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Practical synthesis of aromatic bisabolanes: Synthesis of 1,3,5-bisabolatrien-7-ol, peniciaculin A and B, and hydroxysydonic acid

Arata Yajima [a, *], Izumi Shirakawa [b], Nanami Shiotani [c], Kazuya Ueda [c], Hazuki Murakawa [c], Tatsuo Saito [a], Ryo Katsuta [a], Ken Ishigami [a]

[a] Department of Chemistry for Life Sciences and Agriculture, Tokyo University of Agriculture, 1-1-1 Sakuragaoka, Setagaya-ku, Tokyo, 156-8502, Japan
[b] Graduated School of Agriculture, Tokyo University of Agriculture, 1-1-1 Sakuragaoka, Setagaya-ku, Tokyo, 156-8502, Japan
[c] Department of Fermentation Science, Tokyo University of Agriculture, 1-1-1 Sakuragaoka, Setagaya-ku, Tokyo, 156-8502, Japan

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ABSTRACT

The enantioselective synthesis of aromatic bisabolanes, such as 1,3,5-bisabolatrien-7-ol, peniciaculin A and B, and hydroxysydonic acid, has been described. Our methodology for the total synthesis of aromatic bisabolanes involves the stereoselective construction of the C-7 stereogenic center via a Sharpless asymmetric dihydroxylation reaction, followed by a SmI_2-mediated Julia olefination. Preliminary results obtained for the odor evaluation of 1,3,5-bisabolatrien-7-ol and the confirmation of the absolute configurations of peniciaculin A and B are also described.

1. Introduction

Aromatic bisabolanes are a large family of monocyclic sesquiterpenoids isolated from various sources, such as microorganisms, plants, and insects [1]. Several natural products possess a chiral center at C-7, as epitomized by α-curcumene (**1**) (Fig. 1). Focusing on the absolute configuration at C-7, some of these natural products have been isolated in both their (*R*)- [1a] and (*S*)-forms [1b]. Therefore, aromatic bisabolanes have inspired many synthetic organic chemists to develop enantioselective synthetic methods for accessing the C-7 stereocenter [2]. Another major class of aromatic bisabolanes possesses an additional hydroxy group at C-7 [3]; sydonic acid (**2**) was the first member of this class to be reported [3a]. Because the C-7 stereocenter of aromatic bisabolanes is a benzylic position, it is presumed to be susceptible to biological oxidation. Although there have been many reports on the isolation of C-7-oxidized aromatic bisabolanes from various organisms, the absolute configuration at C-7 for many compounds remains unknown. Among such aromatic bisabolanes, the simplest compound is 1,3,5-bisabolatrien-7-ol (**3**), which was first described as a synthetic intermediate of the bicyclic sesquiterpene calmenene in 1980 [4]. Compound **3** has been isolated from liverwort (*Bazzania tridens*) by Wu et al. [5] and from ginger (*Curcuma amada*) by Padalia et al. [6]. In both cases, no information on the absolute configuration at C-7 was reported. Although the biological activity of **3** has not been reported, it may have some fragrance because **3** has been isolated from the leaf essential oil of mango ginger. These findings have motivated us to study the synthesis of the C-7-oxidized aromatic bisabolanes.

Some studies on the enantioselective synthesis of C-7-oxidized aromatic bisabolanes have been reported [7]. In 2008, Asami et al. reported the first enantioselective synthesis of sydonol (**7**) and curcutetraol (**8**) [7a]. They employed a highly diastereoselective addition of an aryl Grignard reagent to a methyl ketone derivative possessing a chiral aminal moiety, which was derived from proline. Although this methodology would be applicable for the synthesis of other aromatic bisabolanes, the preparation of the starting chiral compound was slightly laborious. Other synthetic approaches include an asymmetric alkylation [7b], Sharpless asymmetric epoxidation (AE) [7c], an asymmetric bromolactonization reaction [7d]. During our studies, Kavanagh and Gilheany reported a synthesis of gossonorol (**9**) utilizing an asymmetric Grignard addition reaction with a chiral aminoalcohol ligand [7e]. They also synthesized **3** with an enantiomeric ratio (er) of 96.5:3.5, which was the

* Corresponding author.
E-mail address: ayaji@nodai.ac.jp (A. Yajima).

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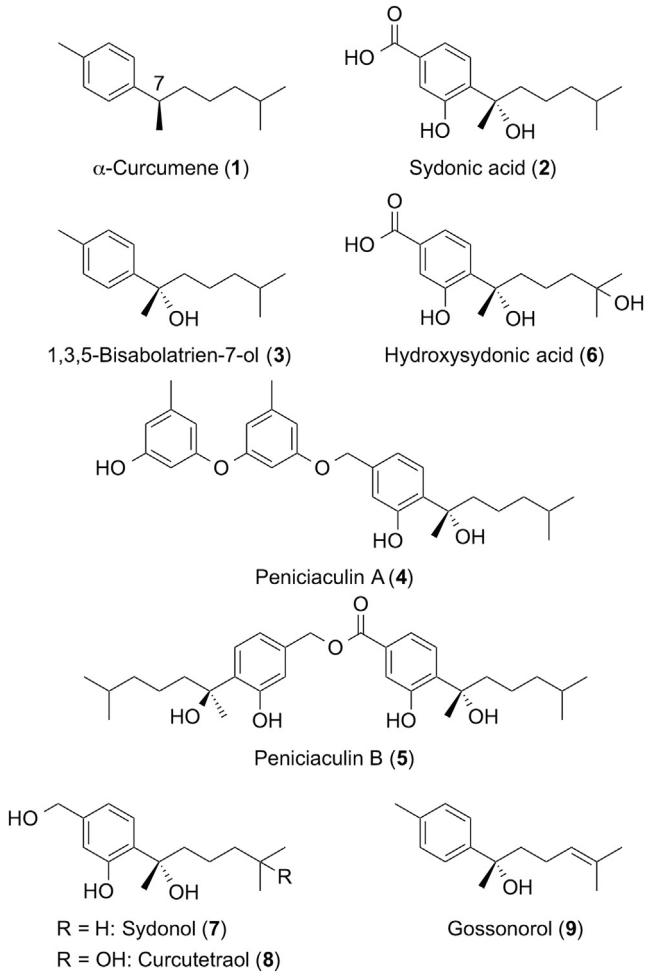


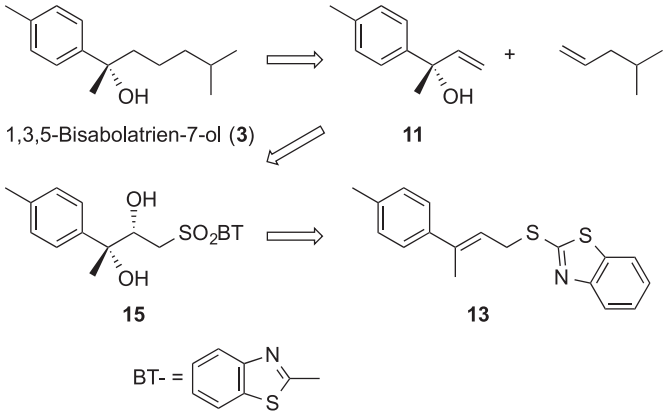
Fig. 1. Structures of natural aromatic bisabolanes.

first report of the enantiomeric synthesis of **3**. Although these methodologies exhibit high selectivity, they all suffer from drawbacks, such as incomplete stereoselectivity, the need to synthesize chiral ligands that are not commercially available, or a lack of applicability toward the synthesis of other compounds owing to their poor substrate scope.

To challenge the construction of the chiral tertiary alcohol moiety found in aromatic bisabolanes, we have employed the Sharpless asymmetric dihydroxylation (AD) reaction because of its high stereoselectivity, wide substrate scope, and simple operation using commercially available reagents. We have previously reported a versatile method for the preparation of chiral secondary benzyl alcohols used for the total synthesis of ganomycin I and fornicin A, in which we employed a Sharpless AD, followed by a Julia–Kocienski olefination reaction [8]. The challenge of this research study was to extend the methodology toward the synthesis of tertiary benzyl alcohols. This paper describes the development of a versatile method for the synthesis of tertiary benzyl alcohols, the total synthesis of 1,3,5-bisabolatrien-7-ol (**3**), peniciaculin A (**4**) and B (**5**), and hydroxysydonic acid (**6**), and our preliminary results on the odor evaluation of both the enantiomers of **3**.

