Extracyclic Stereocontrolled Alkylation of (1*R*,5*S*)-4-Ethyl-6,6-dimethyl-3-(phenylsulfonyl)bicyclo[3.1.1]hept-3-en-2-one. A Highly Stereocontrolled Synthesis of (−)-Kanshone A

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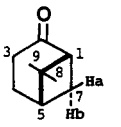
(1*R*,5*S*)-4-Ethyl-6,6-dimethyl-3-(phenylsulfonyl)bicyclo[3.1.1]hept-3-en-2-one (**7**) was prepared from (+)-nopinone (**1**) in six steps and 70% overall yield via (1*R*,5*R*)-6,6-dimethyl-3-(phenylthio)bicyclo-[3.1.1]hept-3-en-2-one (**2**). Alkylation reactions of **7** with alkyl bromides **16** (**a**, allyl; **b**, 3-methyl-2-butenyl; **c**, propargyl; **d**, benzyl bromide) in the presence of K_2CO_3 in MeCN proceeded in regio- and extracyclic stereocontrolled fashion to give, as the major product, mixtures of γ-alkylated products **17a–d** possessing a new chiral center of *R* configuration adjacent to a ring and **18a–d** possessing that of *S* configuration, whose ratios are **17a–18a**, 10:1, **17b–18b**, 7:1; **17c-18c**, 13:1; and **17d-18d**, 18:1, along with α-alkylated products **19a–d** and O-alkylated products **20a,b** on reactions with **16a,b**. In addition, reaction of **7** with methyl bromoacetate (**16e**) provided **17e** as the sole product. In the presence of a combined reagent, K_2CO_3–Cs_2CO_3 (9:1), in MeCN, considerably high diastereoselection was detected, i.e., reactions of **7** with **16a,b** produced mixtures of **17a** and **18a**, and **17b** and **18b**, in 20:1 and 12:1 ratios, respectively. Reaction products were separated by chromatography on silica gel, while the major diastereomers **17a,c–e**, highly crystalline themselves, were readily obtained as pure crystals by recrystallization. Mechanism of diastereoselection and the scope and limitations of the extracyclic stereocontrolled alkylation are briefly discussed. In the application of **17** as the synthetic intermediate for the asymmetric synthesis, starting with (1*R*,5*S*)-6,6-dimethyl-4-[(1*R*)-1-methyl-3-butenyl]-3-(phenylsulfonyl)bicyclo[3.1.1]hept-3-en-2-one (**17a**), (−)-kanshone A (**8**), a nardosinane sesquiterpene, was synthesized in a highly stereoselective fashion in 12 steps via (1*R*,4*R*,5*R*)-4,6,6-trimethyl-4-[(1*R*)-1-methyl-3-butenyl]bicyclo[3.1.1]heptan-2-one (**30**) and its cyclobutane-ring opening product, (4*S*,4a*R*,5*R*)-1-acetoxy-4-isopropenyl-4a,5-dimethyl-3,4,4a,5,6,7-hexahydronaphthalene (**34**).

Introduction

(+)-Nopinone (**1**) is readily accessible in large quantities by ozonolysis of (−)-β-pinene.[1,2] Recently, we have reported that conjugated enones **2** and **3**, obtainable from **1** in a few steps and high overall yields, are useful for the preparation of 4-alkyl- and 4,4-dialkylnopinones, **4** and **5**, respectively, and that enol acetates **6** derived from **5** by desulfonylation followed by boron trifluoride etherate (BF_3·OEt_2)-catalyzed cyclobutane opening with little loss of optical integrity[3] serve as the versatile intermediates for the preparation of optically active carbocycles.[2] These facts indicate that nopinone (**1**) plays an important part in the naturally occurring chiral sources utilizable for asymmetric synthesis. In connection with our program dealing with a search for reactive nopinone derivatives useful as the chiral building blocks,[2,4] we wish to describe that alkylation of enone **7**, readily accessible from **2**, with the representative alkyl halides proceeded in an extracyclic stereocontrolled fashion[5] to give good to high yields of γ-alkylated products **17** possessing a chiral center of *R* configuration adjacent to a ring, and that the product **17a** was utilized as a key intermediate for the highly stereocontrolled synthesis of (−)-kanshone A (**8**).[6]



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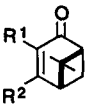
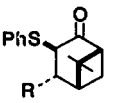


2 R^1=SPh, R^2=H

3 R^1=SO_2Ph, R^2=Me

7 R^1=SO_2Ph, R^2=Et

9 R^1=SO_2Ph, R^2=$CHMe_2$



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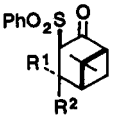

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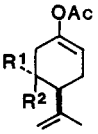

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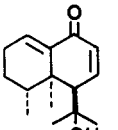

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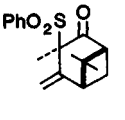

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Our study was founded on the observation made earlier that methylation of the enone **3** with methyl iodide (MeI) in the presence of K_2CO_3 gave 4-isopropyl enone **9** as the major product (70% yield), together with deconjugated ketone **10** (27% yield). This finding is of interest from the features that (1) alkylation of **3** affords a γ-alkylated

(1) Van Der Gen, A.; Van Der Linde, L. M.; Witteveen, J. G.; Boelens, H. *Recl. Trav. Chim. Pay-Bas.* **1971**, *90*, 1031. Banthorpe, D. V.; Wittaker, D. *Chem. Rev.* **1966**, *66*, 647.

(2) Kato, M.; Watanabe, M.; Vogler, B.; Awen, B. Z.; Masuda, Y.; Tooyama, Y.; Yoshikoshi, A. *J. Org. Chem.* **1991**, *56*, 7071.

(3) Kato, M.; Kamat, V. P.; Tooyama, Y.; Yoshikoshi, A. *J. Org. Chem.* **1989**, *54*, 1536. Kato, M.; Watanabe, M.; Vogler, B.; Tooyama, Y.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1990**, 1706. *Idem. Synthesis* **1992**, 1055.

(4) For use of methyl apoverbenone-3-carboxylate, see Liu, H-J.; Chew, S. Y.; Browne, E. N. C. *Tetrahedron Lett.* **1991**, 2005, and refs cited therein.

(5) Bartlett, P. *Tetrahedron* **1980**, *36*, 1.

(6) Reported in part in the preliminary communications: Kato, M.; Watanabe, M.; Awen, B. Z.; Vogler, B. *Tetrahedron Lett.* **1991**, *32*, 7439. Kato, M.; Watanabe, M.; Awen, B. Z. *ibid.* **1991**, *32*, 7443.

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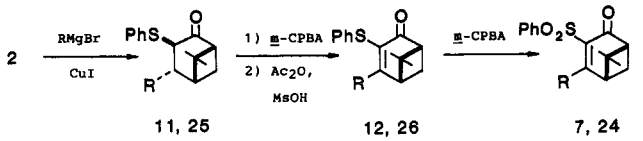
Scheme I



R = Et for 11, 12, and 7

R = $CH_2CH_2CH{=}CH_2$ for 25, 26, and 24

product predominantly rather than an α-alkylated one;[7] (2) 4-ethyl enone **7**, the first product in the above methylation, is reactive to undergo readily the second methylation, giving 4-isopropyl enone **9**, and formation of the latter forces the reaction to completion; and (3) therefore, on alkylation starting with **7** in place of **3**, reactions with alkyl halides other than MeI are expected to occur at the γ-position in a stereoselective fashion based on the well-known reactivity common to the pinane-type compounds; i.e., electrophiles approach the reaction site from the less-hindered side, opposite the *gem*-dimethyl bridge, yielding γ-alkylated products possessing a new chiral center at the α-position of the side chain adjacent to a ring.

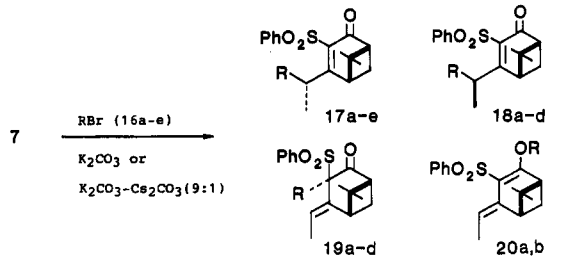
Although one can find in nature a variety of compounds possessing an extracyclic chiral center, one component of which is in general a methyl group as seen, for example, in the steroid side chains, few methods exist for producing this chiral center effectively in one step.[5]

Extracyclic Stereocontrolled Alkylation

Thus, our study began with preparation of **7** from **2**, obtainable from (+)-nopinone (**1**) in three steps and 94% overall yield, according to our synthetic methodology established earlier.[2] Conjugate addition of **2** with ethylmagnesium bromide in the presence of copper(I) iodide (CuI) in THF proceeded in a stereoselective fashion[2] to give (3*R*,4*S*)-4-ethylnopinone **11** as the sole product (Scheme I). The compound **11** was oxidized with *m*-CPBA (1 equiv), and the resulting sulfoxide was subjected to the Pummerer rearrangement with acetic anhydride containing methanesulfonic acid (MsOH), providing enone **12**, which was then oxidized with *m*-CPBA (2 equiv) to give **7** in 74% overall yield from **2**.

