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Synthesis of a Potential Key Intermediate of Akaterpin, Specific Inhibitor of PI-PLC

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Abstract—In order to establish the stereochemistry of akaterpin, a specific inhibitor of PI-PLC, *cis*-decalin **2** and *trans*-decalin **3** were prepared. Comparison of NMR spectra of **2** and **3** with those of akaterpin indicated that the upper decalin has a *cis*-fused structure. Based on the methodology developed here, synthesis of a potential intermediate **32** for the total synthesis of akaterpin was successfully achieved. Further, resolution of β,γ-unsaturated ketone **6** was accomplished using chiral sulfoxyimine.

Phosphatidylinositol (PI) turnover plays an important role in the regulation of cell growth and differentiation.[1] Among several enzymes involved in PI turnover, PI-specific phospholipase C (PI-PLC) hydrolyzes PIP_2 into two important biomolecules, diacylglycerol (DG) and inositol-1,4,5-triphosphate (IP_3). DG activates protein kinase C, and IP_3 releases Ca^{2+} from the endoplasmic reticulum to the cytoplasm. Further, PI-PLC is considered to be a rate-limiting enzyme of PI-turnover; therefore, a selective inhibitor of PI-PLC is considered to be quite useful as a tool for the investigation of signal transduction as well as being of medicinal importance. Akaterpin[2] (**1**) isolated recently by Umezawa as a specific inhibitor of PI-PLC from the marine sponge *Callyspongia* sp. is the most potent inhibitor among several compounds such as fluvirucin B_2[3] and pholipeptin.[4] Further, akaterpin was also found to inhibit neutral sphingomyelinase.

The planar structure of akaterpin containing two decalin rings and a hydroquinone disulfate moiety was elucidated by extensive NMR measurements, although the stereochemistry has remained unknown. The relative stereochemistry of the lower decalin moiety is the same as that of mamanuthaquinone.[5] However, even the relative configuration of the upper decalin has not yet been established. Being interested in the structure and biological activities of akaterpin, we embarked on a synthetic study of akaterpin. In a previous communication,[6] we reported that the relative stereochemistry of the upper decalin moiety was determined to be *cis* by synthesizing *cis*-decalin **2** and *trans*-decalin **3**. This paper describes the details of the synthesis of *cis*-decalin **2** and *trans*-decalin **3**, and the synthesis of a key intermediate for total synthesis of akaterpin. The resolution of a key intermediate for *cis*-decalin is also presented (Fig. 1).

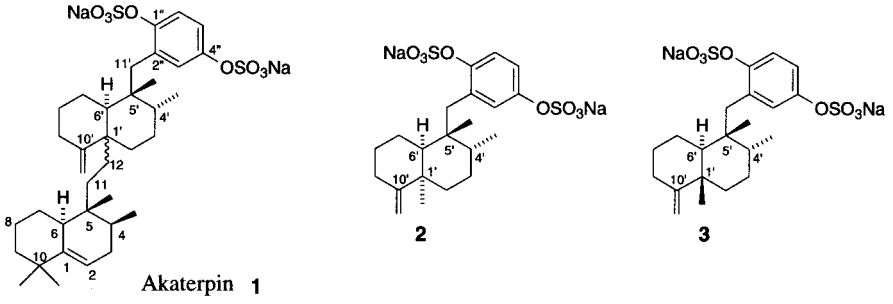

Figure 1.

Keywords: akaterpin; *cis*-decalin; *trans*-decalin; intramolecular Diels–Alder reaction.
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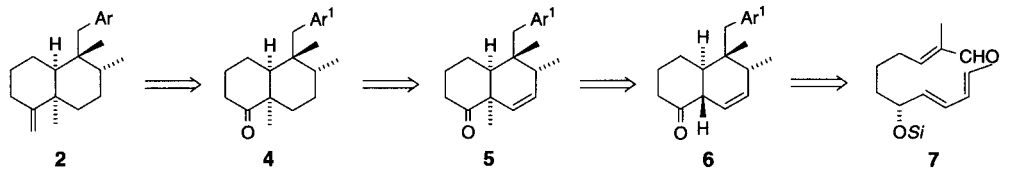


Scheme 1.

Since the relative stereochemistry of the upper decalin has not been established, our initial efforts were focused on the determination of the upper decalin moiety. For this purpose, we decided to synthesize *cis*-decalin **2** and *trans*-decalin **3**. We expected that the spectroscopic comparison of the synthesized decalins with natural akaterpin would provide some information on the stereochemistry.

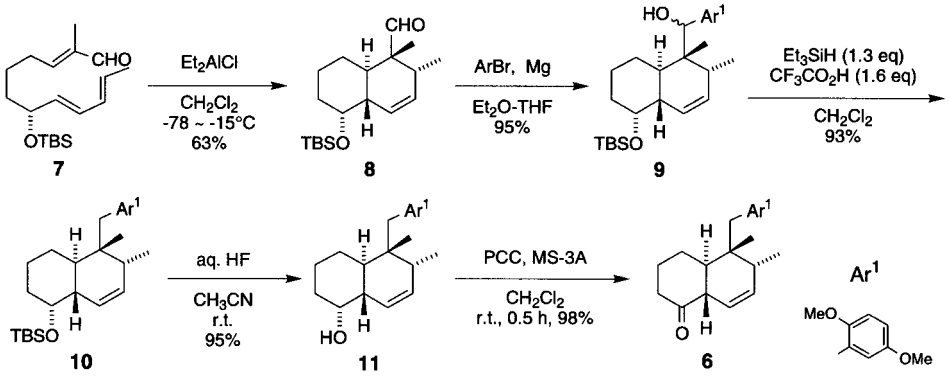
Synthesis of *cis*-Decalin 2

There are many *cis*-fused clerodane diterpenes such as arenarol,[7] popollohuanone E,[8] and (±)-15,16-epoxy-cis-cleroda-3,13(16),14-triene,[9] and several excellent methodologies have been developed for the total synthesis of these natural products.[7–9] Our synthetic strategy for *cis*-decalin **2** is shown in Scheme 1. We envisaged that β,γ-unsaturated ketone **6** might undergo regio- and stereoselective alkylation to afford *cis*-decalin **5**. Unsaturated ketone **6**, in turn, might be derived from trienal **7** through an intramolecular Diels–Alder reaction.[10]

At first, the synthesis of the *cis*-decalin **2** (racemate) is described. According to the procedure reported by Marshall,[10] trienal **7**, prepared from 2,4-hexadienal in **6** steps, was treated with Et_2AlCl to obtain **8** in 63% yield. The structure of **8** was confirmed by comparing the NMR data with those reported by Marshall. After introducing the aromatic moiety by Grignard reaction, dehydroxylation at the benzylic hydroxyl group was examined. Direct dehydroxylation with $LiAlH_4$–$AlCl_3$[11] only resulted in the formation of a complex mixture of products. However, the combination of Et_3SiH[12] (1.3 equiv.) and CF_3CO_2H (1.6 equiv.) was found to be effective giving **10** in 93% yield. No reaction occurred when acetic acid was used instead of CF_3CO_2H. The TBDMS group in **10** was cleaved with HF, and the resulting alcohol **11** was oxidized with PCC to obtain the key intermediate **6** (Scheme 2).

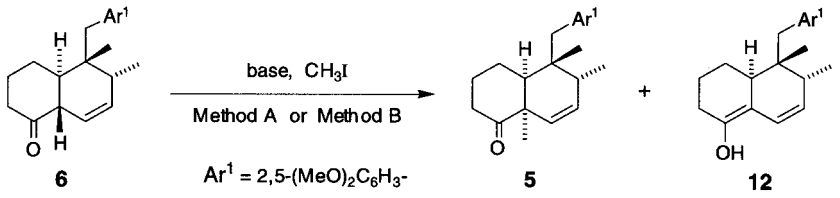
We then investigated the alkylation of β,γ-unsaturated ketone **6**. When a THF solution of enone **6** was added to a THF solution of LDA (Entry 1), no reaction occurred to recover the enone **6**. Then, we attempted methylation under various conditions varying the base, solvent, and order of addition. Some results are summarized in Table 1. We examined two procedures, Method A and B, which are classified according to the order of addition. Method A means that enone **6** was added to a base in a solvent, followed by the addition of MeI. Method B means that base was added to enone **6**, and MeI was finally added to the above reaction mixture. As shown in Table 1, dienol **12** was isolated in most cases. The structure of the dienol **12** was determined by NMR measurement. Thus, in the ^1H NMR spectrum, an OH proton appeared at δ 5.0 as a singlet which disappeared on the addition of D_2O. The IR spectrum also supported the enol structure, showing no C=O absorption. Further, dienol **12** slowly converted to the enone **6** in $CHCl_3$. From these results, we determined the dienol structure although the isolation of dienol is not clear. After a number of experiments, regio- and stereoselective methylation was accomplished by the treatment of **6** with $NaN[Si(CH_3)_3]_2$ as a base and MeI (Method B) to obtain the methylated *cis*-decalin **5** in 83% yield. Regioselectivity and stereoselectivity of the present methylation was excellent, producing **5** as a single isomer. *cis*-Fused structure of **5** was confirmed after transformation to the saturated ketone **4**. Comparison of the results (entry 7, 9, 10) strongly indicated that the choice of base and the order of addition are critical in the present methylation.

Hydrogenation of **5** was next examined. The double bond is sterically hindered, and resisted the hydrogenation using a conventional method such as Pd–C under H_2 atmosphere. Hydrogenation proceeded when $Pd(OH)_2$ was employed as a catalyst. However, two saturated ketones were formed in the hydrogenation. The major isomer was estimated to be the desired **4**, and the minor isomer was found to be **13**,



Scheme 2.

Table 1.



