Journal of the Chinese Chemical Society, **1997**, *44*, 253-260

A Model Study of Intramolecular Asymmetric Radical Cyclizations of α-Ester and α-Amide Radicals

Ru-Long Yeh (葉儒隆), Weir-Torn Jiaang (蔣維棠) and Yeun-Min Tsai* (蔡蘊明)
Department of Chemistry, National Taiwan University, Taipei, Taiwan 10617, R.O.C.

Starting from malonate, a practical route was developed for the synthesis of α-phenylthio acid **3**. Several chiral compounds including (-)-menthol, (-)-8-phenylmenthol and a camphor based oxazolidinone **8** reacted with **3** to give α-phenylthio esters or amide. These sulfides cyclized efficiently when reacted with tributyltin hydride. Among the chiral auxiliaries used, 8-phenylmenthyl group displayed moderate asymmetric induction (64% ee for *cis*-product and 40% ee for *trans*-product). Based on this results, a transition state model was proposed to explain the observed stereoselectivity. In this model, due to π,π-orbital overlap of the phenyl ring and the carbonyl, the *si*-face of the most stable conformer of the radical was shielded. This controlled the carbon-carbon bond formation to occur from the *re*-face.

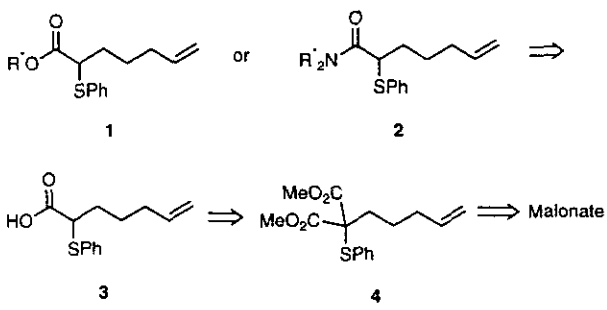
INTRODUCTION

α-Ester radicals[1] are useful reactive intermediates in C-C bond formation for two major reasons. Firstly, the existing ester functionality can easily undergo further synthetic transformations. Secondly, the possibility of incorporating chiral auxiliary at the ester moiety allows the formation of asymmetric radicals. The latter feature attracted the interests of many research groups, including us,[2] to further develop asymmetric radical reactions.[3-5] Similarly, α-amide radicals share the same characteristics and also received wide attentions.[3,4]

There are several approaches to generate the α-ester or α-amide radicals, a popular one being conjugate addition of radicals to α,β-unsaturated esters[6] or amides.[3] Abstraction of the α-hydrogen atom of esters also provides the corresponding α-radicals.[7] Metal oxidation of β-keto esters or amides is an unique way to generate β-keto α-ester or α-amide radicals.[5] Another important approach relies on the reaction of tributyltin hydride with α-halo esters or amides.[8]

Initially, our goal was to search for a suitable chiral auxiliary in order to perform intramolecular asymmetric radical cyclizations of α-ester or α-amide radicals. We decided first to develop a general strategy for the synthesis of a more stable α-halo ester or amide equivalent for our purpose. Since phenylthio compounds have been used to generate radicals,[9] we believed that sulfides **1** and **2** (Scheme I) would be good substitutes for the α-halo analogs. While this work was in progress, others also reported the use of α-phenylthio esters to prepare α-ester radicals.[10,11] It was envisioned sulfides **1** and **2** to derive from the same acid 3. This acid can be prepared using the classical malonate chemistry.

Scheme I



1 2 3 4

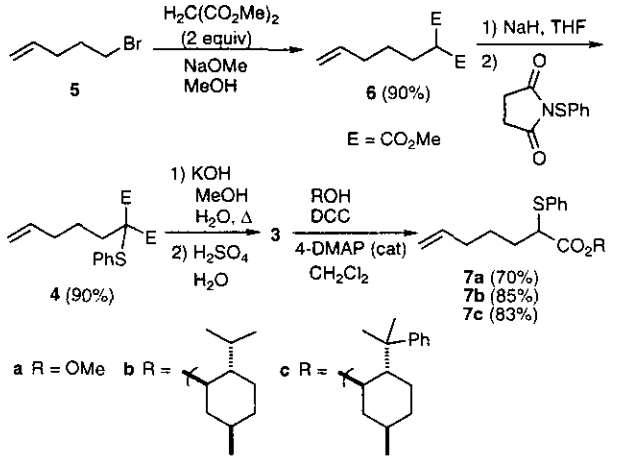
RESULTS AND DISCUSSION

As shown in Scheme II, 4-pentenyl bromide (**5**) was treated with two equivalents of dimethyl sodiomalonate in methanol to give malonate **6** in 90% yield. Sulfenylation of **6** was accomplished by treating **6** with sodium hydride in THF followed by the addition of *N*-(phenylthio)succinimide.[12] Sulfide **4** was obtained in 90% yield. Hydrolysis of **4** with potassium hydroxide in aqueous methanol followed by acidification afforded the corresponding diacid. This diacid decarboxylated easily at room temperature to afford crude acid **3**. Without purification, acid **3** was converted to methyl ester **7a** (70%) by reacting with methanol in the presence of DCC and catalytic amount of 4-DMAP. Similarly, starting from enantiomerically pure (-)-menthol and (-)-8-phenylmenthol,[13] we were able to prepare esters

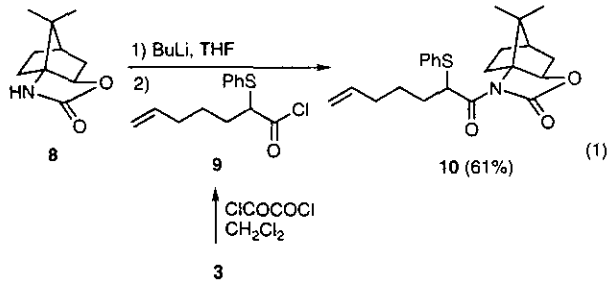
Dedicated to Professor Yu-Shia Cheng on the occasion of her 65th birthday.