With the requisite enone **7** in hand, its alkylation with some representative alkyl halides was carried out next. To establish the optimum reaction conditions, allylation of **7** with allyl bromide (**16a**) was examined in some detail. No reaction occurred upon generation of the enolate anion of **7** with LDA (THF, −78 °C–rt), whereas upon treatment with NaH in refluxing THF there was detected an unstable deconjugated enone **13**[8,9] which regenerated the original enone **7** upon chromatographic purification on silica gel. The compound **13** was obtained in 74% yield upon treatment of **7** with NaH in THF at room temperature. Parallel to these reactions, we prepared enol acetate **14**[9] and enol silyl ether **15**[9] possessing a transoid ethylidene group by treatment of the sodium enolate of **7** with acetyl chloride and *tert*-butyldimethylsilyl chloride (TBDMSCl), respectively. However, attempted allylation of **14** [MeLi (2 equiv)/THF/−40 °C–rt] and **15** ($ZnBr_2$ or $TiCl_4/CH_2Cl_2$/rt)[10] with allyl bromide, respectively, were unsuccessful, resulting in recovery of the original **7**.

Scheme II

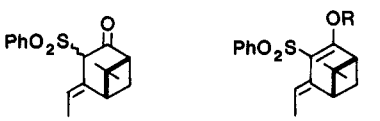


a, R = $CH_2CH{=}CH_2$; b, R = $CH_2CH{=}CMe_2$; c, R = $CH_2C{\equiv}CH$; d, R = CH_2Ph; e, R = CH_2CO_2Me

Table I. Alkylation of 7 with Alkyl Bromides under the K_2CO_3/MeCN Conditions

		product and yield, %			
		17 and 18			
run	alkyl bromide (RBr) 16: R	combined yield of 17 and 18	ratio of 17 and 18[a]	19	20
1	a, $CH_2CH{=}CH_2$	a, 68 (60)[b]	10:1 (20:1)[c]	a, 20	a, 5
2	b, $CH_2CH{=}CMe_2$	b, 62 (50)[b]	7:1 (12:1)[c]	b, 16	b, 5
3	c, $CH_2C{\equiv}CH$	c, 60 (50)[b]	13:1	c, 20	–
4	d, CH_2Ph	d, 87 (80)[b]	18:1	d, 3	–
5	e, CH_2CO_2Me	e, – (65)[b]	–	–	–

[a] The ratio obtained by the ^1H NMR (600 MHz) analysis. [b] Isolated yield of 17. [c] The ratio obtained by alkylation under the K_2CO_3/Cs_2CO_3 (9:1)/MeCN conditions.



Thereafter, potassium bases were shown to be effective for allylations of this type. Although the use of KH or *tert*-BuOK (THF–HMPA) resulted in formation of a mixture of γ- and α-allylated products,[7] formation of intractable byproduct was always a problem. After optimization, it was found that the reaction conditions using K_2CO_3 (10 equiv) in MeCN at 50 °C resulted in allylation smoothly and cleanly to afford an acceptable combined yield (68%) of a diastereomeric mixture of γ-allylated products, **17a** and **18a**, in which the former predominated, along with the α-allylated one **19a** (20%) and a small amount of the unstable O-allylated one **20a** (Scheme II and Table I, run 1). Interestingly, the use of Na_2CO_3 or Li_2CO_3 in place of K_2CO_3 was fruitless, resulting in recovery of **7**.

The γ- and α-allylated products were readily separated by column chromatography on silica gel. However, the two diastereomers **17a** and **18a** proved to be quite difficult to separate, so that the correct product ratio was determined by the ^1H NMR (600 MHz) spectrum analysis of the mixture of the two isomers (*vide infra*). Fortunately, the sulfone **17a** is highly crystalline, and thus a simple

(7) Positioning α and γ are given with respect to the conjugated enone system in **3** and **7**.

(8) For analogous deconjugation, see Ohloff, G.; Giersch, W. *Helv. Chim. Acta* **1977**, *60*, 1496.

(9) Geometry of the ethylidene group was assigned transoid as depicted, judging from less allylic 1,3-strain as well as the chemical shift (ca. δ 6.4) of the olefinic proton with a deshielding due to the proximity of the phenylsulfonyl group (see Experimental Section).

(10) Paterson, I.; Fleming, I. *Tetrahedron Lett.* **1979**, *11*, 993.

Table II. ^{1}H NMR (600 MHz) Data (δ, J in Hz) of 17a–e and 18a–d. An Apoverbenone Moiety and a Phenylsulfonyl Group

	17a	18a	17b	18b	17c	18c	17d	18d	17e	multiplicity[c]
1-H[a] (1H)	2.93	2.98	2.92	2.98	2.96	3.04	3.04	3.08	2.89	t
5-H[a] (1H)	2.65	2.69	2.63	2.67	2.67	2.68	2.57	2.65	2.65	dd
7a-H[a] (1H)	2.72	2.79	2.70	2.79	2.77	2.82	2.66	2.81	2.77	ddd
7b-H[a] (1H)	2.00	2.00	1.87	2.00	2.11	2.01	1.61	2.02	2.06	d
8-H[a] (3H)	0.84	0.85	0.85	0.76	0.90	0.93	0.88	0.85	0.90	s
9-H[a] (3H)	1.43	1.49	1.45	1.45	1.47	1.43	1.47	1.45	1.47	s
ortho-H[b] (2H)	8.05	8.06	8.01	8.06	8.08	8.12	7.74	8.01	8.09	d[d]
meta-H[b] (2H)	7.51	7.51	7.49	7.51	7.51	7.50	7.41	7.50	7.51	dd
para-H[b] (1H)	7.57	7.60	7.55	7.58	7.59	7.57	7.51	7.57	7.57	tt

Side Chain Part[e,f]

	17a	18a	17b	18b	17c	18c	17d	18d	17e
C*H*Me (1H)	4.83 (ddq, 11.0, 7.0, 6.5)	4.71 (ddq, 10.0, 7.0, 6.5)	4.76 (tq, 7.5, 6.5)	4.64 (tq, 7.5, 6.5)	4.98 (ddq, 9.5, 6.0, 7.0)	4.92 (ddq, 9.5, 6.5, 7.0)	5.16 (ddq, 8.5, 7.5, 6.5)	5.05 (ddq, 9.5, 8.2, 6.5)	5.11 (ddq, 10.0, 5.8, 6.5)
CH*Me* (3H)	1.06 (d, 6.5)	1.19 (d, 6.5)	1.05 (d, 6.5)	1.18 (d, 6.5)	1.15 (d, 7.0)	1.30 (d, 7.0)	1.12 (d, 6.5)	1.16 (d, 6.5)	1.15 (d, 6.5)
C*Ha*Hb (1H)	2.25 (dddt 11.0, 10.4, 7.8, 1.5)	2.07 (dddt, 10.4, 10.0, 7.5, 1.5)	2.20[g] (br t, 2 H, 7.5)	2.07[g] (br t, 2 H, 7.5)	2.32 (ddd, 17.0, 9.5, 2.6)	2.32[g] (m, 2H)	2.81 (dd, 13.5, 8.5)	2.59 (dd, 13.5, 9.5)	2.51 (dd, 15.0, 10.0)
CHa*Hb* (1H)	2.32 (dddt, 10.4, 7.0, 6.5, 1.5)	2.19 (dddt, 10.4, 7.0, 6.5, 1.5)			2.50 (ddd, 17.0, 6.0, 2.6)		2.86 (dd, 13.5, 7.0)	2.78 (dd, 13.5, 8.2)	2.57 (dd, 15.0, 5.8)

[a] Protons in the apoverbenone part. [b] Protons in the phenyl part. [c] Coupling constant (J): 1,7b = 5,7b = 0; 1,5 = 1,7a = 6.0; 5,7a = 5.5; 7a,7b = 9.5; o,m = 7.0–7.8; m,p = 7.5; o,p = 1.0–1.5. [d] With fine splittings. [e] Multiplicity and coupling constants are shown in parentheses. [f] Others: **17a**: 5.06 (dq, 1H, 17.1, 1.5), 5.08 (dq, 1H, 10.0, 1.5), 5.88 (dddd, 1H, 17.1, 10.0, 7.8, 6.5); **18a**: 5.11 (dq, 1H, 10.5, 1.5), 5.13 (dq, 1H, 17.5, 1.5), 5.79 (dddd, 1H, 17.5, 10.5, 7.5, 6.5); **17b**; 1.61 (s, 3H), 1.70 (s, 3H), 5.19 (br t, 1H, 7.5); **18b**: 1.63 (s, 3H), 1.70 (s, 3H), 4.99 (br t, 1H, 7.5); **17c**: 2.20 (t, 1H, 2.6); **18c**: 1.99 (t, 1H, 2.6); **17d**: 7.24–7.34 (m, 5H); **18d**: 7.23–7.34 (m, 5H); **17e**: 3.53 (s, 3H). [g] Resonances due to C*HaHb*.

recrystallizaton of this diastereomeric mixture provided the major **17a** as practically pure crystals. The diastereomer **18a** was obtained in a pure form from the filtrate by use of HPLC. The configuration of the newly formed chiral center in the side chain was deduced as *R* for **17a** and as *S* for **18a** from the reaction mechanism, and the validity of this assignment was proven by a chemical transformation of **17a** into a sesquiterpene natural product, (−)-kanshone A (**8**), whose absolute stereostructure has been determined.

