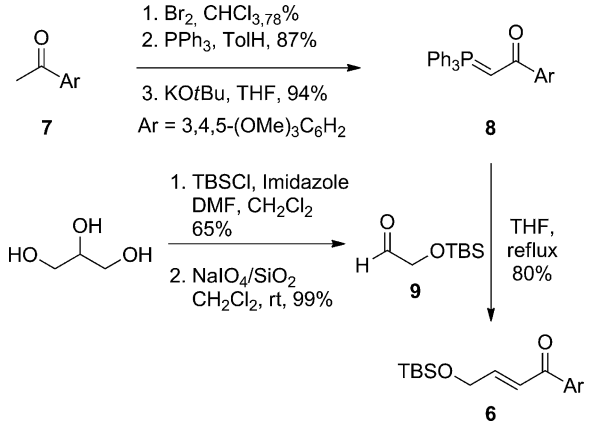


Scheme 1. Retrosynthetic analysis of yangambin **1**.

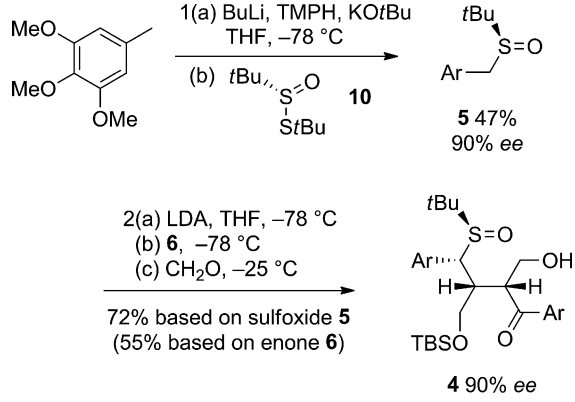
Results and Discussion

Enone **6**, needed for the key conjugate addition/aldol step, was prepared by Wittig reaction with aldehyde **9** and phosphorus ylide **8**, to generate the (*E*)-alkene (Scheme 2). Synthesis of keto ylide **8** was carried out by using standard methods. Treatment of commercially available 3,4,5-trimethoxyacetophenone (**7**) with bromine (1.1 equiv.) afforded the α-bromoketone,[22] which was converted into the phosphonium salt with triphenylphosphine. This phosphonium salt appeared to hydrate rapidly in air when "wet" with solvent, therefore initial filtration under an atmosphere of nitrogen was necessary. Once dry, it was very stable at room temperature. Attempts to deprotonate the phosphonium salt with NaOEt gave ylide that was contaminated with excess base, which caused aldol condensation as a side reaction in the Wittig reaction. Use of *t*BuOK [(1 M solution in tetrahydrofuran (THF)] and aqueous work up proved much better and gave pure ylide **8** in 64% overall yield. Aldehyde **9**[23] was formed by monoprotection of glycerol by using TBSCl, and then oxidation of the diol with silica-gel-supported sodium metaperiodate.[24] The easy non-aqueous work up when the solid-supported oxidising agent was used was the key to obtaining sensitive aldehyde **9** in consistently good yield. Attempts to carry out Wittig reaction in the same pot after deprotonation of phosphonium salt were unsuccessful, but Wittig reaction with pure ylide **8** and aldehyde **9** in THF at reflux temperatures gave desired enone **6** in 80% yield.



Scheme 2. Preparation of enone **6**.

Enantioenriched sulfoxide **5** (90% *ee*) was obtained by deprotonation of trimethoxytoluene and addition of enantioenriched (*R*)-thiosulfinate **10** (obtained by catalytic asymmetric oxidation of the disulfide)[25] to the resulting benzyllithium (Scheme 3).[21] The one-pot reaction that involved deprotonation of sulfoxide **5** and addition of enone **6** in THF at –78 °C, and then trapping of the resulting enolate with gaseous formaldehyde, assembled key intermediate **4**, with excellent diastereoselectivity, and in 72% yield. Though traces of diastereomeric products may have been formed, none could be isolated by chromatography. The gaseous formaldehyde was formed by depolymerisation of paraformaldehyde at 180 °C and was quickly carried into the reaction mixture, which was maintained at –25 °C, through a wide cannula with a steady stream of N_2. This was a tricky operation and by maintaining the enolate at a relatively high temperature, and by using a steady stream of N_2 and a wide cannula, blockage of the cannula resulting from repolymerisation of the formaldehyde could be avoided. Use of solid paraformaldehyde or addition of a preformed solution of formaldehyde in THF at –25 °C to the enolate gave untrapped conjugate adduct along with some unidentified side products.



Scheme 3. Preparation of key intermediate **4**; TMPH = 2,2,6,6-tetramethylpiperidine.

This reaction builds a large degree of molecular complexity by forming two new C–C bonds and three new chiral centres with complete control of configuration and no reduction in *ee*. The relative configurations of the centres α and β to the sulfinyl group were proven by X-ray crystallography of a derivative (see Figure 4). The relative configurations at the centre α and β to the carbonyl were confirmed by successful conversion of this intermediate into yangambin. The stereochemistry at the new chiral centres in aldol adduct **4** can be rationalised in terms of three transition state models (Figure 1). In reactions of anions formed from *tert*-butyl sulfoxides, the configuration at the carbon α to the sulfinyl group can be reliably predicted by using model **11**. In this model the benzylic "carbanion" is planar, the counterion is associated with the sulfoxide oxygen, and the full orbital on C is aligned with the S–O bond.[26,27] The conformer in which the aryl group is *anti* to the *tert*-butyl group is strongly preferred, and the electrophile approaches the face that is less hindered by the *tert*-butyl group.[26,28] In the conjugate addition, we propose that coordination of the sulfinyl oxygen and the carbonyl group of the α,β-unsat-

urated ester with the counterion results in an eight-membered cyclic transition state.[29] The high diastereoselectivity of conjugate addition could then arise from conformation **12**, in which steric interactions between the *tert*-butyl group and the aryl substituent are minimised, and the full p-orbital of the carbanion is still reasonably well aligned with the S–O bond. This transition state would lead to the (*Z*)-enolate intermediate and approach of the electrophile to the less hindered face of favoured conformation **13** gives observed product **4**. It is notable that the large size difference between the silyloxymethyl (R in **13**) and sulfinyl-substituted benzyl groups at the β carbon results in high diastereoselectivity in the enolate reaction.[30,31]

