Preparation of Optically Active Apoverbenone and Verbenone from Nopinone by Use of the Sulfenylation−Dehydrosulfenylation Method. Stability and Reactivity Attributable to Absolute Configuration at the Sulfur Atom in Sulfoxides

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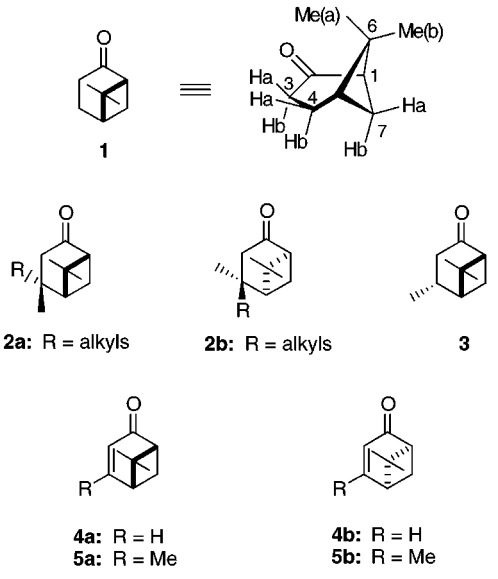
Apoverbenone (**4**) and verbenone (**5**) in optically active forms are potentially useful compounds as the chiral source in enantioselective synthesis. Starting with (+)-nopinone (**1**), readily available from (−)-*β*-pinene, (+)-apoverbenone (**4a**) and (+)-verbenone (**5a**) were prepared in synthetically satisfactory overall yields, using commonly the sulfenylation−dehydrosulfenylation method directed toward construction of an enone function. This methodology could be applicable to preparation of their enantiomers (−)-**4b** and (−)-**5b** on starting with (−)-nopinone. While configuration of the phenylsulfinyl group in sulfoxides **10a**,**b**, and **18a**,**b** were assigned by their ^{1}H NMR spectra and NOE correlations, absolute configurations at the sulfur atom were performed by comparison in ^{1}H NMR spectra with their homologues whose absolute configurations are well-defined, that is, **10a** with **13a**, **10b** with **13b**, **18a** with **19b**, and **18b** with **19a**. As a result, it was proved that, in 3-(phenylsulfinyl)nopinones, thermodynamic stability of isomers is dependent on absolute configuration at the sulfur center; that is, the *trans*-isomer **10a** possesses an R_s-phenylsulfinyl group and the *cis*-isomer **10b** possesses an S_s-phenylsulfinyl group, and it was proved that, in (4*R*)-4-methyl-3-(phenylsulfinyl)nopinones, both *cis*-isomers **18a**,**b** are stable, irrelevant with absolute configurations at the sulfur atom. In elimination of phenylsulfenic acid from sulfoxides **10** and **18**, the use of purified sulfoxides was essential, because the competing Pummerer reaction proceeded to give 3-(phenylthio)verbenone (**11**) as a byproduct, when acidic contaminants were present. The sulfoxides **10a**,**b** and **18a** provided smoothly **4a** and **5a**, respectively, in a syn elimination manner, whereas **18b** gave a mixture of decomposed products as a major part, probably because of instability of **18b** to heat as well as because of its conformational requirement.

Introduction

(+)-Nopinone (**1**) (Chart 1) is readily available in large quantities by ozonolysis of (−)-*β*-pinene. As part of synthetic study on natural products starting with **1**, we have demonstrated that 4,4-disubstituted nopinones **2a**[1] and their enantiomers **2b**[2] served as the versatile key intermediates for the enantioselective syntheses of elemane[1] and nardosinane sesquiterpenes[3] and lobane[4] and clerodane diterpenes.[5] In addition, (4*R*)-methylnopinone (**3**)[6] has been utilized as the key compound for the enantioselective approach to the steroid-D ring.[7] In all preparations of these alkyl-substituted nopinones from **1**, introduction of methyl and other alkyl groups at the C(4) position was achieved by use of the stereoselective conjugate addition of alkyl nucleophiles to an enone function, that is, the conjugate addition of (1*R*,5*R*)-(+)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (apoverbenone; **4a)** with lithium dimethylcuprate for the synthesis of **3** and that of (1*R*,5*R*)-(+)-4,6,6-trimethylbicyclo[3.1.1]hept-3-en-2-one (verbenone; **5a**) with alkyl Grignard reagents in the presence of copper(I) iodide for the synthesis of **2a**. On the other hand, compound **2b** was prepared from **4a** by a sequence of reactions: (i) 1,2-addition of **4a** with

Chart 1



(1) Kato, M.; Watanabe, M.; Vogler, B.; Awen, B. Z.; Masuda, Y.; Tooyama, Y.; Yoshikoshi, A. *J. Org. Chem.* **1991**, *56*, 7071. Kato, M.; Kido, F.; Watanabe, M.; Masuda, Y. Awen, B. Z. *J. Chem. Soc., Perkin Trans. 1.* **1993**, 2831.

(2) Watanabe, M.: Awen, B. Z.; Kato, M. *J. Org. Chem.* **1993**, *58*, 3923.

(3) Kato, M.; Watanabe, M.; Awen, B. Z. *J. Org. Chem.* **1993**, *58*, 5145.

(4) Kosugi, H.; Yamabe, O.; Kato, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 217.

(5) Kato, M.; Kosugi, H.; Kodaira, A.; Hagiwara, H. *Tetrahedron Lett.* **1997**, *38*, 6845.

(6) Hobbs, P. D.; Magnus, P. D. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2870. Konopelski, J. P.; Sundararaman, P.; Barth, G.; Djerassi, C. *J. Am. Chem. Soc.* **1980**, *102*, 2737.

(7) Kosugi, H.; Sugiura, J.; Kato, M. *J. Chem. Soc., Chem. Commun.* **1996**, 2743.

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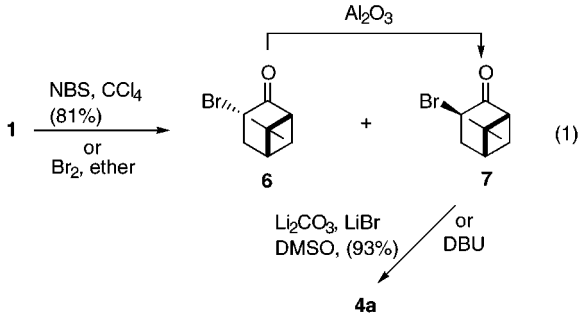
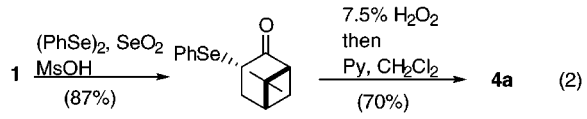
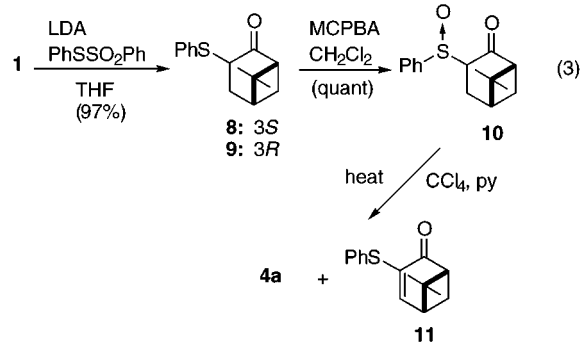
MeLi; (ii) oxidative rearrangement of the resulting allyl alcohol with pyridinium chlorochromate (PCC) with formation of (1*S*,5*S*)-(−)-verbenone **5b**; (iii) subsequent stereoselective conjugate addition with alkyl Grignard reagents to give **2b**.[2]

From the reasons mentioned above, compounds **4a** and **5a** attracted considerable attention as potentially useful synthetic intermediates, and substantial quantities of these were required.

