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The synthesis of the anti-malarial natural product polysphorin and analogues using polymer-supported reagents and scavengers

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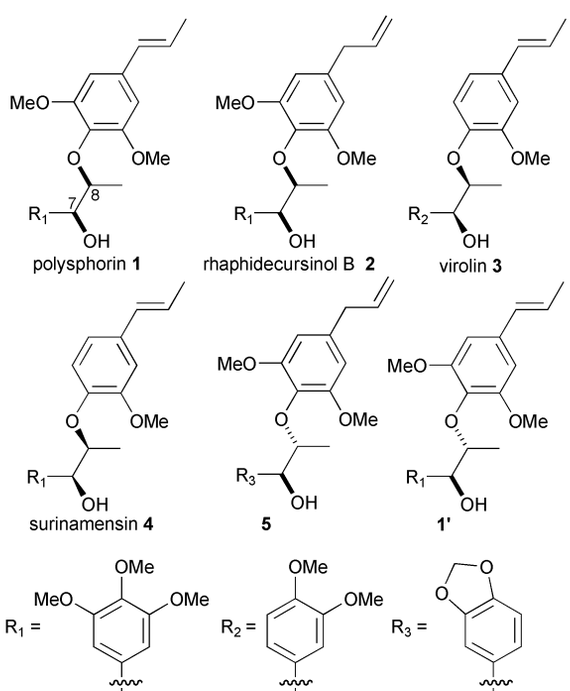
A general asymmetric route to both enantiomers of polysphorin has been developed. The route utilizes polymer-supported reagents, catalysts and scavengers to minimise the need for aqueous work-up and chromatography. This includes application of a method to scavenge 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and a "catch-and-release" procedure to extract the resultant diol following Sharpless asymmetric dihydroxylation. A novel enzymatic selective protection and investigations of a new asymmetric dihydroxylation using microencapsulated osmium tetroxide were also investigated during the course of this study.

Introduction

The neolignan polysphorin (**1**) was isolated from *Piper polysphorum C* in China,[1] and from the leaves and stems of *Rhaphidopora decursiva* in Vietnam.[2] Biological screening has since shown polysphorin (**1**) to possess *in vitro* anti-malarial activity.[2] Several other members of this family of neolignans have also been shown to display interesting biological properties: rhaphidecursinol B (**2**) shows activity against *Plasmodium falciparum*, the parasite responsible for the most severe forms of malaria,[3] but is ten times less active than polysphorin (**1**);[2] neolignans virolin (**3**) and surinamensin (**4**) both show activity against leishmaniasis, another vector-borne disease;[4] a number of neolignans including (**5**) have also been shown to exhibit potent anti-fungal activity.[5]



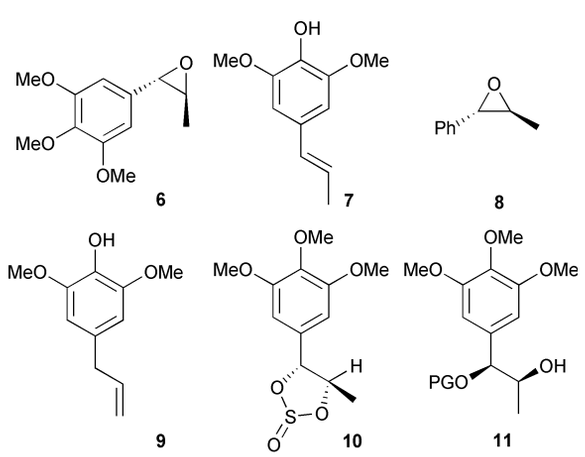
Although the published structure of polysphorin (**1′**) shows an *anti*-relationship between the two chiral centres,[2] our synthetic studies and crystal structures have confirmed that polysphorin in fact possesses a *syn* relationship between the two centres. The published ^{1}H NMR coupling constant of 8.17 Hz between H-7 and H-8 correctly corresponds to the *threo* (*syn*) compound as the *anti* compound should display a ^{1}H NMR coupling constant of approximately 2.5 Hz, based on IR, NMR and conformational studies.[6] Also, since the optical rotation of the sample of polysphorin isolated from natural sources was zero, it was presumed that this material is racemic.

In previous synthetic studies the neolignans were synthesized by oxidative coupling to give rise to racemic mixtures of *syn* and *anti* products.[5–7] Herein the development of a new general asymmetric route towards both enantiomers of polysphorin, plus a small collection of unnatural analogues is described. Polymer-supported reagents and scavengers have been used throughout to facilitate reaction work-up and purification, requiring only filtration to isolate reaction products.[8,9]

Results and discussion

Initial studies were aimed towards producing the *anti*- diastereoisomer of polysphorin (**1′**), based on the published structure. Although it is known that ring opening of secondary epoxides using phenols can sometimes be difficult, the possible reaction of epoxide **6** with phenol **7** posed a strategically attractive route to **1′**. Numerous methods were examined to open model epoxide **8** with phenol **9**, but all proved unsuccessful. Alternative attempts to open a cyclic sulfite **10** also failed to produce the desired product.[10]

Consequently, the target molecule was approached *via* an alternative S_N2 inversion of mono-protected diol **11**. Selective



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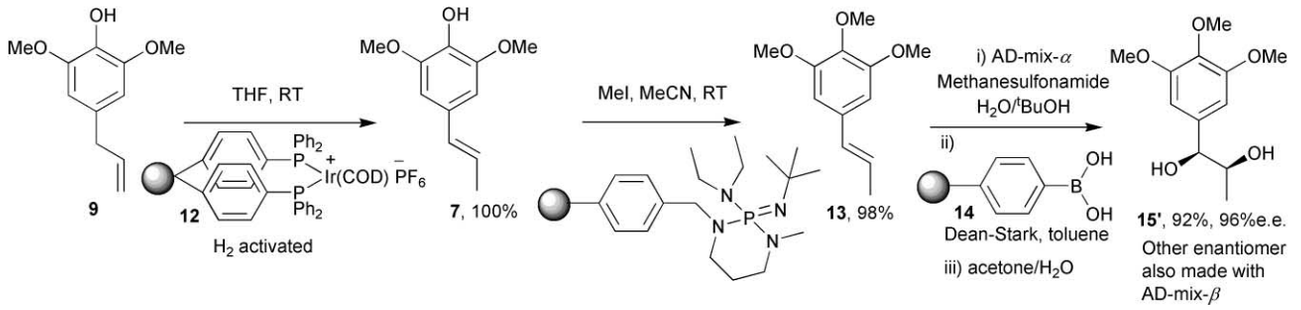
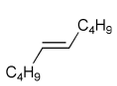
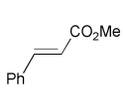
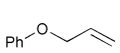


Scheme 1

Table 1 Asymmetric dihydroxylations using Os EnCat [a]

Substrate	Yield (%, isolated)	Ee (%) [b]
	97–99	94
	91	97
	88	>99
	97	90
	96	82
	89	87
	94	>99
	83	51

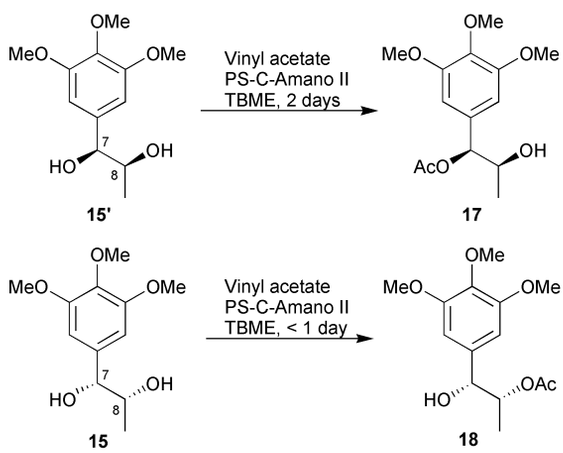
[a] Reagents and conditions: Os EnCat™ 5 mol%, $(DHQD)_2PHAL$ 5 mol%, $MeSO_2NH_2$ 1 eq., $K_3Fe(CN)_6$ 3 eq., K_2CO_3 3 eq., 1 : 1 THF–water, RT, 24–48 h. [b] Ee determined by ^{1}H-NMR analysis of the bis-Mosher ester

isomerisation of phenol **9** to *trans* alkene **7** was effected using a polymer-supported iridium catalyst **12**[9,11] (Scheme 1). Subsequent *O*-methylation using polymer-supported Schwesinger base PS-BEMP and MeI afforded **13** in 98% yield. The asymmetric centres were then installed using a Sharpless asymmetric dihydroxylation.[12] Methods for asymmetric dihydroxylation using polyurea microencapsulated osmium tetroxide (Os EnCat™)[13] were developed for intended application in this step. Prior to this work, Kobayashi *et al*. had reported a similar catalytic asymmetric dihydroxylation using phenoxyethoxymethyl-polystyrene microencapsulated osmium tetroxide.[14] Optimisation studies using Os EnCat™ with *trans*-β-methylstyrene showed that the best yield and ee could be achieved using 5 mol% of catalyst in THF–water (Table 1). This reaction was observed to exhibit a high level of solvent dependency; water–^{t}BuOH mixtures gave no reaction, while water–acetone mixtures provided only 44–50% yield. Eight substrates were screened successfully using the optimized conditions (Table 1). Experiments were also conducted with *trans*-β-methylstyrene to test catalyst recycling and these gave near quantitative yields with no drop in ees over the first three runs. However, on the fourth cycle, the yield dropped dramatically to 19%, indicating that the recycling of the Os EnCat™ was not consistently reproducible for asymmetric application. Similar observations were encountered whilst conducting experiments using $(DHQD)_2PHAL$ and NMO in acetone–water (10 : 1) solvent system. Conversely, when the reagent was recycled using achiral conditions the microcapsules appeared to maintain good activity over five recycles.[13] Overall, the unreliability observed upon recycling of the microcapsules, combined with the fact that chromatography was still required when using Os EnCat™, prompted us to seek an alternative strategy.

