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Stereoselective synthesis of (−)-blepharocalyxin D

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Abstract—The Prins cyclization strategy was successfully applied in the stereoselective synthesis of (−)-blepharocalyxin D (**1**), a cytotoxic dimeric diarylheptanoid isolated from *Alpinia blepharocalyx*.

1. Introduction

A large number of bioactive diarylheptanoid natural products were isolated recently by Kadota and co-workers from the seeds of *Alpinia blepharocalyx* K. Schum, a member of Zingiberaceae family found in China.[1,2] Plants of this family are known to have antihepatotoxic, anti-inflammatory, and stomachic properties. More recently, synthetic investigations[3] by Rychnovsky and co-workers led to revised structures of some of the diarylheptanoids such as calyxins L, F, M, and G (Fig. 1).

Blepharocalyxin D (**1**)[1e,h] is a unique member of dimeric diarylheptanoid natural products isolated from the seeds of *A. blepharocalyx* (Fig. 2). It is an antiproliferative agent (ED_{50} 3.61 μM) against murine colon 26-L5 carcinoma cells. The most characteristic feature of blepharocalyxin D (**1**) is a rare 2,8-dioxabicyclo[4.4.0]decane core, to which four *p*-hydroxyphenyl groups are appended.[4] No general strategy has evolved for generation of this dioxabicyclodecane system, and there have been no advances made toward synthesis of this interesting natural product.[5] Herein, we describe a concise stereoselective synthesis of **1** employing two distinctive Prins cyclization reactions.[6]

In our retrosynthetic analysis, the oxane derivative **A** was considered as a pivotal intermediate in the synthesis of blepharocalyxin D (**1**). A number of different synthetic routes may be considered for the efficient conversion from **A** to

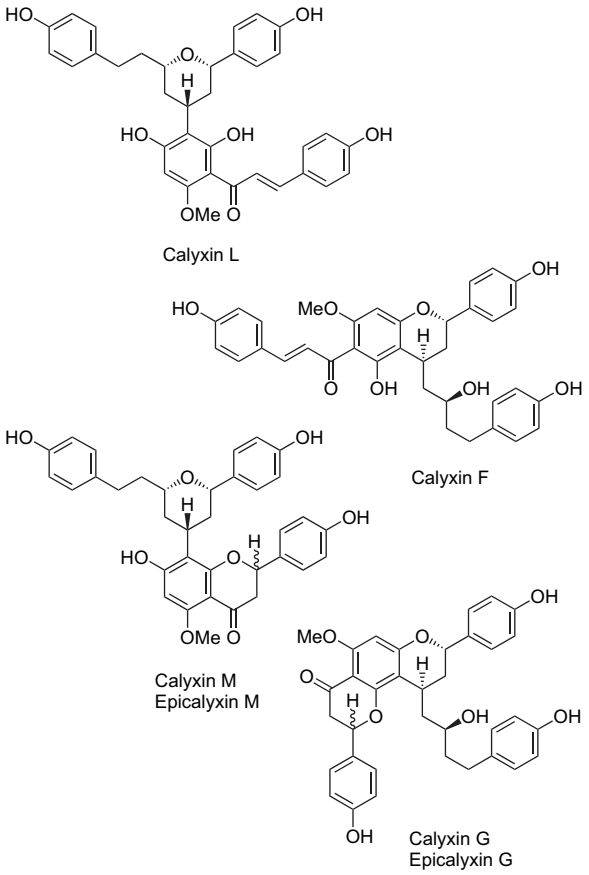

Figure 1. Some diarylheptanoid natural products from *Alpinia blepharocalyx*.

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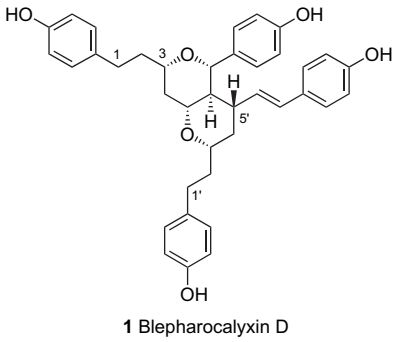


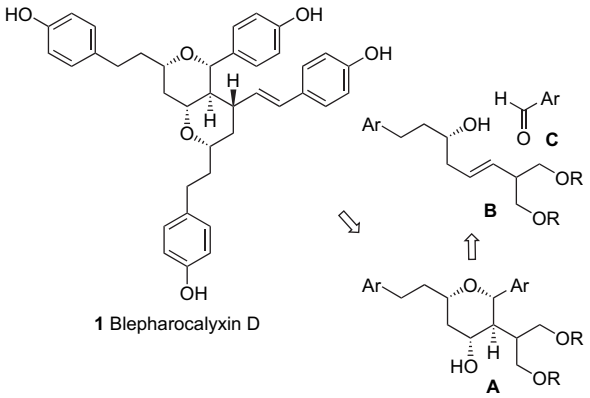
Figure 2. Structure of blepharocalyxin D (**1**).

1. Intermediate **A** may be prepared from homoallylic alcohol **B** and aldehyde **C**. This type of Prins cyclization has already been reported by Willis and co-workers.[7] (Scheme 1).

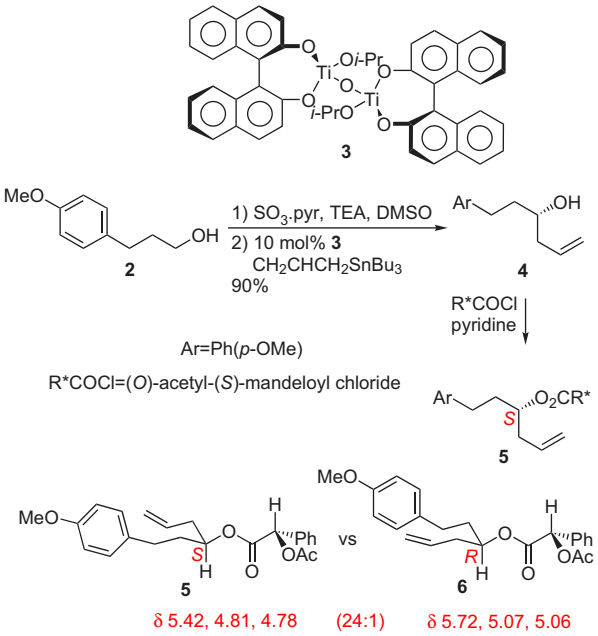
2. Results and discussion

Sulfur trioxide–DMSO oxidation of 3-(*p*-methoxyphenyl)-propan-1-ol (**2**) yielded the corresponding aldehyde, which was converted into homoallylic alcohol **4** (92% ee) via reaction with allyltributylstannane in the presence of 10 mol % catalyst **3** following the Maruoka protocol.[8] The (*S*)-configuration of homoallylic alcohol **4** was confirmed by NMR analysis of the ester derivatives, which were produced via reaction with (*O*)-acetyl-(*S*)-mandeloyl chloride.[9] The NMR spectra of the major product **5** exhibited vinylic proton signals at δ 5.42, 4.81, and 4.78, compared to the signals of the minor isomer **6** at δ 5.72, 5.07, and 5.06 (Scheme 2).

