First Enantioselective Total Synthesis of Both (+)- and (−)-Metachromin A

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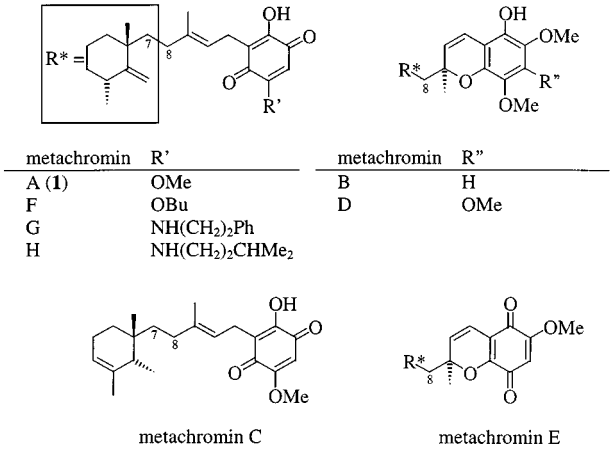
Dedicated to Professor Günter Helmchen on the occasion of his 60th birthday

Keywords: Total synthesis / Natural products / Chiral 1,3-oxazolidines / Terpenoids / Quinones

The antineoplastic agent (–)-metachromin A (**1**) from *Hippospongia metachromia* has been synthesized in enantiomerically pure form in 13% overall yield. A general convergent synthetic strategy for different metachromins using a 2-alkyloxy-3-sulfonyl-1,3-oxazolidine as a chiral dithienium equivalent is presented.

Introduction

The purple-coloured Okinawan marine sponge *Hippospongia metachromia* is the source of a number of structurally related sesquiterpenoid quinones and phenols named metachromins A−H[1] (Figure 1). Due to their interesting biological profiles[1] − exhibiting cytotoxicity against murine leukemia cells and human epidermoid carcinoma cells as well as remarkable coronary vasodilating activity − these compounds represent attractive synthetic targets in medicinal chemistry.



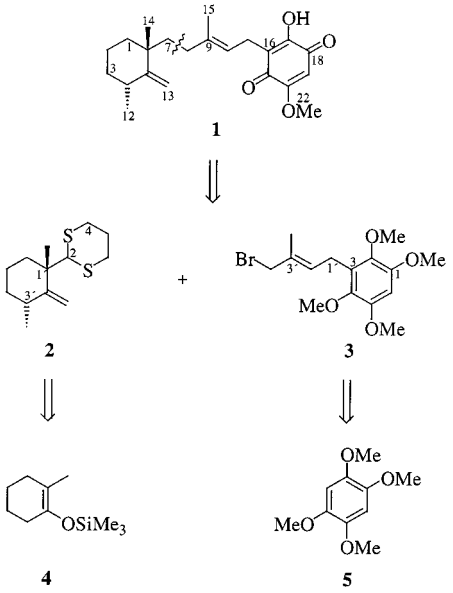
metachromin	R'
A (**1**)	OMe
F	OBu
G	$NH(CH_2)_2Ph$
H	$NH(CH_2)_2CHMe_2$

metachromin	R"
B	H
D	OMe

metachromin C metachromin E

Figure 1. Structures of metachromins

With the exception of metachromin C, all metachromins contain the same chiral fragment R* as part of their biogenetically unusual carbon skeletons. Consequently, a retrosynthetic scission of the C-7−C-8 bond offers a general convergent synthetic strategy suitable for the preparation of seven different metachromins. As a first synthetic target, we chose (−)-metachromin A (**1**), which has previously been synthesized by Correia et al. as a racemic mixture.[2a] More recently, an enantioenriched intermediate of this synthesis has also been prepared.[2b] Our retrosynthetic disassembly is shown in Scheme 1. The two key intermediates **2** and **3** can be elaborated from silyl enol ether **4** and 1,2,4,5-tetramethoxybenzene (**5**), respectively.



Scheme 1. Retrosynthetic analysis of (−)-metachromin A (**1**)

Results and Discussion

To introduce the stereochemical information into the key intermediate **2**, an enantiomerically pure 2-alkyloxy-3-sulfonyl-1,3-oxazolidine **6** was used as a chiral dithienium equivalent. The well-known Lewis acid mediated reaction of chiral, non-racemic 2-alkyloxy-3-sulfonyl-1,3-oxazolidines[3] with prochiral silyl enol ethers generally affords a 1:1 mixture of epimers when it is used for the construction of quaternary carbon centres.[3e,3f] In order to obtain enhanced selectivities, prior conversion of the silyl enol ether **4**[4] into a titanium enolate[5] was essential (Scheme 2). Without further addition of a Lewis acid, this new method provided 79% of an easily separable mixture (*dr* = 81:19)

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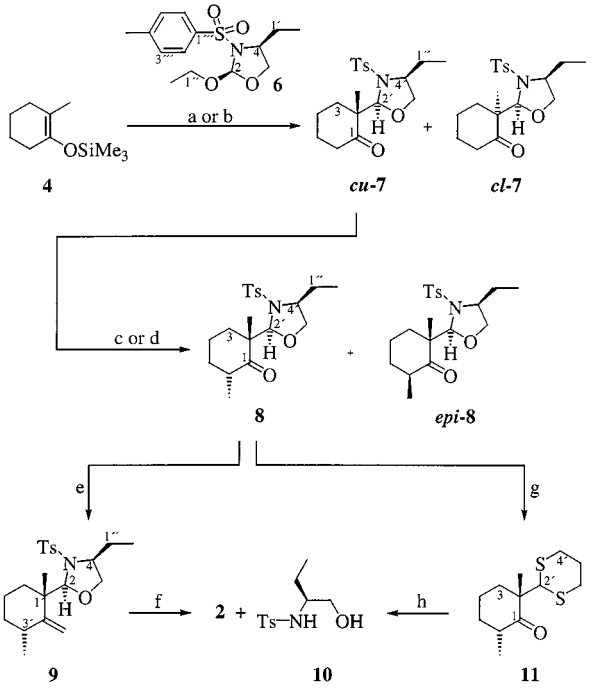
of two epimers at the quaternary carbon centre favouring the desired diastereomer ***cu*-7**. Presumably, coordination of the oxazolidine **6** at the trichlorotitanium enolate and reaction via a cyclic transition state similar to that involved in corresponding aldol reactions[5b−5d] is responsible for the increased selectivity. We plan to study this reaction in more detail in the future.



Scheme 2. Reagents and conditions: (a) **6**, $ZnCl_2{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 15 min, 85%, *dr* = 45:55; (b) $TiCl_4$, CH_2Cl_2, −78 °C, 15 min, room temp., 45 min, then **6**, −78 °C → room temp., 15 h, 79%, *dr* = 81:19; (c) LDA, THF, −78 °C, 1 h, then MeI, 0 °C → room temp., 15 h, 54%, *dr* = 27:73 (+35% ***cu*-7**); (d) KO*t*Bu, 18-crown-6, THF, −40 °C → room temp., 1 h, then MeI, −78 °C → room temp., 15 h, 86%, *dr* = 96:4; (e) $MePPh_3Br$, KO*t*Bu, toluene, reflux, 4 h, 93%, *dr* > 96:4; (f) $H_2C(CH_2SH)_2$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 2 h, 93% **2** + 84% **10**; (g) $H_2C(CH_2SH)_2$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 2 h, 82%; (h) $MePPh_3Br$, KO*t*Bu, toluene, reflux, 4 h, 52%, *dr* = 81:19 (+18% **11**); LDA = lithium diisopropylamide, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl

After separation by flash column chromatography (FCC) on silica gel, the diastereoselective methylation of ***cu*-7** with methyl iodide was efficiently achieved using potassium *tert*-butylate/18-crown-6 for deprotonation (86%, *dr* = 96:4); other bases, such as lithium diisopropylamide (LDA) in THF, gave lower yields and led preferentially to the undesired diastereomer ***epi*-8** (54%, *dr* = 27:73). By exposing the thermodynamically unfavoured diastereomerically pure ***epi*-8** to the same conditions as used for the formation of **8** (KO*t*Bu/18-crown-6/MeI, *then* ***epi*-8**, THF, −78 °C → room temp., 15 h), it was shown that no epimerization occurred. This result suggests that it is the alkylation step which is responsible for the observed selectivity. Most probably, interaction between the alkylating agent and the quasi-axial methyl group[6c] at C-2 favours the formation of **8** when a free enolate is employed (Figure 2). In this case, "equatorial" attack via a twist-boat-like transition state leads to the product.[6] When LDA is used for deprotonation, the lithium presumably creates a steric demand at the enolate oxygen by aggregation and complexation, forcing the methyl group into the axial position via a chair-like transition state.

