Novel Stereocontrolled Approach to *syn*- and *anti*-Oxepene–Cyclogeranyl *trans*-Fused Polycyclic Systems: Asymmetric Total Synthesis of (−)-Aplysistatin, (+)-Palisadin A, (+)-Palisadin B, (+)-12-Hydroxy-Palisadin B, and the AB Ring System of Adociasulfate-2 and Toxicol A

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Abstract: A new stereocontrolled method for the formation of *trans-anti* cyclogeranyl–oxepene systems is described. The demanding stereochemistry is secured by stereoselective coupling of a cyclogeranyl tertiary alcohol with a 1,2-unsymmetrically substituted epoxide, while the formation of the highly strained oxepene is achieved employing ring-closing metathesis. Since the stereochemistry of the *trans*-fused 6,7-ring system is determined by the epoxide, the method also allows the construction of *trans–syn* 6,7-ring systems. This approach leads to the synthesis of the AB fragment of Adociasulfate-2 and Toxicol A, for the first time. The flexibility and efficiency of the presented strategy is demonstrated by the total asymmetric synthesis of (−)-Aplysistatin, (+)-Palisadin A, (+)-12-hydroxy-Palisadin B, and (+)-Palisadin B, employing two similar key intermediates.

Keywords: epoxide opening reaction · natural products · oxepenes · ring-closing metathesis · total synthesis

Introduction

Polycyclic compounds possessing a *trans*-fused oxepane ring abound in nature (Figure 1). They are classified as *trans–syn* systems, such as Brevetoxin B and related *Dinoflagellate* metabolites,[1] and *trans–anti* systems, including the selective kinesin inhibitor Adociasulfate-2,[2] Toxicol A,[3], cytotoxic Aplysistatin, and related bioactive halosesquiterpenoids,[4] for example, Palisadin A, Palisadin B, and 12-hydroxy-Palisadin B.

Regarding the first class, a large number of efficient methodologies for the stereoselective construction of the cyclic ether linkages has been developed,[5] mainly designed and applied for this particular stereochemistry.[6] On the other hand, only limited reports investigate the construction of *trans–anti* systems.[7] Besides the impressive pioneer approaches of Hoye, established more than twenty years ago,[7a] no significant progress has been accomplished since. In his methodology towards the total synthesis of (±)-Aplysistatin, he succeeded in cyclising olefin **I** in 62% yield (Scheme 1a). However, key intermediate **I** was prepared in low stereoselectivity, while in the following syntheses of re-

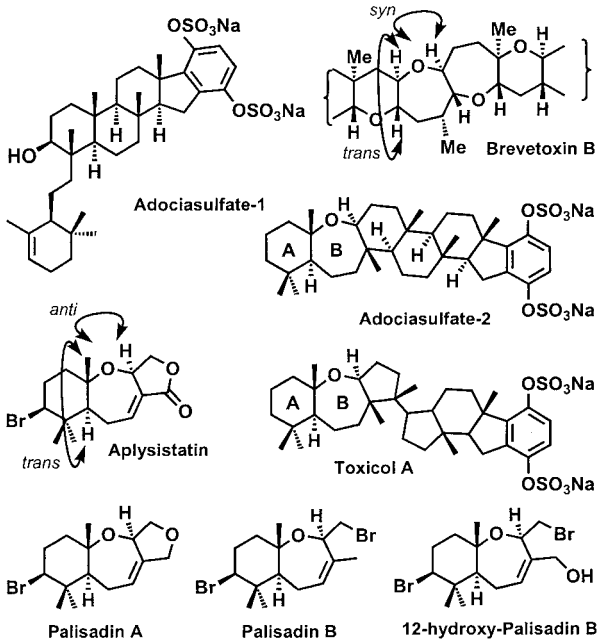

Figure 1. Naturally occurring oxepane-containing fused polycyclic systems.

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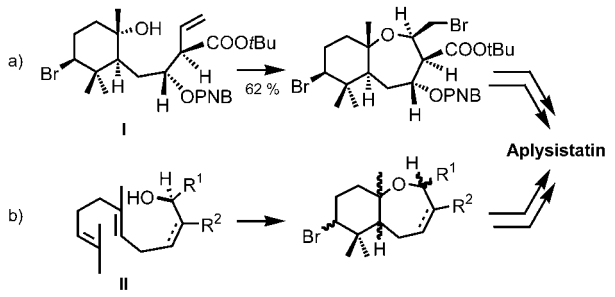


Scheme 1. Previous approaches to Aplysistatin and related halosesquiterpenoids.

lated compounds, based on polyene cyclizations, the stereoselectivities and/or the chemical yields were even lower (Scheme 1b).[7b–f] Evidently the formation of these oxepanes was thermodynamically unfavorable due to the severe repulsion between the 1,3-alkyl substituents adjacent to the ring oxygen atom. Regarding Adociasulfates, Overman et al. have already disclosed a method for the construction of the steroid skeleton in their synthesis of Adociasulfate-1 (Figure 1);[8] however, the problem of the oxepane ring system of Adociasulfate-2 remains to be solved.

Herein, we describe a new stereocontrolled method for the formation of *trans*-fused oxepene–cyclogeranyl systems, as well as its application to the synthesis of the AB fragment of Adociasulfate-2 and Toxicol A, and the synthesis of the title sesquiterpenoids. Some interesting synthetic methods for the construction of commonly used geranyl and cyclogeranyl derivatives are also disclosed.

Abstract in Greek:

Μια νέα στερεοελεγχόμενη μέθοδος παρασκευής *trans-anti* οξεπανικών συστημάτων περιγράφεται στο παρόν άρθρο. Η απαιτητική στερεοχημεία του συστήματος εξασφαλίζεται μέσω στερεοειδικής σύζευξης μιας κυκλογερανυλο-τριτοταγούς αλκοόλης με ένα 1,2-ασύμμετρα υποκατεστημένο εποξείδιο, ενώ ο σχηματισμός του ισχυρά τεταμένου οξεπανίου επιτυγχάνεται με εφαρμογή ολεφινομεταθετικής κυκλοποίησης. Επειδή η στερεοχημεία του σχηματιζόμενου συστήματος *trans*-συμπυκνωμένων 6,7-δακτυλίων καθορίζεται από το εποξείδιο, η παρούσα μέθοδος δύναται επίσης να χρησιμοποιηθεί για την κατασκευή συστημάτων *trans-syn*-6,7-δακτυλίων. Η εφαρμογή της προσέγγισης αυτής οδήγησε στην πρώτη παρασκευή του τμήματος AB του Adociasulfate-2 και της Τοξικόλης A. Η ευελιξία και η αποτελεσματικότητα της νέας στρατηγικής καταδεικνύεται με την ολική ασύμμετρη σύνθεση των φυσικών προϊόντων (−)-Απλυσιστατίνη, (+)-Παλισαδίνη A, (+)-12-υδροξυ-Παλισαδίνη B, (+)-Παλισαδίνη A και (+)-Παλισαδίνη B, μέσω δύο κοινών ενδιαμέσων.

Results and Discussion

Synthetic strategy: In an effort to circumvent the problems encountered by previous approaches, which involved concomitant ether and ring formation (see above), we opted to explore an alternative route, based on a cyclization reaction with only one possible reaction pathway, by securing the sterically demanding stereochemistry of the ether linkages prior to oxepane ring formation. This short and highly convergent strategy (Figure 2) involves two straightforward dis-

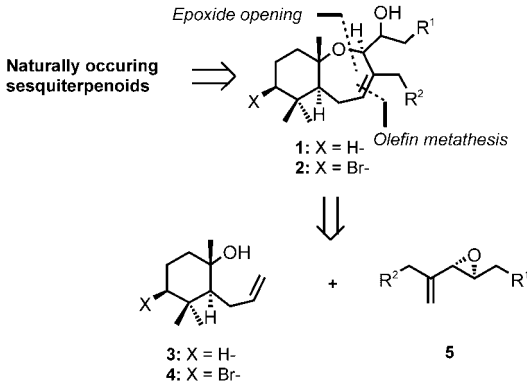
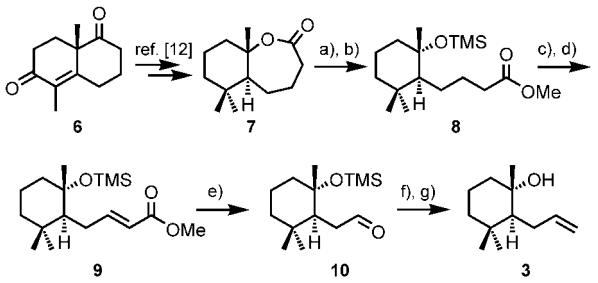


Figure 2. Retrosynthetic analysis of *trans–anti* fused bicyclic key intermediates **1** and **2**.

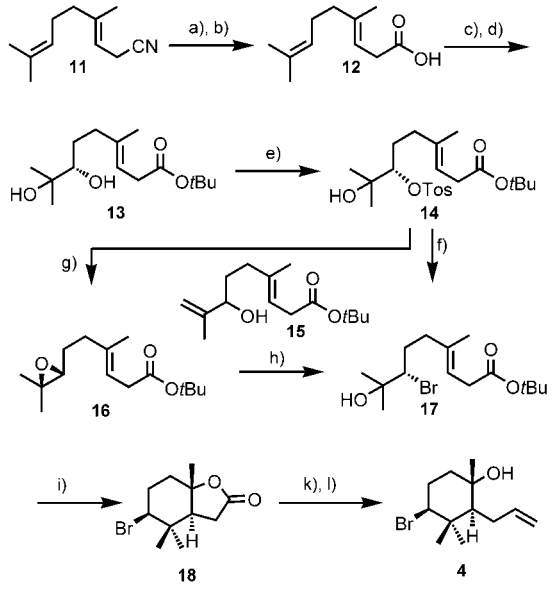
connections, which, however, in terms of the synthesis, requires two challenging bond formations: the demanding stereoselective coupling of a tertiary alcohol with a 1,2-unsymmetrically disubstituted epoxide,[9] and the formation of a sterically crowded oxepene with increased strain, due to the unfavorable 1,3-interaction of alkyl substituents adjacent to the ring oxygen atom.[10] Nonetheless, should this strategy be proved successful, it would be endowed with great flexibility, since it has been designed to allocate most of the remaining functional group modifications on the linear epoxide fragment, allowing the construction of diversified polycyclic systems. In addition, the resulting relative stereochemistry is dictated by the epoxide, allowing the synthesis of both *trans–anti* and *trans–syn* systems in a stereocontrolled fashion.

Enantioselective synthesis of tertiary alcohols 3 and 4: For the synthesis of cyclogeranyl tertiary alcohol **3**,[11] lactone **7**, prepared from the easily accessible (*S*)-(+)-Wieland–Miescher ketone analogue **6** (Scheme 2),[12] was subjected to transesterification and silylation to afford methyl ester **8**. The latter was converted to its olefinic analogue **9** employing the diphenyldiselenide protocol. Ozonolysis coupling of the resulting aldehyde **10** with methylylide and TBAF-mediated (TBAF = tetrabutylammonium fluoride) desilylation afforded key intermediate **3**, in optically pure form and in good overall yield.

On the other hand, for the synthesis of bromocyclogeranyl alcohol **4**, lactone **18** was envisioned as an ideal precursor (Scheme 3). Surprisingly, despite the use of the latter as key intermediate and the amount of chemistry developed



Scheme 2. Asymmetric synthesis of tertiary alcohol **3**. Reagents and conditions: a) K_2CO_3, MeOH, 25 °C, 1.5 h, 96 %; b) TMS–imidazole, 25 °C, 93 %; c) LDA, HMPA, THF, −78 °C, 1.5 h; then PhSeSePh, THF, −78 °C, 30 min, 89 %; d) H_2O_2 (30 %), CH_2Cl_2/H_2O (15:1), 25 °C, 20 min, 95 %; e) O_3, CH_2Cl_2, −78 °C; then PPh_3, −78 °C→25 °C, 93 %; f) $PPh_3CH_3{}^+Br^-$, NaHMDS, THF, 25 °C, 45 min; then **10** in THF, 0 °C, 30 min, 95 %; g) TBAF, THF, 25 °C, 3 h, 96 %. TMS = trimethylsilyl, LDA = lithium diisopropylamide, HMPA = hexamethyl phosphoramide, THF = tetrahydrofuran, NaHMDS = sodium bis(trimethylsilyl)amide, TBAF = tetra-*n*-butyl ammonium fluoride.



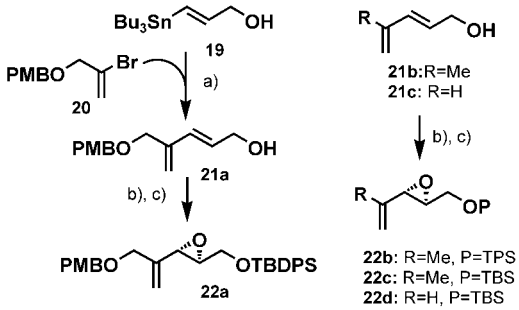
Scheme 3. Asymmetric synthesis of tertiary alcohol **4**. Reagents and conditions: a) DIBAL, CH_2Cl_2, −78 °C, 30 min; then aq. NH_4Cl, 10 % HCl, 25 °C, 20 min; b) Jones reagent, acetone, −20 °C, 60 % from **11**; c) $(TFA)_2O$, *t*BuOH, 25 °C, 15 min, 95 %, see ref. [16a]; d) $K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2PHAL$, $K_2OsO_2(OH)_4$, $CH_3SO_2NH_2$, *t*BuOH/H_2O (2:1), 12 h, 0 °C, 61 %, (75 % based on recovered material), >97 % *ee*; e) Ts_2O, pyridine, 0 °C, 1 h, 86 %; f) LiBr, HMPA, 60 °C, 20 min, **17**: 40 %, **15**: 15 %; g) DBU, DMF, 25 °C, 15 min, 87 %; h) LiBr, PPTS, NMP, 20 °C, 1 h, 85 %; i) $SnCl_4$, CH_3NO_2, 0 °C, 30 min, 60 %; k) DIBAL, CH_2Cl_2, −78 °C, 30 min, 90 %, see ref. [7a]; l) $PPh_3CH_3{}^+Br^-$, NaHMDS, THF, 25 °C, 1 h; then dropwise addition to lactol in THF during 12 h, 60 % (90 % based on recovered lactol). DIBAL = diisobutylaluminum hydride, $(TFA)_2O$ = trifluoroacetic anhydride, $(DHQ)_2PHAL$ = hydroquinine 1,4-phthalazinediyl diether, Ts_2O = *p*-toluenesulfonic anhydride, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMF = *N*,*N*-dimethylformamide, PPTS = pyridinium *p*-toluenesulfonate, NMP = 1-methyl-2-pyrrolidinone.

around similar compounds,[13] to the best of our knowledge there is no reported method for the preparation of its optically pure form.[14] Thus, its synthesis commenced with a straightforward conversion of the easily accessible (*E*)-geranyl nitrile **11**[15] to geometrically pure (*E*)-homogeranic acid **12**, employing diisobutylaluminum hydride (DIBAL-H) reduction with concomitant mild acidic hydrolysis and subsequent "Jones" oxidation of the resulting aldehyde. The above approach was found to be more convenient and scalable than the previously reported ones.[16] Anticipating an acidic hydrolysis at a later step, acid **12** was esterified with *tert*-butanol,[16a] and the appropriate asymmetry was efficiently introduced by applying Sharpless asymmetric dihydroxylation conditions,[17] to afford diol **13** in 61 % yield (75 % based on recovered material, 97 % *ee*). Subsequent selective tosylation furnished optically active monotosylate **14**. Direct bromination of **14** afforded optically active bromohydrine **17** in low yield (~40 %, enantiomeric ratio (*S*)/(*R*) 8:2) together with a substantial amount of allylic alcohol **15** (~15 %). The observed partial retention of stereochemistry, proved at a later step of the synthesis,[18] was attributed to the formation of an epoxide intermediate. Thus, in a second approach, we opted for a two-step double-inversion protocol, involving a base-mediated epoxide formation and subsequent regio- and diastereoselective bromide-induced opening under acidic conditions.[19] To this end, epoxide **16** was prepared in 87 % yield upon treatment of tosylate **14** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Subsequent treatment with LiBr in hexamethylphosphoramide (HMPA), employing camphorosulfonic acid (CSA) led to the regioselective formation of bromohydrin **17** (53 %) together with the dehydrated byproduct **15** (18 %). After considerable experimentation, the formation of the latter was suppressed to less than 5 % by the use of milder acidic conditions (pyridinium *p*-toluenesulfonate (PPTS) in 1-methyl-2-pyrrolidinone (NMP)), leading to bromohydrin **17** in high yield and excellent optical purity.

Gratifyingly, by applying modified Gosselin's conditions[14b] on *tert*-butylate **17**, one-pot deprotection–cyclization was achieved in 60 % yield. Thus, lactone **18** was synthesized in six steps from (*E*)-homogeranic acid **12** in 25 % overall yield and in optically pure form. Target alcohol **4** was finally reached upon reduction of lactone **18** to the corresponding lactol,[7a] followed by one-carbon homologation, in 54 % overall yield for two steps.

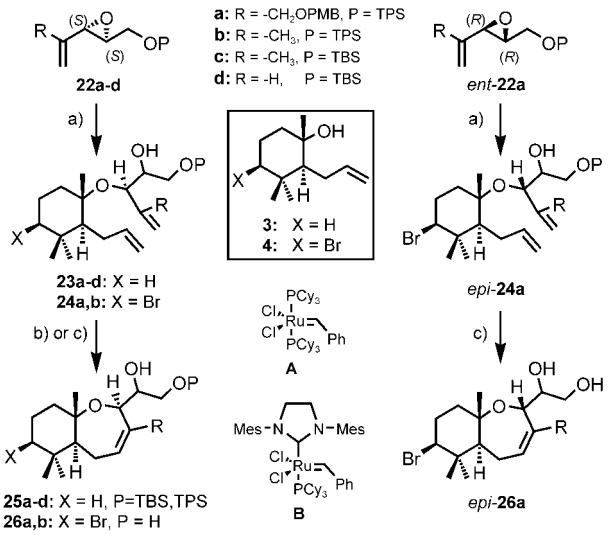
Synthesis of coupling "partners", epoxides 22a–d: The required coupling "partners" for model studies, as well as for the preparation of the title compounds were designed to be allylic epoxides **22a–d**. Their synthesis relied on Sharpless asymmetric epoxidation of the corresponding allylic alcohols **21a–c** (Scheme 4).[20]

Thus, while epoxidation precursors **21b** and **21c** were known,[21] allylic alcohol **21a** was prepared by means of a short synthetic route, involving Stille coupling of vinyl stannane **19**[22] and vinyl bromide **20** in the presence of $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone). Each alcohol was then epoxidized regio- and enantioselectively in the presence of L-(+)-diisopropyltartrate to afford, after silylation with *tert*-butyldimethylsilyl chloride (TBSCl) or *tert*-butyldiphenylsilyl chloride (TPSCl), allylic epoxides **22a–d**. The enantiomeric form of **22a**, *ent*-**22a** (Scheme 5), was similarly prepared as an indicative entry to *trans–syn* 6,7-ring systems.



Scheme 4. Synthesis of allylic epoxide coupling "partners". Reagents and general conditions: a) $[Pd_2(dba)_3]$, CH_2Cl_2, 25 °C, 3 h, 60 %; b) L-(+)-DIPT, $Ti(O\text{-}iPr)_4$, MS 4 Å, *t*BuOOH, −20 °C; c) TPSCl or TBSCl, imidazole, cat. 4-DMAP, DMF, 25 °C, **22a**: 76 %, **22b**: 72 %, **22c**: 75 %, **22d**: 60 % (yields over 2 steps). PMB = *p*-methoxybenzyl, dba = dibenzylideneacetone, DIPT = diisopropyltartrate, TPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, 4-DMAP = 4-dimethylaminopyridine.