The fact that **19a** was recovered unchanged when warmed in xylene at 50 °C, while a low yield (20%) of **17a** was isolated upon reflux, fully supports **17a** to be an alkylation product in the above reaction and not a product which arose from the Cope rearrangement of **19a**.

Reactions of **7** with other alkyl halides **16b–d** and methyl bromoacetate (**16e**) and purification of the products obtained were carried out according to the procedures used for the aforementioned allylation (Scheme II and Table I). All alkylation reactions proceeded in an extracyclic stereocontrolled fashion to give good yields of γ-alkylated products **17b–d**, together with **18b–d** and α-alkylated **19b–d** as the minor product. The O-alkylated product **20b** as the minor product (run 2) was somewhat labile and regenerated partially the starting materials on chromatographic separation. On the other hand, reaction of **7** with methyl bromoacetate provided, as the sole product, the ester **17e** which is homogeneous from the ^{1}H NMR and TLC analyses (run 5).

The ^{1}H NMR (600 MHz) spectral data of **17a–e** and **18a–d** are given in Table II, in which the following characteristic features are detected, i.e., coupling constants $J_{1,7b}$ and $J_{5,7b}$ are 0, since vicinal protons, H(1) and H(7b), and H(5) and H(7b), are at approximately right angles as measured on Dreiding models, so that H(7b) appears as a doublet (9.5 Hz) arising from geminal coupling with H(7a). In addition, $J_{1,5}$ characteristic of the apoverbenone ring system is commonly 6.0 Hz.[11] On the other hand, resonances due to the allylic methine protons in the side chain appear in the range (δ 4.64–5.16) on account of the deshielding arising from the anisotropy of the phenylsulfonyl group. In addition, on comparison of **17** with **18**, chemical shifts due to the secondary methyl group show distinct differences (25–90 Hz), serving as a tool for determining the product ratio in the γ-alkylation.

In the course of the present study, since Lightner and co-worker reported that a combined reagent, K_2CO_3–cesium carbonate (Cs_2CO_3) (a 9:1 ratio) is effective for C-alkylation of pentane-2,4-dione,[12] we applied this reagent to our alkylation. When **7** was reacted with **16c–e** in the presence of this combined reagent (10 equiv), no change was observed in the product composition including the yield, except that the reactions went to completion at room temperature in relatively shorter reaction time; however, surprisingly, considerably high diastereoselection was detected on the reactions with **16a,b** to produce **17a,b** and **18a,b** (Table I, runs 1 and 2, in parentheses), although we have at present no reasonable explanation for this observation. When Cs_2CO_3 alone was employed, no improvement in the yield and diastereoselection on formation of **17a** and **18a** was detected.[13]

A proposed mechanism for the alkylation of **7** is shown in Scheme III. The compound **7** generates a metal-extended enolate **21** possessing a transoid ethylidene group. Because of the steric repulsion between a phenylsulfonyl group and the *gem*-dimethyl bridge in the transition state for an α-alkylation process leading to **19**, the enolate **21** undergoes γ-alkylation preferentially, giving **17** and **18**. In this γ-alkylation step, alkyl halides approach the enolate **21** trans to the bulky *gem*-dimethyl bridge according to the reactivity of pinane-type compounds,[2,14] giving **17** diastereoselectively. From the same reason, the α-alkyl-

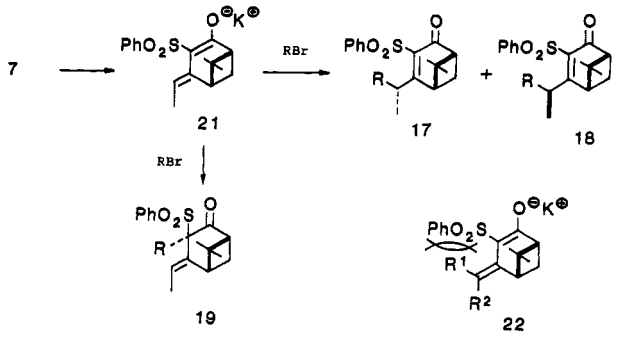
(11) For an analogous example, see Bohlmann, F.; Jakupovic, J.; Schuster, A.; King, R. M.; Robinson, H. *Planta Med.* **1984**, *50*, 202.

(12) Shrout, D. P.; Lightner, D. A. *Synth. Commun.* **1990**, 2075.

(13) Attempted allylation of **7** in the presence of rubidium carbonate (Rb_2CO_3) resulted in recovery of **7**.

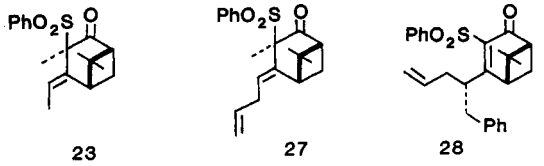
(14) For an analogous example, see Inokuchi, T.; Asanuma, G.; Torii, S. *J. Org. Chem.* **1982**, *47*, 4622.

Scheme III



ation reaction provides 3*R*-nopinone derivative **19**. Retention of the integrity of the newly formed chiral centers in the side chains of **17** and **18** would be accounted for by the consideration that no enolate formation of **17** and **18** under the conditions employed here occurs, because the postulated enolate **22** possesses a severe nonbonded interaction between a phenylsulfonyl group and a cisoid substituent (R^1, Me, or other alkyl functions). In fact, treatment of **17a** with the combined reagent, K_2CO_3–Cs_2CO_3 (9:1), in MeCN (50 °C, 12 h) resulted in complete recovery of the starting material.

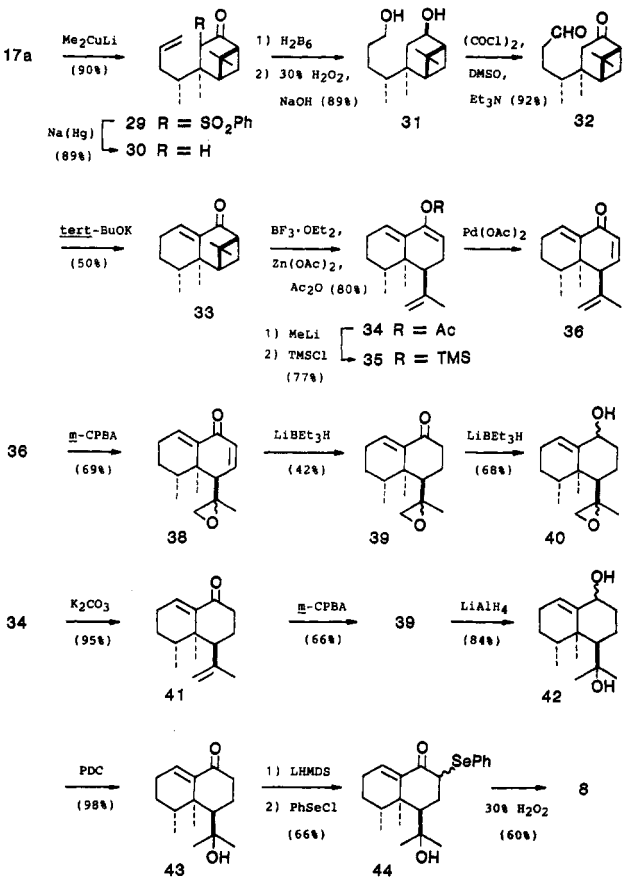
The scope and limitations for the alkylation of this type were examined next. Reaction of **7** with MeI in the presence of K_2CO_3 gave **9** and **23** in 70 and 27% yields, respectively, whereas no reaction occurred when the less reactive alkylating agent butyl bromide was employed. Attempts to make the minor alkylated products **18** rich were carried out by reversing the order of introduction of the two alkyl groups. As shown in Scheme I, chemical transformation of **2** to enone **24** was accomplished by the conjugate addition of **2** with 3-butenylmagnesium bromide followed by the Pummerer reaction and *m*-CPBA oxidation, according to the procedure for the preparation of **7**. Although methylation of **24** with MeI in the presence of K_2CO_3–Cs_2CO_3 (9:1) provided a mixture of γ-methylated products, **18a** and **17a**, and α-methylated product **27** in 61 and 21% yields, respectively, a poor diastereoselection (**18a**/**17a**, 3.8:1) in the γ-alkylation step was detected, indicating that MeI, a reactive and relatively small agent in molecular size, can easily approach the nopinone skeleton from the same direction as the *gem*-dimethyl bridge. The fact that benzylation of **24** with benzyl bromide afforded a mixture (86% yield) of γ-benzylated products (a 20:1 ratio), in which the stereostructure **28** is assigned for the major product, provides unambiguous evidence supporting the above explanation. Finally, attempted methylation of **12** in place of **7** with MeI resulted in recovery of **12**, indicating that the phenylsulfonyl function is essential as an activator for alkylations of this type.