7b (85%) and **7c** (83%). In each case, a mixture of two isomers epimeric at the α-position of ester was obtained. However, since the phenylthio group would be removed during cyclization, these epimers were not separated and used as a mixture.

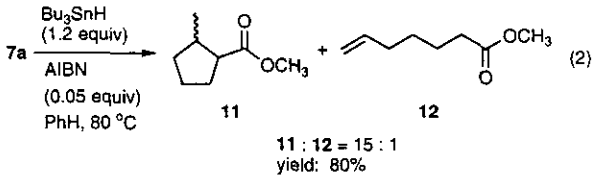
Scheme II



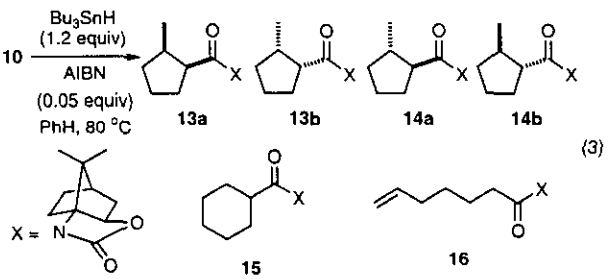
We also transformed acid **3** to the corresponding acid chloride **9** (eq 1) which was then reacted with the lithium anion of oxazolidinone **8**[14] to afford amide **10** in 61% yield from **3**. Again, two epimers were obtained and used as a mixture in the next step.



For the radical cyclization study, we first used methyl ester **7a** as a model for comparison (eq 2). The cyclization was performed by slow addition (6 h) of a solution of tributyltin hydride (0.1 M in benzene) and catalytic amount of AIBN to a solution of **7a** (0.1 M) in refluxing benzene. A mixture of cyclized product **11** and uncyclized product **12** was obtained in 80%. By ^{1}H NMR integration of this mixture, the ratio of **11/12** was determined as 15/1. Ester **11** was a mixture of *cis/trans* isomers as revealed by two methyl doublets at δ 0.85 (J = 7 Hz) and 1.05 (J = 6 Hz). NOe experiments carried out on this mixture showed that irradiation at δ 1.05 resulted in 9% enhancement of a quartet at δ 2.23 (J = 8 Hz, H(1)). On the contrary, irradiation at δ 0.85 did not give any enhancement of the quartet at δ 2.78 (J = 8 Hz, H(1)). These experiments suggested that the one with methyl absorption at δ 1.05 should have a *cis*-relationship with H(1) and belonged to the *trans*-isomer. Integration of the two methyl signals showed the *cis/trans* ratio as 1.5/1. Our result was similar to the cyclization of methyl 2-iodo-6-heptenoate as reported by Curran.[1] However, we did not isolate any 6-*endo* cyclization product.

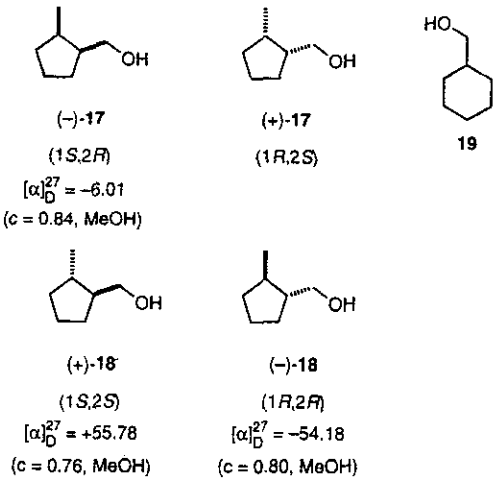


When sulfide **10** was treated with tributyltin hydride under similar conditions (eq 3), uncyclized reduction product **16** was isolated in 3% yield. 5-*Exo* cyclization products **13a** (20%), **14a** (17%), and **14b** (12%) were obtained. In addition, **13b** and 6-*endo* product **15** were isolated (35%) as a mixture in a ratio of 1.5/1 (**13b/15**) as determined by ^{1}H NMR integrations. In order to determine the absolute structures of the cyclization products, we treated these compounds with LAH individually to remove the chiral auxiliary. Thus, alcohols (-)-**17**, (+)-**18** and (-)-**18** were obtained from **13a**, **14a**, and **14b**, respectively. Since the rotation of (+)-**18** was similar as that reported by Brown *et al.* ($[\alpha]_D^{23}$ = +54.95 ± 0.01, c = 1, MeOH),[15] assignments of the absolute structures of **14a** and **14b** can be made. At this stage, we did not know the exact configurations of **13a** and **13b** (*vide infra*). However, pure (-)-**17** was obtained from **13a**, and the maximum rotation of **17** was determined.