Coupling and oxepene ring formation: The stage was now set for the crucial coupling between tertiary alcohols **3** or **4** and allylic epoxides **22a–d** (Scheme 5, Table 1). Initial attempts, involving alcohol **3**, the unsubstituted model epoxide **22d**, and Lewis acids $SnCl_4$, $AlCl_3$, $Sc(OTf)_3$, or $[Pd(PPh_3)_4]$ proved completely unsuccessful as they resulted only in decomposition of the epoxide and/or the alcohol. Utilization of $BF_3{\cdot}OEt_2$ in a 1 M solution of stoichiometric amounts of the coupling "partners", as reported for related substrates,[9a] resulted in slow decomposition of the epoxide, yet at a slower rate, while a small amount of of the desired diene **23d** was observed (10–15 %). The yield of diene **23d** was dramatically increased (60 %) by using twofold excess of alcohol **3** (Table 1, entry 4). More substituted epoxides required practically solvent-free conditions along with excess of alcohol. Thus, each of the substituted ethers **23a–c** (entries 1–3) and **24a**,**b** (entries 5, 6) was isolated in 50–60 % yield, based on the epoxide. It should be noted, that despite the moderate coupling yields, valuable alcohols **3** or **4** could be recovered and recycled to achieve, after three more cycles, a final yield of approximately 80 %, based on the alcohol. In this impressive reaction, a new C–O bond was formed between a tertiary alcohol and a 1,2-unsymmetrically disubstituted epoxide in a completely diastereo- and regioselective fashion, providing direct access to ring-closing metathesis precursors.



Scheme 5. Synthesis of *anti*– and *syn*–*trans*-fused cyclogeranyl–oxepenes. Reagents and general conditions: a) **3** or **4** (2–2.5 equiv), **22a–d** (1.0 equiv, 10 M in CH_2Cl_2), $BF_3{\cdot}OEt_2$ (0.1 equiv), 0 °C, 20–30 min; b) **23a–d**: first- (**A**) or second-generation (**B**) Grubbs catalyst (0.1–0.15 equiv), 35 °C, 1 h; c) **24a**,**b**, *epi*-**24a**: 1) TBAF (1 M solution in THF, 1.0 equiv), THF, 25 °C, 2 h; 2) Second-generation Grubbs catalyst (**B**; 0.1–0.15 equiv), 35 °C, 1 h. [The b),c) reaction sequence was inverted in the case of **24b**.]

Table 1. Yields of dienes and oxepenes prepared according to Scheme 5.

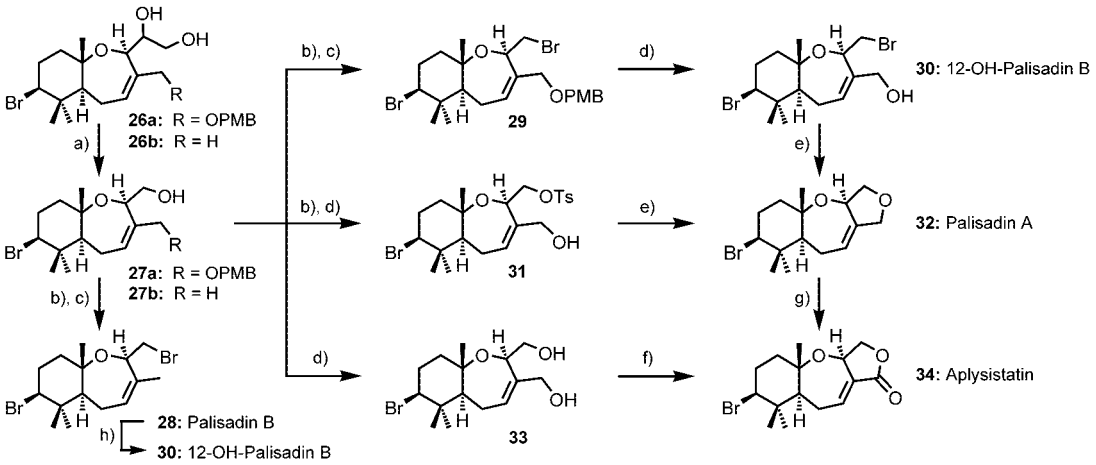
	Coupled pair alcohol + epoxide		Diene	Yields [%][a]	Oxepene	Yield [%]
1	**3**	**22a**	**23a**	56 (80)	**25a**	(78)
2	**3**	**22b**	**23b**	55 (83)	**25b**	(93)
3	**3**	**22c**	**23c**	50 (78)	**25c**	(88)
4	**3**	**22d**	**23d**	60	**25d**	(88)[c]
5	**4**	**22a**	**24a**	50 (80)[b]	**26a**	(80)[d]
6	**4**	**22b**	**24b**	54 (82)	**26b**	(90)
7	**4**	*ent*-**22a**	*epi*-**24a**	48 (75)[b]	*epi*-**26a**	(76)[d]

[a] Yields are based on epoxide. Yields in parentheses are based on alcohol, after four cycles. [b] Yield for coupling and desilylation. [c] Olefin metathesis of this less substituted diene was successfully performed at room temperature, with a first-generation Grubbs catalyst. [d] RCM was performed after desilylation.

To complete the construction of the designed oxepene systems, olefin metathesis was initially attempted with the first-generation Grubbs catalyst (**A**)[23] affording poor yields of the desired products, with the exception of the less-substituted model diene **23d** (Table 1, entry 4). To our delight, the use of second-generation Grubbs catalyst (**B**)[24] converted dienes **23a–c** into the functionalized *trans–anti* cyclogeranyl–oxepene systems **25a–c** (entries 1–3), potential precursors of Adociasulfate-2 and Toxicol A, in high yields. Similarly, bromocyclogeranyl analogues **24a**,**b** were converted to the corresponding *trans–anti* oxepenes **26a**,**b** (entries 5, 6), key intermediates for the title halosesquiterpenoids.

As anticipated, the above reaction sequence constitutes a stereocontrolled method for the construction of either *trans–anti* or *trans–syn* 6,7-ring systems. Indeed, by employing the antipode of the highly substituted epoxide **22a**, that is, (*R*,*R*)-epoxide *ent*-**22a**, the formation of a *trans–syn* bicyclic system, *epi*-**26a**, (Scheme 5) was accomplished in equally high chemical yield and stereospecificity (Table 1, entry 7).

Synthesis of sesquiterpenoids 28, 30, 32 and 34: The generality of the originally designed disconnection and the flexibility of intermediates **26a** and **26b** allowed the synthesis of the title sesquiterpenoids in three or four steps for each compound (Scheme 6). Thus, one-pot periodate cleavage and reduction of diol **26b** to alcohol **27b**, followed by a tosylation–bromination sequence furnished (+)-Palisadin B (**28**). On the other hand, oxidative removal of the *p*-methoxybenzyl group of bromide **29**, similarly prepared from diol **26a**, afforded (+)-12-hydroxy-Palisadin B (**30**). Moreover, con-



Scheme 6. Synthesis of (−)-Aplysistatin, (+)-Palisadin A, (+)-Palisadin B, and (+)-12-hydroxy-Palisadin B. Reagents and conditions: a) $NaIO_4$ (5.8 equiv), $MeOH/H_2O$ (2:1), 25 °C, 20 min; then $NaBH_4$, 0 °C, 1 h, **27a**: 75 %, **27b**: 90 %; b) TsCl, pyridine, CH_2Cl_2, 25 °C, 12 h, 85 % from **27a**, 90 % from **27b**; c) **28**: LiBr, HMPA, 40 °C, 16 h, 75 %, **29**: LiBr, HMPA, 50 °C, 20 h, 80 %; d) DDQ, CH_2Cl_2/H_2O (10:1), 25 °C, **30**: 30 min, 78 %, **31**: 30 min, 80 %, **33**: 3 h, 76 %; e) K_2CO_3 (10 % in MeOH), 30 min, 95 %; f) MnO_2, CH_2Cl_2, 25 °C, 2 h, 93 %; g) PCC, benzene, 25 °C, 48 h, 50 % (90 % based on recovered **32**); h) SeO_2, $EtOH/H_2O$ (8:2), 80 °C, 2 h; then $NaBH_4$, 0 °C, 30 min, 24 %. DDQ = 2,3-dicloro-5,6-dicyano-1,4-benzoquinone, TsCl = *p*-toluenesulfonyl chloride, PCC = pyridinium chlorochromate.

struction of the 6,7,5-tricyclic system of (+)-Palisadin A (**32**) was achieved by a Williamson-type intramolecular etherification of hydroxytosylate **31**. Finally, deprotection of alcohol **27a** to diol **33** and subsequent one-pot oxidative lactonization provided (−)-Aplysistatin (**34**) in 93 % yield. In this interesting cascade of transformations, a selective oxidation of the allylic hydroxyl group of diol **33** occurred, followed by spontaneous formation of a five-membered lactol and further oxidation to the corresponding lactone. Spectroscopical data and optical rotation of synthetic (−)-Aplysistatin (**34**) was identical, in all respects, to those reported.[4a] Although ^1H and ^{13}C NMR spectra of compounds **28**, **30**, and **32** were slightly different from those originally reported by Fenical for the isolated natural products,[4b] they were all successfully converted to **34** by following his protocol for the conversion of natural **30** to **32** and eventually to **34**. Synthetic (+)-Palisadin B was also converted to **30** upon allylic hydroxylation. Furthermore, failing to obtain authentic samples from any source, we compared ^1H and ^{13}C NMR spectra of the title natural products, kindly provided by Prof. T. Higa and Prof. M. Kuniyoshi, with the corresponding synthetic ones and found them identical. Full spectroscopic data of the synthesized natural products are given in the Experimental Section.

Conclusion

In conclusion, we have demonstrated a general stereocontrolled strategy for the construction of either *syn* or *anti trans*-fused cyclogeranyl–oxepenes, by employing epoxide opening by a tertiary alcohol and subsequent ring-closing metathesis. Besides the first total synthesis of (+)-Palisadin B, three related natural products were also synthesized from the same key intermediate **4**. En route, convenient preparation procedures for the commonly used (*E*)-homogeranic acid **12**, optically active lactone **18**, and tertiary alcohols **3** and **4** were also developed.

Completion of the synthesis of Adociasulfate-2 as well as other sesquiterpenoids, elaborating the above strategy, is currently underway.

Experimental Section

General: All reactions were carried out under anhydrous conditions and argon atmosphere using dry, freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium/benzophenone, dichloromethane (CH_2Cl_2) from CaH_2 and toluene from sodium. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. All reagents were purchased at highest commercial quality and used without further purification, unless otherwise stated. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60 F_{254}) by using UV light as visualizing agent and ethanolic phosphomolybdic acid or *p*-anisaldehyde solution and heat as developing agents. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on Bruker AMX-500 or AC-250 instruments, at 25 °C. The following abbreviations were used to explain NMR signal multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dddd = doublet of doublets of doublets of doublets. IR spectra were recorded on a Perkin–Elmer 1600 series FT-IR or Nicolet Magna system 550 FT-IR instruments. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions, while matrix-assisted (MALDI-FTMS) mass spectra were recorded on a PerSeptive Biosystems Voyager IonSpect mass spectrometer. Melting points (m.p.) were recorded on a Gallenkamp melting point apparatus and are uncorrected.

Preparation of methyl ester 8 from lactone 7: Lactone **7** (272 mg, 1.3 mmol) was dissolved in dry methanol (10 mL) and K_2CO_3 (180 mg, 1.3 mmol) was added at ice-bath temperature. The reaction mixture was stirred under argon for 1.5 h at 25 °C, poured in water (30 mL), and ex-

tracted with ethyl acetate (EtOAc) (2×20 mL). The combined organic extracts were washed with water and brine, dried over sodium sulphate, and concentrated in vacuo. The crude mixture was subjected to flash chromatography (silica gel, hexanes/EtOAc 9:1) to afford the corresponding hydroxymethyl ester (302 mg, 96%), as a colorless liquid. R_f= 0.16 (hexanes/EtOAc 9:1); $[\alpha]_D^{20}$=+4.6 (c=5.0 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.63 (s, 3H; CH_3O-), 2.31 (t, ^3J(H,H)=7.4 Hz, 2H; -CH_2COOCH$_3$), 1.84–1.05 (m, 11H; -(CH_2)$_3$-C(CH$_3$)$_2$-CH-, -(CH_2)$_2$-CH$_2$COOCH$_3$), 1.12 (s, 3H; -(CH_3)C-OH), 0.90 (s, 3H; -C(CH_3)$_a$(CH$_3$)$_b$), 0.75 ppm (s, 3H; -C(CH$_3$)$_a$(CH_3)$_b$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ= 174.5, 74.1, 57.1, 51.4, 43.3, 41.5, 35.4, 34.5, 32.7, 27.8, 25.7, 23.3, 21.2, 20.4 ppm; IR (neat): $\tilde{\nu}$=3488, 2950, 2929, 2868, 1742, 1464, 1440, 1367, 1254, 1198, 1167, 1104, 915, 888 cm^{-1}; HRMS (MALDI-FTMS): m/z calcd for $C_{14}H_{26}O_3$ $[M+Na]^+$: 265.1774; found: 265.1777.

Trimethylsilylimidazole (80 μL, 0.42 mmol) was added to the above alcohol (51 mg, 0.21 mmol) under argon, at 25°C. After 30 min of stirring, the reaction was quenched with methanol. The mixture was concentrated in vacuo and subjected to flash chromatography (silica gel, hexanes/EtOAc 95:5) to afford the silylated methyl ester **8** (61.2 mg, 93%) as a colorless liquid. R_f=0.48 (hexanes/EtOAc 9:1); $[\alpha]_D^{20}$=+8.7 (c=7.0 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.66 (s, 3H; CH_3O-), 2.31 (m, 2H; -CH_2COOCH$_3$), 1.91–1.13 (m, 11H; -(CH_2)$_3$–C(CH$_3$)$_2$–CH-, -(CH_2)$_2$CH$_2$COOCH$_3$), 1.17 (s, 3H; -(CH_3)C–OSi(CH$_3$)$_3$), 0.91 (s, 3H; -C(CH_3)$_a$(CH$_3$)$_b$), 0.78 (s, 3H; -C(CH$_3$)$_a$(CH_3)$_b$), 0.08 ppm (s, 9H; -OSi(CH_3)$_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=174.5, 77.7, 57.0, 51.3, 43.3, 41.4, 35.2, 34.9, 33.0, 27.9, 26.2, 23.9, 21.4, 20.5, 2.8, 1.0 ppm; IR (neat): $\tilde{\nu}$=2950, 2867, 1748, 1462, 1436, 1380, 1253, 1164, 1108, 1081, 1052, 1032, 1007, 841, 754 cm^{-1}; MS (ESI): m/z calcd for $C_{17}H_{34}O_3Si$ $[M+Na]^+$: 337; found: 337.

Preparation of α,β-unsaturated methyl ester 9 from ester 8: Methyl ester **8** (113.5 mg, 0.361 mmol) was dissolved in dry THF (1 mL) and hexamethylphosphoramide (HMPA) (82 μL, 0.469 mmol) was added at 25°C under argon. The reaction mixture was cooled to −78°C and a solution of freshly prepared lithium diisopropylamide (LDA) in THF (0.73 M, 634 μL, 0.469 mmol) was added dropwise. After 1.5 h of stirring at −78°C, a solution of diphenyl diselenide (147 mg, 0.469 mmol) in THF (1 mL) was added; the reaction mixture was stirred for 30 min at −78°C and poured in a mixture of a saturated aqueous solution of ammonium chloride (5 mL) and Et_2O (5 mL). The organic phase was separated and the aqueous phase was washed with Et_2O (2×5 mL). The combined organic extracts were washed with water and brine, dried over sodium sulphate, and concentrated in vacuo. Flash chromatography of the crude mixture (silica gel, hexanes/EtOAc 98:2) afforded the α-phenylselenyl ester (151 mg, 89%), as a yellow oil. R_f=0.7 (hexanes/EtOAc 95:5); ^{1}H NMR (250 MHz, $CDCl_3$) (mixture of isomers): δ=7.56 (m, 4H; -SeAr-H), 7.25 (m, 6H; -SeAr-H), 3.72–3.60 (m, 2H; -CH–SePh), 3.60 (2s, 6H; CH_3O-), 2.32–1.15 (m, 22H; -(CH_2)$_3$–C(CH$_3$)$_2$-CH-, -(CH_2)$_2$CH(SePh)COOCH$_3$), 1.13 (s, 6H; -(CH_3)C–OSi(CH$_3$)$_3$), 0.87–0.81 (2s, 6H; -C(CH_3)$_a$(CH$_3$)$_b$), 0.76–0.70 (2s, 6H; -C(CH$_3$)$_a$(CH_3)$_b$-), 0.05 ppm (s, 18H; -OSi(CH_3)$_3$); IR (neat): $\tilde{\nu}$=2953, 2870, 1740, 1480, 1464, 1439, 1256, 1169, 1113, 1072, 1025, 845, 748, 695 cm^{-1}.

The above α-selenyl ester (380 mg, 0.81 mmol) was dissolved in dichloromethane (9 mL), and water (0.61 mL) and a 30% aqueous solution of hydroperoxide (1.84 mL, 16.2 mmol) were added, at 25°C. After 20 min of stirring, the reaction mixture was poured in a 20% aqueous solution of sodium carbonate (10 mL) and extracted with Et_2O (30 mL). The organic phase was separated and the aqueous phase was washed with Et_2O (2× 10 mL). The combined organic extracts were sequentially washed with water, saturated aqueous NH_4Cl, water, and brine, dried over Na_2SO_4, and concentrated in vacuo. Flash column chromatography of the crude mixture (silica gel, hexanes/EtOAc 98:2) afforded pure ester **9** (240 mg, 95%) as a pale yellow oil. R_f=0.7 (hexanes/EtOAc 95:5); $[\alpha]_D^{20}$=−5.1 (c=0.6 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.12 (dt, ^3J(H,H)= 7.4 Hz, ^3J(H,H)=15.6 Hz, 1H; -CH=CHCOOCH$_3$), 5.75 (dt, ^3J(H,H)= 15.6 Hz, ^4J(H,H)=1.5 Hz, 1H, -CH=CHCOOCH$_3$), 3.71 (s, 3H; -COOCH_3), 2.43 (m, 1H; -CH_aH$_b$–CH=CH-), 1.87–1.22 (m, 7H; -(CH_2)$_3$–C(CH$_3$)$_2$–CH-), 1.19 (s, 3H; -(CH_3)C-OSi(CH$_3$)$_3$), 0.92 (s, 3H; -C(CH_3)$_a$(CH$_3$)$_b$), 0.82 (s, 3H; -C(CH$_3$)$_a$(CH_3)$_b$-), 0.08 ppm (s, 9H; -OSi(CH_3)$_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=167.5, 154.0, 118.8, 77.1, 57.4, 51.2, 43.2, 41.5, 35.2, 33.3, 29.6, 23.9, 21.4, 20.4, 2.8 ppm; IR (neat): $\tilde{\nu}$=2950, 2874, 1729, 1656, 1459, 1435, 1252, 1164, 1112, 1073, 1055, 846, 757 cm^{-1}; MS (ESI): m/z calcd for $C_{17}H_{32}O_3Si$ $[M+Na]^+$: 335; found: 335.