TIPS-protection of **4**, hydroboration–oxidation, and sulfur trioxide–DMSO oxidation produced the corresponding aldehyde. The aldehyde was converted into the malonate derivative **7** after Knoevenagel condensation and LDA-mediated deconjugation. Lithium aluminum hydride reduction of **7** and acetylation of the resulting diol produced the homoallylic alcohol diacetate derivative **8**. Reaction of **8** with *p*-anisaldehyde in the presence of boron trifluoride diethyl etherate and trimethylsilyl acetate in acetic acid[10] resulted in the formation of the oxane triacetate product **9** in 35% yield accompanied by diacetate **10** in 60% yield (Scheme 3). Diacetate **10** could be recycled under the same reaction conditions producing **9** in 35% yield. The corresponding

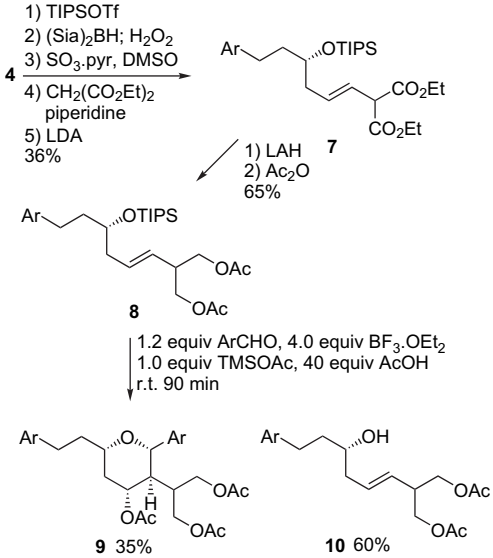


Scheme 1. Retrosynthetic analysis.



Scheme 2. Synthesis of homoallylic alcohol **4**.

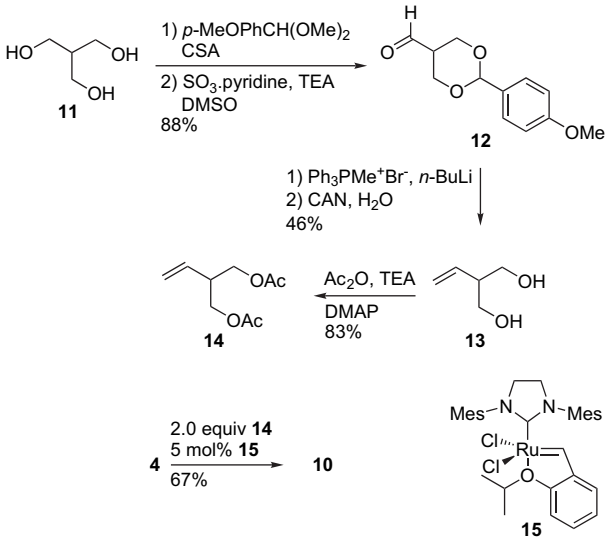
TES derivative could also be converted into oxane triacetate **9** under similar conditions, but the malonate derivative **7** did not serve as a viable precursor for Prins cyclization yielding a complex reaction mixture.



Scheme 3. Synthesis of homoallylic alcohol derivative **8** and Prins cyclization.

The efficacy of olefin cross metathesis reaction was then examined for potential alternative for the laborious route to the pivotal oxane intermediate **9** described above. The required olefin **14** was prepared starting from triol **11**. Cyclic acetal formation and sulfur trioxide–DMSO oxidation yielded aldehyde **12**.[11] Wittig olefination and oxidative deprotection produced diol **13**, from which diacetate **14** was obtained via acetylation. Cross metathesis reaction of **4** with 2 equiv of olefin **14** in the presence of the second generation Hoveyda–Grubbs catalyst (**15**)[12] proceeded smoothly producing

homoallylic alcohol **10** in 67% yield (Scheme 4). Use of the second generation Grubbs catalyst under the identical reaction conditions provided the product **10** in 48% yield. Use of alternative olefin partners, for example, diol **13** or its bis(TBS) ether, led to more sluggish reactions producing the corresponding products in 10–20% yield in the presence of the second generation Grubbs catalyst.

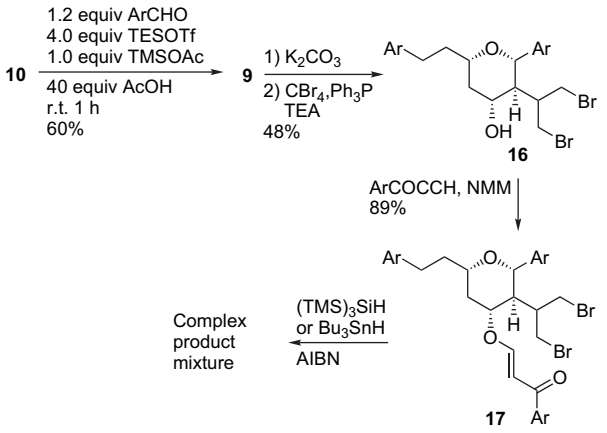


Scheme 4. Improved synthesis of homoallylic alcohol diacetate **10**.

For the crucial Prins cyclization of homoallylic alcohol **10** with *p*-anisaldehyde, reaction conditions of Willis and co-workers[7,10] were modified for maximum efficiency: in our hands, use of 4 equiv of triethylsilyl triflate and 1 equiv of trimethylsilyl acetate in 40 equiv of acetic acid worked best producing the oxane product **9** stereoselectively in 60% yield. No sign of racemization was noticed originating from oxonia-Cope rearrangement.[13] Use of 2 equiv of boron trifluoride diethyl etherate, 4 equiv of trimethylsilyl acetate, and 4 equiv of acetic acid in cyclohexane produced **9** in 18–26% yield. No oxane product was formed in the presence of 4 equiv of trifluoroacetic acid in trifluoromethylbenzene.

At this point, radical cyclization routes toward the required dioxabicyclodecane system were investigated. The triol obtained via exhaustive hydrolysis of triacetate **9** was converted into dibromide **16** in the presence of carbon tetrabromide and triphenylphosphine. Reaction of **16** with (*p*-methoxyphenyl)propynone in the presence of *N*-methylmorpholine produced β-alkoxyvinyl ketone **17**. These type of vinyl ethers are known to be viable precursors for radical cyclization.[14] Unfortunately, reaction of **17** with tris(trimethylsilyl)silane or tributylstannane in the presence of AIBN resulted in the formation of complex product mixtures, and it was not possible to obtain the desired bicyclic product (Scheme 5).

Alternative ways for preparation of the dioxabicyclodecane system were examined and a prominent possibility appeared to be a second Prins cyclization. Exhaustive deacetylation of **9** led to the corresponding triol, which was converted into thionocarbonate **18** in 67% yield. Cyclic acetal formation of **18** with 3-(*p*-methoxyphenyl)propanal was accomplished using ionic liquid [SOClMIm]Cl (**19**),[15] and thermal



Scheme 5. Improved Prins cyclization of **10** and radical cyclization attempted.

elimination was carried out in hot diphenyl ether to provide the seven-membered cyclic acetal **20**.[16] The second Prins reaction proceeded smoothly in the presence of boron trifluoride diethyl etherate producing a mixture of the axial aldehyde **21** (83%) and the equatorial aldehyde **22** (2%). As far as we know, this type of Prins cyclization using methylidene-substituted seven-membered cyclic acetals is unprecedented. The high stereoselectivity is surprising, as the Prins-pinacol sequence on related diol substrates is known to yield mainly equatorial aldehydes.[17,18] The kinetic preference in our case may be explained by the conformational constraints originating from the steric crowding.