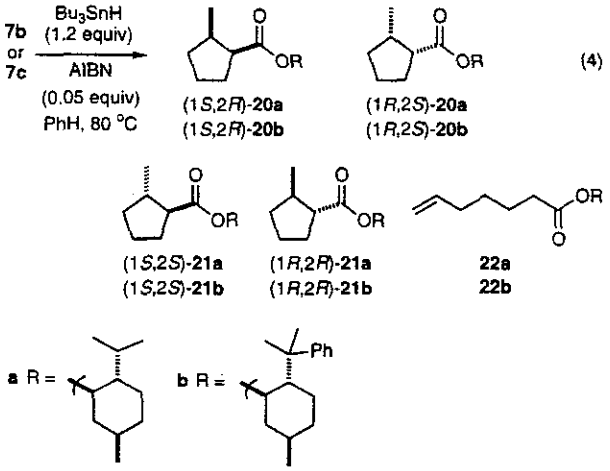


Because we could not separate **13b** and **15**, the mixture was converted to another mixture of (+)-**17** and **19** by the reaction with LAH. The presence of **19** was confirmed by comparing with an authentic sample. Although there was very little chiral-induction for the cyclization, we still obtained useful information about the rotation values of the enatiomers of **17**.

Sulfide **7b** also reacted with tributyltin hydride to give



in 94% yield a mixture of **20a**, **21a** and **22a** (eq 4) in a ratio of 50:42:8, as determined by GC. The mixture was reduced with LAH to afford a mixture of the corresponding alcohols (97%) along with 92% of recovered (-)-menthol. Alcohols **17** and **18** were separated by HPLC and the optical rotations were determined. For the *cis* product **17**, a 16% ee was obtained in favor of (-)-**17**. For the *trans* product **18**, no enantio-selectivity was observed.



On another occasion, we treated the cyclization mixture with potassium hydroxide in aqueous methanol. The hydrolysis required stirring at room temperature for 4 days and then heating at 60-70 °C for 2 days to complete. The crude acid was converted to methyl ester **11** by heating for 22 h in methanol in the presence of sulfuric acid. Analysis of this ester by GC showed that it was a 88:4:8 mixture of *trans*-**11**, *cis*-**11**, and **12**, respectively. This experiment indicated that the *cis*-isomer could be epimerized to the *trans*-isomer. However, for the purpose of retaining the stereochemical information of the cyclization, the hydrolysis process was not a viable method.

Similarly, a mixture of esters **20b**, **21b** and **22b** was obtained in 92% yield from **7c**. Judging by ^{1}H NMR integration, reduction product **22b** was present in 5%. Reduction of the mixture with LAH gave 96% yield of an alcohol mixture in which the ratio of **17/18** was 1.5/1 as determined by HPLC. (-)-8-Phenylmenthol was recovered in 86% yield. Based on the optical rotations, the *cis* alcohol exhibited 64% ee in favor of (-)-**17**. For the *trans* alcohol, a 40% ee was observed in favor of (+)-**18**.

The results of the cyclizations are summarized in Table 1. In all cases, cyclizations were quite efficient and 5-*exo*-cyclizations were preferred with mild *cis*-selectivity. The regioselectivity and stereoselectivity followed the general guidelines of radical cyclizations.[9,16] When (-)-8-phenylmenthyl group was used as chiral auxiliary (entry 4), appreciable asymmetric inductions were observed for **20b** and **21b**.[6,17] In the case of **21b**, the (1*S*,2*S*)-isomer was predominant. This stereoselectivity can be explained by adopting the model proposed for intramolecular Diels-Alder reactions of 8-phenylmenthyl acrylates.[18] There are two most likely conformations **23** and **24** of the 8-phenylmenthyl ester derived radical. In **23** and **24**, s-*cis* conformation is adopted around the C-O single bond.[19] The phenyl ring is parallel to the carbonyl-π system to maintain an effective π,π-orbital overlap. For **24**, the R group is *anti*-periplanar to the carbonyl and exhibits unfavorable steric interaction with the phenyl ring. However, in **23**, the R group is *syn*-periplanar to the carbonyl and the steric interaction with the phenyl ring is minimal. Therefore, conformer **23** is preferred. In **23**, the *si*-face of the radical is shielded by the ring. Thus, the olefin will come in from the *re*-face as in **25** or **26**, leading to the formation of (1*S*,2*S*)-**21b**. Similar control should operate as in **27** or **28**, and this would lead to the formation of (1*S*,2*R*)-**20b**. Based on this analysis, we assigned the *levorotatory* isomer of **17** the configuration (1*S*,2*R*).

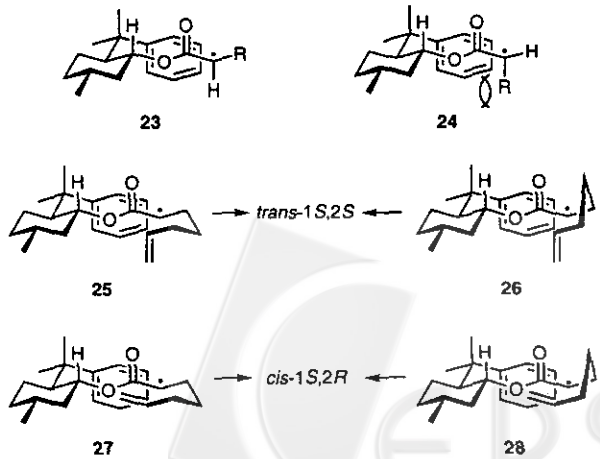


Table 1. Summary of Radical Cyclizations of **7** and **10**

				5-*exo*-cyclizations		
entry	sulfide	6-*endo* cyclization (% yield)	uncyclized product (% yield)[a]	products (% yields; *cis/trans*)	*cis* isomer *1R,2S/1S,2R*	*trans* isomer *1S,2S/1R,2R*
1	**7a**	-	**12** (5)	**11** (75; 1.5/1)[a]	-	-
2[b]	**10**	**15** (14)	**16** (3)	**13+14** (70; 1.4/1)	50/50	52/49
3	**7b**	-	**22a** (8)[c]	**20a+21a** (86; 1.2/1)[c]	42/58[d]	50/50[d]
4	**7c**	-	**22b** (5)	**20b+21b** (87[a]; 1.5/1[d])	18/82[d]	70/30[d]

[a] Calculated from ratio obtained by ^{1}H NMR integration. [b] Based on isolation yields. [c] Determined by GC. [d] Based on the results of LAH reduction of the cyclization products.