A polymer-supported boronic acid **14**, which had previously been applied by Fréchet to separate *cis* and *trans*-cyclohexanediol was considered.[15] It was envisaged that Fréchet's protocol could be adopted for a "catch-and-release" method to purify diol **15′** synthesized by conventional Sharpless asymmetric dihydroxylation (Scheme 1). Following aqueous work-up, diol **15′** was heated to reflux with boronic acid resin **14**. When TLC analysis indicated that all the diol had been effectively captured by the polymer, the solution of impurities was removed by filtration and the remaining polymer beads washed with excess toluene. Subsequent washing using 10 : 1 acetone–water was then used to cleave purified diol **15′**. Release of the diol was much easier on a smaller scale than on a gram scale, where several washes were needed to release all of the clean diol.

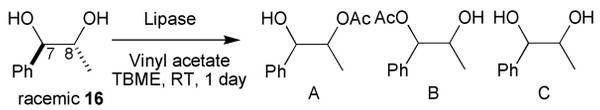
Selective protection of diol **15** was investigated: cleavage of a cyclic silyl ether using BuLi;[16] cleavage of an acetonide using MeMgBr;[17] and reductive cleavage of an orthoester[18] all failed to achieve appreciable selectivity due to difficulty differentiating between the two secondary alcohols.

Consequently, an enzymatic selective protection was investigated. Seven enzymes were screened in combination with racemic diol **16** (Table 2). As anticipated, most lipases only acylated one enantiomer, but at the undesired C-8 position. However, the result using PS–C Amano II from *Pseudomonas cepacia* immobilized on ceramic particles was more successful; one enantiomer was selectively protected at the desired C-7 position and the other enantiomer on the C-8 hydroxyl. The enzyme was tested on enantiomerically enriched diols **15** and **15′** (Scheme 2), made by a Sharpless dihydroxylation



Scheme 2

Table 2 Lipase screening[a]

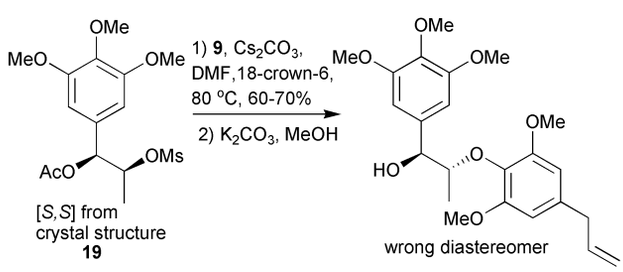


Entry	Lipase	Result
1	Type VII, *Candida rugosa*	A + C (trace B)
2	PS "Amano" from *Pseudomonas cepacia*	A + C
3	PS -C "Amano" II from *Pseudomonas cepacia* immobilised on ceramic particles	A + B
4	Type II, *Porcine pancreas*	A + C (trace B)
5	*Candida cylindrica*, immobilised on Sol–Gel-AK	No reaction
6	*Rhizopus delemar*	No reaction
7	*Candida cylindrica*	A + C (trace B)

[a] Reagents and conditions: lipase (292 mg), diol **16** (0.33 mmol), vinyl acetate (3.5 mmol), TBME (4.5 ml), RT, 17 h.

(~96% ee). Reaction with the 7*R*, 8*R* diol **15** led to the acylation at the undesired C-8 position **18**. Fortunately, reaction with its enantiomer **15′** resulted in selective acylation at the C-7 hydroxyl (**17**). Although we have used enantiomerically enriched diols for the purpose of our synthesis, this novel enzymatic protection could potentially complement existing methods for enzymatic kinetic resolution of racemic diols.[19]

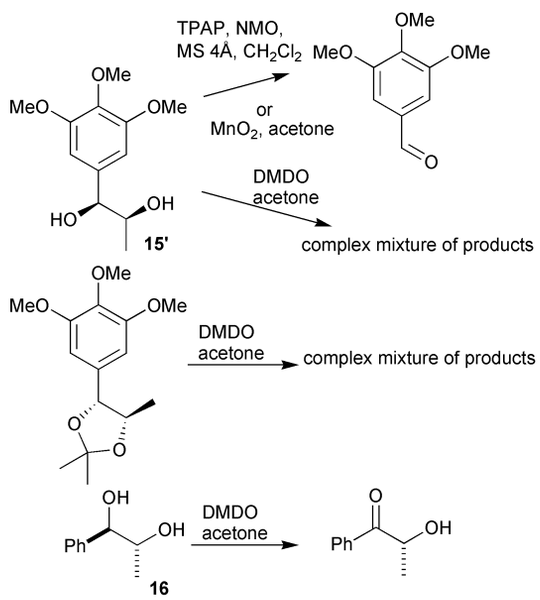
The Mitsunobu reaction between **17** and **9** was investigated. Unfortunately, all tested conditions failed to give any desired product, owing to the low reactivity of phenol **9**. Therefore, stepwise mesylation followed by S_N2 displacement was investigated as an alternative. Most conventional methods for displacing the mesylate failed to initiate a reaction. The only successful conditions applied Cs_2CO_3 and 18-crown-6 (Scheme 3).[20] Unfortunately this led to the wrong diastereoisomer of the natural product rhaphidecursinol B (**2**), exhibiting a ^{1}H-NMR coupling constant of 2.2 Hz between H-7 and H-8.



Scheme 3

It was envisaged that a secondary mesylate would be further activated for displacement if formed on the alcohol adjacent to a carbonyl centre. A stereoselective reduction could then permit access to polysphorin (**1**). Both chelation and non-chelation controlled reductions of similar compounds are known.[5,21] The α-hydroxy ketone **20** was produced by selectively oxidising the benzylic position of diol **15**. Transition metal oxidants such as MnO_2 and tetra-*N*-propylammonium perruthenate (TPAP) unfortunately resulted in diol cleavage in preference to selective oxidation (Scheme 4). Application of dimethyldioxirane (DMDO) to the diol or the corresponding acetonide led to a complex mixture of products, even though the same oxidation was successful when used in combination with diol **16** (Scheme 4).[22]

Fortunately, application of DDQ gave the desired α-hydroxy ketone **20** in 89–94% yield without significant racemisation. As DDQ is notoriously difficult to remove using column chromatography, a mixed resin-bed scavenging method was successfully applied to extract excess DDQ.[23] Polymer-supported ascorbate resin was used to reduce any excess DDQ to DDQH,



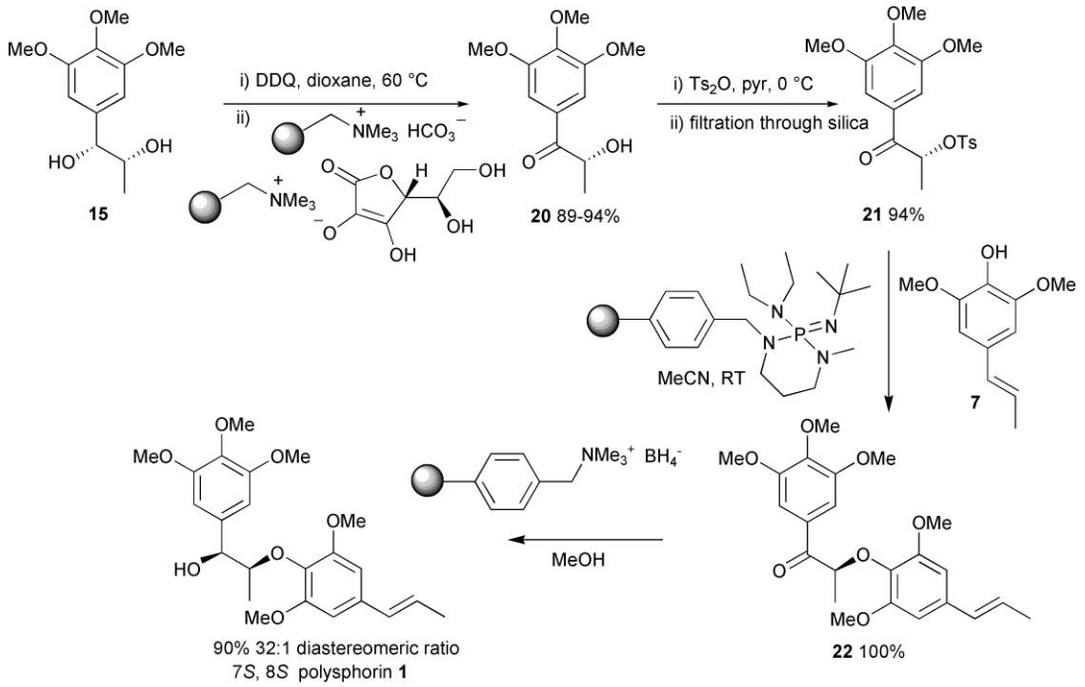
Scheme 4

while polymer-supported bicarbonate was used concurrently to scavenge DDQH, resulting in a clear colourless solution (Scheme 5).

Tosylation of α-hydroxy ketone **20** was achieved in 94% yield using toluenesulfonic anhydride and pyridine, followed by filtration through silica gel. Since a high concentration of both reactants was found to be essential for this reaction, application of PS-DMAP or diethylaminomethyl-polystyrene failed to provide complete conversions as a large amount of solvent was necessary to swell the polymer-supported reagents. Alternative conversion of the α-hydroxy ketone **20** to the corresponding mesylate, bromide or iodide did not give sufficiently clean reactions.