The early preparation of **4a** consisted of bromination of **1** followed by dehydrobromination with bases. First, Grimshaw et al. employed NBS as a brominating reagent to obtain a mixture of (3*S*)- and (3*R*)-bromo ketones **6** and **7**, in which only the latter, **7**, derivable from **6** by epimerization on alumina, underwent dehydrobromination with Li_2CO_3 and LiBr to give **4a** in more than 70% overall yield (eq 1).[8,9] Then, Nishino et al. reported a







sequence of reactions, bromination with bromine followed by heating with DBU to give **4a**, without any description on the overall yield.[10] Recently, we have shown an alternate approach consisting of phenylselenenylation of **1** followed by selenoxide fragmentation (eq 2).[2,11] Although our synthesis provided **4a** in good overall yield (63%), it has its own disadvantages, such as the use of expensive and toxic selenenyl compounds. Herein, we wish to describe not only facile and efficient preparation of **4a** and **5a** from (+)-nopinone (**1**) by use of the sulfenylation−dehydrosulfenylation method[12] as the key unit reaction but also a few attractive findings obtained in the present study, that is, the relationship in thermodynamic stability between configuration of a phenylsulfinyl group at the C(3) position of nopinones and absolute configuration at the sulfur atom. In addition, reactivity resulting from absolute configuration at the sulfur center in the dehydrosulfenylation reaction of (3*R*,4*R*)-3-(phenylsulfinyl)-4-methylnopinones will be discussed.

Results and Discussion

Previously, one (M.K.) of the authors has pointed out that attempted syn elimination reaction of (3*R*)-3-(phenylsulfinyl)nopinone (**10**), prepared from the sulfide **9** by oxidation with MCPBA, proved to be unsuccessful, affording 3-(phenylthio)apoverbenone **(11)** as the major product (49% yield) along with a small amount of the expected **4a** (eq 3).[2] Now, we reinvestigated the phenylsulfenylation−dehydrosulfenylation method in some detail, since formation of the compound **11** could be accounted for by the Pummerer reaction of the sulfoxide **10** with some acidic contaminants, probably *m*-chlorobenzoic acid (MCBA) and/or MCPBA, which were carelessly left unremoved on purification of a mixture of oxidation products.

To avoid contamination of the sulfoxide with some acidic compounds mentioned above, we employed, in the present study, sodium periodate ($NaIO_4$) as an oxidant in place of MCPBA. The sulfides **8** and **9** were prepared from **1** in a 85:15 ratio and 97% yield according to our synthetic procedure established earlier.[1] Treatment of **8** with DBU in boiling benzene led to an equilibrium mixture from which the thermodynamically stable **9** was obtained in 63% yield.[1] The sulfide **9** was oxidized with $NaIO_4$ in aqueous methanol to give in 99% yield a mixture of two diastereomeric sulfoxides **10a**,**b** (a 36:64 ratio) which are readily separable by silica gel chromatography, while upon oxidation of the sulfide **8** under the same reaction conditions a mixture of the same sulfoxides **10a**,**b** (a 72:28 ratio) was obtained in 99% yield (Scheme 1). Table 1 shows the ^{1}H NMR data for the compounds obtained in the present study. Stereochemistry of **10a**,**b** was assigned by their ^{1}H NMR data and NOE correlations, in which the NOEs in **10a** indicate stereochemistry of the C(3)-phenylsulfinyl substituent as *S*, while those in **10b** indicate that as *R*. In addition, as seen in Table 1, the chemical shifts of the C(7)−Hb of **10a** and C(6)−Me(a) of **10b** showed a deshielding effect (0.36 for the former and 0.14 ppm for the latter) by the proximate phenylsulfinyl group, as revealed when compared with those of **10b** and **10a**, respectively. The findings support the above configurational assignment.

Next, assignment of the absolute configuration at the sulfur atom in **10a**,**b** was carried out by the synthesis of their homologues, whose absolute configuration are well-defined, followed by comparison of their ^{1}H NMR spectra with those of **10a**,**b**. The nucleophilic substitution reaction of (−)-(*S*)-menthyl *p*-toluenesulfinate (**12a**)[13] with **1**

(8) Grimshaw, J.; Grimshaw, J. T.; Juneja, H. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 50.

(9) In our repeated runs according to the reported procedures, procurement of the bromo ketone **7** was not necessarily reproducible, so that the reproducibility in the overall yield from **1** to **4a** appeared to be poor.

(10) Nishino, C.; Takayanagi, H. *Agric. Biol. Chem.* **1979**, *43*, 1957.

(11) Related synthesis: Siegel, C.; Gordon, D. H.; Vliss, D. B.; Handrick, G. R. Dalzell, H. C.; Razdan, R. K. *J. Org. Chem.* **1991**, *56*, 6865.

(12) Trost, B. M.; Salzmann, T. N. *J. Am. Chem. Soc.* **1973**, *95*, 6840.

(13) Solladie, G. *Synthesis* **1981**, 185.