Under basic conditions, aldehyde **21** was converted into a product mixture favoring the equatorial aldehyde **22** (**22**, 52%; **21**, 25%). Epimerization at C5′ (from **21** to **22**) was accompanied by the diagnostic upfield shift of the aldehyde proton signals in the ^{1}H NMR spectra: the aldehyde proton of **21** exhibits a singlet at δ 9.68 compared to a doublet at δ 8.38 (J=4.7 Hz) for the same proton of **22**. The axial aldehyde **21** recovered could be recycled to produce an additional amount of **22**. Julia–Julia reaction[19] of the lithiated sulfone **23** with aldehyde **22** proceeded smoothly, and a 77% yield of the (*E*)-olefin **24** was obtained stereoselectively (50:1). Crystals of **24** were obtained from carbon tetrachloride–pentane solution and the crystallographic data confirmed the assigned structure (Fig. 3).

Global demethylation of **24** was not possible under various reaction conditions using Lewis acids: presumably, oxygen atoms in the dioxabicyclodecane system presented more basic sites. Eventually, blepharocalyxin D (**1**) was obtained in acceptable yield using lithium propanethiolate in hot HMPA[20,21] (Scheme 6).

The synthetic sample of blepharocalyxin D (**1**) exhibited variable specific rotation values, particularly in methanol. Some values are $[\alpha]_D^{22}$ −88.1 (*c* 0.43, MeOH), $[\alpha]_D^{22}$ −77.1 (*c* 0.11, MeOH), $[\alpha]_D^{22}$ −89.9 (*c* 0.027, MeOH), $[\alpha]_D^{23}$ −72.9 (*c* 0.32, acetone), and $[\alpha]_D^{24}$ −85.0 (*c* 0.31, MeOH–DCM (1:1)). These values are at odds with the value reported by Kadota and co-workers:[1e,h] $[\alpha]_D^{25}$ +18.5 (*c* 0.025, MeOH). The synthetic sample has (3*S*)-configuration, but at this point, determination of the absolute stereochemistry of the

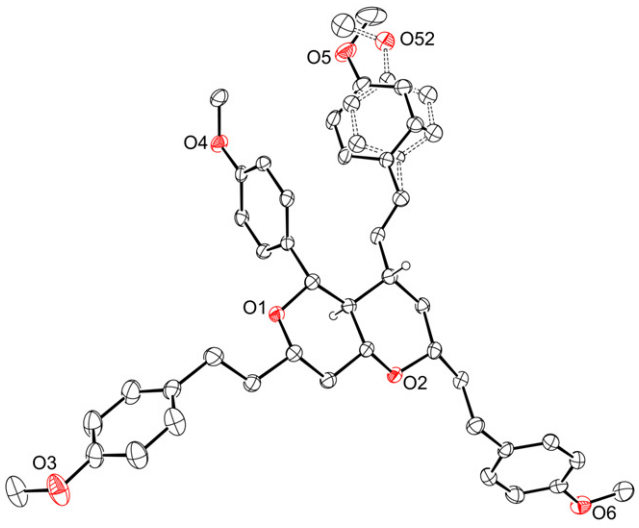
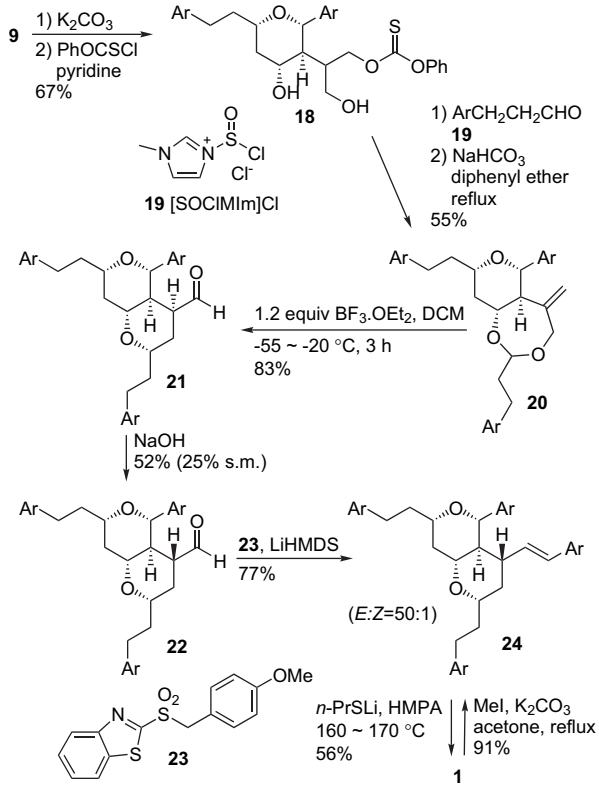


Figure 3. Crystal structure of **24**. (One of the phenyl groups was statistically disordered: the minor part of the disordered phenyl group is shown in broken lines.)



Scheme 6. Synthesis of blepharocalyxin D (**1**) via the second Prins cyclization of **20**.

natural product is not possible. Examples of unreliable optical rotation values of related polyphenols have already been reported by Rychnovsky and co-workers.[3]

A synthetic sample of blepharocalyxin D (**1**) was converted back into the tetramethyl ether derivative **24** using iodomethane and potassium carbonate in hot acetone. The specific rotation of this sample ($[\alpha]_D^{23}$ −87.8 (*c* 0.065, $CHCl_3$)) was almost identical with the value of the original sample ($[\alpha]_D^{14}$ −90.4 (*c* 0.32, $CHCl_3$)) of **24**, which confirms the structure of the synthetic sample of **1** beyond any doubt.

In this synthesis, two oxane rings in blepharocalyxin D (**1**) were constructed via two different types of Prins cyclization reaction. The synthetic scheme adopts a highly modular approach and the strategy may easily be adapted to library synthesis.

3. Experimental

3.1. General

^1H and ^{13}C NMR spectra were obtained on Bruker DPX-300 (300 MHz), Bruker Avance-600 (600 MHz), and JEOL ECX-400 (400 MHz). Chemical shift values were recorded as parts per million relative to tetramethylsilane as an internal standard unless otherwise indicated, and coupling constants in Hertz. Mass spectra were recorded on a JEOL JMS 600W spectrometer using electron impact (EI) or chemical ionization (CI), and JEOL JMS AX505WA spectrometer using fast atom bombardment (FAB) method. Significant fragments are reported in the following fashion: *m*/*z* (relative intensity). Optical rotation data were obtained on a Jasco P-1030 automatic polarimeter.

The progress of the reaction was checked on TLC plates (Merck 5554 Kiesel gel 60 F254), and the spots were visualized under 254 nm UV light and/or by charring after dipping the TLC plate into vanillin solution (9.0 g of vanillin and 1.5 mL of concentrated sulfuric acid in 300 mL of methanol), $KMnO_4$ solution (3 g of $KMnO_4$, 20 g of K_2CO_3, and 5 mL of 5% NaOH solution in 300 mL of water), or phosphomolybdic acid solution (250 mg phosphomolybdic acid in 50 mL ethanol). Column chromatography was performed on silica gel (Merck 9385 Kiesel gel 60) using hexane–EtOAc (v/v) or hexane–acetone (v/v). The solvents were simple distilled unless otherwise noted.

Unless otherwise specified, all reactions were conducted under a slight positive pressure of dry nitrogen. The usual work-up refers to washing the quenched reaction mixture with brine, drying the organic extracts over anhydrous $MgSO_4$ or Na_2SO_4, and evaporating under reduced pressure using a rotary evaporator.

All solvents used in reactions were dried under nitrogen atmosphere. THF was distilled from Na-benzophenone and CH_2Cl_2 was distilled from P_2O_5. Et_2O was distilled from LAH. CH_3CN was distilled from CaH_2 and stored over 4 Å molecular sieves. Pyridine and TEA were distilled over KOH and stored over 4 Å molecular sieves.