6 **5** **12**

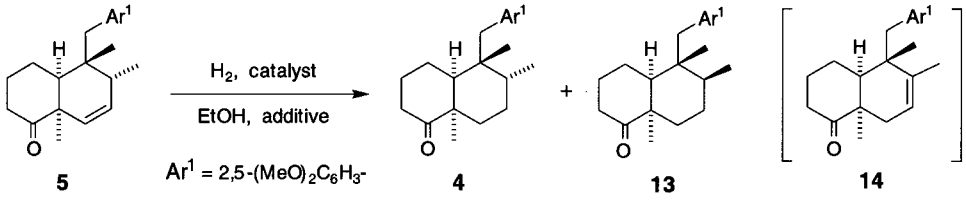
Entry	Method	Base (eq)	Solvent	Temp (°C)	**5** (%)	**12** (%)
1	A	LDA (1.2)	THF	−20	No reaction	
2		*t*-BuOK (1.2)	THF	0	–	30
3		*t*-BuOK (1.2)	THF–HMPA	0	Decomposition	
4		*t*-BuOK (1.2)	*t*-BuOH	rt	Decomposition	
5		KHMDS (1.0)	THF	0	–	40
6		KHMDS (1.0)	THF–HMPA	0	Decomposition	
7		NaHMDS (1.0)	THF	rt	–	35
8	B	*t*-BuOK (1.2)	THF	0	–	43
9		KHMDS (1.0)	THF	0	–	47
10		NaHMDS (1.0)	THF	rt	83	–

epimer at C-4′ (ca 5:1). The minor compound **13** is an intermediate for the first enantioselective synthesis of (+)-arenarol by Terashima.[7c] The undesirable **13** might be produced from **14** which would be formed by the isomerization of **5** prior to the hydrogenation. Addition of Et_3N was not effective for the undesirable epimerization. Separation of the two isomers was difficult, and it was necessary to achieve the hydrogenation without any accompanying epimerization (Table 2).

After a number of unsuccessful experiments, we finally found that Raney-Ni hydrogenation proceeded without accompaniment of the undesirable epimerization. During hydrogenation of the carbon–carbon double bond, ketone was also reduced, affording an epimeric mixture of cyclohexanol; the crude mixture was oxidized with PCC to give **4** in 98% yield. The *cis*-decalin structure of **4** was confirmed by NOE. between benzylic methylene protons and the newly introduced angular Me. Exomethylenation of **4** was achieved by the CH_2Br_2–Zn–$TiCl_4$ method developed by Takai and Nozaki[13] to obtain **15** in 89% yield. Conventional Wittig reaction was not successful, probably due to the steric congestion (Scheme 3).

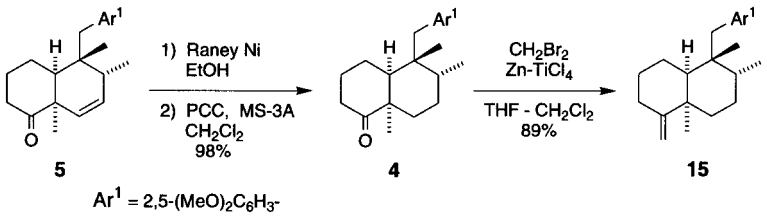
With the complete *cis*-decalin skeleton in hand, the remaining step was the demethylation of the hydroquinone moiety and sulfurization. Demethylation of **15** was found to be very difficult, although a number of alkylative and oxidative demethylation methods have been developed. For example, treatment with TMSI[14] prepared in situ from TMSCl and NaI resulted in the isomerization of *exo* olefin into *endo* olefin. We also attempted various oxidative demethylation methods using CAN, CrO_3,[15] and an Ag complex of picoline dicarboxylic acid.[16] Among them, treatment with CAN afforded quinone in moderate yield (36%). The resulting quinone was immediately reduced with $Na_2S_2O_4$ to obtain

Table 2.



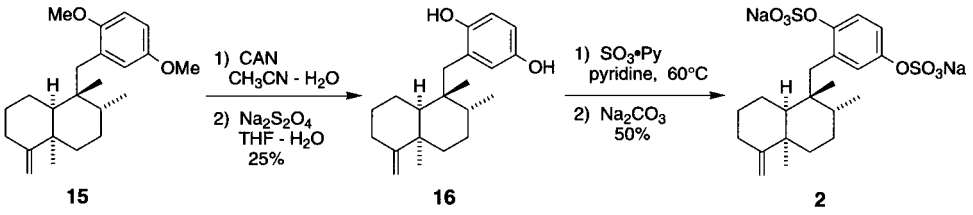
5 **4** **13** **14**

Entry	Catalyst	Additive	Time (h)	Yield (%)	Ratio (**4**:**13**)
1	Pd–C	–	24	No reaction	–
2	$Pd(OH)_2$	–	24	58	5:1
3	$Pd(OH)_2$	Et_3N	24	43	4:1
4	PtO_2	–	6	Decomposition	–



5 **4** **15**

Scheme 3.



Scheme 4.

the desired hydroquinone **16**. Although the yields are not satisfactory, the CAN–$Na_2S_2O_4$ method was employed for the synthesis of *cis*-decalin **2** and *trans*-decalin **3**. For further study towards the total synthesis of akaterpin, other protecting groups such as benzyl and MOM groups are to be employed (Scheme 4).

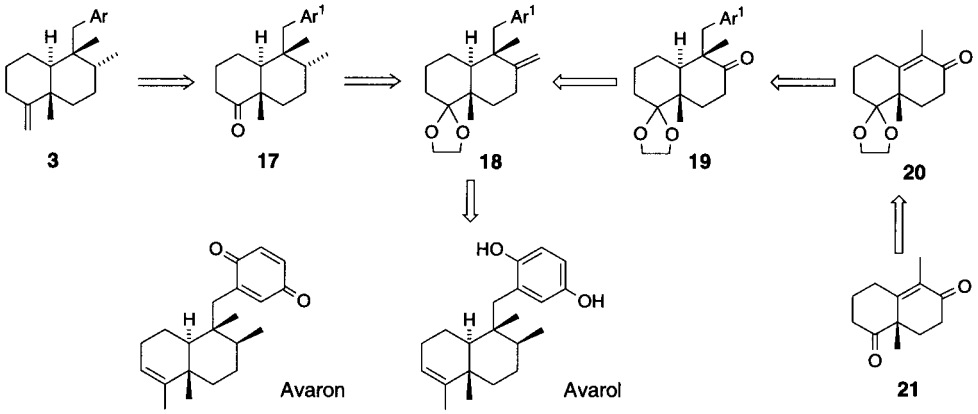
Finally, hydroquinone **16** was reacted with an SO_3·pyridine complex[17] in pyridine at 60°C, followed by treatment with Na_2CO_3 to complete the synthesis of *cis*-decalin **2**. During the sulfurization of hydroquinone, we found that mono-sulfurization products were isolated when sulfurization was carried out at room temperature. This finding will be useful for the study of the structure–activity relationships of akaterpin.

Synthesis of *trans*-Decalin 3

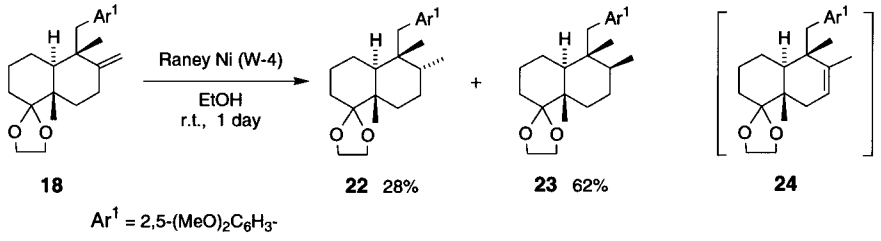
Most clerodane diterpenes have a *trans*-decalin structure. Among them, avarol[18] and avaron[18] are structurally closely related to our target compound **3**. The difference from a stereochemical point of view is that 4,5-dimethyl substituents are *syn* in avaron and avarol whereas *anti* in **3**. In the total synthesis of avarol by Wiemer et al.,[18c] the *trans*-decalin skeleton was constructed by reductive alkylation of enone **20**, and 4,5-*syn* stereochemistry was achieved by a stereoselective hydrogenation of *exo*-methylene **18**. Since the primary purpose of our present study was the determination of the relative stereochemistry of the upper decalin, we decided to follow the procedure developed for avarol and to examine several hydrogenation methods expecting to obtain the desired 4,5-*anti* isomer (Scheme 5).

According to the literature procedure, *exo*-methylene **18** was prepared from Wieland–Miescher ketone analog **21** and subjected to hydrogenation. Although hydrogenation of **18** was reported to produce the 4,5-*syn* dimethyl isomer predominantly,[18] we attempted the hydrogenation of **18** under various conditions to achieve the reversal of stereoselectivity. However, the desired 4,5-*trans* isomer **22** was best obtained in 28% yield by the treatment with Raney-Ni under H_2 atmosphere in EtOH. The major product (62% yield) was an isomeric 4,5-*cis* isomer **23**. The structure of **23** was determined by comparison of the ^{1}H- and ^{13}C NMR data with those reported by Wiemer et al.[18c] Catalytic hydrogenation over palladium catalysts gave an inseparable mixture of the desired **22** and isomerized *endo*-olefin **24** along with **23** (Scheme 6).

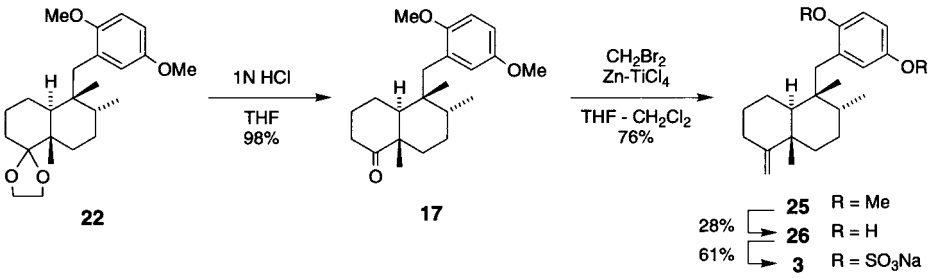
Although we were not able to achieve the reversal of



Scheme 5.

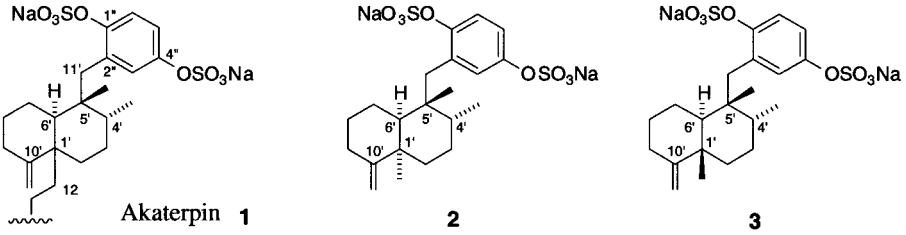


Scheme 6.