Scheme 1

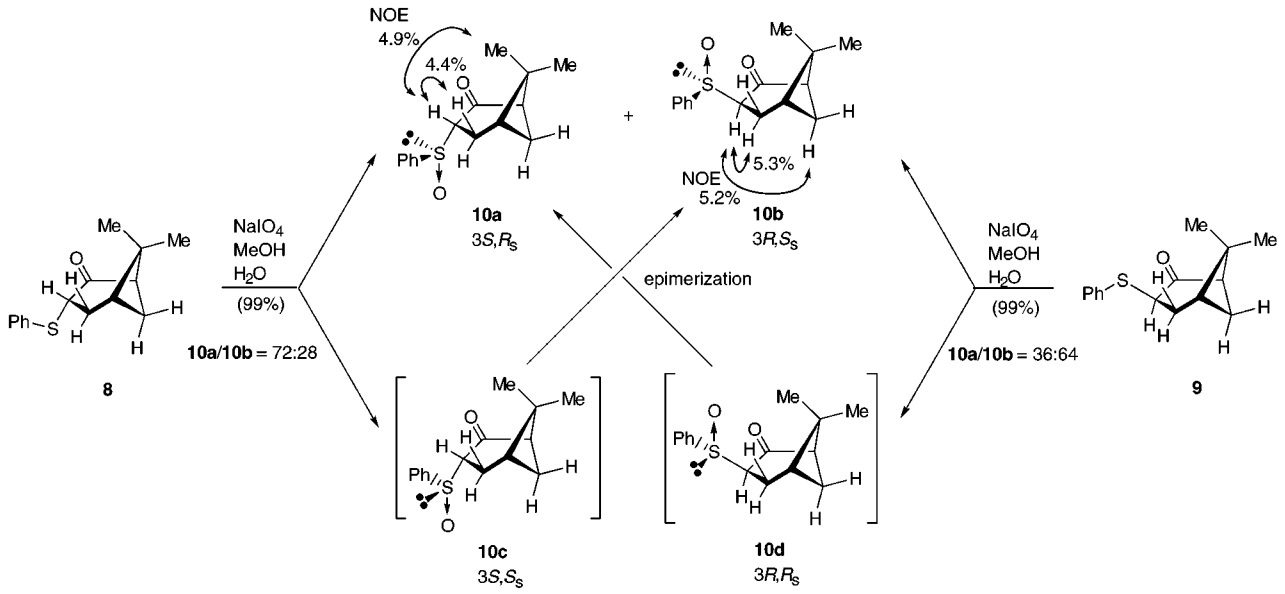


Table 1. ^{1}**H NMR (400 MHz, $CDCl_3$) Data (δ, Multiplicity, and *J* in Hz) of 8, 9, 10a,b, 13a,b, 17, 18a,b, and 19a,b**[a]

	1-H (1H)	3-H (1H)	4-Hb (1H)	4-Ha (1H)	5-H (1H)	7-Ha (1H)	7-Hb (1H)	4-Me (3H)	6-Me(a) (3H)	6-Me(b) (3H)
8	2.68	3.74	2.23	2.14	2.5−2.60		1.88		0.85	1.36
	t	dd	m	ddd	(2H, m)		d		s	s
	5.4	9.5, 2.2		14.5, 3.6 2.4			10.7			
9	2.75	4.18	1.95	2.56	2.25	2.51	1.72		0.82	1.34
	t	dd	ddd	ddd	dddd	ddd	d		s	s
	5,4	10.9, 8,3	13.8, 10.9, 1.5	13.8, 5.5, 3.4	5.4, 5.4, 3.4, 1.5	10.7, 5.4, 5.4	10.7			
10a	2.67	3.43	2.36	1.66	2.20	2.56	1.91		0.85	1.35
	t	dd	dt	ddt	ddt	ddt	d		s	s
	5.6	10.5, 4.4	14.4, 3.6	14.4, 10.5, 2.2	5.6, 3.9, 2.2	11.0, 2.2, 5.6	11.0			
10b	2.74	3.54	1.63	2.49−2.55		2.30	1.55		0.99	1.33
	t	dd	ddd	(2H, m)		dt	d		s	s
	5.1	10.5, 8.5	13.9, 10.5, 4.4			11.0, 5.1	11.0			
17	2.73	3.37		2.44	2.05	2.15	1.70	1.23	0.70	1.34
	t	d		ddq	ddd	ddd	d	d	s	s
	5.4	8.1		8.1, 1.5, 6.6	5.4, 5.1, 1.5	11.0, 5.4, 5.1	11.0	6.6		
18a	2.71	3.27		2.90	2.03	2.46	1.59	0.70	1.02	1.34
	t	d		ddq	ddd	ddd	d	d	s	s
	5.1	6.8		6.9, 1.9, 6.6	5.1, 5.0, 1.9	11.2, 5.1, 5.0	11.2	6.6		
18b	2.57	3.49		2.53	2.00	2.42	1.63	1.12	0.65	1.27
	t	d		ddq	td	ddd	d	d	s	s
	5.4	8.0		8.0, 1.9, 6.6	5.4, 1.9	11.0, 5.4, 5.1	11.0	6.6		
13a	2.66	3.39	2.36	1.67	2.20	2.55	1.92		0.84	1.35
	t	dd	dt	ddt	ddt	ddt	d		s	s
	5.6	10.3, 3.9	14.6, 3.9	14.6, 10.3, 2.2	5.6, 3.9, 2.2	11.2, 2.2, 5.6	11.2			
13b	2.73	3.52	1.64	2.49−2.56		2.30	1.54		0.99	1.33
	t	dd	ddd	(2H, m)		dt	d		s	s
	5.2	10.5, 8.3	13.9, 10.5, 4.4			11.0, 5.1	11.0			
19a	2.57	3.46		2.49	1.98	2.42	1.62	1.10	0.65	1.27
	t	d		ddq	td	ddd	d	d	s	s
	5.3	7.6		8.0, 1.9, 6.6	5.4, 1.9	11.0, 5.4, 5.1	11.0	6.6		
19b	2.69	3.25		2.89	2.02	2.46	1.58	0.73	1.02	1.34
	t	d		ddq	ddd	ddd	d	d	s	s
	5.2	8.0		8.0, 2.0, 6.6	5.3, 5.1, 2.0	11.1, 5.3, 5.1	11.1	6.6		

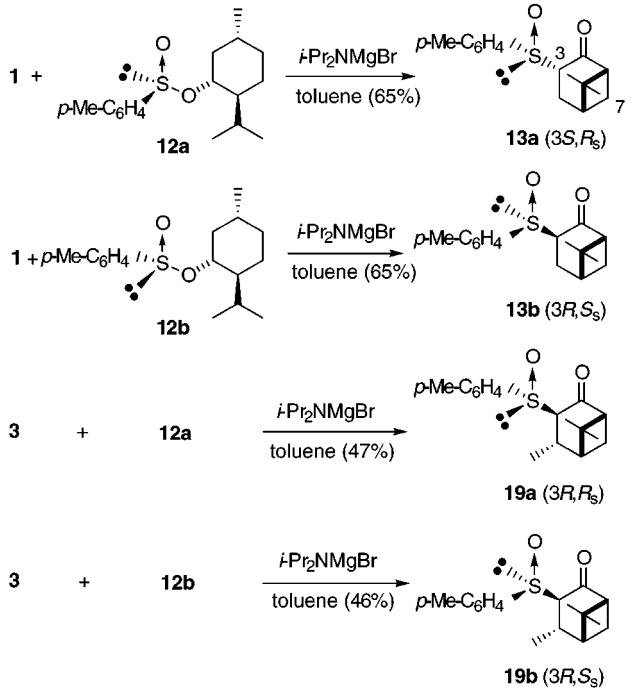
[a] Others: **8**, 7.24−7.37 (3H, m), 7.50−7.55 (2H, m); **9**, 7.22−7.32 (3H, m), 7.47−7.55 (2H, m); **10a**, 7.45−7.56 (3H, m), 7.62−7.65 (2H, m); **10b**, 7.42−7.55 (3H, m), 7.61−7.65 (2H, m); **17**, 7.21−7.30 (3H, m), 7.54−7.50 (2H, m); **18a**, 7.46−7.55 (3H, m), 7.74−7.78 (2H, m); **18b**, 7.46−7.54 (3H, m), 7.75−7.78 (2H, m); **13a**, 2.40 (3H, s), 7.33 (2H, d, 8.6[b]), 7.52 (2H, d, 8.3[b]); **13b**, 2.42 (3H, s), 7.31 (2H, d, 8.1[b]), 7.52 (2H, d, 8.0[b]); **19a**, 2.41 (3H, s); 7.31 (2H, d,[b] 8.0), 7.65 (2H, d,[b] 8.3); **19b**: 2.42 (3H, s), 7.32 (2H, d,[b] 8.0), 7.64 (2H, d,[b] 8.2). [b] With fine splittings.