Synthesis of (−)-Kanshone A

Attention was then focused on the utility of **17a** in natural product synthesis combined with the stereochemical assignment of the newly formed chiral center in the side chain by chemical means. As the target natural product, we chose (−)-kanshone A (**8**), a nardosinane sesquiterpene isolated from *Nardostachys chinensis* (Valerianaceae), with antihepatotoxicity.[15] The structural characteristics of this natural product are an axially oriented 2-hydroxypropyl group, a *cis*-dimethyl group, and a cross-conjugated dienone system. In these, the stereocontrolled construction of the axial disposition for the 2-oxygenated propyl group is anticipated to be difficult.

Scheme IV

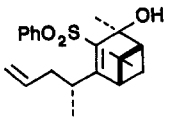


Our synthesis is shown in Schemes IV, in which two kinds of significant advantages are included: (1) the methyl group in the side chain of **17a** acts in **8** as the secondary methyl group being arranged cis with the angular methyl group with the correct absolute configuration; (2) bicyclic enol acetate **34** derived from cyclobutane-ring opening of the tricyclic enone **33** by use of the combined reagent, BF_3·OEt_2/$Zn(OAc)_2$/Ac_2O, which we have developed earlier,[2,3] possesses a nardosinane carbon skeleton flanking an axially oriented isopropenyl group, synthetically equivalent to a 2-hydroxypropyl group.

Conjugate addition of **17a** with Me_2CuLi in THF–ether proceeded in a stereoselective fashion[2] to give the adduct **29** as a diastereomeric mixture with regard to phenylsulfonyl group, one isomer of which is major. It is noteworthy that copper(I)-catalyzed methylation of **17a** with methylmagnesium bromide (THF, −78–0 °C) provided mostly the 1,2-adduct **37**. Desulfonylation of **29** was carried out using Na(Hg) in MeOH in preventing overreduction of the product **30** by monitoring with TLC, affording 4,4-dialkylnopinone **30** in 89% yield based on the consumed **29**. Chemical transformation of a substituted 3-butenyl

(15) Bagchi, A.; Oshima, Y.; Hikino, H. *Phytochemistry* **1988**, *27*, 1199.

group in 30 into the corresponding butanol one was achieved by a sequence of conventional reactions; (1) hydroboration–oxidation of 30 gave high yield of crystalline diol 31, whose stereochemistry of the newly formed secondary hydroxyl group may be assigned as depicted; (2) Swern oxidation of 31 provided the desired keto aldehyde 32, somewhat labile on standing at room temperature.



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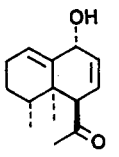
Intramolecular aldol condensation of 32 under basic conditions[16] was then examined. Recovery of 32 was detected under the conditions such as K_2CO_3/MeCN/50 °C and DBU/benzene/reflux, while treatment with KOH in aqueous MeOH or with NaOMe in MeOH provided an intractable mixture of products. Finally, the cyclization product 33 was successfully synthesized with reproducibility in 45–50% isolated yield regardless of the reaction scale, when 32 was treated with *tert*-BuOK in CH_2Cl_2 at room temperature.[17] Careful TLC monitoring revealed that the condensation occurred rapidly and the reaction was mostly complete within a few minutes.

BF_3·OEt_2-promoted cyclobutane opening[3] of 33 proceeded with little loss of optical purity to provide high yield of the nardosinane-type enol acetate 34 with the correct absolute stereostructure necessary for the synthesis of (−)-kanshone A (8). Conversion of 34 into the corresponding silyl enol ether 35 was effected by treatment with MeLi (2 equiv) followed by addition of chlorotrimethylsilane (TMSCl) to the resulting lithium enolate at −78 °C. Dehydrosilylation of 35 with palladium acetate by the Saegusa method[18] gave the cross-conjugated dienone 36 whose physical data including the sign of the optical rotation are in good agreement with those of the authentic 36 derived from the natural 8 by dehydration.[15]

The remaining task of our total synthesis is transformation of the isopropenyl group in 36 to an isopropyl alcohol function. Epoxy dienone 38 was readily available by the regioselective epoxidation of 36 with *m*-CPBA (1 equiv) in CH_2Cl_2. However unfortunately, attempted cleavage of the oxirane ring in 38 with super hydride failed; this reaction resulted in formation of epoxy enone 39, which on further exposure to this reactant provided epoxy alcohol 40, and no oxirane-opening product was detected in spite of a careful inspection of the reaction mixture. This could be accounted for by assuming that an axially oriented substituent, the 1,2-epoxypropane group in this case, at the peri position is usually less reactive because of the steric hindrance. In the course of our studies, Asakawa and co-workers reported the racemic synthesis of 8, wherein attempted conversion of the acetyl group in 45 into a 2-hydroxypropyl unit using a large excess of MeLi resulted mostly in recovery of the starting material.[19] This fact supports our assertion.



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Success of our total synthesis was finally achieved starting with enone 41 as a key synthetic intermediate. The compound 41 was obtained quantitatively by hydrolysis of 34. Regioselective epoxidation of 41 provided epoxy ketone 39 as a single product, and subsequent reduction with lithium aluminum hydride in refluxing THF gave diol 42. Oxidation of 42 with PDC provided dihydrokanshone A (43) in 50% overall yield from 41. Transformation of 43 to (−)-kanshone A (8) was readily performed by a phenylselenenylation–selenoxide elimination sequence;[20] treatment of the lithium enolate of 43 with phenylselenenyl chloride and subsequent exposure of the resulting phenylselenenyl ketone 44 to 30% H_2O_2 gave the desired 8. The IR and ^1H and ^{13}C NMR spectra of the synthetic 8, $[\alpha]^{20}_D$ −245.1° ($CHCl_3$), are in good accordance with those of natural 8, $[\alpha]_D$ −147.8° ($CHCl_3$).[15,21] Although the sign of the specific rotation of natural and synthetic 8 is identical with each other, there is a considerable difference between their values. The natural (−)-kanshone A (8) is reported to be an oil, while our synthetic (−)-8 is crystals, mp 96–97 °C, and homogeneous by the TLC and ^1H NMR analyses. Consequently, we can assume that the natural product is contaminated by a small amount of impurities.

Conclusions

Alkylation of (1*R*,5*S*)-7, readily obtainable in 74% yield from (+)-nopinone (1), with reactive alkyl bromides involving allyl bromide as the representative proceeded in an extracyclic stereocontrolled fashion to give γ-alkylated products 17 in synthetically satisfactory yields. Since our initial investigations confirmed that conjugate addition of enone 3 with some carbon nucleophiles followed by desulfonylation provide 4,4-disubstituted nopinones 5 (R^2 = Me), and that the cyclobutane ring of the latter can be cleaved without any loss of optical purity to produce enol acetates 6 (R^2 = Me),[2] chemical transformations of 17 into 4,4-disubstituted nopinones and cyclobutane opening products corresponding to 5 and 6, respectively, are quite feasible. Especially, the latter products could serve as promising building blocks for asymmetric synthesis. In fact, starting from 17a, a highly stereocontrolled synthesis of (−)-kanshone A (8) was achieved in an optically active form via the 4,4-disubstituted nopinone 30 and the cyclobutane opening product 34.

Experimental Section

General. See ref 2. ^1H NMR spectra were recorded at 90 MHz, unless otherwise stated.

(1*R*,3*R*,4*S*,5*R*)-4-Ethyl-6,6-dimethyl-3-(phenylthio)bicyclo[3.1.1]heptan-2-one (11). To a stirred mixture of CuI (233 mg, 1.22 mmol) in THF (15 mL) at −50 °C was added a 0.91 M solution of ethylmagnesium bromide in THF (13.5 mL, 12.29 mmol), and the resulting mixture was stirred for 30 min. A solution of 2[2]

(16) Although condensation of 32 using *p*-TsOH in CH_2Cl_2 at 50 °C gave 33 in a low yield, the more forcing conditions were not adopted on account of instability of the cyclobutane ring to acid.

(17) On the choice of solvent, use of *tert*-BuOH or benzene in place of CH_2Cl_2 was not necessarily effective in this case.

(18) Ito, Y.; Hirano, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

(19) Tori, M.; Furuta, H.; Asakawa, Y. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1919.

(20) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Org. Chem.* **1974**, *39*, 2133. *Idem. J. Am. Chem. Soc.* **1975**, *97*, 5434.

(21) Spectral data of our synthetic 8 are also identical with those of the synthetic one by Asakawa; see ref 19.

(1.50 g, 6.1 mmol) in THF (2 mL) was added dropwise, and stirring was continued at −50 to −40 °C for 1 h. The reaction mixture was quenched by addition of aqueous NH_4Cl and extracted with AcOEt. Evaporation of the extract followed by purification of the oily residue by chromatography on silica gel (hexane–AcOEt (15:1)) gave **11** (1.28 g, 76%) as crystals: mp 79–80 °C (ether–hexane); $[\alpha]^{20}_D$ +225.6° (*c* 0.25, $CHCl_3$); IR ($CHCl_3$) 1710, 1580, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3H), 0.94 (t, 3 H, J = 6.4 Hz), 1.33 (s, 3 H), 1.4–2.8 (m, 7 H), 3.38 (d, 1 H, J = 7.6 Hz), 7.1–7.4 (m, 3 H), 7.4–7.6 (m, 2 H). Anal. Calcd for $C_{17}H_{22}OS$: C, 74.40; H, 8.08. Found: C, 74.41; H, 8.25.