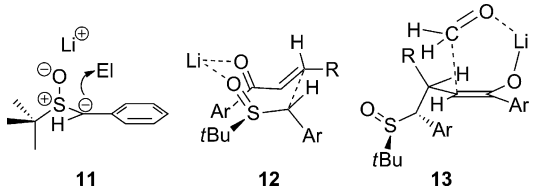
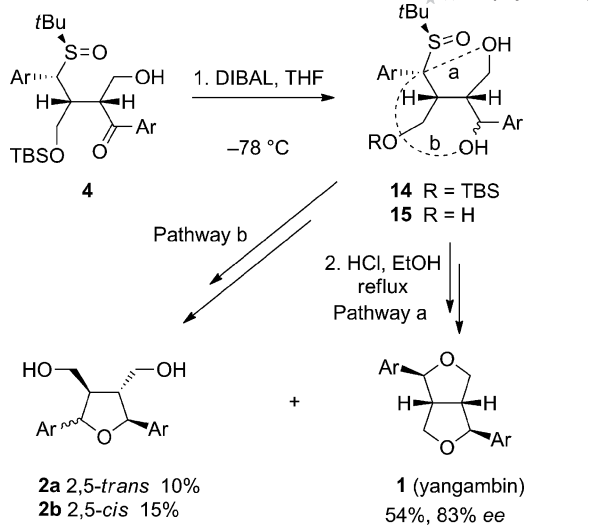


Figure 1. Transition state models for the conjugate addition and the aldol reaction.

The next step was to reduce aldol adduct **4**. Sodium borohydride reduction was complicated by competing retro-aldol reaction under a variety of conditions. By following a literature precedent for reduction of aldols,[32] use of diisobutylaluminium hydride (DIBAL) gave diol **14** in 92% yield, as a 3:2 mixture of diastereomers. The formation of two epimers was of no consequence because that chiral centre undergoes an S_N1 reaction in the final cyclisation. Owing to the acidic workup some of the product diol underwent deprotection to give corresponding triol **15**, which could also be utilised in the next step. By heating the unpurified mixture of reduction products in ethanol heated to reflux with a catalytic amount of HCl, the same conditions used for cyclisation reactions of tetra-ols in Beroza's original synthesis of furofuran lignans,[33] resulted in deprotection of the silyl ether, and closing of both the tetrahydrofuran rings with removal of the sulfur auxiliary to form yangambin **1** in 54% yield over two steps. The structure of the product was confirmed by analysis with published ^{1}H NMR and ^{13}C NMR spectroscopic data.[18] HPLC analysis showed 83% *ee*, and recrystallisation gave enantiopure (+)-yangambin (Scheme 4), albeit in poor yield (35%).

Formation of the tetrahydrofuran rings presumably occurred through formation of benzylic carbocations, which were stabilised by the ring substituents. In the case of the "upper" ring, the acidity of the reaction medium resulted in protonation of the sulfinyl oxygen and cleavage of the C–S bond to form the benzylic carbocation, which reacted with the primary alcohol group to complete the cyclisation (Scheme 4, Pathway a). Similarly, formation of the other tetrahydrofuran ring was achieved by protonation of the benzylic hydroxy group and loss of water to give a stable benzylic carbocation. The hydroxy group, formed by cleavage of the silyl ether under acidic conditions reacted with this benzylic carbocation to form the other tetrahydrofuran ring. The cyclisation reactions gave only the more stable *exo*,*exo* product, in which both aromatic rings are on the less hindered face of the bicyclic ring system. This short (seven steps from ketone **7**) and efficient (15% overall based on ketone **7**) asymmetric synthesis of yangambin is much shorter than the previous synthesis of racemic material,[17] and although longer than the enantioselective oxidative dimerisation strategies reported earlier,[18,19] it is similar in efficiency, and has the advantage that it should be readily adaptable to the synthesis of unsymmetrical furofuran lignans that bear two different aryl groups. In terms of yield and flexibility it compares favourably with other syntheses of furofuran lignans.[1,34–37]



Scheme 4. Completion of the synthesis of (+)-yangambin (**1**).

