Tetrahedron 67 (2011) 6753–6761

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Enantioselective syntheses of the assigned structures of the helibisabonols A and B

Akari Miyawaki, Mayu Osaka, Makoto Kanematsu, Masahiro Yoshida, Kozo Shishido *

Graduate School of Pharmaceutical Sciences, The University of Tokushima, 1-78-1 Sho-machi, Tokushima 770-8505, Japan

ARTICLE INFO

Article history:
Received 3 March 2011
Received in revised form 21 March 2011
Accepted 22 March 2011
Available online 11 April 2011

Keywords:
Total synthesis
Enantioselective synthesis
Sesquiterpene
Desymmetrization
Lipase

ABSTRACT

The enantioselective syntheses of the compounds with the assigned structures of the helibisabonols A and B have been accomplished. Using an enzymatic desymmetrization of the σ-symmetrical diol (route a) and a diastereoselective conjugate addition of the methyl to the enone with a chiral auxiliary (route b) we constructed the key tertiary stereogenic center at the benzylic position (C7) and then used an asymmetric dihydroxylation for assembling the C10 stereogenic center. In addition, possible diastereoisomers of the natural products were prepared and detailed comparisons of the ^{1}H and ^{13}C NMR spectra were conducted. As a result, the structure originally assigned to helibisabonol A may be revised to (7*R*,10*R*)-**1**. In the case of helibisabonol B, the (7*R*,10*R*)-**2** would be reasonable based on a comparison of the NMR data and the biogenetic parallelism with helibisabonol A.

1. Introduction

The sesquiterpenes helibisabonols A (**1**) and B (**2**) were isolated from the extracts of dried leaves of *Helianthus annuus* L. cv. Peredovick® by Macías et al.[1] The structures were elucidated on the basis of extensive NMR and theoretical studies and it was revealed that both are aromatic bisabolene sesquiterpenes with a hydroquinone moiety and two tertiary stereogenic centers at the C7 and C10 positions. The relative stereochemistries of the two chiral centers were deduced to be (7*R**,10*S**) and (7*R**,10*R**), respectively, based on a comparison of the coupling constants between the experimental and the theoretical values. Helibisabonol A (**1**) has been reported to exhibit inhibitory activity against the growth of etiolated wheat coleoptiles, which is called allelopathic activity. Since the helibisabonols are believed to represent the biogenetic precursor of helianane sesquiterpenes (e.g., heliannuols[2] and heliespirones[3]), the development of an efficient and practical synthetic route to both natural products would be valuable. Although both a racemic and an enantioselective synthesis of **1** have been reported by Macías[4] and Sirat,[5] respectively, the synthesis of helibisabonol B (**2**) has never been accomplished. We describe herein the enantioselective syntheses of the assigned structures of the helibisabonols A (**1**) and B (**2**) and the structure elucidation of the natural products by extensive comparisons of the NMR spectra (Fig. 1).

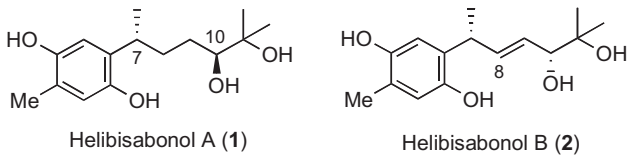


Fig. 1. Structures of the helibisabonols A and B.

2. Results and discussion

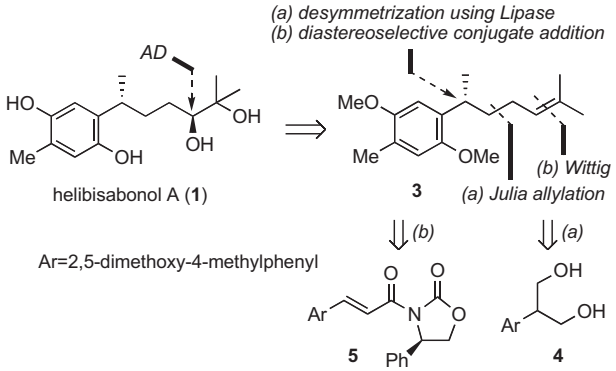
2.1. Enantioselective synthesis of helibisabonol A (1)

For the enantioselective synthesis, the (7*R*,10*S*)-**1** was initially targeted since the absolute configuration at C7 of the biogenetically paralleled heliannuols had been established to be *R*.[6a] Our retrosynthetic analysis of **1** is shown in Scheme 1. We envisaged the C10-*S* stereogenic center of **1** being assembled by dihydroxylation using AD-mix-α. For the preparation of **3** with the C7-*R* configuration, we planned to examine the two strategies that we have already developed; route a: the enzymatic desymmetrization[7] of a σ-symmetrical 2-aryl-1,3-propanediol **4**[6,8] followed by the Julia allylation with prenyl bromide, and route b: the diastereoselective conjugate addition of the methyl to the substrate **5**[9] with a chiral auxiliary followed by Wittig olefination (Scheme 1).

Enzymatic desymmetrization of the prochiral diol **4**, derived from 4-iodo-2,5-dimethoxytoluene via two steps,[6] using PPL (Porcine Pancreatic Lipase) provided the optically active monoacetate

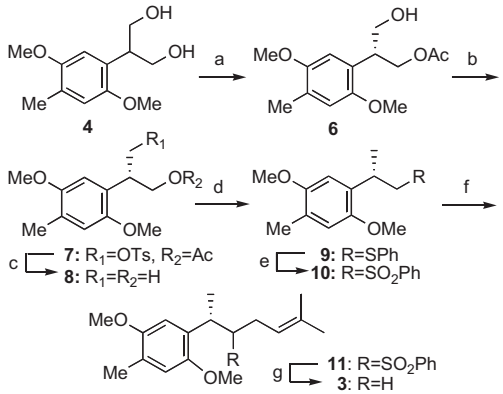
* Corresponding author. Tel.: +81 88 6337287; fax: +81 88 6339575; e-mail address: shishido@ph.tokushima-u.ac.jp (K. Shishido).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.03.064



Scheme 1. Synthetic strategy of **1**.

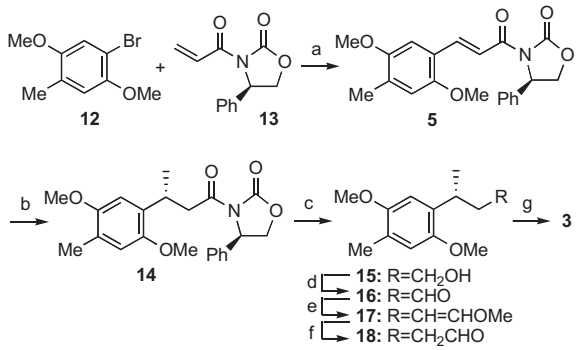
R-**6**[8a] with 84% ee (HPLC, Chiralcel AD), which was converted to the alcohol **8** by tosylation, $NaBH_4$ reduction, and hydrolysis. At this stage, recrystallization rendered **8** optically pure. Phenylsulfenylation followed by *m*-CPBA oxidation of the resulting sulfide **9** produced the sulfone **10**, which was treated with ^{n}BuLi and prenyl bromide in THF/HMPA at −78 °C to give **11**. Finally, desulfonylation using Na/Hg provided **3** in 8% overall yield for nine steps from 4-iodo-2,5-dimethoxytoluene (Scheme 2).



Scheme 2. Preparation of **3** via route a. Reagents and conditions: (a) PPL, vinyl acetate, Et_2O, rt, 34 h, 34% (98% based on recovered **4**), 84% ee (HPLC, Chiralcel AD); (b) TsCl, Et_3N, 4-DMAP, CH_2Cl_2, rt, 2 h, 98%; (c) $NaBH_4$, DMSO, 60 °C, 1.5 h then K_2CO_3, MeOH, H_2O, rt, 3 h, 51% (after recrystallization from *n*-hexane), >99% ee (HPLC, Chiralcel OD); (d) PhSSPh, ^{n}Bu$_3$P, pyridine, rt, 1 h; (e) *m*-CPBA, $KHCO_3$, $CH2Cl_2$, rt, 4 h, 94% (two steps); (f) prenyl bromide, ^{n}BuLi, HMPA, THF, −78 °C, 0.5 h, 76%; (g) Na/Hg, Na_2HPO_4, MeOH, sonication, rt, 8 h, 86%.

Although we could obtain the desired **3**, this route contains two low-yielding steps, **4**→**6** and the preparation of optically pure **8**. Therefore, we tried to find a more efficient route. Substrate **5** for the key diastereoselective conjugate addition was synthesized in 81% yield by the Heck reaction[10,11] of the aryl bromide **12**[12] and the optically active enone **13**[13] with catalytic $Pd(OAc)_2$ and (*o*-tol)$_3$P in the presence of Et_3N. Treatment of a solution of **5** in THF with MeMgBr and $CuBr{\cdot}SMe_2$ at −20 °C produced the methylated product **14** as an inseparable mixture of diastereoisomers (12:1 from ^{1}H NMR in C_6D_6), which was recrystallized immediately from AcOEt and *n*-hexane to give the diastereomerically pure **14** in 71% yield. Reductive removal of the chiral auxiliary with $NaBH_4$ followed by PCC oxidation provided the aldehyde **16**, which was converted to **18** by a standard one-carbon homologation procedure. It was then subjected to the Wittig reaction to produce **3** in 33% overall yield for seven steps from **12** (Scheme 3).

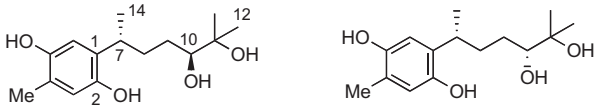
Sharpless dihydroxylation[14] of **3** with AD-mix-α provided the diol **19** with the 10*S* configuration in 91% yield with 93% de (^{1}H NMR). Sequential oxidation with cerium ammonium nitrate (CAN) and reduction of the resulting quinone **20** with $Na_2S_2O_4$[6] gave



Scheme 3. Preparation of **3** via route b. Reagents and conditions: (a) $Pd(OAc)_2$, (*o*-tol)$_3$P, Et_3N, CH_3CN/H_2O (10/1), 80 °C, 2 h, 81%; (b) MeMgBr, $CuBr{\cdot}SMe2$, THF, −20 °C, 0.5 h, 71% (recrystallized from AcOEt/*n*-hexane); (c) $NaBH_4$, THF/H_2O (3/1), 50 °C, 3.5 h, 80%; (d) PCC, CH_2Cl_2, rt, 3 h; (e) $(Ph_3P^+CH_2OCH_3)Cl^-$, NaHMDS, THF, rt, 1 h; (f) 2 N HCl (aq), THF, rt, 6 h, 71% (three steps); (g) $[Ph_3P^+CH(CH3)2]I^-$, ^{t}BuOK, THF, rt, 0.5 h, quant.