2. Results and discussion

Scheme 1 shows our approach for the synthesis of 1,3,5-

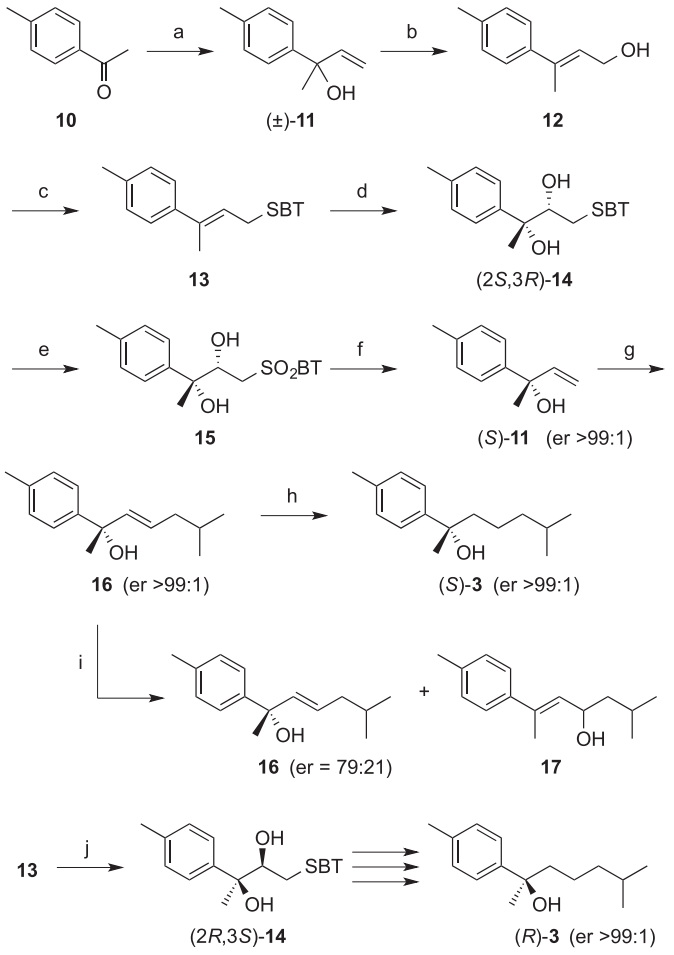


Scheme 1. Retrosynthetic analysis of 1,3,5-bisabolatrien-7-ol (**3**).

bisabolatrien-7-ol (**3**), the first synthetic target of the C-7-oxidized aromatic bisabolenes. We planned to connect the side chain of **3** via an olefin-cross metathesis (CM) reaction. This strategy can be applied for the synthesis of various aromatic bisabolanes by changing the structure of the aromatic segment and sidechain. The aromatic segment bearing a tertiary benzyl alcohol moiety was obtained using a Julia–Kocienski-type olefin formation via Smiles rearrangement of benzothiazolyl (BT) sulfone **15** [8]. The optically active diol **15** could be obtained by the Sharpless AD of alkene **13**.

The synthesis of both the enantiomers of **3** via key intermediate **11** is summarized in Scheme 2. The addition of a vinyl Grignard reagent to commercially available **10** gave racemic **11**. An acid-mediated allylic rearrangement of **11** gave primary alcohol **12**, in which the *Z*-isomer was not observed. After conversion of **12** to its corresponding BT-sulfide (**13**), the key Sharpless AD reaction using AD-mix-α was carried out to give diol **14**. The oxidation of the sulfide moiety in **14** using *m*CPBA gave sulfone **15**, and the DBU-mediated Smiles rearrangement and olefination of **15** gave key tertiary alcohol (*S*)-**11**. The enantiomeric ratio (er) of **11**, which reflects the enantioselectivity of the Sharpless AD reaction of **13,** was determined to be > 99:1 using chiral GC ($[\alpha]_D^{24}$ −26.8 (c = 1.00, $CHCl_3$); Lit [9]. (er = 92:8): $[\alpha]_D^{20}$ −17.4 (c = 1.00, $CHCl_3$)). Although the conversion of **12** to **11** was also possible with good selectivity using the 1-phenyltetrazolyl (PT) group instead of BT, some of the intermediates were highly viscous oils, which were difficult to handle.

Once we obtained the key intermediate **11**, we then attempted to homologate the side chain using CM. During our initial investigations on the reaction conditions, we obtained the desired product **16** in its partially racemized form. Careful analysis of the by-product formed in the reaction revealed the formation of compound **17** [10], which can be attributed to the allylic rearrangement of target product **16**. This indicated that **16** was relatively unstable under acidic conditions and easily generated its corresponding allyl cation intermediate, which can regenerate **16** in its partially racemized form or give **17** via a non-selective hydroxylation of the allyl cation. Because the reaction conditions were unlikely to be acidic, the purification method was scrutinized and the formation of the undesired by-product (**17**) could be completely suppressed by changing the silica gel used for column chromatography to pH-neutral silica. Thus, we obtained product **16** in good yield without any loss of its enantiomeric purity. We confirmed the partial racemization and formation of **17** by exposing the enantiomerically pure **16** to the silica gel previously used in the purification step. Because of its instability, the double bond of **16** was immediately hydrogenated using PtO_2 catalyst to afford (*S*)-1,3,5-

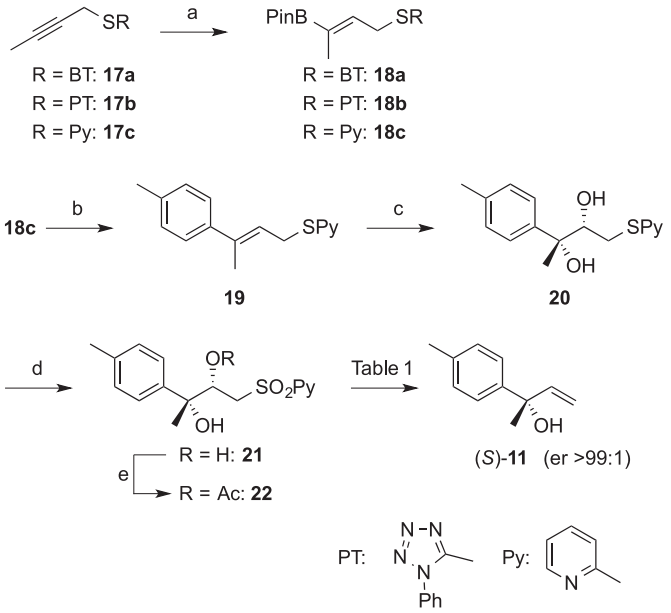


Scheme 2. Synthesis of (*S*)- and (*R*)-**3**. *Reagents, conditions, and yields*: (a) vinylmagnesium bromide, THF, 0 °C (91%); (b) $MeSO_3H$, THF, H_2O (82%); (c) 2-mercaptobenzothiazole, Ph_3P, DEAD, THF, 0–4 °C to room temperature (rt) (73%); (d) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0 °C (98%); (e) *m*CPBA, CH_2Cl_2, −78 °C to rt (80%); (f) DBU, THF, −20 °C (86%); (g) 4-methylpent-1-ene, Grubbs 2nd generation cat., toluene (58%); (h) H_2, PtO_2, EtOH (85%); (i) SiO_2 column chromatography using Silica Gel 60 (Kanto Chemical CO., INC.); (j) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0–4 °C (99%).

bisabolatrien-7-ol (**3**) in its optically pure form. (*R*)-**3** was also synthesized via (2*R*,3*S*)-**14**. The ^1H and ^{13}C NMR spectra of synthetic **3** were in good agreement with those reported in the literature, and the absolute configuration of synthetic **3** was confirmed upon the comparison of its specific optical rotation with that reported in the literature ((*S*)-**3**: $[\alpha]_D^{25}$ −9.5 (c = 1.0, $CHCl_3$); (*R*)-**3**: $[\alpha]_D^{24}$ +9.1 (c = 1.0, $CHCl_3$); Lit [7e].: $[\alpha]_D^{20}$ −2.0 (c = 0.23, $CHCl_3$)). Because no physical data, such as the specific optical rotation or ECD spectrum of the natural product, were available, its absolute configuration could not be determined. After successfully synthesizing both enantiomers of **3**, its odor evaluation was conducted (Table S1). Several panelists noted differences between the odors of the enantiomers and perceived a favorable odor, such as floral, flowery, earthy, and citrus; however, the odor potency was generally weak.