Preparation of aldehyde 10: α,β-Unsaturated methyl ester **9** (2.4 g, 7.68 mmol) was dissolved in dichloromethane (50 mL) and the solution was cooled at −78°C. A stream of ozone was passed through the solution. Immediately after consumption of **9** (monitored by TLC), triphenylphosphine (3 g, 11.5 mmol) was added with stirring. The reaction mixture was brought to room temperature with stirring, concentrated in vacuo, and subjected to flash column chromatography (silica gel, hexanes/EtOAc 9:1) to afford pure aldehyde **10** (1.8 g, 93%) as a pale yellow oil. R_f=0.74 (hexanes/EtOAc 7:3); $[\alpha]_D^{20}$=+47.0 (c=1.3 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=9.58 (dd, ^3J(H,H)=1.1 Hz, ^3J(H,H)=4.8 Hz, 1H; -CH=O), 2.39 (ddd, ^3J(H,H)=4.8 Hz, ^2J(H,H)=15.6 Hz, ^3J(H,H)= 10.1 Hz, 1H; -CH_aH$_b$–CHO), 2.25 (ddd, ^2J(H,H)=15.6 Hz, ^3J(H,H)= 1.2 Hz, ^3J(H,H)=3.7 Hz, 1H; -CH$_a$$H_b$–CHO), 1.94 (dd, ^3J(H,H)=3.7 Hz, ^3J(H,H)=9.7 Hz, 1H; -C(CH$_3$)$_2$–CH-), 1.86 (m, 6H; -(CH_2)$_3$–C(CH$_3$)$_2$-), 1.20 (s, 3H; -(CH_3)C–OSi(CH$_3$)$_3$), 0.95 (s, 3H; -C(CH_3)$_a$(CH$_3$)$_b$), 0.81 (s, 3H; -C(CH$_3$)$_a$(CH_3)$_b$), 0.08 ppm (s, 9H; -OSi(CH_3)$_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=202.8, 76.8, 53.5, 42.9, 41.1, 40.9, 34.6, 33.1, 23.9, 21.3, 20.4, 2.6 ppm; IR (neat): $\tilde{\nu}$=2961, 2936, 1726, 1252, 1161, 1108, 1074, 1021, 843, 757 cm^{-1}; HRMS (MALDI-FTMS): m/z calcd for $C_{14}H_{28}O_2Si$ $[M+H]^+$: 257.1931; found: 257.1942.

Synthesis of tertiary alcohol 3 from aldehyde 10: Sodium bis(trimethylsilyl)amide (1 M solution in THF, 9.1 mL, 9.1 mmol) was added to a solution of triphenylphosphonium bromide (3.75 g, 10.5 mmol) in dry THF (15 mL) at 0°C stirring under argon. After 45 min of stirring at 25°C, a solution of aldehyde **10** in dry THF (25 mL) was added at 0°C. The reaction mixture was stirred for 30 min at this temperature, poured to a saturated solution of NH_4Cl (40 mL), and extracted with Et_2O (2×40 mL). The combined organic extracts were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Subjection of the crude mixture to flash chromatography (silica gel, hexanes/EtOAc 98:2) yielded the pure silylated alkene (1.69 g, 95%) as a colorless liquid. R_f=0.81 (hexanes/EtOAc 95:5); $[\alpha]_D^{20}$=+4.5 (c=0.44 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.94 (m, 1H; -CH=CH$_2$), 4.94 (ddd, ^3J(H,H)=17.1 Hz, ^4J(H,H)=2.2 Hz, ^2J(H,H)=3.7 Hz, 1H; -CH=CH_{trans}H$_{cis}$), 4.83 (ddd, ^3J(H,H)=10.1 Hz, ^4J(H,H)=1.5 Hz, ^2J(H,H)=3.7 Hz, 1H; -CH= CH$_{trans}$$H_{cis}$), 2.34 (m, 1H; -C$H_aH_b$–CH=CH$_2$), 2.04 (m, 1H; -CH$_a$$H_b$–CH= CH$_2$), 1.84–1.20 (m, 7H; -(C$H_2$)$_3$–C(CH$_3$)$_2$–C$H$-), 1.19 (s, 3H; -(C$H_3$)C-OSi(CH$_3$)$_3$), 0.94 (s, 3H; -C(C$H_3$)$_a$(CH$_3$)$_b$), 0.84 (s, 3H; -C(CH$_3$)$_a$(C$H_3$)$_b$), 0.10 ppm (s, 9H; -OSi(CH_3)$_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=142.9, 112.4, 77.5, 57.5, 43.4, 41.8, 35.5, 33.4, 31.1, 24.1, 21.6, 20.6, 2.9 ppm; IR (neat): $\tilde{\nu}$=2958, 2937, 2873, 1638, 1616, 1465, 1380, 1251, 1114, 1073, 1054, 1010, 873, 840, 757 cm^{-1}; HRMS (EI): m/z calcd for $C_{15}H_{30}OSi$ $[M+H]^+$: 255.2139; found: 255.2137.

The above alkene (295 mg, 1.16 mmol) was dissolved in THF (2.3 mL) and TBAF (1 M solution in THF, 1.74 mL, 1.74 mmol) was added at 0°C. The reaction mixture was stirred at 25°C for 3 h, poured in a saturated solution of NH_4Cl (10 mL), and extracted with Et_2O (2×10 mL). The organic extracts were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Flash column chromatography of the crude mixture (silica gel, hexanes/EtOAc 9:1) afforded pure tertiary alcohol **3** (203 mg, 96%) as a colorless liquid. R_f=0.16 (hexanes/EtOAc 9:1); $[\alpha]_D^{20}$=+11.4 (c=1.4 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=6.02 (m, 1H; -CH=CH$_2$), 5.09 (ddd, ^4J(H,H)=3.4 Hz, ^3J(H,H)=17.1 Hz, ^2J(H,H)=1.9 Hz, 1H; -CH=CH_{trans}H$_{cis}$), 4,97 (ddd, ^4J(H,H)=3.0 Hz, ^3J(H,H)=10.1 Hz, ^2J(H,H)=1.9 Hz, 1H; -CH=CH$_{trans}$$H_{cis}$), 2.26 (t, ^3J(H,H)=7.1 Hz, 2H; -CH_2–CH=CH$_2$), 1.84 (brs, -OH), 1.78–1.20 (m, 7H; -(CH_2)$_3$–C(CH$_3$)$_2$–CH-), 1.22 (s, 3H; -(CH_3)C–OH), 0.96 (s, 3H; -C(CH_3)$_a$(CH$_3$)$_b$), 0.83 ppm (s, 3H; -C(CH$_3$)$_a$(CH_3)$_b$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=142.2, 114.5, 74.4, 56.5, 42.6, 41.8, 33.0, 31.1, 23.9, 21.2, 20.1 ppm; IR (neat): $\tilde{\nu}$=3412, 2934, 2869, 1637, 1463, 1391, 1382, 1372, 1102, 914 cm^{-1}; HRMS (EI): m/z calcd for $C_{12}H_{22}O$ $[M+H]^+$: 183.1743; found: 183.1740.

Preparation of pure (*E*)-Homogeranic acid (12): Geranyl nitrile **11** (4.3 gr, 26.3 mmol) was dissolved in dichloromethane (110 mL) and the mixture was cooled at −78°C under argon. A solution of DIBAL-H (1.0 M in CH_2Cl_2, 34.2 mL, 34.2 mmol) was added. After 30 min at −78°C, the reaction mixture was quenched with MeOH and poured in a mixture of EtOAc/$NH_4Cl_{(aq)}$ 1:1 (50 mL). A solution of 10% HCl was then added at room temperature with stirring until the pH of the aqueous phase was

~3–4. Stirring was continued for 20 min at room temperature. Potassium sodium tartrate was then added until the pH of the aqueous phase was ~7–8 and stirring was continued until there was a sufficient separation of the two phases (~1 h). The organic phase was separated and the aqueous phase was washed with EtOAc (2×50 mL). The combined organic extracts were washed with water and brine, dried over sodium sulphate, and concentrated in vacuo at 25–30 °C. The crude aldehyde was immediately dissolved in acetone (150 mL) and cooled at −20 °C. A solution of Jones reagent (8 M) was added portionwise until no aldehyde was traced by TLC (~7 mL). The reaction was then quenched with isopropanol, filtered through Celite, and poured in EtOAc/H_2O 1:1 (200 mL). The organic phase was separated, the aqueous phase was washed with EtOAc (2×50 mL), and the combined organic extracts were washed successively with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture was subjected to flash column chromatography (silica gel, hexanes/EtOAc 9:1) to afford pure (*E*)-homogeranic acid (2.9 g, 60%) as a yellow oil. R_f=0.44 (hexanes/EtOAc 7:3); ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.32 (t, ^3J(H,H)=6.9 Hz, 1H; -C*H*=C(CH$_3$)-), 5.09 (m, 1H; (CH$_3$)$_2$C=C*H*-), 3.09 (d, ^3J(H,H)=6.9 Hz, 2H; -C*H*$_2$−COOH), 2.07 (m, 4H; -C*H*$_2$C*H*$_2$-), 1.68 (s, 3H; (CH$_3$)$_{trans}$(C*H*$_3$)$_{cis}$ C=CH-), 1.64 (s, 3H; -(C*H*$_3$)C=CH-), 1.60 ppm (s, 3H; (C*H*$_3$)$_{trans}$(CH$_3$)$_{cis}$C=CH-); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=178.8, 131.7, 123.9, 114.9, 39.5, 33.5, 26.4, 25.6, 18.7, 17.7, 16.3 ppm; IR (neat): $\tilde{\nu}$=3300, 2973, 2926, 2859, 1712, 1443, 1418, 1383, 1301, 1235 cm^{-1}.

Synthesis of diol 13: (*E*)-Homogeranic *tert*-butylate (1.0 g, 4.2 mmol), prepared from (*E*)-homogeranic acid **12** according to Gosselin,[16a] was dissolved in a mixture of *t*BuOH/H_2O 2:1 (45 mL). After cooling at 0 °C, K_2CO_3 (2.32 g, 16.8 mmol), $K_3Fe(CN)_6$ (5.5 g, 16.8 mmol), hydroquinine 1,4-phthalazinediyl diether ((DHQ)$_2$PHAL; 549 mg, 0.168 mmol), $K_2OsO_2(OH)_4$ (61.9 mg, 0.168 mmol), and $CH_3SO_2NH_2$ (520 mg, 5.46 mmol) were added successively. After 12 h at 0 °C, Na_2SO_3 (2.1 g, 16.8 mmol) was added and stirring was continued for 1 h at this temperature. The reaction mixture was then partitioned between EtOAc (100 mL) and water (100 mL). The organic phase was separated, the aqueous phase was washed with EtOAc (2×50 mL), and the combined organic extracts were washed successively with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture was subjected in flash column chromatography (silica gel, hexanes/EtOAc 6:4) to afford pure diol **13** (699 mg, 61%, 97% *ee*, detected by ^{1}H NMR spectrum of the Mosher ester) as a pale yellow oil and recovered (*E*)-homogeranic *tert*-butylate (293 mg, 75%). R_f=0.22 (hexanes/EtOAc 6:4); $[\alpha]_D^{20}$=−22.0 (*c*=1.3 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.35 (t, ^3J(H,H)=6.9 Hz, 1H; -(CH$_3$)C=C*H*-), 3.34 (d, ^3J(H,H)=10.2 Hz, 1H; -C*H*−OH), 2.95 (d, ^3J(H,H)=6.9 Hz, 2H; -C*H*$_2$−COO(CH$_3$)$_3$), 2.43–2.00 (m, 4H; -C*H*$_2$C*H*$_2$-), 1.63 (s, 3H; -(C*H*$_3$)C=CH-), 1.43 (s, 3H; C(C*H*$_3$)$_3$), 1.18 (s, 3H; -(C*H*$_3$)$_a$(CH$_3$)$_b$C−OH), 1.14 ppm (s, 3H; -(CH$_3$)$_a$(C*H*$_3$)$_b$C-OH); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=172.0, 138.9, 116.8, 80.6, 78.1, 72.9, 36.9, 34.7, 29.5, 28.1, 26.3, 23.2, 16.2 ppm; IR (neat): $\tilde{\nu}$=3447, 2979, 2932, 2874, 1732, 1455, 1368, 1143, 1078, 951, 836, 766 cm^{-1}; HRMS (MALDI-FTMS): *m*/*z* calcd for $C_{15}H_{28}O_4$ [*M*+Na]$^+$: 295.1880; found: 295.1883.

Synthesis of monotosylate 14: *p*-Toluenesulfonyl anhydride (1.6 g, 4.77 mmol) was added at 0 °C to a solution of diol **13** (1.0 g, 3.67 mmol) in pyridine (4.6 mL) under argon. The reaction mixture was stirred for 1 h and then it was partitioned between saturated aqueous solution of NH_4Cl (40 mL) and EtOAc (40 mL). The organic phase was separated and the aqueous phase was washed with EtOAc (2×20 mL). The combined organic extracts were washed successively with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Flash column chromatography (silica gel, hexanes/EtOAc 8:2) of the crude mixture yielded pure monotosylate **14** (4.94 g, 86%) as a pale yellow oil. R_f=0.65 (hexanes/EtOAc 6:4); $[\alpha]_D^{20}$=−18.0 (*c*=0.4 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.82 (d, ^3J(H,H)=8.7 Hz, 2H; Ar*H*), 7.34 (d, ^3J(H,H)=8.7 Hz, 2H; Ar*H*), 5.25 (t, ^3J(H,H)=7.0 Hz, 1H; -C*H*=C(CH$_3$)-), 4.56 (dd, ^3J(H,H)=3.0 Hz, ^3J(H,H)=8.9 Hz, 1H; -C*H*OTs), 2.92 (d, ^3J(H,H)=7.0 Hz, 2H; -C*H*$_2$−COOC(CH$_3$)$_3$), 2.44 (s, 3H; C*H*$_3$Ar), 2.01 (m, 2H; -C*H*$_2$−C(CH$_3$)=CH-), 1.85–1.61 (m, 2H; -CH(OTs)C*H*$_2$-), 1.54 (s, 3H; -C(C*H*$_3$)=CH-), 1.44 (s, 9H; -OC(C*H*$_3$)$_3$), 1.19 (s, 3H; -(C*H*$_3$)$_a$(CH$_3$)$_b$C(OH)-), 1.18 ppm (s, 3H; (CH$_3$)$_a$(C*H*$_3$)$_b$C(OH)-); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=171.6, 144.7, 137.4, 134.5, 129.7, 127.7, 117.1, 90.3, 80.4, 72.2, 35.8, 34.8, 29.1, 28.1, 26.2, 24.6, 21.6, 16.4 ppm; IR (neat): $\tilde{\nu}$=3530, 2978, 2934, 1730, 1367, 1189, 177, 1150, 904, 670, 559 cm^{-1}; HRMS (MALDI-FTMS): *m*/*z* calcd for $C_{22}H_{34}O_6S$ [*M*+Na]$^+$: 449.1968; found: 449.1964.

Synthesis of bromohydrin 17:

Method A—by direct bromination of monotosylate 14: Monotosylate **14** (223 mg, 0.52 mmol) was dissolved in HMPA (0.7 mL) and LiBr (226 mg, 2.6 mmol) was added at 25 °C. The reaction was stirred at 50 °C under argon for 30 min and saturated aqueous NH_4Cl was added. The reaction mixture was extracted with EtOAc (2×20 mL) and the combined organic extracts were washed successively with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture was subjected to flash column chromatography to afford an inseparable mixture of bromohydrin **17** with allylic alcohol **15** (122 mg, **17**/**15** 3:1 detected by ^{1}H NMR spectroscopy). Bromohydrin **17** obtained this way was separated from the allylic alcohol **15** after acetylation of the latter. The enantiomeric excess of **17** was calculated from the diastereomeric excess of oxepene **26b** (*syn*/*anti* 2:8, detected by ^{1}H NMR spectroscopy) prepared after converting **17** to bromoalcohol **4** (**17**→**18**→**4**), subsequent coupling with epoxide **22b** and ring-closing metathesis of the corresponding diene **24b**.

Data for the acetylated form of allylic alcohol ***15***: ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.32 (t, ^3J(H,H)=7.0 Hz, 1H; -C(CH$_3$)=C*H*-), 5.13 (t, ^3J(H,H)=6.4 Hz, 1H; -C*H*(OAc)-), 4.94 (s, 1H; -(CH$_3$)C=CH$_a$H$_b$), 4.89 (s, 1H; -(CH$_3$)C=CH$_a$H$_b$), 2.94 (d, ^3J(H,H)=7.0 Hz, 2H; -C*H*$_2$-COO(CH$_3$)$_3$), 2.06 (s, 3H; -CH(OOCC*H*$_3$)-), 2.01 (m, 2H; -C*H*$_2$−C(CH$_3$)=CH-), 1.75 (m, 2H; -(OAc)CH−C*H*$_2$-), 1.72 (br s, 3H; -(C*H*$_3$)C=CH$_2$), 1.62 (br s, 3H; -(C*H*$_3$)C=CH-), 1.44 ppm (br s, 9H; -C(C*H*$_3$)$_3$).

Method B—by means of epoxide ring opening: DBU (393 mg, 2.58 mmol) was added at 25 °C to a solution of monotosylate **14** (220 mg, 0.516 mmol) in DMF (0.4 mL) under argon. After 15 min of stirring, saturated aqueous solution of NH_4Cl was added. The reaction mixture was extracted with EtOAc (2×20 mL) and the combined organic extracts were washed successively with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture was subjected to flash column chromatography (silica gel, hexanes/EtOAc 95:5) to afford pure epoxide **16** (114 mg, 87%), as a pale yellow oil. R_f=0.8 (hexanes/EtOAc 8:2); $[\alpha]_D^{20}$=+3.0 (*c*=1.2 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.35 (t, ^3J(H,H)=7.1 Hz, 1H; -C(CH$_3$)=C*H*-), 2.96 (d, ^3J(H,H)=7.1 Hz, 2H; -C*H*$_2$−COOC(CH$_3$)$_3$), 2.71 (t, ^3J(H,H)=6.3 Hz, 1H; (CH$_3$)$_2$C−C*H*-), 2.17 (m, 2H; -C*H*$_2$−C(CH$_3$)=CH-), 1.78–1.60 (m, br s, 6H; -C*H*$_2$−CH$_2$−C(C*H*$_3$)=CH-), 1.44 (br s, 9H; -C(C*H*$_3$)$_3$), 1.30 (s, 3H; -C(C*H*$_3$)$_a$(CH$_3$)$_b$), 1.26 ppm (s, 3H; -C(CH$_3$)$_a$(C*H*$_3$)$_b$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=172.0, 138.0, 117.4, 80.8, 64.4, 58.7, 36.6, 35.4, 28.5, 27.7, 25.3, 19.1, 16.8 ppm; HRMS (MALDI-FTMS): *m*/*z* calcd for $C_{15}H_{26}O_3$ [*M*+H]$^+$: 255.1954; found: 255.1960.

LiBr (89 mg, 1.02 mmol) and PPTS (199 mg, 0.79 mmol) were added at 25 °C to a solution of epoxide **16** (200 mg, 0.79 mmol), in NMP (0.22 mL) under argon. After 1 h of stirring, a saturated aqueous solution of $NaHCO_3$ was added, the reaction mixture was extracted with EtOAc (2×10 mL), and the combined organic extracts were washed successively with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Flash column chromatography of the crude mixture (silica gel, hexanes/EtOAc 9:1) yielded bromohydrin **17** (225 mg, 85%, 95% *ee* according to the procedure described above) as an inseparable mixture with allylic alcohol **15** (<5%, detected by ^{1}H NMR spectroscopy). R_f=0.3 (hexanes/EtOAc 8:2); ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.40 (t, ^3J(H,H)=7.1 Hz, 1H; -C(CH$_3$)=C*H*-), 3.99 (dd, ^3J(H,H)=1.9 Hz, ^3J(H,H)=11.0 Hz, 1H; -(Br)C*H*-), 2.97 (d, ^3J(H,H)=7.1 Hz, 2H; -C*H*$_2$−COOC(CH$_3$)$_3$), 2.36 (m, 1H; -C*H*$_a$H$_b$C(CH$_3$)-), 2.17 (m, 1H; -CH$_a$*H*$_b$C(CH$_3$)-), 2.10–1.95 (m, 1H; -(Br)CH−C*H*$_a$H$_b$-), 1.92–1.73 (m, 2H; -(Br)CH−CH$_a$*H*$_b$-), 1.63 (br s, 3H; -(C*H*$_3$)C=CH-), 1.45 (br s, 9H; -C(C*H*$_3$)$_3$), 1.36–1.33 ppm (2s, 6H; -C(OH)(C*H*$_3$)$_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=171.6, 136.8, 117.9, 80.5, 72.4, 70.3, 38.0, 35.0, 31.9, 28.1, 26.5, 26.0, 16.3 ppm; IR (neat): $\tilde{\nu}$=3469, 2977, 2934, 1733, 1369, 1144, 954, 842, 459 cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{15}H_{27}BrO_3$ ([*M*+H]$^+$): 335.1222; found: 335.1229.