(7*R*,10*S*)-helibisabonol A (**1**) in 51% yield for the two steps. Although the optical rotation of the synthetic **1** {$[\alpha]_D^{29}$ −38.9 (*c* 0.68, acetone)} was in close accord with the reported values {$[\alpha]_D^{25}$ −44.9 (*c* 0.1, acetone);[1] $[\alpha]_D$ −31.5 (*c* 0.3, MeOH)[5]}, the ^{1}H and ^{13}C NMR spectra were not identical with those of the natural product (Tables 1 and 2). Notably, the chemical shift of the methine proton H10 at δ 3.30 exhibits a distinctive difference ($\Delta\delta$=0.36 ppm) and the chemical shift differences ($\Delta\delta$) of the three protons at H7, H8, and H10 are >0.05 ppm. In addition, five of the fifteen carbons showed large differences (>0.5 ppm) in the ^{13}C NMR. Therefore, it was deduced that the configuration at C10, which has been elucidated by an ambiguous method,[1] was actually *R*. Thus, we examined the preparation of the 10*R*-diastereoisomer. Treatment of **3** with AD-mix-β at 0 °C provided quantitatively the (7*R*,10*R*)-diol **21** as a single product (^{1}H NMR) and it was similarly converted to (7*R*,10*R*)-**1** {$[\alpha]_D^{29}$ −6.9 (*c* 0.33, acetone)}[15] in 69% yield for the two steps (Scheme 4). The chemical shifts of the ^{1}H NMR were in good accord with those of the natural product except for H10. The chemical shifts in the ^{13}C NMR were identical with those of the natural product except for those of the C7, C9, and C13 carbons, which were

Table 1
Comparison of ^{1}H and ^{13}C NMR chemical shifts of the natural helibisabonol A with synthetic (7*R*,10*S*)- and (7*R*,10*R*)-**1**. The chemical shift difference ($\Delta\delta$) is indicated in parenthesis. Differences $\Delta\delta$ >0.05/0.5 ppm (^{1}H/^{13}C) are marked in bold. Assignments in ^{1}H NMR are supported by 500 MHz H/H-COSY



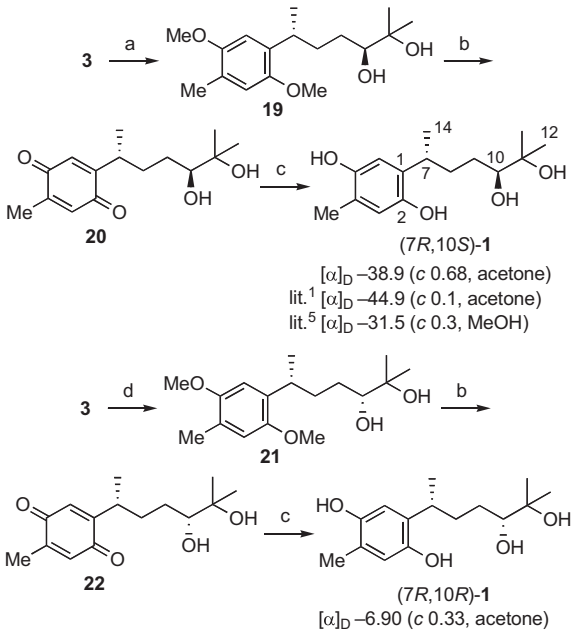
H	Natural	Synthetic		C	Natural	Synthetic	
		(7*R*,10*S*)-**1**	(7*R*,10*R*)-**1**			(7*R*,10*S*)-**1**	(7*R*,10*R*)-**1**
3	6.51	6.55 (+0.04)	6.55 (+0.04)	1	132.1	132.2 (+0.1)	132.4 (+0.3)
6	6.59	6.59 (0)	6.60 (+0.01)	2	147.5	148.0 (+0.5)	147.8 (+0.3)
7	3.06	**3.12** (+**0.06**)	3.11 (+0.05)	3	117.9	118.2 (+0.3)	118.3 (+0.4)
8	1.74	**1.86** (+**0.12**)	1.78 (+0.04)	4	121.9	122.2 (+0.3)	122.2 (+0.3)
8′	1.55	1.54 (−0.01)	1.58 (+0.03)	5	148.8	149.1 (+0.3)	149.1 (+0.3)
9	1.45	1.47 (+0.02)	1.50 (+0.05)	6	113.3	**113.9** (+**0.6**)	113.7 (+0.4)
9′	1.23	1.18 (−0.05)	1.27 (+0.04)	7	29.8[a]	**32.3** (+**2.5**)	**32.3** (+**2.5**)
10	3.66	**3.30** (−**0.36**)	**3.27** (−**0.39**)	8	35.4	35.2 (−0.2)	35.8 (+0.4)
12	1.04	1.05 (+0.01)	1.06 (+0.02)	9	24.4[b]	**30.0** (+**5.6**)	**30.0** (+**5.6**)
13	1.03	1.03 (0)	1.06 (+0.03)	10	79.2	78.9 (−0.3)	79.5 (+0.3)
14	1.09	1.13 (+0.04)	1.14 (+0.05)	11	72.4	72.8 (+0.4)	72.7 (+0.3)
15	2.04	2.08 (+0.04)	2.08 (+0.04)	12	25.5	26.0 (+0.5)	25.8 (+0.3)
C10−OH		3.40	3.59	13	29.0[b]	**24.7** (−**4.3**)	**24.7** (−**4.3**)
C11−OH		3.21	3.27	14	21.1	**22.0** (+**0.9**)	21.4 (+0.3)
				15	15.4	15.8 (+0.4)	15.7 (+0.3)

[a] This may be due to impurity.
[b] These assignments may be reversed.

Table 2
Comparison of the selected *J* values (Hz) of the natural helibisabonol A with synthetic (7*R*,10*S*)- and (7*R*,10*R*)-**1**

H	Natural	Synthetic	
		(7*R*,10*S*)-**1**	(7*R*,10*R*)-**1**
7–8	7.0	7.0	7.0
7–8′	7.6	7.0	7.0
9–10	1.4	2.0	2.0
9′–10	4.9[a]	10.0	10.0
10-OH	—	5.0	5.0

[a] This may be the *J* between H10 and C10–OH.



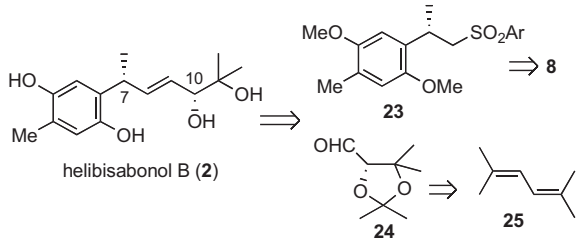
Scheme 4. Syntheses of (7*R*,10*S*)-**1** and (7*R*,10*R*)-**1**. Reagents and conditions: (a) AD-mix-α, $CH_3SO_2NH_2$, ^{t}BuOH, H_2O, 0 °C, 23 h, 91%, 93% de; (b) CAN, CH_3CN, H_2O, 0 °C, 0.5 h, 62% for **20**, 85% for **22**; (c) $Na_2S_2O_4$, THF, H_2O, rt, 10 min, 82% for (7*R*,10*S*)-**1**, 81% for (7*R*,10*R*)-**1**; (d) AD-mix-β, $CH_3SO_2NH_2$, ^{t}BuOH, H2O, 0 °C, 21 h, quant, >99% de.

also different in the (7*R*,10*S*) isomer. We also compared the selected coupling constants between the natural product and the two synthetic compounds (Table 2). The observed H9′–H10 coupling constant (*J*=4.9 Hz) was quite similar to the coupling (*J*=5.0 Hz) between H10 and OH for the synthetic **1**. Therefore, it was thought that the chemical shift at *δ* 3.66 in the ^{1}H NMR of the natural product is not that of H10 but rather that of C10–OH. In our case, the signals of the C10–OH were observed at *δ* 3.40 (doublet, *J*=5.0 Hz, D_2O exchangeable) for the (7*R*,10*S*)-**1** and at *δ* 3.59 (doublet, *J*=5.0 Hz, D_2O exchangeable) for the (7*R*,10*R*)-**1**, respectively. From these data, one may conclude that the structure of helibisabonol A is (7*R*,10*R*)-**1** (Tables 1 and 2).

2.2. Enantioselective synthesis of helibisabonol B (2)

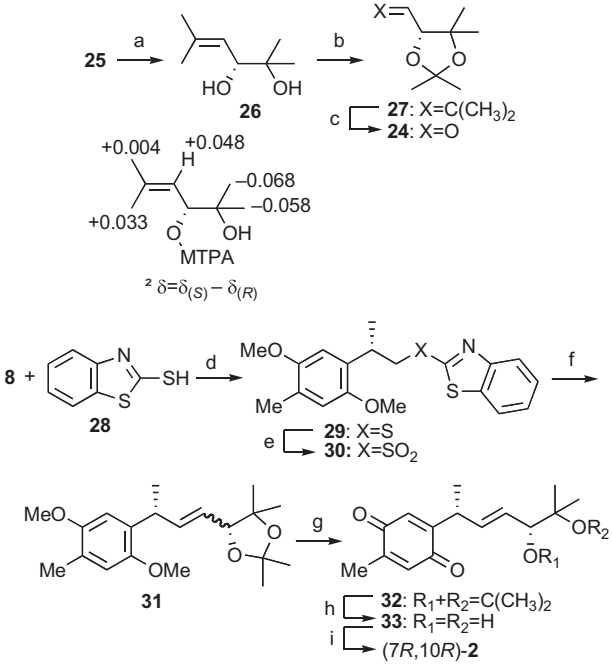
Our retrosynthesis of helibisabonol B (**2**), illustrated in Scheme 5, proposes a convergent strategy employing the Julia coupling of the two chiral building blocks **23** and **24**.[16] The left hand segment **23** would be prepared from the optically active alcohol **8**. The right half aldehyde **24** could be accessed from a commercially available 2,5-dimethylhexa-2,4-diene (**25**) (Scheme 5).

Asymmetric dihydroxylation of **25** with AD-mix-β provided the diol **26**[17] in 79% yield with 93% ee (^{1}H NMR of the MTPA ester). The configuration of a newly generated stereogenic center was confirmed to be *R* by the Kusumi–Mosher method[18] as shown in Scheme 6. After protection of the diol as an acetonide, ozonolysis followed by



Scheme 5. Synthetic strategy of **2**.