Although we accomplished our initial research objective of constructing the tertiary alcohol moiety with high enantioselectivity, the developed synthetic route contains a problematic step of the strong acid-mediated allylic rearrangement, which may be difficult to apply in the synthesis of other target compounds. To avoid these reaction conditions, we investigated the modification of our synthetic route by directly attaching the aliphatic side chain to the aromatic moiety via a Suzuki–Miyaura cross-coupling reaction (Scheme 3). We first selected BT-sulfide **18a** as the substrate for the Suzuki–Miyaura coupling reaction. Unfortunately, we found that the hydroboration of **17a** was problematic. It is well known that internal alkynes without any electronic or steric bias yield a regioisomeric mixture in simple hydroboration reactions [11]. Thus, we applied a regioselective Cu-catalyzed borylation reaction to prepare **18a**. According to Arrayás and Carretero's method [12], **17a** was subjected to the borylation reaction, and we observed the formation of the desired product **18a** upon ^1H NMR analysis of the crude product. The maximum yield of **18a** was estimated to be ~40% along with unreacted **17a** (up to 55%). Although **18a** could be obtained, its isolation from a mixture of **17a** and $B_2(pin)_2$ was difficult using column chromatography. A similar outcome was obtained upon changing the BT-sulfide **17a** substrate to PT-sulfide **17b**. On the other hand, 2-pyridyl (Py) derivative **18c** was obtained in high yield with high regioselectivity using Gómez Arrayás and Carretero's method. Although reports on the utilization of Py-sulfones are rare, Julia et al. reported that Py-sulfones are also applicable in the Julia–Kocienski olefination reaction [13]. Thus, we selected Py-sulfide **18c** and its Suzuki–Miyaura coupling reaction with 4-iodotoluene to give product **19** in good yield under the optimized reaction conditions. After the Sharpless AD reaction and oxidation of the sulfide moiety, the resulting sulfone **21** was treated with various bases such as NaH [13], DBU, *n*-BuLi, NaHMDS, LiHMDS, and *t*-BuOK; however, the desired olefin **11** was not obtained. Although it has been previously reported that the treatment of β-hydroxy Py-sulfones with NaH gives their corresponding olefins, our substrate gave a complex mixture of products under the reaction conditions studied. This was attributed to the additional γ-hydroxy group in **21**.

We next turned our attention towards a reductive elimination reaction (Table 1). According to Fukumoto's conditions [14], the reductive elimination of acetate **22** with SmI_2 in the presence of HMPA gave **11** in 48% yield (entry 1). After extensive investigations on the reaction conditions, we found that HMPA was not required and the maximum yield (59%) for the reaction was obtained by



Scheme 3. Alternative synthesis of a key intermediate **11**. *Reagents, conditions, and yields*: (a) $B_2(Pin)_2$, Cy_3P, *t*-BuONa, CuCl, MeOH, toluene; (b) 4-iodotoluene, $Pd_2(dba)_3$, Ph_3As, Ag_2O, THF, 60 °C (84%); (c) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0–4 °C (quant.); (d) *m*CPBA, CH_2Cl_2, −78 °C to rt (74%); (e) Ac_2O, DMAP, THF, 0 °C (99%).

Table 1
The reductive elimination of **22**.

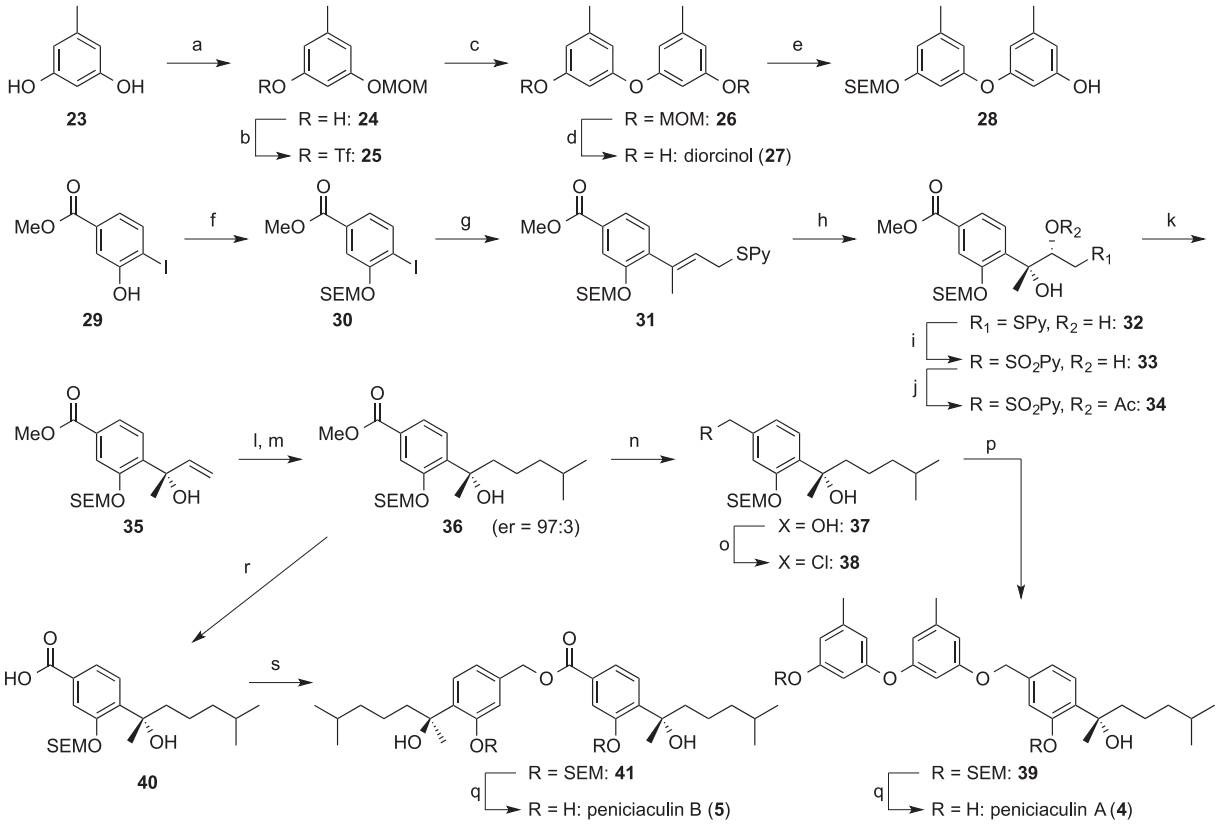
Entry[a]	Additive	Temp. [°C]	Yield [%]	22 recovery [%]
1	HMPA[b]	rt	48	–
2	HMPA[b]	−20	5	25
3	HMPA[b]	−78 to rt	19	–
4	–	rt	31	–
5	–	−20	29	36
6	–	−78 to rt	59	–

[a] 5 eq. of SmI_2 and THF were used for all reactions.
[b] 15 eq.

controlling the reaction temperature (entry 6). Although the isolated yield was moderate even under the optimized conditions, product **11** may be lost during the purification process because of its volatility. The enantiomeric purity of **11** prepared using this modified route was also very high.

To demonstrate the substrate scope of the developed methodology, we synthesized a series of C-7 oxidized aromatic bisabolanes (Scheme 4). We selected peniciaculin A (**4**) and B (**5**) as our next synthetic targets, which possess different substituents on their aromatic ring instead of a methyl group. The peniciaculins are isolated from the culture broth of *Penicillium aculeatum* SD-321, a fungus obtained from deep-sea sediment collected from the South China Sea by Wang et al. [15]. Peniciaculin A exhibits inhibitory activity against some bacteria, such as phytopathogenic bacteria (*Alternaria brassicae*), and peniciaculin B, shows inhibitory activity against a zoonotic aquatic pathogen (*Edwardsiella tarda*). The unique structures of the peniciaculins have been determined using extensive 1D and 2D NMR studies. Peniciaculin A is the first example of a bisabolane analog linked to a diphenyl ether moiety, viz. Diorcinol, (**27**) via an ether bond, and peniciaculin B is the first example of a dimeric bisabolane derivative linked via an ester bond between its corresponding monomers. The absolute configuration at C-7 (C-7′) of peniciaculin A and B was assigned as *S* upon the comparison of their ECD spectra with that of known (+)-sydonol.