Synthesis of optically active bromolactone 18: A solution of bromohydrin **17** (640 mg, 1.91 mmol) in dry CH_3NO_2 (8 mL) was added portionwise to a solution of $SnCl_4$ (1.24 g, 4.75 mmol) in dry CH_3NO_2 (16 mL) at 0 °C under argon. After 30 min of stirring, the reaction mixture was poured in an ice-cold solution of Et_2O/H_2O 1:1 (40 mL). The organic phase was separated, the aqueous phase was washed with diethyl ether (2×20 mL),

and the combined organic extracts were washed successively with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Flash column chromatography of the crude mixture (silica gel, hexanes/EtOAc 9:1) yielded pure bromolactone **5** (299 mg, 60%), as a pale yellow oil with spectroscopical data identical to the reported ones.[4a] $R_f = 0.64$ (hexanes/EtOAc 5:5); $[\alpha]_D^{20} = -24.0$ ($c = 0.8$ in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 3.93$ (dd, $^3J(H,H) = 4.8$ Hz, $^3J(H,H) = 12.0$ Hz, 1H; -C*H*(Br)-), 2.53 (dd, $^3J(H,H) = 13.5$ Hz, $^2J(H,H) = 15.8$ Hz, 1H; -CH_aH_bCO), 2.38 (dd, $^3J(H,H) = 6.9$ Hz, $^2J(H,H) = 15.8$ Hz, 1H; -CH$_a$$H_b$CO), 2.20–1.92 (m, 3H; -C(CH$_3$)$_2$–C*H*-, -CH_2–CH(Br)-), 1.50–1.90 (m, 2H; -CH_2–C(CH$_3$)-O-), 1.37 (s, 3H; -C(CH_3)O-), 1.07 (s, 3H; -C(CH_3)$_a$(CH$_3$)$_b$), 1.02 ppm (s, 3H; -C(CH$_3$)$_a$(CH_3)$_b$); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 175.3$, 84.6, 62.7, 54.4, 38.5, 38.4, 32.3, 30.2, 30.0, 20.4, 17.0 ppm.

Synthesis of optically active tertiary alcohol 4: NaHMDS (1 M solution in THF, 3.3 mL, 3.3 mmol) was added to a solution of $PPh_3CH_3^+Br^-$ (1.57 g, 4.40 mmol) in dry THF (5.3 mL) at 0°C under argon. After stirring at 25°C for 1 h, the solution of the ylide was added to a solution of (3α*S*,5*S*,7α*S*)-5-bromo-octahydro-4,4,7α-trimethylbenzofuran-2-ol (580 mg, 2.20 mmol), prepared from lactone **18** according to Hoye,[7a] in dry THF (4 mL) over a period of 12 h. After addition was completed, the reaction mixture was poured in an aqueous saturated NH_4Cl solution; it was then extracted with EtOAc (2×40 mL). The combined organic extracts were washed successively with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture was subjected to flash column chromatography (silica gel, hexanes/EtOAc 9:1) to afford pure alcohol **4** (345 mg, 60%) as a colorless liquid and recovered lactol (208 mg, 90%). $R_f = 0.5$ (hexanes/EtOAc 7:3); $[\alpha]_D^{20} = +13.0$ ($c = 3.7$ in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 5.97$ (m, 1H; -C*H*=CH$_2$), 5.11 (ddd, $^2J(H,H) = 1.5$ Hz, $^3J(H,H) = 17.2$ Hz, $^4J(H,H) = 3.4$ Hz, 1H; -CH=CH_{trans}H$_{cis}$), 5.00 (ddd, $^2J(H,H) = 1.5$ Hz, $^3J(H,H) = 10.3$ Hz, $^4J(H,H) = 2.9$ Hz, 1H; -CH=CH$_{trans}$$H_{cis}$), 4.00 (dd, $^3J(H,H) = 4.2$ Hz, $^3J(H,H) = 11.9$ Hz, 1H; -C*H*(Br)-), 2.35 (m, 2H; -CH_2–CH=CH$_2$), 2.23–1.91 (m, 2H; -CH_2–CH(Br)-), 1.75 (ddd, $^2J(H,H) = 13.4$ Hz, $^3J(H,H) = 3.2$ Hz, $^3J(H,H) = 3.2$ Hz, 1H; -CH$_{ax}$$H_{eq}$C(OH)-), 1.65–1.46 (m, 2H; -CH_{ax}H$_{eq}$-C(OH), -C(CH$_3$)$_2$–C*H*-), 1.25 (s, 3H; -C(OH)CH_3), 1.14 (s, 3H; -C(CH_3)$_a$(CH$_3$)$_b$), 0.96 ppm (s, 3H; -C(CH$_3$)$_a$(CH_3)$_b$); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 141.2$, 115.1, 73.4, 67.0, 56.5, 43.0, 40.8, 32.1, 32.0, 30.6, 23.7, 17.3 ppm; IR (neat): $\tilde{\nu} = 3444$, 2976, 2953, 2928, 2873, 1637, 1466, 1393, 1372, 1154, 1078, 1004, 985, 915, 708, 582 cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{12}H_{21}BrO$ $[M+H]^+$: 261.0848; found: 261.0854.

Preparation of vinyl bromide 20: Vinyl bromide **20**, was prepared from *p*-methoxybenzyl alcohol and 2,3-dibromobut-1-ene according to reference [20a]. Yellow oil; $R_f = 0.5$ (hexanes/EtOAc 8:2); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.29$ (d, $^3J(H,H) = 8.2$ Hz, 2H; Ar*H*), 6.90 (d, $^3J(H,H) = 8.2$ Hz, 2H; Ar*H*), 5.95 (brs, 1H; -C=CH_aH$_b$), 5.64 (brs, 1H; -C=CH$_a$$H_b$), 4.50 (s, 2H; ArC$H_2$-), 4.11 (s, 2H; -O–C$H_2$–C=C-), 3.81 ppm (s, 3H; CH_3O-Ar); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 159.4$, 129.6, 129.5, 117.7, 113.9, 73.7, 71.7, 55.3 ppm; IR (neat): $\tilde{\nu} = 3001$, 2958, 2935, 2909, 2859, 2835, 1642, 1614, 1589, 1514, 1465, 1303, 1251, 1177, 1085, 1035, 900, 823, 668, 575, 532, 516 cm^{-1}; HRMS (MALDI-FTMS): *m*/*z* calcd for $C_{11}H_{13}BrO_2$ $[M+Na]^+$: 278.9991; found: 278.9992.

Synthesis of allylic alcohol 21a: A mixture of vinyl bromide **20** (225 mg, 0.88 mmol) and 3-tributylstannylprop-2-en-1-ol (608 mg, 1.75 mmol)[22] in dry CH_2Cl_2 (1.7 mL) was stirred at 25°C under argon and $[Pd_2(dba)_3]$ (81 mg, 0.088 mmol) was added. After stirring for 3 h, the reaction mixture was concentrated in vacuo and immediately subjected to flash column chromatography (silica gel, hexanes/EtOAc 7:3) to yield pure allylic alcohol **21a** (124 mg, 60%) as a pale yellow oil. $R_f = 0.31$ (hexanes/EtOAc 6:4); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.27$ (d, $^3J(H,H) = 8.5$ Hz, 2H; Ar*H*), 6.88 (d, $^3J(H,H) = 8.5$ Hz, 2H; Ar*H*), 6.30 (d, ^3J (H,H) = 16.2 Hz, 1H; -C*H*=CH–CH$_2$OH), 5.95 (dt, $^3J(H,H) = 5.6$ Hz, $^3J(H,H) = 16.2$ Hz, 1H; -CH=C*H*–CH$_2$OH), 5.26 (brs, 1H; -C=CH_aH$_b$), 5.20 (brs, 1H; -C=CH$_a$$H_b$), 4.46 (s, 2H; ArC$H_2$), 4.20 (d, $^3J(H,H) = 5.6$ Hz, 2H; -CH_2OH), 4.15 (s, 2H; -OCH_2-), 3.81 ppm (s, 3H; CH_3O); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 159.2$, 141.6, 130.6, 130.2, 129.4, 129.1, 117.5, 113.8, 71.7, 70.0, 63.6, 55.2 ppm; IR (neat): $\tilde{\nu} = 3405$, 2954, 2931, 2856, 1613, 1585, 1514, 1464, 1372, 1302, 1249, 1174, 1091, 1035, 970, 820 cm^{-1}; HRMS (MALDI-FTMS): *m*/*z* calcd for $C_{14}H_{18}O_3$ $[M+Na]^+$: 257.1148; found: 257.1150.

Preparation of the allylic epoxide coupling partners 22a–d: Each of the allylic alcohols **21a–c** was epoxidized and subsequently silylated, as it is described below:

Compound 22a: Ti(O-*i*Pr)$_4$ (336 mg, 1.18 mmol) was added to a mixture of L-(+)-diisopropyltartrate (330 mg, 1.40 mmol) and molecular sieves (MS) 4 Å (250 mg) in dry CH_2Cl_2 (4 mL) at −20°C under argon. After 20 min of stirring, a solution of the allylic alcohol **21a** (513 mg, 2.19 mmol) in dry CH_2Cl_2 (4 mL) was added. The mixture was stirred for 20 min and then an anhydrous solution of *t*BuOOH (5.5 M in decane, 0.8 mL, 4.38 mmol) was added. The reaction was stirred at −20°C for 12 h. Water (13 mL) was added at 0°C and the resulting mixture was brought to 25°C over a period of 30 min. A 30% solution of NaOH in brine was then added and the mixture was vigorously stirred for 1 h at 0°C. After separation of the dichloromethane phase, the aqueous phase was washed with CH_2Cl_2 (4×30 mL) and the combined organic extracts were washed successively with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Flash column chromatography of the crude mixture (silica gel, hexanes/EtOAc 7:3) yielded the pure epoxy alcohol (438 mg, 80%, 95% *ee* determined by the ^{1}H NMR spectrum of Mosher ester) and recovered hydroxydiene **21a** (93 mg, 90%). $R_f = 0.3$ (hexanes/EtOAc 7:3); $[\alpha]_D^{20} = +2.0$ ($c = 0.54$ in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.25$ (d, $^3J(H,H) = 8.5$ Hz, 2H; Ar*H*), 6.88 (d, $^3J(H,H) = 8.5$ Hz, 2H; Ar*H*), 5.36 (brs, 1H; -C=CH_aH$_b$), 5.29 (brs, 1H; -C=CH$_a$$H_b$), 4.46 (d, $^2J(H,H) = 11.1$ Hz, 1H; Ar–CH_aH$_b$O-), 4.40 (d, $^2J(H,H) = 11.1$ Hz, 1H; Ar–CH$_a$$H_b$O-), 3.96 (brs, 2H; ArCH$_2$O–C$H_2$-), 3.93 (dd, $^2J(H,H) = 12.8$ Hz, $^3J(H,H) = 2.0$ Hz, 1H; -CH_aH$_b$OH), 3.81 (s, 3H; CH_3OAr-), 3.67 (dd, $^2J(H,H) = 12.8$ Hz, $^3J(H,H) = 4.2$ Hz, 1H; -CH$_a$$H_b$OH), 3.48 (d, $^3J(H,H) = 1.9$ Hz, 1H; CH$_2$=C–C*H*-(OCH)-), 3.17 ppm (m, 1H; -(-CHO-)–C*H*–CH$_2$OH); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 159.3$, 141.2, 130.0, 129.4, 116.4, 113.8, 71.8, 69.2, 61.4, 59.6, 55.5, 55.3 ppm; IR (neat): $\tilde{\nu} = 3442$, 2995, 2958, 2936, 2855, 2840, 1614, 1516, 1465, 1251, 1087, 1037, 823 cm^{-1}; HRMS (MALDI-FTMS): *m*/*z* calcd for $C_{14}H_{18}O_4$ $[M+Na]^+$: 273.1097; found: 273.1090.

Imidazole (120 mg, 1.76 mmol), *tert*-butyldiphenylchlorosilane (352 mg, 1.28 mmol), and a catalytic amount of 4-dimethylaminopyridine (4-DMAP) were successively added to a solution of the above-mentioned epoxy alcohol (246.8 mg, 0.99 mmol) in anhydrous DMF (0.4 mL) at 0°C under argon. After 30 min of stirring, the reaction mixture was quenched with saturated ammonium chloride solution. EtOAc (25 mL) was added and the organic phase was separated. The aqueous phase was washed with EtOAc (2×20 mL) and the combined organic extracts were washed successively with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture was subjected to flash column chromatography (silica gel, hexanes/EtOAc 9:1) to afford pure allylic epoxide **22a** (455 mg, 95%). $R_f = 0.64$ (hexanes/EtOAc 8:2); $[\alpha]_D^{20} = +0.8$ ($c = 3.2$ in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.71$ (m, 4H; -SiAr*H*), 7.40 (m, 6H; -SiAr*H*), 7.25 (d, $^3J(H,H) = 8.6$ Hz, 2H; CH$_3$OAr*H*), 6.87 (d, $^3J(H,H) = 8.6$ Hz, 2H; CH$_3$OAr*H*), 5.33 (brs, 1H; -C=CH_aH$_b$), 5.28 (brs, 1H; -C=CH$_a$$H_b$), 4.46 (d, $^2J(H,H) = 11.2$ Hz, 1H; Ar–CH_aH$_b$O-), 4.40 (d, ^2J (H,H) = 11.2 Hz, 1H; Ar–CH$_a$$H_b$O-), 3.95 (brs, 2H; ArCH$_2$O–C$H_2$-), 3.88 (dd, $^2J(H,H) = 12.4$ Hz, $^3J(H,H) = 3.2$ Hz, 1H; -CH_aH$_b$OSi-), 3.80 (s, 3H; CH_3OAr-), 3.75 (dd, $^2J(H,H) = 12.4$ Hz, $^3J(H,H) = 3.9$ Hz, 1H; CH$_a$$H_b$OSi-), 3.39 (d, $^3J(H,H) = 2.0$ Hz, 1H; CH$_2$=C–C*H*–(OCH)-), 3.17 (m, 1H; -(-CHO-)–C*H*–CH$_2$OSi), 1.08 ppm (brs, 9H, -C(CH_3)$_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 159.2$, 141.7, 135.6, 135.5, 134.8, 130.1, 129.7, 129.6, 129.3, 127.7, 115.8, 113.8, 71.7, 69.2, 63.7, 59.8, 55.7, 55.2, 26.7, 26.5, 19.2 ppm; HRMS (MALDI-FTMS): *m*/*z* calcd for $C_{30}H_{36}O_4Si$ $[M+Na]^+$: 511.2275; found: 511.2264.

By using D-(−)-diisopropyltartrate, the same procedure was followed to prepare the antipode of **22a**, *ent*-**22a**.

Compounds 22b,c: Epoxidation of allylic alcohol **21b** (300 mg, 3.06 mmol), was performed as described for **21a**, in this case by using L-(+)-diisopropyltartrate (459 mg, 1.96 mmol), Ti(O*i*Pr)$_4$ (470 mg, 1.65 mmol), *t*BuOOH (5.5 M in decane, 1.1 mL, 6.12 mmol) and MS 4 Å (150 mg) in dry CH_2Cl_2 (5 mL). Epoxy alcohol obtained this way was isolated in pure form, as a pale yellow oil (280 mg, 80%, 95% *ee*). $R_f = 0.38$ (hexanes/EtOAc 6:4); $[\alpha]_D^{20} = -13.0$ ($c = 1.1$ in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 5.15$ (brs, 1H; -C=CH_aH$_b$), 5.04 (m, 1H; -C=CH$_a$$H_b$), 3.97 (d, $^2J(H,H) = 12.8$ Hz, 1H; -CH_aH$_b$OH), 3.69 (d, $^2J(H,H) = 12.8$ Hz, 1H;-CH$_a$$H_b$OH), 3.42 (d, $^3J(H,H) = 1.9$ Hz, 1H; CH$_2$=C–C*H*–(OCH)-), 3.15 (m, 1H; -(-CHO-)–C*H*–CH$_2$OH), 1.66 ppm (brs, 3H;

-(CH_3)C=CH_2); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 140.5, 114.9, 61.5, 57.8, 57.7, 16.7 ppm; IR (neat): $\tilde{\nu}$ = 3415, 2924, 2855, 1462, 1376, 1084, 906, 878 cm^{-1}.

For the silylation of the above epoxy alcohol (132 mg, 1.16 mmol) the same procedure as for the synthesis of **22b** was followed, in this case by using imidazole (142 mg, 2.09 mmol), *tert*-butyldiphenylchlorosilane (412 mg, 1.5 mmol) or *tert*-butyldimethylchlorosilane (233 mg, 1.5 mmol), and a catalytic amount of 4-DMAP in anhydrous DMF (0.2 mL) to isolate **22b** (368 mg, 90%) or **22c** (250 mg, 94%), respectively.

Data for 22b: Colorless liquid; R_f = 0.54 (hexanes/EtOAc 8:2); $[\alpha]_D^{20}$ = +1.9 (c = 1.6 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.70 (m, 4H; -SiArH), 7.40 (m, 6H; -SiArH), 5.12 (brs, 1H; -C=CH_aH$_b$), 5.01 (m, 1H; -C=CH$_a$$H_b$), 3.87 (dd, ^2J(H,H) = 11.9 Hz, ^3J(H,H) = 4.2 Hz, 1H; -CH_aH$_b$OSi), 3.78 (dd, ^2J(H,H) = 11.9 Hz, ^3J(H,H) = 5.2 Hz, 1H; -CH$_a$$H_b$OSi-), 3.29 (d, ^3J(H,H) = 1.9 Hz, 1H; CH$_2$=C(-)-CH-(OCH)-), 3.12 (m, 1H; -(-CHO-)-CH-CH$_2$OSi-), 1.64 (brs, 3H, CH$_2$=C(CH_3)-), 1.07 ppm (brs, 9H, -C(CH_3)$_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 141.0, 135.6, 135.5, 133.3, 133.2, 130.0, 129.8, 127.7, 114.5, 63.9, 58.2, 58.0, 29.7, 26.8, 19.3, 16.8 ppm; IR (neat): $\tilde{\nu}$ = 3075, 2963, 2931, 2859, 1477, 1468, 1431, 1116, 891, 742, 701, 510 cm^{-1}; HRMS (EI): m/z calcd for $C_{22}H_{28}O_2Si$ [M+Na]$^+$: 375.1751; found: 375.1759.

Data for 22c: Colorless liquid; R_f = 0.81 (hexanes/EtOAc 6:4); $[\alpha]_D^{20}$ = +0.5 (c = 1.2 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.13 (s, 1H; -C=CH_aH$_b$), 5.00 (brs, 1H; -C=CH$_a$$H_b$), 3.87 (dd, ^2J(H,H) = 11.9 Hz, ^3J(H,H) = 3.0 Hz, 1H; -CH_aH$_b$OSi-), 3.70 (dd, ^2J(H,H) = 11.9 Hz, ^3J(H,H) = 4.8 Hz, 1H; -CH$_a$$H_b$OSi-), 3.29 (d, ^3J(H,H) = 2.2 Hz, 1H; CH$_2$=C(CH$_3$)-CH-(OCH)-), 3.06 (m, 1H; -(-CHO-)-CH-CH$_2$OSi-), 1.64 (brs, 3H; -(CH_3)C=CH$_2$), 0.90 (brs, 9H; -SiC(CH_3)$_3$), 0.08 ppm (2s, 6H; -Si(CH_3)$_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 141.0, 114.0, 63.3, 58.2, 58.1, 25.9, 18.4, 16.8, 3.7 ppm; IR (neat): $\tilde{\nu}$ = 2960, 2930, 2861, 1766, 1481, 1463, 1259, 1147, 1116, 847, 785 cm^{-1}; HRMS (EI): m/z calcd for $C_{12}H_{24}O_2Si$ [M+Na]$^+$: 251.1438; found: 251.1444.