The S_N2 coupling of phenol **7** with tosylate **21** was accomplished in quantitative yield using PS-BEMP phosphazene base. Finally, a non-chelation control polymer-supported borohydride reduction of the resulting ketone **22** yielded the natural product (7*S*, 8*S*)-polysphorin (**1**) in a 13 : 1 to 32 : 1 diastereomeric ratio.[24] A chromatographic separation was carried out at this stage to yield 90% of the desired pure polysphorin (**1**); the NMR spectra matched that of the isolated natural product.[2]

Application of the devised route permitted the synthesis of both enantiomers of polysphorin. Interestingly, these enantiomers displayed complementary optical activity, further confirming that the samples of polysphorin isolated from nature were racemic. A small collection of analogues, including



Scheme 5

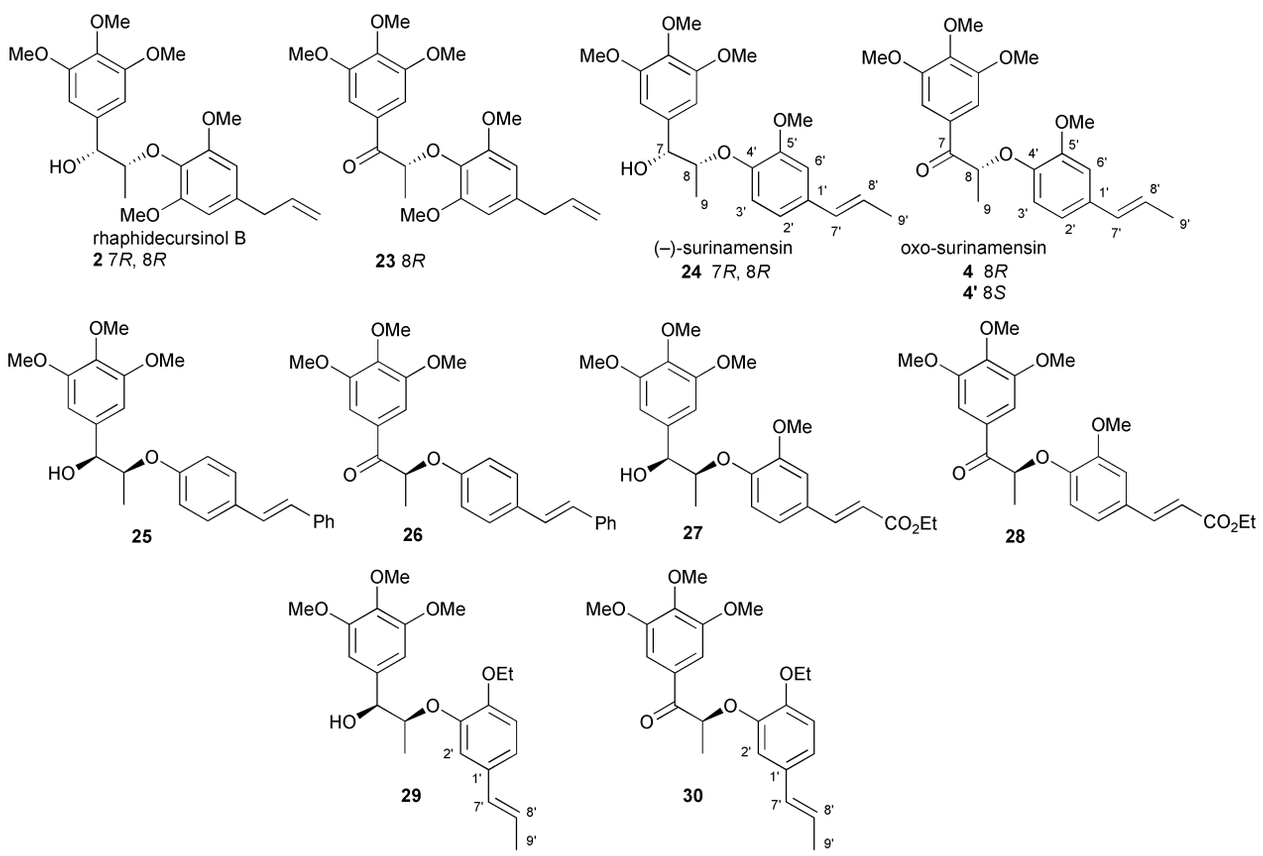


Fig. 1

rhaphidecursinol B (**2**) (Fig. 1) was synthesized under the generic conditions varying the phenol subunit incorporated in the penultimate step.

The relative stereochemistry of this family was proven by the acquisition of a crystal structure of rhaphidecursinol B (**2**) (Fig. 2), which clearly displays a *syn* relationship between the two stereogenic centres. A crystal structure of hydrazone derivative **31** (Fig. 3), synthesized by oxidative cleavage of the double bond in **1**, followed by reaction with *p*-toluenesulfonyl hydrazide (Scheme 6), proved the absolute stereochemistry of (7*R*, 8*R*)-polysphorin.

In conclusion, we have developed a general enantioselective route towards polysphorin and various analogues. Only one aqueous work-up and one chromatographic purification were necessary throughout the whole synthesis due to the multi-step application of polymer-supported reagents, scavengers and catalysts. During the course of this study a novel enzymatic protection was discovered and asymmetric dihydroxylations

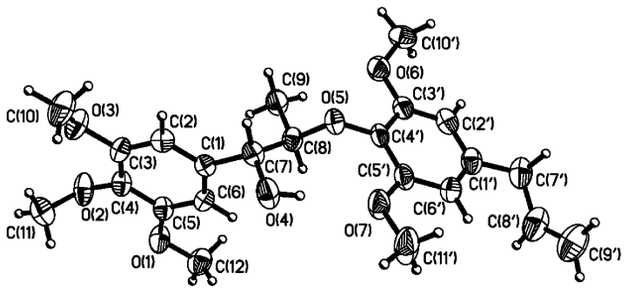


Fig. 2

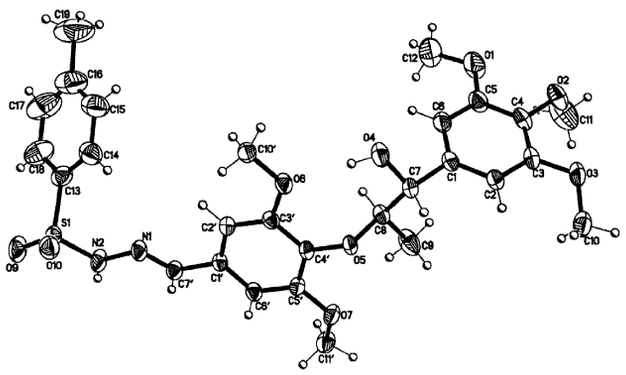
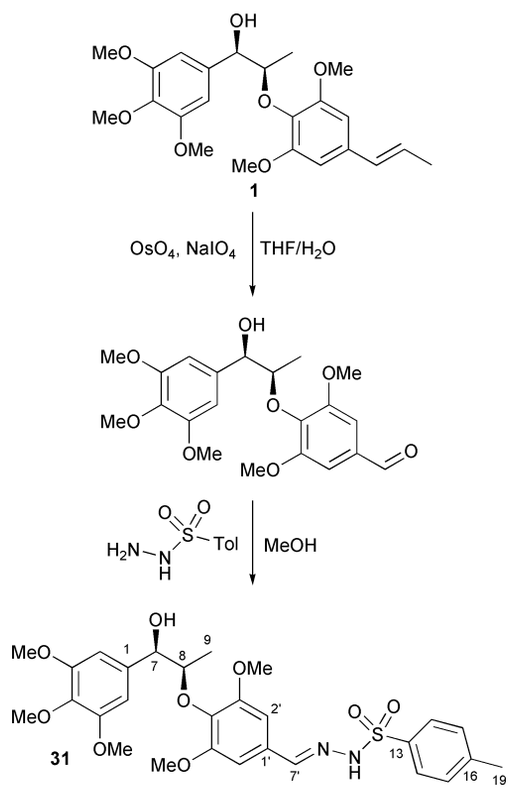


Fig. 3



Scheme 6

using OsEnCat™ were investigated, though these were not utilised in the final synthesis.

Experimental

Unless otherwise specified, reactions involving polymers were carried out on a laboratory shaker IKA 125 at 250 rpm. Moisture sensitive reactions were carried out under an argon atmosphere using oven-dried glassware. Commercially available resins were washed and dried *in vacuo* prior to use. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl; acetonitrile (MeCN), benzene, dichloromethane (CH_2Cl_2), methanol (MeOH) and toluene from calcium hydride. All other solvents and reagents were used as supplied unless otherwise specified. Analytical thin layer chromatography (TLC) was performed using pre-coated glass-backed plates (Merck Kieselgel 60 F254) and visualised by ultra-violet radiation (254 nm), acidic ammonium molybdate(IV) or acidic potassium permanganate(VII) solutions. Optical rotations were determined on a Perkin-Elmer polarimeter Model 343. Infra-red spectra were obtained on Perkin-Elmer Spectrum One FT-IR Universal ATR Sampling Accessory, deposited neat or as a chloroform solution to a diamond/ZnSe plate. ^{1}H-NMR spectra were recorded in $CDCl_3$ on a Bruker Advance DPX-400 spectrometer at 400 MHz with residual chloroform as the internal reference (δ_H = 7.25 ppm). ^{13}C-NMR spectra were recorded in $CDCl_3$ on the same spectrometer at 100 MHz with the central peak of chloroform as the internal reference (δ_C = 77.0 ppm). Where DEPT was taken, the CH and CH_3 carbons are denoted (+) and CH_2 carbons (−). Mass spectra were obtained on a Kratos MS890MS spectrometer (+EI) or a Micromass Q-TOF spectrometer (+ESI) at the Department of Chemistry, University of Cambridge. Optical rotations were measured on a Perkin-Elmer 343 polarimeter using a sodium lamp (λ 589 nm, D-line); $[\alpha]_\lambda^{T^\circ C}$ values are reported in 10^{-1}deg cm^2 g^{-1}, concentration (c) in g per 100 ml. Microanalyses were performed by Medac Ltd., Surrey. X-ray crystal structures were determined at the Department of Chemistry, Lensfield Road, Cambridge. Polymer-supported iridium catalyst **12** was prepared following the previously published procedure.[9]