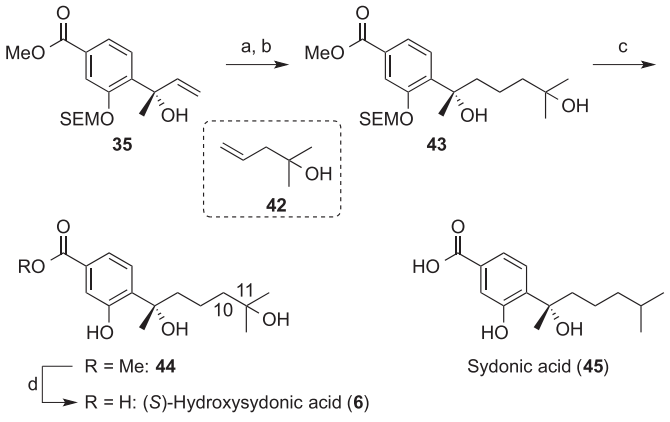
Diorcinol (**27**) was first isolated from *Aspergillus rugulpsus* I.M.I. 84338 by Hassall et al. [16a] and has subsequently been found in various microorganisms [16]. Although Hassall synthesized diorcinol via an Ullman coupling reaction [16a], the yield of the product was very low, and the details of the synthetic procedure were not described. Thus, we synthesized diorcinol via other procedures prior to the preparation of the bisabolane core of peniciaculin A. Monoprotection of the hydroxy group in **23** gave phenol **24**, and the Buchwald–Hartwig etherification between **24** and triflate **25** afforded diaryl ether **26** [17]. Acid hydrolysis of the MOM ether in **26** gave diorcinol (**27**), and monoprotection of the resulting phenolic hydroxy group using a 2-(trimethylsilyl)ethoxymethyl (SEM) group gave **28**, which was used toward the synthesis of peniciaculin A. The bisabolane core moiety was synthesized from known **29** [18]. Protection of the phenolic hydroxy group of **29** as SEM ether was followed by a Suzuki–Miyaura cross coupling with **18c** to afford **31**. Compound **31** was converted to tertiary alcohol **35** using conventional methods. The yield of the final reductive elimination step in this series of transformations was much higher than that of **11**. This confirmed that the low yield of **11** can be attributed



Scheme 4. Synthesis of peniciaculin A (**4**) and B (**5**). *Reagents, conditions, and yields*: (a) NaH, MOMCl, DMF, 0 °C (45%); (b) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C (75%); (c) $Pd(OAc)_2$, tBuXPhos, K_2CO_3, **25**, toluene, 100 °C (79%); (d) HCl aq., MeOH, THF, 50 °C (95%); (e) NaH, SEMCl, THF, (41%); (f) SEMCl, DIPEA, CH_2Cl_2 (quant.); (g) **18c**, $Pd_2(dba)_3$, Ph_3As, Ag_2O, THF, 60 °C (81%); (h) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0–4 °C (98%); (i) *m*CPBA, CH_2Cl_2, −78 °C to rt (99%); (j) Ac_2O, DMAP, THF, 0 °C (quant.); (k) SmI_2, THF, −78 °C to rt (76%); (l) 4-methylpent-1-ene, Grubbs 2nd generation cat., toluene; (m) H_2, PtO_2, EtOH (73%); (n) LAH, Et_2O, 0 °C to rt (82%); (o) MsCl, DMAP, CH_2Cl_2, 0 °C to rt (50%); (p) **28**, K_2CO_3, 18-crown-6, DMF, 90 °C (63%); (q) TBAF, THF, 80 °C (79% for **4**, 87% for **5**); (r) LiOH, THF, MeOH, H_2O, 0 °C to rt (94%); (s) **37**, EDCI, DMAP, CH_2Cl_2, 0 °C to rt (88%).

to its volatility. Because the product of the CM reaction was relatively unstable, the resulting double bond was immediately hydrogenated to give a common intermediate for the peniciaculins (**36**). The enantiomeric ratio of **36** was estimated to be 97:3 using HPLC analysis. Since some decomposed products related to compound **17** were observed in this reaction, we proposed that the reason for the slight decrease in enantiomeric purity was the instability of the target product rather than the Sharpless AD reaction. Intermediate **36** was first reduced using DIBAL to give its corresponding alcohol (**37**). The primary hydroxy group in **37** was selectively converted into its corresponding chloride **38**, and a Williamson etherification between **28** and **38** was carried out to give **39**. Deprotection of the SEM group in **39** using TBAF gave peniciaculin A (**4**). Although the ^{1}H and ^{13}C NMR spectra of the synthetic **4** well supported its structure, slight differences were observed in chemical shifts of aromatic protons between the synthetic compound and the natural product (Table S2). In the ^{1}H NMR spectrum of our synthetic product, the signals derived from the three hydroxy groups of **4** were observed as relatively sharp signals, whereas in the reported spectrum of the natural product, the signals that appear to be hydroxy groups were observed as rather broad signals around 3 ppm. This indicates that the differences of chemical shifts of aromatic protons might be caused by the presence or absence of hydrogen bond(s) due to differences in the acidity or water content of the solution. Because the sign of the specific optical rotation was the same as that of the natural product ($[\alpha]_D^{26} = +9.6$ (c 0.049, MeOH); Lit [15]. $[\alpha]_D^{20} = +4.1$ (c 0.49, MeOH)), we confirmed Wang's assignment of the absolute configuration of natural peniciaculin A. Subsequently, common intermediate **36** was hydrolyzed to give its corresponding acid **40** and esterified with **37** using EDCI to afford **41**. The deprotection of the two SEM groups in **41** using TBAF gave peniciaculin B (**5**) ($[\alpha]_D^{24} = +4.0$ (c 0.34, MeOH); Lit [15]. $[\alpha]_D^{20} = +5.6$ (c 0.34, MeOH)). As the case of peniciaculin A, slight differences were also observed in chemical shifts of aromatic protons between the synthetic peniciaculin B and the natural product (Table S3).

Hydroxysydonic acid (**6**) includes an additional hydroxy group in its side chain, and is therefore considered a good synthetic target to demonstrate the synthetic utility of our methodology (Scheme 5). Hydroxysydonic acid (**6**) was originally isolated from the culture broth of *A. sydowi* in 1978 [3a], and since then it has been identified in a variety of microorganisms [19]. The biological properties of **6**, such as its antibacterial activity against *Staphylococcus aureus* including MRSA, have also been reported. The CM reaction between **35** and homoallyl alcohol **42** [20] proceeded smoothly, followed by a series of conventional transformations, hydrogenation, removal of the SEM group, and hydrolysis, to give (*S*)-hydroxysydonic acid (**6**) ($[\alpha]_D^{19} = +1$ (c 0.3, MeOH); Lit [15]. $[\alpha]_D^{20} = +2.2$ (c 0.49, MeOH)). In their first isolation study on **6**, Hamasaki et al. reported that the specific optical rotation values obtained for natural sydonic acid (**45**) and hydroxysydonic acid were zero [3a]. This indicated that Hamasaki's sydonic acids might be racemates. In 2009, Hashimoto et al. isolated sydonic acid from *Glonium* sp. And proved it to be the optically active (*S*)-isomer ($[\alpha]_D^{20} = +2.73$ (c 2.30, MeOH)) [21]. Thus, they concluded that Hamasaki's sydonic acid was a racemate. Although there are several reports on the isolation of hydroxysydonic acid that was drawn in (*R*)- and (*S*)-forms [19], the absolute configuration of this natural product is unclear. Considering that there is only one report of the actual value of the specific optical rotation of the natural hydroxysydonic acid [15], we speculate that it may be difficult to accurately measure its near-zero value. However, our synthetic (*S*)-**6** sample exhibited a very small yet significantly positive specific optical rotation, we concluded that the absolute configuration of the natural hydroxysydonic acid is *S*.



Scheme 5. Synthesis of hydroxysydonic acid (**6**). Reagents, conditions, and yields: (a) **42**, Grubbs 2nd generation cat., toluene; (b) H_2, PtO_2, EtOH (74% in 2 steps); (c) TBAF, THF, 80 °C (98%); (d) LiOH aq., THF (97%).