(1*R*,5*S*)-4-Ethyl-6,6-dimethyl-3-(phenylthio)bicyclo[3.1.1]hept-3-en-2-one (12). To a stirred solution of **11** (1.0 g, 3.6 mmol) in CH_2Cl_2 (20 mL) was added dropwise at 0 °C a solution of *m*-CPBA (80% purity, 787 mg, 3.6 mmol) in CH_2Cl_2 (15 mL), and stirring was continued at 0 °C for 1 h and then at rt for 30 min. The precipitate was filtered off, and the filtrate was washed successively with aqueous Na_2SO_3, aqueous $NaHCO_3$, and brine, dried, and then filtered. To the filtrate was added acetic anhydride (0.7 mL, 6.85 mmol) and MsOH (126 μL, 1.8 mmol). The resulting solution was stirred at 0 °C for 1 h, allowed to warm to rt, and stirred for an additional 15 h. Water (15 mL) was added, the mixture was stirred for 30 min, and the aqueous layer was separated and extracted with CH_2Cl_2. The combined extracts were washed successively with aqueous K_2CO_3 and brine and dried. Removal of the solvent followed by chromatography of the oil residue on silica gel (hexane–ether (5:1)) afforded **12** (838 mg, 85%) as an oil: $[\alpha]^{20}_D$ +73.3° (*c*, 0.20, $CHCl_3$); IR (film) 1687, 1581, 741, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 3 H), 1.05 (t, 3 H, J = 6.8 Hz), 1.54 (s, 3 H), 2.0–3.1 (m, 6 H), 7.0–7.4 (m, 5 H). Anal. Calcd for $C_{17}H_{20}OS$: C, 74.96; H, 7.40. Found: C, 75.05; H, 7.72.

(1*R*,5*S*)-4-Ethyl-6,6-dimethyl-3-(phenylsulfonyl)bicyclo[3.1.1]hept-3-en-2-one (7). To a stirred solution of **12** (838 mg, 3.0 mmol) in CH_2Cl_2 (20 mL) was added at 0 °C a solution of *m*-CPBA (1.73 g, 8.0 mmol) in CH_2Cl_2 (6 mL), and the resulting mixture was stirred at 0 °C for 30 min and then at rt for 2 h. The precipitate was filtered off, and the filtrate was washed successively with aqueous Na_2SO_3, aqueous K_2CO_3, and brine, and dried. Evaporation of the solvent left a crystalline residue which was filtered through a short silica gel column (hexane–AcOEt (4:1)) to afford **7** (728 mg, 80%) as crystals: mp 137–138 °C (ether–hexane); $[\alpha]^{20}_D$ +136.7° (*c*, 0.15, $CHCl_3$); IR ($CHCl_3$) 1690, 1570, 1320, 1300, 1150, 640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (s, 3 H), 1.25 (t, 3 H, J = 7.3 Hz), 1.46 (s, 3 H), 1.98–2.20 (m, 1 H), 2.60–2.90 (m, 3 H), 2.95–3.35 (m, 2 H), 7.35–7.70 (m, 3 H), 7.90–8.18 (m, 2 H). Anal. Calcd for $C_{17}H_{20}O_3S$: C, 67.08; H, 6.62. Found: C, 67.24; H, 6.70.

Starting with **2** (6.00 g), the sulfone **7** (4.40 g) was prepared in 74% overall yield, wherein purification of the crude products, **11** and **12**, was carried out by using filtration through a short silica gel column (hexane–AcOEt (4:1)).

(1*R*,5*S*)-2-Acetoxy-4-[(*E*)-ethylidene]-6,6-dimethyl-3-(phenylsulfonyl)bicyclo[3.1.1]hept-2-ene (14). A mixture of **7** (50 mg, 0.16 mmol) and NaH (20.2 mg, 0.48 mmol) in THF (2 mL) was stirred at rt for 2 h. To this solution was added acetyl chloride (46 μL, 0.64 mmol), and the resulting solution was stirred for an additional 1 h. AcOEt (10 mL) was added and the resulting solution was washed successively with water and brine and dried. Evaporation of the solvent followed by chromatography of the oily residue on silica gel (hexane–AcOEt (2:1)) gave **14** (52 mg, quant) as an oil: $[\alpha]^{20}_D$ −49.8° (*c*, 0.14, $CHCl_3$); IR (film) 1765, 1590 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.76 (s, 3 H, 8-H), 1.35 (s, 3 H, 9-H), 1.62 (d, 1 H, J = 9.6 Hz, 7b-H), 1.64 (d, 3 H, J = 7.2 Hz, =CMe), 2.40 (dd, 1 H, J = 6.0, 5.4 Hz, 5-H), 2.53 (ddd, 1 H, J = 9.6, 6.0, 5.4 Hz, 7a-H), 3.09 (t, 1 H, J = 6.0 Hz, 1-H), 6.49 (q, 1 H, J = 7.2 Hz, =C*H*Me), 7.51 (dd, 2 H, J = 7.2, 1.2 Hz, *m*-H), 7.58 (tt, 1 H, J = 7.2, 1.2 Hz, *p*-H), 7.95 (dd, 2 H, J = 7.2, 1.2 Hz, *o*-H). Anal. Calcd for $C_{19}H_{22}O_4S$: C, 65.88; H, 6.40. Found: C, 65.62; H, 6.60.

(1*R*,5*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-4-[(*E*)-ethylidene]-3-(phenylsulfonyl)bicyclo[3.1.1]hept-2-ene (15). According to the procedure described for preparation of **14**, **7** (50 mg, 0.16 mmol) was treated with NaH (20.2 mg, 0.48 mmol) in THF (2 mL), followed by addition of TBDMSCl (84 mg, 0.56 mmol), giving **15** (58 mg, 86%) as an oil: $[\alpha]^{20}_D$ −42.8° (*c*, 0.15, $CHCl_3$); IR (film) 1560, 1150, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.25 and 0.27 (s each, 6 H in total), 0.39 (s, 9 H), 0.67 (s, 3 H), 1.32 (s, 3 H), 1.46 (d, 1 H, J = 9.0 Hz), 1.63 (d, 3 H, J = 7.2 Hz), 2.38–2.52 (m, 2 H), 3.12 (t, 1 H, J = 6.0 Hz), 6.46 (q, 1 H, J = 7.2 Hz), 7.38–7.55 (m, 3 H), 7.8–7.9 (m, 2 H). Anal. Calcd for $C_{23}H_{34}O_3SiS$: C, 65.99; H, 8.12. Found: C, 65.88; H, 8.20.

Reaction of 7 with Alkyl Bromides. General Procedure. Method A using K_2CO_3: A mixture of **7** (304 mg, 1.0 mmol), K_2CO_3 (1.38 g, 10.0 mmol), and alkyl bromide **16a–d** (10.0 mmol) in MeCN (10 mL) was stirred at 50 °C for 5 h, and filtered through a short Celite 545 column with MeCN washing. Concentration of the filtrate left a crystalline residue which was chromatographed on silica gel (hexane–AcOEt (5:1)) to give a mixture of γ-alkylated products **17** and **18**, α-alkylated product **19**, and O-alkylated product **20** on reactions with **16a,b**. Reaction with methyl bromoacetate (**16e**) was carried out similarly to give **17e**.

Method B using K_2CO_3–Cs_2CO_3: A mixture of **7** (304 mg, 1.0 mmol), K_2CO_3 (124 mg, 0.9 mmol), Cs_2CO_3 (33 mg, 0.1 mmol), and alkyl bromide or methyl bromoacetate (10.0 mmol) in MeCN (10 mL) was stirred at rt for 5 h. Workup followed by separation of the products were performed according to the procedures mentioned in method A.

The correct product ratio of **17** and **18** was obtained from the integral ratio in the ^1H NMR spectrum of the mixture of the two, wherein a pair of doublets due to two kinds of secondary methyl groups were adopted on acccount of large differences in their chemical shifts. While **17a,c–e** were obtained as pure crystals by recrystallization (hexane–ether) of the above diastereomeric mixture, oily **17b** and the minor **18a–d** were obtained from the mixture by use of HPLC (hexane–AcOEt (5:1)). In a large-scale preparation, most of **17a,c–e** were isolated by recrystallization of the crystalline residue obtained from the extract. The yields of the products and the ratio of **17** and **18** are shown in Table I. ^1H NMR (600 MHz) data of **17a–e** and **18a–d** are summarized in Table II. ^1H NMR (90 MHz) data of **19a–d** and **20a,b**, and other physical data of **17–20** are described below.

(1*R*,5*S*)-6,6-Dimethyl-4-[(1*R*)-1-methyl-3-butenyl]-3-(phenylsulfonyl)bicyclo[3.1.1]hept-3-en-2-one (17a): 60% isolated yield; crystals; mp 115–116 °C (ether–hexane); $[\alpha]^{20}_D$ + 158.6° (*c* 0.77, $CHCl_3$); IR ($CHCl_3$) 1690, 1640, 1155 cm^{-1}. Anal. Calcd for $C_{20}H_{24}O_3S$: C, 69.73; H, 7.02. Found: C, 69.58; H, 7.05.