Scheme 7.

Table 3.



Position	Akaterpin	*cis*-Decalin **2**	Δδ	*trans*-Decalin **3**	Δδ
4′-Me	1.15 d	1.13 d	−0.02	1.17 d	+0.02
5′-Me	1.03 s	0.96 s	−0.07	0.89 s	−0.14
10′-CH_2	4.76 br s	4.75 br s	−0.01	4.52 br s	−0.24
	4.73 br s	4.67 br s	−0.06	4.46 br s	−0.27
11′	3.32 d	3.26 d	−0.06	3.34 d	+0.02
	2.40 d	2.53 d	+0.13	2.33 d	−0.07
3″	7.30 d (2.4 Hz)	7.31 d (3.0 Hz)	+0.01	7.34 d (3.0 Hz)	+0.04
5″	7.09 dd (2.4, 8.5 Hz)	7.08 dd (3.0, 8.9 Hz)	−0.01	7.08 dd (3.0, 8.9 Hz)	−0.01
6″	7.38 d (8.5 Hz)	7.38 d (8.9 Hz)	0.00	7.38 d (8.9 Hz)	0.00

selectivity, we proceeded with the synthesis of *trans*-decalin **3**. After deprotection of ethylene ketal in **22**, the resulting ketone **17** was converted to *trans*-decalin **3** by a similar procedure to that for *cis*-decalin **2** (Scheme 7).

Comparison of NMR of 2 and 3 with those of Akaterpin

We were thus able to synthesize both *cis*-decalin **2** and *trans*-decalin **3** in a stereochemically unambiguous manner.

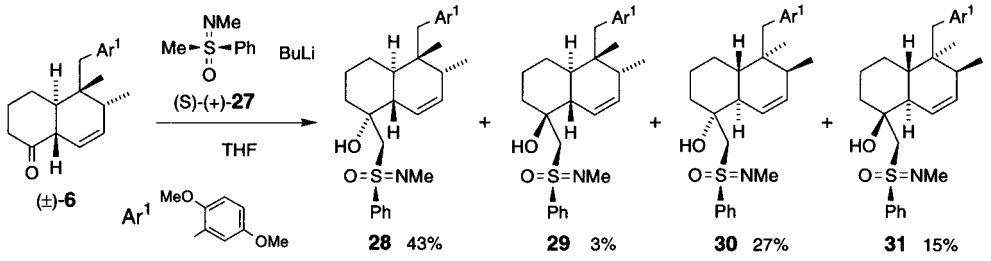
Table 4.

Position	Akaterpin	*cis*-Decalin **2**	Δ ppm	*trans*-Decalin **3**	Δ ppm
1′	44.1	42.6	−1.5	42.1	−2.0
4′	38.6	39.1	+0.5	37.0	−1.6
4′-Me	16.5	16.5	0.0	16.8	+0.3
5′	43.1	41.3	−1.8	42.1	−1.0
5′-Me	25.2	25.4	+0.2	20.8	−4.4
6′	47.0	47.0	0.0	19.6	+2.6
7′	22.4	23.2	+0.8	23.1	+0.7
8′	25.7	26.1	+0.4	26.6	+0.9
9′	34.0	33.4	-0.6	34.1	+0.1
10′	153.4	157.2	+3.8	161.5	+8.1
10′-CH_2	109.4	106.3	−3.1	102.4	−7.0
11′	37.3	36.6	−0.7	36.5	−0.8
1″	150.1	150.1	0.0	150.2	+0.1
2″	135.2	135.4	+0.2	135.3	+0.1
3″	125.1	125.2	+0.1	124.6	−0.5
4″	149.9	149.9	0.0	150.1	+0.2
5″	120.4	120.3	−0.1	120.3	−0.1
6″	123.2	123.2	0.0	123.1	−0.1

The NMR spectra of **2** and **3** were then compared with those of akaterpin. Tables 3 and 4 show the representative data of ^1H NMR (500 MHz, CD_3OD) and ^{13}C NMR (125 MHz, CD_3OD), respectively. As shown in Table 3, differences in chemical shifts of the exomethylene protons (10′-CH_2) are most diagnostic. Differences in the chemical shift of 10′-CH_2 protons are 0.24 and 0.27 ppm in *trans*-decalin **3**, whereas, at most, 0.06 ppm in *cis*-decalin **2**. These data strongly indicate the *cis* configuration of the upper decalin of akaterpin. This conclusion was also supported by ^{13}C NMR spectra. Chemical shift differences of 5′-Me, 6′, 10′ and 10′-H_2 in **3** are apparently larger than in **2**.

Resolution of β,γ-unsaturated ketone 6

Based on the above conclusion that the upper decalin moiety of akaterpin has *cis* stereochemistry, we next attempted the resolution of intermediates of *cis*-decalin. Since the absolute stereochemistry was not determined, both enantiomers of the upper decalin are required. Therefore, we employed a resolution strategy rather than the alternative enantioselective approach. Resolution of β,γ-unsaturated ketone **6** seemed most desirable because **6** might serve as a potential intermediate for the total synthesis of akaterpin. Thus, the introduction of a lower decalin moiety into **6** might be possible by either direct alkylation or a stepwise method. Among several methodologies for the resolution of a ketone, the use of chiral sulfoxyimine developed by Johnson[19] was found to be successful in our case. When



Scheme 8.

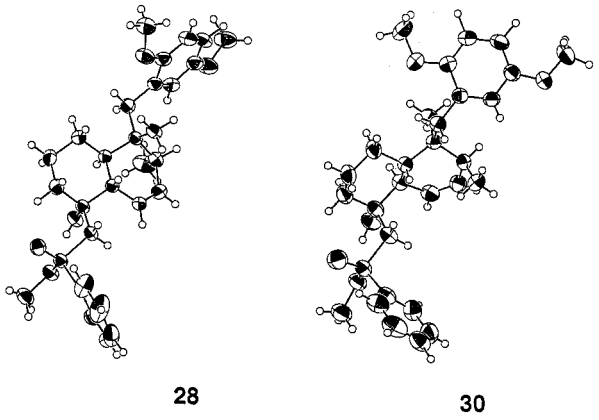


Figure 2.

racemic unsaturated ketone **6** was reacted with lithio derivative of (*S*)-(+)-27, four possible stereoisomers of the sulfoxyimine adducts were isolated in total 88% yield. These isomers were separated by chromatography on silica gel, and the yield of each isomer is shown in Scheme 8.

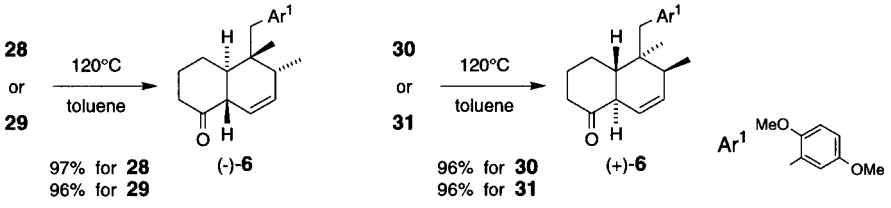
Relative as well as absolute stereochemistry of each isomer was established as follows: The structures of **28** and **30** were determined by X-ray crystallographic analysis (Fig. 2).

These stereochemically established isomers **28** and **30** were separately subjected to thermal elimination affording (−)-6 ($[\alpha]_D$=−3.4° (*c* 1.02, $CHCl_3$)) and (+)-6 ($[\alpha]_D$=+3.3° (*c* 0.57, $CHCl_3$)), respectively. These enantiomers were cleanly separated on HPLC using chiral column (Daicel AD, eluent; *n*-hexane/*i*-PrOH: 9:1; flow rate; 0.5 ml/min; t_R of (+)-6, 13 min; t_R of (−)-6, 20 min). Thermal elimination of the remaining sulfoxyimine adducts **29** and **31** also proceeded almost quantitatively to obtain (−)-6 and (+)-6, respectively. Resolution of key intermediate **6** was thus established (Scheme 9).

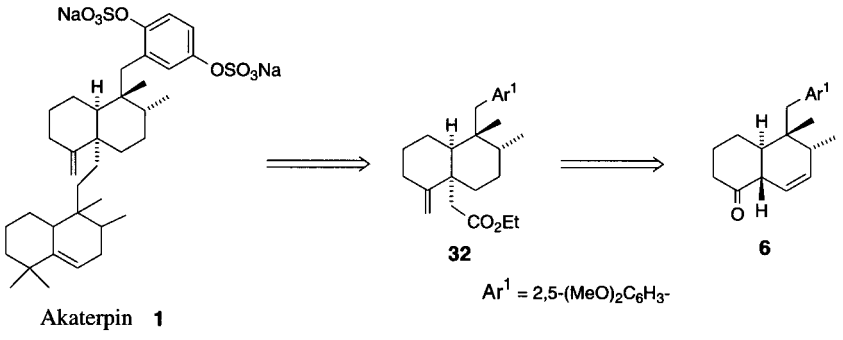
Introduction of Acetate Unit into 6 and Synthesis of a Potential Key Intermediate 32

We envisaged that *cis*-decalin **32** with an ethoxycarbonyl group might serve as a potential intermediate for the synthesis of akaterpin. One plausible approach might be the construction of the lower decalin by intermolecular Diels–Alder reaction reported by Danishefsky in the synthesis of mamanuthaquinone.[5] We then attempted introduction of an acetate unit into **6** and transformation of the derived *cis*-decalin into the key intermediate **32** (Scheme 10).