3. Conclusion

In summary, we have developed a versatile method for the highly enantioselective synthesis of C-7-oxidized aromatic bisabolanes employing a Sharpless asymmetric dihydroxylation reaction, followed by a SmI_2-mediated reductive elimination. Using this methodology, we first synthesized 1,3,5-bisabolatrien-7-ol (**3**). In our odor evaluation of **3**, several panelists noted differences in the odor between its enantiomers and perceived some favorable odors. Although the odor potency of 1,3,5-bisabolatrien-7-ol was relatively weak, a detailed odor study is currently underway in our laboratory. We then synthesized peniciaculin A (**4**) and B (**5**), which possess various functionalities on their aromatic rings. The absolute configurations of these natural products were confirmed using their ECD spectra and a comparison of their specific optical rotations. Hydroxysydonic acid (**6**), which possesses a hydroxy group on its side chain, was also synthesized. Our synthetic (*S*)-hydroxysydonic acid exhibited a small yet positive specific optical rotation, and we concluded that the absolute configuration of the natural hydroxysydonic acid is *S*. Because Hansen et al. reported the selective dehydration of Δ10,11 of a compound similar to **44** in the presence of the C-7 hydroxy group in their synthesis of gossonol [7d], our methodology could be applicable toward the synthesis of gossonol.

4. Experimental section

4.1. General

Melting points were uncorrected values. Optical rotations were recorded with a JASCO P-2100 polarimeter. IR spectra were measured with a JASCO FT/IR-4100 spectrophotometer. ^{1}H and ^{13}C NMR were recorded on JEOL JNM ECX-400 and ECZ-600 spectrometers. Chemical shifts (δ) were referenced to the residual solvent peaks as the internal standard ($CDCl_3$: $\delta_H = 7.26$, $\delta_C = 77.0$, CD_3OD: $\delta_H = 3.30$, $\delta_C = 49.0$, DMSO-d_6: $\delta_H = 2.50$, $\delta_C = 39.52$, acetone-d_6: $\delta_C = 29.82$). Mass spectra were recorded on a JEOL JMS-T100LP and JMS-T100LC. GC analyses were performed by Shimadzu GC-2010. HPLC analysis were performed by JASCO EXTREMA (PU-4180 as a pump and MD-4015 as a detector). Column chromatography was performed using Wako C200 and Kanto silica gel 60 N. Flash column chromatography was performed by Biotage Isolera One. Anhydrous tetrahydrofuran (THF), CH_2Cl_2, ether, and toluene were purchased from FUJIFILM Wako Pure Chemical.

4.2. Typical procedure for the synthesis of 1,3,5-bisabolatrien-7-ol

4.2.1. (E)-2-((3-(p-Tolyl)but-2-en-1-yl)thio)benzo[d]thiazole (**13**)

Under Ar atmosphere, to a stirred solution of **12** (7.20 g, 44.3 mmol), Ph_3P (11.6 g, 44.3 mmol), and 2-mercaptobenzothiazole (7.41 g, 44.3 mmol) in THF (30 mL) was added a solution of diethyl azodicarboxylate (DEAD) in toluene (40%, 26.2 mL, 57.6 mmol) at 0 °C. After stirring for overnight at room temperature (rt), the reaction mixture was quenched with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with H_2O and brine and dried with Na_2SO_4. After concentration under reduced pressure, the residue was chromatographed on silica gel (hexane/EtOAc = 20:1) to give **13** (10.1 g, 73%) as a pale yellow amorphous solid.

IR (KBr): ν_{max} (cm^{-1}) = 2950, 1455, 1427, 996; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.17 (s, 3H), 2.33 (s, 3H), 4.20 (d, J = 7.8 Hz, 2H), 5.99 (t, J = 7.8 Hz, 1H), 7.13 (d, J = 8.2 Hz, 2H), 7.29 (m, 3H), 7.42 (dd, J = 7.8, 7.8 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 16.1, 21.0, 32.3, 120.1, 121.0, 121.5, 124.2, 125.7 (x2), 126.0, 129.0 (x2), 135.4, 137.2, 139.7, 140.2, 153.3, 166.6; HRMS (DART-TOF) *m/z* calcd. for $C_{18}H_{18}NS_2^+$ $[M+H]^+$ 312.0873, found 312.0860.

4.2.2. (2S,3R)-1-(Benzo[d]thiazol-2-ylthio)-3-(p-tolyl)butane-2,3-diol (**14**)

To a stirred solution of **13** (2.20 g, 7.06 mmol), in *t*-BuOH/H_2O (v/v = 1:1, 340 mL) were added methanesulfonamide (67.2 mg, 706 mmol) and AD-mix-β (15.4 g) at 0 °C. After stirring for 38 h at 4 °C, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with H_2O and brine and dried with Na_2SO_4. After concentration under reduced pressure, the residue was chromatographed on silica gel (hexane/EtOAc = 3:1) to give (2*S*,3*R*)-**14** (2.38 g, 98%) as a colorless oil.

$[\alpha]_D^{24}$ −12 (c = 1.0, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) = 3371, 2985, 2896, 1456, 1422; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.66 (s, 3H), 2.35 (s, 3H), 2.91 (s, 1H), 3.30 (dd, J = 9.2, 14.7 Hz, 1H), 3.45 (dd, J = 2.3, 14.7 Hz, 1H), 4.18 (m, 1H), 5.03 (d, J = 2.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.30 (m, 1H), 7.41 (m, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.2 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 21.0, 24.6, 36.3, 76.4, 79.2, 121.0, 121.2, 124.6, 125.6 (x2), 126.2, 129.0 (x2), 135.3, 136.9, 141.7, 152.2, 168.4; HRMS (DART-TOF) *m/z* calcd. for $C_{18}H_{20}NO_2S_2^+$ $[M+H]^+$ 346.0930, found 346.0921.

4.2.3. (2S,3R)-1-(Benzo[d]thiazol-2-ylsulfonyl)-3-(p-tolyl)butane-2,3-diol (**15**)

To a stirred solution of (2*S*,3*R*)-**14** (31.4 mg, 90.9 μmol), in CH_2Cl_2 (1.4 mL) was added *m*-chloroperbenzoic acid (*m*CPBA) (70%, 44.9 mg, 182 μmol) at −78 °C. After stirring for 8 h at 4 °C, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine and dried with Na_2SO_4. After concentration under reduced pressure, the residue was chromatographed on silica gel (hexane/EtOAc = 1:1) to give (2*S*,3*R*)-**14** (27.3 mg, 80%) as colorless amorphous solids.

$[\alpha]_D^{24}$ −6.5 (c = 1.0, $CHCl_3$); IR (KBr): ν_{max} (cm^{-1}) = 3547, 3406, 2930, 1465, 1312, 1145, 1095; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.58 (s, 3H), 2.30 (s, 3H), 2.50 (s, 1H), 3.38 (d, J = 3.2 Hz, 1H), 3.51 (dd, J = 10.1, 15.1 Hz, 1H), 3.76 (d, J = 15.6 Hz, 1H), 4.53 (m, 1H), 7.09 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 7.63 (m, 2H), 8.00 (d, J = 8.2 Hz, 1H), 8.17 (d, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 20.8, 26.7, 57.9, 73.1, 74.6, 123.5, 125.0, 126.2 (x2), 128.0, 128.2, 128.3 (x2), 135.8, 136.5, 141.5, 152.3, 167.4; HRMS (DART-TOF) *m/z* calcd. for $C_{18}H_{20}NO_4S_2^+$ $[M+H]^+$ 378.0828, found 378.0818.

4.2.4. (S)-2-(p-Tolyl)but-3-en-2-ol (**11**)

Method A: Under Ar atmosphere, to a stirred solution of (2*S*,3*R*)-**15** (302 mg, 801 μmol) in THF (20 mL) was added 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) (242 μL, 1.62 mmol) at −20 °C. After stirring for 3 h, the reaction mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/EtOAc = 20:1) to give (*S*)-**11** (111 mg, 86%) as a colorless oil. The enantiomeric purity of the product was determined by GC analysis. Column: Chirasil Dex CB (25 m × 0.25 mm, 0.25 μm thickness), carrier gas: He (110 kPa), 100 °C (15 min) to 190 °C (0.8 °C/min), t_R (*S*)-**11** = 35.4 (>99%), t_R (*R*)-**11** = 36.1 (<1%).

Method B: Under Ar atmosphere, to a stirred solution of SmI_2 in THF (0.1 M, 4.66 mL, 466 μmol) was added dropwise a solution of (2*S*,3*R*)-**22** (33.9 mg, 93.3 μmol) in THF (1.5 mL) at −78 °C. After stirring for 20 min at rt, the reaction mixture was quenched with a drop of saturated aqueous NH_4Cl, and the mixture was poured into water. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with saturated aqueous NH_4Cl and dried with Na_2SO_4. After concentration under reduced pressure, the residue was chromatographed on silica gel (mixed with a few drops of Et_3N) (hexane/EtOAc = 20:1) to give (*S*)-**11** (8.9 mg, 59%) as a colorless oil. The enantiomeric purity of the product was determined by GC analysis. Column: Chirasil Dex CB (25 m × 0.25 mm, 0.25 μm thickness), carrier gas: He (110 kPa), 100 °C (15 min) to 190 °C (0.8 °C/min), t_R (*S*)-**11** = 35.4 (>99%), t_R (*R*)-**11** = 36.1 (<1%).