Two minor products were formed in the final step of the synthesis. Subsequent work with racemic precursor allowed them to be identified as 2,5-diaryltetrahydrofurans **2a** (10%) and **2b** (15%), which arise from substitution of the sulfinyl group by the secondary alcohol (Scheme 4, Pathway b). Both isomers of the 2,5-diaryltetrahydrofuran were fully characterised. The ^{1}H NMR spectrum of 2,5-diaryltetrahydrofuran **2a** was simple, as expected from its C_2-symmetry. A more complex spectrum was observed for unsymmetrical isomer **2b**, and its structure was confirmed by X-ray crystallography (Figure 2). Closely related 2,5-diaryl-

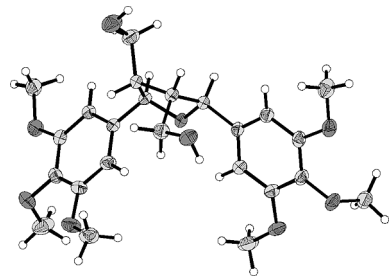


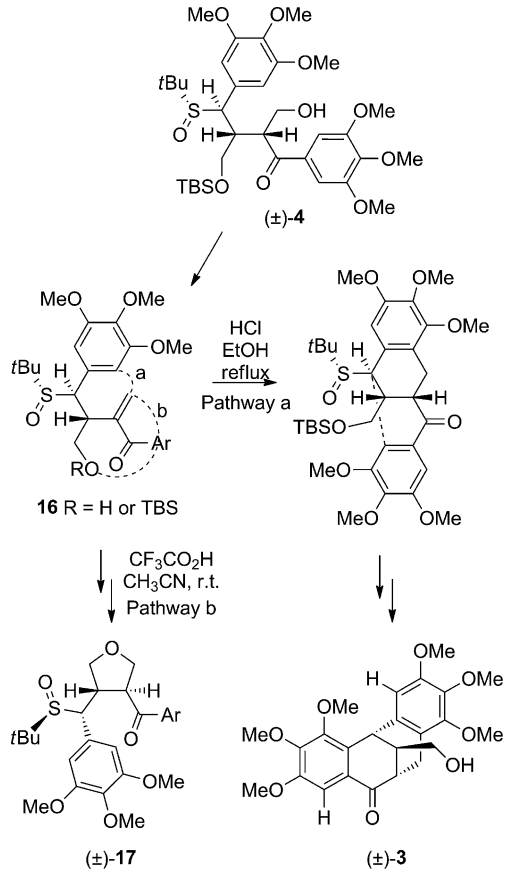
Figure 2. X-ray crystal structure of tetrahydrofuran **2b**.

tetrahydrofurans have been isolated from the Chinese shrub *Neoalsomitra integrifoliola*,[38] the Japanese plant *Glechoma hederacea* L.[39] and from non-centrifuged cane sugar (*Saccharum officinarum* L.),[40] and several syntheses of such lignans have been recorded.[41,42] Less heavily oxygenated 2,5-diaryltetrahydrofurans, such as veraguensin, have attracted much interest because they exhibit diverse and potent biological activities.[8]

The formation of these two diastereomeric tetrahydrofurans could be a consequence of kinetically controlled cyclisation of the mixture of epimeric alcohols **15** (Scheme 4, Pathway b), or of equilibration of the products under the reaction conditions. When the mixture of 2,5-diaryl tetrahydrofurans was re-subjected to the reaction conditions, there was no change in the diastereomer ratio, though traces of yangambin were formed after long reaction times at higher acid concentration. Also, yangambin was unchanged on prolonged heating in ethanolic HCl. These results show that the cyclisations were kinetically controlled. We did not attempt to modify the synthetic route to obtain 2,5-diaryltetrahydrofurans selectively, but more recent work has shown that is possible to obtain closely related compounds efficiently and selectively.[43]

After identification of the 2,5-diaryltetrahydrofuran side products, we sought ways to avoid their formation. Attempts were made to form one tetrahydrofuran ring by acid catalysed cyclisation of conjugate addition/aldol adduct (±)-**4** (readily available racemic material was used in this exploratory work), which cannot give a 2,5-diaryltetrahydrofuran. However, reaction of ketone (±)-**4** in ethanolic HCl at reflux temperatures gave a relatively complex mixture, and the ^{1}H NMR spectrum did not show peaks indicative of the desired tetrahydrofuran. After column chromatography one major product was isolated and the ^{1}H NMR spectrum showed some surprising features: there were two singlets in aromatic region, but each integrated for only one hydrogen. There were also multiplets indicating the presence of two methylene and three methine units. These features suggested that a double electrophilic aromatic substitution had occurred, with the most likely electrophilic centres being the carbon beta to the carbonyl, after dehydration to give enone **16**, and a benzylic carbon that bears the sulfinyl group. Double cyclisation in this way would produce bridged bicyclic structure (±)-**3** (Scheme 5, Pathway a).

The 1D and 2D NMR spectroscopic data, and the mass spectrometry data, were fully consistent with the proposed structure (Figure 3). The relative stereochemistry at C^{13} was established by using NOE experiments. Irradiation of the signal arising from the H^{13} proton caused enhancement of the signals for H^6 and both of the H^7 protons. Irradiation of one of the H^{14} signals resulted in small enhancements of the H^6 signal, but not of either of the H^7 signals. Similarly, irradiation of the other H^{14} signal resulted in almost no enhancements of either the H^7 or the H^6 signals. These results strongly indicate that C^{14} and C^7 are relatively far apart from each other, i.e. that they have a *trans* relationship.



Scheme 5. Cyclisation reactions of aldol **4**.

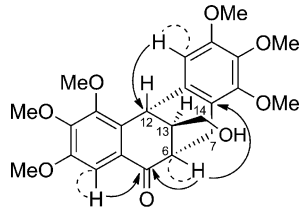


Figure 3. Some important HMBC (arrows) and HSQC (dashed arcs) correlations in compound **3**.