Compound 22d: (−)-(2*S*,3*S*)-2,3-Epoxypent-4-en-1-ol (100 mg, 1.0 mmol)[20c] was silylated, as described above in this case by using imidazole (122 mg, 1.8 mmol), *tert*-butyldimethylchlorosilane (196 mg, 1.3 mmol), and a catalytic amount of 4-DMAP in anhydrous DMF (0.2 mL) to isolate pure vinyl epoxide **22d** (204 mg, 60% for two steps) as a colorless liquid. R_f = 0.42 (hexanes/EtOAc 95:5); $[\alpha]_D^{20}$ = −12.0 (c = 4.5 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.57 (m, 1H; CH$_2$=CH-), 5.47 (dd, ^2J(H,H) = 1.9 Hz, ^3J(H,H) = 17.1 Hz, 1H; CH$_{cis}$$H_{trans}$=CH-), 5.27 (dd, ^2J(H,H) = 1.9 Hz, ^3J(H,H) = 10.1 Hz, 1H; CH_{cis}H$_{trans}$=CH-), 3.86 (dd, ^3J(H,H) = 3.0 Hz, ^2J(H,H) = 11.9 Hz, 1H; -CH_aH$_b$OSi-), 3.70 (dd, ^3J(H,H) = 4.5 Hz, ^2J(H,H) = 11.9 Hz, 1H; -CH$_a$$H_b$OSi-), 3.28 (dd, ^3J(H,H) = 1.9 Hz, ^3J(H,H) = 7.1 Hz, 1H; CH$_2$=CH-CH-(OCH)-), 3.00 (m, 1H; -(-CHO-)-CH-CH$_2$OSi), 0.90 (brs, 9H; -SiC(CH_3)$_3$), 0.07 ppm (s, 6H; -Si(CH_3)$_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 135.2, 119.5, 62.9, 60.2, 56.1, 25.8, 18.3, 3.7 ppm; IR (neat): $\tilde{\nu}$ = 2958, 2930, 2861, 1644, 1474, 1460, 1261, 1145, 1110, 839, 778, 665 cm^{-1}; HRMS (EI): m/z calcd for $C_{12}H_{24}O_2Si$ [M+Na]$^+$: 237.1282; found: 237.1278.

Representative procedure for coupling of tertiary alcohols 3 or 4 with allylic epoxides 22a–d: A solution of redistilled BF_3·OEt_2 (0.08–0.15 mmol) in dry dichloromethane (0.01–1 mL) was added to a mixture of alcohol (2.0–2.5 mmol) and epoxide (1 mmol) at 0°C under argon. The reaction was monitored by TLC. After 15–30 min at 0°C, the reaction was quenched with 5% solution of Et_3N in diethyl ether. The mixture was concentrated in vacuo and fitered through a short silica gel column to afford the corresponding diene and recovered alcohol.

Compound 23a: Coupling of alcohol **3** (40 mg, 0.22 mmol) with allylic epoxide **22a** (43 mg, 0.088 mmol) was performed as described above, by using BF_3·OEt_2 (1.5 μL, 0.012 mmol) in dry CH_2Cl_2 (9 μL), to afford after purification diene **23a** (34 mg, 56%) as pale yellow oil and recovered alcohol **3** (30 mg, 93%). R_f = 0.33 (hexanes/EtOAc 8:2); $[\alpha]_D^{20}$ = +1.6 (c = 0.4 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.69 (m, 4H; -SiArH), 7.40 (m, 6H; -SiArH), 7.26 (d, ^3J(H,H) = 8.2 Hz, 2H; CH$_3$OAr-H), 6.87 (d, ^3J(H,H) = 8.2 Hz, 2H; CH$_3$OAr-H), 5.81 (m, 1H; -CH=CH$_2$), 5.26 (brs, 1H; -C=CH_aH$_b$), 5.16 (brs, 1H; -C=CH$_a$$H_b$), 4.88 (dd, ^3J(H,H) = 17.0 Hz, ^2J(H,H) = 1.5 Hz, 1H; -CH=CH$_{cis}$$H_{trans}$), 4.76 (dd, ^3J(H,H) = 10.0 Hz, ^2J(H,H) = 1.5 Hz, 1H; -CH=CH_{cis}H$_{trans}$), 4.45 (brs, 2H; Ar-CH_2-O-), 4.30 (d, ^3J(H,H) = 4.8 Hz, 1H; -O-CH-CH(OH)-), 4.10 (d, ^2J(H,H) = 13.0 Hz, 1H; CH$_2$=C-CH_aH$_b$-O-), 3.97 (d, ^2J(H,H) = 13.0 Hz, 1H; CH$_2$=C-CH$_a$$H_b$-O-), 3.79 (s, 3H; C$H_3$O-Ar-CH$_2$-), 3.63 (m, 3H; -C$H$(OH)-C$H_2$O-Si-), 2.86 (d, ^3J(H,H) = 3.7 Hz, 1H; -CH(OH)-CH$_2$O-Si-), 2.31–1.90 (m, 2H; -CH_2-CH=CH$_2$), 1.80–1.11 (m, 7H; -(CH_2)$_3$-, -C(CH$_3$)$_2$-CH-), 1.57 (brs, 3H; -(CH_3)C-O-), 1.07 (brs, 9H; -Si-C(CH_3)$_3$), 0.90 (s, 3H; -C(CH_3)$_a$(CH$_3$)$_b$), 0.81 ppm (s, 3H; -C(CH$_3$)$_a$(CH_3)$_b$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 159.2, 145.9, 143.1, 133.4, 135.6, 134.8, 130.3, 129.6, 129.3, 127.7, 127.6, 115.1, 113.7, 112.3, 80.3, 74.2, 72.5, 72.3, 67.8, 64.5, 55.7, 55.2, 41.6, 38.9, 35.4, 33.3, 30.9, 26.7, 26.5, 21.4, 20.0, 18.6 ppm; IR (neat): $\tilde{\nu}$ = 3423, 2960, 2933, 2857, 1619, 1516, 1472, 1432, 1392, 1382, 1253, 1115, 825, 759, 742, 702 cm^{-1}; HRMS (MALDI-FTMS): m/z calcd for $C_{42}H_{58}O_5Si$ [M+Na]$^+$: 693.3946; found: 693.3951.

Compound 23b: Coupling of alcohol **3** (400 mg, 2.19 mmol) with allylic epoxide **22b** (309 mg, 0.88 mmol) was performed as described above, by using BF_3·OEt_2 (8.6 μL, 0.07 mmol) in dry CH_2Cl_2 (88 μL) to afford, after purification, diene **23b** (259 mg, 55%) as a colorless liquid and recovered alcohol **3** (295 mg, 95%). R_f = 0.6 (hexanes/EtOAc 9:1); $[\alpha]_D^{20}$ = +1.2 (c = 1.1 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.66 (m, 4H; -SiAr-H), 7.39 (m, 6H; -SiAr-H), 5.84 (m, 1H; -CH=CH$_2$), 4.90 (brs, 2H; -C(CH$_3$)=CH_2), 4.86 (d, ^3J(H,H) = 16.2 Hz, 1H; -CH=CH_{trans}H$_{cis}$), 4.76 (d, ^3J(H,H) = 10.0 Hz, 1H; -CH=CH$_{trans}$$H_{cis}$), 4.05 (d, ^3J(H,H) = 6.3 Hz, 1H; -O-CH-CH(OH)-), 3.80–3.54 (m, 3H; -CH(OH)-CH_2OSi-), 2.37 (d, ^3J(H,H) = 3.3 Hz, 1H; -CH(OH)-), 2.18 (m, 1H; -CH_aH$_b$-CH=CH$_2$), 1.98 (m, 1H; -CH$_a$$H_b$-CH=CH$_2$), 1.74 (brs, 3H; -(C$H_3$)C=CH$_2$)), 1.64–1.11 (m, 7H; -(CH_2)$_3$-, -C(CH$_3$)$_2$-CH-), 1.07 (brs, 9H; -SiC(CH_3)$_3$), 1.04 (s, 3H; -(CH_3)C-O-), 0.90 (s, 3H; -C(CH_3)$_a$(CH$_3$)$_b$), 0.81 ppm (s, 3H; -C(CH$_3$)$_a$(CH_3)$_b$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 146.2 , 143.0, 135.6, 133.4, 133.3, 129.6, 127.7, 112.3, 80.1, 74.1, 73.2, 64.7, 55.7, 41.7, 38.8, 35.4, 33.3, 30.9, 26.9, 21.4, 20.0, 19.2, 18.5 ppm; IR (neat): $\tilde{\nu}$ = 3576, 3078, 2939, 2863, 1476, 1461, 1429, 1115, 1067, 1052, 906, 761, 701, 507, 439 cm^{-1}; HRMS (MALDI-FTMS): m/z calcd for $C_{34}H_{50}O_3Si$ [M+Na]$^+$: 557.3421; found: 557.3438.

Compound 23c: Coupling of alcohol **3** (40 mg, 0.22 mmol) with allylic epoxide **22c** (20 mg, 0.09 mmol) was performed as described above, by using BF_3·OEt_2 (0.9 μL, 0.008 mmol) in dry CH_2Cl_2 (10 μL) to afford, after purification, diene **23c** (19 mg, 50%) as a colorless liquid and recovered alcohol **3** (29 mg, 92%). R_f = 0.32 (hexanes/EtOAc 9:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.92 (m, 1H; -CH=CH$_2$), 4.95 (d, ^3J(H,H) = 19.0 Hz, 1H; -CH=CH_{trans}H$_{cis}$), 4.84 (d, ^3J(H,H) = 10.0 Hz, 1H; -CH=CH$_{trans}$$H_{cis}$), 4.92 (brs, 1H; -C(CH$_3$)=C$H_aH_b$), 4.90 (brs, 1H; -C(CH$_3$)=CH$_a$$H_b$), 4.00 (d, ^3J(H,H) = 6.3 Hz, 1H; -O-CH-CH(OH)-), 3.69 (dd, ^3J(H,H) = 4.4 Hz, ^2J(H,H) = 10.0 Hz, 1H; -CH_aH$_b$-O-Si-), 3.60 (dd, ^3J(H,H) = 5.6 Hz, ^2J(H,H) = 10.0 Hz, 1H; -CH$_a$$H_b$-O-Si-), 3.53 (m, 1H; -C$H$(OH)-CH$_2$-OSi-), 2.32 (m, 1H; -C$H_aH_b$-CH=CH$_2$), 2.06 (m, 1H; -CH$_a$$H_b$-CH=CH$_2$), 1.77 (brs, 3H; -(C$H_3$)C=CH$_2$), 1.51–1.08 (m, 7H; -(C$H_2$)$_3$-, -C(CH$_3$)$_2$-C$H$-), 1.13 (s, 3H; -(C$H_3$)C-O-), 0.92 (s, 3H; -C(CH_3)$_a$(CH$_3$)$_b$), 0.90 (brs, 9H; -SiC(CH_3)$_3$), 0.84 (s, 3H; -C(CH$_3$)$_a$(CH_3)$_b$), 0.06 ppm (s, 6H; -Si(CH_3)$_2$); HRMS (MALDI-FTMS): calcd for $C_{24}H_{46}O_3Si$ [M+Na]$^+$: 433.3109; found: 433.3130.

Compound 23d: Coupling of alcohol **3** (40 mg, 0.22 mmol) with allylic epoxide **22d** (23.5 mg, 0.11 mmol) was performed as described above, by using BF_3·OEt_2 (1.1 μL, 0.009 mmol) in dry CH_2Cl_2 (11 μL) to afford, after purification, diene **23d** (26 mg, 60%) as a colorless liquid and recovered alcohol **3** (26 mg, 93%). R_f = 0.32 (hexanes/EtOAc 9:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.84 (m, 2H; -CH$_2$-CH=CH$_2$, -O-CH-CH=CH$_2$), 5.22 (d, ^3J(H,H) = 17.5 Hz, 1H; -CH$_2$-CH=CH_{trans}H$_{cis}$), 5.16 (d, ^3J(H,H) = 10.0 Hz, 1H, -O-CH-CH=CH$_{trans}$$H_{cis}$), 5.00 (d, ^3J(H,H) = 19.2 Hz, 1H; -O-CH-CH=CH_{trans}H$_{cis}$), 4.93 (d, ^3J(H,H) = 10.0 Hz, 1H; -CH$_2$-CH=CH$_{trans}$$H_{cis}$), 4.11 (dd, ^3J(H,H) = 4.5 Hz, ^3J(H,H) = 6.7 Hz, 1H; -O-CH-CH(OH)-), 3.65–3.54 (m, 3H; -CH(OH)-CH_2O-Si-), 2.04 (m, 2H; -CH_2-CH=CH$_2$), 1.81–1.20 (m, 7H; -(CH_2)$_3$-, -C(CH$_3$)$_2$-CH-), 1.25 (s, 3H; -(CH_3)C-O-), 1.13 (s, 3H; -C(CH_3)$_a$(CH$_3$)$_b$), 0.90 (brs, 9H; -SiC(CH_3)$_3$), 0.81 (s, 3H; -C(CH$_3$)$_a$(CH_3)$_b$), 0.07 ppm (s, 6H; -Si(CH_3)$_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 157.3, 139.0, 116.2, 114.2, 80.5, 74.8, 71.8, 63.5, 56.2, 41.3, 39.5, 35.3, 33.1, 32.5, 29.7, 26.2, 25.9, 21.5, 20.1, 18.7, 3.7, 1.0 ppm; HRMS (MALDI-FTMS): m/z calcd for $C_{23}H_{44}O_3Si$ [M+Na]$^+$: 419.2952; found: 419.2964.

Compound 24a: Coupling of alcohol **4** (431 mg, 1.65 mmol) with allylic epoxide **22a** (323 mg, 0.66 mmol) was performed as described above, by using BF_3·OEt_2 (12 μL, 0.093 mmol) in dry CH_2Cl_2 (67 μL) to afford, after purification, a mixture of diene **24a** with the starting bromoalcohol

4. Since complete separation of **24a** and **4** was impossible, the mixture of the two compounds was used in the next step, without futher purification. Thus, it was dissolved in THF (1 mL), cooled at 0°C, and TBAF (1 M solution in THF, 660 μL, 0.66 mmol) was added. Stirring was continued for 3 h. The reaction mixture was partitioned between a saturated ammonium chloride solution and ethyl acetate. After separation of the organic phase, the aqueous phase was washed with EtOAc (2×20 mL) and the combined organic extracts were washed successively with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture was subjected to flash column chromatography (silica gel, hexanes/EtOAc 6:4) to afford the pure desilylated form of diene **24a** (169 mg, 50% over two steps), as a yellow oil and recovered alcohol **4** (246 mg, 95%). R_f=0.25 (hexanes/EtOAc 6:4); $[\alpha]_D^{20}=-1.4$ (c=0.9 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.26 (d, ^3J(H,H)=8.6 Hz, 2H; Ar*H*), 6.89 (d, ^3J(H,H)=8.6 Hz, 2H; Ar*H*), 5.84 (m, 1H; -C*H*=CH$_2$), 5.32 (brs,1H; -C=C*H*$_a$H$_b$), 5.24 (brs, 1H; -C=CH$_a$*H*$_b$), 4.99 (dd, ^2J(H,H)= 1.5 Hz, ^3J(H,H)=17.4 Hz, 1H; -CH=C*H*$_{trans}$H$_{cis}$), 4.89 (dd, ^2J(H,H)= 1.5 Hz, ^3J(H,H)=10.2 Hz, 1H; -CH=CH$_{trans}$*H*$_{cis}$), 4.52 (d, ^2J(H,H)= 11.9 Hz, 1H; Ar−C*H*$_a$H$_b$O-), 4.45 (d, ^2J(H,H)=11.9 Hz, 1H; Ar−CH$_a$*H*$_b$O-), 4.13 (d, ^3J(H,H)=6.0 Hz, 1H; -*OCH*−CH(OH)-), 4.05 (d, ^2J(H,H)=11.5 Hz, 1H; CH$_2$=C−C*H*$_a$H$_b$OCH$_2$-), 3.92 (d, ^2J(H,H)= 11.5 Hz, 1H; CH$_2$=C−CH$_a$*H*$_b$OCH$_2$-), 3.86 (dd, ^3J(H,H)=4.9 Hz, ^3J(H,H)=12.8 Hz, 1H; -C*H*(Br)-), 3.81 (s, 3H; C*H*$_3$O-Ar), 3.70–3.50 (m, 3H; -C*H*(OH)−C*H*$_2$OH), 2.50–2.33 (m, 2H; -C*H*−CH=CH$_2$), 2.22–2.00 (m, 2H; -C*H*$_2$−CH(Br)-), 1.93 (ddd, ^2J(H,H)=13.4 Hz, ^3J(H,H)= 13.4 Hz, ^3J(H,H)=3.4 Hz, 1H; -C*H*$_{ax}$H$_{eq}$−C(CH$_3$)O), 1.71 (ddd, ^2J(H,H)=13.4 Hz, ^3J(H,H)=3.5 Hz, ^3J(H,H)=3.5 Hz, 1H; -CH$_{ax}$*H*$_{eq}$-C(CH$_3$)O-), 1.50 (m, 1H; -C(CH$_3$)$_2$−C*H*-), 1.18 (s, 3H; -(C*H*$_3$)C−O-), 1.07 (s, 3H; -C(C*H*$_3$)$_a$(CH$_3$)$_b$), 0.96 ppm (s, 3H; -C(CH$_3$)$_a$(C*H*$_3$)$_b$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=159.3, 146.0, 141.8, 129.4, 129.3, 117.8, 113.8, 113.4, 79.5, 73.1, 72.7, 69.7, 66.7, 62.9, 56.5, 55.2, 41.1, 39.4, 31.8, 31.7, 30.5, 18.0, 17.7 ppm; IR (neat): $\tilde{\nu}$=3425, 2955, 2933, 2876, 1615, 1514, 1465, 1386, 1250, 1084, 1042, 912, 821, 736, 703 cm^{-1}; HRMS (MALDI-FTMS): m/z calcd for $C_{26}H_{39}BrO_5$ $[M+Na]^+$: 533.1873; found: 533.1871.