(1*R*,5*S*)-6,6-Dimethyl-4-[(1*S*)-1-methyl-3-butenyl]-3-(phenylsulfonyl)bicyclo[3.1.1]hept-3-en-2-one (18a): oil; $[\alpha]^{20}_D$ +131.7° (*c* 0.10, $CHCl_3$); IR (film) 1691, 1639, 1154 cm^{-1}; HRMS calcd for $C_{20}H_{24}O_3S$ 344.1446, found 344.1441.

(1*R*,3*R*,5*S*)-3-Allyl-4-[(*E*)-ethylidene]-6,6-dimethyl-3-(phenylsulfonyl)bicyclo[3.1.1]heptan-2-one (19a): 20% yield; crystals; mp 64–65 °C (ether–hexane); $[\alpha]^{20}_D$ + 37.1° (*c* 0.21, $CHCl_3$); IR ($CHCl_3$) 1710, 1620, 1300, 1140, 920, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 3 H), 1.38 (s, 3 H), 1.81 (d, 3 H, J = 6.5 Hz), 2.4–2.75 (m, 3 H), 3.06 (d, 2 H, J = 7.3 Hz), 3.30 (t, 1 H, J = 5.5 Hz), 4.88–5.15 (m, 2 H), 5.50–5.90 (m, 1 H), 6.68 (q, 1 H, J = 6.5 Hz), 7.5–7.8 (m, 3 H), 7.9–8.1 (m, 2 H). Anal. Calcd for $C_{20}H_{24}O_3S$: C, 69.73; H, 7.02. Found: C, 69.70; H, 7.00.

Allyl (1*R*,5*S*)-6,6-Dimethyl-4-[(*E*)-ethylidene]-3-(phenylsulfonyl)bicyclo[3.1.1]hept-2-en-2-yl Ether (20a): 5% yield; unstable oil; IR ($CHCl_3$) 1620, 1150, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.67 (s, 3 H), 1.32 (s, 3 H), 1.67 (d, 3 H, J = 6.5 Hz), 2.35–2.75 (m, 3 H), 3.13 (t, 1 H, J = 5.5 Hz), 4.30 (m, 2 H), 4.95–5.25 (m, 2 H), 5.48–5.90 (m, 1 H), 6.67 (q, 1 H, J = 6.5 Hz), 7.4–7.6 (m, 3 H), 7.85–8.02 (m, 2 H).

(1*R*,5*S*)-6,6-Dimethyl-4-[(1*R*)-1,4-dimethyl-3-pentenyl]-3-(phenylsulfonyl)bicyclo[3.1.1]hept-3-en-2-one (17b): 50% isolated yield; oil; $[\alpha]^{20}_D$ + 112.9° (*c* 1.80, $CHCl_3$); IR ($CHCl_3$) 1690, 1560, 1300, 1150 cm^{-1}. Anal. Calcd for $C_{22}H_{28}O_3S$; C, 70.94; H, 7.58. Found: C, 70.56; H, 7.66.

(1*R*,5*S*)-6,6-Dimethyl-4-[(1*S*)-1,4-dimethyl-3-pentenyl]-3-(phenylsulfonyl)bicyclo[3.1.1]hept-3-en-2-one (18b): oil; $[\alpha]^{20}_D$ + 134.0° (*c* 0.32, $CHCl_3$); IR (film) 1691, 1559, 1305, 1150 cm^{-1}; HRMS calcd for $C_{22}H_{28}O_3S$ 372.1759, found 372.1749.

(1*R*,3*R*,5*S*)-4-[(*E*)-Ethylidene]-6,6-dimethyl-3-(3-methyl-2-butenyl)-3-(phenylsulfonyl)bicyclo[3.1.1]heptan-2-one (19b): 16% yield; oil; $[\alpha]^{20}_D$ +49.6° (*c* 0.64, $CHCl_3$); IR (film) 1710, 1580, 1300, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (s, 3 H), 1.40 (s, 3 H), 1.50 (br s, 3 H), 1.65 (s with fine splittings, 3 H), 1.82 (d, 3 H, J = 6.8 Hz), 2.42–2.80 (m, 3 H), 2.98 (m, 2 H), 3.31 (t,

1 H, J = 6.0 Hz), 5.48 (br t, 1 H, J = 7.4 Hz), 6.70 (q, 1 H, J = 6.8 Hz), 7.4–7.7 (m, 3 H), 7.9–8.05 (m, 2 H). Anal. Calcd for $C_{22}H_{28}O_3S$: C, 70.94; H, 7.58. Found: C, 70.94; H, 7.50.

(1*R*,5*S*)-4-[(*E*)-Ethylidene]-6,6-dimethyl-3-(phenylsulfonyl)bicyclo[3.1.1]hept-2-en-2-yl 3-Methyl-2-butenyl Ether (20b): 5% yield; unstable oil; IR (film) 1680, 1300, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.70 (s, 3 H), 1.35 (s, 3 H), 1.60 (s, 6 H), 1.75 (d, 3 H, J = 6.8 Hz), 2.2–2.8 (m, 3 H), 3.18 (t, 1 H, J = 5.5 Hz), 4.3 (m, 2 H), 4.08 (m, 1 H), 6.73 (q, 1 H, J = 6.8 Hz), 7.43–7.7 (m, 3 H), 7.9–8.05 (m, 2 H).

(1*R*,5*S*)-6,6-Dimethyl-4-[(1*R*)-1-methyl-3-butynyl]-3-(phenylsulfonyl)bicyclo[3.1.1]hept-3-en-2-one (17c): 50% isolated yield; crystals, mp 168–169 °C (ether–hexane); $[\alpha]^{20}_D$ 169.1° (c 0.19, $CHCl_3$); IR (film) 3100, 1690, 1560, 1300, 1150 cm^{-1}. Anal. Calcd for $C_{20}H_{22}O_3S$: C, 70.23; H, 6.48. Found: C, 70.55; H, 6.30.

(1*R*,5*S*)-6,6-Dimethyl-4-[(1*S*)-1-methyl-3-butynyl]-3-(phenylsulfonyl)bicyclo[3.1.1]hept-3-en-2-one (18c): crystals; mp 110–111 °C (ether–hexane); $[\alpha]^{20}_D$ +65.3° (c 0.10, $CHCl_3$); IR (film) 3100, 1691, 1565, 1305, 1152 cm^{-1}; HRMS calcd for $C_{20}H_{22}O_3S$ 342.1290, found 342.1306.

(1*R*,3*R*,5*S*)-4-[(*E*)-Ethylidene]-6,6-dimethyl-3-(phenylsulfonyl)-3-(2-propynyl)bicyclo[3.1.1]heptan-2-one (19c): 20% yield; oil; $[\alpha]^{20}_D$ +70.4° (c 0.56, $CHCl_3$); IR (film) 3100, 1710, 1580, 1300, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 3 H), 1.45 (s, 3 H), 1.83 (d, 3 H, J = 6.5 Hz), 2.08 (t, 1 H, J = 2.2 Hz), 2.5–2.83 (m, 3 H), 3.22 (dd, 2 H, J = 7.5, 2.2 Hz), 3.38 (t, 1 H, J = 5.5 Hz), 6.88 (q, 1 H, J = 6.5 Hz), 7.5–7.8 (m, 3 H), 8.0–8.2 (m, 2 H). Anal. Calcd for $C_{20}H_{22}O_3S$: C, 70.23; H, 6.48. Found: C, 70.07; H, 6.49.

(1*R*,5*S*)-6,6-Dimethyl-4-[(1*R*)-1-methyl-2-phenylethyl]-3-(phenylsulfonyl)bicyclo[3.1.1]hept-3-en-2-one (17d): 80% isolated yield; crystals; mp 108–109 °C (ether–hexane); $[\alpha]^{20}_D$ +65.0° (c 0.14, $CHCl_3$); IR (neat) 1690, 1300, 1150 cm^{-1}. Anal. Calcd for $C_{24}H_{26}O_3S$: C, 73.06; H, 6.64. Found: C, 73.29; H, 6.79.

(1*R*,5*S*)-6,6-Dimethyl-4-[(1*S*)-1-methyl-2-phenylethyl]-3-(phenylsulfonyl)bicyclo[3.1.1]hept-3-en-2-one (18d): oil; $[\alpha]^{20}_D$ +226.2° (c, 0.12, $CHCl_3$); IR (film) 1691, 1305, 1151 cm^{-1}; HRMS calcd for $C_{24}H_{26}O_3S$ 394.1603, found 394.1610.

(1*R*,3*R*,5*S*)-3-Benzyl-4-[(*E*)-ethylidene]-6,6-dimethyl-3-(phenylsulfonyl)bicyclo[3.1.1]heptan-2-one (19d): 3% yield; oil; IR (film) 1710, 1570, 1300, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 3 H), 1.58 (s, 3 H), 1.89 (d, 3 H, J = 6.5 Hz), 1.9–2.2 (m, 2 H), 2.50 (t, 1 H, J = 5.8 Hz), 3.00 (t, 1 H, J = 5.5 Hz), 3.53 (br s, 2 H), 6.60 (q, 1 H, J = 6.5 Hz), 6.9–8.0 (m, 10 H). Anal. Calcd for $C_{24}H_{26}O_3S$: C, 73.06; H, 6.64. Found: C, 73.35; H, 6.79.