in the presence of (diisopropylamino)magnesium bromide[14] provided in 65% yield (3*S*,R_s)-*p*-tolyl sulfoxide (**13a**), whose R_f value on TLC agreed very closely with that of **10a** (Scheme 2).[15] Similarly, the reaction of (+)-(*R*)-menthyl *p*-toluenesulfinate (**12b**)[13] with the magnesium salt of **1** gave in 65% yield (3*R*,S_s)-**13b**,[16] whose R_f value agreed very closely with that of **10b**. As seen in

(14) Carreno, M. C.; Garcia Ruano, J. L.; Rubio, A. *Tetrahedron Lett.* **1987**, *28*, 4861.

(15) Attempted substitution reaction using LDA in place of (diisopropylamino)magnesium bromide proved to be unsuccessful, because the reaction was sluggish and a large portion of **1** was recovered.

Scheme 2



Scheme 3

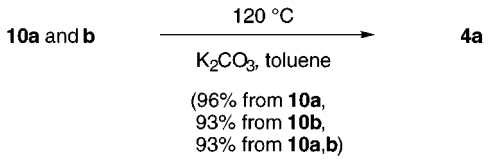
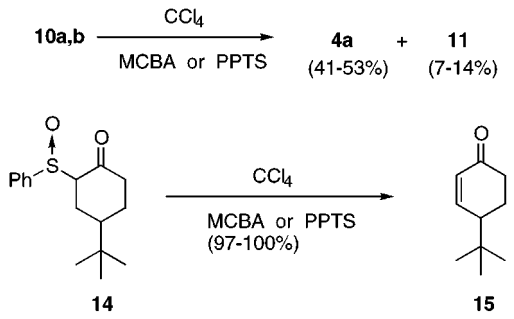


Table 1, the ^{1}H NMR spectra of **13a**,**b** are very closely similar in chemical shifts and coupling patterns to those of **10a**,**b**, respectively, except for the aromatic part, respectively, suggesting configuration at the sulfur center in **10a,b** being *R* and *S*, respectively. The above findings indicate that the initial products **10c**,**d**, which would be produced by $NaIO_4$ oxidation of **8** and **9**, respectively, are thermodynamically unstable to lead readily to **10b** and **10a**, respectively, by concomitant epimerization, during the time the oxidation reaction proceeds.

Each of the sulfoxides **10a**,**b**, obtained by purification with silica gel chromatography, was subjected to the syn elimination reaction under heating at 120 °C in toluene in the presence of K_2CO_3 (5 equiv), thus giving **4a** as the sole product in 96 and 93% yields from **10a,b**, respectively (Scheme 3).[17] Finally, from the standpoint of the practical preparation, a mixture of **10a**,**b** was heated to provide **4a** in 93% yield. This yield is equivalent to 89% overall yield on starting from **1**. In the syn elimination reaction, it was proved that when the sulfoxide is employed without purification, the reaction shows the marked tendency to produce a mixture of **4a** and the Pummerer reaction product **11**. Then, the elimination reaction of the mixture of **10a**,**b** was carried out in boiling CCl_4 in the presence of MCBA (0.1 equiv) and PPTS (0.1 equiv) as the representative of weak organic acids, giving **4a** and **11** in 41 and 7% and 53 and 14% yields, respectively (Scheme 4). Contrary to these observations, it is worth mentioning that, upon heating 2-(phenylsulfinyl)-4-*tert*-butylcyclohexanone (**14**) under the same reaction conditions, 4-*tert*-butylcyclohex-2-en-1-one (**15**) was produced in nearly quantitative yield, and no Pummerer reaction product could be detectable despite careful inspection of the reaction mixture.

Scheme 4



As a consequence of observations mentioned above, while we have developed the efficient preparation of **4a** from **1** using the sulfenylation−dehydrosulfenylation method, it was proved that transformation of sulfoxides **10** into apoverbenone (**4a**) is affected by the presence of acidic contaminants in the reaction media, probably by the reason described in our preceding report;[2] that is, the bridges, especially, the *gem*-dimethyl bridge in **10**, would somewhat hinder formation of the cyclic transition state necessary for the syn elimination between a phenylsulfinyl function and a *β*-hydrogen atom, and thus, the competing Pummerer reaction proceeds to give **11**, when acidic contaminants are present.

It is well-known that (−)-*β*-pinene, a synthetic precursor of (−)-nopinone (mirror image of **1**), is scarcely found in nature.[18] However, a 5-step chemical transformation of (+)-α-pinene into (−)-nopinone in more than 70% overall yield has been accomplished by Lavallee et al.[19] This fact implies that (−)-apoverbenone (**4b**) could be obtainable in more than 60% overall yield on application of the present sequence of reactions to (−)-nopinone as the starting material.

Verbenones **5a**,**b** are natural products and both available commercially. However, these compounds with high optical purity are high in price. For the synthesis of (−)-verbenone (**5b**), a few chemical transformations from (−)-α-pinene have been reported,[18] and we have recently shown the efficient 2 step chemical transformation of **4a** into **5b**, as aforementioned.[2] Then, to synthesize its enantiomer (+)-**5a**, the present sulfenylation−dehydrosulfenylation method was applied to (4*R*)-methylnopinone (**3**). Phenylsulfenylation of the lithium enolate of **3** with *S*-phenyl benzenethiosulfonate[20] provided, in 93% combined yield, sulfides **16** and **17** as an inseparable mixture (a 4:6 ratio from the ^{1}H NMR analysis) (Scheme 5). Treatment of the mixture **16** and **17** with DBU in boiling benzene resulted in smooth epimerization of **16**, because of a steric interaction between the phenylsulfenyl and

(16) The products **13b** and **19a,b** are thermodynamically stable compounds, and their production is attributable to concomitant epimerization of a *p*-tolylsulfinyl group in the initial products, (3*S*,S_s)-, (3*S*,R_s)-, and (3S, S_s)-*p*-tolyl sulfoxides, for the formation of **13b**, **19a**, and **19b**, respectively.

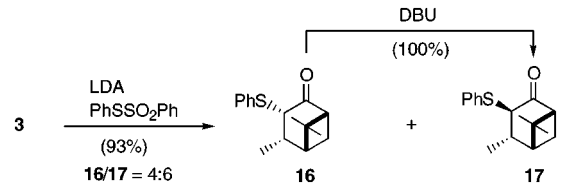
(17) Attempted syn elimination under the mild reaction conditions; heating in CCl_4 containing pyridine proved to be impractical, because the reaction was sluggish.