A literature search for this structure revealed that a small family of lignans have this bridged bicyclic structure,[44] and one of them, lirionol, a phenol that has been isolated from the bark of *Liriodendron* tulipfera is very closely related to our compound **3**.[44] The only other members of this family are lanceolatanins, isolated from *Cunninghamia lanceolata*,[45] which are used in Chinese medicine for the treatment of arthritis, and hernia, but the same dibenzobicyclo[3.3.1] framework is present in several other bioactive natural products.[46–48] Only one synthesis of this type of lignan has been reported,[49] though Pelter obtained a related compound.[50] Formation of this kind of lignan in just one operation from the conjugate addition/aldol adduct, albeit in modest yield (40%), might allow the synthesis of other members of this lignan family in a relatively efficient manner.

Treatment of aldol (±)-**4** with trifluoroacetic acid in acetonitrile at room temperature gave a different outcome. Tetrahydrofuran (±)-**17** was formed in 52% yield, presumably by a sequence that involves dehydration to give enone **16**, desilylation, and tetrahydrofuran formation by intramolecular conjugate addition of the alcohol to the enone (Scheme 5, Pathway b). The structure of the product was determined by X-ray crystallography (Figure 4). Removal of the sulfinyl group from this structure would give compounds belonging to another large family of lignans.[51,52]

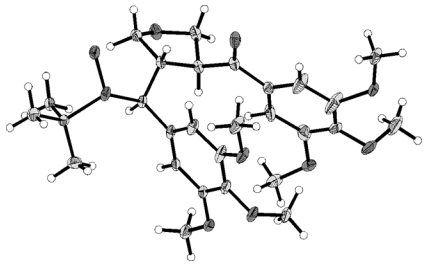


Figure 4. X-ray crystal structure of compound(±)-**17**.

The reactions described above illustrate the variety of cyclisation pathways available to intermediates such as **4** and **15**, which contain several electrophilic and nucleophilic sites. Triol derivative **15** can form stabilised benzylic carbocations under acidic conditions and the alcohols are the most reactive nucleophiles, which thus lead to the formation of stable tetrahydrofuran structures (Scheme 4). In contrast, aldol **4** first undergoes rapid dehydration to give very reactive enone **16**, which then undergoes intramolecular conjugate addition by either an activated aromatic (Scheme 5, Pathway a), or an alcohol (Scheme 5, Pathway b). The dominance of Pathway b under mild conditions may be ascribed to greater nucleophilicity of the alcohol than the aromatic ring. It is possible that Pathway b also occurs in ethanolic HCl at reflux temperatures, but that it is reversible, and the product of irreversible C–C bond formations (Pathway a) eventually predominates. Caution should be exercised in interpreting these cyclisation pathways because the outcome is very sensitive to the reaction conditions, and even to the nature of the "spectator group" on the sulfoxide (*t*Bu in this case), and further studies are needed to obtain a fuller understanding.

Conclusions

In conclusion, enantioselective total synthesis of (+)-yangambin was completed in good yield and enantioselectivity by using an enantioenriched benzyl *tert*-butyl sulfoxide as precursor. Complete asymmetric induction was achieved in the one-pot formation of a conjugate addition/aldol adduct, which was efficiently converted into yangambin. The formation of (±)-2,5-diaryltetrahydrofuran type structures, and of a lignan of the lirionol family, demonstrates the versatility of the multifunctional intermediates, and opens up new possibilities for enantioselective synthesis of several subclasses of lignans.

The power of the sulfoxide-based strategy described above derives from three key features. First, the enantioenriched sulfoxide precursor is easily prepared from a starting material obtained by catalytic asymmetric oxidation. Second, the tandem conjugate addition/aldol reaction of the sulfoxide-stabilised anion rapidly builds molecular complexity and takes place with excellent acyclic stereocontrol. Finally, the sulfinyl group acts as a good leaving group to allow formation of C–O and C–C bonds. The sulfinyl group does not just act as a chiral auxiliary in these syntheses, it is better regarded as a removable chiral functional group that plays a crucial role in the control of both the reactivity and the stereochemistry of the intermediates. Further work to exploit the use of sulfoxides in this way is in progress.

Experimental Section

General Experimental Methods: All reagents were purchased from commercial suppliers and used as received, unless otherwise stated. All reactions were carried out under a nitrogen atmosphere in oven-dried or flame-dried glassware, and all moisture sensitive liquids and solutions were transferred through syringe or cannula. Enantioenriched sulfoxide **5**[25] was prepared by earlier reported methods. The concentration of butyllithium solution in hexane was determined by titration with diphenylacetic acid in THF before use.[53] Flash column chromatography was performed by using silica 60 (40–63 microns). Assignments of the signals in the ^{1}H NMR spectra are supported by gCOSY and HSQCAD spectra. For HPLC analyses CHIRALPAK® IB column was used, and detection was by UV analysis at three wavelengths, 210.8, 230.8 and 254.8 nm. Mass spectrometric data were obtained by using electrospray ionisation, and high-resolution mass spectra were collected on a TOF spectrometer.

2-Bromo-1-(3,4,5-trimethoxyphenyl)ethanone:[22] To a solution of 3,4,5-trimethoxyacetophenone **9** (5.00 g, 23.78 mmol) in $CHCl_3$ (50 mL) at 0 °C was added a solution of Br_2 (1.34 mL, 26.16 mmol) in $CHCl_3$ (18 mL) over 45 min. The reaction mixture was stirred for 15 min at room temperature, before it was concentrated in vacuo to yield crude bromo ketone. Purification by silica gel chromatography on silica with 2:1 pentane/EtOAc yielded the bromo ketone as an off white solid (5.36 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.92 (s, 6 H, O*Me*), 3.94 (s, 3 H, O*Me*), 4.41 (s, 2 H, CH_2Br), 7.24 (s, 2 H, H^{Ar}) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 30.3 (CH_2), 56.3 (CH_3), 60.9 (CH_3), 106.5 (CH), 128.9 (C), 143.4 (C), 153.1 (C), 190.2 (C) ppm. MS (ES): *m*/*z* [M + H]$^+$ 310.92. HRMS: calcd. for $C_{11}H_{13}O_4NaBr$ [M + H]$^+$ 310.9895; found 310.9893.