Methyl (2*R*)-2-[(1*R*,5*S*)-6,6-dimethyl-3-(phenylsulfonyl)-2-oxobicyclo[3.1.1]hept-3-en-4-yl]butanoate (17e): 65% yield; crystals, mp 122–123 °C (ether–hexane); $[\alpha]^{20}_D$ +54.8° (c 0.12, $CHCl_3$); IR (neat) 1736, 1691, 1305, 1153 cm^{-1}. Anal. Calcd for $C_{20}H_{24}O_5S$: C, 63.85; H, 6.42. Found: C, 63.89; H, 6.48.

Cope Rearrangement of 19a. A mixture of **19a** (35 mg) and a catalytic amount of hydroquinone in xylene (2 mL) was gently refluxed for 5 h. Concentration under reduced pressure followed by chromatography of the residue on silica gel (hexane–AcOEt (5:1)) gave **17a** (7 mg, 20%) whose ^{1}H NMR spectrum is identical with that of the authentic sample.

(1*R*,4*R*,5*R*)-4,6,6-Trimethyl-4-[(1*R*)-1-methyl-3-butenyl]bicyclo[3.1.1]heptan-2-one (30). To a stirred suspension of CuI (4.57 g, 24.0 mmol) in ether (120 mL) at 0 °C was added dropwise a 0.94 M solution of MeLi in ether (50 mL, 47.0 mmol). After the mixture was stirred briefly, a solution of **17a** (2.77 g, 8.0 mmol) in THF (20 mL) was added, and stirring was continued for an additional 1 h. The reaction mixture was quenched with aqueous NH_4Cl and the product was extracted with ether. Removal of the solvent left an oil which was chromatographed on silica gel (hexane–AcOEt (8:1)) to give **(1*R*,3*RS*,4*R*,5*S*)-4,6,6-trimethyl-4-[(1*R*)-1-methyl-3-butenyl]-3-(phenylsulfonyl)bicyclo[3.1.1]heptan-3-one (29)** (2.60 g, 90%) as crystals, mp 43–44 °C (ether–hexane); IR (film) 3070, 1710, 1640, 1300, 1140, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (s, with splittings, 6 H, CMe, CH*Me*), 1.37 (s, 3 H), 1.52 (s, 3 H), 1.8–2.9 (m, 7 H), 3.88 (s, 1 H), 5.0, 5.13, and 5.18 (br s each, 2 H in total), 5.58–6.0 (m, 1 H), 7.5–7.75 (m, 3 H), 7.77–7.95 (m, 2 H). Anal. Calcd for $C_{21}H_{28}O_3S$: C, 69.96; H, 7.76. Found: C, 69.90; H, 7.93.

To a stirred suspension of 6% Na (Hg) (37.8 g, 169 mmol) in MeOH (100 mL) was added dropwise at −50 °C a solution of **29** (6.10 g, 16.9 mmol) in MeOH (10 mL), and the resulting mixture was allowed to warm to −20 °C for 1.5 h. The reaction mixture was quenched with aqueous NH_4Cl and the mixture was filtered through a small bed of Celite 545. Water was added to the filtrate and the product was extracted with ether. Evaporation of the solvent followed by chromatography of the residue on silica gel (hexane–AcOEt (15:1)) gave **30** (2.75 g, 89% based on the consumed starting material) and unreacted **29** (1.02 g). **30**: oil; $[\alpha]^{20}_D$ +34.9° (c 0.15, $CHCl_3$); IR (film) 3080, 1710, 1635, 905 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80 (d, 3 H, J = 6.5 Hz), 0.90 (s, 3 H), 1.03 (s, 3 H), 1.35 (s, 3 H), 1.43–2.65 (m, 9 H), 4.90, 5.03, and 5.08 (br s each, 2 H in total), 5.51–5.98 (m, 1 H). Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 82.02; H, 11.25.

(1*R*,2*R*,4*R*,5*R*)-[(1*R*)-4-Hydroxy-1-methylbutyl]-4,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (31). To a stirred solution of **30** (2.75 g, 12.4 mmol) in THF (70 mL) was added at 0 °C dropwise a 1.0 M solution of diborane in THF (29.7 mL, 29.7 mmol). The resulting mixture was stirred at 0 °C for 5 h and then at rt for 15 h and recooled to 0 °C. Water (1 mL) was added with stirring, 3 M NaOH (40 mL) followed by 30% H_2O_2 (12.6 mL) was added, and stirring was continued at 0 °C for 4 h and at rt for 20 h. The reaction mixture was filtered through a small bed of Celite 545, and the product was extracted with AcOEt. Removal of the solvent left a solid whose recrystallization from AcOEt–hexane gave **31** (2.06 g). A crystalline residue obtained from the filtrate was chromatographed on silica gel (hexane–AcOEt (1:3)) to give **31** (576 mg). The total yield of **31** was 2.64 g (89%): mp 120–121 °C (AcOEt–hexane); IR (KBr) 3250, 1060, 1040, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.78 (d, 3 H, J = 6.5 Hz), 0.80 (s, 3 H), 1.20 (s, 3 H), 1.26 (s, 3 H), 1.1–2.37 (m, 13 H), 3.64 (t, 2 H, J = 5.4 Hz), 4.24 (m, 1 H). Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.94; H, 11.74. Found: C, 75.27; H, 11.65.

(4*R*)-4-[(1*R*,4*R*,5*R*)-4,6,6-Trimethyl-2-oxobicyclo[3.1.1]hept-4-yl]pentanal (32). To a stirred solution of oxalyl dichloride (834 μL, 9.71 mmol) in CH_2Cl_2 (20 mL) was added at −78 °C a solution of DMSO (1.38 mL, 19.36 mmol) in CH_2Cl_2 (5 mL). After the solution was stirred briefly, a solution of **31** (584 mg, 2.42 mmol) in CH_2Cl_2 (5 mL) was added dropwise and the resulting mixture was stirred at −78 °C for 1 h. Et_3N (3.38 mL, 24.2 mmol) was added, and stirring was continued for 20 min and then at 0 °C for 30 min. The reaction mixture was diluted with ether and washed succesively with 5% aqueous HCl, water, and brine and dried. Evaporation of the solvent followed by chromtography of the residue on silica gel (hexane–AcOEt (3:1)) gave **32** (530 mg, 92%) as an oil: $[\alpha]^{20}_D$ +84.3° (c 0.39, $CHCl_3$); IR (film) 2700, 1710, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82 (d, 3 H, J = 6.5 Hz), 0.93 (s, 3 H), 1.00 (s, 3 H), 1.35 (s, 3 H), 1.2–2.7 (m, 11 H), 9.78 (t, 1 H, J = 2.2 Hz). The compound **32** was used for the next reaction without further purification because of instability on heating.

(2*R*,4*S*,4a*R*,5*R*)-3,3,4a,5-Tetramethyl-2,4-methano-3,4,4a,5,6,7-hexahydronaphthalen-1(2*H*)-one (33). A mixture of **32** (521 mg, 2.20 mmol) and *tert*-BuOK (249 mg, 2.20 mmol) in CH_2Cl_2 (100 mL) was stirred at rt for 10 min and poured into water. The aqueous layer was separated and extracted with CH_2Cl_2. The combined CH_2Cl_2 solutions were washed with brine and dried. Removal of the solvent left an oil which was chromatographed on silica gel (hexane–AcOEt (6:1)) to give **33** (241 mg, 50%) as an oil: $[\alpha]^{20}_D$ +13.6° (c 0.28, $CHCl_3$); IR (film) 1690(s), 1625(s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (d, 3 H, J = 6.5 Hz), 0.95 (s, 3 H), 1.01 (s, 3 H), 1.36 (s, 3 H), 1.3–2.8 (m, 9 H), 6.77 (t, 1 H, J = 4.3 Hz). Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.26; H, 10.50.

(4*S*,4a*R*,5*R*)-1-Acetoxy-4-isopropenyl-4a,5-dimethyl-3,4,4a,5,6,7-hexahydronaphthalene (34). A suspension of **33** (241 mg, 1.10 mmol) and zinc acetate (210 mg, 1.10 mmol) in acetic anhydride (2 mL) was stirred at 0 °C as freshly distilled BF_3·OEt_2 (53.8 μL, 0.44 mmol) was added, and the resulting mixture was stirred at 0 °C for 10 min and then at rt for 24 h. To this mixture was added water (5 mL), and the resulting mixture was stirred at rt for 30 min and extracted with ether. The combined extracts were washed successively with aqueous $NaHCO_3$, water, and brine and dried. Concentration of the extract left an oil which was chromatographed on silica gel (hexane–AcOEt (6:1)) to give **34** (228 mg, 80%) as an oil: $[\alpha]^{20}_D$ −5.0° (c 0.33, $CHCl_3$); IR (film) 3050, 1755, 1660, 1630, 1170,

1010, 890 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (d, 3 H, J = 6.5 Hz), 1.07 (s, 3 H), 1.72 (s with fine splittings, 3 H), 1.3–2.9 (m, 8 H), 2.18 (s, 3 H), 4.70–4.80 (m, 2 H), 5.35 (m, 1 H), 5.68 (t, 1 H, J = 4.7 Hz). Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.41; H, 9.29. Found: C, 78.60; H, 9.41.