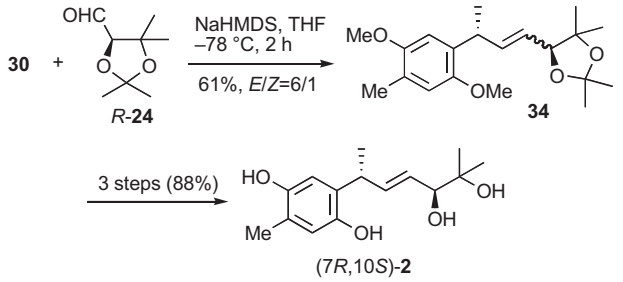
reductive workup produced the right hand segment *S*-aldehyde **24**.[16] We next examined the Julia coupling[19] for the installation of the *E*-alkene. The reaction of **10** with **24** using the three-step sequence (1. ^{n}BuLi, THF, −78 °C; 2. BzCl, 4-DMAP, THF, rt; 3. Na/Hg, Na_2HPO_4, MeOH, rt) produced the alkene **31** as an inseparable mixture of *E*/*Z* isomers (4.4:1) in 17% yield. Higher yield was obtained using the modified Julia olefination;[20] treatment of the sulfone **30**, prepared from **8** by sequential sulfenylation with benzo[*d*]thiazole-2-thiol (**28**) and oxidation of the resulting **29** with ammonium heptamolybdate tetrahydrate/H_2O_2, with **24** in the presence of NaHMDS provided **31** as a 3:1 mixture of *E* and *Z* isomers in 60% yield. Cleavage of methyl ethers on the aryl ring was realized via a two-step sequence.[6] Oxidation of **31** with CAN produced the quinone **32** quantitatively. At this stage, *E* and *Z* isomers could be separated by HPLC. The acetonide moiety of the *E*-isomer was hydrolyzed and the resulting diol **33** was reduced with $Na_2S_2O_4$ to give the (7*R*,10*R*)-helibisabonol B (**2**), {$[\alpha]_D^{27}$ +0.9 (*c* 0.47, acetone), lit.[1] $[\alpha]_D^{25}$ −7.2 (*c* 0.1, acetone)}, which is the assigned structure[1] (Scheme 6).



Scheme 6. Synthesis of (7*R*,10*R*)-helibisabonol B (**2**). Reagents and conditions: (a) AD-mix-β, $CH_3SO_2NH_2$, ^{t}BuOH, H_2O, 0 °C, 20 h, 79%, 93% ee; (b) $(CH_3)_2C(CH_3)_2$, *p*-TsOH, acetone, rt, 8 h, quant.; (c) O_3 then Me_2S, CH_2Cl_2, −78 °C, 68%; (d) diisopropyl azodicarboxylate, Ph_3P, THF, rt, 2.5 h, 91%; (e) ammonium heptamolybdate tetrahydrate, 30% H_2O_2 (aq), EtOH, rt, 4 h, 93%; (f) NaHMDS, *S*-**24**, THF, −78 °C, 1 h, 60%. *E*/*Z*=3/1; (g) CAN, CH_3CN, H_2O, rt, 0.5 h, quant; (h) 10% HCl (aq), MeOH, rt, 5 h, 98%; (i) $Na_2S_2O_4$, THF, H_2O, rt, 0.5 h, 95%.

As in the case of helibisabonol A, we also prepared the diastereomeric (7*R*,10*S*)-**2** for comparison purposes. According to the procedure described above, **30** was condensed with *R*-**24**, prepared by using AD-mix-α for the asymmetric dihydroxylation, to give

a 6:1 mixture of the *E*/*Z* isomers of **34**, which were separated by HPLC, in 61% yield. The desired *E*-isomer of **34** was then converted to (7*R*,10*S*)-**2**, {[α]$_D$ −23.1 (*c* 0.66, acetone)}, via the same three-step sequence (Scheme 7).



Scheme 7. Synthesis of (7*R*,10*S*)-helibisabonol B (**2**).

Comparison of the ^{1}H and ^{13}C NMR chemical shifts between the natural helibisabonol B and the two synthetic diastereoisomers (7*R*,10*R*)- and (7*R*,10*S*)-**2** is shown in Table 3. They showed similar chemical shift differences (Δδ) both in the ^{1}H and ^{13}C NMR, except for the C7 and C10 chemical shifts in the ^{13}C NMR, which may be due to impurities. The *J* values for the selected protons of the natural and synthetic compounds were also similar (Table 4). Although it was difficult to determine the structure of helibisabonol B from these data, the (7*R*,10*R*)-**2**, which was originally assigned to the natural product, would be a more reasonable structure from the point of view of biogenetic parallelism with the helibisabonol A (Tables 3 and 4).

Table 4
Comparison of the selected *J* values (Hz) of the natural helibisabonol B with synthetic (7*R*,10*R*)- and (7*R*,10*S*)-**2**

H	Natural	Synthetic	
		(7*R*,10*R*)-**2**	(7*R*,10*S*)-**2**
7–8	6.6	6.5	6.0
7–14	6.6	7.0	7.0
8–9	15.5	15.5	15.5
9–10	7.7	7.0	7.0
10-OH	—	4.0	4.0

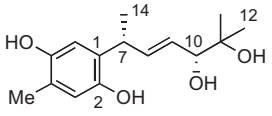
diastereoisomers for both natural products and made a detailed comparison of the NMR data. As a result, it would be reasonable that the structure of helibisabonol A is (7*R*,10*R*)-**1** and that of helibisabonol B is (7*R*,10*R*)-**2**.

4. Experimental

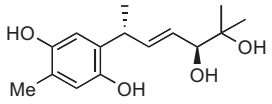
4.1. General

All nonaqueous reactions were carried out under a positive atmosphere of argon in dried glassware unless otherwise indicated. Materials were obtained from commercial suppliers and used without further purification except when otherwise noted. Solvents were dried and distilled according to standard protocols. The phrase 'residue upon workup' refers to the residue obtained when the organic layer was separated and dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. Column chromatography was performed on silica gel, and flash column chromatography was performed on silica gel using the indicated solvent.

Table 3
Comparison of ^{1}H and ^{13}C NMR chemical shifts of the natural helibisabonol B with synthetic (7*R*,10*R*)- and (7*R*,10*S*)-**2**. Assignments in ^{1}H NMR are supported by 500 MHz H/H-COSY



(7*R*,10*R*)-**2**



(7*R*,10*S*)-**2**

H	Natural	Synthetic		C	Natural	Synthetic	
		(7*R*,10*R*)-**2**	(7*R*,10*S*)-**2**			(7*R*,10*R*)-**2**	(7*R*,10*S*)-**2**
3	6.52	6.58 (+0.06)	6.57 (+0.05)	1	132.1	130.8 (−1.3)	130.6 (−1.5)
6	6.49	6.57 (+0.08)	6.57 (+0.08)	2	147.5	147.7 (+0.2)	147.5 (0)
7	3.70	3.79 (+0.09)	3.79 (+0.09)	3	117.9	118.2 (+0.3)	118.1 (+0.2)
8	5.81	5.85 (+0.04)	5.87 (+0.06)	4	121.9	122.7 (+0.8)	122.7 (+0.8)
9	5.46	5.55 (+0.09)	5.54 (+0.08)	5	148.8	149.1 (+0.3)	148.9 (+0.1)
10	3.78	3.80 (+0.02)	3.79 (+0.01)	6	113.3	114.6 (+1.3)	114.5 (+1.2)
12	1.07	1.09 (+0.02)	1.11 (+0.04)	7	28.9[a]	35.4 (+6.5)	35.4 (+6.5)
13	1.02	1.07 (+0.05)	1.08 (+0.06)	8	138.2	137.4 (−0.8)	137.5 (−0.7)
14	1.26	1.24 (−0.02)	1.24 (−0.02)	9	127.7	128.9 (+1.2)	128.6 (+0.9)
15	2.10	2.08 (−0.02)	2.08 (−0.02)	10	31.9[a]	80.1 (+48.2)	80.0 (+48.1)
				11	72.4	72.7 (+0.3)	72.6 (+0.2)
				12	26.3	24.7 (−1.6)	24.6 (−1.7)
				13	26.5	26.3 (−0.2)	26.2 (−0.3)
				14	20.8	20.4 (−0.4)	20.3 (−0.5)
				15	15.4	15.8 (+0.4)	15.7 (+0.3)

[a] These may be due to impurities.

3. Conclusion

In conclusion, we have completed the enantioselective total syntheses of the assigned structures of the helibisabonols A and B using two key reactions, lipase-mediated desymmetrization and diastereoselective conjugate addition, for the construction of the tertiary carbon stereogenic center at the benzylic position (C7). In addition, we also have prepared two corresponding

*4.1.1. (R)-2-(2,5-Dimethoxy-4-methylphenyl)-3-hydroxypropyl acetate (**6**).* To a stirred solution of diol **4** (3.35 g, 14.8 mmol) in Et_2O (70 mL) were added PPL (6.70 g) and vinyl acetate (2.73 mL, 29.6 mmol) at rt. After stirring was continued for 34 h at the same temperature, the reaction mixture was filtered through a pad of Celite. The resulting solution was evaporated in vacuo, the residue was chromatographed on silica gel with hexane/AcOEt (2:1 v/v) as eluent to give monoacetate **6** (1.30 g, 34%, 84% ee) as a yellow oil

and some starting material was recovered (2.12 g, 64%); $[\alpha]_D^{25}$ +12.9 (*c* 1.0 in $CHCl_3$); IR (neat): 3457, 1738, 1211, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.89 (1H, s, D_2O exchangeable), 2.05 (3H, s), 2.21 (3H, s), 3.53 (1H, quint, *J*=5.9 Hz), 3.78 (6H, s), 3.85 (2H, d, *J*=6.0 Hz), 4.42 (1H, dd, *J*=7.7 and 10.9 Hz), 4.36 (1H, dd, *J*=5.9 and 10.9 Hz), 6.72 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2 (CH_3), 21.0 (CH_3), 41.1 (CH), 56.1 (CH_3), 56.2 (CH_3), 63.2 (CH_2), 64.5 (CH_2), 111.4 (CH), 114.3 (CH), 124.8 (Cq), 126.2 (Cq), 151.2 (Cq), 151.8 (Cq), 171.4 (Cq); MS (EI) *m*/*z* 268 $[M]^+$; HRMS (EI) *m*/*z* calcd for $C_{14}H_{20}O_5$ $[M]^+$ 268.1311, found 268.1317. Enantiomeric excess was determined by HPLC analysis [Chiralcel AD, 3% isopropanol/hexane, 1.0 mL/min, λ=254 nm, retention times 27.1 min (*S*) and 31.9 min (*R*)].