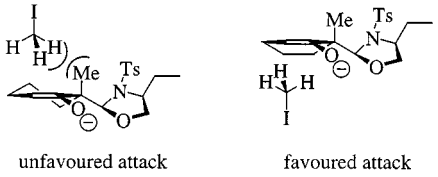


Figure 2. Proposed transition states for the methylation of the enolate of ***cu*-7**

Olefination of the strongly sterically hindered ketone **8** under the conditions established by Fitjer[7] furnished product **9** in 93% yield. Only traces of ***epi*-9**, formed by epimerization at C-3′ under the basic conditions, were detected by NMR (*dr* > 96:4). This ***epi*-9** could not be removed from **9** by FCC, but was lost during the ensuing steps. The relative and absolute configuration of the intermediate **9** was elucidated by X-ray crystal structure analysis[8] (Figure 3), which showed the desired *trans* arrangement of the two methyl groups at the cyclohexane moiety. Finally, thiolysis[3d] with 1,3-propanedithiol resulted in the formation of **2** (93%). The chiral auxiliary, sulfonamide **10**, was recovered in 84% yield. Interestingly, the last two steps could be performed in reverse order. Because of the steric hindrance at the cyclohexane ring in **8**, selective thiolysis of the oxazolidine group was possible, leading to ketone **11** (82%); unfortunately, subsequent olefination afforded the product **2** in only 52% yield as a mixture of epimers (*dr* = 80:20). Following the first route, the key intermediate **2** was synthesized in enantiomerically pure form from the silyl enol ether **4** in only four steps in 46% overall yield.

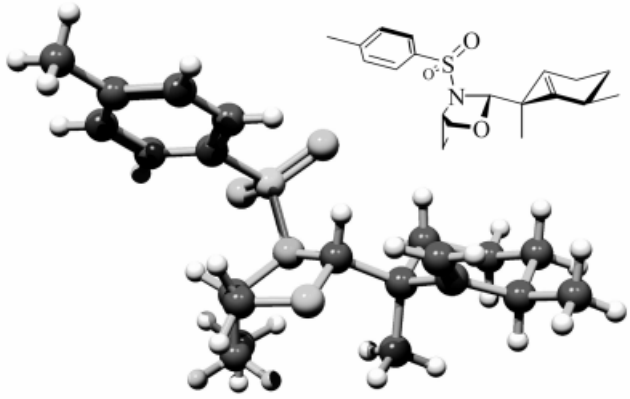
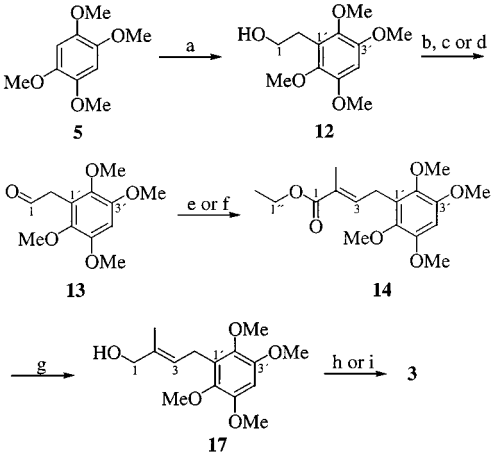


Figure 3. X-ray structure analysis of **9**

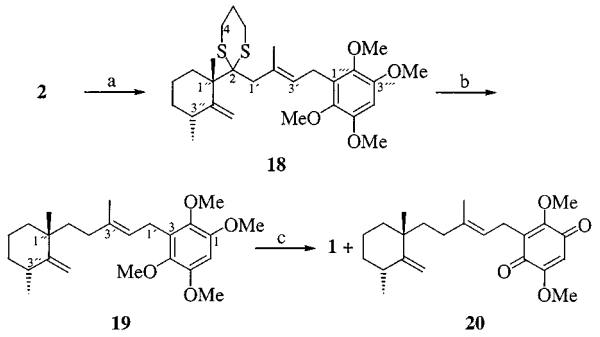
The five steps required for the elaboration of the second fragment **3** from 1,2,4,5-tetramethoxybenzene (**5**)[9] gave an overall yield of 47% (Scheme 3). *ortho*-Lithiation of **5** with *n*-butyllithium and subsequent reaction with oxirane produced the alcohol **12** in 80% yield. Only a Swern oxidation[10] at −30 °C afforded the aldehyde **13** in a satisfactory yield of 79%. Other methods, such as pyridinium chlorochromate (PCC)[11] or Dess−Martin periodinane (DMP) oxidation,[12] gave lower yields (52% and 56%, respectively). The (*E*)-configured trisubstituted double bond moiety

could be introduced by either a Horner−Wadsworth−Emmons reaction[13] with phosphonate **15** [92%, (*E*)/(*Z*) = 95:5] or a Wittig reaction[14] with the commercially available ylide **16** [92%, (*E*)/(*Z*) = 98:2] furnishing the ester **14**. An NOE of 3% between the signals of the methyl group at C-2 and the C-4 methylene group proved the (*E*) configuration of the double bond. Subsequent chemoselective reduction with diisobutylaluminium hydride[15] (DIBAL-H) and bromination of the resulting alcohol **17** via the mesylate with lithium bromide led to the allyl bromide **3** in good yield (82% over two steps).



Scheme 3. Reagents and conditions: (a) *n*BuLi, LiCl, THF, 0 °C, 30 min, then ethylene oxide, −78 °C, 30 min, room temp., 3 h, 80%; (b) DMP, CH_2Cl_2, room temp., 2 h, 56%; (c) PCC, NaOAc, CH_2Cl_2, room temp., 5 h, 52%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C → −30 °C, 1 h, then NEt_3, room temp., 1 h, 79%; (e) $(EtO)_2$-P(O)CH(Me)COOEt (**15**), LiCl, DBU, MeCN, room temp., 1 h, 92%, (*E*)/(*Z*) = 95:5; (f) Ph_3P=C(Me)COOEt (**16**), CH_2Cl_2, reflux, 3 h, 92%, (*E*)/(*Z*) = 98:2; (g) DIBAL-H, CH_2Cl_2, −78 °C, 2.5 h, 92%; (h) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 30 min, 83%; (i) MsCl, NEt_3, CH_2Cl_2, −40 °C, 1.5 h, then LiBr, THF, 0 °C, 2.5 h, 89%; DMP = Dess−Martin periodinane, PCC = pyridinium chlorochromate, DMSO = dimethyl sulfoxide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIBAL-H = diisobutylaluminium hydride, Ms = methanesulfonyl

With the required building blocks in hand, their coupling could be accomplished by alkylation of the lithiated dithiane **2** with the bromide **3** (85%) (Scheme 4). Selective lithiation of the neopentylic dithiane[16] moiety without concomitant deprotonation at the allylic position was achieved using *tert*-butyllithium/hexamethylphosphoric triamide (HMPTA) at low temperature.[16e] As expected, the selective desulfuration of the product **18** caused some difficulties due to the dithiane ring being adjacent to a quaternary carbon centre and the presence of two reactive double bonds. The use of Raney nickel (W2,[17] freshly prepared), even after its deactivation in boiling acetone,[18] led to reduction and isomerization of the double bonds but not to complete desulfuration. Treatment with hydrazine[19] resulted in complete decomposition of the compound. Birch conditions,[20] at the temperature of boiling ammonia as well as at −50 °C, led to reduction of the electron-rich benzene ring, while at −78 °C a mixture of compounds with only one reductively cleaved C−S bond was detected. The same mixture was obtained when **18** was treated with tributylstannane/2,2′-azobisisobutyronitrile (AIBN) in benzene[21] at 80 °C for 12 h (80%). Consequently, much more vigorous conditions of neat tributylstannane at 120 °C for 30 h (addition of AIBN every two hours) were required, under which the desired precursor **19** was obtained in excellent yield (95%). Unfortunately, the final oxidation with cerium(IV) ammonium nitrate (CAN)[9] in acetonitrile/water produced only 37% of (−)-metachromin A (**1**) along with 34% of the known[1] methyl ether **20**. Isolation and separation of the two products was accomplished by FCC on RP-18 silica gel. All attempts to achieve a selective demethylation[9,22] of **20** have hitherto met with failure.



Scheme 4. Reagents and conditions: (a) *t*BuLi, HMPTA, THF, −78 °C, 2.5 h, then **3**, −78 °C, 3 h, 85%; (b) Bu_3SnH, AIBN, 120 °C, 30 h, 95%; (c) CAN, MeCN/H_2O, 70:30, −7 °C, 1.5 h, room temp., 2 h, 37% **1** + 34% **20**; HMPTA = hexamethylphosphoric triamide, AIBN = 2,2′-azobisisobutyronitrile, CAN = cerium(IV) ammonium nitrate

An exact mass, a correct elemental analysis, and the melting point proved the correct molecular formula and high purity of the synthesized (−)-metachromin A (**1**). The spectroscopic data (^1H NMR, ^{13}C NMR, IR) were identical in all respects to those provided by Prof. Correia.[2] The specific optical rotation $[\alpha]_D^{27} = -17.6$ of the synthetic **1** was higher than the value reported[1] for natural **1** ($[\alpha]_D^{27} = -11$). Starting from the 2-alkyloxy-1,3-oxazolidine ***ent*-6**, (+)-metachromin A (***ent*-1**, $[\alpha]_D^{27} = +17.3$) was similarly synthesized.