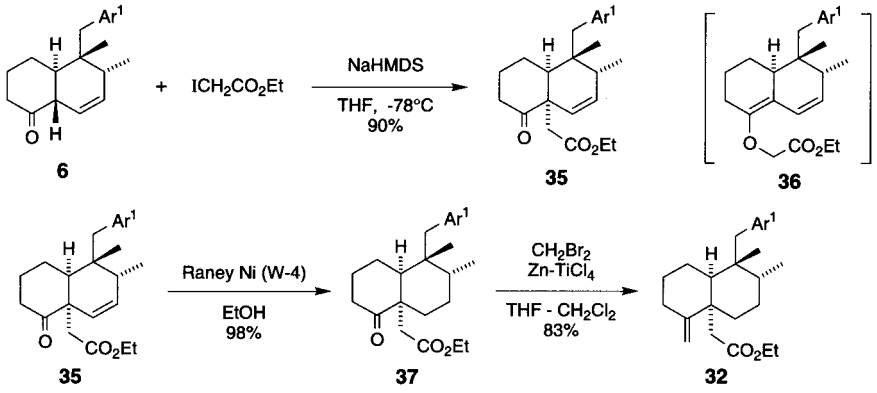
Following the procedure developed above, alkylation of **6** was first attempted. When ethyl bromoacetate was used as



Scheme 9.



Scheme 10.



Scheme 11.

an electrophile, *O*-alkylation product **36** was isolated in 83% yield along with a small amount of dienol **12**. However, the desired *C*-alkylation product **35** was obtained in 90% yield when ethyl iodoacetate was employed as an electrophile. The resulting unsaturated ketoester **35** was reduced to saturated ketoester **37** with Raney Ni. In this case, progress of hydrogenation was carefully monitored by TLC in order to avoid the accompanying reduction of the cyclohexanone part which resulted in the undesirable formation of lactone. Finally, ketoester **37** was treated with CH_2Br_2–Zn–$TiCl_4$ to obtain the key intermediate **32** in high yield (Scheme 11).

Conclusion

In this paper, we have described that the upper decalin moiety of akaterpin has a *cis* configuration. We further disclosed our efforts toward the total synthesis by achieving the synthesis of the potential key intermediate **32**. Additional characteristic features described herein are (i) *cis*-decalin **2** was synthesized by developing the regio- and stereoselective methylation of β,γ-unsaturated ketone **6**, (ii) resolution of β,γ-unsaturated ketone **6** was accomplished using a chiral sulfoxyimine method.

Experimental

All ^{1}H- and ^{13}C NMR spectra were measured in $CDCl_3$ with TMS and the solvent peak as internal standards, and recorded on a JEOL JMN-EX270 spectrometer or JEOL JMN-GS×500. IR spectra were recorded on Horiba FT-210 or Hitachi 215 infrared spectrometer. Mass spectra (MS) were obtained on a Hitachi M-80 spectrometer. Optical rotations were measured on a JASCO DIP-360 digital polarimeter. Column chromatography was carried out on Fujisilisiachem K.K.BW-127ZH. Analytical thin-layer chromatography (TLC) was performed on Merck precoated silica gel HF_{254} plates, and compounds were visualized by UV illumination (254 nm) or by heating to 150°C after spraying phosphomolybdic acid in ethanol. Dry diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium-benzophenone ketyl, and dry benzene (PhH) and dichloromethane (CH_2Cl_2) were distilled from calcium hydride, respectively, under an inert atmosphere. All other organic solvents and reagents were obtained from commercial sources and used without further purification. Organic extracts were dried over sodium sulfate (Na_2SO_4), filtered, and concentrated using a rotary evaporator at <40°C bath temperature. Involatile oils and solids were vacuum dried at <2 mmHg.

***trans*-5α-(*tert*-Butyldimethylsilyloxy)-1α-[(2,5-dimethoxyphenyl)-hydroxymethyl]-1,2,4a,5,6,7,8,8a-octahydro-1β,2α-dimethylnaphthalene (9).** To a vigorously stirred mixture of Mg turnings (0.78 g, 32 mmol) in 30 ml of refluxing ether containing 0.3 ml of 1,2-dibromoethane (1.4 mmol) was added, dropwise, a solution of 1-bromo-2,5-dimethoxy benzene (3.5 g, 32 mmol) in 30 ml of THF over 2 h. After the mixture was refluxed for 30 min and cooled to 0°C, a solution of *trans*-5α-(*tert*-Butyldimethylsilyloxy)-1,2,4a,5,6,7,8,8a-octahydro-1β,2α-dimethylnaphthalene-1α-carbaldehyde **8** (1.73 g, 5.36 mmol) in 17 ml of THF was added over 10 min with stirring. Thirty minutes later, the excess reagent was quenched by the addition of MeOH (6 ml). The resulting solution was poured through a glass-wool plug into a separatory funnel containing 100 ml of ether and 100 ml of saturated aqueous NH_4Cl solution. The aqueous phase was extracted with two additional 100 ml portions of ether. The combined extract was washed with 200 ml of saturated aqueous NaCl solution, dried and concentrated. The residue was purified by chromatography on 100 g of silica gel by using 1:30 ether–hexane as eluent, affording **9** (diastereomeric mixture, 2.34 g, 95%) as a colorless oil. IR (neat) 3506, 2929, 2856, 1494, 1463, 1254, 1218 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.03 (3H, s, Si–CH_3), 0.04 (3H×1/2, s, Si–CH_3), 0.05 (3H×1/2, s, Si–CH_3), 0.70 (3H×1/2, s, 1-CH_3), 0.89 (3H, d, *J*=6.9 Hz, 2-CH_3), 0.90 (9H, s, *t*-Bu), 1.08 (3H×1/2, s, 1-CH_3), 1.20–1.98 (8H, m, 2,4a,6,7,8-H), 2.15–2.27 (1H×1/2, m, 8a-H), 2.34–2.40 (1H×1/2, m, 8a-H), 3.76 (3H×1/2, s, OCH_3), 3.77 (3H×1/2, s, OCH_3), 3.78 (3H×1/2, s, OCH_3), 3.79 (3H×1/2, s, OCH_3), 4.05 (1H, br.s, 5-H), 5.20–5.60 (3H, m, 3,4-H, C*H*–OH), 6.75–6.78 (2H, m, 3′,4′-H), 7.21 (1H×1/2, d, *J*=2.6 Hz, 6′-H), 7.24 (1H×1/2, d, *J*=2.6 Hz, 6′-H); MS *m/z* 460 (M^+); High resolution MS calcd for $C_{27}H_{44}O_4Si$ (M^+) 460.3009, found 460.3007.

***trans*-5α-(*tert*-Butyldimethylsilyloxy)-1α-[(2,5-dimethoxyphenyl)-methyl]-1,2,4a,5,6,7,8,8a-octahydro-1β,2α-dimethylnaphthalene (10).** To a solution of **9** (0.94 g, 2.04 mmol) in 30 ml of dry CH_2Cl_2 were added 0.4 ml (2.6 mmol) of triethylsilane and 0.24 ml (3.3 mmol) of

trifluoroacetic acid. The solution was stirred for 10 h at rt under Ar gas and quenched by the addition of saturated aqueous $NaHCO_3$ solution (50 ml). The aqueous phase was extracted with two 50 ml portions of ether. The combined extract was washed with 100 ml of saturated aqueous NaCl solution, dried and concentrated. The residue was purified by chromatography on 50 g of silica gel by using 1:2 chloroform–hexane as eluent, affording **10** (0.84 g, 93%) of as a colorless oil. IR (neat) 2954, 2929, 2858, 1496, 1464, 1254, 1222 cm^{-1}; ^1H NMR (270 MHz): 0.02 (3H, s, Si–CH_3), 0.04 (3H, s, Si–CH_3), 0.75 (3H, s, 1-CH_3), 0.90 (9H, s, *t*-Bu), 1.10 (3H, d, *J*=6.9 Hz, 2-CH_3), 1.41–1.98 (9H, m, 2,4a,6,7,8,8a-H), 2.38 (1H, d, *J*=13.9 Hz, Ar-CH*H*), 3.03 (1H, d, *J*=13.9 Hz, Ar-C*H*H), 3.75 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.02 (1H, br.s, 5-H), 5.20–5.24 (1H, m, 3 or 4-H), 5.55–5.64 (1H, m, 3 or 4-H), 6.68 (1H, dd, *J*=3.0, 8.6 Hz, 4′-H), 6.77 (1H, d, *J*=8.6 Hz, 3′-H), 6.92 (1H, d, *J*=3.0 Hz, 6′-H); ^{13}C NMR (67.5 MHz) δ −4.63, 14.16, 17.73, 18.11, 21.37, 25.64, 25.86, 32.18, 34.11, 34.72, 38.24, 38.46, 45.97, 55.53, 55.85, 71.23, 110.23, 111.14, 117.45, 128.09, 130.21, 132.99, 152.77, 152.94; MS *m/z* 444 (M^+); High resolution MS calcd for $C_{27}H_{44}O_3Si$ (M^+) 444.3060, found 444.3062.

***trans*-1α-[(2,5-Dimethoxyphenyl)methyl]-1,2,4α,5,6,7,8,8a-octahydro-1β,2α-dimethyl-5α-naphthalenol (11).** To a solution of **10** (0.24 g, 0.54 mmol) in 4 ml of CH_3CN was added 0.2 ml of 46% aqueous HF. The solution was stirred for 20 h at rt and quenched by the addition of saturated aqueous $NaHCO_3$ solution (10 ml). The aqueous phase was extracted with two 20 ml portions of AcOEt. The combined extract was washed with 40 ml of saturated aqueous NaCl solution, dried and concentrated. The residue was purified by chromatography on 20 g of silica gel by using 1:5 ether–hexane as eluent, affording **11** (0.17 g, 95%) as a white solid. Mp 94–96°C; IR (neat) 3456, 2931, 2870, 1497, 1458, 1226 cm^{-1}; ^1H NMR (270 MHz): 0.79 (3H, s, 1-CH_3), 1.14 (3H, d, *J*=6.9 Hz, 2-CH_3), 1.26–2.03 (9H, m, 2,4a,6,7,8,8a-H), 2.40 (1H, d, *J*=14.2 Hz, Ar-C*H*H), 3.03 (1H, d, *J*=14.2 Hz, Ar-CH*H*), 3.75 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.05 (1H, br.s, 5-H), 5.30–5.34 (1H, m, 3 or 4-H), 5.78–5.82 (1H, m, 3 or 4-H), 6.69 (1H, dd, *J*=3.0, 8.9 Hz, 4′-H), 6.78 (1H, d, *J*=8.9 Hz, 3′-H), 6.92 (1H, d, *J*=3.0 Hz, 6′-H); ^{13}C NMR (67.5 MHz) δ 17.68, 18.02, 21.29, 25.48, 32.22, 32.29, 34.77, 38.37, 38.49, 45.43, 55.51, 55.78, 0.49, 110.31, 11.14, 117.37, 126.02, 129.79, 136.46, 152.59, 152.92; MS *m/z* 330 (M^+); High resolution MS calcd for $C_{21}H_{30}O_3$ (M^+) 330.2193, found 330.2200.