*4.1.2. (S)-2-(2,5-Dimethoxy-4-methylphenyl)-3-(tosyloxy)propyl acetate (**7**).* To a stirred solution of monoacetate **6** (1.84 g, 6.87 mmol) in CH_2Cl_2 (30 mL) were added NEt_3 (4.79 mL, 34.4 mmol), TsCl (3.93 g, 20.6 mmol), and catalytic amount of 4-DMAP at rt. After stirring was continued for 2 h at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (1:1 v/v) as eluent to give tosylate **7** (2.84 g, 98%) as a yellow oil; $[\alpha]_D^{27}$ +4.6 (*c* 0.8 in $CHCl_3$); IR (neat): 1741, 1365, 1177, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.98 (3H, s), 2.19 (3H, s), 2.43 (3H, s), 3.62 (1H, m), 3.67 (3H, s), 3.72 (3H, s), 4.28 (4H, m), 6.53 (1H, s), 6.60 (1H, s), 7.26 (2H, d, *J*=8.2 Hz), 7.65 (2H, d, *J*=8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2 (CH_3), 20.8 (CH_3), 21.6 (CH_3), 38.3 (CH), 55.9 (CH_3), 56.0 (CH_3), 63.4 (CH_2), 69.7 (CH_2), 111.4 (CH), 114.0 (CH), 122.5 (Cq), 126.6 (Cq), 127.9 (CH), 129.6 (CH), 132.9 (Cq), 144.6 (Cq), 150.8 (Cq), 151.6 (Cq), 170.7 (Cq); MS (EI) *m*/*z* 422 $[M]^+$; HRMS (EI) *m*/*z* calcd for $C_{21}H_{26}O_7S$ $[M]^+$ 422.1399, found 422.1410.

*4.1.3. (S)-2-(2,5-Dimethoxy-4-methylphenyl)propan-1-ol (**8**).* To a stirred solution of tosylate **7** (1.90 g, 4.49 mmol) in DMSO (10 mL) was added $NaBH_4$ (0.68 g, 18.0 mmol) at rt, and stirring was continued for 1.5 h at 60 °C. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with brine. The residue upon workup was dissolved in MeOH/H_2O (5:1, 18 mL) and added K_2CO_3 (1.24 g, 8.98 mmol) at rt. After stirring was continued for 3 h at the same temperature, the reaction mixture was extracted with AcOEt. The combined extracts were washed with brine. The residue upon workup was recrystallized from hexane to give alcohol **8** (0.48 g, 51%, >99% ee, two steps) as colorless crystals; mp 78.0–79.5 °C (recrystallized from hexane); $[\alpha]_D^{25}$ −12.7 (*c* 1.0 in $CHCl_3$); IR (neat): 3274, 1209, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, d, *J*=6.8 Hz), 1.54 (1H, s, D_2O exchangeable), 2.21 (3H, s), 3.42 (1H, m), 3.69 (2H, d, *J*=6.8 Hz), 3.78 (3H, s), 3.80 (3H, s), 6.70 (1H, s), 6.71 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1 (CH_3), 16.7 (CH_3), 35.5 (CH), 56.1 (CH_3), 56.3 (CH_3), 68.0 (CH_2), 110.3 (CH), 114.4 (CH), 125.3 (Cq), 129.8 (Cq), 151.1 (Cq), 152.0 (Cq); MS (EI) *m*/*z* 210 $[M]^+$; HRMS (EI) *m*/*z* calcd for $C_{12}H_{18}O_3$ $[M]^+$ 210.1256, found 210.1245. Enantiomeric excess was determined by HPLC analysis [Chiralcel OD, 1% isopropanol/hexane, 0.5 mL/min, λ=254 nm, retention times 57.2 min (*S*) and 52.5 min (*R*)].

*4.1.4. (S)-1,4-Dimethoxy-2-methyl-5-[1-(phenylsulfonyl)propan-2-yl]benzene (**10**).* To a stirred solution of alcohol **8** (75.7 mg, 0.36 mmol) in pyridine (1.5 mL) were added PhSSPh (236 mg, 1.08 mmol) and $^nBu_3P$ (0.27 mL, 1.08 mmol) at rt, and stirring was continued for 1 h at the same temperature. The reaction mixture was diluted with Et_2O and washed with 15% aqueous NaOH, 10% aqueous HCl and brine. The residue upon workup was dissolved in CH_2Cl_2 (1.5 mL) and added $KHCO_3$ (22 mg, 0.22 mg) and *m*-CPBA (216 mg, 0.81 mmol) at rt. After stirring was continued for 4 h at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (7:3 v/v) as eluent to give sulfone **10** (113 mg, 94% two steps) as a colorless oil; $[\alpha]_D^{25}$ −6.6 (*c* 1.2 in $CHCl_3$); IR (neat): 1365, 1177, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (3H, d, *J*=7.3 Hz), 2.13 (3H, s), 3.31 (1H, m), 3.51 (1H, m), 3.58 (3H, s), 3.64 (1H, m), 3.74 (3H, s), 6.45 (1H, s), 6.53 (1H, s), 7.44 (2H, m), 7.75 (1H, m), 7.77 (2H, d, *J*=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0 (CH_3), 19.9 (CH_3), 31.2 (CH), 55.5 (CH_3), 56.1 (CH_3), 61.6 (CH_2), 111.1 (CH), 113.9 (CH), 125.8 (Cq), 127.9 (CH), 128.7 (CH), 128.9 (Cq), 133.0 (CH), 139.9 (Cq), 150.3 (Cq), 151.6 (Cq); MS (EI) *m*/*z* 334 $[M]^+$; HRMS (EI) *m*/*z* calcd for $C_{18}H_{22}O_4S$ $[M]^+$ 334.1239, found 334.1259.

*4.1.5. (S)-1,4-Dimethoxy-2-methyl-5-[6-methyl-3-(phenylsulfonyl)hept-5-en-2-yl]benzene (**11**).* To a stirred solution of sulfone **10** (70.5 mg, 0.21 mmol) in THF (1.5 mL) and HMPA (0.3 mL) was added dropwise 1.43 M solution of ^nBuLi in hexane (0.22 mL, 0.32 mmol) at −78 °C. After stirring was continued for 20 min at the same temperature and further 30 min at 0 °C, prenyl bromide (0.073 mL, 0.63 mmol) was added dropwise and stirring was continued for 30 min at −78 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (9:1 v/v) as eluent to give sulfone **11** (64.5 mg, 76%) as a colorless oil; IR (neat): 1211, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, s), 1.38 (1.5H, s), 1.41 (1.5H, s), 1.43 (1.5H, d, *J*=7.2 Hz), 1.57 (1.5H, d, *J*=7.2 Hz), 2.16 (3H, s), 2.22 (0.5H, m), 2.37 (1H, m), 2.68 (0.5H, m), 3.59 (1H, m), 3.61 (1.5H, s), 3.69 (1.5H, s), 3.75 (1.5H, s), 3.77 (1.5H, s), 3.80 (1H, m), 4.71 (0.5H, m), 4.90 (0.5H, s), 6.52 (0.5H, s), 6.54 (0.5H, s), 6.63 (0.5H, s), 6.66 (0.5H, s), 7.58 (3H, m), 7.81 (1H, d, *J*=7.3 Hz), 7.85 (1H, d, *J*=7.3 Hz); MS (EI) *m*/*z* 402 $[M]^+$; HRMS (EI) *m*/*z* calcd for $C_{23}H_{30}O_4S$ $[M]^+$ 402.1865, found 402.1888.

*4.1.6. (R)-1,4-Dimethoxy-2-methyl-5-(6-methylhept-5-en-2-yl)benzene (**3**).* To a stirred solution of sulfone **11** (24.3 mg, 0.06 mmol) in MeOH (0.2 mL) were added Na_2HPO_4 (34.3 mg, 0.24 mmol) and Na/Hg (364.5 mg) at rt and sonicated for 8 h. The reaction mixture was filtered through a pad of Celite and the resulting solution was extracted with AcOEt. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (9:1 v/v) as eluent to give alkene **3** (13.6 mg, 86%) as a colorless oil; $[\alpha]_D^{25}$ −29.3 (*c* 1.0 in $CHCl_3$); IR (neat): 1209, 105 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (3H, d, *J*=6.8 Hz), 1.51 (1H, m), 1.54 (3H, s), 1.63 (1H, m), 1.67 (3H, s), 1.89 (2H, m), 2.20 (3H, s), 3.14 (1H, sext, *J*=7.3 Hz), 3.76 (3H, s), 3.78 (3H, s), 5.12 (1H, m), 6.67 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1 (CH_3), 17.6 (CH_3), 21.3 (CH_3), 25.7 (CH_3), 26.4 (CH_2), 31.9 (CH), 37.3 (CH_2), 56.1 (CH_3), 56.4 (CH_3), 109.8 (CH), 114.4 (CH), 124.2 (Cq), 124.9 (CH), 131.1 (Cq), 134.0 (Cq), 150.9 (Cq), 151.9 (Cq); MS (EI) *m*/*z* 262 $[M]^+$; HRMS (EI) *m*/*z* calcd for $C_{17}H_{26}O_2$ $[M]^+$ 262.1933, found 262.1933.

*4.1.7. (R,E)-3-[3-(2,5-Dimethoxy-4-methylphenyl)acryloyl]-4-phenyloxazolidin-2-one (**5**).* To a stirred solution of 1-bromo-2,5-dimethoxy-4-methylbenzene (**12**) (1.98 g, 8.58 mmol) and (*R*)-3-acryloyl-4-phenyloxazolidin-2-one (**13**) (1.86 g, 8.58 mmol) in MeCN/H_2O (10:1, 40 mL) were added $Pd(OAc)_2$ (192.58 mg, 0.86 mmol), (*o*-tol)$_3$P (522 mg, 1.7 mmol), and Et_3N (2.391 mL, 0.017 mmol) at rt, and allowed to warm to 80 °C. After being stirred at the same temperature for 2 h, the resultant mixture was added water and CH_2Cl_2 and then extracted with CH_2Cl_2. The combined extracts were washed with brine, the residue upon workup was chromatographed on silica gel with hexane/AcOEt (4:1 v/v) as a eluent to give a enone **5** (2.564 g, 81%) as a yellow solid; $[\alpha]_D^{29}$ −5.17 (*c* 0.95 in $CHCl_3$); mp 55.5–59.5 °C; IR (neat) 2958, 1781, 1705, 1505, 1465, 1384, 1209, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.24 (3H, s), 3.82 (3H, s), 3.82 (3H, s), 4.31 (1H, dd, *J*=8.8 and 4.0 Hz), 4.73

(1H, t, *J*=8.8 Hz), 5.57 (1H, dd, *J*=8.8 and 4.0 Hz), 6.72 (1H, s), 7.02 (1H, s), 7.30–7.39 (5H, m), 7.93 (1H, d, *J*=16.0 Hz), 8.12 (1H, d, *J*=16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7 (CH_3), 55.8 (CH_3), 56.0 (CH_3), 57.8 (CH_3), 69.8 (CH_2), 109.8 (CH), 114.4 (CH), 115.7 (CH), 121.1 (Cq), 125.9 (CH), 128.5 (CH), 129.0 (CH), 131.8 (Cq), 139.3 (Cq), 142.0 (CH), 151.7 (Cq), 153.0 (Cq), 153.9 (Cq), 165.2 (Cq); HRMS (ESI) calcd for $C_{21}H_{21}NO_5Na$ $[M+Na]^+$ 390.1317, found 390.1310.