(3,4,5-Trimethoxybenzoylmethyl)triphenylphosphonium Bromide: A solution of triphenylphosphine (3.77 g, 14.41 mmol) in toluene (40 mL) was added to a vigorously stirred solution of the bromide (4.16 g, 14.41 mmol) in toluene (40 mL) at room temperature to give an instant white precipitate. The mixture was stirred for a further 40 min before the reaction mixture was cooled in ice for 1 h prior to filtration under nitrogen to afford the product as a white powder (6.85 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = δ = 3.90 (s, 3 H, O*Me*), 4.01 (s, 6 H, O*Me*), 6.41 (d, *J* = 12.3 Hz, 2 H, CH_2P), 7.43–7.99 (m, 17 H, H^{Ar}) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 38.9 (*J* = 61.9 Hz, CH_2), 57.2 (CH_3), 60.9 (CH_3), 107.4 (CH), 119 (d, *J* = 89.5 Hz, C), 128.4 (d, *J* = 12.2 Hz, CH), 130 (d, *J* = 13.1 Hz, CH), 130.3 (d, *J* = 5.8 Hz, C), 131.9 (CH), 132 (d, *J* = 9.9 Hz, CH), 134 (d, *J* = 10.7 Hz, CH), 134.6 (d, *J* = 3.1 Hz, CH), 143.9 (C), 153.2 (C), 191.1 (C) ppm. MS (ES): *m*/*z* [M]$^+$

471.12. HRMS: calcd. for $C_{29}H_{28}O_4P$ $[M]^+$ 471.1725; found 471.1703. $C_{29}H_{28}BrO_4P$ (551.42): calcd. C 63.17, H 5.12; found C 63.20, H 5.15.

3,4,5-Trimethoxybenzoylmethylenetriphenylphosphorane (8): To a suspension of the phosphonium salt (1.07 g, 1.94 mmol) in THF (15 mL), was added a solution of *t*BuOK in THF (1.0 M, 1.94 mL, 1.94 mmol) over 10 min at room temperature under N_2 atmosphere. The dark brown solution that resulted was stirred for a further 15 min, before water (4 mL) was added. The layers were separated and the organic phase was washed with water (4 mL) and concentrated in vacuo gave pure ylide **8** as yellow foam (0.86 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, O*Me*), 3.90 (s, 6 H, O*Me*), 4.36 (d, J = 24.6 Hz, 1 H, C*H*P), 7.24 (s, 2 H, H^{Ar}CO), 7.43–7.84 (m, 15 H, H^{Ar}) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 50.46 (J = 113 Hz, CH), 56.2 (CH_3), 60.8 (CH_3), 104.2 (d, J = 1.2 Hz, CH), 127 (d, J = 91.3 Hz, C), 128.4 (d, J = 12.1 Hz, CH), 128.6 (d, J = 12.3 Hz, CH), 128.8 (d, J = 12.3 Hz, CH), 131.1 (d, J = 9.9 Hz, CH), 132 (d, J = 2.9 Hz, CH), 136.9 (d, J = 14.7 Hz, C), 139.3 (C), 152.5 (C), 184 (d, J = 3.4 Hz, C) ppm. MS (ES): *m*/*z* $[M + H]^+$ 471.13. HRMS: calcd. for $C_{29}H_{28}O_4P$ $[M + H]^+$ 471.1725; found 471.1732. $C_{29}H_{27}O_4P$ (470.50): calcd. C 74.03, H 5.78; found C 73.76, H 5.72.

***tert*-Butyldimethylsiloxyacetaldehyde (9):**[23] To a solution of glycerol (9.7 mL, 131 mmol), and imidazole (1.35 g, 19.89 mmol) in a mixture of CH_2Cl_2 (20 mL) and dimethyl formamide (DMF; 8 mL) a solution of *tert*-butyldimethylsilyl chloride (TBSCl; 1.00 g, 6.63 mmol) in the minimum amount of CH_2Cl_2 (≈ 1 mL) was added dropwise at room temperature. Further addition of DMF was necessary to affect complete solution (the mixture appeared somewhat cloudy). The mixture was stirred for 1 h, before water (50 mL) was added. The mixture was then concentrated in vacuo, and extracted with Et_2O (3× 15 mL), and organic phase was washed with water (3× 10 mL) to remove any DMF that remained. The organic phase was dried with magnesium sulfate and concentrated in vacuo to yield the crude monoprotected glycerol as a clear oil (0.83 g, 62%). To a vigorously stirred suspension of silica gel-supported $NaIO_4$[24] (5.38 g) in CH_2Cl_2 (17 mL) in a 50 mL round bottomed flask was added a solution of monoprotected glycerol (0.57 g, 2.69 mmol) in CH_2Cl_2 (15 mL). The reaction was monitored by TLC until the starting material had disappeared (generally 40–50 min). The mixture was filtered through a sintered glass funnel, and the silica gel was thoroughly washed with CH_2Cl_2 (10× 3 mL). The organic phase was dried with magnesium sulfate and concentrated in vacuo to afford glycol aldehyde **9** as colourless syrup (0.47 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 [s, 6 H, Si(CH_3)$_2$], 0.83 [s, 9 H, SiC(CH_3)$_3$], 4.11 (s, 2 H, CH_2O), 9.60 (s, 1 H, *H*CO) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 0.00 (CH_3), 23.7 (C), 31.1 (CH_3), 75 (CH_2), 207.6 (CH) ppm. MS (ES): *m*/*z* $[M – H]^–$ 173.15. HRMS: calcd. for $C_8H_{17}O_2Si$ $[M – H]^–$ 173.0998; found 173.0999.