***trans*-1α-[(2,5-Dimethoxyphenyl)methyl]-1,2,4a,7,8,8a-hexahydro-1β,2α-dimethyl-5(6*H*)-naphthalenone (6).** To a suspension of PCC (1.6 g, 5.8 mmol) in 48 ml of CH_2Cl_2 were added 3.2 g of MS-3A powder and a solution of **11** (1.05 g, 3.2 mmol) in 16 ml of CH_2Cl_2 at 0°C. This reaction mixture was stirred for 1 h at rt, diluted by the addition of ether (30 ml), and filtered through a short column of silica gel. The column was eluted with excess ether. The combined eluates were concentrated in vacuo. The residue was purified by chromatography on 30 g of silica gel by using 1:3 ether–hexane as eluent, affording **6** (1.02 g, 98%) as white solid. Mp 119–121°C; IR (neat) 2964, 2921, 2845, 1720, 1707, 1378, 1303, 1220 cm^{-1}; ^1H NMR (270 MHz) δ 0.89 (3H, s, 1-CH_3), 1.09 (3H, d, *J*=6.9 Hz, 2-CH_3), 1.43–1.97 (6H, m, 2,7,8,8a-H), 2.11–2.22 (1H, m, 6-H), 2.35–2.41 (1H, m, 6-H), 2.44 (1H, d, *J*=13.9 Hz, Ar-C*H*H), 2.87–2.92 (1H, m, 4a-H), 3.07 (1H, d, *J*=13.9 Hz, Ar-CH*H*), 3.76 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 5.73–5.75 (2H, m, 3,4-H), 6.71 (1H, dd, *J*=3.0, 8.9 Hz, 4′-H), 6.79 (1H, d, *J*=8.9 Hz, 3′-H), 6.91 (1H, d, *J*=3.0 Hz, 6′-H); ^{13}C NMR (67.5 MHz) δ 17.52, 24.94, 26.26, 32.67, 38.08, 39.27, 40.94, 43.81, 52.42, 55.54, 55.76, 110.53, 111.12, 117.41, 120.0, 129.13, 134.36, 152.47, 152.97, 211.78; MS *m/z* 328 (M^+); High resolution MS calcd for $C_{21}H_{28}O_3$ (M^+) 328.2036, found 328.2025.

***cis*-1α-[(2,5-Dimethoxyphenyl)methyl]-1,2,4a,7,8,8a-hexahydro-1β,2α,4aα-trimethyl-5(6*H*)-naphthalenone (5).** To a solution of **6** (1.02 g, 3.1 mmol) in 100 ml of dry THF was added 3.1 ml (3.1 mmol) of $NaN[Si(CH_3)_3]_2$ as a 1.0 M solution in THF at rt. The solution was stirred for 20 min at rt under Ar gas and then 3.4 ml (31 mmol) of CH_3I was added. After being stirred for 10 h at rt under Ar, the reaction mixture was diluted by the addition of H_2O (20 ml). The aqueous phase was extracted with two 20 ml portions of AcOEt. The combined extract was washed with 40 ml of saturated aqueous NaCl solution, dried and concentrated. The residue was purified by chromatography on 30 g of silica gel by using 1:20 AcOEt–hexane as eluent, affording **5** (883 mg, 83%) as a white solid. Mp 60–61°C; IR (neat) 2968, 2921, 2830, 1703, 1693, 1377, 1220 cm^{-1}; ^1H NMR (270 MHz) δ 0.80 (3H, s, 1-CH_3), 1.11 (3H, d, *J*=6.9 Hz, 2-CH_3), 1.38 (3H, s, 4a-CH_3), 1.85–2.35 (7H, m, 2,6,7,8,8a-H), 2.44 (1H, d, *J*=13.5 Hz, Ar-CHH), 2.57–2.66 (1H, m, 6-H), 3.09 (1H, d, *J*=13.5 Hz, Ar-CHH), 3.74 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 5.68–5.79 (2H, m, 3,4-H), 6.70 (1H, dd, *J*=3.0, 8.9 Hz, 4′-H), 6.77 (1H, d, *J*=8.9 Hz, 3′-H), 6.84 (1H, d, *J*=3.0 Hz, 6′-H); MS *m/z* 342 (M^+); High resolution MS calcd for $C_{22}H_{30}O_3$ (M^+) 342.2193, found 342.2189.

***cis*-1α-[(2,5-Dimethoxyphenyl)methyl]-octahydro-1β,2α,4aα-trimethyl-5(6*H*)-naphthalenone (4).** To a solution of **5** (10 mg, 30 μmol) in 1 ml of ethanol were added one drop of Raney-Ni (W-4). This reaction mixture was stirred for 12 h at rt under H_2 gas, filtered through a celite-pad, and then was concentrated in vacuo to give a crude product. To a solution of PCC (25 mg, 116 μmmol) in 1 ml of CH_2Cl_2 was added 50 mg of MS-3A powder and a solution of the crude product (10 mg) in 3 ml of CH_2Cl_2 at 0°C. This reaction mixture was stirred for 1 h at rt, diluted by the addition of ether (5 ml), and filtered through a short column of silica gel. The column was eluted with excess ether. The combined eluates were concentrated. The residue was purified by chromatography on 1 g of silica gel by using 1:10 AcOEt–hexane as eluent, affording **4** (9.8 mg, 98%) as a white solid. Mp 104–108°C; IR (neat) 2935, 2881, 1701, 1707, 1589, 1498, 1463, 1222 cm^{-1}; ^1H NMR (270 MHz) δ 0.82 (3H, s, 1-CH3), 1.07 (3H, d, *J*=6.9 Hz, 2-CH3), 1.21–1.39 (2H, m, 3-H), 1.34 (3H, s, 4a-CH_3), 1.53–2.18 (8H, m, 2,4,7,8,8a-H), 2.06–2.34 (1H, m, 6-H), 2.44 (1H, d, *J*=13.5 Hz, Ar-C*H*H), 2.52–2.62 (1H, m, 6-H), 3.04 (1H, d, *J*=13.5 Hz, Ar-CH*H*), 3.75 (6H, s, OCH_3×2), 6.69 (1H, dd, *J*=3.0, 8.9 Hz, 4′-H), 6.76 (1H, d, *J*=8.9 Hz, 3′-H), 6.81 (1H, d, *J*=3.0 Hz, 6′-H); MS *m/z* 344 (M^+); High resolution MS calcd for $C_{22}H_{32}O_3$ (M^+) 344.2349, found 344.2350.

***cis*-1α-[(2,5-Dimethoxyphenyl)methyl]-decahydro-1β, 2α,4aα-trimethyl-5-methylenenaphthalene (15).** To a suspension of Zn (800 mg, 12.5 mmol) in 5 ml of THF were added 0.4 ml (5.8 mmol) of CH_2Br_2, 3.1 ml (3.1 mmol) of $TiCl_4$ as a 1.0 M solution in CH_2Cl_2 and a solution of **4** (120 mg, 0.35 mmol) in 4.5 ml of THF at rt. This reaction mixture was stirred for 1 h at rt, diluted by the addition of ether (30 ml), and poured through a glass-wool plug into a separator funnel containing 10 ml of ether and 10 ml of 1 N aqueous HCl solution. The aqueous phase was extracted with two additional 10 ml portions of ether. The combined extract was washed with 20 ml of saturated aqueous NaCl solution, dried and concentrated. The residue was purified by chromatography on 10 g of silica gel by using 1:25 AcOEt–hexane as eluent, affording **15** (106 mg, 89%) as a white solid. Mp 48–49°C; IR (neat) 2935, 2831, 1498, 1463, 1282, 1222 cm^{-1}; ^1H NMR (270 MHz) δ 0.92 (3H, s, 1-CH_3), 1.09 (3H, d, J=6.9 Hz, 2-CH_3), 1.25 (3H, s, 4a-CH_3), 1.41–1.92 (10H, m, 2,3,4,7,8,8a-H), 2.15–2.23 (1H, m, 6-H), 2.35–2.45 (1H, m, 6-H), 2.42 (1H, d, J=13.9 Hz, Ar-C*H*H), 3.04 (1H, d, J=13.9 Hz, Ar-CH*H*), 3.74 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 4.69 (1H, br.s, 5 =C*H*H), 4.75 (1H, br.s, 5 =CH*H*), 6.67 (1H, dd, J=3.0, 8.9 Hz, 4′-H), 6.75 (1H, d, J=8.9 Hz, 3′-H), 6.85 (1H, d, J=3.0 Hz, 6′-H); MS *m/z* 342 (M^+); High resolution MS calcd for $C_{23}H_{34}O_2$ (M^+) 342.2557, found 342.2545.

***cis*-1α-[(2,5-Dihydroxyphenyl)methyl]-decahydro-1β, 2α,4aα-trimethyl-5-methylenenaphthalene (16).** To a solution of **15** (44 mg, 0.128 mmol) in 9 ml of CH_3CN was added, dropwise, a solution of CAN (195 mg, 0.355 mmol) in 4.5 ml of H_2O over 1 h. This solution was stirred for 1 day at rt, diluted with 10 ml of H_2O, and extracted with 30 ml of ether. The extract was washed with 30 ml of saturated aqueous NaCl solution, dried and concentrated to give a crude product.