Enantiomeric excesses were calculated from chiral HPLC using a chiralcel OD-H column (flow rate 0.5 mL/min), or from ^1H NMR spectra of the (*O*)-acetyl-(*S*)-mandelate derivatives.

3.1.1. Homoallylic alcohol 4. Triethylamine (14.7 mL, 105 mmol) and SO_3·pyridine (8.38 g, 52.6 mmol) were added to a solution of alcohol **2** (4.37 g, 26.3 mmol) in

DMSO–CH_2Cl_2 (1:1, 50 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 20 min at this temperature. The reaction was quenched by addition of saturated NH_4Cl solution (40 mL) at 0 °C. The reaction mixture was extracted with CH_2Cl_2 (3×40 mL). The organic extracts were washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (Hex–EtOAc, 2:1) gave 3-(*p*-methoxyphenyl)propanal (4.14 g, 96%). R_f 0.68 (Hex–EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.82 (s, 1H), 7.12 (d, 2H, J=8.5 Hz), 6.84 (d, 2H, J=8.5 Hz), 3.79 (s, 3H), 2.91 (t, 2H, J=7.3 Hz), 2.75 (t, 2H, J=7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.7, 157.9, 132.2, 129.1, 113.8, 55.0, 45.3, 27.1. IR (neat): ν_{max}=3001, 2935, 2835, 2725, 1724, 1612, 1583, 1514, 1466, 1408, 1389, 1248, 1034 cm^{-1}. MS *m*/*z* (CI, relative intensity): 165 (M^++1, 15), 149 (23), 141 (34), 121 (100), 85 (9), 71 (8). HRMS (CI) calcd for $C_{10}H_{13}O_2$ (M^++1) 165.0915, found 165.0915.

A solution of $TiCl_4$ (0.099 mL, 0.90 mmol) in CH_2Cl_2 (18 mL) at 0 °C was treated with $Ti(O^iPr)_4$ (0.804 mL, 2.70 mmol) under Ar. The mixture was allowed to warm to room temperature and stirred for 1 h at this temperature. Silver oxide (Ag_2O, 0.417 g, 1.80 mmol) was added at room temperature and the whole reaction mixture was stirred for 5 h with exclusion of direct light. The reaction mixture was diluted with CH_2Cl_2 (36 mL) and treated with (*R*)-BINOL (1.03 g, 3.60 mmol) at room temperature for 2 h to furnish catalyst **3**. The catalyst **3** thus generated was cooled to −15 °C and treated with 3-(*p*-methoxyphenyl)-propanal (2.96 g, 18.0 mmol) in CH_2Cl_2 (1 mL) and allyltributylstannane (11 mL, 36 mmol). The reaction mixture was allowed to warm to 0 °C and stirred for 7 h. The reaction was quenched with saturated $NaHCO_3$ (40 mL) and the reaction mixture was extracted with ether (3×40 mL). The organic extracts were dried over Na_2SO_4 and concentrated. Flash chromatography of the residue on silica gel (Hex–EtOAc, 2:1) gave homoallylic alcohol **4** (3.5 g, 94%, 92% ee). R_f 0.44 (Hex–EtOAc, 2:1). The enantiomeric excess was determined by chiral HPLC (Chiralcel OD-H, 10% isopropanol/hexane, 0.5 mL/min): t_R=10.0 min (*S*-isomer), 10.9 min (*R*-isomer). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (d, 2H, J=8.4 Hz), 6.83 (d, 2H, J=8.4 Hz), 5.82 (ddt, 1H, J=16.9, 10.1, 7.1 Hz), 5.14 (d, 2H, J=12.6 Hz), 3.78 (s, 3H), 3.71–3.62 (m, 1H), 2.80–2.58 (m, 2H), 2.30 and 2.19 (ABX_2, 2H, J_{AB}=13.3, J_{AX}=7.0, J_{BX}=7.2 Hz), 1.79–1.67 (m, 2H), 1.57 (d, 1H, J=4.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7, 134.6, 134.0, 129.3, 118.3, 113.8, 69.8, 55.2, 42.0, 38.6, 31.1. IR (neat): ν_{max}=3348, 3072, 3032, 3003, 2927, 1612, 1514, 1469, 1454, 1335, 1300, 1246, 1034 cm^{-1}. MS *m*/*z* (EI, relative intensity): 206 (M^+, 22), 188 (5), 147 (20), 122 (11), 121 (100), 91 (4), 70 (4). HRMS (EI) calcd for $C_{13}H_{18}O_2$ (M^+) 206.1307, found 206.1307. $[\alpha]_D^{11}$ −19.5 (*c* 0.55, $CHCl_3$).

3.1.2. (*O*)-Acetyl-(*S*)-mandelate 5. Oxalyl chloride (0.634 mL, 7.30 mmol) was added to a solution of (*S*)-(+)-(*O*)-acetylmandelic acid (141 mg, 0.730 mmol) in CH_2Cl_2 (0.5 mL) at room temperature. The reaction mixture was stirred for 1.5 h and the residual oxalyl chloride was thoroughly evaporated in vacuo. Homoallylic alcohol **4** (15 mg, 0.073 mmol) in CH_2Cl_2 (0.5 mL) and pyridine (0.018 mL, 0.22 mmol) were then added. The reaction mixture was stirred for 10 min and concentrated. Flash column chromatography (Hex–EtOAc, 2:1) gave (*O*)-acetyl-(*S*)-mandelate **5**. R_f 0.61 (Hex–EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48–7.36 (m, 6H), 7.06 (d, 2H, J=8.4 Hz), 6.81 (d, 2H, J=8.4 Hz), 5.94–5.89 (m, 1H), 5.42 (ddt, 1H, J=16.4, 10, 7.2 Hz), 4.98–4.92 (m, 1H), 4.81 (d, 1H, J=9.5 Hz), 4.78 (d, 1H, J=17.2 Hz), 3.78 (s, 3H), 3.72 (s, 1H), 2.65–2.51 (m, 2H), 2.20 (s, 6H), 1.92–1.79 (m, 2H).

3.1.3. Alcohol 10. Olefin **14** (20 mg, 0.11 mmol) and homoallylic alcohol **4** (11 mg, 0.053 mmol) were added to a solution of the Hoveyda–Grubbs second generation catalyst **15** (2 mg, 5 mol %) in CH_2Cl_2 (1 mL) at room temperature under Ar. The reaction mixture was stirred for 24 h at this temperature. Concentration and purification of the residue by flash column chromatography (Hex–EtOAc, 2:1) gave alcohol **10** (13 mg, 67%). R_f 0.22 (Hex–EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (d, 2H, J=8.5 Hz), 6.83 (d, 2H, J=8.6 Hz), 5.70–5.56 (m, 1H), 5.42 (dd, 1H, J=15.5, 8.0 Hz), 4.15–4.02 (m, 4H), 3.79 (s, 3H), 3.62 (br, 1H), 2.79–2.58 (m, 3H), 2.27 and 2.15 (ABX_2, 2H, J_{AB}=13.5, J_{AX}=6.3, J_{BX}=7.1 Hz), 2.04 (s, 6H), 1.77–1.69 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.94, 170.92, 157.7, 133.9, 130.1, 130.0, 129.2, 113.7, 69.8, 64.15, 64.11, 55.2, 41.2, 40.8, 38.6, 31.0, 20.8. IR (neat): ν_{max}=3464, 2935, 1739, 1612, 1583, 1514, 1466, 1367, 1246, 1178, 1038 cm^{-1}. MS *m*/*z* (CI, relative intensity): 365 (M^++1, 5), 305 (29), 287 (49), 227 (100), 147 (18), 140 (18), 121 (61). HRMS (CI) calcd for $C_{20}H_{29}O_6$ (M^++1) 365.1964, found 365.1964. $[\alpha]_D^{27}$ −4.6 (*c* 0.78, $CHCl_3$).