(18) Thomas, A. F.; Bessiere, Y. *The Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wieley-Interscience: New York, 1988; Vol. 7, p 275. Banthorpe, D. V.; Ekundayo, O.; Njar, V. C. O. *Phytochemistry* **1984**, *23*, 291.

(19) Lavallee, P.; Gouthillier, G. *J. Org. Chem.* **1986**, *51*, 1362.

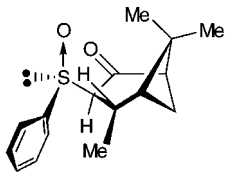
(20) Trost, B. M.; Massiot, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 4405.

Scheme 5



C(4)-methyl groups in the close neighborhood, to give the thermodynamically stable **17** as the sole product in nearly quantitative yield. On oxidation with $NaIO_4$, the compound **17** provided sulfoxides **18a**,**b** (a 68:32 ratio) as a separable diastereomeric mixture in 98% combined yield (Scheme 6). Stereochemical assignments of the phenylsulfinyl group in **18a**,**b** were unambiguously established by their ^{1}H NMR data (Table 1) and NOE correlations as shown in the structures of **18a**,**b**. With respect to configuration at the sulfur center, (3*R*,R_s)-**19a** and (3*R*,S_s)-**19b** were prepared from the nucleophilic substitution reaction of (−)-(*S*)- and (+)−(*R*)-menthyl *p*-toluenesulfinate **12a,b**[13] with **3**, respectively (Scheme 2).[16] As seen in Table 1, a marked spectral resemblance between **18b** and **19a** and **18a** and **19b** except for the aromatic part indicates the absolute configuration at the sulfur atom of **18a**,**b** as being *S* and *R*, respectively. It is worth mentioning that oxidation of a mixture **16** and **17** afforded a mixture of the same sulfoxides **18a**,**b** (a 82:18 ratio) in nearly quantitative yield, and no other configurational isomers were detected by careful inspection of the reaction mixture. The findings suggest that the initial products of **16**, (3*S*,R_s)-**18c** and (3*S*,S_s)-**18d**, easily isomerize to the stable **18b** and **18a**, respectively, while the oxidation reaction proceeds.

The chemical shift (δ 0.70) of the C(4)-Me of **18a** shows a considerable upfield shift (ca. 0.4 ppm) by the shielding effect of a benzene ring, in comparison with that of **18b** (δ 1.12). In addition, the C(4)-H(a) and the C(6)-Me(a) protons in **18b** occur at δ 2.53 and 0.65, respectively, while those in **18a** occur at δ 2.90 and 1.02, respectively, probably because of the deshielding effect due to the proximate phenylsulfinyl function. Judging from the above findings as well as the repulsive behavior between the polar carbonyl and sulfinyl functions, conformation of the major product **18a** was surmised as depicted in **20**.



20

It is of interest to note that, as shown in Scheme 7, upon heating **18** under the same reaction conditions as those for the conversion from **10** to **4a**, phenylsulfenic acid elimination reaction of the major diastereomer **18a** proceeded smoothly to give **5a** in 76% yield, whereas that of the minor **18b** was not only sluggish but also somewhat affected by heat to give, after 11 h, a mixture of a few decomposed products[21] along with the desired **5a** (17% yield). Consequently, heating a mixture of **18a**,**b**, which was carried out from the preparative point of view, resulted in procurement of **5a** only in 53% yield. After considerable experimentation, the reaction conditions with heating at 95 °C in toluene in the presence of K_2CO_3 (12 equiv) for 2 days was employed as optimum, thus providing **5a** in 92% from **18a**, 40% from **18b**, and 82% yields from a mixture of **18a**,**b**. The last yield is equivalent to 61% overall yield on starting from **1**.

In conclusion, using the sulfenylation−dehydrosulfenylation method, we have developed the convenient preparation of (+)-apoverbenone (**4a**) and (+)-verbenone (**5a)** from (+)-nopinone (**1)** as a common starting material**.** As this methodology could be applicable to preparation of their enantiomers (−)-**4a** and (−)-**5a** on starting with (−)-nopinone, the present synthetic approach may be practically useful for a laboratory scale preparation of **4** and **5** in optically active forms on account of its simplicity of operation, safety in handling, and synthetically satisfactory overall yield.

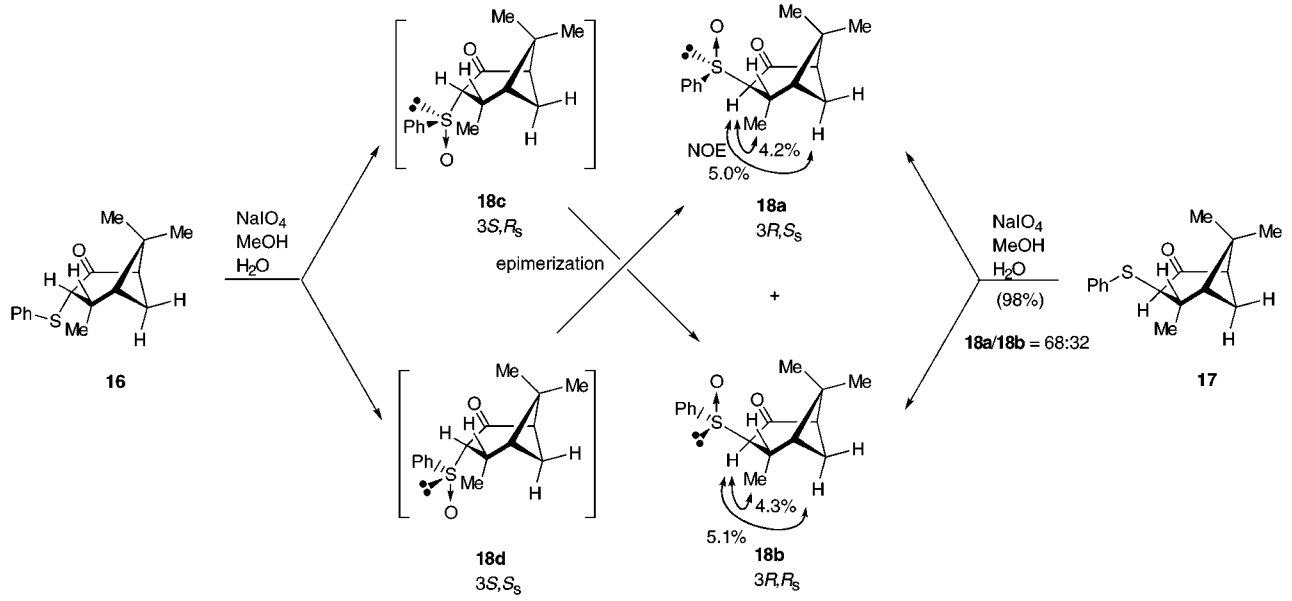
A few interesting chemical behaviors characteristic of the compounds possessing a 6,6-dimethylbicyclo[3.1.1]-heptane skeleton were found in this study. With respect to configuration of the substituent in 3-substituted nopinones, it is known that methylation,[22] bromination,[9] and phenylsulfenylation[1] of **1** give exclusively the thermodynamically less stable trans-substituted products as the initial product, which easily epimerize to the stable cis-isomers with bases or acids.[23] On the contrary, phenylselenenylation provides a trans-substituted product as a stable form.[2] It is worth mentioning that, in 3-(phenylsulfinyl)nopinones, absolute configuration at the sulfur center controls thermodynamic stability of isomers; that is, the stable trans-isomer possesses a R_s-phenylsulfinyl group, and the stable cis-isomer possesses a S_s-phenylsulfinyl group, as seen in the oxidation reaction of **8** and **9** (Scheme 1) and the nucleophilic substitution reactions of **12a**,**b** with **1** (Scheme 2). On the other hand, in the case of (4*R*)-4-methyl-3-(phenylsulfinyl)nopinones, cis-isomers are thermodynamically stable, irrelevant of the absolute configuration at the sulfur atom, as seen in Schemes 2 and 6, probably because steric hindrance between the phenylsulfinyl and methyl groups stimulates a trans-isomer to a cis-isomer in isomerization. In the phenylsulfenic acid elimination from the sulfoxids, the bridges, especially the *gem*-dimethyl bridge, in 3-(phenylsulfinyl)nopinones have a tendency to hinder formation of the cyclic transition state between a phenylsulfinyl function and a β-hydrogen atom, thus producing the Pummerer reaction product **11** as a byproduct when acidic contaminants are present, as seen in transformation of **10** into **4a** (Scheme 4). In addition, the syn elimination reactions of (4*R*)-4-methyl-3-(phenylsulfinyl)-nopinones are affected by absolute configuration at the sulfur center, as seen in heating of **18a**,**b** at 120 °C (Scheme 7); that is, the former **18a** provided **5a** in high yield, whereas the latter **18b** gave mainly thermal decomposition products which may be produced via the phenylsulfinyl radical process, probably because of instability of **18b** to heat as well as the conformational requirement.