Preparation of 2,6-dimethoxy-4-(*E*)-propenyl-phenol 7[6]

Hydrogen was bubbled through a suspension of catalyst **12** (1.27 g, 0.8 mmol based on Ir content) and THF (17 ml) until the polymer turned from red to chrome yellow. The suspension was flushed with argon before addition of 4-allyl-2,6-dimethoxyphenol (2 g, 10 mmol) and the resulting suspension was agitated under an atmosphere of argon at RT. After 24 h, the polymer was removed by filtration and washed with THF. The filtrate was concentrated *in vacuo* to give the title compound as a colourless oil with a 60 : 1 *trans* : *cis* selectivity. Crude mass recovery was quantitative. ν_{max} /cm^{-1} 3470 br (OH), 1653 (alkene C=C), 1603, 1516 (Ar C=C), 961 (*trans* HC=CH); δ_H(400 MHz, $CDCl_3$) 6.55 (2 H, s, Ar–H), 6.29 (1 H, dq, *J* 15.7, 1.8, C*H*=CHCH$_3$), 6.07 (1 H, dq, *J* 15.7, 6.6, CH=C*H*CH$_3$), 5.46 (1 H, s, O*H*), 3.87 (6 H, s, OCH$_3$), 1.85 (3 H, dd, *J* 6.6, 1.8, CH=CHC*H*$_3$); δ_C($CDCl_3$) 147.1, 134.0, 130.9, 129.6, 123.8, 102.7, 56.2, 18.2; Found (ESI): [M + Na]$^+$ 217.0841, $C_{11}H_{14}O_3Na$ requires 217.0838.

Preparation of 1,2,3-trimethoxy-5-(*E*)-propenyl-benzene 13[25]

PS-BEMP (Fluka, 2.2 mmolg^{-1} base, 14 g, 31 mmol) and iodomethane (0.71 ml, 11 mmol) was added to a solution of 2,6-dimethoxy-4-(*E*)-propenyl-phenol **7** (2 g, 10 mmol) in acetonitrile (40 ml). The resulting suspension was agitated under an atmosphere of argon at RT. After 2 h, the spent polymer was removed by filtration to yield the title compound as a yellow oil (2.1 g, 98%); ν_{max} /cm^{-1} 1580 (Ar C=C), 1505 (Ar C=C); δ_H(400 MHz, $CDCl_3$) 6.55 (2 H, s, Ar–H), 6.32 (1 H, d, *J* 15.7, C*H*=CHCH$_3$), 6.14 (1 H, dq, *J* 15.7, 6.5, CH=C*H*CH$_3$), 3.85 (6 H, s, OC*H*$_3$), 3.82 (3 H, s, OC*H*$_3$), 1.87 (3 H, d, *J* 6.6, CH$_3$); δ_C($CDCl_3$) 153.3, 137.3, 133.8, 130.9+, 125.3+, 103.0+, 60.9+, 56.1+, 18.3+; Found (ESI): [M + Na]$^+$ 231.0992, $C_{12}H_{16}O_3Na$ requires 231.0997.

Preparation of polymer-supported boronic acid 14[26]

Bromopolystyrene (Fluka 1% DVB, 4 mmolg^{-1} Br, 40 g, 160 mmol) was swelled in THF (250 ml) and *n*BuLi (192 mmol)

added slowly at RT. The beads were allowed to stir at RT for 3 h. Approximately 50 ml of the solution was removed *via* syringe before the remaining suspension was cooled to −78 °C. Trimethyl borate (22.4 g, 216 mmol) was added dropwise over 45 min at −78 °C and the resulting suspension allowed to warm to RT and stir for 24 h. The reaction was quenched by addition of 1 M HCl (150 ml). The beige beads were washed with 1 M HCl, water, THF and ether before they were dried under vacuum. Elemental analysis indicated 0.53% B corresponding to a loading of 0.49 mmol g^{-1} B.

Polymer-supported boronic acid is also commercially available from Lancaster Synthesis, catalogue number 19459.

Preparation of 1-(3,4,5-trimethoxy-phenyl)-propane-1*R*,2*R* diol 15

A suspension of AD-mix-β (10.1 g), methanesulfonamide (685 mg, 7.2 mmol) in water (21 ml) and ^{t}BuOH (21 ml) was cooled to 0 °C before 1,2,3-trimethoxy-5-(*E*)-propenyl-benzene (**13**) (1.5 g, 7.2 mmol) was added. The reaction was allowed to warm to RT and stir over 16 h before it was quenched by addition of sodium sulfite (10.5 g). After the suspension was stirred for 20 min, the product was extracted with ethyl acetate and methanesulfonamide removed with 2 M KOH. The combined organic layers were dried (brine, Na_2SO_4) and concentrated *in vacuo* to yield a yellow oil. The crude yellow oil was dissolved in toluene (110 ml) and polymer-supported boronic acid added (15.6 g) before the suspension was heated to relux with a Dean–Stark apparatus for 24 h. When TLC analysis showed that no diol product was present in the solution, the polymer beads were isolated and washed with toluene. Finally, the polymer beads were washed with a 10 : 1 acetone : water solution until all the diol product has been cleaved from the polymer beads. The filtrate was dried with $MgSO_4$ and concentrated *in vacuo* to yield a colourless oil (1.44 g, 83%); $[a]_D^{25}$ −28 (*c* 0.805, $CHCl_3$); ν_{max} /cm^{-1} 3446 br (OH), 1592 (Ar C=C), 1508 (Ar C=C); δ_H(400 MHz, $CDCl_3$) 6.52 (2H, s, Ar–H), 4.25 (1 H, d, *J* 7.3, ArC*H*OH), 3.81 (1 H, m, CH_3CHOH), 3.81 (6 H, s, OCH_3), 3.79 (3 H, s, OCH_3), 3.36 (1 H, br s, O*H*), 3.07 (1 H, br s, O*H*), 1.04 (3 H, d, *J* 6.59, CH_3); δ_C($CDCl_3$) 153.2, 137.7, 136.8, 103.8, 79.5, 72.1, 60.8, 56.1, 18.9; Found (EI): $[M]^+$ 242.1158, $C_{12}H_{18}O_5$ requires 242.1154.

The (1*S*, 2*S*)-enantiomer **15′** was prepared in the same way using AD-mix-α; $[a]_D^{25}$ +25 (*c* 1.081, $CHCl_3$).

Preparation of acetic acid 2*S*-hydroxy-1*S*-(3,4,5-trimethoxy-phenyl)-propyl ester 17

Diol **15′** (780 mg, 3.2 mmol) was dissolved in ^{t}butyl methyl ether (30 ml). Lipase PS-C Amano II immobilized on ceramic particles (3.2 g) and vinyl acetate (2.77 g, 32 mmol) was added to this solution and the resulting suspension was allowed to stir at RT. After 48 h, the lipase beads were removed by filtration and the resulting filtrate concentrated *in vacuo* to yield a colourless oil. Purification by silica gel chromatography (3 : 1 EtOAc : petrol ether) yielded the title product as a colourless oil (755 mg, 83%). R_f (1 : 1 EtOAc : petroleum ether) = 0.12. $[a]_D^{20}$ +59.0 (*c* 0.583, $CHCl_3$); ν_{max} /cm^{-1} 3474 br (OH), 1735 (C=O), 1592 (Ar C=C), 1508 (Ar C=C); δ_H(400 MHz, $CDCl_3$) 6.53 (2H, s, Ar–H), 5.45 (1H, d, *J* 7.0, H-7), 4.02 (1H, dq, *J* 7.0, 6.6, H-8), 3.85 (6H, s, OCH_3), 3.82 (3H, s, OCH_3), 2.13 (3H, s, C=OCH_3), 1.10 (3H, d, *J* 6.6, H-9); δ_C($CDCl_3$) 170.3, 153.4, 138.1, 133.2, 104.3+, 80.6+, 70.1+, 60.8+, 56.2+, 21.2+, 18.9+; Found (ESI): $[M + Na]^+$ 307.1146, $C_{14}H_{20}O_6Na$ requires 307.1158.

Preparation acetic acid 2*R*-hydroxy-1*R*-methyl-2-(3,4,5-trimethoxy-phenyl)-ethyl ester 18

Diol **15** (30 mg, 0.12 mmol) was dissolved in ^{t}butyl methyl ether (2 ml). Lipase PS-C Amano II immobilized on ceramic particles (131 mg) and vinyl acetate (113 mg, 1.31 mmol) was added to this solution and the resulting suspension was agitated at RT After 17 h, the lipase beads were removed by filtration and the resulting filtrate concentrated *in vacuo* to yield a colourless oil. Purification by silica gel chromatography (3 : 1 EtOAc : petrol ether) yielded the title product as a colourless oil (33 mg, 94%). R_f (3 : 1 EtOAc : petroleum ether) = 0.30. $[a]_D^{25}$ −31.0 (*c* 0.8, $CHCl_3$); ν_{max} /cm^{-1} 3488 br (OH), 1735 (C=O), 1592 (Ar C=C), 1506 (Ar C=C); δ_H(400 MHz, $CDCl_3$) 6.57 (2 H, s, Ar–H), 5.05 (1 H, dq, *J* 7.3, 6.6, H-8), 4.52 (1 H, dd, *J* 7.3, 3.3, H-7), 3.85 (6 H, s, OCH_3), 3.83 (3 H, s, OCH_3), 2.47 (1 H, d, *J* 3.3, O*H*), 2.09 (3 H, s, C=OCH_3), 1.10 (3 H, d, *J* 6.6, H-9); δ_C($CDCl_3$) 170.8, 153.4, 138.0, 135.7, 104.0+, 77.3+, 74.6+, 60.8+, 56.2+, 21.3+, 16.6+; Found (ESI): $[M + Na]^+$ 307.1140, $C_{14}H_{20}O_6Na$ requires 307.1158.