In conclusion, a very practical synthesis of 2-phenylthio-6-heptenoic acid (**3**) was developed. Esters and amide derived from **3** underwent radical cyclizations effectively. Among the chiral auxiliaries we used, 8-phenylmenthyl group expressed appreciable amount of chiral induction. A model was suggested to explain the observed selectivity.

EXPERIMENTAL SECTION

^{1}H and ^{13}C NMR spectra were recorded on Varian EM-390 (operating at 90 MHz) or Bruker AC-200 (operating at 200 and 50 MHz) spectrometers with tetramethysilane (TMS) or $CHCl_3$ as internal standards and $CDCl_3$ as the solvent. Infrared spectra were taken on a Perkin-Elmer 938G instrument. Mass spectra were recorded on a Finigan TSQ-46C spectrometer. Exact masses were recorded on JEOL JMS-HX 110 or SX-102A spectrometers. Combustion analyses done on a Perkin-Elmer 240C instrument. High-pressure liquid chromatography (HPLC) was carried out on a Hitachi L-6200 chromatograph equipped with a refractive index detector. The samples were analyzed and/or separated on a Hibar Lichrosorb Si 60 (7 μm) column (25 cm × 1 cm) with the indicated eluent with a 5 mL/min flow rate. Gas chromatography was performed on a Shimadzu GC-8A chromatograph with a flow rate of 27 mL/min. The samples were analyzed on a 3 M × 3.3 mm column packed with 10% SE-30 on Chromosorb W (80-100 mesh). Optical rotation was recorded on a Jasco DIP-360 spectrometer. Melting points were measured with a Mel-Temp apparatus and are uncorrected. Benzene and THF were distilled from sodium bezophenone ketyl under N_2. All reactions were performed under a blanket of N_2 or Ar.

Dimethyl 2-(4-pentenyl)propanedioate (6)

To 45 mL of anhydrous methanol cooled at 0 °C was carefully added 1.84 g (80 mmol) of sodium. When the sodium disappeared, dimethyl malonate (9.15 mL, 80 mmol) was added in one portion at room temperature. Bromide **5** (4.76 mL, 40 mmol) was then added in one portion and the resulting solution was stirred under reflux for 3.5 h. The reaction mixture was partitioned between 150 mL of water and 200 mL of ether. The organic layer was washed with brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. The residual oil was chromatographed over silica gel (eluted with hexane/ethyl acetate, 92/8) to give 7.2 g (90%) of **6** as a light yellow liquid: IR (neat) 3077, 2951, 1737, 1639, 1431, 1312, 1219, 1156, 1058, 1003, 915, 856 cm^{-1}; ^{1}H NMR (CCl_4, 90 MHz) δ 1.15-2.27 (m, 6 H), 3.22 (t, J = 8 Hz, 1 H, H(2)), 4.67-5.00 (m, 2 H, =CH_2), 5.73 (ddt, J = 17, 10, 6 Hz, 1 H, -CH=); MS *m/z* (rel intensity) 201 (M^++1, 7), 145 (41), 136 (55), 132 (100), 108 (57), 100 (44), 81 (45), 67 (41), 59 (36), 54 (43); HRMS calcd for $C_{10}H_{17}O_4$ *m/z* 201.1127, found 201.1127.

Dimethyl 2-(4-pentenyl)-2-phenylthiopropanedioate (4)

To 216 mg (5.42 mmol) of sodium hydride (60% dispersion in mineral oil) was added a solution of 0.900 g (4.50 mmol) of **6** in 7 mL of THF. The resulting mixture was stirred until the sodium hydride all disappeared and then cooled in an ice-water bath. A solution of *N*-phenylthiosuccinimide (1.12 g, 5.41 mmol) in 7 mL of THF was added dropwise and the resulting mixture was stirred at 0 °C for

another 1 h. The reaction mixture was partitioned between 60 mL of water and 60 mL of ether. The organic layer was washed with brine (30 mL), dried ($MgSO_4$) and concentrated in vacuo. The residual oil was chromatographed over silica gel (eluted with hexane/ethyl acetate, 92/8) to give 1.25 g (90%) of **4** as an yellow liquid: IR (neat) 3163, 3073, 2952, 2943, 1732, 1639, 1470, 1438, 1248, 1131, 916, 751, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.45-1.70 (m, 2 H), 1.86-2.16 (m, 4 H), 3.73 (s, 6 H, Me), 4.90-5.12 (m, 2 H, $=CH_2$), 5.79 (ddt, J = 17, 10, 6 Hz, 1 H, -CH=), 7.24-7.55 (m, 5 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.4, 33.1, 33.3, 52.9, 65.3, 115.1, 128.8, 129.4, 129.9, 136.9, 137.8, 168.9; MS *m/z* (rel intensity) 308 (M^+, 22), 240 (80), 208 (100), 189 (29), 167 (35), 135 (76), 109 (54), 79 (56); HRMS calcd for $C_{16}H_{20}O_4S$ *m/z* 308.1082, found 308.1091.