Conclusion

A general convergent synthetic strategy for the stereocontrolled preparation of different metachromins is presented. As an example, (−)-metachromin A (**1**) has been synthesized in enantiomerically pure form in seven steps from the silyl enol ether **4** in 13% overall yield. The use of a 2-alkyloxy-3-sulfonyl-1,3-oxazolidine **6** as a chiral dithienium equivalent, which constitutes a new method for the stereoselective construction of quaternary carbon centres, allowed the efficient preparation of the common chiral part of seven of the metachromins.

Thus, the alkylation of chiral dithianes, in turn obtained from enantiomerically pure 3-sulfonyl-1,3-oxazolidines, and subsequent reduction (or hydrolysis) represents a valuable strategy for the enantioselective synthesis of natural products.

Experimental Section

General Remarks: All solvents were dried and purified prior to use: Et_2O and toluene were distilled from sodium benzophenone ketyl. THF was distilled from potassium benzophenone ketyl. CH_2Cl_2, NEt_3, and DMSO were distilled from CaH_2. MeCN was distilled from P_4O_{10}. All commercially available reagents were used without purification. LiCl and LiBr were dried for 15 h at 150 °C under reduced pressure. All reactions were performed under Ar in flame-dried glassware and were monitored by thin-layer chromatography (TLC, silica gel 60 F_{254} or RP-18 F_{254}s, Merck). − Flash column chromatography (FCC) was performed on Merck silica gel 60, 0.040−0.063 mm, or LiChroprep RP-18, 0.040−0.063 mm; PE = light petroleum ether, b.p. 36−46 °C. − NMR: Bruker ARX 300, AM 360 (NOE experiments), and AMX 400 (2D spectra); Varian Unity Plus 600 (2D spectra); for ^{1}H NMR, $CDCl_3$ as solvent (δ_H = 7.24); for ^{13}C NMR, $CDCl_3$ as solvent (δ_C = 77.0). − IR: Nicolet 5DXC. Optical rotations: Perkin−Elmer polarimeter 341. − MS: Finnigan MAT 8200. − Elemental analysis: Heraeus CHN-O-Rapid. − Melting points: Gallenkamp MFB 595, uncorrected values. − GC: Hewlett−Packard 6890, HP1701.

(+)-(2*R*,4*S*)-4-Ethyl-2-ethyloxy-3-[(4-methylphenyl)sulfonyl]-1,3-oxazolidine (6): To a solution of (*S*)-2-aminobutanol (5.00 g, 56.1 mmol) and NEt_3 (8.40 mL, 60.3 mmol) in CH_2Cl_2 (75 mL), a solution of *p*TsCl (11.0 g, 57.7 mmol) in CH_2Cl_2 (75 mL) was slowly added at 0 °C. After stirring at room temperature for 18 h, the reaction mixture was washed with aqueous 2 N HCl (3 × 150 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude tosylate was dissolved in triethyl orthoformate (150 mL), three drops of MsOH were added, and the mixture was stirred for 3 h at room temperature. K_2CO_3 (1.00 g) was then added and the resulting suspension was stirred for 10 min. Filtration and removal of the triethyl orthoformate in vacuo gave the crude products **6** and ***epi*-6** as a viscous oil {16.2 g, 54.1 mmol, 96%, **6**/***epi*-6** = 85:15 [^{1}H NMR (2-H)]}. The epimeric mixture was dissolved in hexanes at 50 °C and the resulting solution was cooled to −30 °C for 4 h. Filtration gave diastereomerically pure **6** (13.5 g, 45.1 mmol, 80%, *dr* = 99:1) as colourless crystals. − R_f = 0.43 (SiO_2, Et_2O/PE, 1:1). − M.p. 57.9−58.7 °C (hexanes). − $[\alpha]_D^{20}$ = +15.9 (*c* = 0.90, CH_2Cl_2); ***ent*-6:** $[\alpha]_D^{20}$ = −15.4 (*c* = 1.00, CH_2Cl_2). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, ^3J = 7.6 Hz, 3 H, 2′-H_3), 1.22 (t, ^3J = 6.9 Hz, 3 H, 2″-H_3), 1.51−1.66 (m, 1 H, 1′-H_2), 1.82−1.96 (m, 1 H, 1′-H_2), 2.41 (s, 3 H, 4‴-CH_3), 3.53−3.72 (m, 3 H, 1″-H_2, 4-H), 3.74−3.89 (m, 2 H, 5-H_2), 6.02 (s, 1 H, 2-H), 7.26−7.30 (m, 2 H, 3‴-H, 5‴-H), 7.69−7.73 (m, 2 H, 2‴-H, 6‴-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.8 (q, C-2′), 14.9 (q, C-2″), 21.4 (q, 4‴-CH_3), 27.4 (t, C-1′), 59.4 (t, C-1″), 61.6 (d, C-4), 70.3 (t, C-5), 108.0 (d, C-2), 127.5 (d, C-2‴, C-6‴), 129.7 (d, C-3‴, C-5‴), 135.6 (s, C-4‴), 144.3 (s, C-1‴). − IR (KBr): $\tilde{\nu}$ = 2980, 2900, 1560, 1360, 1170, 815 cm^{-1}. − EI-MS: *m*/*z* (%) = 299 (0.6) [M^+], 254 (99), 196 (58), 155 (60), 91 (100). − $C_{14}H_{21}NO_4S$ (299.39): calcd. C 56.17, H 7.07, N 4.68; found C 56.24, H 7.08, N 4.92.