*4.1.8. (R)-3-[(R)-3-(2,5-Dimethoxy-4-methylphenyl)butanoyl]-4-phenyloxazolidin-2-one (**14**).* To a stirred solution of $CuBr\cdot SMe_2$ (5.67 g, 27.6 mmol) in THF/Me_2S (2.5:1, 43 mL) was added dropwise 1.06 M solution of MeMgBr in THF (27.1 mL, 28.7 mmol) at −4 °C. After being stirred at the same temperature for 10 min, the resultant mixture was cooled to −20 °C. To the reaction mixture was added dropwise a solution of enone **5** (3.4 g, 9.45 mmol) in THF at the same temperature and the stirring was continued for 30 min. The resultant mixture was quenched with pH 7 phosphate buffer and extracted with hexane/AcOEt (1:1 v/v). The combined extracts were washed with brine, the residue upon workup was recrystallized from hexane/AcOEt to give a **14** (2.52 g, 71%) as a colorless solid; $[\alpha]_D^{26}$ −72.89 (*c* 0.81 in $CHCl_3$); mp 116.1–116.5 °C; IR (neat) 2958, 1781, 1705, 1505, 1465, 1384, 1209, 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$,) δ 1.20 (3H, d, *J*=7.2 Hz), 2.19 (3H, s), 3.17 (1H, dd, *J*=16.8 and 7.6 Hz), 3.42 (1H, dd, *J*=16.8 and 7.6 Hz), 3.64–3.72 (1H, m), 3.76 (3H, s), 3.76 (3H, s), 4.22 (1H, dd, *J*=8.8 and 3.6 Hz), 4.59 (1H, t, *J*=8.8 Hz), 5.36 (1H, dd, *J*=8.8 and 3.6 Hz), 6.66 (1H, s), 6.68 (1H, s), 7.23–7.37 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0 (CH_3), 20.7 (CH_3), 29.9 (CH), 41.5 (CH_2), 56.1 (CH_3), 56.2 (CH_3), 57.6 (CH), 69.8 (CH_2), 110.3 (CH), 114.4 (CH), 124.8 (Cq), 125.8 (CH), 128.5 (CH), 129.0 (CH), 131.6 (Cq), 139.1 (Cq), 150.6 (Cq), 151.6 (Cq), 153.7 (Cq), 171.7 (Cq); HRMS (ESI) calcd for $C_{22}H_{25}NO_5Na$ $[M+Na]^+$ 406.1630, found 406.1622.

*4.1.9. (R)-3-(2,5-Dimethoxy-4-methylphenyl)butan-1-ol (**15**).* To a stirred solution of oxazolidinone **14** (3.73 g, 9.74 mmol) in THF/H_2O (3:1, 40 mL) was added $NaBH_4$ (1.84 g, 48.7 mmol) at rt. After stirring was continued for 3.5 h at 50 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with AcOEt. The combined extracts were washed with brine, the residue upon workup was chromatographed on silica gel with hexane/AcOEt (7:3 v/v) as eluent to give alcohol **15** (1.74 g, 80%) as a colorless oil; $[\alpha]_D^{28}$ −39.0 (*c* 1.34 in $CHCl_3$); IR (neat) 3735, 2956, 2360, 1506, 1457, 1397, 1208, 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, d, *J*=7.2 Hz), 1.59 (1H, br, D_2O exchangeable), 1.56–1.65 (1H, m), 1.88–1.96 (1H, m), 2.21 (3H, s), 3.33–3.40 (2H, m), 3.50–3.56 (1H, m), 3.79 (3H, s), 3.80 (3H, s), 6.67 (1H, s), 6.70 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0 (CH_3), 21.2 (CH_3), 27.6 (CH), 41.0 (CH_2), 56.0 (CH_3), 56.5 (CH_3), 60.9 (CH_2), 109.3 (CH), 114.2 (CH), 124.7 (Cq), 132.3 (Cq), 150.4 (Cq), 152.2 (Cq); HRMS (ESI) calcd for $C_{13}H_{20}O_3Na$ $[M+Na]^+$ 247.1310, found 247.1315.

*4.1.10. (R)-1,4-Dimethoxy-2-(5-methoxypent-4-en-2-yl)-5-methylbenzene (**17**).* To a stirred solution of alcohol **15** (1.00 g, 4.46 mmol) in CH_2Cl_2 (18 mL) was added PCC (1.44 g, 6.69 mmol) at 0 °C and stirring was continued for 3 h at rt. The reaction mixture was treated with silica gel, and filtered through a pad of Celite. The resulting solution was evaporated in vacuo to give crude aldehyde **16** (0.97 g) as a brown oil, which was used to the next reaction without further purification.

To a stirred solution of methoxymethyltriphenylphosphonium chloride (4.53 g, 13.4 mmol) in THF (16 mL) was added dropwise 1.09 M solution of NaHMDS in THF (12.3 mL, 13.4 mmol) at 0 °C. After stirring was continued for 15 min, crude aldehyde **16** (0.97 g) in THF (2 mL) was dropwise at the same temperature. After further stirring was continued for 1 h at rt, the reaction mixture was quenched with brine and extracted with AcOEt. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (95:5 v/v) as eluent to give methylenolether **17** (1.6 g) as a colorless oil; IR (neat) 2933, 1654, 1506, 1466, 1398, 1208, 1048 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (3H, d, *J*=7.2 Hz), 2.04–2.11 (0.55H, m), 2.20 (3H, s), 2.19–2.27 (0.45H, m), 2.31–2.37 (1H, m), 3.15 (1H, sext, *J*=7.2 Hz), 3.47 (1.65H, s), 3.56 (1.35H, s), 3.77 (3H, s), 3.79 (3H, s), 4.28 (0.45H, q, *J*=6.4 Hz), 4.68 (0.55H, dt, *J*=12.8 and 7.2 Hz), 5.86 (0.45H, d, *J*=6.4 Hz), 6.27 (0.55H, d, *J*=12.8 Hz), 6.66 (0.55H, s), 6.68 (1H, s), 6.72 (0.45H, s); HRMS (ESI) calcd for $C_{15}H_{22}O_3Na$ $[M+Na]^+$ 273.1467, found 273.1466.

*4.1.11. (R)-4-(2,5-Dimethoxy-4-methylphenyl)pentanal (**18**).* To a stirred solution of methylenolether **17** (1.6 g) in THF (15 mL) was added 2 N aqueous HCl (3 mL) at 0 °C. After stirring was continued for 6 h at rt, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (95:5 v/v) as eluent to give aldehyde **18** (0.75 g, 71% three steps) as a colorless oil; $[\alpha]_D^{28}$ −11.7 (*c* 0.63 in $CHCl_3$); IR (neat) 2930, 2360, 1718, 1506, 1457, 1398, 1209, 1046 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, d, *J*=6.8 Hz), 1.81–1.96 (2H, m), 2.20 (3H, s), 2.22–2.43 (2H, m), 3.18 (1H, sext, *J*=6.8 Hz), 3.75 (3H, s), 3.79 (3H, s), 6.64 (1H, s), 6.68 (1H, s), 9.69 (1H, t, *J*=1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1 (CH_3) 21.0 (CH_3), 29.5 (CH_2), 31.5 (CH), 42.1 (CH_2), 56.1 (CH_3), 56.2 (CH_3), 109.6 (CH), 114.2 (CH), 124.8 (Cq), 132.0 (Cq), 150.8 (Cq), 151.9 (Cq), 202.9 (CH); HRMS (ESI) calcd for $C_{14}H_{20}O_3Na$ $[M+Na]^+$ 259.1310, found 259.1310.

*4.1.12. (R)-1,4-Dimethoxy-2-methyl-5-(6-methylhept-5-en-2-yl)benzene (**3**).* To a stirred solution of isopropyltriphenylphosphonium iodide (4.01 g, 9.28 mmol) in THF (12 mL) was added ^{t}BuOK (1.04 g, 9.28 mmol) at 0 °C. After stirring was continued for 15 min, aldehyde **18** (0.73 g, 3.09 mmol) in THF (3 mL) was dropwise at the same temperature. After stirring was continued for 0.5 h at rt, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with AcOEt. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (98:2 v/v) as eluent to give alkene **3** (0.82 g, quant.) as a colorless oil. Spectra data coincides with those of the described above.

*4.1.13. (3S,6R)-6-(2,5-Dimethoxy-4-methylphenyl)-2-methylheptane-2,3-diol (**19**).* To a stirred solution of AD-mix-α (295 mg, 0.38 mmol) and $CH_3SO_2NH_2$ (18.0 mg, 0.19 mmol) in ^{t}BuOH/H_2O (1:1, 1 mL) was added alkene **3** (49.4 mg, 0.19 mmol) at 0 °C. After stirring was continued for 23 h at the same temperature, the reaction mixture was quenched with saturated aqueous Na_2SO_3 and stirred for 1 h at 0 °C. After further stirring was continued for 1 h at rt, the reaction mixture was extracted with $CHCl_3$. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (6:4 v/v) as eluent to give diol **19** (51.1 mg, 91%, 93% de) as a colorless oil; $[\alpha]_D^{26}$ −40.9 (*c* 1.3 in $CHCl_3$); IR (neat): 3418, 2955, 1504, 1466, 1399, 1208 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (3H, s), 1.13 (3H, s), 1.21 (3H, d, *J*=6.8 Hz), 1.15–1.28 (1H, m), 1.38–1.46 (1H, m), 1.58–1.67 (1H, m), 1.81–1.90 (1H, m), 2.00–2.20 (2H, br, D_2O exchangeable), 2.20 (3H, s), 3.15–3.24 (1H, m), 3.39 (1H, dd, *J*=10.4 and 1.6 Hz), 3.76 (3H, s), 3.79 (3H, s), 6.67 (1H, s), 6.68 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1 (CH_3), 21.6 (CH_3), 23.2 (CH_2), 26.4 (CH_3), 29.6 (CH_3), 31.6 (CH), 34.1 (CH_2), 56.1 (CH_3), 56.3 (CH_3), 73.1 (Cq), 78.4 (CH), 109.7 (CH), 114.2 (CH), 124.4 (Cq), 133.2 (Cq), 150.7 (Cq), 151.9 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{17}H_{29}O_4$ $[M+H]^+$ 297.2066, found 297.2066.