Preparation of polymer-supported ascorbate [23]

Ambersep 900 OH^- (Acros, 35 g) was placed in a sintered funnel and washed with a 0.4 M ascorbic acid solution (1.2 l) over a 1.5 h period. The resulting beige beads were then washed with water (1 l), MeOH (500 ml) and acetone (500 ml) and dried *in vacuo* for 24 h; ν_{max} /cm^{-1} 3281 br (OH), 1788 (C=O), 1725 (C=O).

Preparation of polymer-supported bicarbonate

Chloride on polymer-support (Fluka, 4 mmol g^{-1}, 50 g) was placed in a sintered funnel and washed with a saturated $NaHCO_3$ solution until the filtrate tested negative for Cl^-. The polymer beads were washed with water, acetone, ether and dried *in vacuo* for 24 h.

(Polystyrylmethyl)trimethylammonium bicarbonate is also available from Merck Biosciences, catalogue number 01–64–0419.

Preparation of 2*R*-hydroxy-1-(3,4,5-trimethoxy-phenyl)-propan-1-one 20

Diol **15** (1.3 g, 5.36 mmol) was dissolved in dioxane (26 ml). DDQ (1.83 g, 8 mmol) was added and the resulting mixture was allowed to stir at 60 °C for 12 h. The solution was concentrated *in vacuo* and redissolved in CH_2Cl_2 (100 ml). Polymer-supported ascorbate (18.9 g) and polymer-supported bicarbonate (15.2 g) were added to the solution and the resulting suspension was allowed to stir at RT for 2 h, when TLC analysis indicated that all DDQ and DDQH had been scavenged by the polymers. The purple and yellow polymer beads were removed by filtration to leave a pale yellow filtrate. Concentration *in vacuo* yielded a pale yellow oil (1.14 g, 89%); $[a]_D^{25}$ +48 (*c* 0.8, $CHCl_3$); ν_{max} /cm^{-1} 3475 br (OH), 1678 (C=O), 1585 (Ar C=C), 1505 (Ar C=C); δ_H(400 MHz, $CDCl_3$) 7.15 (2 H, s, Ar–H), 5.10 (1 H, dq, *J* 7.0, 6.6, C*H*OHMe), 3.92 (3 H, s, OCH_3), 3.90 (6 H, s, OCH_3), 3.74 (1 H, d, *J* 6.6, O*H*), 1.44 (3 H, d, *J* 7.0, CH_3); δ_C($CDCl_3$) 201.1, 153.2, 143.4, 128.3, 106.2+, 69.0+, 60.9+, 56.4+, 22.6+; Found (EI): $[M]^+$ 240.1004, $C_{12}H_{16}O_5$ requires 240.0998.

The 2*S* enantiomer was prepared in the same way using 1-(3,4,5-trimethoxy-phenyl)-propane-1*S*,2*S* diol **15′** as the starting material. $[a]_D^{25}$ −45 (*c* 1.143, $CHCl_3$).

Preparation of toluene-4-sulfonic acid 1*R*-methyl-2-oxo-2-(3,4,5-trimethoxy-phenyl)-ethyl ester 21

A solution of 2*R*-hydroxy-1-(3,4,5-trimethoxy-phenyl)-propan-1-one (**20**) (293 mg, 1.22 mmol) in pyridine (1.5 ml) was cooled to 0 °C before *p*-toluenesulfonic anhydride (600 mg, 1.85 mmol) was added to the solution. The resulting suspension was allowed to stir at 0 °C for 1 h. Filtration through a plug of silica (1 : 1 $CHCl_2$: ether) and concentration *in vacuo* yielded a yellow oil (455 mg, 94%); $[a]_D^{25}$ −3.1 (*c* 2.0, $CHCl_3$); ν_{max} /cm^{-1} 1695 (C=O), 1583 (Ar C=C), 1505 (Ar C=C), 1128 (SO_2O); δ_H(400 MHz, $CDCl_3$) 7.75 (2 H, d, *J* 8.4, Ar–H), 7.28 (2 H, d,

J 8.4, Ar–H), 7.21 (2 H, s, Ar–H), 5.76 (1 H, q, *J* 7.0, C*H*MeOTs), 3.92 (3 H, s, OCH_3), 3.89 (6 H, s, OCH_3), 2.41 (3 H, s, Ar–CH_3), 1.55 (3 H, d, *J* 7.0, CH_3); δ_C($CDCl_3$) 193.3, 153.1, 145.0, 143.4, 133.6, 129.8+, 128.7, 127.8+, 106.6+, 77.06+, 60.9+, 56.4+, 21.6+, 18.4+; Found (ESI): $[M + Na]^+$ 417.0992, $C_{19}H_{22}O_7SNa$ requires 417.0984.

The 1*S* enantiomer was prepared in the same way using 2*S*-hydroxy-1-(3,4,5-trimethoxy-phenyl)-propan-1-one as the starting material; $[a]_D^{25}$ +3.0 (*c* 0.713, $CHCl_3$).

Preparation of 2*S*-(2,6-dimethoxy-4-propenyl-phenoxy)-1-(3,4,5-trimethoxy-phenyl)-propane-1-one 22

Phenol **6** (33 mg, 0.17 mmol) and PS-BEMP (Fluka, 2.2 mmol g^{-1} base, 94 mg, 0.21 mmol) was added to a solution of toluene-4-sulfonic acid 1*R*-methyl-2-oxo-2-(3,4,5-trimethoxy-phenyl)-ethyl ester (**21**) (68 mg, 0.17 mmol) in acetonitrile (3 ml). The resulting suspension was allowed to stir at RT. After 15 h, the polymer beads were removed by filtration and washed with ether and CH_2Cl_2. The filtrate was concentrated *in vacuo* to yield a yellow oil. Crude mass recovery was quantitative. The crude product was used directly in the next reaction. A small amount of material was purified by column chromatography (100 : 1 CH_2Cl_2 : ether) for characterisation. R_f (1 : 1 ether : petroleum ether) = 0.14. $[a]_D^{25}$ −59 (*c* 2.35, $CHCl_3$); ν_{max} /cm^{-1} 1683 (C=O), 1582 (Ar C=C), 1503 (Ar C=C); δ_H(400 MHz, $CDCl_3$) 7.49(2 H, s, Ar–H), 6.52 (2 H, s, Ar–H), 6.30 (1 H, d, *J* 15.7, H-7′), 6.13 (1 H, dq, *J* 15.7, 6.2, H-8′), 5.27 (1 H, q, *J* 7.0, H-8), 3.90 (3 H, s, OCH_3), 3.87 (6 H, s, OCH_3), 3.74 (6 H, s, OCH_3), 1.85 (3 H, d, *J* 6.2, H-9′), 1.54 (3 H, d, *J* 7.0, H-9); δ_C($CDCl_3$) 197.4, 153.2, 152.8, 142.5, 134.6, 134.0, 130.8+, 130.5, 125.4+, 107.1+, 102.8+, 80.7+, 60.9+, 56.2+, 55.8+, 18.3+, 17.8+; Found (ESI): $[M + Na]^+$ 439.1747, $C_{23}H_{28}O_7Na$ requires 439.1733.

The 2*R* enantiomer was prepared in the same way using toluene-4-sulfonic acid 1*S*-methyl-2-oxo-2-(3,4,5-trimethoxy-phenyl)-ethyl ester as the starting material; $[a]_D^{25}$ +60 (*c* 0.88, $CHCl_3$).

(7*S*, 8*S*)-Polysphorin 1[2]

Polymer-supported borohydride (Aldrich, 2.5 $mmolg^{-1}$ on Amberlite IRA-400, 82 mg, 0.2 mmol) was added to a solution of 2*S*-(2,6-dimethoxy-4-propenyl-phenoxy)-1-(3,4,5-trimethoxy-phenyl)-propane-1-one (**22**) (17 mg, 0.041 mmol) in methanol (0.8 ml) and the resulting suspension was stirred at RT. After 16 h, the polymer beads were removed by filtration and washed with methanol. The filtrate was concentrated *in vacuo* to give a 32 : 1 mixture of diastereoisomers in favour of the title product. The diastereoisomers were separated by preparative TLC (eluent: 3 : 1 ether : petroleum ether) to yield the title product as a viscous white oil (16 mg, 96%). R_f (3 : 1 ether : petroleum ether) = 0.23. Mp 107–108 °C; $[a]_D^{25}$ +95 (*c* 0.8, $CHCl_3$); ν_{max} /cm^{-1} 3471 br (OH), 1582 (Ar C=C), 1503 (Ar C=C); δ_H(400 MHz, $CDCl_3$) 6.58 (2 H, s, Ar–H), 6.57 (2 H, s, Ar–H), 6.33 (1 H, d, *J* 15.7, H-7′), 6.16 (1 H, dq, *J* 15.7, 6.6, H-8′), 4.88 (1 H, s, O*H*), 4.58 (1 H, d, *J* 8.4, H-7), 3.96 (1 H, dq, *J* 8.4, 6.2, H-8), 3.88 (6 H, s, OCH_3), 3.84 (6 H, s, OCH_3), 3.81 (3 H, s, OCH_3), 1.88 (3 H, d, *J* 6.6, H-9′), 1.21 (3 H, d, *J* 6.2, H-9); δ_C($CDCl_3$) 153.1, 152.8, 137.6, 136.4, 136.1, 133.9, 130.8, 125.6+, 104.4+, 103.0+, 86.4+, 79.4+, 60.8+, 56.1+, 56.0+, 18.3+, 17.7+; Found (ESI): $[M + Na]^+$ 441.1907, $C_{23}H_{30}O_7Na$ requires 441.1889.