(−)-(2*R*)-2-{(2*S*,4*S*)-4−Ethyl-3-[(4-methylphenyl)sulfonyl]-1,3-oxazolidin-2-yl}-2-methylcyclohexan-1-one (*cu*-7) and (−)-(2*S*)-2-{(2*S*,4*S*)-4-Ethyl-3-[(4-methylphenyl)sulfonyl]-1,3-oxazolidin-2-yl}-2-methylcyclohexan-1-one (*cl*-7): To a cold (−78 °C) solution of silyl enol ether **4**[4] (4.61 g, 25.0 mmol) in CH_2Cl_2 (200 mL), $TiCl_4$ (2.75 mL, 25.1 mmol) was added dropwise. After stirring for 15 min at −78 °C, the reaction mixture was allowed to warm to room temperature and stirred for a further 45 min. The deep-red solution was then cooled to −78 °C once more, whereupon a solution of 2-alkyloxy-1,3-oxazolidine **6** (7.49 g, 25.0 mmol) in CH_2Cl_2 (50 mL) was slowly added. The resulting mixture was allowed to warm to room temperature over a period of 15 h. The reaction was then stopped by the addition of 2 N HCl (250 mL) and the aqueous layer was extracted with CH_2Cl_2 (4 × 150 mL). The combined organic layers were stirred with K_2CO_3 (3.00 g) for 15 min, then the suspension was filtered and the solvent was removed in vacuo to leave the crude product {***cu*-7**/***cl*-7**, 81:19 [^{1}H NMR (2′-H)]}. Purification by FCC (1130 cm^3 SiO_2, gradient Et_2O/PE, 1:5 → Et_2O/PE, 1:4) yielded diastereomerically pure ***cu*-7** (5.93 g, 16.2 mmol, 65%) as colourless crystals. − R_f = 0.37 (SiO_2, Et_2O/PE, 1:1). − M.p. 97.0−98.5 °C (Et_2O/PE, 1:4). − $[\alpha]_D^{20}$ = −24.8 (*c* = 1.30, CH_2Cl_2); ***ent*-cu-7:** $[\alpha]_D^{20}$ = +25.6 (*c* = 0.94, CH_2Cl_2). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, ^3J = 7.4 Hz, 3 H, 2″-H_3), 1.08 (s, 3 H, 2-CH_3), 1.42−1.57 (m, 2 H, 3-H_2, 1″-H_2), 1.61−1.79 (m, 3 H, 5-H_2, 4-H_2, 1″-H_2), 1.83−1.99 (m, 2 H, 5-H_2, 4-H_2), 2.28−2.53 (m, 3 H, 6-H_2, 3-H_2), 2.38 (s, 3 H, 4‴-CH_3), 3.05−3.11 (m, 1 H, 5′-H_2), 3.50−3.57 (m, 2 H, 4′-H, 5′-H_2), 5.36 (s, 1 H, 2′-H), 7.28−7.37 (m, 2 H, 3‴-H, 5‴-H), 7.68−7.77 (m, 2 H, 2‴-H, 6‴-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.8 (q, C-2″), 20.7 (q, 2-CH_3), 21.0 (t, C-4), 21.6 (q, 4‴-CH_3), 25.9 (t, C-5), 27.4 (t, C-1″), 34.3 (t, C-3), 39.5 (t, C-6), 52.8 (s, C-2), 62.2 (d, C-4′), 69.4 (t, C-5′), 93.6 (d, C-2′), 128.2 (d, C-2‴, C-6‴), 129.9 (d, C-3‴, C-5‴), 134.4 (s, C-4‴), 144.2 (s, C-1‴), 212.1 (s, C-1). − IR (KBr): $\tilde{\nu}$ = 2900 s, 2850 s, 1690 s, 1585 w, 1430 m, 1330 s, 1150 s, 1100 s, 975 s, 800 w, 650 s cm^{-1}. − EI-MS: *m*/*z* (%) = 364 (0.1) [M^+ − H], 254 (100), 210 (43), 155 (64), 91 (76). − $C_{19}H_{27}NO_4S$ (365.50): calcd. C 62.44, H 7.45, N 3.83; found C 62.36, H 7.46, N 3.60. − ***cl*-7** (1.32 g, 3.61 mmol, 14%, colourless crystals). − R_f = 0.32 (SiO_2, Et_2O/PE, 1:1). − M.p. 136.5−137.5 °C (Et_2O/PE, 1:4). − $[\alpha]_D^{20}$ = −23.8 (*c* = 0.96, CH_2Cl_2); ***ent*-cl-7:** $[\alpha]_D^{20}$ = +22.2 (*c* = 0.94, CH_2Cl_2). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.78 (t, ^3J = 7.6 Hz, 3 H, 2″-H_3), 1.21 (s, 3 H, 2-CH_3), 1.36−1.63 and 1.65−1.93 (2 m, 3 H and 4 H, 5-H_2, 4-H_2, 3-H_2, 1″-H_2), 2.05−2.16 (m, 1 H, 3-H_2), 2.41 (s, 3 H, 4‴-CH_3), 2.42−2.53 (m, 1 H, 6-H_2), 2.59−2.71 (m, 1 H, 6-H_2), 3.23−3.31 (m, 1 H, 5′-H_2), 3.55−3.66 (m, 2 H, 4′-H, 5′-H_2), 5.69 (s, 1 H, 2′-H), 7.28−7.36 (m, 2 H, 3‴-H, 5‴-H), 7.70−7.79 (m, 2 H, 2‴-H, 6‴-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.8 (q, C-2″), 20.1 (q, 2-CH_3), 20.8 (t, C-4), 21.6 (q, 4‴-CH_3), 26.7 (t, C-5), 27.0 (t, C-1″), 34.7 (t, C-3), 39.6 (t, C-6), 53.6 (s, C-2), 62.1 (d, C-4′), 70.1 (t, C-5′), 94.3 (d, C-2′), 128.5 (d, C-2‴, C-6‴), 129.9 (d, C-3‴, C-5‴), 134.9 (s, C-4‴), 144.3 (s, C-1‴), 212.8 (s, C-1). − IR (KBr): $\tilde{\nu}$ = 2920 s, 2850 s, 1680 s, 1585 w, 1440 m, 1330 s, 1150 s, 970 s, 800 w, 655 s cm^{-1}. − EI-MS: *m*/*z* (%) = 364 (0.1) [M^+ − H], 254 (92), 210 (19), 155 (55), 91 (100). − $C_{19}H_{27}NO_4S$ (365.50): calcd. C 62.44, H 7.45, N 3.83; found C 62.35, H 7.41, N 3.77.

(+)-(2*R*,6*R*)-2-{(2*S*,4*S*)-4-Ethyl-3-[(4-methylphenyl)sulfonyl]-1,3-oxazolidin-2-yl}-2,6-dimethylcyclohexan-1-one (8) and (−)-(2*R*,6*S*)-2-{(2*S*,4*S*)-4-Ethyl-3-[(4-methylphenyl)sulfonyl]-1,3-oxazolidin-2-yl}-2,6-dimethylcyclohexan-1-one (*epi*-8): A solution of 18-crown-6 (6.39 g, 24.2 mmol) and KO*t*Bu (2.71 g, 24.1 mmol) in THF (80 mL) was cooled until the onset of cloudiness (ca. −40 °C). The ketone ***cu*-7** (5.90 g, 16.1 mmol) in THF (40 mL) was then added at such a rate that the mixture did not solidify during the course of the addition. The orange solution thus obtained was stirred at room temperature for 1 h. It was then cooled to −78 °C, whereupon MeI (10.1 mL, 162 mmol) was added. After allowing the mixture to warm to room temperature over a period of 15 h, satd. aqueous NH_4Cl (150 mL) was added and vigorous stirring was maintained. The aqueous layer was subsequently extracted with Et_2O (5 × 150 mL). The combined organic layers were dried with Na_2SO_4 and the solvents were removed in vacuo. The crude product {**8**/***epi*-8**, 96:4 [^{1}H NMR (2′H)]} was subjected to FCC (1130

cm³ SiO_2, gradient Et_2O/PE, 1:5 → Et_2O/PE, 1:3). The diastereomerically pure product **8** (5.10 g, 13.4 mmol, 83%) was obtained as a resinous colourless oil. − R_f = 0.38 (SiO_2, Et_2O/PE, 1:1). − $[\alpha]_D^{20}$ = +35.5 (*c* = 2.90, CH_2Cl_2); ***ent*-8:** $[\alpha]_D^{20}$ = −35.1 (*c* = 0.73, CH_2Cl_2). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, ^3J = 7.5 Hz, 3 H, 2′′-H_3), 1.00 (d, ^3J = 6.4 Hz, 3 H, 6-CH_3), 1.07 (s, 3 H, 2-CH_3), 1.35−1.40 (m, 2 H, 5-H_2, 3-H_2), 1.50−1.56 (m, 1 H, 1′′-H_2), 1.68−1.74 (m, 2 H, 4-H_2, 1′′-H_2), 2.03−2.09 (m, 2 H, 5-H_2, 4-H_2), 2.58−2.66 (m, 2 H, 6-H, 3-H_2), 2.43 (s, 3 H, 4′′′-CH_3), 3.07 (dd, ^2J = 8.6 Hz, ^3J = 6.1 Hz, 1 H, 5′-H_2), 3.53 (dd, ^2J = 8.6 Hz, ^3J = 2.6 Hz, 1 H, 5′-H_2), 3.54−3.60 (m, 1 H, 4′-H), 5.46 (s, 1 H, 2′-H), 7.31−7.38 (m, 2 H, 3′′′-H, 5′′′-H), 7.71−7.78 (m, 2 H, 2′′′-H, 6′′′-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.8 (q, C-2′′), 15.0 (q, 6-CH_3), 19.3 (q, 2-CH_3), 20.9 (t, C-4), 21.6 (q, 4′′′-CH_3), 26.9 (t, C-1′′), 35.8 (t, C-5), 36.6 (t, C-3), 43.1 (d, C-6), 53.6 (s, C-2), 62.5 (d, C-4′), 69.7 (t, C-5′), 93.3 (d, C-2′), 128.2 (d, C-2′′′, C-6′′′), 130.0 (d, C-3′′′, C-5′′′), 134.1 (s, C-4′′′), 144.4 (s, C-1′′′), 213.1 (s, C-1). − IR (film): ṽ = 2920 m, 2850 m, 1700 s, 1590 w, 1450 m, 1340 s, 1160 s, 1120 m, 1080 m, 1000 m, 855 w, 820 m, 700 m, 660 s cm^{-1}. − EI-MS: *m*/*z* (%) = 254 (100), 224 (14), 173 (5), 155 (45), 91 (65). − $C_{20}H_{29}NO_4S$ (379.52): calcd. C 63.30, H 7.70, N 3.69; found C 63.45, H 7.92, N 3.88. − ***epi*-8** (205 mg, 0.54 mmol, 3.3%, colourless solid). − R_f = 0.48 (SiO_2, Et_2O/PE, 1:1). − M.p. 71.8−72.6 °C (Et_2O/PE, 1:3). − $[\alpha]_D^{20}$ = −78.6 (*c* = 0.74, CH_2Cl_2); ***ent-epi*-8:** $[\alpha]_D^{20}$ = +74.5 (*c* = 0.96, CH_2Cl_2). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, ^3J = 7.4 Hz, 3 H, 2′′-H_3), 1.08 (d, ^3J = 6.5 Hz, 3 H, 6-CH_3), 1.18 (s, 3 H, 2-CH_3), 1.46−1.61 (m, 2 H, 5-H_2, 1′′-H_2), 1.68−1.87 (m, 4 H, 4-H_2, 3-H_2, 1′′-H_2), 1.91−2.01 (m, 1 H, 5-H_2), 2.29−2.39 (m, 1 H, 3-H_2), 2.44−2.59 (m, 1 H, 6-H), 2.40 (s, 3 H, 4′′′-CH_3), 3.09−3.15 (m, 1 H, 5′-H_2), 3.50−3.59 (m, 2 H, 4′-H, 5′-H_2), 5.39 (s, 1 H, 2′-H), 7.30−7.37 (m, 2 H, 3′′′-H, 5′′′-H), 7.70−7.80 (m, 2 H, 2′′′-H, 6′′′-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.7 (q, C-2′′), 15.2 (q, 6-CH_3), 20.9 (t, C-4), 21.2 (q, 2-CH_3), 21.5 (q, 4′′′-CH_3), 27.9 (t, C-1′′), 33.6 (t, C-5), 34.4 (t, C-3), 41.5 (d, C-6), 52.2 (s, C-2), 62.0 (d, C-4′), 69.2 (t, C-5′), 94.4 (d, C-2′), 128.3 (d, C-2′′′, C-6′′′), 129.8 (d, C-3′′′, C-5′′′), 134.5 (s, C-4′′′), 143.9 (s, C-1′′′), 214.4 (s, C-1). − IR (KBr): ṽ = 2920 m, 2850 m, 1690 s, 1590 w, 1450 m, 1340 s, 1160 s, 1090 m, 1080 m, 1000 m, 820 m, 660 s. − EI-MS: *m*/*z* (%) = 254 (100), 224 (60), 173 (5), 155 (48), 125 (9), 91 (71). − $C_{20}H_{29}NO_4S$ (379.52): calcd. C 63.30, H 7.70, N 3.69; found C 63.57, H 7.47, N 3.66.