2-Phenylthio-6-hetenoic acid (3)

To a solution of 1.80 g (5.84 mmol) of **4** in 5 mL of methanol/water (5/1) was added 1.08 g (19.2 mmol) of potassium hydroxide and the resulting mixture was heated under reflux for 16 h. The resulting mixture was concentrated in vacuo to remove methanol. The residual aqueous solution was washed with hexane (15 mL × 3) and then diluted with 3 mL of THF/water (1/1) followed by the addition of 6 mL of a 3 N sulfuric acid aqueous solution. The resulting mixture was stirred at room temperature for 20 min and then extracted with dichloromethane (30 mL × 2). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give 1.39 g (100%) of crude **3** as an yellow oil: IR (neat) 2925 (br), 1708, 1480, 1438, 1413, 1283, 1189, 993, 748, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.42-2.18 (m, 6 H), 3.63 (t, J = 8 Hz, 1 H, H(1)), 4.91-5.12 (m, 2 H, $=CH_2$), 5.78 (ddt, J = 18, 10, 6 Hz, 1 H, -CH=), 7.23-7.40 (m, 3 H, ArH), 7.40-7.57 (m, 2 H, ArH), 9.92 (br s, 1 H, OH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.3, 30.8, 33.1, 50.6, 115.2, 128.1, 129.0, 132.8, 137.8, 178.3. This material was used directly in the next step without further purification.

General procedure for the preparation of ester of acid 3

To a solution of 0.90 mmol of alcohol, 0.90 mmol of DCC and catalytic amount of 4-DMAP in 1 mL of dichloromethane was added 0.70 mmol of the crude acid **3** in 1 mL of dichloromethane. The resulting mixture was stirred at room temperature for 30-45 min, diluted with 10 mL of ether, filtered, and the filtrate was concentrated in vacuo. The resulting residual material was chromatographed over silca gel with suitable hexane/ethyl acetate mixture as eluent to afford the desired ester.

Methyl 2-phenylthio-6-heptenoate (7a)

Compound **7a** was prepared according to the general procedure in 70% yield as a colorless liquid: IR (neat) 2946, 2856, 1733, 1479, 1436, 1260, 1214, 1190, 1155, 1025, 914, 748, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.39-2.00 (m, 4 H), 2.07 (q, J = 8 Hz, 2 H), 3.65 (t, J = 9 Hz, 1 H, SCH), 3.66 (s, 3 H, OMe), 4.91-5.06 (m, 2 H, $=CH_2$), 5.77 (ddt, J = 18, 10, 6 Hz, 1 H, -CH=), 7.26-7.36 (m, 3 H, ArH), 7.37-7.49 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.4, 31.1, 33.1, 50.7, 52.1, 115.0, 127.9, 128.9, 132.8, 133.4, 137.8, 172.7; MS *m/z* (rel intensity) 250 (M^+, 14), 182 (9), 123 (39), 110 (48), 81 (100), 55 (29); HRMS calcd for $C_{14}H_{18}O_2S$ *m/z* 250.1028, found 250.1022.

(1*R*,2*S*,5*R*)-Menthyl (2*R*)- and (2*S*)-2-phenylthio-6-heptenoate (7b)

Compound **7b** was prepared according to the general procedure in 85% yield as a colorless liquid: IR (neat) 2957, 2929, 2870, 1719, 1454, 1438, 1259, 1167, 1149, 917, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.62-0.70 (two overlapped d, J = 6 Hz, at 0.65 and 0.68, 3 H, C(5)-Me of menthyl), 0.73-2.00 (m, 19 H), 2.08 (q, J = 7 Hz, 2 H, allylic-CH_2), 3.63-3.75 (two overlapped t, J = 6 Hz, at 3.68 and 3.69, 1 H, SCH), 4.65 (td, J = 11, 4 Hz, 1 H, OCH), 4.91-5.10 (m, 2 H, $=CH_2$), 5.77 (ddt, J = 17, 10, 7 Hz, 1 H, -CH=), 7.21-7.37 (m, 3 H, ArH), 7.37-7.55 (m, 2 H, ArH). Anal. Calcd for $C_{23}H_{34}O_2S$: C, 73.70; H, 9.15. Found: C, 73.22; H, 8.87.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl (2*R*)- and (2*S*)-2-phenylthio-6-heptenoate (7c)

Compound **7c** was prepared according to the general procedure in 83% yield as a colorless liquid: IR (neat) 3057, 2923, 2118, 1721, 1438, 1248, 1155, 911, 765, 747, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.49-2.18 (m overlapped with d, J = 6 Hz, at 0.84, and two s at 1.18 and 1.24, 23 H), 3.26 (t, J = 7 Hz, 1 H, SCH), 4.78 (td, J = 11, 4 Hz, 1 H, OCH), 4.89-5.10 (m, 2 H, $=CH_2$), 5.73 (ddt, J = 17, 10, 7 Hz, 1 H, -CH=), 7.04-7.56 (m, 10 H, ArH). Anal. Calcd for $C_{29}H_{38}O_2S$: C, 77.29; H, 8.50. Found: C, 76.89; H, 9.05.