*4.1.14. 2-[(2R,5S)-5,6-Dihydroxy-6-methylheptan-2-yl]-5-methylcyclohexa-2,5-diene-1,4-dione (**20**).* To a stirred solution of diol **19** (25.8 mg, 0.09 mmol) in CH_3CN/H_2O (4:1, 0.4 mL) was added CAN (95.5 mg, 0.17 mmol) at 0 °C, and stirring was continued for 30 min at the same temperature. The resulting solution was diluted with

water and extracted with Et_2O. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (1:1 v/v) as eluent to give quinone **20** (14.4 mg, 62%) as a yellow oil; $[\alpha]_D^{28}$ −26.9 (*c* 0.77 in $CHCl_3$); IR (neat): 3434, 2969, 1654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, s), 1.15 (3H, d, *J*=6.8 Hz), 1.20 (3H, s), 1.20–1.27 (1H, m), 1.43–1.52 (2H, m), 1.77–1.87 (1H, m), 1.87 (1H, br s, D_2O exchangeable), 2.04 (3H, d, *J*=2.0 Hz), 2.28 (1H, br s, D_2O exchangeable), 2.96 (1H, sext, *J*=6.8 Hz), 3.34 (1H, dd, *J*=10.4 and 2.0 Hz), 6.54 (1H, s), 6.60 (1H, d, *J*=2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4 (CH_3), 19.8 (CH_3), 23.2 (CH_3), 26.5 (CH_3), 29.2 (CH_2), 31.4 (CH), 33.1 (CH_2), 73.1 (Cq), 78.5 (CH), 131.3 (CH), 133.7 (CH), 145.3 (Cq), 153.8 (Cq), 187.5 (Cq), 188.5 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{23}O_4$ $[M+H]^+$ 267.1596, found 267.1604.

*4.1.15. 2-[(2R,5S)-5,6-Dihydroxy-6-methylheptan-2-yl]-5-methylbenzene-1,4-diol (7R,10S-**1**).* To a stirred solution of quinone **20** (14.4 mg, 0.05 mmol) in THF (0.2 mL) were added $Na_2S_2O_4$ (28.3 mg, 0.16 mmol) in H_2O (0.1 mL) at 0 °C, and stirring was continued for 10 min at rt. The resulting solution was diluted with water and extracted with AcOEt. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (3:7 v/v) as eluent to give tetraol 7*R*,10*S*-**1** (11.9 mg, 82%) as a colorless oil; $[\alpha]_D^{29}$ −38.9 (*c* 0.68 in acetone); IR (neat): 3373, 2967, 1703, 1420, 1195 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3) δ 1.03 (3H, s), 1.05 (3H, s), 1.13 (3H, d, *J*=7.0 Hz), 1.16–1.21 (1H, m), 1.45–1.50 (1H, m), 1.51–1.57 (1H, m), 1.82–1.90 (1H, m), 2.08 (3H, s), 3.12 (1H, sext, *J*=7.0 Hz), 3.21 (1H, s, D_2O exchangeable), 3.30 (1H, ddd, *J*=10.0, 5.0 and 2.0 Hz), 3.40 (1H, d, *J*=5.0 Hz, D_2O exchangeable), 6.55 (1H, s), 6.59 (1H, s), 7.27 (1H, s, D_2O exchangeable), 7.28 (1H, s, D_2O exchangeable); ^{13}C NMR (125 MHz, CD_3COCD_3) δ 15.8 (CH_3), 22.0 (CH_3), 24.7 (CH_3), 26.0 (CH_3), 30.0 (CH_2), 32.3 (CH), 35.2 (CH_2), 72.8 (Cq), 78.9 (CH), 113.9 (CH), 118.2 (CH), 122.2 (Cq), 132.2 (Cq), 148.0 (Cq), 149.1 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{25}O_4$ $[M+H]^+$ 269.1753, found 269.1757.

*4.1.16. (3R,6R)-6-(2,5-Dimethoxy-4-methylphenyl)-2-methylheptane-2,3-diol (**21**).* By following the same procedure described for **19**, diol **21** was prepared from alkene **3** with AD-mix-β: quantitative yield, >99% de; colorless oil; $[\alpha]_D^{26}$ −6.89 (*c* 1.2 in $CHCl_3$); IR (neat): 3422, 2956, 1504, 1466, 1398, 1208 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, s), 1.15 (3H, s), 1.21 (3H, d, *J*=6.8 Hz), 1.22–1.37 (1H, m), 1.37–1.49 (1H, m), 1.56–1.70 (1H, m), 1.70–1.83 (1H, m), 2.20 (3H, s), 2.39 (1H, br, D_2O exchangeable), 2.67 (1H, br, D_2O exchangeable), 3.15–3.20 (1H, m), 3.36 (1H, d, *J*=9.6 Hz), 3.77 (3H, s), 3.78 (3H, s), 6.67 (1H, s), 6.68 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0 (CH_3), 20.8 (CH_3), 23.0 (CH_2), 26.3 (CH_3), 29.5 (CH_3), 31.4 (CH), 34.6 (CH_2), 56.1 (CH_3), 56.4 (CH_3), 73.0 (Cq), 78.6 (CH), 109.4 (CH), 114.3 (CH), 124.4 (Cq), 133.6 (Cq), 150.3 (Cq), 151.9 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{17}H_{29}O_4$ $[M+H]^+$ 297.2066, found 297.2075.

*4.1.17. 2-[(2R,5R)-5,6-Dihydroxy-6-methylheptan-2-yl]-5-methylcyclohexa-2,5-diene-1,4-dione (**22**).* By following the same procedure described for **20**, quinone **22** was prepared from **21**: yield 85%; yellow oil; $[\alpha]_D^{25}$ +10.8 (*c* 0.58 in $CHCl_3$); IR (neat): 3421, 2970, 1654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, d, *J*=6.8 Hz), 1.15 (3H, s), 1.20 (3H, s), 1.34–1.49 (2H, m), 1.57–1.64 (2H, m), 1.96 (1H, br s, D_2O exchangeable), 2.04 (3H, d, *J*=1.6 Hz), 2.46 (1H, br s, D_2O exchangeable), 2.96 (1H, sext, *J*=6.8 Hz), 3.39 (1H, d, *J*=10.0 Hz), 6.53 (1H, s), 6.60 (1H, d, *J*=1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4 (CH_3), 18.7 (CH_3), 23.3 (CH_3), 26.6 (CH_3), 29.0 (CH_2), 30.9 (CH), 32.9 (CH_2), 73.0 (Cq), 77.9 (CH), 131.1 (CH), 133.8 (CH), 145.4 (Cq), 153.9 (Cq), 187.7 (Cq), 188.4 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{23}O_4$ $[M+H]^+$ 267.1596, found 267.1588.

*4.1.18. 2-[(2R,5R)-5,6-Dihydroxy-6-methylheptan-2-yl]-5-methylbenzene-1,4-diol (7R,10R-**1**).* By following the same procedure described for 7*R*,10*S*-**1**, 7*R*,10*R*-**1** was prepared from **22**: yield 81%; colorless oil; $[\alpha]_D^{29}$ −6.9 (*c* 0.33 in acetone); IR (neat): 3367, 2963, 1703, 1419, 1193 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3) δ 1.06 (6H, s), 1.14 (3H, d, *J*=7.0 Hz), 1.22–1.31 (1H, m), 1.50 (1H, dddd, *J*=15.5, 10.0, 5.5 and 2.0 Hz), 1.58 (1H, dddd, *J*=13.5, 10.0, 7.5 and 5.5 Hz), 1.78 (1H, dddd, *J*=13.5, 10.0, 7.0 and 5.5 Hz), 2.08 (3H, s), 3.11 (1H, sext, *J*=7.0 Hz), 3.27 (1H, s, D_2O exchangeable), 3.27 (1H, ddd, *J*=10.0, 5.0 and 2.0 Hz), 3.59 (1H, d, *J*=5.0 Hz, D_2O exchangeable), 6.55 (1H, s), 6.60 (1H, s), 7.26 (1H, s, D_2O exchangeable), 7.36 (1H, s, D_2O exchangeable); ^{13}C NMR (125 MHz, CD_3COCD_3) δ 15.7 (CH_3), 21.4 (CH_3), 24.7 (CH_3), 25.8 (CH_3), 30.0 (CH_2), 32.3 (CH), 35.8 (CH_2), 72.7 (Cq), 79.5 (CH), 113.7 (CH), 118.3 (CH), 122.2 (Cq), 132.4 (Cq), 147.8 (Cq), 149.1 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{25}O_4$ $[M+H]^+$ 269.1753, found 269.1758.

*4.1.19. (S)-2-[2-(2,5-Dimethoxy-4-methylphenyl)propylthio]benzo[d]thiazole (**29**).* To a stirred solution of alcohol **8** (264 mg, 1.25 mmol) in THF (10 mL) were added 2-benzothiazolethiol **28** (251 mg, 1.50 mmol) and Ph_3P (393 mg, 1.50 mmol) at rt. After the solution was cooled to 0 °C, DIAD (0.32 mL, 1.63 mmol) was added dropwise and the mixture was stirred for 2.5 h at rt. The reaction mixture was quenched with 1 N aqueous NaOH and extracted with Et_2O. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (95:5 v/v) as eluent to give sulfide **29** (409 mg, 91%) as a colorless oil; $[\alpha]_D^{29}$ −31.8 (*c* 0.87 in $CHCl_3$); IR (neat): 2931, 2829, 1504, 1462, 1427, 1398, 1209, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (3H, d, *J*=6.8 Hz), 2.20 (3H, s), 3.56–3.63 (2H, m), 3.66–3.70 (1H, m), 3.77 (3H, s), 3.78 (3H, s), 6.69 (1H, s), 6.70 (1H, s), 7.27 (1H, td, *J*=8.0 and 1.2 Hz), 7.39 (1H, td, *J*=8.0 and 1.2 Hz), 7.72 (1H, dd, *J*=8.0 and 1.2 Hz), 7.85 (1H, dd, *J*=8.0 and 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1 (CH_3), 19.6 (CH_3), 33.4 (CH), 40.1 (CH_2), 56.1 ($CH_3\times2$), 110.2 (CH), 114.2 (CH), 120.8 (CH), 121.3 (CH), 124.0 (CH), 125.5 (Cq), 125.9 (CH), 130.2 (Cq), 135.2 (Cq), 150.8 (Cq), 151.7 (Cq), 153.3 (Cq), 167.7 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{19}H_{22}NO_2S_2$ $[M+H]^+$ 360.1092, found 360.1102.