The 7*R*, 8*R* enantiomer was prepared in the same way using 2*R*-(2,6-dimethoxy-4-propenyl-phenoxy)-1-(3,4,5-trimethoxy-phenyl)-propane-1-one as starting material. The diastereoisomeric ratio was 15:1 in favour of the 7*R*, 8*R* isomer; $[a]_D^{25}$ −87 (*c* 0.34, $CHCl_3$).

The following analogues of compounds **22** and **1** were made using the same general methods. The coupling phenol was varied to produce analogues of **22** and subsequent reduction of these analogues using polymer-supported borohydride produced analogues of **1**.

Preparation of 2*R*-(4-allyl-2,6-dimethoxy-phenoxy)-1-(3,4,5-trimethoxy-phenyl)-propane-1-one 23[27]

Phenol **9** (100 mg, 0.52 mmol) and PS-BEMP (Fluka, 2.2 mmol g^{-1} base, 282 mg, 0.62 mmol) was added to a solution of toluene-4-sulfonic acid 1*S*-methyl-2-oxo-2-(3,4,5-trimethoxy-phenyl)-ethyl ester (204 mg, 0.52 mmol) in acetonitrile (5 ml) and the resulting suspension was allowed to stir at RT. After 15 h, the polymer beads were removed by filtration and washed with ether and CH_2Cl_2. The filtrate was concentrated *in vacuo* to yield a yellow oil. Crude mass recovery was quantitative. The crude product was used directly in the next reaction. A small amount of material was purified by column chromatography (100 : 1 CH_2Cl_2 : ether) for characterisation. R_f (100 : 1 CH_2Cl_2 : ether) = 0.09. $[a]_D^{25}$ +44.5 (*c* 1.47, $CHCl_3$); ν_{max} /cm^{-1} 1683 (C=O), 1588 (Ar C=C), 1504 (Ar C=C); δ_H(400 MHz, $CDCl_3$) 7.51 (2 H, s, Ar–H), 6.37 (2 H, s, Ar–H), 5.93 (1 H, m, H-8′), 5.24 (1 H, q, *J* 6.6, H-8), 5.10 (1 H, d, *J* 17.2, H-9′), 5.08 (1 H, d, *J* 8.1, H-9′), 3.90 (3 H, s, OCH_3), 3.87 (6 H, s, OCH_3), 3.72 (6 H, s, OCH_3), 3.31 (2 H, d, *J* 7.0, H-7′), 1.54 (3 H, d, *J* 7.0, H-9); δ_C($CDCl_3$) 197.5, 153.2, 152.8, 142.2, 134.1+, 136.11, 133.8, 130.5, 116.1–, 107.2+, 105.4+, 80.8+, 60.9+, 56.2+, 55.9+, 40.5–, 17.9+; Found (ESI): $[M + Na]^+$ 439.1713, $C_{23}H_{28}O_7Na$ requires 439.1733.

(7*R*, 8*R*)-Rhaphidecursinol B 2[2]

Polymer-supported borohydride (Aldrich, 2.5 mmol g^{-1} on Amberlite IRA-400, 529 mg, 1.3 mmol) was added to a solution of 2*R*-(4-allyl-2,6-dimethoxy-phenoxy)-1-(3,4,5-trimethoxy-phenyl)-propane-1-one (**23**) (110 mg, 2.6 mmol) in methanol (2.5 ml) and the resulting suspension was stirred at RT. After 16h, the polymer beads were removed by filtration and washed with methanol. The filtrate was concentrated *in vacuo* to give a 25 : 1 mixture of diastereoisomers in favour of the title product. The diastereoisomers were separated by preparative TLC (eluent: 2.5 : 1 ether : petroleum ether) to yield the title product as a white solid (86 mg, 79%). R_f (3 : 1 ether : petroleum ether) = 0.23. Mp 81–82 °C; $[a]_D^{25}$ −58.2 (*c* 5.26, $CHCl_3$); ν_{max} /cm^{-1} 3469 br (OH), 1589 (Ar C=C), 1502 (Ar C=C); δ_H(400 MHz, $CDCl_3$) 6.57 (2 H, s, Ar–H), 6.43 (2 H, s, Ar–H), 5.95 (1 H, m, H-8′), 5.11 (1 H, dd, *J* 16.8, 1.5, H-9′), 5.01 (1 H, dd, *J* 8.4, 1.5, H-9′), 4.91 (1 H, s, O*H*), 4.58 (1 H, d, *J* 8.1, H-7), 3.95 (1 H, dq, *J* 8.1, 6.2, H-8), 3.85 (6 H, s, OCH_3), 3.83 (6 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 3.33 (2 H, d, *J* 7.0, H-7′), 1.20 (3 H, d, *J* 6.2, H-9); δ_C($CDCl_3$) 153.1, 152.7, 137.0+, 136.4, 135.9, 135.2, 134.6, 116.1–, 105.5+, 104.4+. 86.2+, 79.3+, 60.7+, 56.1+, 55.9+, 40.4−, 17.6+; Found (ESI): $[M + Na]^+$ 441.1895, $C_{23}O_7H_{30}Na$ requires 441.1889.

Crystal data: $C_{23}H_{30}O_7$, *M* = 418.47, monoclinic, *a* = 12.334(3), *b* = 12.813(3), *c* = 14.026(3), *β* = 91.62(3)°, *U* = 2215.9(8) Å^3, *T* = 180(2) K, space group *P*2(1), *Z* = 4, *μ* = 0.092 mm^{-1}, 10958 reflections collected, 6652 independent reflections (R_{int} = 0.0959). The final *wR*(F^2) was 0.1715. †

2-Methoxy-4-propenyl-phenol[28]

Hydrogen was bubbled through a suspension of catalyst **12** (225 mg, 0.15 mmol) and THF (4 ml) until the polymer turned from red to chrome yellow. The suspension was flushed with argon before eugenol (300 mg, 1.83 mmol) was added and the resulting suspension was agitated under an atmosphere of argon at RT. After 24 h, the polymer was removed by filtration and washed with THF. The filtrate was concentrated *in vacuo* to

† CCDC reference numbers 216370–216371. See http://www.rsc.org/suppdata/ob/b3/b308761a/ for crystallographic data in .cif or other electronic format.

give the title compound as a yellow oil with a 50 : 1 *trans* : *cis* selectivity. Crude mass recovery was quantitative; ν_{max} /cm^{-1} 3507 br (OH), 1596 (Ar C=C), 1510 (Ar C=C); δ_H(400 MHz, $CDCl_3$) 6.89 (1 H, s, Ar–H), 6.84 (2 H, s, Ar–H), 6.33 (1 H, dd, *J* 15.7, 1.5, C*H*=CHCH$_3$), 6.59 (1 H, dq, *J* 15.7, 6.6, 1.46, CH=C*H*CH$_3$), 5.57 (1 H, s, O*H*), 3.90 (3 H, s, OC*H*$_3$), 1.86 (3 H, dd, *J* 6.6, 1.5, CH=CHC*H*$_3$); δ_C($CDCl_3$) 146.5, 144.8, 130.7, 130.7, 123.4, 119.3, 114.3, 107.9, 55.8, 18.3; Found (EI): [M]$^+$ 164.0837, $C_{10}H_{12}O_2$ requires 164.0837.

(8*R*)-Oxo-surinamensin 4[29]

PS-BEMP (Fluka, 2.2 mmol g^{-1} base, 90 mg, 0.20 mmol) and 2-methoxy-4-propenyl-phenol (27 mg, 0.17 mmol) was added to a solution of toluene-4-sulfonic acid 1*S*-methyl-2-oxo-2-(3,4,5-trimethoxy-phenyl)-ethyl ester (65 mg, 0.165 mmol) in acetonitrile (3 ml) and the resulting suspension was allowed to stir at RT. After 15 h, the polymer beads were removed by filtration and washed with ether and CH_2Cl_2. The filtrate was concentrated *in vacuo* to yield a yellow oil. Crude mass recovery was quantitative. The crude product was used directly in the next reaction. A small amount of material was purified by column chromatography (100 : 1 CH_2Cl_2 : ether) for characterisation. R_f (100 : 1 CH_2Cl_2 : ether) = 0.40 (streaks). $[\alpha]_D^{25}$ +1.2 (*c* 0.325, $CHCl_3$); ν_{max} /cm^{-1} 1686 (C=O), 1582 (Ar C=C), 1506 (Ar C=C); δ_H(400 MHz, $CDCl_3$) 7.45 (2 H, s, Ar–H), 6.85 (1 H, s, Ar–H), 6.74 (2 H, s, Ar–H), 6.27 (1 H, d, *J* 15.7, H-7′), 6.06 (1 H, dq, *J* 15.7, 6.4, H-8′), 5.32 (1 H, q, *J* 6.8, H-8), 3.89 (3 H, s, OC*H*$_3$), 3.86 (6 H, s, OC*H*$_3$), 3.82 (3 H, s, OC*H*$_3$), 1.82 (3 H, d, *J* 6.4, H-9′), 1.71 (3 H, d, *J* 6.8, H-9); δ_C($CDCl_3$) 198.0, 152.9, 149.7, 145.8, 142.9, 132.6, 130.4+, 120.1, 124.4+, 118.6+, 115.6+, 109.4+, 106.7+, 78.8+, 60.8+, 55.1+, 55.6+, 19.0+, 18.3+; Found (ESI): [M + Na]$^+$ 409.1628, $C_{22}H_{26}O_6Na$ requires 409.1627.

8*S*-Oxo-surinamensin (**4′**) was prepared in the same way using toluene-4-sulfonic acid 1*R*-methyl-2-oxo-2-(3,4,5-trimethoxy-phenyl)-ethyl ester as starting material; $[\alpha]_D^{25}$ −1.5 (*c* 0.7, $CHCl_3$).