Compound 24b: Coupling of alcohol **4** (230 mg, 0.88 mmol) with allylic epoxide **22b** (123 mg, 0.35 mmol) was performed as described for **23a**, by using $BF_3{\cdot}OEt_2$ (4.5 μL, 0.035 mmol) in dry CH_2Cl_2 (40 μL) to afford, after purification, diene **24b** (117 mg, 54%) as a pale yellow oil and recovered alcohol **4** (167 mg, 93%). R_f=0.42 (hexanes/EtOAc 9:1); $[\alpha]_D^{20}=+1.3$ (c=0.8 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.65 (m, 4H; -SiAr*H*), 7.39 (m, 6H; -SiAr*H*), 5.76 (m, 1H; -C*H*=CH$_2$), 4.91 (brs, 1H; -(CH$_3$)C=C*H*$_a$H$_b$), 4.90 (brs, 1H; -(CH$_3$)C=CH$_a$*H*$_b$), 4.88 (dd, ^2J(H,H)= 1.5 Hz, ^3J(H,H)=17.2 Hz, 1H; -CH=C*H*$_{trans}$H$_{cis}$), 4.79 (dd, ^2J(H,H)= 1.5 Hz, ^3J(H,H)=10.1 Hz, 1H; -CH=CH$_{trans}$*H*$_{cis}$), 4.00 (d, ^3J(H,H)= 6.2 Hz, 1H; -OC*H*−CH(OH)-), 3.91 (dd, ^3J(H,H)=4.5 Hz, ^3J(H,H)= 12.9 Hz, 1H; -C*H*(Br)-), 3.80–3.60 (m, 2H; -C*H*$_2$−OSi-), 3.57 (m, 1H; -C*H*(OH)−CH$_2$−OSi-), 2.35–2.00 (m, 5H; -CH(O*H*)-, -C*H*$_2$−CHBr, -C*H*$_2$−CH=CH$_2$), 1.92 (ddd, ^2J(H,H)=13.2 Hz, ^3J(H,H)=13.2 Hz, ^3J(H,H)=3.5 Hz, 1H; -C*H*$_{ax}$H$_{eq}$−C(CH$_3$)O-), 1.76 (ddd, ^2J(H,H)= 13.2 Hz, ^3J(H,H)=3.8 Hz, ^3J(H,H)=3.8 Hz, 1H; -CH$_{ax}$*H*$_{eq}$−C(CH$_3$)O-), 1.72 (brs, 3H, -C=C(C*H*$_3$)-), 1.51 (m, 1H; -C(CH$_3$)$_2$−C*H*-), 1.25 (s, 3H; -(C*H*$_3$)C−O-), 1.08 (s, 3H; -C(C*H*$_3$)$_a$(CH$_3$)$_b$), 1.07 (brs, 9H, -C(C*H*$_3$)$_3$), 0.93 ppm (s, 3H; -C(CH$_3$)$_a$(C*H*$_3$)$_b$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ= 146.0, 141.9, 135.6, 135.5, 129.7, 127.7, 113.8, 113.1, 79.0, 74.4, 72.8, 67.0, 64.6, 56.4, 41.1, 39.4, 31.8,31.7, 30.6, 26.9, 18.4, 18.1, 17.8 ppm; IR (neat): $\tilde{\nu}$=3573, 3071, 2958, 2931, 2859, 1475, 1464, 1427, 1392, 1116, 1078, 1055, 908, 763, 741, 701, 616 cm^{-1}; HRMS (MALDI-FTMS): m/z calcd for $C_{34}H_{49}BrO_3Si$ $[M+Na]^+$: 635.2526; found: 635.2511.

Representative procedure for oxepene ring formation through ring-closing metathesis: Second-generation Grubbs catalyst (**B** in Scheme 5; 1.7 mg, 0.002 mmol) was added to a solution of diene **23a** (8.5 mg, 0.013 mmol) in CH_2Cl_2 (2.2 mL) at 25°C under argon. The mixture was stirred at 35°C for 1 h. After cooling at 25°C, the reaction was stirred in air for 16 h and concentrated in vacuo. Purification by flash column chromatography silica gel, hexanes/EtOAc 8:2) yielded oxepene **25a** (7 mg, 78%) as a pale yellow oil. R_f=0.21 (hexanes/EtOAc 8:2); ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.69 (m, 4H; -Si−Ar*H*), 7.39 (m, 6H; -Si−Ar*H*), 7.24 (d, ^3J(H,H)=8.6 Hz, 2H; CH$_3$OAr*H*), 6.86 (d, ^3J(H,H)=8.6 Hz, 2H; CH$_3$OAr*H*), 5.77 (d, ^3J(H,H)=7.8 Hz, 1H; -C*H*=C-), 4.50 (brs, 1H; -O−C*H*−CH(OH)-), 4.35 (brs, 2H; -CH$_2$−O−C*H*$_2$−Ar), 4.07 (m, 3H; -CH=C−C*H*$_2$−O-, -C*H*(OH)-), 3.87–3.72 (m, brs, 4H; C*H*$_3$OAr−CH$_2$-, -C*H*$_a$H$_b$O−Si-), 3.65 (dd, ^3J(H,H)=7.4 Hz, ^2J(H,H)=11.2 Hz, 1H; -CH$_a$*H*$_b$O-Si-), 2.63 (d, ^3J(H,H)=7.6 Hz, 1H; -CH(O*H*)-), 2.23 (m, 1H; -C*H*$_a$H$_b$−CH=C-), 2.01 (m, 1H; -CH$_a$*H*$_b$−CH=C-), 1.71 (d, ^3J(H,H)= 10.0 Hz, 1H; -C(CH$_3$)$_2$−C*H*-), 1.14–1.16 (m, 6H; -(C*H*$_2$)$_3$-), 1.12 (s, 3H; -(C*H*$_3$)C−O-), 1.04 (brs, 9H; -SiC(C*H*$_3$)$_3$), 0.91 (s, 3H; -C(C*H*$_3$)$_{eq}$(CH$_3$)$_{ax}$), 0.76 ppm (s, 3H; -C(CH$_3$)$_{eq}$(C*H*$_3$)$_{ax}$); IR (neat): $\tilde{\nu}$=2963, 2931, 2859, 1517, 1465, 1431, 1263, 1249, 1111, 1075, 1039, 821, 806, 705 cm^{-1}; HRMS (MALDI-FTMS): m/z calcd for $C_{40}H_{54}O_5Si$ $[M+Na]^+$: 665.3633; found: 665.3640.

Compound 25b: Ring-closing metathesis of diene **23b** (400 mg, 0.75 mmol) was performed as described above, in this case by using second-generation Grubbs catalyst (**B** in Scheme 5; 64 mg, 0.075 mmol) in CH_2Cl_2 (115 mL) to afford, after purification, oxepene **25b** (354 mg, 93%) as a colorless oil. R_f=0.5 (hexanes/EtOAc 9:1); $[\alpha]_D^{20}=-5.0$ (c= 0.1 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.72 (m, 4H; -Si−Ar−*H*), 7.30 (m, 6H; -Si−Ar−*H*), 5.46 (d, ^3J(H,H)=8.2 Hz, 1H; -C*H*=C(CH$_3$)-), 4.35 (brs, 1H; -O−C*H*−CH(OH)-), 3.95 (m, 1H; -C*H*(OH)−CH$_2$−O−Si-), 3.79 (dd, ^2J(H,H)=10.8 Hz, ^3J(H,H)=3.7 Hz, 1H; -CH(OH)−C*H*$_a$H$_b$−OSi-), 3.68 (dd, ^2J(H,H)=10.8 Hz, ^3J(H,H)=7.8 Hz, 1H; -CH(OH)−CH$_a$*H*$_b$−OSi-), 2.46 (d, ^3J(H,H)=7.8 Hz, 1H; -CH(O*H*)−CH$_2$OSi-), 2.15 (m, 1H; -C*H*$_a$H$_b$−CH=C(CH$_3$)-), 1.91 (dd, ^2J(H,H)=17.1 Hz, ^3J(H,H)= 8.2 Hz, 1H; -CH$_a$*H*$_b$−CH=C(CH$_3$)-), 1.64 (d, ^3J(H,H)=10.0 Hz, 1H; -C(CH$_3$)$_2$−C*H*-), 1.55 (brs, 3H; -CH=C(C*H*$_3$)-), 1.66–1.14 (m, 6H; -(C*H*$_2$)$_3$-), 1.12 (s, 3H; -(C*H*$_3$)C−O-), 1.07 (s, 9H; -SiC(C*H*$_3$)$_3$), 0.91 (s, 3H; -C(C*H*$_3$)$_{eq}$(CH$_3$)$_{ax}$), 0.76 ppm (s, 3H; -C(CH$_3$)$_{eq}$(C*H*$_3$)$_{ax}$): ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=136.3, 135.7, 133.6, 129.6, 129.5, 129.1, 127.6, 127.5, 78.3, 72.8, 72.4, 65.1, 52.8, 40.8, 36.1, 35.1, 33.0, 26.8, 24.3, 22.1, 20.9, 20.8, 19.2 ppm; IR (neat): $\tilde{\nu}$=3654, 2963, 2933, 2856, 1476, 1465, 1426, 1113, 1079, 705, 506, 487 cm^{-1}; HRMS (MALDI-FTMS): m/z calcd for $C_{32}H_{46}O_3Si$ $[M+Na]^+$: 529.3108; found: 529.3111.

Compound 25c: Ring-closing metathesis of diene **23c** (62.5 mg, 0.152 mmol) was performed as described for **23a**, in this case by using second-generation Grubbs catalyst (**B** in Scheme 5; 13 mg, 0.015 mmol) in CH_2Cl_2 (25 mL) to afford, after purification, oxepene **25c** (51 mg, 88%) as a colorless oil. R_f=0.28 (hexanes/EtOAc 9:1); $[\alpha]_D^{20}=-2.3$ (c= 0.4 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.52 (d, ^3J(H,H)=7.8 Hz, 1H; -C*H*=C(CH$_3$)-), 4.34 (brs, 1H; -O−C*H*−CH(OH)-), 3.85 (m, 1H; -C*H*(OH)−CH$_2$O−Si-), 3.74 (dd, ^2J(H,H)=10.5 Hz, ^3J(H,H)=3.0 Hz, 1H; -C*H*$_a$H$_b$−O−Si-), 3.58 (dd, ^2J(H,H)=10.5 Hz, ^3J(H,H)=7.8 Hz, 1H; -CH$_a$*H*$_b$−O−Si-), 2.45 (d, ^3J(H,H)=7.1 Hz, 1H; -CH(O*H*)−CH$_2$−O−Si-), 2.20 (m, 1H; -C*H*$_a$H$_b$−CH=C(CH$_3$)-), 1.94 (dd, ^2J(H,H)=17.2 Hz, ^3J(H,H)=7.8 Hz, 1H; -CH$_a$*H*$_b$−CH=C(CH$_3$)-), 1.74 (brs, 3H; -CH=C(C*H*$_3$)-), 1.69 (d, ^3J(H,H)=10.0 Hz, 1H; -C(CH$_3$)$_2$−C*H*-), 1.65–1.05 (m, 6H; -(C*H*$_2$)$_3$-), 1.19 (s, 3H; -(C*H*$_3$)C−O-), 0.93 (s, 3H; -C(C*H*$_{3eq}$)(CH$_{3ax}$)), 0.90 (brs, 9H; -SiC(C*H*$_3$)$_3$), 0.77 (s, 3H; -C(CH$_3$)$_{eq}$(C*H*$_3$)$_{ax}$), 0.07 ppm (brs, 6H; -Si(C*H*$_3$)$_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=136.7, 129.2, 78.4, 72.6, 72.5, 64.6, 52.6, 40.9, 36.3, 35.1, 33.0, 25.9, 24.5, 22.2, 21.1, 21.0, 20.9, 3.7, 3.6 ppm; IR (neat): $\tilde{\nu}$=3658, 2954, 2929, 2855, 1463, 1257, 1107, 1078, 840, 779 cm^{-1}; HRMS (MALDI-FTMS): m/z calcd for $C_{22}H_{42}O_3Si$ $[M+Na]^+$: 405.2795; found: 405.2785.

Compound 25d: Ring-closing metathesis of diene **23d** (22 mg, 0.055 mmol) was performed as described for **23a**, in this case by using first-generation Grubbs catalyst (**A** in Scheme 5;6.4 mg, 0.008 mmol) in CH_2Cl_2 (9 mL) at 25°C for 1 h to afford, after purification, oxepene **25d** (17 mg, 88%) as a colorless liquid. R_f=0.27 (hexane/EtOAc 9:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.84 (m, 2H; -CH$_2$−C*H*=C*H*-), 4.26 (brs, 1H; -O−C*H*−CH(OH)-), 3.76 (dd, ^3J(H,H)=3.7 Hz, ^2J(H,H)= 10.0 Hz, 1H; -C*H*$_a$H$_b$−O−Si-), 3.67 (dd, ^3J(H,H)=5.2 Hz, ^2J(H,H)= 10.0 Hz, 1H; -CH$_a$*H*$_b$−O−Si-), 3.47 (m, 1H; -C*H*(OH)-), 2.46 (d, ^3J(H,H)=6.3 Hz, 1H; -CH(O*H*)-), 2.33–2.04 (m, 2H; -CH$_2$−CH=CH-), 1.84 (d, ^3J(H,H)=10.0 Hz, 1H; -C(CH$_3$)$_2$−C*H*-), 1.70–1.12 (m, 6H; -(C*H*$_2$)$_3$-), 1.21 (s, 3H; -(C*H*$_3$)C−O-), 0.95 (s, 3H; -C(C*H*$_3$)$_{eq}$(CH$_3$)$_{ax}$), 0.91 (brs, 9H; -SiC(C*H*$_3$)$_3$), 0.80 (s, 3H; -C(CH$_3$)$_{eq}$(C*H*$_3$)$_{ax}$), 0.08 ppm (brs, 6H; -Si(C*H*$_3$)$_2$); HRMS (MALDI-FTMS): m/z calcd for $C_{21}H_{40}O_3Si$ $[M+Na]^+$: 391.2639; found: 391.2632.

Compound 26a: Ring-closing metathesis of the desilylated form of diene **24a** (67 mg, 0.131 mmol) was performed as described for **23a**, in this case by using the second-generation Grubbs catalyst (**B** in Scheme 5; 17 mg, 0.020 mmol) in CH_2Cl_2 (21 mL) to afford, after purification, oxepene **26a** (51 mg, 80%) as a pale yellow oil. R_f=0.2 (hexanes/EtOAc 6:4); $[\alpha]_D^{20}=$

−3.7 (c=1.2 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.23 (d, ^3J(H,H)=8.6 Hz, 2H; Ar*H*), 6.88 (d, ^3J(H,H)=8.6 Hz, 2H; Ar*H*), 5.88 (d, ^3J(H,H)=8.2 Hz, 1H; -C=C*H*-), 4.52 (brs, 1H; -O-C*H*-), 4.39 (s, 2H; ArCH_2-O-), 4.06 (d, ^2J(H,H)=11.2 Hz, 1H; -CH_aH$_b$OPMB), 3.87 (dd, ^3J(H,H)=4.9 Hz, ^3J(H,H)=12.9 Hz, 1H; -C*H*(Br)-), 3.84 (d, ^2J(H,H)=11.2 Hz, 1H; -CH_aH$_b$OPMB), 3.81 (s, 3H; CH_3O-Ar), 3.73–3.60 (m, 2H; -C*H*(OH)-CH_aH$_b$OH), 3.53 (d, ^2J(H,H)=8.2 Hz, 1H; -CH$_a$H$_b$OH), 2.58 (brs, 1H; -CH(O*H*)-), 2.39–2.22 (m, 2H, -CH_2CH=C-), 2.20–1.98 (m, 2H; -CH_2CH(Br)-), 1.84 (ddd, ^2J(H,H)=13.4 Hz, ^3J(H,H)=13.4 Hz, ^3J(H,H)=3.5 Hz, 1H; -CH_{ax}H$_{eq}$−C(CH$_3$)O-), 1.81 (d, ^3J(H,H)=9.7 Hz, 1H; -C(CH$_3$)$_2$−C*H*-), 1.50 (ddd, ^2J(H,H)=13.4 Hz, ^3J(H,H)=3.4 Hz, ^3J(H,H)=3.4 Hz, 1H; -CH$_{ax}$H$_{eq}$−C(CH$_3$)O-), 1.26 (s, 3H; -C(CH_3)−O-), 1.12 (s, 3H; -C(CH_3)$_{eq}$(CH$_3$)$_{ax}$), 0.89 ppm (s, 3H; -C(CH$_3$)$_{eq}$(CH_3)$_{ax}$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=159.4, 137.1, 135.2, 129.6, 129.4, 113.9, 78.1, 74.0, 73.2, 71.9, 70.2, 65.5, 64.0, 55.3, 52.0, 40.7, 36.5, 32.7, 30.5, 25.7, 22.2, 18.0 ppm; IR (neat): $\tilde{\nu}$=3409, 2937, 2875, 1614, 1520, 1457, 1390, 1374, 1251, 1174, 1155, 1063, 1040, 872, 822 cm^{-1}; HRMS (MALDI-FTMS): m/z calcd for $C_{24}H_{35}BrO_5$ $[M+Na]^+$: 505.1560; found: 505.1588.

Compound 26b: Ring-closing metathesis of diene **24b** (130 mg, 0.212 mmol) was performed as described for **23a**, in this case by using the second-generation Grubbs catalyst (**B** in Scheme 5; 27 mg, 0.030 mmol) in CH_2Cl_2 (35 mL) to afford, after purification, silylated oxepene (112 mg, 90%) as a pale yellow oil. TBAF (1M solution in THF, 0.11 mL, 0.11 mmol) was added to a solution of the silylated oxepene (55.6 mg, 0.095 mmol) in THF (0.16 mL) at 25°C. After 2 h of stirring, the reaction mixture was partitioned between a saturated ammonium chloride solution and ethyl acetate. The organic phase was separated, the aqueous phase was washed with EtOAc (2×10 mL), and the combined organic extracts were washed successively with water and brine, dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography on the crude mixture (hexanes/EtOAc 7:3) afforded pure **26b** (29.7 mg, 90%), as a pale yellow oil. R_f=0.65 (hexanes/EtOAc 6:4); $[\alpha]_D^{20}$=+3.5 (c=1.2 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.61 (d, ^3J(H,H)=8.1 Hz, 1H; -C=C*H*-), 4.50 (brs, 1H; -O−C*H*−CH(OH)-), 3.95–3.72 (m, 3H; -C*H*(Br)-, -CH_2OH), 3.61 (ddd, ^3J(H,H)=3.9 Hz, ^3J(H,H)=10.2 Hz, ^3J(H,H)=10.5 Hz, 1H; -C*H*(OH)-), 2.73 (d, ^3J(H,H)=10.3 Hz, 1H; -CH(O*H*)-), 2.59 (d, ^3J(H,H)=10.4 Hz, 1H; -CH$_2$O*H*), 2.39–2.22 (m, 2H; -CH_aH$_b$CH=C-, -CH_aH$_b$CH(Br)-), 2.21–1.94 (m, 2H; -CH$_a$H$_b$CH=C-, CH$_a$H$_b$CH(Br)-), 1.85 (ddd, ^2J(H,H)=12.9 Hz, ^3J(H,H)=12.9 Hz, ^3J(H,H)=4.3 Hz, 1H; -CH_{ax}H$_{eq}$-C(CH$_3$)O-), 1.72 (d, ^3J(H,H)=10.2 Hz, 1H; -C(CH$_3$)$_2$-C*H*-), 1.62 (brs, 3H; -CH=C-CH_3), 1.49 (ddd, ^2J(H,H)=12.9 Hz, ^3J(H,H)=3.4 Hz, ^3J(H,H)=3.4 Hz, 1H; -CH$_{ax}$H$_{eq}$−C(CH$_3$)O-), 1.27 (s, 3H; -C(CH_3)−O-), 1.11 (s, 3H; -C(CH_3)$_{eq}$(CH$_3$)$_{ax}$), 0.89 ppm (s, 3H; -C(CH$_3$)$_{eq}$(CH_3)$_{ax}$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=135.1, 129.9, 78.1, 76.1, 70.1, 65.7, 63.3, 53.3, 40.7, 36.4, 32.7, 30.6, 25.3, 22.5, 20.8, 18.1 ppm; IR (neat): $\tilde{\nu}$=3397, 2972, 2947, 2923, 2874, 1464, 1456, 1386, 1377, 1151, 1056, 1030, 768, 703, 692 cm^{-1}; HRMS (MALDI-FTMS): m/z calcd for $C_{16}H_{27}BrO_3$ $[M+Na]^+$: 369.1036; found: 369.1038.