3.1.4. Aldehyde 12. Anisaldehyde dimethylacetal (0.77 mL, 4.5 mmol) and CSA (44 mg, 0.19 mmol) were added to a solution of triol **11** (401 mg, 3.78 mmol) in CH_2Cl_2 (20 mL) at room temperature. The reaction mixture was stirred for 2 h. The reaction was quenched by addition of TEA (0.6 mL). Concentration and purification by flash column chromatography (Hex–EtOAc, 1:1) gave the cyclic acetal alcohol (835 mg, 98%). R_f 0.22 (Hex–EtOAc, 1:1).

Triethylamine (4.37 mL, 31.3 mmol) and SO_3·pyridine (2.5 g, 16 mmol) were added to a solution of cyclic acetal alcohol (1.76 g, 7.84 mmol) in DMSO–CH_2Cl_2 (1:1, 18 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 20 min. The reaction was quenched by addition of saturated NH_4Cl solution (15 mL) at 0 °C. The reaction mixture was extracted with CH_2Cl_2 (3×15 mL). The organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash chromatography (Hex–EtOAc, 1:1) gave aldehyde **12** (1.58 g, 91%). R_f 0.37 (Hex–EtOAc, 1:1).

3.1.5. Diol 13. A solution of *n*-BuLi (2.5 M in hexane, 1.46 mL) was added dropwise to a solution of $PPh_3Me^+Br^-$ (1.45 g, 4.07 mmol) in THF (6 mL) at −78 °C under Ar. The reaction mixture was stirred for 20 min at this temperature. The ylide thus generated was treated with aldehyde **12** (452 mg, 2.03 mmol) in THF (4 mL). The reaction mixture was stirred for 1 h at −78 °C and warmed to 0 °C over 30 min. The reaction mixture was diluted with ether

(10 mL) and treated with acetone (10 mL). The reaction mixture was filtered through a short pad of silica gel. Concentration of the filtrate and purification of the residue by flash chromatography (Hex–EtOAc, 4:1) gave a mixture of the cyclic acetal olefins (isomer-1 (*cis*), 86 mg, 19%; isomer-2 (*trans*), 172 mg, 39%). Isomer-1, R_f 0.65 (Hex–EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, 2H, J=8.6 Hz), 6.89 (d, 2H, J=8.6 Hz), 5.53 (ddd, 1H, J=17.5, 10.3, 7.4 Hz), 5.39 (s, 1H), 5.17 (d, 1H, J=18.8 Hz), 5.15 (d, 1H, J=9.5 Hz), 4.21 (dd, 2H, J=11.5, 4.7 Hz), 3.80 (s, 3H), 3.70 (t, 2H, J=11.4 Hz), 2.86–2.80 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.0, 133.6, 130.9, 127.4, 118.0, 113.7, 101.2, 71.3, 55.3, 38.9. Isomer-2, R_f 0.57 (Hex–EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, 2H, J=8.6 Hz), 6.89 (d, 2H, J=8.6 Hz), 6.38 (ddd, 1H, J=17.6, 10.2, 7.6 Hz), 5.50 (s, 1H), 5.28 (d, 1H, J=17.4 Hz), 5.21 (d, 1H, J=10.5 Hz), 4.19–4.10 (m, 4H), 3.80 (s, 3H), 2.19–2.17 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.0, 138.3, 131.1, 127.4, 116.0, 113.6, 101.7, 71.0, 55.3, 38.5. IR (neat): ν_{max}=3070, 2964, 2910, 2850, 1614, 1518, 1464, 1387, 1304, 1248, 1171, 1032 cm^{-1}. MS *m*/*z* (CI, relative intensity): 221 (M^++1, 100), 220 (17), 219 (14), 137 (31), 113 (61), 67 (13). HRMS (CI) calcd for $C_{13}H_{17}O_3$ (M^++1) 221.1178, found 221.1178.

Ceric ammonium nitrate (6.8 g, 12 mmol) was added to a solution of the olefin isomers (544 mg, 2.47 mmol) in CH_3CN–H_2O (9:1, 56 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 20 min. The reaction mixture was diluted with EtOAc and treated with saturated $NaHCO_3$ (40 mL) at 0 °C. The mixture was extracted with EtOAc (3×40 mL) and the organic extracts were dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by flash chromatography (Hex–EtOAc, 1:1) gave diol **13** (205 mg, 81%). R_f 0.11 (Hex–EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.77–5.65 (m, 1H), 5.21 (dd, 1H, J=11, 0.7 Hz), 5.20 (d, 1H, J=16.9 Hz), 3.76 (d, 4H, J=6.2 Hz), 2.54 (dq, 1H, J=6.4, 6.4 Hz), 2.21 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 118.1, 64.7, 47.5. IR (neat): ν_{max}=3400, 2927, 1643, 1425, 1032 cm^{-1}. MS *m*/*z* (CI, relative intensity): 103 (M^++1, 16), 89 (21), 85 (69), 67 (100), 57 (58), 55 (46), 54 (20). HRMS (CI) calcd for $C_5H_{11}O_2$ (M^++1) 103.0759, found 103.0759.

3.1.6. Olefin 14. Acetic anhydride (0.16 mL, 1.7 mmol), TEA (0.38 mL, 2.8 mmol), and DMAP (4.2 mg, 0.035 mmol) were added to a solution of diol **13** (70.6 mg, 0.690 mmol) in CH_2Cl_2 (7 mL) at room temperature. The reaction mixture was stirred for 1 h, quenched with saturated NH_4Cl (10 mL), and extracted with CH_2Cl_2 (3×10 mL). The organic extracts were dried over $MgSO_4$ and concentrated. Flash column chromatography (Hex–EtOAc, 2:1) gave olefin **14** (107 mg, 83%). R_f 0.57 (Hex–EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.72 (ddd, 1H, J=17.6, 10, 7.7 Hz), 5.193 (d, 1H, J=16 Hz), 5.186 (d, 1H, J=11.8 Hz), 4.18–4.07 (m, 4H), 2.75 (dq, 1H, J=6.5, 6.5 Hz), 2.06 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 134.6, 118.2, 63.9, 41.8, 20.8. IR (neat): ν_{max}=3084, 2958, 1745, 1645, 1427, 1381, 1367, 1227, 1039 cm^{-1}. MS *m*/*z* (CI, relative intensity): 187 (M^++1, 2), 127 (100), 89 (6), 85 (4), 67 (12), 61 (4). HRMS (CI) calcd for $C_9H_{15}O_4$ (M^++1) 187.0970, found 187.0970.