(−)-Surinamensin 24

Polymer-supported borohydride (Aldrich, 2.5 mmol g^{-1} on Amberlite IRA-400, 160 mg, 0.4 mmol) was added to a solution of 8*R*-surinamensin (**4**) (30 mg, 0.078 mmol) in methanol (1 ml) and the resulting suspension was stirred at RT. After 16 h, the polymer beads were removed by filtration and washed with methanol. The filtrate was concentrated *in vacuo* to give an 8 : 1 mixture of inseparable diastereoisomers in favour of the title product. A small proportion of pure title compound was isolated (8 mg) by preparative TLC (eluent: 1 : 1 ethyl acetate : petroleum ether) to yield the title product as a colourless oil. R_f (2 : 1 ether : petroleum ether) = 0.20. $[\alpha]_D^{25}$ −3.9 (*c* 0.615, $CHCl_3$); ν_{max} /cm^{-1} 3496 br (OH), 1591 (Ar C=C), 1508 (Ar C=C); δ_H(400 MHz, $CDCl_3$) 6.94 (1 H, d, *J* 8.2, H-3′), 6.92 (1 H, d, *J* 1.6, H-6′), 6.86 (1 H, dd, *J* 8.2, 1.6, H-2′), 6.61 (2 H, s, H-2), 6.36 (1 H, d, *J* 15.9, H-7′), 6.15 (1 H, dq, *J* 15.9, 6.6, H-8′), 4.60 (1 H, d, *J* 8.2, H-7), 4.10 (2 H, m, O*H* and H-8), 3.92 (3 H, s, OC*H*$_3$), 3.86 (6 H, s, OC*H*$_3$), 3.83 (3 H, s, OC*H*$_3$), 1.88 (3 H, d, *J* 6.6, H-9′), 1.20 (3 H, d, *J* 6.0, H-9); δ_C($CDCl_3$) 153.2, 150.8, 146.7, 135.6, 133.6, 130.4, 125.0, 119.1, 118.8, 109.2, 104.4, 84.1, 78.7, 60.8, 56.1, 55.7, 18.3, 17.2; Found (ESI): [M + Na]$^+$ 411.1788, $C_{22}H_{28}O_6Na$ requires 411.1784.

Preparation of 2*S*-[4-((*E*)-styryl)-phenoxy]-1-(3,4,5-trimethoxy-phenyl)-propan-1-one 26

PS-BEMP (Fluka, 2.2 mmol g^{-1} base, 55 mg, 0.122 mmol) and *trans*-4-hydroxystilbene (20 mg, 0.101 mmol) was added to a solution of toluene-4-sulfonic acid 1*R*-methyl-2-oxo-2-(3,4,5-trimethoxy-phenyl)-ethyl ester (**21**) (40 mg, 0.101 mmol) in acetonitrile (2 ml) and the resulting suspension was allowed to stir at RT. After 15 h, the polymer beads were removed by filtration and washed with ether and CH_2Cl_2. The filtrate was concentrated *in vacuo* to yield a colourless oil. Crude mass recovery was quantitative. The crude product was filtered through a plug of silica (eluent: 100 : 1 CH_2Cl_2 : ether); $[\alpha]_D^{25}$ 0 (*c* 0.2, $CHCl_3$); ν_{max} /cm^{-1} 1688 (C=O), 1582 (Ar C=C), 1507 (Ar C=C); δ_H(400 MHz, $CDCl_3$) 7.21–7.46 (9 H, m, Ar–H), 6.86–7.03 (4 H, m, Ar–H and *HC*=*CH*), 5.88 (1H, q, *J* 6.8, H-8), 3.91 (3H, s, OC*H*$_3$), 3.87 (6 H, s, OC*H*$_3$), 1.73 (3 H, d, *J* 6.8, H-9); δ_C($CDCl_3$) 197.6, 157.1, 153.1, 143.3, 137.5, 131.0, 128.9, 128.6+, 127.9+, 127.3+, 127.1+, 126.3+, 115.2+, 106.6+, 77.4+, 60.9+, 56.3+, 19.0+; Found (ESI): [M + Na]$^+$ 419.1844, $C_{26}H_{26}O_5Na$ requires 419.1858.

Preparation of 2*S*-[4-((*E*)-styryl)-phenoxy]-1-(3,4,5-trimethoxy-phenyl)-propan-1*S*-ol 25

Polymer-supported borohydride (Aldrich, 2.5 mmolg^{-1} on Amberlite IRA-400, 86 mg, 0.22 mmol) was added to a solution of 2*S*-[4-((*E*)-styryl)-phenoxy]-1-(3,4,5-trimethoxy-phenyl)-propan-1-one (**26**) (18 mg, 0.04 mmol) in methanol (0.4 ml) and CH_2Cl_2 (0.4 ml) and the resulting suspension was stirred at RT. After 16 h, the polymer beads were removed by filtration and washed with methanol. The filtrate was concentrated *in vacuo* to give a colourless oil with a 3 : 1 mixture of inseparable diastereoisomers in favour of the title product. The crude yield was quantitative; ν_{max} /cm^{-1} 3436 br (OH), 1594 (Ar C=C), 1507 (Ar C=C); δ_H(400 MHz, $CDCl_3$) 7.53–6.91 (9 H, m, Ar–H and C*H*=C*H*), 6.66 (2 H, s, H-2 and H-6), 4.64 (1 H, dd, *J* 7.3, 2.2, H-7), 4.44 (1 H, m, H-8), 3.89 (6 H, s, OC*H*$_3$), 3.85 (3 H, s, OC*H*$_3$), 2.98 (1 H, d, *J* 2.2, O*H*), 1.18 (3 H, d, *J* 6.1, H-9); δ_C($CDCl_3$) 157.3, 153.3, 138.0, 137.5, 135.4, 131.0, 128.7+, 128.0+, 127.8+, 127.4+, 127.2+, 126.3+, 116.5+, 104.4+, 79.0+, 78.2+, 60.8+, 56.2+, 16.0+; Found (ESI): [M + Na]$^+$ 443.1831, $C_{26}H_{28}O_5Na$ requires 443.1834.

Preparation of (*E*)-3-{3-methoxy-4-[1*S*-methyl-2-oxo-2-(3,4,5-trimethoxy-phenyl)-ethoxy-phenyl}-acrylic acid ethyl ester 28

Ethyl-4-hydroxy-3-methoxy-cinnamate (22 mg, 0.098 mmol) and PS-BEMP (Fluka, 2.2 mmol g^{-1} base, 55 mg, 0.12 mmol) was added to a solution of toluene-4-sulfonic acid 1*R*-methyl-2-oxo-2-(3,4,5-trimethoxy-phenyl)-ethyl ester (**21**) (39 mg, 0.098 mmol) in acetonitrile (2 ml) and the resulting suspension was allowed to stir at RT. After 15 h, the polymer beads were removed by filtration and washed with ether and CH_2Cl_2. The filtrate was concentrated *in vacuo* to yield a colourless oil. Crude mass recovery was quantitative. The crude product was used directly in the next reaction. A small amount of material was purified by column chromatography (100 : 1 CH_2Cl_2 : ether) to yield an amorphous white solid for characterisation. R_f (100 : 1 CH_2Cl_2 : ether) = 0.04. $[\alpha]_D^{25}$ −2.6 (*c* 0.765, $CHCl_3$); ν_{max} /cm^{-1} 1705 (C=O), 1583 (Ar C=C), 1508 (Ar C=C); δ_H(400 MHz, $CDCl_3$) 7.55 (1 H, d, J 15.9, H-8′), 7.42 (2 H, s, Ar–H), 7.02(1H, d, *J* 1.6, H-6′), 6.97 (1 H, dd, *J* 8.3, 1.6, H-2′), 6.76 (1 H, d, *J* 8.3, H-3′), 6.26 (1 H, d, *J* 15.9, H-7′), 5.39 (1 H, q, *J* 6.9, H-8), 4.22 (2 H, q, *J* 7.1, C*H*$_2$), 3.89 (3 H, s, OC*H*$_3$), 3.87 (6 H, s, OC*H*$_3$), 3.85 (3 H, s, OC*H*$_3$), 1.74 (3 H, d, *J* 6.9, H-9), 1.30 (3 H, t, *J* 7.1, CH$_2$C*H*$_3$); δ_C($CDCl_3$) 197.4, 167.0, 153.0, 149.7, 148.7, 144.1+, 143.2, 128.8, 128.6, 122.2+, 116.6+, 114.6+, 110.6+, 106.7+, 78.6+, 60.9+, 60.3−, 56.2+, 55.8+, 19.1+, 14.3+; Found (ESI): [M + Na]$^+$ 467.1678, $C_{24}H_{28}O_8Na$ requires 467.1682.