(*E*)-4-(*tert*-Butyldimethylsiloxy)-1-(3,4,5-trimethoxyphenyl)but-2-en-1-one (6): To a solution of phosphorane **8** (3.91 g, 8.31 mmol) in THF (40 mL) at room temperature, was added a solution of aldehyde **9** (2.0 g, 11.63 mmol) in THF (8 mL). The reaction mixture was stirred at reflux temperatures for 3 h. After this time, it was concentrated in vacuo and the residue was subjected to silica gel chromatography with 5:1 pentane/EtOAc to yield title compound **6** as a clear oil (2.35 g, 80%), m.p. 151–154 °C (toluene/cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.00 [s, 6 H, Si(CH_3)$_2$], 0.84 [s, 9 H, SiC(CH_3)$_3$], 3.79 (s, 9 H, O*Me*), 4.32–4.35 (br. s, 2 H, CH_2O), 7.0 (dt, J = 15.1, 3.0 Hz, 1 H, C*H*), 7.08–7.16 (m, 3 H, C*H*, H^{Ar}) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 0.00 (CH_3), 23.71 (C), 31.2 (CH_3), 61.6 (CH_3), 66.3 (CH_3), 67.9 (CH_2), 111.31 (CH), 128.2 (CH), 138.4 (C), 147.7 (C), 152.8 (CH), 158.4 (C), 194.2 (C) ppm. MS (ES): *m*/*z* $[M + H]^+$ 367.09. HRMS: calcd. for $C_{19}H_{31}O_5Si$ $[M + H]^+$ 367.1941; found 367.1943.

(2*R*,3*R*,4*R*)-3-[(*tert*-Butyldimethylsilyloxy)methyl]-4-[(*S*)-*tert*-butylsulfinyl]-2-(hydroxymethyl)-1,4-bis(3,4,5-trimethoxyphenyl)butanone (4): Paraformaldehyde (732 mg, 24.4 mmol) was added to a 25 mL two-necked flask, which was connected to another 25 mL two-necked flask by a wide cannula, which was connected in turn to a bubbler, and the whole system was flushed with N_2. In the second flask, a solution of *n*,*n*-diisopropylamine (0.51 mL, 3.66 mmol) in THF (10 mL) was cooled to –78 °C and then a precooled solution of BuLi in hexane (2.5 M, 1.36 mL, 3.41 mmol) was added and the mixture was stirred for 10 min. A precooled solution of enantioenriched sulfoxide **5** (90% *ee*, 0.7 g, 2.44 mmol) in THF (5 mL) was added dropwise by cannula. After 15 min, a precooled solution of the enone **6** (1.16 g, 3.17 mmol) in THF (5 mL) was added slowly and the reaction mixture was stirred for another 15 min. After this time, the solution was quickly warmed to –25 °C. The paraformaldehyde was depolymerised by heating at 180 °C and carried into the second flask through a wide cannula by using a steady stream of N_2. The reaction mixture was warmed to –15 °C and quenched with saturated $NaHCO_3$ (7 mL), and warmed to room temperature. The reaction mixture was poured into water (7 mL) and extracted with CH_2Cl_2 (3× 30 mL). The combined extracts were dried with magnesium sulfate and concentrated in vacuo. Purification by silica gel chromatography with 1:4 pentane/EtOAc yielded title compound **4** as a white foam (1.13 g, 72%). $[\alpha]_D$ = +31.7 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 3 H, $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$), 0.85 [s, 9 H, $SiC(CH_3)_3$], 0.97 {s, 9 H, $[SOC(CH_3)_3]$}, 3.02 (t, J = 6.6 Hz, 1 H, OH), 3.05–3.12 (m, 1 H, $CHCH_2OTBS$), 3.52–3.60 (m, 1 H, CH_2OTBS), 3.68 (s, 3 H, OMe), 3.79 (s, 6 H, OMe), 3.82–3.92 (m, 10 H, 3× OMe, CH_2OTBS), 4.10–4.27 (m, 4 H, $CHCH_2OH$, CHS), 6.55 (s, 2 H, H^{Ar}), 7.15 (s, 2 H, H^{Ar}) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 0.00 ($SiCH_3$), 0.10 ($SiCH_3$), 23.6 [$SiC(CH_3)_3$], 29 [$SiC(CH_3)_3$], 31.3 [$SOC(CH_3)_3$], 50.3 (CH), 55.6 (CH), 61.6 (OCH_3), 61.7 (OCH_3), 61.7 [$SOC(CH_3)_3$], 64.8 (CH), 66.2 (OCH_3), 66.3 (OCH_3), 66.9 (CH_2OH), 67.3 ($CH_2OTBDMS$), 111.4 (CH^{Ar}), 112.5 (CH^{Ar}), 137.7 (C^{Ar}), 138 (C^{Ar}), 143.2 (C^{Ar}), 147.9 (C^{Ar}), 158.4 (C^{Ar}), 158.8 (C^{Ar}), 206.9 (C=O) ppm. HRMS: calcd. for $C_{34}H_{54}O_{10}NaSiS$ $[M + H]^+$ 705.3105; found 705.3122. $C_{34}H_{54}O_{10}SSi$ (682.94): calcd. C 59.80, H 7.97; found C 60.03, H 8.06. HPLC (CHIRALPAK® IB Column, 80:20 heptane/EtOH; 1.0 mL/min), t_R(major enantiomer) = 7.03 min, t_R(minor enantiomer) = 10.64 min, 90% *ee*.