Compound *epi*-**26a**: Ring-closing metathesis of *epi*-**24a** (14 mg, 0.027 mmol), prepared from alcohol **4** and *ent*-**22a** (see procedure for **24a**), was performed according to the procedure described for **26a**, in this case by using the second-generation Grubbs catalyst (**B** in Scheme 5; 3.4 mg, 0.004 mmol) in CH_2Cl_2 (4.5 mL) to afford, after purification, oxepene *epi*-**26a** (10 mg, 76%) as a yellow oil. R_f=0.11 (hexanes/EtOAc 7:3); $[\alpha]_D^{20}$=+52.0 (c=0.2 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.24 (d, ^3J(H,H)=8.6 Hz, 2H; Ar*H*), 6.88 (d, ^3J(H,H)=8.6 Hz, 2H; Ar*H*), 6.07 (t, ^3J(H,H)=6.3 Hz, 1H; -C*H*=C-), 4.51 (brs, 1H; -O−C*H*−CH(OH)-), 4.46 (d, ^2J(H,H)=11.2 Hz, 1H; -O−CH_aH$_b$−Ar), 4.38 (d, ^2J(H,H)=11.2 Hz, 1H; -O−CH$_a$H$_b$−Ar), 4.25 (d, ^2J(H,H)=11.5 Hz, 1H; -CH=C−CH_aH$_b$−O-), 3.86 (m, 1H; -C*H*(OH)-), 3.94 (dd, ^3J(H,H)=4.8 Hz, ^3J(H,H)=11.9 Hz, 1H; -C*H*(Br)-), 3.84 (d, ^2J(H,H)=11.5 Hz, 1H; -CH=C−CH$_a$H$_b$−O-), 3.80 (s, 3H; CH_3O−Ar-), 3.69 (m, 2H; -CH_2OH), 2.59–1.93 (m, 4H; -CH_2−CH=C-, -CH_2−CH(Br)-), 1.69 (ddd, ^2J(H,H)=13.0 Hz, ^3J(H,H)=3.7 Hz, ^3J(H,H)=3.7 Hz, 1H; -CH$_{ax}$H$_{eq}$−C(CH$_3$)O-), 1.59 (m, 1H; -C(CH$_3$)$_2$−C*H*-), 1.51 (ddd, ^2J(H,H)=13.0 Hz, ^3J(H,H)=13.0 Hz, ^3J(H,H)=3.4 Hz, 1H; -CH$_{ax}$H$_{eq}$−C(CH$_3$)O-), 1.38 (s, 3H; -(CH_3)C−O-), 1.11 (s, 3H; -C(CH_3)$_{eq}$(CH$_3$)$_{ax}$), 0.89 ppm (s, 3H; -C(CH$_3$)$_{eq}$(CH_3)$_{ax}$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=139.2, 137.2, 129.7, 129.0, 114.0, 79.3, 73.5, 72.6, 71.8, 70.3, 66.5, 64.3, 55.3, 54.4, 42.5, 40.2, 32.1, 30.0, 26.0, 18.9, 17.3 ppm; IR (neat): $\tilde{\nu}$=3374, 2959, 2926, 2857, 2121, 1612, 1514, 1464, 1249, 1078, 1038, 756 cm^{-1}; HRMS (MALDI-FTMS): m/z calcd for $C_{24}H_{35}BrO_5$ $[M+Na]^+$: 505.1560; found: 505.1564.

Synthesis of alcohols 27a and 27b:

Compound 27a: $NaIO_4$ (24 mg, 0.112 mmol) was added to a solution of diol **26a** (9 mg, 0.019 mmol) in a mixture of MeOH/H_2O 2:1 (1.5 mL) at 25°C. After 20 min of stirring the reaction mixture was cooled at 0°C and $NaBH_4$ (10 mg, 0.3 mmol) was added. Stirring was continued for 1 h. A saturated aqueous solution of NH_4Cl (5 mL) was then added and the mixture was extracted with EtOAc (2×5 mL). The combined organic extracts were washed successively with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Flash column chromatography of the crude mixture (silica gel, hexanes/EtOAc 7:3) afforded pure alcohol **27a** (6.5 mg, 75%) as a pale yellow oil. R_f=0.46 (hexanes/EtOAc 6:4); $[\alpha]_D^{20}$=−1.4 (c=2.0 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.24 (d, ^3J(H,H)=8.6 Hz, 2H; Ar*H*), 6.87 (d, ^3J(H,H)=8.6 Hz, 2H; Ar*H*), 5.85 (d, ^3J(H,H)=7.9 Hz, 1H; -C=C*H*-), 4.43 (brs, 1H; -O−C*H*−CH$_2$OH), 4.39 (s, 2H; ArCH_2−O-), 3.97 (d, ^2J(H,H)=11.2 Hz, 1H; -CH_aH$_b$O-CH$_2$OPMB), 3.88 (dd, ^3J(H,H)=4.8 Hz, ^3J(H,H)=12.5 Hz, 1H; -C*H*(Br)-), 3.80 (brs, m, 4H; CH_3OAr, -CH$_a$H$_b$OH), 3.76 (d, ^2J(H,H)=11.2 Hz, 1H; -CH$_a$H$_b$OCH$_2$OPMB), 3.62 (dd, ^2J(H,H)=10.9 Hz, ^3J(H,H)=6.8 Hz, 1H; -CH$_a$H$_b$OH), 2.27–2.01 (m, 2H; -CH_2CH=C-), 2.45–2.28 (m, 2H; -CH_2CH(Br)-), 1.79 (ddd, ^2J(H,H)=13.2 Hz, ^3J(H,H)=13.2 Hz, ^3J(H,H)=3.8 Hz, 1H; -CH_{ax}H$_{eq}$−C(CH$_3$)O-), 1.87 (d, ^3J(H,H)=9.7 Hz, 1H; C(CH$_3$)$_2$-C*H*-), 1.50 (ddd, ^2J(H,H)=13.2 Hz, ^3J(H,H)=3.4 Hz, ^3J(H,H)=3.4 Hz, 1H; -CH$_{ax}$H$_{eq}$-C(CH$_3$)O-), 1.29 (s, 3H; -C(CH_3)-O-), 1.12 (s, 3H; -C(CH_3)$_{eq}$(CH$_3$)$_{ax}$), 0.90 ppm (s, 3H; -C(CH$_3$)$_{eq}$(CH_3)$_{ax}$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=159.3, 137.3, 133.8, 129.9, 129.5, 113.8, 77.6, 72.8, 72.0, 70.1, 65.8, 63.4, 55.2, 52.1, 40.7, 36.8, 32.7, 30.5, 25.8, 22.1, 18.0 ppm; IR (neat): $\tilde{\nu}$=3464, 2952, 2926, 2855, 1612, 1515, 1464, 1249, 1174, 1152, 1065, 1036, 821, 759, 701 cm^{-1}; HRMS (MALDI-FTMS): m/z calcd for $C_{23}H_{33}BrO_4$ $[M+Na]^+$: 475.1454; found: 475.1458.

Compound 27b: The above procedure was followed with diol **26b** (11.7 mg, 0.034 mmol), $NaIO_4$ (43.2 mg, 0.202 mmol), $NaBH_4$ (15.5 mg, 0.408 mmol), in MeOH (1.8 mL) and H_2O (0.9 mL). Alcohol **27b** was isolated as pale yellow oil (9.7 mg, 90%). R_f=0.65 (hexanes/EtOAc 6:4); $[\alpha]_D^{20}$=−0.8 (c=1.0 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.56 (d, ^3J(H,H)=8.2 Hz, 1H; -C=C*H*-), 4.36 (brs, 1H; -O−C*H*−CH$_2$OH), 3.91 (dd, ^3J(H,H)=4.8 Hz, ^3J(H,H)=12.7 Hz, 1H; -C*H*(Br)-), 3.72 (m, 1H; -CH_aH$_b$OH), 3.52 (dd, ^2J(H,H)=11.2 Hz, ^3J(H,H)=8.8 Hz, 1H; -CH$_a$H$_b$-OH), 2.40–2.19 (m, 2H; -CH_2CH(Br)-), 2.19–2.00 (m, 2H; -CH_2CH=C-), 1.85 (d, ^3J(H,H)=10.0 Hz, 1H; -C(CH$_3$)$_2$−C*H*-), 1.82 (ddd, ^2J(H,H)=13.2 Hz, ^3J(H,H)=13.2 Hz, ^3J(H,H)=5.2 Hz, 1H; -CH_{ax}H$_{eq}$−C(CH$_3$)O-), 1.61 (brs, 3H; -CH=C(CH_3)-), 1.51 (ddd, ^2J(H,H)=13.2 Hz, ^3J(H,H)=3.5 Hz, ^3J(H,H)=3.5 Hz, 1H; -CH$_{ax}$H$_{eq}$−C(CH$_3$)O-), 1.31 (s, 3H; -C(CH_3)−O-), 1.13 (s, 3H; -C(CH_3)$_{eq}$(CH$_3$)$_{ax}$), 0.91 ppm (s, 3H; -C(CH$_3$)$_{eq}$(CH_3)$_{ax}$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=135.8, 128.6, 77.7, 71.3, 66.1, 63.5, 52.7, 40.7, 37.0, 32.8, 30.6, 25.8, 22.2, 19.9, 18.0 ppm; IR (neat): $\tilde{\nu}$=3476, 2977, 2947, 2871, 1468, 1453, 1384, 1225, 1154, 1064, 1030, 965, 871, 770, 703, 627, 582 cm^{-1}; HRMS (MALDI-FTMS): m/z calcd for $C_{15}H_{25}BrO_2$ $[M+Na]^+$: 339.0930; found: 339.0942.

Synthesis of (+)-Palisadin B (28): Pyridine (3.5 μL, 0.044 mmol) and TsCl (7.1 mg, 0.037 mmol) were added to a solution of alcohol **27b** (9.1 mg, 0.029 mmol) in dry CH_2Cl_2 (0.1 mL) at 25°C under argon. After 12 h of stirring, a saturated ammonium chloride solution (5 mL) was added. The reaction was extracted with ethyl acetate (2×5 mL) and the combined organic extracts were washed successively with water and brine dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography of the crude mixture (silica gel, hexanes/EtOAc 8:2) afforded the pure tosylated form of alcohol **27b** (12.3 mg, 90%) as a pale yellow oil. R_f=0.4 (hexanes/EtOAc 8:2); $[\alpha]_D^{20}$=+40.4 (c=1.1 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.79 (d, ^3J(H,H)=8.4 Hz, 2H; Ar*H*), 7.33 (d, ^3J(H,H)=8.4 Hz, 2H; Ar*H*), 5.53 (d, ^3J(H,H)=7.8 Hz, 1H; -C=C*H*-), 4.51 (brs, 1H; -O−C*H*−CH$_2$OTs), 4.28 (dd, ^2J(H,H)=10.4 Hz, ^3J(H,H)=3.0 Hz, 1H; -CH_aH$_b$−OTs-), 3.92 (dd, ^2J(H,H)=10.4 Hz, ^3J(H,H)=8.6 Hz, 1H; -CH$_a$H$_b$OTs-) 3.86 (dd, ^3J(H,H)=5.2 Hz, ^3J(H,H)=12.9 Hz, 1H; -C*H*(Br)-), 2.44 (s, 3H; CH_3−Ar-), 2.31–2.15 (m, 2H; -CH_2CH(Br)-), 2.15–1.97 (m, 2H; -CH_2CH=C-), 1.75 (d, ^3J (H,H)=9.6 Hz, 1H; -C(CH$_3$)$_2$−C*H*-), 1.69 (ddd, ^2J (H,H)=12.9 Hz, ^3J(H,H)=12.9 Hz, ^3J(H,H)=4.8 Hz, 1H; -CH_{ax}H$_{eq}$−C(CH$_3$)O-), 1.59 (brs, 3H; -CH=C(CH_3)-), 1.44 (ddd, ^2J(H,H)=12.9 Hz, ^3J(H,H)=3.5 Hz, ^3J(H,H)=

3.5 Hz, 1H; -$CH_{ax}H_{eq}$–$C(CH_3)$O-), 1.16 (s, 3H; -$C(CH_3)$–O-), 1.10 (s, 3H; -$C(CH_3)_{eq}(CH_3)_{ax}$), 0.87 ppm (s, 3H; -$C(CH_3)_{eq}(CH_3)_{ax}$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 144.7, 134.5, 130.0, 129.7, 129.6, 128.0, 77.6, 71.2, 68.6, 66.1, 52.3, 40.7, 36.4, 32.8, 30.6, 25.9, 21.8, 21.6, 20.5, 17.9 ppm; IR (neat): $\tilde{\nu}$ = 2953, 2918, 2849, 1599, 1454, 1445, 1362, 1189, 1176, 1151, 1098, 1085, 984, 759, 669, 555, 571 cm^{-1}; HRMS (MALDI-FTMS): *m*/*z* calcd for $C_{22}H_{31}BrO_4S$ $[M+Na]^+$: 493.1018; found: 493.1031.

The above tosylated alcohol (11.0 mg, 0.023 mmol), was dissolved in HMPA (70 μL), and LiBr (10 mg, 0.12 mmol), was added. The reaction mixture was stirred at 40 °C, under argon, for 16 h. A saturated aqueous solution of sodium bicarbonate (10 mL) was added to the warm solution and the mixture was extracted with ethyl acetate (2×10 mL). The combined organic extracts were washed successively with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Subjection of the crude mixture to flash column chromatography (silica gel, hexanes/EtOAc 95:5) afforded pure (+)-Palisadin B (**28**) as a pale yellow oil (6.5 mg, 75%). R_f = 0.67 (hexanes/EtOAc 9:1); $[\alpha]_D^{20}$ = +6.5 (*c* = 0.4 in $CHCl_3$), (lit.:[4b] $[\alpha]_D$ = +8.8 (*c* = 1.3 in $CHCl_3$)); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.61 (d, ^3J(H,H) = 7.8 Hz, 1H; -C=C*H*-), 4.49 (brs, 1H; -O–C*H*–CH_2Br), 3.91 (dd, ^3J(H,H) = 5.2 Hz, ^3J(H,H) = 12.9 Hz, 1H; -C*H*(Br)-), 3.69 (dd, ^2J(H,H) = 10.4 Hz, ^3J(H,H) = 2.6 Hz, 1H; -C$H_a$$H_b$Br), 3.37 (dd, ^2J(H,H) = 10.4 Hz, ^3J(H,H) = 8.6 Hz, 1H; -CH_aH_bBr), 2.42–2.22 (m, 2H; -CH_a-H_bCH(Br)-, -C$H_a$$H_b$CH=C-), 2.21–1.94 (m, 2H; -CH_aH_bCH(Br)-, -CH_aH_bCH=C-), 1.80 (ddd, ^2J(H,H) = 12.9 Hz, ^3J(H,H) = 12.9 Hz, ^3J(H,H) = 4.4 Hz, 1H; -C$H_{ax}H_{eq}$–$C(CH_3)$O-), 1.77 (d, ^3J(H,H) = 9.7 Hz, 1H; -$C(CH_3)_2$–C*H*-), 1.69 (brs, 3H; -CH=C(CH_3)-), 1.65 (ddd, ^2J(H,H) = 12.9 Hz, ^3J(H,H) = 3.5 Hz, ^3J(H,H) = 3.5 Hz, 1H; -$CH_{ax}H_{eq}$–$C(CH_3)$O-), 1.30 (s, 3H; -$C(CH_3)$–O-), 1.12 (s, 3H; -$C(CH_3)_{eq}(CH_3)_{ax}$), 0.90 ppm (s, 3H; -$C(CH_3)_{eq}(CH_3)_{ax}$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 136.1, 129.4, 77.5, 70.7, 66.3, 52.8, 40.8, 36.7, 36.2, 32.9, 30.7, 25.9, 22.0, 21.0, 18.0 ppm; IR (neat): $\tilde{\nu}$ = 2971, 2924, 2859, 1455, 1386, 1374, 1155, 1086, 1055, 865, 769, 672 cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{15}H_{24}Br_2O_2$, $[M+H]^+$: 380.0350; found: 380.0190.

Synthesis of bromide 29: Alcohol **26a** (11 mg, 0.025 mmol) was tosylated following the procedure described for **26b**, in this case by using TsCl (6.1 mg, 0.032 mmol) and pyridine (3 μL, 0.038 mmol) in dry CH_2Cl_2 (0.11 mL). Tosylated form of alcohol **26b** was isolated as a pale yellow oil (13 mg, 85%). R_f = 0.23 (hexanes/EtOAc 7:3); $[\alpha]_D^{20}$ = +13.6 (*c* = 0.5 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.76 (d, ^3J(H,H) = 8.6 Hz, 2H; -SO_2–Ar*H*), 7.30 (d, ^3J(H,H) = 8.6 Hz, 2H; -SO_2–Ar*H*), 7.19 (d, ^3J(H,H) = 8.6 Hz, 2H; CH_3OAr*H*), 6.87 (d, ^3J(H,H) = 8.6 Hz, 2H; CH_3OAr*H*), 5.79 (d, ^3J(H,H) = 7.5 Hz, 1H; -C=C*H*-), 4.58 (brs, 1H; -O–C*H*–CH_2OSO_2-), 4.41 (dd, ^2J(H,H) = 10.5 Hz, ^3J(H,H) = 2.8 Hz, 1H; -C$H_a$$H_b$$OSO_2$-), 4.34 (d, ^2J(H,H) = 11.2 Hz, 1H; -C$H_a$$H_b$OArOC$H_3$), 4.27 (d, ^2J(H,H) = 11.2 Hz, 1H; -CH_aH_bOArOCH_3), 4.03 (dd, ^2J(H,H) = 10.5 Hz, ^3J(H,H) = 8.6 Hz, 1H; -$CH_aH_b$$OSO_2$-), 3.85 (dd, ^3J(H,H) = 4.7 Hz, ^3J(H,H) = 12.5 Hz, 1H; -C*H*(Br)-), 3.82 (s, 3H; CH_3OAr), 3.80 (d, ^2J(H,H) = 10.7 Hz, 1H; -C$H_a$$H_b$-OPMB), 3.74 (d, ^2J(H,H) = 10.7 Hz, 1H; -CH_aH_bOPMB), 2.43 (s, 3H; CH_3–ArSO_2-), 2.34–2.18 (m, 2H; -CH_2CH(Br)-), 2.18–1.96 (m, 2H; -CH_2CH=C-), 1.76 (d, ^3J(H,H) = 9.8 Hz, 1H; $C(CH_3)_2$–C*H*-), 1.67 (ddd, ^2J(H,H) = 12.9 Hz, ^3J(H,H) = 12.9 Hz, ^3J(H,H) = 3.8 Hz, 1H; -C$H_{ax}H_{eq}$–$C(CH_3)$O-), 1.44 (ddd, ^2J(H,H) = 12.9 Hz, ^3J(H,H) = 3.5 Hz, ^3J(H,H) = 3.5 Hz, 1H; -$CH_{ax}H_{eq}$-$C(CH_3)$O-), 1.16 (s, 3H; -$C(CH_3)$-O-), 1.09 (s, 3H; -$C(CH_3)_{eq}(CH_3)_{ax}$), 0.87 ppm (s, 3H; -$C(CH_3)_{eq}(CH_3)_{ax}$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 159.3, 144.5, 136.0, 134.6, 133.3, 129.8, 129.5, 128.0, 113.9, 77.2, 72.7, 71.3, 67.7, 65.9, 55.3, 51.8, 40.7, 36.2, 32.7, 30.6, 25.9, 21.7, 21.6, 17.9 ppm; IR (neat): $\tilde{\nu}$ = 2950, 2862, 1614, 1589, 1514, 1464, 1361, 1248, 1177, 976, 818, 665, 554 cm^{-1}; HRMS (MALDI-FTMS): *m*/*z* calcd for $C_{30}H_{39}BrO_6S$ $[M+Na]^+$: 629.1543; found: 629.1551.