3.1.7. Oxane 9. Anisaldehyde (0.0053 mL, 0.047 mmol) and TMSOAc (0.0060 mL, 0.039 mmol) were added to a solution of homoallylic alcohol **10** (14 mg, 0.039 mmol) in AcOH (0.090 mL, 1.6 mmol) at room temperature. TESOTf (0.040 mL, 0.16 mmol) was added dropwise to the resulting solution at the same temperature. The reaction mixture was stirred for 1 h, diluted with CH_2Cl_2 (2 mL), and treated with TEA (0.1 mL). Concentration and purification of the residue by flash column chromatography (Hex–EtOAc, 1:1) gave oxane **9** (13 mg, 60%). R_f 0.57 (Hex–EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, 2H, J=9.3 Hz), 7.03 (d, 2H, J=8.6 Hz), 6.91 (d, 2H, J=8.6 Hz), 6.80 (d, 2H, J=8.6 Hz), 5.02 (dt, 1H, J=10.8, 4.7 Hz), 4.24 (d, 1H, J=10.5 Hz), 4.10 (dd, 1H, J=11, 7.9 Hz), 3.96 (dd, 1H, J=11, 7.0 Hz), 3.87 (d, 2H, J=6.0 Hz), 3.82 (s, 3H), 3.78 (s, 3H), 3.51–3.41 (m, 1H), 2.69–2.52 (m, 2H), 2.25–2.20 (m, 1H), 2.14 (t, 1H, J=11.3 Hz), 2.08 (s, 3H), 2.03 (s, 3H), 1.97 (s, 3H), 1.94–1.89 (m, 1H), 1.87–1.80 (m, 1H), 1.75–1.64 (m, 1H), 1.43 (q, 1H, J=11.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 170.0, 159.7, 157.8, 133.8, 131.8, 129.3, 129.0, 114.1, 113.7, 81.1, 74.3, 72.3, 64.4, 62.0, 55.3, 55.2, 45.8, 37.8, 37.3, 36.2, 30.4, 21.4, 20.8. IR (neat): ν_{max}=2952, 2837, 1739, 1612, 1585, 1514, 1464, 1367, 1246, 1178, 1036 cm^{-1}. MS *m*/*z* (FAB, relative intensity): 542 (M^+, 4), 483 (10), 282 (11), 154 (60), 121 (100), 69 (64), 55 (76), 43 (61). HRMS (FAB) calcd for $C_{30}H_{38}O_9$ (M^+) 542.2516, found 542.2523. $[\alpha]_D^{13}$ −22.6 (*c* 0.55, $CHCl_3$).

3.1.8. Thionocarbonate 18. Potassium carbonate (1.53 g, 11.1 mmol) was added to a solution of oxane **9** (602 mg, 1.11 mmol) in MeOH (30 mL) at room temperature. The reaction mixture was stirred for 3 h, concentrated, and diluted with H_2O (20 mL). The reaction mixture was extracted with ether (3×20 mL), the organic extracts were dried over $MgSO_4$, and filtered. Concentration and purification of the residue by flash chromatography (Hex–acetone, 1:1) gave the corresponding triol (392 mg, 85%). R_f 0.26 (Hex–acetone, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, 2H, J=8.0 Hz), 7.04 (d, 2H, J=8.6 Hz), 6.87 (d, 2H, J=8.6 Hz), 6.79 (d, 2H, J=8.6 Hz), 4.98 (br, 1H), 4.31 (br, 1H), 4.11 (d, 1H, J=10.4 Hz), 3.78 (s, 3H), 3.76 (s, 3H), 3.69 (br, 2H), 3.60 (d, 1H, J=8.3 Hz), 3.41–3.34 (m, 2H), 3.20 (br, 1H), 2.68–2.52 (m, 2H), 2.02 (dd, 1H, J=12.0, 3.6 Hz), 1.93–1.81 (m, 1H), 1.77–1.65 (m, 2H), 15.9–1.58 (m, 1H), 1.42 (q, 1H, J=11.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4, 157.7, 134.0, 132.7, 129.3, 129.0, 114.0, 113.7, 81.6, 74.5, 68.2, 64.0, 60.2, 55.22, 55.20, 51.5, 41.1, 40.8, 37.4, 30.4. IR (neat): ν_{max}=3334, 2937, 1612, 1585, 1514, 1464, 1369, 1300, 1248, 1178, 1034 cm^{-1}. MS *m*/*z* (FAB, relative intensity): 417 (M^++1, 6), 399 (10), 191 (12), 154 (25), 121 (100), 55 (24), 43 (17). HRMS (FAB) calcd for $C_{24}H_{33}O_6$ (M^++1) 417.2277, found 417.2290. $[\alpha]_D^{13}$ −50.9 (*c* 0.56, $CHCl_3$).

Phenyl chlorothionoformate (0.0061 mL, 0.044 mmol) and pyridine (0.0060 mL, 0.073 mmol) were added to a solution of triol (15 mg, 0.037 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 20 min. Concentration and purification of the residue by flash chromatography (Hex–acetone, 1:1) gave thionocarbonate **18** (16 mg, 80%). R_f 0.42 (Hex–acetone, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (t, 2H,

J=7.7 Hz), 7.29 (d, 1H, J=7.0 Hz), 7.27 (d, 2H, J=6.8 Hz), 7.07 (d, 2H, J=8.4 Hz), 7.04 (d, 2H, J=7.5 Hz), 6.90 (d, 2H, J=8.6 Hz), 6.81 (d, 2H, J=8.5 Hz), 4.81–4.70 (m, 1H), 4.42 (dd, 1H, J=10.9, 5.9 Hz), 4.13 (d, 1H, J=10.4 Hz), 4.04–3.99 (m, 1H), 3.84–3.76 (m, 8H), 3.48–3.41 (m, 1H), 3.03 (br, 1H), 2.63 (t, 2H, J=7.5 Hz), 2.17 (br, 1H), 2.09–2.02 (m, 2H), 1.97–1.84 (m, 1H), 1.81–1.69 (m, 2H), 1.52 (q, 1H, J=11.9 Hz).

3.1.9. Acetal 20. A solution of thionyl chloride (0.123 mL, 1.72 mmol) in CH_3CN (0.2 mL) was treated dropwise with 1-methylimidazole (0.134 mL, 1.72 mmol) at room temperature. The reaction mixture was stirred for 12 h and concentrated. Residual CH_3CN, thionyl chloride, and 1-methylimidazole were removed in vacuo at 150 °C. The ionic liquid **19** generated was diluted with CH_2Cl_2 (3 mL). The resulting solution was treated with 3-(*p*-methoxyphenyl)propanal (24 mg, 0.15 mmol) and thionocarbonate **18** (68 mg, 0.12 mmol) in CH_2Cl_2 (3 mL). The mixture was heated under reflux for 90 min and treated with H_2O (6 mL). The reaction mixture was extracted with ether (3×6 mL) and the organic extracts were dried over Na_2SO_4. Concentration and purification of the residue by flash chromatography (Hex–EtOAc, 2:1) gave the corresponding cyclic acetal (60 mg, 69%). R_f 0.44 (Hex–EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (t, 2H, J=7.8 Hz), 7.30–7.23 (m, 3H), 7.12–7.00 (m, 6H), 6.89 (d, 2H, J=8.5 Hz), 6.83 (d, 2H, J=8.3 Hz), 6.81 (d, 2H, J=8.4 Hz), 4.50 (t, 1H, J=5.1 Hz), 4.31 (t, 1H, J=10.4 Hz), 4.07 (dd, 1H, J=13.3, 2.8 Hz), 3.97 (d, 1H, J=10.2 Hz), 3.86–3.78 (m, 11H), 3.63 (dd, 1H, J=10.3, 4.5 Hz), 3.44–3.37 (m, 1H), 2.70–2.62 (m, 4H), 2.07–2.00 (m, 1H), 1.96–1.87 (m, 3H), 1.82–1.73 (m, 2H), 1.66–1.52 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.2, 159.7, 157.8, 157.7, 153.3, 133.9, 133.7, 131.8, 129.4, 129.3, 129.0, 126.4, 121.9, 114.1, 113.8, 113.7, 105.9, 82.7, 79.0, 74.6, 73.9, 66.9, 55.3, 55.2, 50.2, 39.3, 39.1, 37.4, 36.4, 30.4, 29.9. IR (neat): ν_{max}=2951, 2835, 1612, 1585, 1512, 1464, 1379, 1298, 1246, 1201, 1136, 1036 cm^{-1}. MS *m*/*z* (FAB, relative intensity): 698 (M^+, 2), 535 (9), 399 (8), 173 (15), 121 (100), 55 (20), 43 (13). HRMS (FAB) calcd for $C_{41}H_{46}O_8S$ (M^+) 698.2913, found 698.2928.