To a solution of the crude quinone in 3 ml of THF was added a solution of $Na_2S_2O_4$ (200 mg) in 1 ml of H_2O. The solution was stirred for 10 min at rt, diluted with 5 ml of H_2O, and extracted with 10 ml of AcOEt. The extract was washed with 30 ml of saturated aqueous NaCl solution, dried and concentrated. The residue was purified by chromatography on 5 g of silica gel by using 1:5 AcOEt–hexane as eluent, affording **16** (10 mg, 25%) as a yellow oil. IR (neat) 3481, 3417, 3373, 2956, 2873, 1635, 1452, 1215 cm^{-1}; ^1H NMR (270 MHz) δ 0.98 (3H, s, 1-CH_3), 1.10 (3H, d, J=6.9 Hz, 2-CH_3), 1.26 (3H, s, 4a-CH_3), 1.45–1.93 (10H, m, 2,3,4,7,8,8a-H), 2.14–2.23 (1H, m, 6-H), 2.35–2.45 (1H, m, 6-H), 2.39 (1H, d, J=13.9 Hz, Ar-C*H*H), 2.97 (1H, d, J=13.9 Hz, Ar-CH*H*), 4.35–4.41 (2H, m, OH), 4.71 (1H, br.s, 5 =C*H*H), 4.77 (1H, br.s, 5 =CH*H*), 6.53 (1H, dd, J=3.0, 8.9 Hz, 4′-H), 6.61 (1H, d, J=8.9 Hz, 3′-H), 6.75 (1H, d, J=3.0 Hz, 6′-H); MS *m/z* 314 (M^+); High resolution MS calcd for $C_{21}H_{30}O_2$ (M^+) 314.2155, found 314.2163.

***cis*-1α-[(2,5-bis(Sodiumoxysulfonyloxy)phenyl]methyl-decahydro-1β,2α,4aα-trimethyl-5-methylenenaphthalene (2).** To a solution of SO_3·pyridine (26 mg, 64 mmol) in 1 ml of pyridine was added a solution of **16** (10 mg, 32 mmol) in 3 ml of pyridine. This solution was stirred for 4 h at 80°C under Ar gas, cooled to rt, and 2 ml of H_2O and 200 mg of Na_2CO_3 were added. The reaction mixture was stirred for 30 min at 60°C and concentrated The residue was purified by chromatography on 1 g of silica gel by using 2:1 chloroform–methanol as eluent, affording **2** (8.1 mg, 50%) as white solid. Mp>240°C; IR (neat) 3467, 2927, 2873, 1556, 1485, 1460, 1261, 1232 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) d 0.96 (3H, s, 1-CH_3), 1.13 (3H, d, J=6.9 Hz, 2-CH_3), 1.25 (3H, s, 4a-CH_3), 1.51–2.06 (10H, m, 2,3,4,7,8,8a-H), 2.14–2.20 (1H, m, 6-H), 2.40–2.50 (1H, m, 6-H), 2.53 (1H, d, J=14.0 Hz, Ar-C*H*H), 3.26 (1H, d, J=14.0 Hz, Ar-CH*H*), 4.67 (1H, br.s, 5 =C*H*H), 4.75 (1H, br.s, 5 =CH*H*), 7.08 (1H, dd, J=3.0, 8.9 Hz, 4′-H), 7.31 (1H, d, J=3.0 Hz, 6′-H), 7.38 (1H, d, J=8.9 Hz, 3′-H); ^{13}C NMR (125 MHz, CD_3OD) d 16.5 (2-CH_3), 23.2 (8), 25.4 (1-CH_3), 26.1 (7), 27.0 (3), 32.3 (4), 32.5 (4a-CH_3), 33.4 (6), 36.6 (Ar-CH_2), 39.1 (2), 41.3 (1), 42.6 (4a), 47.0 (8a), 106.3 (5 =CH_2), 120.3 (4′), 123.2 (3′), 125.2 (6′), 135.4 (1′), 149.9 (5′), 150.1 (2′), 157.2 (5); FABMS *m/z* 541 $(M+Na)^+$; High resolution FABMS calcd for $C_{21}H_{28}O_8S_2Na_3$ $(M+Na)^+$ 541.0918, found 541.0914.

***trans*-1α-[(2,5-Dimethoxyphenyl)methyl]-octahydro-1β, 2α,4ab-trimethyl-5(6*H*)-naphthalenone ethylene ketal (22).** To a solution of *trans*-1α-[(2,5-dimethoxy-phenyl)-methyl]-octahydro-1β,4aβ-dimethyl-2-methylene-5(6*H*)-naphthalenone ethylene ketal (300 mg, 0.777 mmol) in 10 ml of ethanol were added two drops of Raney-Ni. This reaction mixture was stirred for 12 h at rt under H_2 gas, filtered through a celite-pad and concentrated. The residue was purified by chromatography on 40 g of silica gel by using 1:20 AcOEt–hexane as eluent, affording **22** (83 mg, 28%) as a colorless oil and 188 mg (62%) of the stereo-isomer **23**. 22: IR (neat) 2950, 2879, 1497, 1466, 1224 cm^{-1}; ^1H NMR (270 MHz) δ 0.82 (3H, s, 1-CH_3), 1.12 (3H, s, 4a-CH_3), 1.18 (3H, d, J=6.9 Hz, 2-CH_3), 1.25–1.91 (12H, m, 2,3,4,6,7,8,8a-H), 2.28 (1H, d, J=13.9 Hz, ArC*H*H), 3.03 (1H, d, J=13.9 Hz, ArCH*H*), 3.74 (3H, s, O–CH_3), 3.75 (3H, s, O–CH_3), 3.77–4.00 (4H, m, O-CH_2), 6.67 (1H, dd, J=3.0,8.9 Hz, 4′-H), 6.75 (1H, d, J=8.9 Hz, 3′-H), 6.88 (1H, d, J=3.0 Hz, 6′-H); MS *m/z* 388 (M^+); High resolution MS calcd for $C_{24}H_{36}O_4$ (M^+) 388.2611, found 388.2602. 23: ^1H NMR (270 MHz) δ 0.81 (3H, s, 1-CH_3), 0.94 (3H, d, J=5.6 Hz, 2-CH_3), 1.05 (3H, s, 4a-CH_3), 1.20–1.71 (11H, m, 2,3,4,6,7,8-H), 1.94 (1H, d, J=13.6 Hz, 8a-H), 2.63 (2H, s, Ar-CH_2), 3.78 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.70–3.85 (4H, m, OCH_2), 6.65–6.86 (3H, m, 3′,4′,6′-H).

***trans*-1α-[(2,5-Dimethoxyphenyl)methyl]-octahydro-1β, 2α,4aβ-trimethyl-5(6*H*)-naphthalenone (17).** To a solution of **22** (55 mg, 0.142 mmol) in 10 ml of THF was added a solution of 1 N aqueous HCl solution (5 ml). This reaction mixture was stirred for 10 min at rt, and quenched by the addition of saturated aqueous $NaHCO_3$ solution (10 ml). The aqueous phase was extracted with two 10 ml portions of ether. The combined extract was washed with 20 ml of saturated aqueous NaCl solution, dried and concentrated. The residue was purified by chromatography on 10 g of silica gel by using 1:25 AcOEt–hexane as eluent, affording **17** (48 mg, 98%) as a colorless oil. IR (neat) 2950, 2833, 1705, 1589, 1497, 1463, 1282, 1223 cm^{-1}; ^1H NMR (270 MHz) δ 0.93 (3H, s, 1-CH_3), 1.15 (3H, s, 4a-CH_3),

1.20 (3H, d, J=6.9 Hz, 2-CH_3), 1.22–2.10 (10H, m, 2,3,4,7,8,8a-H), 2.17–2.35 (1H, m, 6H), 2.28 (1H, d, J=13.9 Hz, ArC*H*H), 2.50–2.63 (1H, m, 6H), 3.03 (1H, d, J=13.9 Hz, Ar-CH*H*), 3.74 (3H, s, O–CH_3), 3.75 (3H, s, O-CH_3), 6.67 (1H, dd, J=3.0, 8.9 Hz, 4′-H), 6.75 (1H, d, J=8.9 Hz, 3′-H), 6.85 (1H, d, J=3.0 Hz, 6′-H); MS m/z 344 (M^+); High resolution MS calcd for $C_{22}H_{32}O_3$ (M^+) 344.2349, found 344.2341.

***trans*-1α-[(2,5-Dimethoxyphenyl)methyl]-decahydro-1β,2α,4aβ-trimethyl-5-methylenenaphthalene (25).** To a suspension of Zn (125 mg, 1.98 mmol) in 2 ml of THF were added 45 ml (0.6 mmol) of CH_2Br_2, 0.48 ml (0.48 mml) of $TiCl_4$ as a 1.0 M solution in CH_2Cl_2, and a solution of **17** (15 mg, 44 mmol) in 1.5 ml of THF at rt. This reaction mixture was stirred for 1 h at rt, diluted by the addition of ether (20 ml), and poured through a glass-wool plug into a separatory funnel containing 10 ml of ether and 10 ml of 1N aqueous HCl solution. The aqueous phase was extracted with two additional 10 ml portions of ether. The combined extract was washed with 20 ml of saturated aqueous NaCl solution, dried and concentrated. The residue was purified by chromatography on 1 g of silica gel by using 1:25 AcOEt–hexane as eluent, affording **25** (11.5 mg, 76%) as a white solid. Mp 32–34°C; IR (neat) 2941, 2831, 1498, 1463, 1381, 1282, 1225 cm^{-1}; ^1H NMR (270 MHz) δ 0.86 (3H, s, 1-CH_3), 1.12 (3H, s, 4a-CH_3), 1.15 (3H, d, J=6.9 Hz, 2-CH_3), 1.22–1.98 (10H, m, 2,3,4,7,8,8a-H), 2.13–2.40 (2H, m, 6-H), 2.22 (1H, d, J=13.9 Hz, ArC*H*H), 3.03 (1H, d, J=13.9 Hz, ArCH*H*), 3.74 (3H, s, O-CH_3), 3.75 (3H, s, O-CH_3), 4.49 (1H, br.s, 5 =C*H*H), 4.54 (1H, br.s, 5 =CH*H*), 6.68 (1H, dd, J=3.0, 8.9 Hz, 4′-H), 6.75 (1H, d, J=8.9 Hz, 3′-H), 6.88 (1H, d, J=3.0 Hz, 6′-H); MS m/z 342 (M^+); High resolution MS calcd for $C_{23}H_{34}O_2$ (M^+) 342.2557, found 342.2564.

***trans*-1α-[(2,5-Dihydroxyphenyl)methyl]-decahydro-1β,2α,4aβ-trimethyl-5-methylenenaphthalene (26).** To a solution of **25** (42 mg, 0.12 mmol) in 12 ml of CH_3CN was added, dropwise, a solution of CAN (134 mg, 0.246 mmol) in 6 ml of H_2O over 1 h. This solution was stirred for 1 day at rt, diluted with 10 ml of H_2O, and extracted with 30 ml of ether. The extract was washed with 30 ml of saturated aqueous NaCl solution, dried and concentrated to give a crude product.