$[\alpha]_D^{24}$ −26.8 (c = 1.00, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) = 3404, 2981, 2359, 1512; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.65 (s, 3H), 1.83 (s, 1H), 2.34 (s, 3H), 5.13 (dd, J = 0.9, 10.5 Hz, 1H), 5.29 (dd, J = 0.9, 17.4 Hz, 1H), 6.17 (dd, J = 10.5, 17.4 Hz, 1H), 7.16 (d, J = 7.8 Hz, 2H), 7.36 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 21.0, 29.3, 74.6, 112.1, 125.1 (x2), 128.9 (x2), 136.6, 143.5, 145.0; HRMS (ESI-TOF) *m/z* calcd. for $C_{11}H_{14}ONa^+$ $[M+Na]^+$ 185.0937, found 185.0958.

4.2.5. (S,E)-6-Methyl-2-(p-tolyl)hept-3-en-2-ol (**16**)

Under Ar atmosphere, to a degassed and stirred solution of (*S*)-**11** (480 mg, 2.96 mmol) in toluene (29 mL) were added 4-methylpent-1-ene (1.88 mL, 14.8 mmol) and Grubbs 2nd catalyst (75.3 mg, 88.8 μmol). After stirring for 3 h, additional 4-methylpent-1-ene (1.88 mL, 14.8 mmol) and Grubbs 2nd catalyst (75.3 mg, 88.8 μmol) were added to the reaction mixture. After stirring for overnight, the reaction mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/EtOAc = 30:1) to give (*S*)-**16** (374 mg, 58%) as a colorless oil.

$[\alpha]_D^{23}$ −2.9 (c = 1.0, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) = 3424, 2956, 1172; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 0.89 (d, J = 6.4 Hz, 6H), 1.60−1.68 (m, 1H), 1.62 (s, 3H), 1.78 (s, 1H), 1.94 (dd, J = 6.9, 6.9, 2H), 2.34 (s, 3H), 5.65 (dt, J = 15.6, 6.9 Hz, 1H), 5.76 (d, J = 15.6 Hz, 1H), 7.14 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 21.0, 22.3, 22.4, 28.3, 29.9, 41.6, 74.3, 125.1 (x2), 127.6, 128.8 (x2), 136.3, 138.2, 144.4; HRMS (ESI-TOF) *m/z* calcd. for $C_{15}H_{22}ONa^+$ $[M+Na]^+$ 241.1563, found 241.1600.

4.2.6. (S)-1,3,5-Bisabolatrien-7-ol (**3**)

Under Ar atmosphere, to a degassed and stirred solution of (*S*)-**16** (220 mg, 1.01 mmol) in EtOH (44 mL) was added PtO_2 (132 mg, 581 mmol), and the reaction flask was flushed with hydrogen. After stirring for 3 h under a hydrogen balloon, the reaction mixture was filtered over a pad of Celite and washed with ethyl acetate. After concentration of the filtrate under reduced pressure, the residue

was chromatographed on silica gel (hexane/EtOAc = 30:1) to give (*S*)-**3** (188 mg, 85%) as a colorless oil.

$[\alpha]_D^{25}$ −9.5 (c = 1.0, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) = 3412, 2952, 1463, 1370; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 0.81 (d, *J* = 6.9 Hz, 6H), 1.13 (m, 2H), 1.26 (m, 2H), 1.49 (m, 1H), 1.54 (s, 3H), 1.65 (s, 1H), 1.76 (m, 2H), 2.34 (s, 3H), 7.15 (d, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 20.9, 21.8, 22.5, 22.6, 27.8, 30.1, 39.2, 44.3, 74.6, 124.7 (x2), 128.8 (x2), 136.0, 145.2; HRMS (ESI-TOF) *m/z* calcd. for $C_{15}H_{24}ONa^+$ $[M+Na]^+$ 243.1719, found 243.1732. The enantiomeric purity of the product was determined by GC analysis. Column: Chirasil Dex CB (25 m × 0.25 mm, 0.25 μm thickness), carrier gas: He (110 kPa), 100 °C (10 min) to 190 °C (1.0 °C/min), t_R (*S*)-**3** = 55.0 (>99%), t_R (*R*)-**3** = 55.4 (<1%).

4.2.7. (E)-2-((3-(p-Tolyl)but-2-en-1-yl)thio)pyridine (**19**)

Under Ar atmosphere, to a mixture of **18c** (1.00 g, 3.43 mmol), 4-iodotoluene (824 mg, 44.3 mmol), $Pd_2(dba)_3$ (236 mg, 257 μmol), Ph_3As (158 mg, 515 mmol), and Ag_2O (1.99 g, 8.58 mmol) was added a degassed THF (40 mL). After stirring for 26 h at 60 °C, the reaction mixture was diluted with EtOAc. The mixture was filtered over a pad of Celite and washed with ethyl acetate. After concentration of the filtrate under reduced pressure, the residue was chromatographed on silica gel (hexane/ether = 10:1) to give **19** (739 mg, 84%) as a pale yellow oil.

IR (ATR): ν_{max} (cm^{-1}) = 3043, 3024, 2991, 2918, 1577, 1555, 1452, 1412; ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) = 2.14 (s, 3H), 2.33 (s, 3H), 4.02 (d, *J* = 7.5 Hz, 2H), 5.94 (m, 1H), 6.99 (m, 1H), 7.11 (d, *J* = 7.5 Hz, 2H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.38 (m, 2H), 7.47 (dd, *J* = 2.1, 7.5, 8.3 Hz, 1H), 8.45 (dd, *J* = 2.1, 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 16.0, 21.0, 28.9, 119.4, 121.8, 122.3, 125.6 (x2), 128.8 (x2), 135.9, 136.8, 138.3, 140.1, 149.4, 159.1; HRMS (ESI-TOF) *m/z* calcd. for $C_{16}H_{17}NNaS_2^+$ $[M+Na]^+$ 278.0974, found 278.0971.

4.3. Typical procedure for the synthesis of peniciaculins A and B

4.3.1. 5,5′-Oxybis(1-(methoxymethoxy)-3-methylbenzene) (**26**)

Under Ar atmosphere, to a mixture of $Pd(OAc)_2$ (1.5 mg, 6.5 μmol), *t*BuXPhos (5.5 mg, 13 μmol), and K_3PO_4 (55 mg, 260 μmol) was added a solution of **23** (27.0 mg, 160 μmol) and **24** (44.0 mg, 130 μmol) in degassed toluene (2 mL). After stirring for 16 h at 100 °C, the reaction mixture was cooled to rt and diluted with ether. The organic layer was washed with 1 M NaOH and brine and dried with $MgSO_4$. After concentration under reduced pressure, the residue was chromatographed on silica gel (hexane/ether = 20:1) to give **26** (32.6 mg, 79%) as a colorless oil.

IR (film): ν_{max} (cm^{-1}) = 2919, 1588, 1467; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.29 (s, 6H), 3.47 (s, 6H), 5.13 (s, 4H), 6.47 (s, 2H), 6.53 (s, 2H), 6.61 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 21.6, 56.0, 94.4, 104.6, 111.7, 113.1, 140.6, 157.9, 158.2; HRMS (DART-TOF) *m/z* calcd. for $C_{18}H_{23}O_5^+$ $[M+H]^+$ 319.1540, found 319.530.

4.3.2. Diorcinol (**27**)

To a stirred solution of **26** (177 mg, 557 μmol) in THF/MeOH (v/v = 1:1, 10 mL) was added 1 N HCl (5 mL, 5 mmol). After stirring for 20 h at 50 °C, the reaction mixture was poured into H_2O, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with H_2O and brine and dried with Na_2SO_4. After concentration under reduced pressure, the residue was chromatographed on silica gel (hexane/EtOAc = 10:1) to give **27** (123 mg, 95%) as a colorless oil.

IR (film): ν_{max} (cm^{-1}) = 3366, 1592, 1464, 1322; ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) = 2.27 (s, 6H), 4.5–4.9 (br, 2H), 6.30 (dd, *J* = 2.3, 2.3 Hz, 2H), 6.40 (d, *J* = 2.3 Hz, 2H), 6.41 (br. d, *J* = 2.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 21.4, 103.4, 111.1, 112.2, 141.0, 156.4, 158.0; HRMS (DART-TOF) *m/z* calcd. for $C_{14}H_{15}O_3^+$ $[M+H]^+$ 231.1016, found 231.1003.