A solution of the cyclic acetal (1.01 g, 1.44 mmol) in diphenyl ether (20 mL) was treated with $NaHCO_3$ (0.61 g, 7.2 mmol). The reaction mixture was heated under reflux for 3 h. Flash chromatography (Hex–EtOAc, 2:1) gave the methylidene-substituted cyclic acetal **20** (619 mg, 79%). R_f 0.49 (Hex–EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, 2H, J=8.3 Hz), 7.08 (d, 4H, J=8.2 Hz), 6.83 (t, 6H, J=8.2 Hz), 4.96 (s, 1H), 4.77 (s, 1H), 4.63 (t, 1H, J=5.5 Hz), 4.39 (d, 1H, J=10.7 Hz), 4.21 and 4.07 (ABq, 2H, J=12.6 Hz), 3.78 (s, 9H), 3.54–3.41 (m, 2H), 2.71–2.62 (m, 5H), 2.08 (dd, 1H, J=12.8, 3.1 Hz), 1.99–1.87 (m, 3H), 1.80–1.69 (m, 1H), 1.56 (q, 1H, J=11.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 157.8, 157.7, 145.4, 134.0, 133.7, 132.4, 129.4, 129.3, 129.2, 116.6, 113.84, 113.79, 113.74, 113.65, 100.2, 80.7, 79.9, 74.8, 74.6, 55.24, 55.19, 51.9, 38.3, 37.5, 37.4, 30.5, 30.0.

3.1.10. Aldehyde 21. A solution of acetal **20** (619 mg, 1.14 mmol) in CH_2Cl_2 (20 mL) was cooled to −55 °C and treated dropwise with $BF_3\cdot OEt_2$ (0.173 mL, 1.36 mmol). The reaction mixture was stirred for 3 h at the same temperature, allowed to warm to −20 °C, and stirred for 15 min. The reaction was quenched with saturated NH_4Cl (20 mL) and the reaction mixture was extracted with CH_2Cl_2 (3×20 mL). The organic extracts were dried over Na_2SO_4. Purification by flash chromatography (Hex–EtOAc, 2:1) gave aldehyde **21** (526 mg, 83%). R_f 0.51 (Hex–EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.68 (s, 1H), 7.23 (d, 2H, J=7.1 Hz), 7.07 (d, 4H, J=8.5 Hz), 6.87 (d, 2H, J=6.8 Hz), 6.81 (d, 4H, J=8.6 Hz), 4.65 (d, 1H, J=10.5 Hz), 3.84–3.75 (m, 10H), 3.60–3.53 (m, 1H), 3.44–3.35 (m, 1H), 2.76–2.53 (m, 4H), 2.32 (t, 1H, J=4.2 Hz), 2.06–2.01 (m, 1H), 1.99–1.94 (m, 1H), 1.91–1.80 (m, 1H), 1.78–1.73 (m, 3H), 1.66–1.62 (m, 1H), 1.55–1.43 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.3, 159.5, 157.8, 157.7, 134.1, 134.0, 131.7, 129.33, 129.26, 128.5, 114.0, 113.80, 113.76, 78.5, 75.0, 74.3, 72.7, 55.3, 55.2, 49.1, 45.7, 38.6, 38.0, 37.8, 31.8, 30.7, 30.5. IR (neat): ν_{max}=2935, 2835, 1720, 1612, 1583, 1514, 1464, 1300, 1246, 1178, 1068, 1036 cm^{-1}. MS *m*/*z* (FAB, relative intensity): 545 (M^++1, 11), 307 (25), 289 (12), 154 (100), 121 (70), 107 (21), 89 (16). HRMS (FAB) calcd for $C_{34}H_{41}O_6$ (M^++1) 545.2903, found 545.2894. $[\alpha]_D^{16}$ −32.1 (*c* 0.23, $CHCl_3$).

3.1.11. Aldehyde 22. A solution of aldehyde **21** (526 mg, 0.970 mmol) in THF (15 mL) was treated with NaOH solution (2 N, 15 mL). The reaction mixture was heated under reflux for 4 h and treated with saturated NH_4Cl (20 mL). The mixture was extracted with ether (3×20 mL), the organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash chromatography (Hex–EtOAc, 2:1) gave aldehyde **22** (272 mg, 52%). R_f 0.37 (Hex–EtOAc, 2:1). Aldehyde **21** (133 mg, 25%) was also recovered. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (d, 1H, J=4.7 Hz), 7.21 (br, 2H), 7.10–7.06 (m, 4H), 6.86–6.80 (m, 6H), 3.91 (d, 1H, J=9.6 Hz), 3.79 (s, 9H), 3.58–3.51 (m, 1H), 3.36–3.28 (m, 2H), 2.75–2.57 (m, 4H), 2.24–2.13 (m, 1H), 2.06 (dd, 1H, J=12.2, 2.1 Hz), 2.01–1.87 (m, 2H), 1.85–1.77 (m, 2H), 1.74–1.61 (m, 2H), 1.50–1.41 (m, 1H), 1.31 (q, 1H, J=11.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.0, 160.1, 157.83, 157.75, 134.0, 133.7, 131.0, 129.33, 129.30, 113.8, 113.7, 82.0, 77.9, 75.2, 74.7, 55.25, 55.21, 49.7, 47.6, 37.9, 37.73, 37.65, 32.2, 30.5, 30.4. IR (neat): ν_{max}=2937, 2837, 1720, 1612, 1583, 1512, 1464, 1300, 1246, 1176, 1132, 1034 cm^{-1}. MS *m*/*z* (EI, relative intensity): 544 (M^+, 20), 526 (14), 366 (24), 323 (11), 147 (14), 121 (100). HRMS (EI) calcd for $C_{34}H_{40}O_6$ (M^+) 544.2825, found 544.2825. $[\alpha]_D^{16}$ −30.0 (*c* 0.34, $CHCl_3$).

3.1.12. Sulfone 23. A solution of 2-mercaptobenzothiazole (3.03 g, 18.1 mmol) and diethyl azodicarboxylate (2.85 mL, 18.1 mmol) in THF (20 mL) was added to a solution of *p*-methoxybenzyl alcohol (1.81 mL, 14.5 mmol) and PPh_3 (4.75 g, 18.1 mmol) in THF (20 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 6 h. The reaction mixture was concentrated and purified by flash chromatography (Hex–EtOAc, 2:1) to give the corresponding sulfide (4.16 g, 100%). R_f 0.71 (Hex–EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, 1H, J=8.1 Hz), 7.72 (dd, 1H, J=8.0, 0.6 Hz), 7.43–7.33 (m, 3H), 7.30–7.23 (m, 1H), 6.86–6.82 (m, 2H), 4.54 (s, 1H), 3.76 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 159.1, 153.1, 135.2,

130.3, 127.9, 126.0, 124.2, 121.4, 120.9, 114.0, 55.2, 37.2. IR (neat): ν_{max}=3047, 2962, 2927, 2837, 1614, 1516, 1456, 1427, 1309, 1257, 1037 cm^{-1}. MS *m/z* (CI, relative intensity): 288 (M^++1, 34), 410 (12), 409 (27), 408 (100), 289 (8), 287 (21), 121 (44). HRMS (CI) calcd for $C_{15}H_{14}NOS_2$ (M^++1) 288.0517, found 288.0517.