(−)-(2*S*,4*S*)-2-[(1*S*,3*R*)-1,3-Dimethyl-2-methylenecyclohexyl]-4-ethyl-3-[(4-methylphenyl)sulfonyl]-1,3-oxazolidine (9): A mixture of $MePPh_3Br$ (7.15 g, 20.0 mmol) and KO*t*Bu (2.22 g, 19.8 mmol) in toluene (80 mL) was refluxed for 1 h. Most of the solvent was then distilled off and a solution of ketone **8** (5.00 g, 13.2 mmol) in toluene (50 mL) was slowly added to the boiling mixture. Again, most of the toluene was removed and the concentrated mixture was refluxed for 4 h. After cooling to room temperature, brine (150 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (4 × 150 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. The crude product {**9**/***epi*-9**, > 96:4 [^{1}H NMR (2-H)]} was purified by FCC (1130 cm³ SiO_2, Et_2O/PE, 1:5) to give **9** together with traces of ***epi*-9** (4.65 g, 12.3 mmol, 93%, *dr* > 96:4) as colourless crystals. − R_f = 0.55 (SiO_2, Et_2O/PE, 1:1). − M.p. 174.9−175.5 °C (Et_2O/PE, 1:5). − $[\alpha]_D^{20}$ = −44.7 (*c* = 0.68, CH_2Cl_2); ***ent*-9:** $[\alpha]_D^{20}$ = +44.1 (*c* = 1.00, CH_2Cl_2). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, ^3J = 7.6 Hz, 3 H, 2′′-H_3), 1.02 (d, ^3J = 6.7 Hz, 3 H, 3′-CH_3), 1.08 (s, 3 H, 1′-CH_3), 1.46−1.61 and 1.61−1.88 (2 m, 2 H and 6 H, 3′-H, 4′-H_2, 5′-H_2, 6′-H_2, 1′′-H_2), 2.25−2.42 (m, 1 H, 6′-H_2), 2.43 (s, 3 H, 4′′′-CH_3), 3.25−3.31 (m, 1 H, 5-H_2), 3.56−3.68 (m, 2 H, 4-H, 5-H_2), 4.81 (s, 1 H, 2′-CH_2), 4.94 (s, 1 H, 2′-CH_2), 5.41 (s, 1 H, 2-H), 7.28−7.38 (m, 2 H, 3′′′-H, 5′′′-H), 7.70−7.80 (m, 2 H, 2′′′-H, 6′′′-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.9 (q, C-2′′), 18.0 (q, 3′-CH_3), 19.4 (q, 1′-CH_3), 21.3 (t, C-5′), 21.5 (q, 4′′′-CH_3), 27.3 (t, C-1′′), 34.1 (d, C-3′), 37.0 and 37.2 (2 t, C-4′, C-6′), 46.2 (s, C-1′), 62.1 (d, C-4), 70.5 (t, C-5), 97.8 (d, C-2), 105.3 (t, 2′-CH_2), 128.5 (d, C-2′′′, C-6′′′), 129.8 (d, C-3′′′, C-5′′′), 134.7 (s, C-4′′′), 144.0 (s, C-1′′′), 157.0 (s, C-2′). − IR (KBr): ṽ = 2950 s, 2910 s, 2860 s, 1650 m, 1590 m, 1330 s, 1160 s, 1100 s, 970 s, 890 s, 810 m, 660 s cm^{-1}. − EI-MS: *m*/*z* (%) = 254 (100), 173 (5), 155 (53), 123 (4), 91 (75). − $C_{21}H_{31}NO_3S$ (377.55): calcd. C 66.81, H 8.28, N 3.71; found C 66.80, H 8.25, N 3.93.

X-ray Structure Analysis of 9:[8] Data were collected on an Enraf−Nonius CAD4 diffractometer. $C_{21}H_{31}NO_3S$, crystal size 0.35 × 0.25 × 0.20 mm, M_r = 377.53 gmol^{-1}, orthorhombic, space group $P2_12_12_1$ (No. 19), *a* = 11.534(1), *b* = 12.404(1), *c* = 14.629(1) Å, *V* = 2092.9(3) Å³, *Z* = 4, $\rho_{calcd.}$ = 1.198 g cm^{-3}, λ = 1.54178 Å, *T* = 223 K, μ = 1.522 mm^{-1}, empirical absorption correction based on ψ scan data (0.618 ≤ *C* ≤ 0.751), ω/2θ scans, total no. of reflections collected (+*h*, −*k*, −*l*) 2418, $[\sin\Theta/\lambda]_{max}$ = 0.62 Å^{-1}, 2418 independent reflections and 2279 observed reflections [$I \geq 2\sigma(I)$], 240 refined parameters, R = 0.040, R_w^2 = 0.114, max. residual electron density ρ = 0.33 (−0.33) eÅ^{-3}, Flack parameter −0.01(2).

(+)-(2*S*,6*R*)-2-(1,3-Dithian-2-yl)-2,6-dimethylcyclohexan-1-one (11): To a solution of oxazolidine **8** (975 mg, 2.57 mmol) and 1,3-propanedithiol (0.52 mL, 5.2 mmol) in CH_2Cl_2 (50 mL), $BF_3{\cdot}Et_2O$ (0.64 mL, 5.1 mmol) was added dropwise at 0 °C. After 2 h at this temperature, satd. aqueous $NaHCO_3$ (50 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo. FCC (440 cm³ SiO_2, gradient Et_2O/PE, 1:10 → Et_2O/PE, 1:3) gave **11** (518 mg, 2.12 mmol, 82%) as a colourless solid. − R_f = 0.43 (SiO_2, Et_2O/PE, 1:1). − $[\alpha]_D^{20}$ = +160 (*c* = 1.18, CH_2Cl_2). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99 (d, ^3J = 6.2 Hz, 3 H, 6-CH_3), 1.13 (s, 3 H, 2-CH_3), 1.24−1.35 (m, 2 H, 3-H_2, 5-H_2), 1.55−1.64 (m, 1 H, 4-H_2), 1.72−1.94 (m, 2 H, 4-H_2, 5′-H_2), 2.00−2.13 (m, 2 H, 5-H_2, 5′-H_2), 2.37 (dq, ^2J = 14.1 Hz, ^3J = 3.3 Hz, 1 H, 3-H_2), 2.61−2.75 (m, 1 H, 6-H), 2.84−2.95 (m, 4 H, 4′-H_2, 6′-H_2), 4.63 (s, 1 H, 2′-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.0 (q, 6-CH_3), 19.2 (q, 2-CH_3), 20.6 (t, C-4), 26.4 (t, C-5′), 31.5 and 31.6 (2 t, C-4′, C-6′), 36.6 (t, C-5), 38.1 (t, C-3), 41.6 (d, C-6), 53.8 (s, C-2), 54.9 (d, C-2′), 213.1 (s, C-1). − IR (KBr): ṽ = 2940 s, 1709 s, 1450 m, 1420 m, 1380 m, 1280 m cm^{-1}. − EI-MS: *m*/*z* (%) = 244 (27) [M$^+$], 121 (25), 119 (100), 106 (13). − $C_{12}H_{20}OS_2$ (244.42): calcd. C 58.97, H 8.25; found C 59.01, H 8.44.