Preparation of (*E*)-3-(4-[2*S*-hydroxy-1*S*-methyl-2-(3,4,5-trimethoxy-phenyl)-ethoxy]-3-methoxy-phenyl}-acrylic acid ethyl ester 27

Polymer-supported borohydride (Aldrich, 2.5 mmolg^{-1} on Amberlite IRA-400, 157 mg, 0.39 mmol) was added to a solution of (*E*)-3-{3-methoxy-4-[1*S*-methyl-2-oxo-2-(3,4,5-trimethoxy-phenyl)-ethoxy-phenyl}-acrylic acid ethyl ester (**28**)

(35 mg, 0.08 mmol) in methanol (1 ml) and CH_2Cl_2 (0.2 ml) and the resulting suspension was stirred at RT. After 16 h, the polymer beads were removed by filtration washed with methanol. The filtrate was concentrated *in vacuo* to give a colourless oil with a 6 : 1 mixture of inseparable diastereoisomers in favour of the title product. The crude yield was quantitative; ν_{max} /cm^{-1} 3484 br (OH), 1705 (C=O), 1633 (alkene C=C), 1594 (Ar C=C), 1508 (Ar C=C); δ_H(400 MHz, $CDCl_3$) 7.62 (1 H, d, *J* 16.1, H-8′), 7.10–7.05 (2 H, m, Ar–H), 6.96 (1 H, d, *J* 8.8, Ar–H), 6.61 (2 H, s, Ar–H), 6.32 (1 H, d, *J* 16.1, H-7′), 4.64 (1 H, d, *J* 6.9, H-7), 4.50–4.41 (3 H, m, OC*H*$_2$CH$_3$ and H-8), 3.91 (3 H, s, OC*H*$_3$), 3.85 (6 H, s, OC*H*$_3$), 3.82 (3 H, s, OC*H*$_3$), 3.72 (1 H, s, O*H*), 1.33 (3 H, t, *J* 7.1, OCH$_2$C*H*$_3$), 1.21 (3 H, d, *J* 6.2, H-9); δ_C($CDCl_3$) 167.0, 153.3, 150.8, 149.6, 144.1+, 138.0, 135.3, 129.3, 122.2+, 117.5+, 116.9+, 110.6+, 104.4+, 82.9+, 78.4+, 60.8+, 60.4−, 56.2+, 55.9+, 16.8+, 14.3+; Found (ESI): [M + Na]$^+$ 469.1821, $C_{24}H_{30}O_8Na$ requires 469.1838.

Preparation of 2*S*-((*E*)-2-ethoxy-5-propenyl-phenoxy)-1-(3,4,5-trimethoxy-phenyl)-propane-1-one 30

PS-BEMP (Fluka, 2.2 mmol g^{-1} base, 90 mg, 0.198 mmol) and *trans*-2-ethoxy-5-(1-propenyl)-phenol (29 mg, 0.165 mmol) was added to a solution of toluene-4-sulfonic acid 1*R*-methyl-2-oxo-2-(3,4,5-trimethoxy-phenyl)-ethyl ester (**21**) (65 mg, 0.165 mmol) in acetonitrile (3 ml) and the resulting suspension was allowed to stir at RT. After 15 h, the polymer beads were removed by filtration and washed with ether and CH_2Cl_2. The filtrate was concentrated *in vacuo* to yield a yellow oil. Crude mass recovery was quantitative. The crude product was filtered through a plug of silica (eluent: 100 : 1 CH_2Cl_2 : ether); $[a]_D^{25}$ 0 (*c* 0.67, $CHCl_3$); ν_{max} /cm^{-1} 1689 (C=O), 1582 (Ar C=C), 1507 (Ar C=C); δ_H(400 MHz, $CDCl_3$) 7.44 (2 H, s, Ar–H), 6.82 (3 H, m, Ar–H), 6.23 (1 H, dd, *J* 15.7, 1.6, H-7′), 6.00 (1 H, dq, *J* 15.7, 6.6, H-8′), 5.33 (1 H, q, *J* 6.9, H-8), 4.034 (1 H, q, *J* 7.0, OC*H*-H′CH$_3$), 4.028 (1 H, q, *J* 7.0, OCH*H*′CH$_3$), 3.90 (3 H, s, OC*H*$_3$), 3.86 (6 H, s, OC*H*$_3$), 1.80 (3 H, d, *J* 6.6, 1.6, H-9′), 1.70 (3 H, d, *J* 6.9, H-9), 1.35 (3 H, t, *J* 7.0, OCHH′C*H*$_3$); δ_C($CDCl_3$) 198.2, 152.9, 148.5, 147.3, 142.9, 131.4, 130.2+, 129.4, 124.2+, 120.4+, 114.4+, 113.91+, 106.89+, 79.39+, 64.55−, 60.89+, 56.24+, 19.12+, 18.30+, 14.83+; Found (ESI): [M + Na]$^+$ 423.1801, $C_{23}H_{28}O_6Na$ requires 423.1784.

Preparation of 2*R*-((*E*)-2-ethoxy-5-propenyl-phenoxy)-1-(3,4,5-trimethoxy-phenyl)-propan-1*R*-ol 29

Polymer-supported borohydride (Aldrich, 2.5 mmol g^{-1} on Amberlite IRA-400, 582 mg, 1.45 mmol) was added to a solution of 2*R*-((E)-2-ethoxy-5-propenyl-phenoxy)-1-(3,4,5-trimethoxy-phenyl)-propane-1-one (**30**) (117 mg, 0.29 mmol) in methanol (5 ml) and the resulting suspension was stirred at RT. After16 h, the polymer beads were removed by filtration and washed with methanol. The filtrate was concentrated *in vacuo* to give, as a colourless oil, a 7 : 1 mixture of inseparable diastereoisomers in favour of the title product; ν_{max} /cm^{-1} 3483 br (OH), 1591 (Ar C=C), 1508 (Ar C=C); δ_H(400 MHz, $CDCl_3$) 7.02 (1 H, s, Ar–H), 6.97 (1 H, d, *J* 8.2, Ar–H), 6.84 (1 H, d, *J* 8.2, Ar–H), 6.60 (2 H, s, Ar–H), 6.30 (1 H, d, *J* 15.7, H-7′), 6.08 (1 H, dq, *J* 15.7, 6.6, H-8′), 4.58 (1 H, d, *J* 8.3, H-7), 4.42 (1 H, br s, O*H*), 4.02–4.14 (3 H, m, OC*H*$_2$CH$_3$ and H-8), 3.85 (6 H, s, OC*H*$_3$), 3.82 (3 H, s, OC*H*$_3$), 1.85 (3 H, d, *J* 6.6, H-9′), 1.49 (3 H, t, *J* 6.9, OCH$_2$C*H*$_3$), 1.21 (3 H, d, *J* 6.2, H-9); δ_C($CDCl_3$) 153.2, 149.4, 148.0, 137.8, 135.7, 131.6, 130.1, 124.3, 121.3, 117.7, 113.1, 104.5, 84.9, 79.0, 64.4, 60.8, 56.1, 18.3, 17.6, 14.8; Found (ESI): [M + Na]$^+$ 425.1941, $C_{23}H_{30}O_6Na$ requires 425.1940.

2*R*-[2,6-Dimethoxy-4-(*p*-toluenesulfonyl-hydrazonomethyl)-phenoxy]-1-(3,4,5-trimethoxy-phenyl-propan-1*R*-ol 31

Osmium tetroxide (5% in ^{t}BuOH, 5 mg, 1 μmol) was added to a solution of (7*R*, 8*R*) polysphorin (20 mg, 0.048 mmol) and sodium periodate (31 mg, 0.14 mmol) in THF (0.4 ml) and water (0.2 ml). The resulting mixture was allowed to stir at RT. After 20 min, the reaction was diluted with CH_2Cl_2 and quenched with a saturated solution of $Na_2S_2O_3$. The aqueous layer was separated, extracted with CH_2Cl_2, washed with brine and dried ($MgSO_4$) before the solvent was removed *in vacuo* and the resulting residue was filtered through a plug of silica (3 : 1 ether : petroleum ether). A portion of the crude product (9.6 mg, 0.02 mmol) was dissolved in dry methanol (0.3 ml) and *p*-toluenesulfonyl hydrazide (4.4 mg, 0.02 mmol) was added to this solution. The reaction mixture was allowed to stir at RT for 45 min before the solvent was removed under a gentle stream of air and the resulting residue was purified by silica gel column chromatography (5 : 1 ether : hexane) to yield a white solid (12 mg, 88%). Single crystals of the title compound were obtained by evaporation from a solution of ethyl acetate. R_f (5 : 1 ether : hexane) = 0.08. $[a]_D^{25}$ −42 (*c* 0.17, $CHCl_3$); ν_{max} /cm^{-1} 3472 br (OH), 1592 (C=N/Ar C=C), 1579 (Ar C=C), 1501 (Ar C=C), 1333 (–SO_2–N), 1166 (–SO_2–N); δ_H(600 MHz, $CDCl_3$) 7.86 (2 H, d, *J* 8.2, H-14, H-18), 7.69 (1 H, s, H-7′), 7.66 (1 H, s, N*H*), 7.32 (2 H, d, *J* 8.2, H-15, H-17), 6.85 (2 H, s, Ar–H), 6.56 (2 H, s, Ar–H), 4.66 (1 H, br s, O*H*), 4.60 (1 H, d, *J* 8.2, H-7), 4.03 (1 H, dq, *J* 6.6, 8.2, H-8), 3.89 (6 H, s, OC*H*$_3$), 3.84 (6 H, s, OC*H*$_3$), 3.81 (3 H, s, OC*H*$_3$), 2.42 (3 H, s, H-19), 1.22 (3 H, d, *J* 6.6, H-9); δ_C($CDCl_3$) 153.1, 152.9, 147.5+, 144.4, 139.1, 137.6, 136.0, 135.2, 129.7+, 128.6, 127.9+, 104.5+, 104.2+, 86.5+, 79.2+, 60.8+, 56.2+, 56.1+, 21.6+, 17.7+; Found (ESI): [M + Na]$^+$ 597.1903, $C_{23}H_{34}N_2O_9SNa$ requires 597.1883.

Crystal data: $C_{23}H_{34}N_2O_9S$, *M* = 574.63, monoclinic, *a* = 22.4427(4), *b* = 11.0768(3), *c* = 12.8817(2), *β* = 114.475(2)°, *U* = 2914.55(10) Å^3, *T* = 180(2) K, space group *C*2, *Z* = 4, *μ* = 0.166 mm^{-1}, 14205 reflections collected, 6477 independent reflections (R_{int} = 0.0345). Flack parameter[30] = 0.05(7). The final *wR*(F^2) was 0.0951. †

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