(21) Among the products, thermal decomposition products **3**, **4a**, **17**, and **18a** were identified by the spectral comparison with authentic samples.

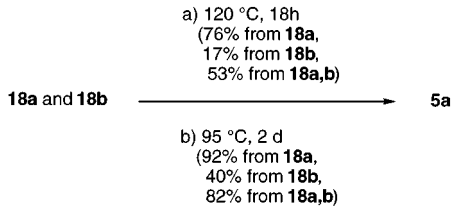
(22) Konopelski, J. P.; Djerassi, C. *J. Org. Chem*. **1980**, *45*, 2297.

(23) The terms trans and cis refer to whether the substituent points away from (trans) or toward (cis) the *gem*-dimethyl bridge.

Scheme 6



Scheme 7



Experimental Section

General Methods. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz. All reactions were carried out under dry N_2 or Ar atmosphere. Na_2SO_4 was used for drying of extracts. Column chromatography was performed on 70−230 mesh silica gel (Merck). Medium-pressure chromatography (MPLC) utilized a 22 ϕ × 300 mm silica gel (10 μm) column. Solvent for elution are shown in parentheses. Ether refers to diethyl ether.

Preparation of (1*R*,3*S*,5*R*)-6,6-Dimethyl-3-(phenylthio)bicyclo[3.1.1]heptan-2-one (8) and (1*R*,3*R*,5*R*)-6,6-Dimethyl-3-(phenylthio)bicyclo[3.1.1]heptan-2-one (9). The compounds **8** and **9** were prepared from **1**[24] in 82 and 14% yields, respectively, according to our synthetic procedure established earlier.[1] Treatment of **8** with DBU in boiling benzene provided an equilibrium mixture of **8** and **9** from which **9** was isolated in 63% yield by silica gel chromatography.

(1*R*,3*S*,5*R*,*R*$_s$)- and (1*R*,3*R*,5*R*,*S*$_s$)-6,6-Dimethyl-3-(phenylsulfoxy)bicyclo[3.1.1]heptan-2-one (10a,b). A mixture of **8** (1.00 g, 4.06 mmol), $NaIO_4$ (1.30 g, 6.09 mmol), and 50% aqueous methanol (48 mL) was stirred at 0 °C for 1 d and extracted with CH_2Cl_2. The combined extracts were washed successively with water and brine and dried. Concentration of the extract left a crystalline residue which was chromatographed on silica gel (AcOEt−hexane, 1:5) to give **10a** (756 mg, 71%) and **10b** (294 mg, 28%).

10a: crystals; mp 97 °C; $[\alpha]^{15}_D$ = +421.3 (*c* 0.56, $CHCl_3$); IR (KBr) 1709, 1086, 1048, 985, 749, 696 cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_2S$: C, 68.67; H, 6.91; S, 12.22. Found: C,68.27; H,7.02; S, 12.16.

10b: crystals; mp 126−127 °C; $[\alpha]^{15}_D$ = −315.3 (*c* 0.92, $CHCl_3$); IR (KBr) 1711, 1085, 1033, 760, 697 cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_2S$: C, 68.67; H, 6.91; S, 12.22. Found: C, 68.57; H, 6.84;, S, 12.42.

Similarly, the compound **9** (260 mg, 1.06 mmol) was treated with $NaIO_4$ (338 mg, 1.58 mmol) in 50% methanol (12 mL) to give **10a** (99 mg, 36%) and **10b** (175 mg, 63%).

(+)-Apoverbenone (4a). Method 1. From 10a,b. A suspension of **10a** (5.0 g, 19.06 mmol), K_2CO_3 (13.2 g, 95.5 mmol), and toluene (70 mL) was heated at 120 °C with stirring for 4 h. After being cooled to room temperature, the reaction mixture was charged on a silica gel column (SiO_2, 300 g).[25] Toluene was eluted off by use of hexane as an eluent, and then the product was eluted with AcOEt−hexane (1:6), giving **4a** (2.50 g, 96%), $[\alpha]^{15}_D$ = +288.4 (*c* 0.84, $CHCl_3$). IR and ^{1}H NMR spectra of **4a** were identical with those of the authentic sample.[2]

Similarly, a mixture of **10b** (4.80 g, 18.29 mmol) and K_2CO_3 (12.65 g, 91.5 mmol) was heated in toluene (70 mL) to give **4a** (2.31 g, 93%).

Method 2. From a Mixture of 10a,b. A mixture (a 36:64 ratio) of **10a**,**b** (10.5 g, 40 mmol), K_2CO_3 (17.29 g, 200 mmol), and toluene (100 mL) was heated at 120 °C with stirring for 4 h. Aqueous workup followed by chromatography of a residue on silica gel gave **4a** (5.09 g, 93%).