4.3.3. Methyl (S)-4-(2-hydroxybut-3-en-2-yl)-3-((2-(trimethylsilyl) ethoxy)methoxy)benzoate (**35**)

Under Ar atmosphere, to a stirred solution of SmI_2 in THF (0.1 M, 143 mL, 14.3 mmol) was added dropwise a solution of **34** (1.50 g, 2.86 mmol) in THF (8 mL) at −78 °C. After stirring for 20 min at rt, the reaction mixture was quenched with a drop of saturated aqueous NH_4Cl, and the mixture was poured into water. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with saturated aqueous NH_4Cl and dried with Na_2SO_4. After concentration under reduced pressure, the residue was chromatographed on silica gel (mixed with a few drops of Et_3N) (hexane/EtOAc = 3:1) to give **35** (769 mg, 76%) as a colorless oil.

$[\alpha]_D^{26}$ −20.2 (c = 1.00, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) = 3523, 2953, 1731, 1576, 1438; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 0.00 (s, 9H), 0.97 (dd, *J* = 7.3, 8.2 Hz, 2H), 1.69 (s, 3H), 3.77 (m, 2H), 3.91 (s, 3H), 4.06 (s, 1H), 5.07 (d, *J* = 10.5 Hz, 1H), 5.14 (d, *J* = 17.4 Hz, 1H), 5.31 (d, *J* = 6.9 Hz, 1H), 5.34 (d, *J* = 6.9 Hz, 1H), 6.19 (dd, *J* = 10.5, 17.4 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.68 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.78 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = −1.5 (x3), 17.9, 27.4, 52.1, 67.1, 74.8, 92.9, 112.0, 115.3, 123.1, 126.7, 130.5, 139.1, 144.5, 154.6, 166.6; HRMS (ESI-TOF) *m/z* calcd. for $C_{18}H_{28}O_5NaSi^+$ $[M+Na]^+$ 375.1598, found 375.1599.

4.3.4. Methyl (S)-4-(2-hydroxy-6-methylheptan-2-yl)-3-((2-(trimethylsilyl)ethoxy)methoxy)benzoate (**36**)

Under Ar atmosphere, to a degassed and stirred solution of **35** (207 mg, 586 mmol) in toluene (4 mL) were added 4-methylpent-1-ene (371 μL, 2.93 mmol) and Grubbs 2nd catalyst (14.9 mg, 17.6 μmol). After stirring for 11 h, additional 4-methylpent-1-ene (371 μL, 2.93 mmol) and Grubbs 2nd catalyst (14.9 mg, 17.6 μmol) were added to the reaction mixture. After stirring for 9 h, the reaction mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/EtOAc = 4:1) to give crude product as a pale brown oil. Under Ar atmosphere, to a degassed and stirred solution of the obtained crude product in EtOH (5 mL) was added PtO_2 (26.9 mg, 118 μmol), and the reaction flask was flushed with hydrogen. After stirring for 40 min under a hydrogen balloon, the reaction mixture was filtered over a pad of Celite and washed with ethyl acetate. After concentration of the filtrate under reduced pressure, the residue was chromatographed on silica gel (hexane/EtOAc = 5:1) to give **36** (177 mg, 73%) as a colorless oil.

$[\alpha]_D^{26}$ +6.3 (c = 1.0, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) = 3527, 2953, 1725, 1575, 1293; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 0.00 (s, 9H), 0.81 (d, *J* = 6.4 Hz, 6H), 0.99 (t, *J* = 8.5 Hz, 2H), 1.08–1.23 (m, 4H), 1.47 (m, 1H), 1.60 (s, 3H), 1.82 (m, 1H), 1.98 (m, 1H), 3.54 (s, 1H), 3.79 (t, *J* = 8.5 Hz, 2H), 3.90 (s, 3H), 5.34 (d, *J* = 6.9 Hz, 1H), 5.36 (d, *J* = 6.9 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.67 (dd, *J* = 1.8, 8.2 Hz, 1H), 7.78 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = −1.4 (x3), 18.0, 22.1, 22.6 (x2), 27.5, 27.8, 39.4, 42.2, 52.1, 67.0, 75.2, 92.9, 115.0, 123.0, 127.0, 130.0, 140.5, 154.5, 166.7; HRMS (ESI-TOF) *m/z* calcd. for $C_{22}H_{38}O_5NaSi^+$ $[M+Na]^+$ 433.2381, found 433.2427. The enantiomeric purity of the product was determined by HPLC analysis. Column: Chiralpack IB (250 mm × 4.6 mm), solvent: hexane/2-propanol = 95:5, 0.6 mL/min, t_R (*S*)-**36** = 16.6 (98%), t_R (*R*)-**36** = 11.1 (2%).

4.3.5. (S)-6-Methyl-2-(4-((3-methyl-5-(3-methyl-5-((2-(trimethylsilyl)ethoxy)methoxy)phenoxy)phenoxy)methyl)-2-((2-(trimethylsilyl)ethoxy)methoxy)phenyl)heptan-2-ol (**39**)

Under Ar atmosphere, to a stirred solution of **38** (6.7 mg, 17 μmol) and **28** (7.2 mg, 20 μmol) in DMF (1 mL) were added K_2CO_3

(3.5 mg, 17 μmol) and 18-crown-6 (0.7 mg, 2.5 μmol). After stirring for 3 h at 55 °C, additional K_2CO_3 (9.1 mg, 66 μmol) and 18-crown-6 (6.6 mg, 25 μmol) were added to the reaction mixture. After stirring for 17 h at 90 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried with Na_2SO_4. After concentration under reduced pressure, the residue was chromatographed on silica gel (hexane/EtOAc = 5:1) to give **39** (7.6 mg, 63%) as a colorless oil.

$[\alpha]_D^{28}$ +3.6 (c = 0.5, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) = 3555, 2952, 1732, 1602, 1505; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 0.002 (s, 9H), 0.003 (s, 9H), 0.82 (d, 6.9 Hz, 6H), 0.97 (m, 4H), 1.08−1.32 (m, 4H), 1.49 (m, 1H), 1.57 (s, 3H), 1.82 (m, 1H), 1.93 (m, 1H), 2.29 (s, 6H), 3.71−3.81 (m, 5H), 4.95 (s, 2H), 5.17 (s, 2H), 5.31 (d, J = 6.9 Hz, 1H), 5.32 (d, J = 6.9 Hz, 1H), 6.44 (s, 1H), 6.47 (s, 2H), 6.53 (s, 1H), 6.55 (s, 1H), 6.62 (s, 1H), 7.03 (d, J = 7.8 Hz, 1H), 7.19 (s, 1H), 7.32 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = −1.4 (x6), 18.0, 21.6, 21.7, 22.2, 22.6 (x2), 27.6, 27.9, 29.7, 39.5, 42.5, 66.3, 66.8, 69.8, 75.1, 92.9 (x2) 103.0, 104.7, 110.6, 111.8, 112.3, 113.0, 113.6, 120.7, 127.0, 135.1, 136.8, 140.5 (x2), 154.9, 157.8, 158.1, 158.5, 159.9; HRMS (ESI-TOF) *m/z* calcd. for $C_{41}H_{64}O_7NaSi_2^+$ $[M+Na]^+$ 747.4083, found 747.4083.

4.3.6. (S)-Peniciaculin A (*4*)

Under Ar atmosphere, to a stirred solution of **39** (9.8 mg, 14 μmol) in THF (1.5 mL) was added tetra-*n*-butylammonium fluoride (TBAF) in THF (1.0 M, 41 μL, 41 μmol). After stirring for 1 h, an additional TBAF in THF (1.0 M, 95 μL, 95 μmol) was added to the reaction mixture. After stirring for 15 h at 80 °C, the reaction mixture was quenched with H_2O, and the aqueous layer was extracted with ether. The combined organic layer was washed with saturated aqueous NH_4Cl and brine and dried with Na_2SO_4. After concentration under reduced pressure, the residue was chromatographed on silica gel (hexane/EtOAc = 2:1) to give **4** (5.0 mg, 79%) as amorphous solids.