***N*-[(2*R*)- and (2*S*)-2-Phenylthio-6-heptenoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-oxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (10)**

To a solution of 664 mg (2.86 mmol) of crude acid **3** in 4 mL of dichloromethane was added 0.5 mL (5.73 mmol) of oxalyl chloride. The reaction mixture was stirred at room temperature for 18 h and then concentrated in vacuo. The residual dark orange liquid was dissolved in 5 mL of THF

and used in the following step.

To 511 mg (2.82 mmol) of **8** in 6 mL of THF was added dropwise 2.1 mL (3.26 mmol) of *n*-butyllithium (1.55 M in hexane). The resulting solution was stirred at room temperature for 10 min followed by slow addition of the acid chloride solution prepared above. After another 30 min, the reaction mixture was poured into a mixture of 10 mL of 0.3 N sulfuric acid and 30 mL of dichloromethane. The aqueous phase was extracted with dichloromethane (30 mL × 2). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residual orange oil was chromatographed over silica gel (eluted with hexane/ethyl acetate, 96/4) to give 683 mg (61%) of **10** as a pale yellow oil: IR (neat) 3072, 2958, 1776, 1701, 1481, 1451, 1436, 1356, 1302, 1273, 1250, 1228, 1199, 1186, 1175, 1078, 1024, 764, 748, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.94-1.17 (two overlapped s of equal intensity at 0.97 and 1.00, 3 H, Me), 1.10 (s, 3 H, Me), 1.17-2.34 (m, 12 H), 2.80 (td, J = 12, 5 Hz, 0.5 H, bridgehead-CH), 2.90 (td, J = 12, 5 Hz, 0.5 H, bridgehead-CH), 3.96 (dd, J = 8, 4 Hz, 0.5 H, OCH), 4.24 (dd, J = 8, 4 Hz, 0.5 H, OCH), 4.87-5.25 (m overlapped with two t, J = 6 Hz, at 5.11 and 5.20, 3 H, $=CH_2$ and SCH), 5.75 (ddt, J = 17, 11, 7 Hz, 1 H, -CH=), 7.22-7.57 (m, 5 H, ArH). Anal. Calcd for $C_{23}H_{29}O_3SN$: C, 69.13; H, 7.32; N, 3.50. Found: C, 68.78; H, 7.41; N, 3.32.

Radical cyclization of ester 7a

To a solution of 191 mg (0.76 mmol) of **7a** in 7.7 mL of benzene under reflux was added over 6 h a solution of tributyltin hydride (0.27 mL, 1.0 mmol) and AIBN (7.2 mg, 0.044 mmol) in 7.7 mL of benzene. The resulting solution was concentrated in vacuo to give a colorless liquid. To the liquid was added a few drops of triethylamine[1] and the resulting mixture was chromatographed over silica gel to give 86.7 mg (80%) of a mixture of **11** and **12**.[1] The ratio of **11/12** was 15/1 as determined by ^1H NMR integration. Characteristic ^1H NMR ($CDCl_3$, 200 MHz) of **11**: δ 0.85 (d, J = 7 Hz, 1.8 H, *cis*-Me), 1.05 (d, J = 6 Hz, 1.2 H, *trans*-Me), 1.10-2.37 (m, 7 H, with a q, J = 8 Hz, revealed when irradiating at δ 1.05 during a nOe experiment), 2.78 (q, J = 8 Hz, 0.6 H, *cis*-C(=O)CH), 3.63 (s, 1.8 H, *cis*-OMe), 3.65 (s, 1.2 H, *trans*-OMe).

Radical cyclization of ester 10

Sulfide **10** (663 mg, 1.66 mmol) was cyclized under the same condition for the cyclization of **7a** except that the addition of the tin hydride solution was completed over 8.6 h. The crude product was purified over silica gel and then by HPLC (eluted with hexane/ethyl acetate, 97/3) to give 97 mg (20%) of **13a** (R_t = 16.3 min), 82 mg (17%) of **14a** (R_t = 18.2 min), 60 mg (12%) of **14b** (R_t = 21.5 min), 168 mg (35%) of a mixture of **15** (R_t = 23.9 min) and **13b** (R_t = 25.0 min), and 13 mg (3%) of **16** (R_t = 48.8 min). The ratio of **15/13b** was 4/6 as determined by ^1H NMR integration.

***N*-[(1*S*,2*R*)-2-methylcyclopentylcarbonyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-oxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (13a)**

White solid, mp 118-119 °C; $[\alpha]_D^{27}$ +54.08 (c = 1.5, $CHCl_3$); IR ($CHCl_3$) 2959, 1779, 1691, 1377, 1319, 1293, 1276, 1249, 1233, 1200, 1177, 1157, 1071, 1052, 1035, 762 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.83 (d, J = 8 Hz, 3 H, Me on cyclopentane), 1.04 (s, 3 H, Me), 1.16 (s, 3 H, Me), 1.19-2.17 (m, 11 H), 2.27 (dq, J = 14, 4 Hz, 1 H, bridgehead-CH), 2.43 (septet, J = 9 Hz, 1 H, Me-CH-), 2.92 (td, J = 12, 5 Hz, 1 H), 4.12 (q, J = 8 Hz, 1 H, C(=O)CH), 4.22 (dd, J = 8, 4 Hz, 1 H, OCH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.4, 19.2, 21.7, 23.5, 25.6, 26.0, 26.6, 34.2, 34.7, 36.3, 42.5, 47.8, 48.1, 72.6, 84.5, 176.0, 209.5. Anal. Calcd for $C_{27}H_{25}O_3N$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.01; H, 8.90; N, 4.79.