*4.1.20. (S)-2-[2-(2,5-Dimethoxy-4-methylphenyl)propylsulfonyl]benzo[d]thiazole (**30**).* To a stirred solution of sulfide **29** (163 mg, 0.45 mmol) in EtOH (2 mL) was added dropwise solution of ammonium heptamolybdate tetrahydrate (56.0 mg, 0.045 mmol) in 30% aqueous H_2O_2 (0.44 mL, 4.54 mmol) at rt, and stirring was continued for 4 h at the same temperature. The resulting mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (8:2 v/v) as eluent to give sulfone **30** (164 mg, 93%) as a colorless oil; $[\alpha]_D^{28}$ −0.55 (*c* 0.62 in $CHCl_3$); IR (neat): 2934, 1505, 1469, 1401, 1329, 1211, 1143, 1045, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (3H, d, *J*=6.8 Hz), 1.95 (3H, s), 3.59 (3H, s), 3.61–3.69 (2H, m), 3.73 (3H, s), 4.22–4.30 (1H, m), 6.24 (1H, s), 6.54 (1H, s), 7.55 (1H, ddd, *J*=8.1, 7.0 and 1.2 Hz), 7.60 (1H, ddd, *J*=8.1, 7.2 and 1.2 Hz), 7.92 (1H, dd, *J*=7.0 and 1.2 Hz), 8.13 (1H, dd, *J*=7.2 and 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9 (CH_3), 19.9 (CH_3), 31.9 (CH), 55.4 (CH_3), 56.0 (CH_3), 60.0 (CH_2), 111.6 (CH), 113.4 (CH), 122.0 (CH), 125.1 (CH), 126.0 (Cq), 127.3 (CH), 127.5 (Cq), 127.6 (CH), 137.2 (Cq), 150.3 (Cq), 151.3 (Cq), 152.5 (Cq), 166.3 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{19}H_{22}NO_4S_2$ $[M+H]^+$ 392.0990, found 392.0973.

*4.1.21. (R)-5-[(R,E)-3-(2,5-Dimethoxy-4-methylphenyl)but-1-enyl]-2,2,4,4-tetramethyl-1,3-dioxolane (**31**).* To a stirred solution of sulfone **30** (105 mg, 0.26 mmol) in THF (1.0 mL) was added dropwise 1.1 M solution of NaHMDS in THF (0.35 ml, 0.39 mmol) at −78 °C. After stirring was continued for 15 min, a solution of (*S*)-2,2,5,5-tetramethyl-1,3-dioxolane-4-carbaldehyde *S*-**24** (62 mg, 0.39 mmol) in THF (0.5 mL) was added dropwise to this reaction mixture at the same temperature, and stirring was continued for 1 h at rt. The

reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (95:5 v/v) as eluent to give *E*- and *Z*-alkene **31** (52.3 mg, 60%, *E*/*Z*=3:1) as a colorless oil; IR (neat): 2979, 1504, 1208, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (2.25H, s), 1.14 (0.75H, s), 1.22 (2.25H, s), 1.30 (0.75H, s), 1.33 (2.25H, d, *J*=6.0 Hz), 1.35 (0.75H, d, *J*=6.0 Hz), 1.36 (2.25H, s), 1.38 (0.75H, s), 1.46 (3H, s), 2.19 (0.75H, s), 2.20 (2.25H, s), 3.76 (2.25H, s), 3.77 (2.25H, s), 3.79 (0.75H, s), 3.80 (0.75H, s), 3.92 (1H, dq, *J*=6.0 and 2.0 Hz), 4.17 (0.75H, dd, *J*=8.0 and 0.8 Hz), 4.82 (0.25H, d, *J*=8.8 Hz), 5.32 (0.25H, dd, *J*=11.2 and 8.8 Hz), 5.50 (0.75H, ddd, *J*=15.6, 8.0 and 2.0 Hz), 5.70 (0.25H, dd, *J*=11.2 Hz), 5.98 (0.75H, ddd, *J*=15.6, 6.0 and 0.8 Hz), 6.64 (0.75H, s), 6.67 (0.25H, s), 6.68 (0.75H, s), 6.71 (0.25H, s); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{31}O_4$ $[M+H]^+$ 335.2222, found 335.2216.

*4.1.22. 2-Methyl-5-[(R,E)-4-((R)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)but-3-en-2-yl]cyclohexa-2,5-diene-1,4-dione (**32**).* To a stirred solution of alkene **31** (45.8 mg, 0.14 mmol) in CH_3CN/H_2O (4:1, 0.5 mL) was added CAN (150 mg, 0.27 mmol) at 0 °C, and stirring was continued for 30 min at the same temperature. The resulting solution was diluted with water and extracted with Et_2O. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (9:1 v/v) as eluent to give quinone **32** (43.0 mg, quant.) as a yellow oil. The *E*, *Z* isomer of **32** were partially separated with HPLC column (Mightysil, 10% AcOEt/hexane, 10 mL/min, λ=254 nm); $[\alpha]_D^{23}$ +6.6 (*c* 0.91 in $CHCl_3$); IR (neat): 2979, 1656, 1369 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, s), 1.22 (3H, s), 1.26 (3H, d, *J*=6.8 Hz), 1.36 (3H, s), 1.46 (3H, s), 2.04 (3H, d, *J*=1.2 Hz), 3.68 (1H, quint, *J*=6.8 Hz), 4.14 (1H, d, *J*=7.6 Hz), 5.58 (1H, dd, *J*=15.6 and 7.6 Hz), 5.80 (1H, dd, *J*=15.6 and 6.8 Hz), 6.54 (1H, s), 6.60 (1H, d, *J*=1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4 (CH_3), 18.5 (CH_3), 23.6 (CH_3), 25.8 (CH_3), 27.0 (CH_3), 28.4 (CH_3), 34.4 (CH), 80.9 (Cq), 84.3 (CH), 107.4 (Cq), 126.3 (CH), 131.5 (CH), 133.7 (CH), 135.7 (CH), 145.4 (Cq), 151.7 (Cq), 186.8 (Cq), 188.3 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{18}H_{25}O_4$ $[M+H]^+$ 305.1753, found 305.1763.

*4.1.23. 2-[(2R,5R,E)-5,6-Dihydroxy-6-methylhept-3-en-2-yl]-5-methylcyclohexa-2,5-diene-1,4-dione (**33**).* To a stirred solution of quinone **32** (9.8 mg, 0.03 mmol) in MeOH (0.2 mL) was added 10% aqueous HCl (0.2 mL) at rt, and stirring was continued for 5 h at the same temperature. The resulting solution was diluted with water and extracted with AcOEt. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (1:1 v/v) as eluent to give diol **33** (7.8 mg, 98%) as a yellow oil; $[\alpha]_D^{26}$ +23.9 (*c* 0.66 in $CHCl_3$); IR (neat): 3426, 2973, 2360, 1654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, s), 1.18 (3H, s), 1.25 (3H, d, *J*=7.2 Hz), 1.96 (1H, br s, D_2O exchangeable), 2.04 (3H, d, *J*=1.2 Hz), 2.14 (1H, br s, D_2O exchangeable), 3.65 (1H, dq, *J*=7.2 and 6.8 Hz), 3.78 (1H, d, *J*=7.2 Hz), 5.61 (1H, dd, *J*=15.6 and 7.2 Hz), 5.74 (1H, dd, *J*=15.6 and 6.8 Hz), 6.52 (1H, s), 6.59 (1H, d, *J*=1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4 (CH_3), 18.7 (CH_3), 23.7 (CH_3), 26.4 (CH_3), 34.5 (CH), 72.8 (Cq), 79.2 (Cq), 129.8 (CH), 131.5 (CH), 133.7 (CH), 134.9 (CH), 145.4 (Cq), 151.8 (Cq), 186.9 (Cq), 188.3 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{21}O_4$ $[M+H]^+$ 265.1440, found 265.1431.

*4.1.24. 2-[(2R,5R,E)-5,6-Dihydroxy-6-methylhept-3-en-2-yl]-5-methylbenzene-1,4-diol (7R,10R-**2**).* To a stirred solution of diol **33** (3.9 mg, 0.01 mmol) in THF (0.2 mL) were added $Na_2S_2O_4$ in H_2O (0.1 mL) at 0 °C, and stirring was continued for 30 min at rt. The resulting solution was diluted with water and extracted with AcOEt. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (3:7 v/v) as eluent to give 7*R*,10*R*-**2** (3.8 mg, 95%) as a colorless oil; $[\alpha]_D^{27}$ +0.9 (*c* 0.47 in acetone); IR (neat): 3367, 2972, 1703, 1418 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3) δ 1.07 (3H, s), 1.09 (3H, s), 1.24 (3H, d, *J*=7.0 Hz), 2.08 (3H, s), 3.22 (1H, s, D_2O exchangeable), 3.71 (1H, d, *J*=4.0 Hz, D_2O exchangeable), 3.76–3.81 (1H, m), 3.80 (1H, dd, *J*=7.0 and 2.0 Hz), 5.55 (1H, ddd, *J*=15.5, 7.0, and 1.5 Hz), 5.85 (1H, ddd, *J*=15.5, 6.5 and 1.0 Hz), 6.57 (1H, s), 6.58 (1H, s), 7.33 (1H, s, D_2O exchangeable), 7.37 (1H, s, D_2O exchangeable); ^{13}C NMR (125 MHz, CD_3COCD_3) δ 15.8 (CH_3), 20.4 (CH_3), 24.7 (CH_3), 26.3 (CH_3), 35.4 (CH), 72.7 (Cq), 80.1 (CH), 114.6 (CH), 118.2 (CH), 122.7 (Cq), 128.9 (CH), 130.8 (Cq), 137.4 (CH), 147.7 (Cq), 149.1 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{23}O_4$ $[M+H]^+$ 267.1596, found 267.1591.