(4*S*,4a*R*,5*R*)-4-Isopropenyl-4a,5-dimethyl-1,4,4a,5,6,7-hexahydronaphthalen-1-one (36). A 0.94 M solution of MeLi in ether (556 μL, 0.59 mmol) was added to ether (1 mL) with stirring at −78 °C as a solution of **34** (70 mg, 0.26 mmol) in ether (2 mL) was added dropwise. After being stirred for 30 min, TMSCl (748 μL, 0.59 mmol) followed by Et_3N (868 μL) and HMPA (43 μL) was added to the reaction mixture, and stirring was continued for an additional 3 h at −78 to 0 °C. Pentane was added, and the solid was filtered off. The filtrate was washed successively with cold 5% HCl, 5% $NaHCO_3$, water, and brine and dried over Na_2SO_4. Removal of the solvent followed by distillation of the oily residue gave the silyl enol ether **35** (60 mg, 77%) as an oil: bp 100 °C/1 Torr (bath temperature); ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 9 H), 0.90 (d, 3 H, J = 7.0 Hz), 1.04 (s, 3 H), 1.2–2.4 (m, 8 H), 1.63 (s, 3 H), 4.82 and 5.58 (s, with fine splittings, 1 H each), 5.59 (t, 1 H, J = 2.9 Hz), 6.68 (t, 1 H, J = 4.0 Hz).

A mixture of **35** (145 mg, 0.49 mmol) and palladium acetate (146 mg, 0.65 mmol) in MeCN (3 mL) was stirred at rt for 20 h, poured into water, and the product was extracted with ether. Concentration of the extract gave an oil which was chromatographed on silica gel (hexane–AcOEt (20:1)) to give **36** (17 mg) as an oil. The IR and ^{1}H NMR spectra of the synthetic **36**, $[\alpha]^{20}_D$ −320.8° (*c* 0.24, $CHCl_3$), were identical with those of the authentic sample, $[\alpha]_D$ −355.4° (*c* 0.44, $CHCl_3$), derived from the natural kanshone A (**8**).[15]

(4*S*,4a*R*,5*R*)-4-Isopropenyl-4a,5-dimethyl-3,4,4a,5,6,7-hexahydronaphthalen-1(2*H*)-one (41). A mixture of **34** (95 mg, 0.36 mmol) and K_2CO_3 (152 mg, 1.1 mmol) in MeOH (5 mL) was stirred at rt for 20 h. Water was added to the reaction mixture, and the product was extracted with ether. Concentration of the extract followed by chromatography of the oily residue on silica gel (hexane–AcOEt (6:1)) gave **41** (75 mg, 95%) as an oil: $[\alpha]^{20}_D$ −41.5° (*c* 0.21, $CHCl_3$); IR (film) 1680(s), 1620(s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (d, 3 H, J = 6.5 Hz), 0.98 (s, 3 H), 1.75 (s with fine splittings, 3 H), 1.3–2.6 (m, 10 H), 4.70 (br s, 1 H), 4.88 (br s, 1 H), 6.62 (t, 1 H, J = 4.7 Hz). Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.74; H, 10.16.

(4*R*,4a*R*,5*R*)-4-[(1*R*,*S*)-1-Methyl-1,2-epoxyethyl]-4a,5-dimethyl-3,4,4a,5,6,7-hexahydronaphthalen-1(2*H*)-one (39). A solution of **41** (45 mg, 0.21 mmol) and *m*-CPBA (61 mg, 0.24 mmol) in CH_2Cl_2 (5 mL) was stirred at 0 °C for 5 h and at rt for 15 h, washed successively with aqueous Na_2SO_3, aqueous $NaHCO_3$, water, and brine, and dried. Removal of the solvent followed by chromatography of the oily residue on silica gel (hexane–AcOEt (6:1)) gave **39** (31 mg, 66%) as crystals: mp 109–110 °C (ether–hexane); $[\alpha]^{20}_D$ +9.9° (*c* 0.28, $CHCl_3$); IR (neat) 1680(s), 1620(s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (d, 3 H, J = 6.5 Hz), 1.00 (s, 3 H), 1.26 (s, 3 H), 1.4–2.9 (m, 12 H), 6.80 (t, 1 H, J = 4.7 Hz). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.87; H, 9.46. Found: C, 76.58; H, 9.45.

(4*R*,4a*R*,5*R*)-4-(1-Hydroxy-1-methylethyl)-4a,5-dimethyl-3,4,4a,5,6,7-hexahydronaphthalen-1(2*H*)-one (43). To a stirred mixture of lithium aluminum hydride (32 mg, 0.83 mmol) in THF (4 mL) was added at 0 °C a solution of **39** (39 mg, 0.17 mmol) in THF (1 mL), and the reaction mixture was stirred at 0 °C for 5 min and then gently refluxed for 4 h. After being cooled to 0 °C, wet ether followed by water was added and the product was extracted with ether. Removal of the solvent followed by chromatography of the residue on silica gel (hexane–AcOEt (2:1)) gave **(1*RS*,4*R*,4a*R*,5*R*)-4-(1-Hydroxy-1-methylethyl)-4a,5-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-1-ol (42)** (32 mg, 84%) as crystals: mp 121–122 °C (ether–hexane); IR (neat) 3400, 3300, 1130, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (d, 3 H, J = 6.5 Hz), 1.03 (s, 3 H), 1.33 (s, 6 H), 1.2–2.8 (m, 13 H), 4.40 (br m, 1 H), 5.90 (m, 1 H). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.57; H, 10.99. Found: C, 75.50; H, 10.86.

A mixture of **42** (7.8 mg, 0.03 mmol), PDC (61.8 mg, 0.16 mmol), molecular seives 4A (31 mg), and CH_2Cl_2 (2 mL) was stirred at rt for 2 h and filtered through a short silica gel column (CH_2Cl_2). Evaporation of the solvent left an oil which was purified by preparative TLC (hexane–AcOEt (1:1)) to give **43** (7.6 mg, 98%) as crystals: mp 83–84 °C (ether–hexane); $[\alpha]^{20}_D$ +68.4° (*c* 0.11, $CHCl_3$); IR (neat) 3454, 1677(s), 1613(s), 1138 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 3 H, J = 6.5 Hz), 1.02 (s, 3 H), 1.32 (s, 3 H), 1.36 (s, 3 H), 1.2–2.8 (m, 11 H), 6.76 (t, 1 H, J = 3.8 Hz). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.23. Found: C, 76.49; H, 10.14.

(−)-Kanshone A (8). A 5.4 M solution of LHMDS in THF (20 μL, 0.11 mmol) was added to THF (0.6 mL) at 0 °C with stirring as a solution of **43** (8.6 mg, 0.036 mmol) in THF (1.5 mL) followed by HMPA (100 μL) was added dropwise. After stirring for 1 h, a solution of phenylselenenyl chloride (21.3 mg, 0.11 mmol) in THF (0.4 mL) was added, and stirring was continued for an additional 3 h. The reaction mixture was diluted with ether and washed successively with water and brine and dried. Evaporation of the solvent left an oil which was purified by preparative TLC (hexane–AcOEt (2:1)) to give **(2*RS*,4a*R*,5*R*)-4-(1-hydroxy-1-methylethyl)-4a,5-dimethyl-2-(phenylseleno)-3,4,4a,5,6,7-hexahydronaphthalen-1(2*H*)-one (44)** (7.6 mg, 66%) as an oil: IR (film) 3490, 1675, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 and 0.95 (s each, 6 H in total), 1.21 (s, 3 H), 1.26 (s, 3 H), 1.3–2.8 (m, 9 H), 4.27 (t, 1 H, J = 7.2 Hz), 6.78 (t, 1 H, J = 4.0 Hz), 7.2–7.4 (m, 3 H), 7.5–7.75 (m, 2 H).

A solution of **44** (7.6 mg, 0.02 mmol) and pyridine (60 μL) in THF (1.5 mL) was stirred at 0 °C as 30% H_2O_2 (60 μL) was added, and the resulting mixture was stirred at rt for 40 min. Workup in a usual manner gave an oily residue which was purified by preparative TLC (hexane–AcOEt (4:1)) to give **8** (2.8 mg, 60%) as crystals: mp 96–98 °C (ether–hexane); $[\alpha]^{20}_D$ −245.1° (*c* 0.39, $CHCl_3$); IR (film) 3435, 1663, 1625, 1602, 1465, 1386, 1273, 1149, 831 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02 (d, 3 H, J = 6.5 Hz), 1.08 (s, 3 H), 1.18 (s, 3 H), 1.24 (s, 3 H), 2.4–2.7 (m, 3 H), 2.1–2.4 (m, 2 H), 2.5–2.75 (m, 2 H), 6.16 (dd, 1 H, J = 10.0, <1.0 Hz), 6.95 (dd, 1 H, J = 10.0, 7.0 Hz), 7.00 (t, 1 H, J = 4.0 Hz). The IR and ^{1}H NMR spectra of the synthetic **8** is identical with those of the natural **8**, $[\alpha]_D$ −147.8° (*c* 0.35, $CHCl_3$).[15]

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Supplementary Material Available: Experimental details and characterization of **9**, **13**, **23–28**, and **37–40** and copies of ^{1}H NMR spectra of **18a–d** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.