(−)-2-[(1*S*,3*R*)-1,3-Dimethyl-2-methylenecyclohexyl]-1,3-dithiane (2). − Method A: To a stirred solution of oxazolidine **9** (4.11 g, 10.9 mmol) and 1,3-propanedithiol (2.21 mL, 22.0 mmol) in CH_2Cl_2 (200 mL), $BF_3{\cdot}Et_2O$ (2.75 mL, 21.7 mmol) was added dropwise at 0 °C. After stirring for 2 h, satd. aqueous $NaHCO_3$ (50 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (4 × 100 mL). The combined organic layers were dried with Na_2SO_4 and the solvents were removed in vacuo. Purification of the crude product by FCC (780 cm³ SiO_2, gradient PE → Et_2O/PE, 1:10 → Et_2O) yielded **2** (2.46 g, 10.1 mmol, 93%) as a volatile oil and amino alcohol **10** (2.22 g, 9.12 mmol, 84%) as a white solid. − **Method B:** A mixture of $MePPh_3Br$ (785 mg, 2.20 mmol) and KO*t*Bu (245 mg, 2.18 mmol) in toluene (20 mL) was refluxed for 1 h. Most of the solvent was then distilled off and a solution of ketone **11** (355 mg, 1.45 mmol) in toluene (10 mL) was slowly added to the boiling mixture. Again, most of the toluene was distilled

off and the concentrated mixture was refluxed for 4 h. After cooling to room temperature, brine (30 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. The crude product [^{1}H NMR (2-H): **2**/***epi*-2**, 81:19] was purified by FCC (250 cm^3 SiO_2, gradient Et_2O/PE, 1:10 → Et_2O/PE, 1:5) to give a mixture of **2** and ***epi*-2** (183 mg, 0.75 mmol, 52%, *dr* = 80:20) as a volatile colourless liquid, along with diastereomerically pure **11** (65 mg, 0.26 mmol, 18%). − R_f = 0.64 (SiO_2, Et_2O/PE, 1:1). − $[\alpha]_D^{20}$ = −3.1 (*c* = 0.80, CH_2Cl_2); ***ent*-2:** $[\alpha]_D^{20}$ = +1.75 (*c* = 1.10, CH_2Cl_2). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (d, ^3J = 6.7 Hz, 3 H, 3′-CH_3), 1.05−1.20 (m, 1 H, 4′-H_2), 1.23 (s, 3 H, 1′-CH_3), 1.49−1.74 (m, 4 H, 4′-H_2, 5′-H_2, 6′-H_2), 1.75−1.90 (m, 2 H, 5-H_2, 6′-H_2), 2.02−2.10 (m, 1 H, 5-H_2), 2.30−2.43 (m, 1 H, 3′-H), 2.84−2.92 (m, 4 H, 4-H_2, 6-H_2), 4.32 (s, 1 H, 2-H), 4.92 (d, ^2J = 1.4 Hz, 1 H, 2′-CH_2), 5.11 (s, 1 H, 2′-CH_2). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7 (q, 3′-*C*H_3), 20.8 (t, C-5′), 24.3 (q, 1′-CH_3), 26.4 (t, C-5), 31.8 and 32.0 (2 t, C-4, C-6), 34.9 (d, C-3′), 35.9 (t, C-4′), 37.4 (t, C-6′), 44.9 (s, C-1′), 60.4 (d, C-2), 108.5 (t, 2′-*C*H_2), 154.3 (s, C-2′). − IR (film): $\tilde{\nu}$ = 3080 w, 2900 s, 1620 m, 1440 m, 1410 m, 1270 m, 1180 w, 1050 w, 900 s, 770 m cm^{-1}. − EI-MS: *m*/*z* (%) = 242 (8) [M$^+$], 121 (9), 119 (100), 106 (3). − $C_{13}H_{22}S_2$ (242.44): calcd. C 64.40, H 9.15; found C 64.83, H 9.28.

2-(2,3,5,6-Tetramethoxyphenyl)ethan-1-ol (12): A solution of 1,2,4,5-tetramethoxybenzene[9] (**5**) (1.98 g, 10.0 mmol) and LiCl (1.27 g, 30.0 mmol) in THF (100 mL) was cooled to 0 °C, whereupon a 1.6 M solution of *n*BuLi in hexane (6.90 mL, 11.0 mmol) was added dropwise. After stirring at room temperature for 30 min, the reaction mixture was cooled to −78 °C and transferred by means of a cannula into a solution of ethylene oxide (ca. 5 g, 114 mmol) in THF (30 mL). The resulting mixture was stirred at −78 °C for 30 min and thereafter at room temperature for a further 3 h. 2 N aqueous HCl (50 mL) was then added at 0 °C and the heterogeneous mixture was stirred for 30 min. The aqueous layer was subsequently extracted with Et_2O (4 × 150 mL), the combined organic layers were dried ($MgSO_4$), and the solvents were evaporated in vacuo. FCC (850 cm^3 SiO_2, gradient Et_2O/PE, 2:1 → Et_2O) provided alcohol **12** (1.94 g, 8.00 mmol, 80%) as a waxy solid. − R_f = 0.23 (SiO_2, Et_2O). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04 (s, 1 H, 1-OH), 2.94 (t, ^3J = 6.6 Hz, 2 H, 2-H_2), 3.76 (s, 6 H, 2′-OCH_3, 6′-OCH_3), 3.77 (t, ^3J = 6.6 Hz, 2 H, 1-H_2), 3.83 (s, 6 H, 3′-OCH_3, 5′-OCH_3), 6.44 (s, 1 H, 4′-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.0 (t, C-2), 56.3 (q, 3′-OCH_3, 5′-OCH_3), 60.9 (q, 2′-OCH_3, 6′-OCH_3), 63.4 (t, C-1), 97.9 (d, C-4′), 126.9 (s, C-1′), 141.3 (s, C-2′, C-6′), 149.0 (s, C-3′, C-5′). − IR (film): $\tilde{\nu}$ = 3400 s, 2920 s, 1590 m, 1480 s, 1360 s, 1230 s, 1080 s, 850 w cm^{-1}. − EI-MS: *m*/*z* (%) = 242 (100) [M$^+$], 227 (45), 211 (9), 195 (37), 181 (35), 166 (11), 153 (60), 139 (18), 125 (16). − $C_{12}H_{18}O_5$ (242.27): calcd. C 59.49, H 7.48; found C 59.57, H 7.38.

2-(2,3,5,6-Tetramethoxyphenyl)ethanal (13): To a cooled (−60 °C) solution of $(COCl)_2$ (2.00 mL, 22.9 mmol) in CH_2Cl_2 (100 mL), a solution of DMSO (3.24 mL, 45.7 mmol) in CH_2Cl_2 (20 mL) was added dropwise and the resulting mixture was stirred for 15 min. Then, a solution of alcohol **12** (2.76 g, 11.4 mmol) in CH_2Cl_2 (30 mL) was slowly added. The reaction mixture was allowed to warm to −30 °C over a period of 1 h, NEt_3 (12.7 mL, 91.1 mmol) was added, and the resulting solution was stirred for 1 h at room temperature. 2 N aqueous HCl (100 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) and the solvents were evaporated. The crude product was purified by FCC (850 cm^3 SiO_2, gradient Et_2O/PE, 1:2 → Et_2O/PE, 1:1) to furnish aldehyde **13** (2.15 g, 8.95 mmol, 79%) as a colourless oil. − R_f = 0.27 (SiO_2, Et_2O/PE, 1:1). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.70 (s, 8 H, 2-H_2, 2′-OCH_3, 6′-OCH_3), 3.85 (s, 6 H, 3′-OCH_3, 5′-OCH_3), 6.50 (s, 1 H, 4′-H), 9.68 (t, ^3J = 1.5 Hz, 1 H, 1-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.5 (t, C-2), 56.4 (q, 3′-OCH_3, 5′-OCH_3), 60.8 (q, 2′-OCH_3, 6′-OCH_3), 98.9 (d, C-4′), 121.2 (s, C-1′), 141.2 (s, C-2′, C-6′), 148.9 (s, C-3′, C-5′), 199.5 (d, C-1). − IR (film): $\tilde{\nu}$ = 2920 s, 1710 s, 1590 m, 1480 s, 1340 m, 1225 s, 1070 s, 1000 m, 960 w, 845 w. − EI-MS: *m*/*z* (%) = 240 (100) [M$^+$], 225 (38), 196 (28), 182 (72), 167 (20), 153 (23). − $C_{12}H_{16}O_5$ (240.26): calcd. C 59.99, H 6.71; found C 60.14, H 6.80.