A solution of the sulfide (3.32 g, 11.0 mmol) in CH_2Cl_2 (40 mL) was treated with *m*-CPBA (9.45 g, 54.8 mmol) and $NaHCO_3$ (9.20 g, 110 mmol) at room temperature. The reaction mixture was stirred for 5 h and treated with the aqueous solution saturated with $NaHCO_3$ and $Na_2S_2O_3$ (30 mL). The reaction mixture was extracted with EtOAc (3×40 mL). The organic extracts were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by flash chromatography (Hex–EtOAc, 2:1) gave sulfone **23** (3.50 g, quant.). R_f 0.43 (Hex–EtOAc, 2:1). ^1H NMR (300 MHz, $CDCl_3$): δ 8.25 (d, 1H, *J*=7.9 Hz), 7.96–7.93 (m, 1H), 7.67–7.55 (m, 2H), 7.18 (d, 2H, *J*=8.7 Hz), 6.79 (d, 2H, *J*=8.7 Hz), 4.70 (s, 2H), 3.76 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 160.3, 152.6, 137.1, 132.3, 127.9, 127.6, 125.4, 122.3, 118.1, 114.4, 60.4, 55.2. IR (neat): ν_{max}=3020, 2974, 2927, 2843, 1610, 1514, 1466, 1325, 1257, 1147, 1026 cm^{-1}. MS *m/z* (CI, relative intensity): 320 (M^++1, 14), 440 (32), 257 (13), 256 (77), 122 (9), 121 (100). HRMS (CI) calcd for $C_{15}H_{14}NO_3S_2$ (M^++1) 320.0415, found 320.0415.

3.1.13. Tetramethyl blepharocalyxin D (24). A solution of sulfone **23** (248 mg, 0.780 mmol) in THF (10 mL) was cooled to −78 °C and treated dropwise with LiHMDS (1.0 M in THF, 1.62 mL) under Ar. The reaction mixture was stirred for 20 min and treated with aldehyde **22** (353 mg, 0.650 mmol) in THF (10 mL). The reaction mixture was stirred for 3 h at the same temperature and allowed to warm to room temperature, stirred for 3 h, and treated with H_2O (15 mL). The reaction mixture was extracted with ether (3×20 mL), the organic extracts were dried over $MgSO_4$, and concentrated. Purification of the residue by flash chromatography (Hex–EtOAc, 2:1) gave tetramethyl blepharocalyxin D (**24**, 323 mg, 77%). R_f 0.57 (Hex–EtOAc, 2:1). ^1H NMR (300 MHz, $CDCl_3$): δ 7.14 (br, 1H), 7.08 (t, 5H, *J*=8.8 Hz), 6.81 (t, 4H, *J*=7.5 Hz), 6.72–6.65 (m, 6H), 5.70 (d, 1H, *J*=15.8 Hz), 4.98 (dd, 1H, *J*=15.8, 8.8 Hz), 3.94 (d, 1H, *J*=9.7 Hz), 3.78 (d, 6H, *J*=2.2 Hz), 3.75 (s, 3H), 3.52–3.42 (m, 5H), 3.37–3.29 (m, 1H), 2.75–2.57 (m, 4H), 2.16–2.02 (m, 2H), 1.98–1.86 (m, 1H), 1.84–1.75 (m, 2H), 1.73–1.57 (m, 3H), 1.54–1.50 (m, 1H), 1.29 (q, 1H, *J*=12.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 158.3, 157.62, 157.57, 134.11, 134.08, 133.2, 132.2, 130.4, 129.33, 129.31, 126.9, 126.7, 113.7, 113.6, 113.2, 82.7, 79.1, 75.6, 74.8, 55.2, 54.8, 51.0, 41.9, 40.3, 38.1, 37.8, 37.6, 30.6, 30.4. IR (neat): ν_{max}=2997, 2933, 2835, 1738, 1707, 1610, 1583, 1512, 1464, 1360, 1300, 1246, 1176, 1036 cm^{-1}. MS *m/z* (EI, relative intensity): 648 (M^+, 67), 338 (9), 308 (9), 174 (16), 147 (15), 121 (100). HRMS (EI) calcd for $C_{42}H_{48}O_6$ (M^+) 648.3451, found 648.3451. $[\alpha]_D^{14}$ −90.4 (*c* 0.32, $CHCl_3$).

3.1.14. Blepharocalyxin D (1). A solution of *n*-PrSLi (3 M in HMPA, 1 mL) was added to a solution of **24** (33 mg, 0.05 mmol) in HMPA (1.8 mL). The reaction mixture was heated under reflux for 3 h at 160–180 °C. The reaction was quenched with saturated aqueous NH_4Cl solution (3 mL) and H_2O (2 mL), and the mixture was extracted with EtOAc (3×5 mL). The organic extracts were dried over Na_2SO_4. Concentration and purification of the residue by flash chromatography ($CHCl_3$–MeOH, 10:1) gave blepharocalyxin D (**1**, 17 mg, 56%). R_f 0.2 ($CHCl_3$–MeOH, 10:1). ^1H NMR (300 MHz, CD_3OD): δ 7.08 (br, 2H), 6.98 (t, 4H, *J*=7.8 Hz), 6.70–6.52 (m, 10H), 5.75 (d, 1H, *J*=15.8 Hz), 5.00 (dd, 1H, *J*=15.7, 8.6 Hz), 3.97 (d, 1H, *J*=9.8 Hz), 3.53–3.48 (m, 2H), 3.41–3.34 (m, 1H), 2.70–2.52 (m, 4H), 2.20–2.11 (m, 1H), 2.01–1.97 (m, 1H), 1.88–1.78 (m, 1H), 1.75–1.66 (m, 2H), 1.63–1.56 (m, 2H), 1.54–1.46 (m, 2H), 1.26 (q, 1H, *J*=12.1 Hz). ^{13}C NMR (75 MHz, CD_3OD): δ 158.2, 157.0, 156.38, 156.35, 134.23, 134.19, 133.5, 132.7, 131.0, 130.4, 130.3, 128.6, 128.0, 116.1, 116.0, 115.7, 84.4, 80.6, 77.3, 76.4, 52.2, 43.1, 41.8, 39.4, 39.2, 31.8, 31.6. IR (neat): ν_{max}=3375, 3022, 2976, 2931, 1660, 1614, 1514, 1446, 1383, 1230, 1101 cm^{-1}. MS *m/z* (FAB, relative intensity): 591 (M^-−1, 3), 306 (57), 266 (56), 199 (35), 153 (100), 113 (73), 46 (32). HRMS (FAB) calcd for $C_{38}H_{39}O_6$ (M^-−1) 591.2747, found 591.2734.

3.1.15. Tetramethyl blepharocalyxin D (24) from 1. A mixture of blepharocalyxin D (**1**, 1.3 mg, 0.0022 mmol), K_2CO_3 (3.0 mg, 0.022 mmol), and MeI (0.01 mL, 0.022 mmol) in acetone (2 mL) was heated under reflux for 4 h. The reaction mixture was filtered to remove K_2CO_3 and concentrated. The residue was dissolved in EtOAc and washed with water. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Purification by flash chromatography (Hex–EtOAc, 2:1) gave tetramethyl blepharocalyxin D (**24**, 1.3 mg, 91%). $[\alpha]_D^{23}$ −87.8 (*c* 0.065, $CHCl_3$).

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2007.02.028.

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