(1*R*,3*S*,4*S*,5*R*)-4,6,6-Trimethyl-3-(phenylthio)bicyclo[3.1.1]heptan-2-one (16) and (1*R*,3*R*,4*S*,5*R*)-4,6,6-Trimethyl-3-(phenylthio)bicyclo[3.1.1]heptan-2-one (17). According to our synthetic procedure established earlier[6] with a slight modification, a solution of 1.05 M MeLi in ether (16.8 mL, 17.64 mmol) was added dropwise at 0 °C to a stirred mixture of copper(I) iodide (1.68 g, 8.82 mmol) in ether (20 mL). Stirring was continued for an additional 1 h, after which the reaction mixture was treated with a solution of **4a** (1.04 g, 7.67 mmol) in ether (5 mL). The reaction mixture was stirred for an additional 2 h, quenched with aqueous NH_4-Cl, and extracted with ether. The combined extracts were washed successively with water and brine and dried. Evaporation of the extract followed by distillation of an oily residue by use of the Kugelrohr apparatus (140 °C, 19 Torr) gave (1*R*,4*R*,5*R*)-4,6,6-trimethylbicyclo[3.1.1]heptan-2-one **(3)** (1.07 g, 92%), $[\alpha]^{15}_D$ = +50.1 (*c* 0.99, $CHCl_3$). IR and ^{1}H NMR spectra of **3** were identical with those of the authentic sample.[7]

To a stirred solution of diisopropylamine (0.92 mL, 5.96 mmol) in THF (5 mL) was added dropwise at 0 °C a solution of 1.66 M BuLi in hexane (3.6 mL, 5.98 mmol). After 30 min,

(24) In the present study, (+)-nopinone, $[\alpha]^{15}_D$ = +34.0 (*c* 1.10, $CHCl_3$) and 98% ee, was used.

(25) As verbenone is volatile, evaporative removal of toluene from the extract was avoided in the purification step.

a solution of **3** (750 mg, 4.97 mmol) in THF (5 mL) was added dropwise at − 78 °C, and stirring was continued for an additional 1 h. To the reaction mixture was added a solution of *S*-phenyl benzenethiosulfonate[20] (1.51 g, 5.47 mmol) in THF (5 mL), and stirring was continued for an additional 6 h, during which the reaction temperature rose slowly to room temperature. The reaction mixture was quenched with aqueous NH_4Cl and extracted with CH_2Cl_2, and the combined extracts were washed successively with water and brine and dried. Evaporation of the extract followed by purification of a residue with silica gel chromatography (AcOEt−hexane, 1: 10) gave an oily mixture of **16** and **17** (1.19 g, 93%, a 4:6 ratio), ^{1}H NMR ($CDCl_3$): δ 0.70 (s, 1.8H) and 0.84 (s, 1.2H), 1.23 (s, 1.8H), 1.26 (s, 1.2H), 1.34 (s, 1.8H), 1.36 (s, 1.2H), 1.70 (d, J = 11.0 Hz, 0.6H), 1.87 (d, J = 11.0 Hz, 0.4H), 1.93 (dt, J = 11.0, 5.4 Hz, 0.4H), 2.05 (ddd, J = 5.4, 5.1, 1.5 Hz, 0.6H), 2.15 (ddd, J = 11.0, 5.4, 5.1 Hz, 0.6H), 2.42−2.48 (m, 1H), 2.66−2.75 (m, 1.4H), 3.37 (d, J = 8.1 Hz, 0.6H), 3.73 (d, J = 8.6 Hz, 0.4H), 7.21−7.33 (m, 3H), 7.53−7.56 (m, 2H).

A mixture of **16** and **17** (520 mg, 2.00 mmol) was dissolved in benzene (6 mL) containing DBU (321 mg, 2.0 mmol), and the reaction mixture was heated at 85 °C for 2 h. Aqueous workup followed by chromatography of a residue on silica gel (AcOEt−hexane, 1: 10) gave **17** (513 mg, 99%) as an oil: $[\alpha]^{15}_D$ = +220.5 (*c* 0.41, $CHCl_3$); IR (film) 1716, 1590, 1198, 1160, 1026, 746, 691 cm^{-1}. Anal. Calcd for $C_{16}H_{20}OS$: C, 73.82; H, 7.74; S, 12.30. Found: C, 73.54; H, 7.61; S, 12.44.

(1*R*,3*R*,4*S*,5*R*,*S*$_s$)- and (1*R*,3*R*,4*S*,5*R*,*R*$_s$)-4,6,6-Trimethyl-3-(phenylsulfoxy)bicyclo[3.1.1]heptan-2-one (18a,b). Method 1. From 17. A mixture of **17** (4.20 g, 16.10 mmol) and $NaIO_4$ (5.18 g, 24.15 mmol) in 50% aqueous methanol (52 mL) was stirred at 0 °C for 1 d and extracted with CH_2Cl_2. The combined extracts were washed successively with water and brine and dried. Concentration of the extract followed by chromatography of a residue on silica gel (AcOEt−hexane, 1:3) gave **18a** (2.97 g, 67%) and **18b** (1.40 g, 31%).

18a: crystals, mp 131−133 °C; $[\alpha]^{15}_D$ = −188.7 (*c* 0.48, $CHCl_3$); IR (KBr) 1711, 1086, 1030, 996, 744, 698 cm^{-1}. Anal. Calcd for $C_{16}H_{20}OS$: C, 69.54; H, 7.30; S, 11.58. Found: C, 69.53; H, 7.24; S, 11.30.

18b: crystals, mp 106−107 °C; $[\alpha]^{15}_D$ = +180.2 (*c* 0.57, $CHCl_3$); IR (KBr) 1706, 1080, 1046, 1034, 990, 762, 696 cm^{-1}. Anal. Calcd for $C_{16}H_{20}OS$: C, 69.54; H, 7.30; S, 11.58. Found: C, 69.43; H, 7.20; S, 11.38.

Method 2. From a Mixture of 16 and 17. Similarly, a mixture (a 4:6 ratio) of **16** and **17** (1.04 g, 4.0 mmol) was treated with $NaIO_4$ (1.28 g, 6.0 mmol) in 50% aqueous methanol (12 mL) to give **18a** (914 mg, 85%) and **18b** (131 mg, 12%).

(+)-Verbenone (5a). Method 1. Heating at 120 °C. A mixture of **18a** (51 mg, 0.18 mmol), K_2CO_3 (1.28 g, 0.90 mmol), and toluene (10 mL) was heated with stirring at 130 °C for 18 h. After cooling, the reaction mixture was chromatographed on silica gel (AcOEt−hexane, 1:9) according to the manner described for preparation of **4a** from **10a**, giving **5a** (20 mg, 76%), $[\alpha]^{15}_D$ = +257.4 (*c* 0.47, $CHCl_3$). IR and ^{1}H NMR spectra of **5a** were identical with those of the authentic sample.

Similarly, heating a mixture of **18b** (400 mg, 1.45 mmol), K_2CO_3 (1.0 mg, 7.25 mmol), and toluene (10 mL) gave **5a** (38 mg, 17%).

Similarly, heating a mixture (a 68:32 ratio) of **18a**,**b** (250 mg, 0.91 mmol) with K_2CO_3 (413 mg, 4.55 mmol), in toluene (10 mL) gave **5a** (59 mg, 53%).