*4.1.25. (S)-5-[(R,E)-3-(2,5-Dimethoxy-4-methylphenyl)but-1-enyl]-2,2,4,4-tetramethyl-1,3-dioxolane (**34**).* By following the same procedure described for **31**, alkene **34** was prepared from **30** and *R*-**24**: yield 61%, *E*/*Z*=6:1; colorless oil. The *E*, *Z* isomer of **34** were partially separated with HPLC column (Mightysil, 8% AcOEt/hexane, 10 mL/min, λ=254 nm); *E*-alkene: $[\alpha]_D^{25}$ +29.8 (*c* 0.67 in $CHCl_3$); IR (neat): 2979, 1504, 1398, 1376, 1209, 1043, 989 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, s), 1.25 (3H, s), 1.32 (3H, d, *J*=6.8 Hz), 1.36 (3H, s), 1.46 (3H, s), 2.20 (3H, s), 3.76 (3H, s), 3.78 (3H, s), 3.93 (1H, dquint, *J*=6.8 and 1.2 Hz), 4.19 (1H, d, *J*=8.4 Hz), 5.48 (1H, ddd, *J*=15.6, 8.4 and 1.2 Hz), 6.03 (1H, dd, *J*=15.6 and 6.8 Hz), 6.59 (1H, s), 6.69 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1 (CH_3), 19.7 (CH_3), 23.6 (CH_3), 25.8 (CH_3), 27.0 (CH_3), 28.5 (CH_3), 34.6 (CH), 56.0 (CH_3), 56.2 (CH_3), 80.9 (Cq), 85.0 (CH), 107.2 (Cq), 110.2 (CH), 114.1 (CH), 123.1 (CH), 124.9 (Cq), 131.3 (Cq), 140.2 (CH), 150.4 (Cq), 151.7 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{31}O_4$ $[M+H]^+$ 335.2222, found 335.2232. *Z*-Alkene: $[\alpha]_D^{28}$ −93.0 (*c* 0.28 in $CHCl_3$); IR (neat): 2979, 1504, 1466, 1397, 1369, 1208, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, s), 1.07 (3H, s), 1.32 (3H, dd, *J*=6.8 and 1.2 Hz), 1.41 (3H, s), 1.46 (3H, s), 2.19 (3H, s), 3.77 (3H, s), 3.78 (3H, s), 4.22–4.26 (1H, m), 4.68 (1H, dd, *J*=9.8 and 0.8 Hz), 5.38 (1H, ddd, *J*=10.8, 9.8 and 1.2 Hz), 5.97 (1H, ddd, *J*=10.8, 6.8 and 0.8 Hz), 6.66 (1H, s), 6.68 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1 (CH_3), 22.4 (CH_3), 23.5 (CH_3), 25.5 (CH_3), 27.2 (CH_3), 28.6 (CH_3), 31.3 (CH), 55.9 (CH_3), 56.2 (CH_3), 79.0 (Cq), 81.2 (CH), 107.3 (Cq), 110.3 (CH), 114.0 (CH), 123.3 (CH), 124.8 (Cq), 132.6 (Cq), 140.9 (CH), 149.9 (Cq), 151.8 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{31}O_4$ $[M+H]^+$ 335.2222, found 335.2233.

*4.1.26. 2-Methyl-5-[(R,E)-4-((S)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)but-3-en-2-yl]cyclohexa-2,5-diene-1,4-dione (7R,10S-**32**).* By following the same procedure described for **32**, 7*R*,10*S*-**32** was prepared from **34**: 92% yield; yellow oil; $[\alpha]_D^{26}$ +20.8 (*c* 0.82 in $CHCl_3$); IR (neat): 2979, 1656, 1369, 913 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (3H, s), 1.25 (3H, s), 1.26 (3H, d, *J*=6.8 Hz), 1.35 (3H, s), 1.44 (3H, s), 2.04 (3H, d, *J*=1.6 Hz), 3.68 (1H, dquint, *J*=6.8 and 0.8 Hz), 4.15 (1H, d, *J*=7.6 Hz), 5.52 (1H, ddd, *J*=15.6, 7.6, and 0.8 Hz), 5.85 (1H, dd, *J*=15.6 and 6.8 Hz), 6.51 (1H, s), 6.60 (1H, d, *J*=1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4 (CH_3), 18.8 (CH_3), 23.6 (CH_3), 25.8 (CH_3), 27.0 (CH_3), 28.4 (CH_3), 34.4 (CH), 80.9 (Cq), 84.2 (CH), 107.4 (Cq), 126.0 (CH), 131.7 (CH), 133.6 (CH), 135.9 (CH), 145.4 (Cq), 151.7 (Cq), 186.8 (Cq), 188.3 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{18}H_{25}O_4$ $[M+H]^+$ 305.1753, found 305.1765.

*4.1.27. 2-[(2R,5S,E)-5,6-Dihydroxy-6-methylhept-3-en-2-yl]-5-methylcyclohexa-2,5-diene-1,4-dione (7R,10S-**33**).* By following the same procedure described for **33**, 7*R*,10*S*-**33** was prepared from 7*R*,10*S*-**32**: yield 96%; yellow oil; $[\alpha]_D^{25}$ +1.4 (*c* 0.70 in $CHCl_3$); IR (neat): 3419, 2974, 1653, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, s), 1.21 (3H, s), 1.24 (3H, d, *J*=6.8 Hz), 2.06 (3H, d, *J*=1.6 Hz), 2.43 (1H, br s, D_2O exchangeable), 2.44 (1H, br s, D_2O exchangeable), 3.65 (1H, dquint, *J*=6.8 and 1.2 Hz), 3.89 (1H, d, *J*=6.8 Hz), 5.61 (1H, ddd, *J*=15.6, 6.8, and 1.2 Hz), 5.75 (1H, dd, *J*=15.6 and 6.8 Hz), 6.52 (1H, s), 6.60 (1H, d, *J*=1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4 (CH_3), 18.8 (CH_3), 23.8 (CH_3), 26.5 (CH_3), 34.5 (CH), 72.8 (Cq), 79.2 (Cq), 129.6

(CH), 131.6 (CH), 133.7 (CH), 134.9 (CH), 145.5 (Cq), 151.8 (Cq), 187.0 (Cq), 188.3 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{21}O_4$ $[M+H]^+$ 265.1440, found 265.1440.

*4.1.28. 2-[(2R,5S,E)-5,6-Dihydroxy-6-methylhept-3-en-2-yl]-5-methylbenzene-1,4-diol (7R,10S-**2**).* By following the same procedure described for 7*R*,10*R*-**2**, 7*R*,10*S*-**2** was prepared from 7*R*,10*S*-**33**: quantitative yield; colorless oil; $[\alpha]_D^{27}$ −23.1 (*c* 0.66 in acetone); IR (neat): 3373, 2973, 1703, 1193 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3) δ 1.08 (3H, s), 1.11 (3H, s), 1.24 (3H, d, *J*=7.0 Hz), 2.08 (3H, s), 3.21 (1H, s, D_2O exchangeable), 3.72 (1H, d, *J*=4.0 Hz, D_2O exchangeable), 3.77–3.82 (1H, m), 3.79 (1H, dd, *J*=7.5 and 7.5 Hz), 5.54 (1H, ddd, *J*=15.5, 7.0, and 1.5 Hz), 5.87 (1H, ddd, *J*=15.5, 6.0, and 1.0 Hz), 6.57 (2H, s), 7.33 (1H, s, D_2O exchangeable), 7.37 (1H, s, D_2O exchangeable); ^{13}C NMR (125 MHz, CD_3COCD_3) δ 15.7 (CH_3), 20.3 (CH_3), 24.6 (CH_3), 26.2 (CH_3), 35.4 (CH), 72.6 (Cq), 80.0 (CH), 114.5 (CH), 118.1 (CH), 122.7 (Cq), 128.6 (CH), 130.6 (Cq), 137.4 (CH), 147.5 (Cq), 148.9 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{23}O_4$ $[M+H]^+$ 267.1596, found 267.1602.

Acknowledgements

We thank Dr. Takashi Ooi of the University of Tokushima for NMR analyses. This work was supported financially by a Grant-in-Aid for the Promotion of Basic and Applied Research for Innovations in the Bio-oriented Industry (BRAIN).

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.03.064.

References and notes

1. Macías, F. A.; Torres, A.; Galindo, J. L. G.; Varela, R. M.; Álvarez, J. A.; Molinillo, J. M. G. *Phytochemistry* **2002**, *61*, 687–692.
2. For a review, see: Vyvyan, J. R. *Tetrahedron* **2002**, *58*, 1631–1646.
3. (a) Macías, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G. *Tetrahedron Lett.* **1998**, *39*, 427–430; (b) Macías, F. A.; Galindo, J. L. G.; Valela, R. M.; Torres, A.; Molinillo, J. M. G.; Fronczek, F. R. *Org. Lett.* **2006**, *8*, 4513–4516.
4. Macías, F. A.; Marín, D.; Chinchilla, D.; Molinillo, J. M. G. *Tetrahedron Lett.* **2002**, *43*, 6417–6420.
5. Sirat, H. M.; Hong, N. M.; Jauri, M. H. *Tetrahedron Lett.* **2007**, *48*, 457–460.
6. (a) Takabatake, K.; Nishi, I.; Shindo, M.; Shishido, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1807–1808; (b) Yoshimura, T.; Kishuku, H.; Kamei, T.; Takabatake, K.; Shindo, M.; Shishido, K. *ARKIVOC* **2003**, *8*, 247–255.
7. For reviews, see: (a) Shishido, K.; Bando, T. *J. Mol. Catal. B: Enzym.* **1998**, *5*, 183–186; (b) Shishido, K. *Chem. Ind.* **2004**, *55*, 623–633; (c) Kamei, T.; Morimoto, S.; Shishido, K. *J. Synth. Org. Chem. Jpn.* **2006**, *64*, 1021–1031.
8. (a) Kishuku, H.; Shindo, M.; Shishido, K. *Chem. Commun.* **2003**, 350–351; (b) Morimoto, S.; Shindo, M.; Shishido, K. *Heterocycles* **2005**, *66*, 69–73; (c) Morimoto, S.; Shindo, M.; Yoshida, M.; Shishido, K. *Tetrahedron Lett.* **2006**, *47*, 7353–7356.
9. Osaka, M.; Kanematsu, M.; Yoshida, M.; Shishido, K. *Tetrahedron: Asymmetry* **2010**, *21*, 2319–2320 and references are cited therein.
10. (a) Burke, T. R.; Liu, D. G.; Gao, Y. *J. Org. Chem.* **2000**, *65*, 6288–6292; (b) Gao, Y.; Wei, C.; Burke, T. R. *Org. Lett.* **2001**, *3*, 1617–1620.
11. For a review, see: Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.
12. Yoshida, M.; Shoji, Y.; Shishido, K. *Org. Lett.* **2009**, *11*, 1441–1443.
13. Kise, N.; Mimura, R. *Tetrahedron: Asymmetry* **2007**, *18*, 988–993.
14. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–3547.
15. The synthesis of (7*R*,10*R*)-**1** was reported by Sirat et al.,[5] however the optical rotation was not mentioned in the literature.
16. Krief, A.; Froidbise, A. *Tetrahedron* **2004**, *60*, 7637–7658.
17. Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570–7571.
18. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
19. Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, *16*, 4833–4836.
20. (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175–1178; (b) For a review, see: Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585.