(2*R*)-2-{(1*R*,2*R*)-3-(*tert*-Butyldimethylsiloxy)-1-[(*S*)-*tert*-butylsulfinyl]-1-(3,4,5-trimethoxyphenyl)propan-2-yl}-1-(3,4,5-trimethoxyphenyl)propane-1,3-diol (14): To a solution of aldol **4** (483 mg, 0.70 mmol) in THF (9 mL) at –78 °C, was added a solution of DIBAL in toluene (1 M, 2.1 mL, 2.1 mmol) and the reaction mixture was stirred for 3.5 h before being quenched with 5% HCl solution. The reaction mixture was extracted with CH_2Cl_2 (3× 15 mL), washed with NaCl (3 mL). The organic extracts were dried with magnesium sulfate and concentrated in vacuo. Purification by silica gel chromatography with 1:4 pentane/EtOAc yielded sulfoxide **14** as a white foam (450 mg, 92%).

(+)-Yangambin (1): Crude sulfoxide **14** (450 mg) was dissolved in ethanolic HCl (7 mL of EtOH: 7 drops HCl), and the mixture was heated to reflux for 50 min. The mixture was cooled, diluted with water (4 mL), and extracted with CH_2Cl_2 (3× 5 mL). The organic extracts were dried with magnesium sulfate and concentrated in vacuo to yield the crude title compound. This was purified by silica

gel chromatography with 1:2 pentane/EtOAc to yield title compound **1** as a white solid (150 mg, 54%), m.p. (pentane/EtOAc) 114–115 °C. $[\alpha]_D$ = +47.6 (*c* = 1, $CHCl_3$); ref.[18] +44 (*c* = 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.09 (ddd, 2 H, m, C*H*CH), 3.82 (s, 6 H, 2× O*Me*), 3.87 (s, 12 H, 4× O*Me*), 3.94 (dd, *J* = 3.5, 9.2 Hz, 2 H, OCH*H*), 4.31 (dd, *J* = 6.8, 9.1 Hz, 2 H, OC*H*H), 4.75 (d, *J* = 4.1 Hz, 2 H, ArC*H*), 6.56 (s, 4 H, H^{Ar}) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 54.2 (*C*HC*H*), 56.0 (*m*-OMe), 60.8 (*p*-OMe), 72.0 (CH_2O), 85.8 (Ar*C*H), 102.5 (CH^{Ar}), 136.7 (C^{Ar}), 137.5 (C^{Ar}), 153.3 (C^{Ar}) ppm. MS (ES): *m*/*z* [M + H]$^+$469.09. HRMS: calcd. for $C_{24}H_{30}O_8Na$ [M + H]$^+$ 469.1838; found 469.1838. $C_{24}H_{30}O_8$ (446.50): calcd. C 64.56, H 6.77; found C 64.55, H 6.82. HPLC (CHIRALPAK® IB Column, 60:40 heptane/EtOH; 1.0 mL/min), t_R(major enantiomer) = 8.38 min, t_R(minor enantiomer) = 13.52 min, 83% *ee*.

When this reaction was carried out with racemic starting material *rac*-[(2S,3R,4R,5S)-2,5-bis(3,4,5-trimethoxyphenyl)tetrahydrofuran-3,4-diyl]dimethanol (**2a**) was also isolated as a white solid in 10% yield. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.28–2.38 (m, 2 H, C*H*, C*H*), 3.28–3.41 (br. s, 2 H, O*H*), 3.64–3.72 (m, 2 H, CH_2OH), 3.84–3.88 (m, 20 H, 6× O*Me*, CH_2OH), 4.79 (d, *J* = 8.8 Hz, 2 H, C*H*O,C*H*O), 6.61 (s, 4 H, H^{Ar}) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 56.2 (*m*-OCH_3), 56.8 (CH, CH), 60.8 (*p*-OCH_3), 62.9 (CH_2), 83.4 (CH,CH), 103.1 (CH^{Ar}), 137.2 (C^{Ar}), 137.6 (C^{Ar}), 153.3 (C^{Ar}) ppm. MS (ES): *m*/*z* [M + H]$^+$ 487.14. HRMS: calcd. for $C_{24}H_{32}O_9Na$ [M + H]$^+$ 487.1944; found 487.1941.

When this reaction was carried out with racemic starting material *rac*-[(2S,3R,4R,5R)-2,5-bis(3,4,5-trimethoxyphenyl)tetrahydrofuran-3,4-diyl]dimethanol (**2b**) was also isolated as a white solid in 15% yield. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.24–2.34 (m, 1 H, C*H*), 2.57–2.67 (m, 1 H, C*H*), 3.15–3.22 (br. t, 1 H, CH_2OH), 3.41 (dd, *J* = 4.7, 10.7 Hz, 1 H, CH_2OH), 3.67 (dd, *J* = 8.5, 10.5 Hz, 1 H, CH_2OH), 3.83 (s, 4 H, O*Me*, obscured CH_2OH), 3.85 (s, 9 H, O*Me*), 3.88 (s, 6 H, O*Me*), 4.55 (d, *J* = 9.1 Hz, 1 H, C*H*O), 5.13 (d, *J* = 8.4 Hz, 1 H, C*H*O), 6.62 (s, 2 H, H^{Ar}), 6.73 (s, 2 H, H^{Ar}) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 50.7 (CH), 54.8 (CH), 56.0 (OCH_3), 56.1 (OCH_3), 60.85 (OCH_3), 60.89 (OCH_3), 63.1 (CH_2), 63.5 (CH_2), 81.4 (CH), 82.6 (CH), 103.4 (CH^{Ar}), 103.6 (CH^{Ar}), 134.4 (C^{Ar}), 135.9 (C^{Ar}), 137.8 (C^{Ar}), 153.1 (C^{Ar}), 153.3 (C^{Ar}) ppm. MS (ES): *m*/*z* [M + H]$^+$ 487.14. HRMS: calcd. for $C_{24}H_{32}O_9Na$ [M + H]$^+$ 487.1944; found 487.1943.