The above tosylate (5.5 mg, 0.009 mmol) was brominated following the procedure described for the synthesis of (+)-Palisadin B, in this case by using anhydrous LiBr (3.7 mg, 0.043 mmol) in HMPA (30 μL) at 50 °C for 20 h. Subjection of the crude mixture to flash column chromatography (silica gel, hexanes/EtOAc 9:1) afforded pure bromide **29** (3.7 mg, 80%) as a yellow oil. R_f = 0.62 (hexanes/EtOAc 8:2); $[\alpha]_D^{20}$ = −1.1 (*c* = 0.4 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.23 (d, ^3J(H,H) = 8.6 Hz, 2H; CH_3OAr*H*), 6.89 (d, ^3J(H,H) = 8.6 Hz, 2H; CH_3OAr*H*), 5.85 (d, ^3J(H,H) = 7.5 Hz, 1H; -C=C*H*-), 4.56 (brs, 1H; -O-C*H*-CH_2Br), 4.41 (d, ^2J(H,H) = 11.5 Hz, 1H; -C$H_a$$H_b$OPMB), 4.38 (brs, 2H; CH_2OAr), 3.88 (dd, ^3J(H,H) = 4.8 Hz, ^3J(H,H) = 12.8 Hz, 1H; -C*H*(Br)-), 3.81 (s, 3H; CH_3O–Ar), 3.80 (dd, ^2J(H,H) = 10.4 Hz, ^3J(H,H) = 2.8 Hz, 1H; -C$H_a$$H_b$Br), 3.79 (d, ^2J(H,H) = 11.5 Hz, 1H; -CH_aH_bOPMB), 3.42 (dd, ^2J(H,H) = 10.4 Hz, ^3J(H,H) = 8.5 Hz, 1H; -CH_aH_bBr), 2.46–2.22 (m, 2H; -CH_2CH(Br)-), 2.21–2.00 (m, 2H; -CH_2CH=C-), 1.78 (d, ^3J(H,H) = 9.4 Hz, 1H; -$C(CH_3)_2$-C*H*-), 1.77 (ddd, ^2J(H,H) = 12.5 Hz, ^3J(H,H) = 12.5 Hz, ^3J(H,H) = 3.8 Hz, 1H; -C$H_{ax}H_{eq}$–$C(CH_3)$O-), 1.64 (ddd, ^2J(H,H) = 12.5 Hz, ^3J(H,H) = 3.5 Hz, ^3J(H,H) = 3.5 Hz, 1H; -$CH_{ax}H_{eq}$-$C(CH_3)$O-), 1.29 (s, 3H; -$C(CH_3)$-O-), 1.12 (s, 3H; -$C(CH_3)_{eq}(CH_3)_{ax}$), 0.90 ppm (s, 3H; -$C(CH_3)_{eq}(CH_3)_{ax}$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 159.4, 137.7, 129.5, 113.9, 77.5, 73.2, 71.9, 69.6, 66.1, 55.3, 52.3, 40.8, 36.6, 35.9, 32.9, 30.6, 25.9, 22.0, 18.0 ppm; IR (neat): $\tilde{\nu}$ = 2957, 2925, 2852, 1616, 1589, 1514, 1463, 1455, 1440, 1386, 1248, 1172, 1153, 1053, 1037, 827, 759, 668 cm^{-1}; HRMS (MALDI-FTMS): *m*/*z* calcd for $C_{23}H_{32}Br_2O_3$ $[M+Na]^+$: 537.0610; found: 537.0603.

Synthesis of (+)-12-hydroxy-Palisadin B (30): 2,3-Dicloro-5,6-dicyano-1,4-benzoquinone (DDQ; 5.9 mg, 0.026 mmol) was added to a solution of bromide **29** (6.6 mg, 0.013 mmol) in a mixture of CH_2Cl_2/H_2O 10:1 (0.1 mL) at 25 °C. After 30 min of vigorous stirring, a saturated solution of sodium bicarbonate (5 mL) was added. The reaction was extracted with EtOAc (2×5 mL) and the combined organic extracts were washed successively with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Flash column chromatography of the crude mixture (silica gel, hexanes/EtOAc 9:1) afforded pure (+)-12-hydroxy-Palisadin B (**30**) (4.0 mg, 78%) as a yellow oil. R_f = 0.28 (hexanes/EtOAc 8:2); $[\alpha]_D^{20}$ = +17.0 (*c* = 0.28 in $CHCl_3$) (lit.:[4b] $[\alpha]_D$ = +19.7 (*c* = 0.4 in $CHCl_3$)); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.88 (d, ^3J(H,H) = 7.8 Hz, 1H; -C=C*H*-), 4.66 (brs, 1H; -O–C*H*-CH_2Br), 4.20 (d, ^2J(H,H) = 12.8 Hz, 1H; -C$H_a$$H_b$-OH), 4.00 (d, ^2J(H,H) = 12.8 Hz, 1H; -CH_aH_bOH), 3.90 (dd, ^3J(H,H) = 4.8 Hz, ^3J(H,H) = 11.9 Hz, 1H; -C*H*(Br)-), 3.89 (dd, ^2J(H,H) = 10.4 Hz, ^3J(H,H) = 2.6 Hz, 1H; -C$H_a$$H_b$Br), 3.49 (dd, ^2J(H,H) = 10.4 Hz, ^3J(H,H) = 8.9 Hz, 1H; -CH_aH_bBr), 2.40–2.02 (m, 4H; -CH_2CH(Br)-, -CH_2CH=C-), 1.83 (ddd, ^2J(H,H) = 13.4 Hz, ^3J(H,H) = 13.4 Hz, ^3J(H,H) = 4.1 Hz, 1H; -C$H_{ax}H_{eq}$–$C(CH_3)$O-), 1.82 (d, ^3J(H,H) = 9.7 Hz, 1H; -$C(CH_3)_2$–C*H*-), 1.67 (ddd, ^2J(H,H) = 12.7 Hz, ^3J(H,H) = 3.7 Hz, ^3J(H,H) = 3.7 Hz, 1H; -$CH_{ax}H_{eq}$–$C(CH_3)$O-), 1.31 (s, 3H; -$C(CH_3)$–O-), 1.13 (s, 3H; -$C(CH_3)_{eq}(CH_3)_{ax}$), 0.91 ppm (s, 3H; -$C(CH_3)_{eq}(CH_3)_{ax}$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 140.4, 133.2, 77.6, 69.5, 66.1, 66.0, 52.3, 40.8, 36.6, 35.8, 32.9, 30.7, 25.9, 22.0, 18.0 ppm; IR (neat): $\tilde{\nu}$ = 3411, 2973, 2951, 2928, 2874, 1468, 1390, 1377, 1151, 1090, 1054, 1000, 871, 759 cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{15}H_{24}Br_2O_2$ $[M+Na]^+$: 417.0035; found: 417.0036.

Synthesis of hydroxytosylate 31: DDQ (4.6 mg, 0.020 mmol) was added to a solution of the tosylated form of alcohol **27a** (5.5 mg, 0.009 mmol), prepared as described in the synthesis of bromide **29**, in a mixture of CH_2Cl_2/H_2O 10:1 (0.1 mL) at 25 °C. After 30 min of vigorous stirring, a saturated solution of sodium bicarbonate (5 mL) was added. The reaction mixture was extracted by ethyl acetate (2×5 mL), and the combined organic extracts were washed successively with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography to the crude mixture (silica gel, hexanes/EtOAc 8:2) afforded pure **31** (3.7 mg, 80%) as a yellow oil. R_f = 0.22 (hexanes/EtOAc 8:2); $[\alpha]_D^{20}$ = +26.0 (*c* = 0.3 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.80 (d, ^3J(H,H) = 8.2 Hz, 2H; -SO_2–Ar*H*), 7.33 (d, ^3J(H,H) = 8.2 Hz, 2H; -SO_2–Ar*H*), 5.82 (d, ^3J(H,H) = 7.8 Hz, 1H; -C*H*=C–CH_2OH), 4.67 (brs, 1H; -O–C*H*–CH_2–OSO_2-), 4.47 (dd, ^2J(H,H) = 10.2 Hz, ^3J(H,H) = 2.9 Hz, 1H; -C$H_a$$H_b$–$OSO_2$-), 4.08 (dd, ^2J(H,H) = 10.2 Hz, ^3J(H,H) = 8.2 Hz 1H; -CH_aH_b–OSO_2-), 4.04 (d, ^2J(H,H) = 10.5 Hz, 1H; -C$H_a$$H_b$–OH), 3.93 (d, ^2J(H,H) = 10.5 Hz, 1H; -CH_aH_b–OH), 3.87 (dd, ^3J(H,H) = 4.8 Hz, ^3J(H,H) = 12.9 Hz, 1H; -C*H*(Br)-), 2.44 (s, 3H; CH_3–ArSO_2-), 2.36–2.00 (m, 4H; -CH_2CH(Br)-, -CH_2CH=C-), 1.80 (d, ^3J(H,H) = 9.6 Hz, 1H; -$C(CH_3)_2$–C*H*-), 1.72 (ddd, ^2J(H,H) = 13.5 Hz, ^3J(H,H) = 13.5 Hz, ^3J(H,H) = 4.8 Hz, 1H; -C$H_{ax}H_{eq}$–$C(CH_3)$O-), 1.48 (ddd, ^2J(H,H) = 13.5 Hz, ^3J(H,H) = 3.2 Hz, ^3J(H,H) = 3.2 Hz, 1H; -$CH_{ax}H_{eq}$–$C(CH_3)$O-), 1.19 (s, 3H; -$C(CH_3)$–O-), 1.10 (s, 3H; -$C(CH_3)_{eq}(CH_3)_{ax}$), 0.88 ppm (s, 3H; -$C(CH_3)_{eq}(CH_3)_{ax}$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 144.7, 138.8, 133.7, 129.7, 128.0, 77.7, 71.3, 68.0, 65.9, 65.5, 51.9, 40.7, 36.3, 32.7, 30.6, 25.9, 21.7, 21.6, 17.9 ppm; HRMS (MALDI-FTMS): *m*/*z* calcd for $C_{22}H_{31}BrO_5S$ $[M+Na]^+$: 509.0968; found: 509.0977.

Synthesis of (+)-Palisadin A (32):

Method A: Tosylate **31** (8.0 mg, 0.016 mmol) was treated with a 10% solution of anhydrous potassium carbonate in dry MeOH (1 mL) for 30 min at 25 °C. The reaction mixture was then partitioned between EtOAc

(5 mL) and water (5 mL). After separation of the organic phase, the aqueous phase was washed with ethyl acetate (2×5 mL), and the combined organic extracts were washed successively with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Subjection of the crude mixture to flash chromatography (silica gel, hexanes/EtOAc 95:5) afforded (+)-Palisadin A (**32**) (4.8 mg, 96%), as a pale yellow oil.

Method B: The above procedure was followed, treating (+)-12-hydroxy-Palisadin B (**30**) (5 mg, 0.013 mmol) with a 10% solution of anhydrous potassium carbonate in dry MeOH (1 mL) for 30 min. (+)-Palisadin A (**32**) was isolated as a pale yellow oil (3.9 mg, 95%). R_f=0.6 (hexanes/EtOAc 8:2); $[\alpha]_D^{20}$=+15.7 (c=0.2 in $CHCl_3$) (lit.:[4b] $[\alpha]_D$=+19.5, (c=1.5 in $CHCl_3$)); ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.55 (m, 1H; -C*H*=C-), 4.83 (brs, 1H; -O−C*H*−CH_2−O-), 4.42 (d, ^2J(H,H)=12.9 Hz, 1H; -CH=C−CH_aH$_b$−O-), 4.34 (d, ^2J(H,H)=12.9 Hz, 1H; -CH=C−CH$_a$$H_b$−O-), 4.07 (dd, ^2J(H,H)=8.2 Hz, ^3J(H,H)=8.2 Hz, 1H; -O-CH-CH_aH$_b$-O-), 3.96 (dd, ^3J(H,H)=4.8 Hz, ^3J(H,H)=12.7 Hz, 1H; -C*H*(Br)-), 3.44 (dd, ^2J(H,H)=8.2 Hz, ^3J(H,H)=8.2 Hz, 1H; -O−CH−CH$_a$$H_b$-), 2.45–2.01 (m, 5H; -C(CH$_3$)$_2$−C*H*-, -CH_2CH(Br), -CH_2CH=C-), 1.80 (ddd, ^2J(H,H)=13.0 Hz, ^3J(H,H)=13.0 Hz, ^3J(H,H)=4.4 Hz, 1H; -CH_{ax}H$_{eq}$−C(CH$_3$)O-), 1.56 (ddd, ^2J(H,H)=13.0 Hz, ^3J(H,H)=3.3 Hz, ^3J(H,H)=3.3 Hz, 1H; -CH$_{ax}$$H_{eq}$−C(CH$_3$)O-), 1.28 (s, 3H; -C(C$H_3$)-O), 1.17 (s, 3H; -C(C$H_3$)$_{eq}$-(CH$_3$)$_{ax}$), 0.94 ppm (s, 3H; -C(CH$_3$)$_{eq}$(CH_3)$_{ax}$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=141.9, 121.1, 78.0, 72.0, 71.0, 70.1, 66.3, 51.8, 41.0, 37.5, 32.7, 30.8, 26.3, 21.9, 18.0 ppm; IR (neat): $\tilde{\nu}$=2976, 2946, 2917, 2852, 1464, 1386, 1152, 1103, 1059, 918, 869, 768, 703, 624, 583 cm^{-1}; HRMS (EI): m/z calcd for $C_{15}H_{23}BrO_2$ $[M+Na]^+$: 337.0077; found: 337.0077.

Synthesis of diol 33: DDQ (47.7 mg, 0.21 mmol) was added to a solution of alcohol **27a** (9.4 mg, 0.021 mmol) in a mixture of CH_2Cl_2/H_2O 10:1 (0.11 mL) at 25°C. After 3 h of vigorous stirring, a saturated solution of sodium bicarbonate (10 mL) was added. The reaction was extracted by ethyl acetate (3×5 mL), and the combined organic extracts were washed successively with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography of the crude mixture (silica gel, hexanes/EtOAc 6:4) afforded pure diol **33** (5.3 mg, 76%), as a pale yellow oil. R_f=0.16 (hexanes/EtOAc 6:4); $[\alpha]_D^{20}$=+5.0 (c=0.3 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.90 (d, ^3J(H,H)=7.8 Hz, 1H; -C*H*=C-), 4.48 (brs, 1H; -O−C*H*−CH_2OH), 4.09 (d, ^2J(H,H)=11.9 Hz, 1H; -CH=C−CH_aH$_b$OH), 3.99 (d, ^2J(H,H)=11.9 Hz, 1H; -CH=C−CH$_a$$H_b$OH), 3.90 (dd, ^3J(H,H)=4.8 Hz, ^3J(H,H)=12.5 Hz, 1H; -C*H*(Br)-), 3.84 (dd, ^2J(H,H)=10.8 Hz, ^3J(H,H)=3.4 Hz, 1H; -O−CH−CH_aH$_b$OH), 3.73 (dd, ^2J(H,H)=10.8 Hz, ^3J(H,H)=6.2 Hz, 1H; -O−CH−CH$_a$$H_b$−OH), 2.49–2.08 (m, 4H; -CH_2CH(Br)-, -CH_2CH=C-), 1.88 (d, ^3J(H,H)=9.7 Hz, 1H; -C(CH$_3$)$_2$−C*H*-), 1.80 (ddd, ^2J(H,H)=13.2 Hz, ^3J(H,H)=13.3 Hz, ^3J(H,H)=3.5 Hz, 1H; -CH_{ax}H$_{eq}$−C(CH$_3$)O-), 1.53 (ddd, ^2J(H,H)=13.2 Hz, ^3J(H,H)=3.3 Hz, ^3J(H,H)=3.3 Hz, 1H; -CH$_{ax}$$H_{eq}$−C(CH$_3$)O-), 1.31 (s, 3H; -C(C$H_3$)−O-), 1.14 (s, 3H; -C(C$H_3$)$_{eq}$(CH$_3$)$_{ax}$), 0.92 ppm (s, 3H; -C(CH$_3$)$_{eq}$(CH_3)$_{ax}$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=140.0, 133.4, 77.7, 69.8, 65.8, 65.4, 63.9, 52.1, 40.7, 36.9, 32.7, 30.6, 25.9, 22.1, 18.0 ppm; IR (neat): $\tilde{\nu}$=3384, 2956, 2927, 2876, 2857, 1466, 1386, 1373, 1263, 1220, 1153, 1066, 1055, 998, 758 cm^{-1}; HRMS (MALDI-FTMS): m/z calcd for $C_{15}H_{25}BrO_3$ $[M+Na]^+$: 355.0879; found: 335.0880.

Synthesis of (−)-Aplysistatin (34):

Method A: Diol **33** (5 mg, 0.015 mmol) was dissolved in CH_2Cl_2 (0.1 mL), and MnO_2 (85%) (15 mg, 0.15 mmol) was added at 25°C. After 2 h of stirring, the reaction mixture was filtered through a short pad of Celite and the filtrate was concentrated in vacuo. Flash column chromatography (silica gel, hexanes/EtOAc 8:2) afforded (−)-Aplysistatin (**34**) (4.6 mg, 93%) as a white solid.

Method B: Pyridinium chlorochromate (PCC; 16 mg, 0.079 mmol) was added to a solution of (+)-Palisadin A (**32**) (5 mg, 0.016 mmol) in dry benzene (0.1 mL). The mixture was stirred for 48 h at 25°C and filtered through a short pad of Celite; the filtrate was concentrated in vacuo. Flash column chromatography of the crude mixture (silica gel, hexanes/EtOAc 8:2) afforded (−)-Aplysistatin (2.4 mg, 50%) as a white solid and recovered (+)-Palisadin A (2 mg, 90%). R_f=0.67 (hexane-ethyl acetate 6:4); m.p.=157–159° (lit.:[4e] 160–161°); $[\alpha]_D^{20}$=−27.5 (c=0.38 in MeOH) (lit.:[4e] $[\alpha]_D$=−29, (c=0.030 in MeOH)); ^{1}H NMR (250 MHz, $CDCl_3$): δ=6.95 (m, 1H; -C*H*=C-), 5.14 (m, 1H; -O−C*H*−CH_2−O-), 4.49 (dd, ^2J(H,H)=8.9 Hz, ^3J(H,H)=8.9 Hz, 1H; -O−CH−CH_aH$_b$−O-), 3.92 (dd, ^3J(H,H)=4.5 Hz, ^3J(H,H)=12.7 Hz, 1H; -C*H*(Br)-), 3.87 (dd, ^2J(H,H)=8.9 Hz, ^3J(H,H)=7.0 Hz, 1H; -O−CH−CH$_a$$H_b$−O-), 2.60–2.51 (m, 2H; -CH_2CH=C-), 2.29 (dddd, ^2J(H,H)=13.5 Hz, ^3J(H,H)=4.1 Hz, ^3J(H,H)=4.1 Hz, ^3J(H,H)=4.1 Hz, 1H; -CH$_{ax}$$H_{eq}$−CH(Br)-), 2.11 (dddd, ^2J(H,H)=13.5 Hz, ^3J(H,H)=13.5 Hz, ^3J(H,H)=13.5 Hz, ^3J(H,H)=4.1 Hz, 1H; -CH_{ax}H$_{eq}$−CH(Br)-), 2.05 (dd, ^3J(H,H)=4.1 Hz, ^3J(H,H)=7.8 Hz, 1H; -C(CH$_3$)$_2$−C*H*-), 1.79 (ddd, ^2J(H,H)=12.7 Hz, ^3J(H,H)=12.7 Hz, ^3J(H,H)=3.4 Hz, 1H; -CH_{ax}H$_{eq}$−C(CH$_3$)O-), 1.62 (ddd, ^2J(H,H)=12.7 Hz, ^3J(H,H)=3.7 Hz, ^3J(H,H)=3.7 Hz, 1H; -CH$_{ax}$$H_{eq}$−C(CH$_3$)O-), 1.29 (s, 3H; -C(C$H_3$)−O-), 1.18 (s, 3H; -C(C$H_3$)$_{eq}$(CH$_3$)$_{ax}$), 0.96 ppm (s, 3H; -C(CH$_3$)$_{eq}$(CH_3)$_{ax}$); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=169.2, 143.1, 131.9, 79.0, 69.9, 66.8, 65.1, 51.2, 41.0, 37.6, 32.4, 30.7, 27.2, 21.7, 18.0 ppm; IR (neat): $\tilde{\nu}$=2984, 2945, 2928, 1758, 1675, 1391, 1381, 1230, 1206, 1118, 1018, 998, 752, 708, 594 cm^{-1}; HRMS (MALDI-FTMS): m/z calcd for $C_{15}H_{21}BrO_3$ $[M+H]^+$: 329.0747; found: 329.0756.

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