Ethyl (*E*)-2-Methyl-4-(2,3,5,6-tetramethoxyphenyl)-2-butenoate (14): Ylide **16** (2.55 g, 7.03 mmol) was treated with a solution of aldehyde **13** (1.30 g, 5.41 mmol) in CH_2Cl_2 (70 mL) and the resulting mixture was refluxed for 3 h. Satd. brine (100 mL) was then added, the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. FCC (440 cm^3 SiO_2, gradient Et_2O/PE, 1:3 → Et_2O/PE, 1:2) furnished ester **14** [1.61 g, 4.96 mmol, 92%, (*E*)/(*Z*) = 98:2 (GC)] as a colourless solid. − R_f = 0.32 (SiO_2, Et_2O/PE, 1:1). − M.p. 54.7−55.3 °C (Et_2O/PE, 1:2). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, ^3J = 7.2 Hz, 3 H, 2′′-H_3), 1.99 (d, ^4J = 1.2 Hz, 3 H, 2-CH_3), 3.52 (dd, ^3J = 7.2 Hz, *J* = 0.9 Hz, 2 H, 4-H_2), 3.74 (s, 6 H, 2′-OCH_3, 6′-OCH_3), 3.82 (s, 6 H, 3′-OCH_3, 5′-OCH_3), 4.22 (q, ^3J = 7.2 Hz, 2 H, 1′′-H_2), 6.44 (s, 1 H, 4′-H), 6.74 (m, 1 H, 3-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.4 (q, C-2′′), 14.2 (q, 2-CH_3), 24.3 (t, C-4), 56.3 (q, 3′-OCH_3, 5′-OCH_3), 60.3 (t, C-1′′), 60.8 (q, 2′-OCH_3, 6′-OCH_3), 97.8 (d, C-4′), 127.2 and 127.4 (2 s, C-2, C-1′), 140.6 (d, C-3), 141.17 (s, C-2′, C-6′), 148.9 (s, C-3′, C-5′), 168.2 (s, C-1). − IR (KBr): $\tilde{\nu}$ = 2910 s, 1695 s, 1630 w, 1590 w, 1480 s, 1340 m, 1230 s, 1050 s, 960 w, 800 w cm^{-1}. − EI-MS: *m*/*z* (%) = 323 (100) [M$^+$ − H], 308 (5), 292 (4), 278 (12), 247 (11), 235 (59), 220 (18). − $C_{17}H_{24}O_6$ (324.38): calcd. C 62.95, H 7.46; found C 63.01, H 7.68.

(*E*)-2-Methyl-4-(2,3,5,6-tetramethoxyphenyl)-2-buten-1-ol (17): A 1.0 M solution of DIBAL-H in CH_2Cl_2 (28.4 mL, 28.4 mmol) was added dropwise to a solution of ester **14** (1.84 g, 5.67 mmol) in CH_2Cl_2 (50 mL) at −78 °C. After stirring for 2.5 h at this temperature, the reaction mixture was hydrolyzed by the addition of H_2O (15 mL) and allowed to warm to room temperature. 2 N aqueous HCl (100 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. Purification of the crude product by FCC (500 cm^3 SiO_2, Et_2O/PE, 3:1) yielded alcohol **17** (1.47 g, 5.21 mmol, 92%) as a colourless oil. − R_f = 0.29 (SiO_2, Et_2O). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 1 H, 1-OH), 1.82 (d, ^4J = 0.3 Hz, 3 H, 2-CH_3), 3.39 (d, ^3J = 7.2 Hz, 2 H, 4-H_2), 3.74 (s, 6 H, 2′-OCH_3, 6′-OCH_3), 3.82 (s, 6 H, 3′-OCH_3, 5′-OCH_3), 3.95 (s, 2 H, 1-H_2), 5.45 (td, ^3J = 7.2 Hz, ^4J = 0.3 Hz, 1 H, 3-H), 6.41 (s, 1 H, 4′-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (q, 2-CH_3), 23.3 (t, C-4), 56.3 (q, 3′-OCH_3, 5′-OCH_3), 60.8 (q, 2′-OCH_3, 6′-OCH_3), 68.9 (t, C-1), 97.3 (d, C-4′), 125.0 (d, C-3), 129.1 (s, C-1′), 134.6 (s, C-2), 141.0 (s, C-2′, C-6′), 148.9 (s, C-3′, C-5′). − IR (film): $\tilde{\nu}$ = 3400 s, 2910 s, 1590 m, 1450 s, 1340 m, 1230 s, 1050 s, 830 w cm^{-1}. − EI-MS: *m*/*z* (%) = 282 (100) [M$^+$], 249 (8), 233 (16), 209 (12), 202 (20), 181 (11), 178 (16). − $C_{15}H_{22}O_5$ (282.34): calcd. C 63.81, H 7.85; found C 63.71, H 7.92.

3-[(*E*)-4-Bromo-3-methyl-2-butenyl]-1,2,4,5-tetramethoxybenzene (3): To a solution of alcohol **17** (1.00 g, 3.54 mmol) in CH_2Cl_2 at −40 °C, NEt_3 (0.78 mL, 5.6 mmol) followed by MsCl (0.36 mL, 4.7 mmol) were added. After stirring for 1.5 h, a solution of LiBr

(1.23 g, 14.2 mmol) in THF (25 mL) was added and the resulting mixture was stirred for 2.5 h at 0 °C. It was then poured into PE (250 mL) and extracted with H_2O (4 × 200 mL). Drying (Na_2SO_4) of the organic layer and evaporation of the solvents afforded an adequately pure crude product (1.20 g, 3.48 mmol, 98%). FCC (310 cm^3 SiO_2, Et_2O/PE, 1:2) provided the bromide **3** (1.09 g, 3.16 mmol, 89%) as a colourless oil. − R_f = 0.40 (SiO_2, Et_2O/PE, 1:1). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.90 (d, ^4J = 0.3 Hz, 3 H, 3′-CH_3), 3.38 (d, ^3J = 7.2 Hz, 2 H, 1′-H_2), 3.73 (s, 6 H, 2-OCH_3, 4-OCH_3), 3.82 (s, 6 H, 1-OCH_3, 5-OCH_3), 3.93 (s, 2 H, 4′-H_2), 5.63 (td, ^3J = 7.2 Hz, ^4J = 0.3 Hz, 1 H, 2′-H), 6.42 (s, 1 H, 6-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7 (q, 3′-CH_3), 24.0 (t, C-1′), 41.8 (t, C-4′), 56.3 (q, 1-OCH_3, 5-OCH_3), 60.8 (q, 2-OCH_3, 4-OCH_3), 97.5 (d, C-6), 128.1 (s, C-3), 130.0 (d, C-2′), 131.4 (s, C-3′), 141.0 (s, C-2, C-4), 148.9 (s, C-1, C-5). − IR (film): $\tilde{\nu}$ = 2905 s, 1580 m, 1450 s, 1345 m, 1200 s, 1050 s, 1000 w, 830 w cm^{-1}. − EI-MS: *m*/*z* (%) = 344/346 (100/98) [M^+], 265 (69), 250 (32), 234 (56), 219 (20), 203 (20), 191 (20), 187 (18). − $C_{15}H_{21}O_4Br$ (345.24): calcd. C 52.19, H 6.13; found C 52.24, H 6.30.

(+)-2-[(1*S*,3*R*)-1,3-Dimethyl-2-methylenecyclohexyl]-2-[(*E*)-2-methyl-4-(2,3,5,6-tetramethoxyphenyl)-2-butenyl]-1,3-dithiane (18): A 1.7 M solution of *t*BuLi in pentane (1.23 mL, 2.09 mmol) was slowly added to a solution of dithiane **2** (485 mg, 2.00 mmol) in THF (40 mL) and HMPTA (1.04 mL, 5.98 mmol) at −78 °C. The yellow mixture thus obtained was stirred for 2.5 h and then a solution of bromide **3** (691 mg, 2.00 mmol) in THF (8 mL) was added dropwise. After stirring for a further 3 h at −78 °C, MeOH/H_2O (1:1, 10 mL) was added and the reaction mixture was allowed to warm to room temperature. The mixture was passed through a pad of silica gel eluting with Et_2O/PE, 1:1, so as to remove HMPTA, the solvents were evaporated, and the residue was subjected to FCC (500 cm^3 SiO_2, Et_2O/PE, 1:10). The dithiane **18** (864 mg, 1.70 mmol, 85%) was obtained as a resinous colourless oil. − R_f = 0.40 (SiO_2, Et_2O/PE, 1:1). − $[\alpha]_D^{20}$ = +31.1 (*c* = 0.63, CH_2Cl_2); ***ent*-18:** $[\alpha]_D^{20}$ = −28.8 (*c* = 0.86, CH_2Cl_2). − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.83−1.04, 1.55−1.80, 1.80−1.98, and 2.05−2.15 (4 m, 1 H, 5 H, 1 H, and 1 H, 4′′-H_2, 5′′-H_2, 6′′-H_2, 5-H_2), 0.96 (d, ^3J = 6.4 Hz, 3 H, 3′′-CH_3), 1.34 (s, 3 H, 1′′-CH_3), 2.14 (s, 3 H, 2′-CH_3), 2.16−2.31 (m, 1 H, 3′′-H), 2.46−2.61, 2.61−2.85, and 2.85 −3.05 (3 m, 1 H, 3 H, and 2 H, 4-H_2, 6-H_2, 1′-H_2), 3.39 (d, ^3J = 6.9 Hz, 2 H, 4′-H_2), 3.76 (s, 6 H, 2′′′-OCH_3, 6′′′-OCH_3), 3.81 (s, 6 H, 3′′′-OCH_3, 5′′′-OCH_3), 4.94 (d, ^2J = 1.4 Hz, 1 H, 2′′-CH_2), 5.53−5.62 (m, 2 H, 2′′-CH_2, 3′-H), 6.41 (s, 1 H, 4′′′-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3 (q, 2′-CH_3), 19.9 (q, 3′′-CH_3), 20.4 (q, 1′′-CH_3), 22.3, 22.7, 27.2, and 27.9 (4 t, C-4, C-5, C-6, C-5′′), 24.0 (t, C-4′), 34.0 and 36.9 (2 t, C-4′′, C-6′′), 34.8 (d, C-3′′), 47.5 (t, C-1′), 54.3 (s, C-1′′), 56.4 (q, 3′′′-OCH_3, 5′′′-OCH_3), 60.8 (q, 2′′′-OCH_3, 6′′′-OCH_3), 66.7 (s, C-2), 97.6 (d, C-4′′′), 108.7 (t, 2′′-CH_2), 129.6 and 131.7 (2 s, C-2′, C-1′′′), 129.9 (d, C-3′), 141.4 (s, C-2′′′, C-6′′′), 148.9 (s, C-3′′′, C-5′′′), 153.4 (s, C-2′′). − IR (film): $\tilde{\nu}$ = 2980 s, 1580 w, 1450 m, 1335 w, 1210 m, 1045 m cm^{-1}. − EI-MS: *m*/*z* (%) = 506 (14) [M^+], 383 (45), 241 (49), 211 (50), 196 (37), 181 (21), 153 (20), 133 (23), 125 (27), 123 (31), 119 (43). − HRMS ($C_{28}H_{42}O_4S_2$): calcd. 506.2524; found 506.2526. − $C_{28}H_{42}O_4S_2$ (506.78): calcd. C 66.36, H 8.35; found C 66.96, H 8.29.