***N*-[(1*S*,2*S*)-2-methylcyclopentylcarbonyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-oxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (14a)**

White solid, mp 66.0-66.5 °C; $[\alpha]_D^{27}$ +145.63 (c = 1.8, $CHCl_3$); IR ($CHCl_3$) 2959, 2931, 1775, 1696, 1393, 1316, 1303, 1292, 1275, 1251, 1079 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.99 (d, J = 7 Hz, 3 H, Me on cyclopentane), 1.02 (s, 3 H, Me), 1.13 (s, 3 H, Me), 1.18-1.40 (m, 3 H), 1.65-2.14 (m, 7 H), 2.14-2.44 (m, 3 H), 2.89-3.07 (m, 1 H), 3.43 (q, J = 8 Hz, 1 H, C(=O)CH), 4.24 (dd, J = 8, 4 Hz, 1 H, OCH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.1, 19.2, 21.7, 24.3, 26.0, 30.9, 34.5, 34.7, 38.9, 42.5, 48.2, 51.8, 72.4, 84.5, 177.9, 209.5. Anal. Calcd for $C_{27}H_{25}O_3N$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.19; H, 8.77; N, 4.71.

***N*-[(1*R*,2*R*)-2-methylcyclopentylcarbonyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-oxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (14b)**

White solid, mp 78-79 °C; $[\alpha]_D^{27}$ +4.58 (c = 1.3, $CHCl_3$); IR ($CHCl_3$) 2959, 1773, 1697, 1491, 1452, 1372, 1316, 1291, 1275, 1251, 1232, 1175, 1159, 1079, 1013, 997 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.80-1.50 (m overlapped with d, J = 7 Hz, at 1.06, and two s at 1.05 and 1.14, 13 H), 1.55-2.48 (m, 9 H), 2.89-3.09 (m, 1 H), 3.60 (q, J = 7 Hz, 1 H, C(=O)CH), 4.22 (dd, J = 8, 4 Hz, 1 H, OCH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.1, 19.3, 21.7, 24.2, 26.0, 30.6,

34.1, 34.7, 38.4, 42.4, 48.2, 51.3, 72.5, 84.2, 98.0, 177.8, 209.5. Anal. Calcd for $C_{27}H_{25}O_3N$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.89; H, 8.83; N, 4.70.

***N*-[(1*R*,2*S*)-2-methylcyclopentylcarbonyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-oxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (13b) and *N*-cyclohexylcarbonyl-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-oxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (15)**

Characteristic ^{1}H NMR ($CDCl_3$, 200 MHz) signals of **13b**: δ 2.64 (septet, J = 8 Hz, 1 H, Me-CH-), 3.82 (q, J = 8 Hz, 1 H, C(=O)CH). Characteristic ^{1}H NMR ($CDCl_3$, 200 MHz) signals of **15**: δ 3.49 (tt, J = 11, 3 Hz, 1 H, C(=O)CH). Anal. Calcd for $C_{27}H_{25}O_3N$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.13; H, 8.95; N, 4.61.

***N*-6-heptenoyl-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-oxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (16)**

IR (neat) 2927, 1780, 1702, 1637, 1370, 1303, 1274, 1251, 1228, 1200, 1175, 1078 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.72-2.28 (m overlapped with two s at 0.95 and 1.06, and dq, J = 14, 4 Hz, at 2.18, 18 H), 2.66-3.05 (m, 3 H), 4.16 (dd, J = 8, 4 Hz, 1 H, OCH), 4.82-5.02 (m, 2 H, $=CH_2$), 5.74 (ddt, J = 17, 10, 7 Hz, 1 H, -CH=); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.2, 21.6, 23.8, 25.8, 26.0, 28.3, 33.5, 34.7, 36.3, 42.4, 48.2, 72.2, 84.6, 114.6, 138.5, 174.5, 209.5; MS *m/z* (rel intensity) 292 (25), 291 (M^+, 4), 181 (100), 122 (9), 111 (31), 55 (53); HRMS calcd for $C_{17}H_{25}O_3$ *m/z* 291.1836, found 291.1830.

General procedure for the LAH reduction of cyclized amides or esters

To a solution of the ester or amide (0.214 mmol) in ether (0.05 M) was added LAH (0.685 mmol) at 0 °C. The resulting mixture was stirred at the same temperature for 10 min and then warmed up to room temperature by itself. To the reaction mixture was added in sequence 8 mL of ether, 0.026 mL of water, 0.026 mL of 15% NaOH solution, and some $MgSO_4$. The mixture was then filtered and the filtrate was concentrated in vacuo. The residual liquid was chromatographed over silica gel to separate the chiral auxiliary and the alcohol.

(1*S*,2*S*)-(+)-*trans*-(2-Methylcyclopentyl)methanol ((+)-18)

This material was obtained from **14a** via LAH reduction and was identical to that reported by Brown;[15] $[\alpha]_D^{27}$ +55.78 (c = 0.76, MeOH).

(1*R*,2*R*)-(-)-*trans*-(2-Methylcyclopentyl)methanol ((-)-18)

This material was obtained from **14b** via LAH reduction and was identical to (+)-**18** except for the optical rotation: $[\alpha]_D^{27}$ -54.18 (c = 0.80, MeOH).