***rac*-(6*R*,12*R*,13*S*)-13-(Hydroxymethyl)-1,2,3,8,9,10-hexamethoxy-6,7-dihydro-6,12-methanodibenzo[a,d][8]annulen-5(12*H*)-one (*O*,*O*-Dimethyllirionol) [(±)-3]:** Sulfoxide **(±)-4** (215 mg, 0.31 mmol) was dissolved in ethanolic HCl (4 mL of EtOH/6 drops conc. HCl), the mixture was heated at reflux temperatures for 50 min. The mixture was cooled, diluted with water (2 mL), and extracted with CH_2Cl_2 (3× 5 mL). The organic extracts were dried with magnesium sulfate and concentrated in vacuo to yield the crude title compound. The crude compound was purified by silica gel chromatography on silica with 1:1 pentane/EtOAc to yield title compound **(±)-3** as a white solid (56 mg, 40%). ^1H NMR (500 MHz, $CDCl_3$): δ = δ = 2.58–2.63 (m, 1 H, CH), 2.96–3.04 (m, 2 H, CH, CH_2), 3.08 (dd, *J* = 17.2, 7.1 Hz, 1 H, CH_2), 3.58 (dd, *J* = 10.2, 9.8 Hz, 1 H, CH_2OH), 3.68 (ddd, *J* = 10.2, 6.2, 2.7 Hz, 1 H, CH_2OH), 3.79 (s, 3 H, OMe), 3.80 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 3.94 (s, 3 H, OMe), 4.03 (s, 3 H, OMe), 4.52 (br. s, 1 H, CH), 6.84 (s, 1 H, H^{Ar}), 7.29 (s, 1 H, H^{Ar}) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 27.2 (CH_2), 32.8 (CH), 41.5 (CH), 42.3 (CH), 54.9 (CH_3), 59.2 (CH_3), 59.6 (CH_3), 59.8 (CH_3), 60.3 (CH_3), 62.9 (CH_2OH), 104.6 (CH^{Ar}), 106.4 (CH^{Ar}), 117.8 (C^{Ar}), 125.2 (C^{Ar}), 132.9 (C^{Ar}), 135.1 (C^{Ar}), 139.7 (C^{Ar}), 146.6 (C^{Ar}), 148.9 (C^{Ar}), 150.5 (C^{Ar}), 150.8 (C^{Ar}), 151.0 (C^{Ar}), 198.6 (C=O) ppm. MS (ES): *m*/*z* [M + H]$^+$ 445.14. HRMS: calcd. for $C_{24}H_{29}O_8$ [M + H]$^+$ 445.1862; found 445.1860.

((3*RS*,4*RS*)-4-{(*RS*)-[(*SR*)-*tert*-Butylsulfinyl](3,4,5-trimethoxyphenyl)methyl}tetrahydrofuran-3-yl)(3,4,5-trimethoxyphenyl)methanone [(±)-17]: To a stirred solution of aldol **(±)-4** (335 mg, 0.47 mmol) in acetonitrile (3 mL) trifluoroacetic acid (55 mg, 36 μL, 0.48 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 3 h and the reaction mixture was poured onto water, quenched with $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (3× 5 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo to yield a mixture (2:1) of cyclised compounds with the above compound as the major product. The crude mixture was purified by using column chromatography on silica (1:1, pentane/ethyl acetate) to yield title compound **(±)-17** (132 mg, 0.24 mmol, 52%), m.p. (toluene/cyclohexane) 158–161 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.12 [s, 9 H, $C(CH_3)_3$], 3.47 (obscured, 1 H, CH), 3.51 (s, 3 H, OMe), 3.73 (s, 6 H, OMe), 3.83 (s, 6 H, OMe), 3.85 (s, 3 H, OMe), 3.95 (m, 3 H, obscured, CH_2O,CH), 4.11 (bdd, 2 H,CH_2O), 4.39 (d, 1 H, CHSO), 6.34 (s, 2 H, H^{Ar}), 6.78 (s, 2 H, H^{Ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = ppm 23.80 [$C(CH_3)_3$], 29.90 [$C(CH_3)_3$] 43.79, 49.36, 56.21 (CH_3), 56.31 (2× CH_3), 56.56 (CH_3), 60.58 (2× CH_3), 103.94 (2× CH^{Ar}), 107.64 (2× CH^{Ar}), 116.57 (C^{Ar}) 131.60 (2× C^{Ar}), 139.01 (C^{Ar}), 153.41 (2× C^{Ar}), 153.71 (2× C^{Ar}), 191.22 (C=O) ppm. IR (KBr) $\tilde{\nu}$ = 2950, 2840, 1587, 1506, 1464, 1410, 1148 cm^{-1}. $C_{28}H_{38}O_9S$ (550.66): calcd. C 61.07, H 6.96; found C 60.96, H 6.72.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra for compounds **1**, **2a**, **2b**, **3**, **4**, **6**, **8** and **9**. X-ray crystal structures for compounds **2b** and **17**.

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