(−)-3-{(*E*)-5-[(1*R*,3*R*)-1,3-Dimethyl-2-methylenecyclohexyl]-3-methyl-2-pentenyl}-1,2,4,5-tetramethoxybenzene (19): Dithiane **18** (740 mg, 1.46 mmol) was dissolved in Bu_3SnH (5.80 mL, 21.6 mmol) and the resulting solution was heated to 120 °C for 30 h. Initially, and then at intervals of 2 h, 1 mg portions of solid AIBN were added. The crude reaction mixture was subsequently subjected to FCC (500 cm^3 SiO_2, Et_2O/PE, 1:9) to yield **19** (560 mg, 1.39 mmol, 95%) as a resinous colourless oil. − R_f = 0.47 (SiO_2, Et_2O/PE, 1:1). − $[\alpha]_D^{20}$ = −15.2 (*c* = 0.79, CH_2Cl_2); ***ent*-19:** $[\alpha]_D^{20}$ = +15.2 (*c* = 0.86, CH_2Cl_2) . − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.81−1.00, 1.10−1.30, 1.40−1.75, and 1.75−1.80 (4 m, 1 H, 1 H, 5 H, and 1 H, 4′′-H_2, 5′′-H_2, 6′′-H_2, 5′-H_2), 0.99 (s, 3 H, 1′′-CH_3), 1.00 (d, ^3J = 6.4 Hz, 3 H, 3′′-CH_3), 1.79 (s, 3 H, 3′-CH_3), 1.93−2.00 (m, 2 H, 4′-H_2), 2.26−2.34 (m, 1 H, 3′′-H), 3.37 (d, ^3J = 6.4 Hz, 2 H, 1′-H_2), 3.74 (s, 6 H, 2-OCH_3, 4-OCH_3), 3.82 (s, 6 H, 1-OCH_3, 5-OCH_3), 4.65 (s, 1 H, 2′′-CH_2), 4.67 (s, 1 H, 2′′-CH_2), 5.13−5.23 (m, 1 H, 2′-H), 6.41 (s, 1 H, 6-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3 (q, 3′-CH_3), 19.6 (q, 3′′-CH_3), 21.8 (t, C-5′′), 23.7 (t, C-1′), 24.7 (q, 1′′-CH_3), 34.0 (d, C-3′′), 39.2 (s, C-1′′), 34.0, 37.2, 38.7, and 40.1 (4 t, C-4′, C-5′, C-4′′, C-6′′), 56.4 (q, 1-OCH_3, 5-OCH_3), 60.8 (q, 2-OCH_3, 4-OCH_3), 97.4 (d, C-6), 103.4 (t, 2′′-CH_2), 122.9 (d, C-2′), 130.2 (s, C-3), 135.8 (s, C-3′), 141.3 (s, C-2, C-4), 149.0 (s, C-1, C-5), 159.8 (s, C-2′′). − IR (film): $\tilde{\nu}$ = 2930 s, 2850 s, 1639 w, 1604 m, 1487 s, 1467 s, 1425 s, 1343 m, 1246 s, 1095 s, 1088 s, 1019 m, 978 w, 895 w cm^{-1}. − EI-MS: *m*/*z* (%) = 402 (100) [M^+], 278 (59), 263 (24), 247 (29), 233 (37), 211 (70), 196 (66), 191 (33), 181 (35), 171 (34), 123 (33), 109 (57), 95 (66). − HRMS ($C_{25}H_{38}O_4$): calcd. 402.2770; found 402.2780.

(−)-Metachromin A (1): To a solution of compound **19** (474 mg, 1.17 mmol) in MeCN (10 mL), a solution of CAN (1.61 g, 2.94 mmol) in MeCN/H_2O (7:3, 10 mL) was added over a period of 1.5 h (syringe pump) at −7 °C. The resulting reaction mixture was stirred at room temperature for 2 h. The organic layer was then washed with H_2O (2 × 20 mL) and the aqueous layers were extracted with Et_2O (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and the solvents were removed in vacuo. FCC (80 cm^3 RP-18, gradient MeCN/H_2O, 2:1 → MeCN/H_2O, 3:1) afforded metachromin A (**1**, 154 mg, 0.43 mmol, 37%) and the methyl ether **20** (162 mg, 0.40 mmol, 34%) as orange oils. Both compounds were crystallized from Et_2O/PE to give orange needles. − R_f = 0.43 (RP-18, MeCN/H_2O, 9:1). − M.p. 80.7−81.2 °C (Et_2O) (ref.[1] 80−82 °C). − $[\alpha]_D^{27}$ = −17.6 (*c* = 0.94, $CHCl_3$) {ref.[1] $[\alpha]_D^{27}$ = −11.0 (*c* = 1.00, $CHCl_3$)}; ***ent*-1:** $[\alpha]_D^{27}$ = +17.3 (*c* = 0.55, $CHCl_3$). − ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87−1.02, 1.13−1.22, 1.41−1.65, and 1.65−1.75 (4 m, 1 H, 1 H, 5 H, and 1 H, 1-H_2, 2-H_2, 3-H_2, 7-H_2), 0.98 (s, 3 H, 14-H_3), 0.99 (d, ^3J = 6.4 Hz, 3 H, 12-H_3), 1.73 (s, 3 H, 15-H_3), 1.91−1.96 (m, 2 H, 8-H_2), 2.27−2.32 (m, 1 H, 4-H), 3.13 (d, ^3J = 7.2 Hz, 2 H, 11-H_2), 3.82 (s, 3 H, 22-H_3), 4.65 (s, 1 H, 13-H_2), 4.67 (s, 1 H, 13-H_2), 5.13 (td, ^3J = 7.2 Hz, ^4J = 1.0 Hz, 1 H, 10-H), 5.81 (s, 1 H, 19-H), 7.26 (s, 1 H, OH). − ^{13}C NMR (100 MHz, $CDCl_3$):[23] δ = 16.3 (q, C-15), 19.6 (q, C-12), 21.8 (t, C-11), 24.7 (q, C-14), 34.0 (d, C-4), 39.2 (s, C-6), 21.8, 34.0, 37.2, 38.7, and 40.0 (5 t, C-1, C-2, C-3, C-7, C-8), 56.7 (q, C-22), 102.2 (d, C-19), 103.3 (t, C-13), 118.3 (s, C-9), 118.8 (d, C-10), 138.3 (s, C-16), 151.2, 159.2, and 161.1 (3 s, C-5, C-17, C-20), 181.4 and 183.0 (2 s, C-18, C-21). − IR (film): $\tilde{\nu}$ = 3346 s, 2920 s, 2856 s, 1649 s, 1607 s, 1450 w, 1387 m, 1308 m, 1230 m, 1202 m, 1039 w cm^{-1}. − EI-MS: *m*/*z* (%) = 358 (16) [M^+], 234 (13), 219 (40), 207 (38), 189 (68), 180 (48), 170 (54), 168 (81), 133 (22), 123 (31), 119 (33), 109 (100), 95 (69). − HRMS ($C_{22}H_{30}O_4$): calcd. 358.2144; found 358.2149. − $C_{22}H_{30}O_4$ (358.48): calcd. C 73.71, H 8.44; found C 73.45, H 8.71.

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