$[\alpha]_D^{26}$ +9.6 (c = 0.049, MeOH); IR (KBr): ν_{max} (cm^{-1}) = 3404, 2924, 2851, 1585; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) = 0.785 (d, J = 6.4 Hz, 3H), 0.783 (d, J = 6.4 Hz, 3H), 1.05 (m, 2H), 1.23 (m, 2H), 1.44 (m, 1H), 1.48 (s, 3H), 1.64 (m, 1H), 1.88 (m, 1H), 2.18 (s, 3H), 2.23 (s, 3H), 4.94 (s, 2H), 5.65 (s, 1H), 6.17 (s, 1H), 6.24 (s, 1H), 6.35 (s, 1H), 6.37 (s, 1H), 6.42 (s, 1H), 6.60 (s, 1H), 6.76 (s, 1H), 6.78 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 9.41 (s, 1H), 9.86 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 21.1 21.2, 21.3, 22.4, 22.5, 27.3, 28.6, 38.8, 41.9, 69.0, 75.2, 102.8, 102.9, 109.9, 110.5, 111.2, 111.6, 115.2, 117.8, 126.6, 131.8, 136.3, 140.1, 140.2, 155.0, 157.46, 157.53, 158.4, 159.5; HRMS (ESI-TOF) *m/z* calcd. for $C_{29}H_{36}O_5Na^+$ $[M+Na]^+$ 487.2455, found 487.2442.

4.3.7. 4-((S)-2-Hydroxy-6-methylheptan-2-yl)-3-((2-(trimethylsilyl)ethoxy)methoxy)benzyl 4-((S)-2-hydroxy-6-methylheptan-2-yl)-3-((2-(trimethylsilyl)ethoxy)methoxy)benzoate (*41*)

To a stirred solution of **37** (21.4 mg, 53.9 μmol) and **40** (20.6 mg, 67.1 μmol) in CH_2Cl_2 (1.5 mL) were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (21.9 mg, 112 μmol) and DMAP (2.8 mg, 22 μmol) at 0 °C. After stirring for 19 h at rt, the reaction mixture was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried with Na_2SO_4. After concentration under reduced pressure, the residue was chromatographed on silica gel (hexane/EtOAc = 4:1) to give **41** (34.7 mg, 88%) as a colorless oil.

$[\alpha]_D^{26}$ +4.5 (c = 1.0, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) = 3521, 2953, 1722, 1614, 1575; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = −0.005 (s, 9H), −0.001 (s, 9H), 0.81 (d, J = 6.4 Hz, 6H), 0.82 (d, J = 6.4 Hz, 6H), 0.98 (t, J = 8.0 Hz, 4H), 1.08−1.27 (m, 8H), 1.48 (m, 2H), 1.58 (s, 3H), 1.59 (s, 3H), 1.81 (m, 2H), 1.95 (m, 2H), 3.53 (s, 1H), 3.71 (s, 1H), 3.78 (t, J = 8.0 Hz, 4H), 5.31−5.38 (m, 4H), 5.32 (s, 2H), 7.06 (d, J = 7.8 Hz, 1H), 7.23 (s, 1H), 7.33 (d, J = 8.2 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.70 (dd, J = 1.4, 8.2 Hz, 1H), 7.81 (d, J = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = −1.4 (x6), 17.99, 18.03, 22.1, 22.2, 22.6 (x4), 27.6 (x2), 27.8 (x2), 39.38, 39.44, 42.2, 42.5, 66.3, 66.8, 67.0, 75.0, 75.2, 92.94, 92.96 114.0, 115.1, 121.1, 123.0, 126.95, 127.03, 130.0, 135.3, 136.1, 140.7, 154.4, 154.8, 166.0; HRMS (ESI-TOF) *m/z* calcd. for $C_{42}H_{72}O_8NaSi_2^+$ $[M+Na]^+$ 783.4658, found 783.4625.

4.3.8. (7S,7′S)-Peniciaculin B (*5*)

Under Ar atmosphere, to a stirred solution of **41** (32.6 mg, 42.8 μmol) in THF (1.5 mL) was added TBAF in THF (1.0 M, 428 μL, 428 μmol). After stirring for 6 h at rt and 15 h at 80 °C, the reaction mixture was quenched with H_2O, and the aqueous layer was extracted with ether. The combined organic layer was washed with brine and dried with Na_2SO_4. After concentration under reduced pressure, the residue was chromatographed on silica gel (hexane/EtOAc = 2:1) to give **5** (18.6 mg, 87%) as amorphous solids.

$[\alpha]_D^{24}$ +4.0 (c = 0.34, MeOH); IR (KBr): ν_{max} (cm^{-1}) = 3459, 2953, 2868, 1698, 1577, 1507; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) = 0.76 (d, J = 6.5 Hz, 3H), 0.770 (d, J = 6.5 Hz, 3H), 0.772 (d, J = 6.5 Hz, 3H), 0.78 (d, J = 6.5 Hz, 3H), 0.94 (m, 1H), 1.05 (m, 5H), 1.26 (m, 2H), 1.42 (m, 2H), 1.49 (s, 3H), 1.50 (s, 3H), 1.65 (m, 2H), 1.88 (m, 1H), 1.97 (dd, J = 4.1, 12.8, 12.8 Hz, 1H), 5.20 (s, 2H), 5.47 (s, 1H), 5.66 (s, 1H), 6.78 (s, 1H), 6.81 (d, J = 7.8 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 1.3 Hz, 1H), 7.39 (dd, J = 1.3, 7.8 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 9.89 (s, 1H), 10.01 (d, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 21.3 (x2), 22.3, 22.4, 22.5 (x2), 27.22, 27.24, 28.2, 28.6, 38.8 (x2), 41.1, 41.8, 65.6, 74.5, 75.1, 115.4, 116.3, 118.0, 119.6, 126.8, 127.3, 128.8, 132.1, 135.6, 138.7, 154.6, 155.0, 165.5; HRMS (ESI-TOF) *m/z* calcd. for $C_{30}H_{44}O_6Na^+$ $[M+Na]^+$ 523.3030, found 523.3013.

4.4. (S)-Hydroxysydonic acid (*6*)

To a stirred solution of **44** (197 mg, 665 μmol) in THF/H_2O (v/v = 1:1, 2 mL) was added LiOH·H_2O (159 mg, 6.65 mmol) at 0 °C. After stirring for 16 h at rt, the reaction mixture was quenched with saturated aqueous NH_4Cl. The aqueous layer was acidified with 1 N HCl and extracted with EtOAc. The combined organic layer was washed with brine and dried with Na_2SO_4. After concentration under reduced pressure, the residue was chromatographed on silica gel (hexane/EtOAc = 1:2) to give **6** (182 mg, 97%) as colorless solids.

M.p. 131−132 °C; $[\alpha]_D^{19}$ +1.0 (c = 1.0, MeOH); IR (film): ν_{max} (cm^{-1}) = 3212, 2970, 2926, 1686, 1574, 1369, 1294, 1217; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) = 0.97 (s, 3H), 0.98 (s, 3H), 1.05 (m, 1H), 1.18−1.34 (m, 3H), 1.50 (s, 3H), 1.65 (dd, J = 3.6, 12.4, 12.4 Hz, 1H), 1.93 (dd, J = 4.0, 10.0, 12.7 Hz, 1H), 4.00 (s, 1H), 5.50 (s, 1H), 7.29 (d, J = 1.4 Hz, 1H), 7.33 (dd, J = 1.4, 7.8 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 9.98 (s, 1H); ^1H NMR (400 MHz, CD_3OD): δ (ppm) = 1.10 (s, 3H), 1.11 (s, 3H), 1.28 (m, 1H), 1.35−1.47 (m, 3H), 1.61 (s, 3H), 1.80 (m, 1H), 1.98 (m, 1H), 7.29 (d, J = 8.2 Hz, 1H), 7.37 (d, J = 1.6 Hz, 1H), 7.44 (dd, J = 1.6, 8.2 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ (ppm) 19.5, 29.7 (x2), 44.3, 44.9, 70.1, 78.6, 118.7, 121.0, 127.6, 131.3, 136.7, 157.3, 167.4; ^{13}C NMR (100 MHz, CD_3OD): δ (ppm) 20.0, 28.8, 29.1, 29.2, 43.9, 45.0, 71.4, 77.8, 118.6, 121.5, 127.8, 131.6, 138.0, 156.9, 169.8 (See Tables S4 and S5); HRMS (ESI-TOF) *m/z* calcd. for $C_{15}H_{21}O_5^-$ $[M-H]^-$ 281.1394, found 281.1395.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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