Method 2. Heating at 95 °C. A mixture of **18a** (365 mg, 1.32 mmol), K_2CO_3 (2.19 g, 15.8 mmol), and toluene (27 mL) was heated at 95 °C with stirring for 2 d and cooled to room temperature. Aqueous workup followed by chromatography of a residue on silica gel (AcOEt−hexane, 1:9) gave **5a** (155 mg, 78%, 92% based on consumed **18a**) and **18a** (55 mg).

Similarly, heating a mixture of **18b** (226 mg, 0.82 mmol), K_2CO_3 (1.357 g, 9.82 mmol) and toluene (22 mL) gave **5a** (47 mg, 38%, 40% based on consumed **18b**) and **18b**(10 mg).

Similarly, heating a mixture (a 68:32 ratio) of **18a,b** (153 mg, 0.55 mmol) with K_2CO_3 (918 mg, 6.64 mmol), in toluene (15 mL) gave **5a** (61 mg, 72%, 82% based on consumed **18a,b**) and **18a,b** (16 mg).

Heating of 10a,b in the Presence of MCBA and PPTS. A solution of **10a**,**b** (290 mg, 1.11 mmol) and MCBA (17 mg, 0.11 mmol) in CCl_4 (7 mL) was gently refluxed for 7 h. After being cooled to room temperature, the reaction mixture was filtered through a short silica gel column (AcOEt). Concentration of the filtrate left an oily residue which was purified by MPLC (AcOEt−hexane, 1:4) to give **4a** (63 mg, 41%) and **11** (19 mg, 7%).

Similarly, heating a solution of **10a**,**b** (146 mg, 0.56 mmol) and PPTS (14 mg, 0.06 mmol) in CCl_4 (6 mL) gave **4a** (41 mg, 53%) and **11** (19 mg, 14%).

Heating of 2-(Phenylsulfoxy)-4-*tert*-butylcyclohexanone (14) in the Presence of MCBA and PPTS. The compound **14** was prepared from 4-*tert*-butylcyclohexanone according to the reported procedures.[8] A solution of **14** (584 mg, 2.10 mmol) and MCBA (33 mg, 0.21 mmol) in CCl_4 (10 mL) was gently refluxed for 1 h and cooled to room temperature. The reaction mixture was washed successively with water and brine and dried. Concentration followed by chromatography of a residue on silica gel (benzene−ether, 10:1) gave **15** (309 mg, 97%). IR and ^{1}H NMR spectra of **15** were identical with those of the authentic sample.

Similarly, heating of a solution of **14** (216 mg, 0.78 mmol) and PPTS (20 mg, 0.08 mmol) in CCl_4 (10 mL) gave **15** (119 mg, quantitative).

(1*R*,3*S*,5*R*,*R*$_s$)-6,6-Dimethyl- and (1*R*,3*R*,4*S*,5*R*,*R*$_s$)-4,6,6-Trimethyl-3-(*p*-tolylsulfoxy)bicyclo[3.1.1]heptan-2-one (13a and 19a). To a stirred 2.35 M solution of ethylmagnesium bromide in ether (1.7 mL, 4.0 mmol) was added diisopropylamine (0.56 mL, 4.0 mmol). After evaporation of ether by N_2 steam, toluene (10 mL) was added. To the resulting suspension, a solution of **1** (415 mg, 3.0 mmol) in toluene (3 mL) was added dropwise at 0 °C, and stirring was continued for an additional 1.5 h. A solution of (*S*)-menthyl-*p*-toluenesufinate **12a**[13] (877 mg, 3.0 mmol) in toluene (3 mL) was added to the reaction mixture, and stirring was continued for an additional 15 h, during which the reaction temperature rose slowly to room temperature. The reaction was quenched by addition of aqueous NH_4Cl. The organic layer was separated, washed successively with water and brine, and dried. Concentration followed by chromatography of a residue on silica gel (AcOEt−hexane, 1:10) gave **13a** (543 mg, 65%) as crystals: mp 125−126 °C; $[\alpha]^{16}_D$ = +435.0 (*c* 1.12, $CHCl_3$); IR (KBr) 1713, 1594, 1039, 818 cm^{-1}. Anal. Calcd for $C_{16}H_{20}O_2S$: C, 69.53; H, 7.29; S, 11.60. Found: C, 69.13; H, 7.14; S, 11.36.

Similarly, treatment of **3** (457 mmg, 3.0 mmol) with (diisopropylamino)magnesium bromide, prepared from ethylmagnesium bromide (1.7 mL, 4.0 mmol) and diisopropylamine (0.56 mL, 4.0 mmol) in toluene (10 mL), followed by addition of a solution of **12a** (877 mg, 3.0 mmol) in toluene (3 mL) gave **19a** (407 mg, 47%) as crystals: mp 118 °C; $[\alpha]^{16}_D$ = +186.8 (*c* 1.13, $CHCl_3$); IR (KBr) 1706, 1597, 1048, 825 cm^{-1}. Anal. Calcd for $C_{17}H_{22}O_2S$: C, 70.31; H, 7.64; S, 11.04. Found: C, 70.22; H, 7.50; S, 10.92.

(1*R*,3*R*,5*R*,*S*$_s$)-6,6-Dimethyl- and (1*R*,3*R*,4*S*,5*R*,*S*$_s$)-4,6,6-Trimethyl-3-(*p*-tolylsulfoxy)bicyclo[3.1.1]heptan-2-one (13b and 19b). According to the procedure for the synthesis of **13a** from **1**, treatment of **1** (276 mg, 2.0 mmol) with (diisopropylamino)magnesium bromide, prepared from ethylmagnesium bromide (3 mL, 3.0 mmol) and diisopropylamine (0.56 mL, 4.0 mmol) in toluene (10 mL), followed by addition of a solution of (*R*)-menthyl-*p*-toluenesufinate (**12b**)[13] (585 mg, 2.0 mmol) in toluene (3 mL) gave **13b** (361 mg, 65%) as crystals: mp 164−65 °C; $[\alpha]^{19}_D$ = −348 (*c* 0.96, $CHCl_3$); IR (KBr) 1717, 1595, 1050, 816 cm^{-1}. Anal. Calcd for $C_{16}H_{20}O_2S$: C, 69.53; H, 7.29; S, 11.60. Found: C, 69.23; H, 7.36; S, 11.38.

Similarly, treatment of **3** (152 mg, 1.0 mmol) with (diisopropylamino)magnesium bromide, prepared from ethylmagnesium bromide (1.5 mL, 1.5 mmol) and diisopropylamine (0.28 mL, 2.0 mmol) in toluene (6 mL), followed by addition of a

solution of **12b**[13] (293 mg, 1.0 mmol) in toluene (2 mL) gave **19b** (134 mg, 46%) as crystals: mp 160 °C; $[\alpha]^{25}_{D} = -207$ (*c* 0.48, $CHCl_3$); IR (KBr) 1709, 1042, 819 cm^{-1}. Anal. Calcd for $C_{17}H_{22}O_2S$: C, 70.31; H, 7.64; S, 11.04. Found: C, 70.24; H, 7.62; S, 10.95.

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