(1*S*,2*R*)-(-)-*cis*-(2-Methylcyclopentyl)methanol ((-)-17)[20]

This material was obtained from **13a** via LAH reduction: $[\alpha]_D^{27}$ -6.01 (c = 0.84, MeOH); IR (neat) 3679, 3617, 2957, 1630, 1012 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.85 (d, J = 6.5 Hz, 3 H, Me), 1.12-1.85 (m, 7 H), 1.90-2.25 (m, 2 H), 3.50 (dd, J = 11, 7 Hz, 1 H, OCH), 3.67 (dd, J = 11, 7 Hz, 1 H, OCH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.9, 22.8, 27.3, 33.9, 34.9, 45.4, 64.1.

Radical cyclization of ester 7c

Sulfide **7c** (275 mg, 0.611 mmol) was cyclized under the same condition for the cyclization of **7a**. The crude product was purified over silica gel to give 192 mg (92%) of a mixture of **20b**, **21b**, and **22b** as a light yellow oil. The ratio of (**20b** + **21b**)/**22b** was 19/1 as determined by ^{1}H NMR integration. The mixture was directly subjected to LAH reduction according to the general procedure to give 62 mg (96%) of a mixture of **17**, **18** and 6-heptenol, in addition to 112 mg (86%) of recovered (-)-8-phenylmenthol. Alcohols **17** and **18** (**17**/**18** = 1.5/1) were separated by HPLC (eluted with hexane/ethyl acetate, 8/2) to give **18** (40% ee): R_t = 10.0 min; $[\alpha]_D^{33}$ +21.91 (c = 1.4, MeOH), and **17** (63% ee): R_t = 10.8 min; $[\alpha]_D^{29}$ -3.83 (c = 2.7, MeOH).

ACKNOWLEDGMENT

We thank the National Science Council of the Republic of China for financial support. A gift of oxazolidinone **8** from Prof. Tu-Hsin Yan (National Chung-Hsing University) is gratefully acknowledged.

Received October 1, 1996.

Key Words

Asymmetric radical; Radical cyclization; 8-Phenylmenthol; Chiral auxiliary; Tributyltin hydride; α-Ester radical; α-Amide radical.

REFERENCES

1. Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.
2. Chen, M.-Y.; Fang, J.-M.; Tsai, Y.-M.; Yeh, R.-L. *J.*

Chem. Soc. Chem. Commun. **1991**, 1603.
3. Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296.
4. Smadja, W. *Synlett* **1994**, 1.
5. Snider, B. B. *Chem. Rev.* **1996**, *96*, 339.
6. For example, see: Crich, D.; Davies, J. W. *Tetrahedron Lett.* **1987**, *28*, 4205.
7. Rawal, V. H.; Newton, R. C.; Krishnamurthy, V. *J. Org. Chem.* **1990**, *55*, 5181.
8. For example, see: Stork, G.; Mah, R. *Heterocycles* **1989**, *28*, 723.
9. Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: New York, **1992**, chap 7.
10. (a) Takasu, M.; Wakabayashi, H.; Furuta, K.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 6943. (b) Posner, G. H.; Asirvatham, E.; Hamill, T. G.; Webb, K. S. *J. Org. Chem.* **1990**, *55*, 2132. (c) Renaud, P.; Schubert, S. *Synlett* **1990**, 624. (d) Beckwith, A. L. J.; Chai, C. L. L. *Tetrahedron*, **1993**, *49*, 7871. (e) Sato, T.; Chono, N.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc. Perkin Trans. I*, **1995**, 1115.
11. For the use of α-phenylselenenyl esters or amides, see: (a) Hart, D. J.; Krishnamurthy, R. *J. Org. Chem.* **1992**, *57*, 4457. (b) Radinov, R.; Mero, C. L.; McPhail, A. T.; Porter, N. A. *Tetrahedron Lett.* **1995**, *36*, 8183. For xanthates, see ref 2.
12. Kwiatkowski, S.; Syed, A.; Brock, C.; Watt, D. S. *Synthesis* **1989**, 818.
13. Ort, O. *Org. Syn.* **1987**, *65*, 203.
14. Yan, T.-H.; Tan, C.-W.; Lee, H.-C.; Lo, H.-C.; Huang, T.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 2613.
15. Brown, H. C.; Naik, R. G.; Bakshi, R. K.; Pyun, C.; Singaram, B. *J. Org. Chem.* **1985**, *50*, 5586.
16. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: New York, **1986**, chap 4.
17. (a) Hamon, D. P. G.; Razzino, P.; Massy-Westropp, R. A. *J. Chem. Soc. Chem. Commun.* **1991**, 332. (b) Hamon, D. P. G.; Massy-Westropp, R. A.; Razzino, P. *J. Chem. Soc. Chem. Commun.* **1991**, 722. (c) Hamon, D. P. G.; Massy-Westropp, R. A.; Razzino, P. *Tetrahedron*, **1993**, *49*, 6419. (d) Snider, B. B.; Zhang, Q. *Tetrahedron Lett.* **1992**, *33*, 5921. (e) Zhang, Q.; Mohan, R. M.; Cook, L.; Kazanis, S.; Peisach, D.; Foxman, B. M.; Snider, B. B. *J. Org. Chem.* **1993**, *58*, 7640.
18. Oppolzer, W.; Kurth, M.; Reichlin, D.; Chapuis, C.; Mohnhaupt, M.; Moffatt, F. *Helv. Chim. Acta* **1981**, *64*, 2802.
19. Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: New York, **1983**, chap 3.
20. Richter, W. J.; Richter, B. *Israel J. Chem.* **1976/77**, *15*, 57.