To a solution of the crude quinone in 3 ml of THF was added a solution of $Na_2S_2O_4$ (200 mg) in 1 ml of H_2O. The solution was stirred for 10 min at rt, diluted with 5 ml of H_2O, and extracted with 10 ml of AcOEt. The extract was washed with 30 ml of saturated aqueous NaCl solution, dried and concentrated. The residue was purified by chromatography on 5 g of silica gel by using 1:5 AcOEt–hexane as eluent, affording **26** (11 mg, 28%) as a yellow oil. IR (neat) 3475, 2931, 1635, 1504, 1452, 1381, 1194 cm^{-1}; ^1H NMR (270 MHz) δ 0.92 (3H, s, 1-CH_3), 1.13 (3H, s, 4a-CH_3), 1.16 (3H, d, J=6.9 Hz, 2-CH_3), 1.19–2.04 (10H, m, 2,3,4,7,8,8a-H), 2.09–2.40 (2H, m, 6-H), 2.23 (1H, d, J=13.9 Hz, ArC*H*H), 2.91 (1H, d, J=13.9 Hz, ArCH*H*), 4.34 (1H, br.s, OH), 4.39 (1H, br.s, OH), 4.50 (1H, br.s, 5 =C*H*H), 4.55 (1H, br.s, 5 =CH*H*), 6.54 (1H, dd, J=3.0, 8.9 Hz, 4′-H), 6.62 (1H, d, J=8.9 Hz, 3′-H), 6.78 (1H, d, J=3.0 Hz, 6′-H); MS m/z 314 (M^+); High resolution MS calcd for $C_{21}H_{30}O_2$ (M^+) 314.2244, found 314.2245.

***trans*-1α-[(2,5-bis(Sodiumoxysulfonyloxy)phenyl]methyl-decahydro-1β,2α,4aβ-trimethyl-5-methylenenaphthalene (3).** To a solution of SO_3·pyridine (26 mg, 64 mmol) in 1 ml of pyridine was added a solution of **26** (10 mg, 32 mmol) in 3 ml of pyridine. The solution was stirred for 4 h at 80°C under Ar gas, cooled to rt, and 2 ml of H_2O and 200 mg of Na_2CO_3 were added. The reaction mixture was stirred for 30 min at 60°C and concentrated. The residue was purified by chromatography on 1 g of silica gel by using 2:1 chloroform–methanol as eluent, affording **3** (10 mg, 61%) as white solid. Mp>240°C; IR (neat) 3471, 2931, 1564, 1485, 1380, 1257, 1232 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) d 0.89 (3H, s, 1-CH_3), 1.14 (3H, s, 4a-CH_3), 1.17 (3H, d, J=6.9 Hz, 2-CH_3), 1.20–2.04 (10H, m, 2,3,4,7,8,8a-H), 2.07–2.15 (1H, m, 6-H), 2.30–2.40 (1H, m, 6-H), 2.33 (1H, d, J=14.0 Hz, ArC*H*H), 4.46 (1H, br.s, 5 =C*H*H), 4.52 (1H, br.s, 5 =CH*H*), 7.08 (1H, dd, J=3.0, 8.9 Hz, 4′-H), 7.34 (1H, d, J=3.0 Hz, 6′-H), 7.38 (1H, d, J=8.9 Hz, 3′-H); ^{13}C NMR (125 MHz, CD_3OD) d 16.8 (2-CH_3), 20.8 (1-CH_3), 22.5 (4a-CH_3), 23.1 (8), 26.6 (7), 30.0 (3), 31.2 (4), 34.1 (6), 36.5 (Ar-CH_2), 37.0 (2), 42.1 (1), 42.1 (4a), 49.6 (8a), 102.4 (5 =CH_2), 120.3 (4′), 123.1 (3′), 124.6 (6′), 135.3 (1′), 150.1 (5′), 150.2 (2′), 161.5 (5); FABMS m/z 541 $(M+Na)^+$; High resolution FABMS calcd for $C_{21}H_{28}O_8S_2Na_3$ $(M+Na)^+$ 541.0955, found 541.0959.

Optical resolution of ketone 6 by addition of sulfoxyimine

To a solution of (*S*)-(+)-*N*,*S*-dimethyl-*S*-phenylsulfoxyimine (71 mg, 0.4 mmol) in 4 ml of dry THF was added 0.4 ml (0.4 mmol) of *n*-BuLi as a 1.0 M solution in *n*-hexane at 0°C. The solution was stirred for 30 min at 0°C under Ar gas, and then ketone **6** (65 mg, 0.2 mmol) was added as a solution of THF at −78°C. After being stirred for 1 h at −78°C under Ar, the reaction mixture was quenched by the addition of sat NH_4Cl aq. The aqueous phase was extracted with two additional 10 ml portions of ether. The combined extract was washed with 20 ml of saturated aqueous NaCl solution, dried and concentrated. The residue was purified by chromatography on 10 g of silica gel by using 1:25 AcOEt–hexane as eluent, affording **28** (42 mg, 43%) as a white solid, **29** (3 mg, 3%) as a white solid, **30** (25 mg, 27%) as a white solid, **31** (14 mg, 15%) as a white solid.

28. Mp 163°C; $[\alpha]_D^{23}$=+57° (c 0.18, $CHCl_3$); IR (neat) 3418, 2956, 1654, 1496, 1222, 1138 cm^{-1}; ^1H NMR (270 MHz) δ 0.73 (3H, s, 1-CH_3), 1.16 (3H, d, J=6.9 Hz, 2-CH_3), 1.58–2.09 (8H, m, 2,6,7,8,8a-H), 2.41 (1H, d, J=13.8 Hz, ArC*H*H), 2.60 (3H, s, N-CH_3), 2.70–2.81 (1H, m, 4a-H), 2.90 (1H, d, J=13.5 Hz, C*H*HS), 3.03 (1H, d, J=13.8 Hz, ArCH*H*), 3.73 (1H, d, J=13.5 Hz, CH*H*S), 3.75 (6H, s, OCH×32), 5.34–5.38 (1H, m, 4-H), 5.70–5.81 (1H, m, 3-H), 6.68 (1H, dd, J=3.0, 8.9 Hz, 4′-H), 6.76 (1H, d, J=8.9 Hz, 3′-H), 6.90 (1H, d, J=3.0 Hz, 6′-H), 7.57–7.63 (3H, m, S-*Ar*), 7.86–7.90 (2H, m, S-*Ar*); MS m/z 497 (M^+).

29. Mp 110–114°C; $[\alpha]_D^{23}$=+27° (c 0.08, $CHCl_3$); IR (neat) 3421, 2931, 1654, 1496, 1222, 1138 cm^{-1}; ^1H NMR

(270 MHz) δ 0.76 (3H, s, 1-CH_3), 1.04 (3H, d, J=6.9 Hz, 2-CH_3), 1.20–2.08 (8H, m, 2,6,7,8,8α-H), 2.31 (1H, d, J=13.8 Hz, ArC*H*H), 2.77 (3H, s, N-CH_3), 2.92 (1H, d, J=13.8 Hz, ArCH*H*), 3.32 (1H, d, J=13.5 Hz, C*H*HS), 3.56 (1H, d, J=13.5 Hz, CH*H*S), 3.70 (6H, s, OCH×32), 5.68–5.81 (2H, m, 3,4-H), 6.68 (1H, dd, J=3.0, 8.9 Hz, 4′-H), 6.74 (1H, d, J=8.9 Hz, 3′-H), 6.85 (1H, d, J=3.0 Hz, 6′-H), 7.57–7.63 (3H, m, S-*Ar*), 7.86–7.90 (2H, m, S-*Ar*); MS *m*/*z* 497 (M^+).

30. Mp 167°C; $[\alpha]_D^{23}=-45°$ (*c* 0.21, $CHCl_3$); IR (neat) 3423, 2932, 1654, 1496, 1222, 1138 cm^{-1}; ^1H NMR (270 MHz), δ 0.78 (3H, s, 1-CH_3), 0.93 (3H, d, J=6.9 Hz, 2-CH_3), 1.20–2.08 (8H, m, 2,6,7,8,8a-H), 2.31 (1H, d, J=13.8 Hz, ArC*H*H), 2.60 (3H, s, N-CH_3), 2.98 (1H, d, J=13.8 Hz, ArCH*H*), 3.23–3.25 (2H, m, CH_2S), 3.73 (6H, s, OCH_3×2), 5.60–5.70 (1H, m, 3-H), 5.75–5.81 (1H, m, 4-H), 6.67 (1H, dd, J=3.0, 8.9 Hz, 4′-H), 6.75 (1H, d, J=8.9 Hz, 3′-H), 6.86 (1H, d, J=3.0 Hz, 6′-H), 7.56–7.67 (3H, m, S-*Ph*), 7.87–7.92 (2H, m, S-*Ph*); MS *m*/*z* 497 (M^+).

31. Mp 122–124°C; $[\alpha]_D^{23}=-40°$ (*c* 2.16, $CHCl_3$); IR (neat) 3401, 3019, 1497, 1215, 1136 cm^{-1}; ^1H NMR (270 MHz), δ 0.74 (3H, s, 1-CH_3), 1.13 (3H, d, J=6.9 Hz, 2-CH_3), 1.61–2.07 (8H, m, 2,6,7,8,8α-H), 2.30–2.36 (1H, m, 4a-H), 2.39 (1H, d, J=13.8 Hz, ArC*H*H), 2.72 (3H, s, N-CH_3), 2.99 (1H, d, J=13.8 Hz, ArCH*H*), 3.31 (1H, d, J=14.2 Hz, C*H*HS), 3.73 (6H, s, OCH×32), 3.72 (1H, d, J=14.2 Hz, C*H*HS), 5.47–5.51 (1H, m, 4-H), 5.74–5.81 (1H, m, 3-H), 6.68 (1H, dd, J=3.0, 8.9 Hz, 4′-H), 6.76 (1H, d, J=8.9 Hz, 3′-H), 6.90 (1H, d, J=3.0 Hz, 6′-H), 7.52–7.61 (3H, m, S-*Ar*), 7.84–7.88 (2H, m, S-*Ar*); MS *m*/*z* 497 (M^+).

X-Ray diffraction study

28. $C_{29}H_{39}O_4SN$: colorless crystal (0.30×0.35×0.20 mm, grown from dichloromethane), $C_{29}H_{39}O_4SN$, M 497.70, orthorhombic, space group $P2_12_12_1$, a=18.236(4) Å, b=18.277(4) Å, c=8.087(2) Å, V=2696(1) Å, Z=4, D=1.23 g/cm^3, F(000)=1071, T=293 K. A Mac Science MXC18 diffractometer and graphite monochromated CuKα radiation, l=1.54178 Å, was used for all measurements. Cell constants and an orientation matrix for data collection were obtained from a least-squares refinement using the setting angles of 20 carefully centered reflections.

30. $C_{29}H_{39}O_4SN$: colorless crystal (0.40×0.30×0.44 mm, grown from dichloromethane), $C_{29}H_{39}O_4SN$, M 497.70, orthorhombic, space group $P2_12_12_1$, a=14.412(4) Å, b=21.788(5) Å, c=8.619(3) Å, V=2706(1) Å, Z=4, D=1.22 g/cm^3, F(000)=1071, T=293 K. A Mac Science MXC18 diffractometer and graphite monochromated CuKα radiation, l=1.54178 Å, was used for all measurements. Cell constants and an orientation matrix for data collection were obtained from a least-squares refinement using the setting angles of 20 carefully centered reflections.

(−)-(1*S*,2*R*,4a*R*,5*S*,8a*R*)-*trans*-1α-[(2,5-Dimethoxyphenyl)-methyl]-1,2,4a,7,8,8a-hexahydro-1β,2α-dimethyl-5(6*H*)-naphthalenone ((−)-6). A solution of **28** (210 mg, 0.43 mmol) in deoxygenated toluene (15 ml) was heated 120°C in a sealed tube for 3 h, cooled, and concentrated. The residue was purified by chromatography on 1 g of silica gel by using 1:15 AcOEt–hexane as eluent, affording **6** (135 mg, 97%) as a white solid.

A solution of **29** (14 mg, 29 mmol) in deoxygenated toluene (3 ml) was heated 120°C in a sealed tube for 20 h, cooled, and concentrated. The residue was purified by chromatography on 1 g of silica gel by using 1:15 AcOEt–hexane as eluent, affording **6** (9.2 mg, 97%) as a white solid. Mp 119–121°C; $[\alpha]_D=-3.4°$ (*c* 1.02, $CHCl_3$).

(+)-(1*R*,2*S*,4a*S*,5*R*,8a*S*)-*trans*-1b-[(2,5-Dimethoxyphenyl)-methyl]-1,2,4a,7,8,8a-hexahydro-1α,2β-dimethyl-5(6*H*)-naphthalenone ((+)-6). A solution of **30** (125 mg, 0.26 mmol) in deoxygenated toluene (15 ml) was heated 120°C in a sealed tube for 10 h, cooled, and concentrated. The residue was purified by chromatography on 10 g of silica gel by using 1:15 AcOEt–hexane as eluent, affording **6** (82 mg, 96%) as a white solid.

A solution of **31** (70 mg, 0.15 mmol) in deoxygenated toluene (10 ml) was heated 120°C in a sealed tube for 12 hrs, cooled, and concentrated. The residue was purified by chromatography on 10 g of silica gel by using 1:15 AcOEt–hexane as eluent, affording **6** (47 mg, 96%) as a white solid. Mp 118–120°C, $[\alpha]_D=+3.3°$ (*c* 0.57, $CHCl_3$).

***cis*-1α-[(2,5-Dimethoxyphenyl)methyl]-1,2,4a,7,8,8a-hexahydro-1β,2α-dimethyl-4aα-(ethylcarboxylate)-methyl-5(6*H*)-naphthalenone (35).** To a solution of **6** (164 mg, 0.5 mmol) in 8 ml of dry THF was added 0.5 ml (0.5 mmol) of $NaN\{Si(CH_3)_3\}_2$ as a 1.0 M solution in THF at rt. The solution was stirred for 20 min at rt under Ar gas and then 0.165 ml (1.4 mmol) of ICH_2CO_2Et was added at −78°C. After being stirred for 1 h at −78°C under Ar, the reaction mixture was diluted by the addition of H_2O (4 ml). The aqueous phase was extracted with two 10 ml portions of AcOEt. The combined extract was washed with 10 ml of saturated aqueous NaCl solution, dried and concentrated. The residue was purified by chromatography on 10 g of silica gel by using 1:15 AcOEt–hexane as eluent, affording **35** (188 mg, 90%) as a white solid. Mp 30–34°C; IR (neat) 2956, 2881, 2832, 1731, 1702, 1589, 1496, 1454, 1369, 1336, 1218, 1051 cm^{-1}; ^1H NMR (270 MHz) δ 1.01 (3H, s, 1-CH_3), 1.09 (3H, d, J=6.9 Hz, 2-CH_3), 1.16 (3H, t, J=6.8 Hz, OCH_2CH_3),1.79–2.16 (5H, m, 2,7,8,8a-H), 2.27–2.34 (1H, m, 8a-H), 2.49–2.64 (2H, m, 6-H), 2.53 (1H, d, J=15.1 Hz, ArC*H*H), 2.73 (1H, d, J=15.6 Hz, 4a-C*H*H), 2.92 (1H, d, J=15.1 Hz, ArCH*H*), 3.74 (3H, s, O–CH_3), 3.76 (3H, s, O–CH_3), 3.88–4.05 (2H, m, OCH_2CH_3), 5.47–5.51 (1H, m, 4-H), 5.69–5.72 (1H, m, 3-H), 6.67 (1H, dd, J=3.0, 8.9 Hz, 4′-H), 6.76 (1H, d, J=3.0 Hz, 6′-H), 6.86 (1H, d, J=8.9 Hz, 3′-H); MS *m*/*z* 414 (M^+); High resolution MS calcd for $C_{25}H_{34}O_5$ (M^+) 414.2406, found 414.2402.

***cis*-1α-[(2,5-Dimethoxyphenyl)methyl]-decahydro-1β,2α-dimethyl-4aα-(ethylcarboxylate)methyl-5(6*H*)-naphthalenone (37).** To a solution of **35** (80 mg, 0.19 mmol) in 3 ml of ethanol was added ca. 90 mg of Raney-Ni (W-4). This reaction mixture was stirred for 3days at rt under H_2 gas, filtered through a celite-pad, and then was concentrated and purified by chromatography on 10 g of silica gel by using 1:10 AcOEt–hexane as eluent,

affording **37** (79 mg, 98%) as a white solid. Mp 42–45°C; IR (neat) 2929, 1726, 1461, 1272, 1122 cm^{-1}; ^1H NMR (270 MHz) δ 0.86 (3H, s, 1-CH_3), 1.00 (3H, d, J=6.9 Hz, 2-CH_3), 1.18 (3H, t, J=6.8 Hz, OCH_2CH_3), 1.34–2.06 (10H, m, 2,3,4,7,8,8a-H), 2.54–2.58 (2H, m, 6-H), 2.59 (1H, d, J=13.9 Hz, ArC*H*H), 2.90 (1H, d, J=13.9 Hz, ArCH*H*), 3.07 (1H, d, J=16.3 Hz, 4a-C*H*H), 3.75 (6H, s, O–CH×32), 3.97–4.05 (2H, m, OCH_2CH_3), 6.67 (1H, dd, J=3.0, 8.9 Hz, 4′-H), 6.73 (1H, d, J=3.0 Hz, 6′-H), 6.75 (1H, d, J=8.9 Hz, 3′-H); MS m/z 416 (M^+); High resolution MS calcd for $C_{25}H_{36}O_5$ (M^+) 416.2563, found 416.2567.

***cis*-1α-[(2,5-Dimethoxyphenyl)methyl]-decahydro-1β, 2α-dimethyl-4aα-(ethylcarboxylate)methyl-5-methyl-enenaphthalene (32).** To a suspension of Zn (183 mg, 2.8 mmol) in 5 ml of THF were added 66 ml (0.94 mmol) of CH_2Br_2, 0.7 ml (0.7 mml) of $TiCl_4$ as a 1.0 M solution in CH_2Cl_2 and a solution of **37** (23 mg, 55 mmol) in 3 ml of THF at rt. This reaction mixture was stirred for 1 h at rt, diluted by the addition of ether (10 ml), and poured through a glass-wool plug into a separatory funnel containing 5 ml of ether and 10 ml of 1N aqueous HCl solution. The aqueous phase was extracted with two additional 10 ml portions of ether. The combined extract was washed with 20 ml of saturated aqueous NaCl solution, dried and concentrated. The residue was purified by chromatography on 10 g of silica gel by using 1:25 AcOEt–hexane as eluent, affording **32** (19 mg, 83%) as a white solid. Mp 55–57°C; IR (neat) 2958, 2854, 1720, 1641, 1498, 1222 cm^{-1}; ^1H NMR (270 MHz) δ 0.83 (3H, s, 1-CH_3), 1.12 (3H, d, J= 6.9 Hz, 2-CH_3), 1.20 (3H, t, J=6.8 Hz, OCH_2CH_3), 1.34–2.06 (12H, m, 2,3,4,6,7,8,8a-H), 2.32 (1H, d, J=13.9 Hz, ArC*H*H), 2.37 (1H, d, J=16.3 Hz, 4a-C*H*H), 2.88 (1H, d, J=13.9 Hz, ArCH*H*), 3.07 (1H, d, J=16.3 Hz, 4a-C*H*H), 3.75 (6H, s, O-CH×32), 4.07 (2H, q, J=6.9 Hz, OCH_2CH_3), 4.80 (2H, s, C=CH_2), 6.68 (1H, dd, J=3.0, 8.9 Hz, 4′-H), 6.75 (1H, d, J=3.0 Hz, 6′-H), 6.83 (1H, d, J=8.9 Hz, 3′-H); MS m/z 414 (M^+); High resolution MS calcd for $C_{26}H_{38}O_4$ (M^+) 414.2416, found 414.2412.

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