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Diastereoselective Radical Cyclization Using a Chiral α-Methyl-α,β-unsaturated Ester: Controlling the Stereochemistry at both the α- and β-Positions

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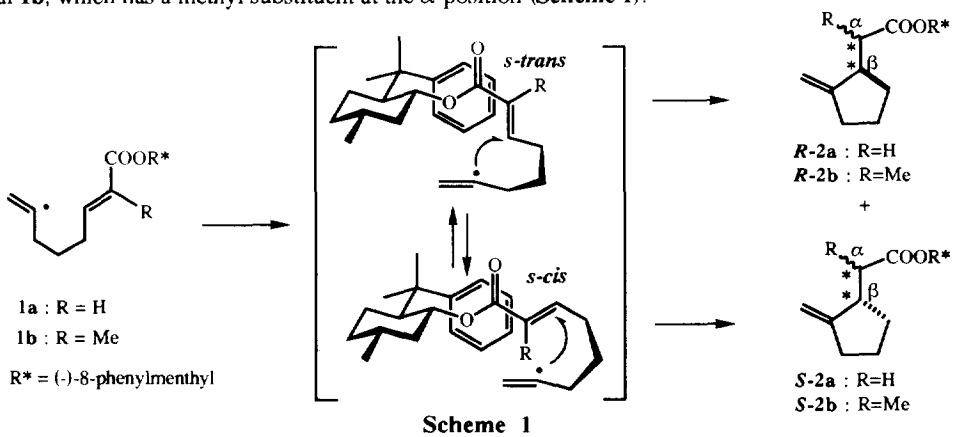
Abstract: Diastereoselective radical cyclizations of (-)-8-phenylmenthyl 2-methyl-2-octene-7-ynoate (**9**) and (-)-8-phenylmenthyl 7-iodo-2-methyl-2,7-octadienoate (**10**) were investigated. The best results were obtained in the cyclization of **10** at -98°C. A mixture of four diastereomers was obtained at a yield of 72% and with a diastereoselectivity of 78:12:9:1. The main product was (*S*)-2-[(*R*)-2-methylene-cyclopentyl]propionate (**3a**). The diastereoselectivities at the α- and β-positions were 90:10 and 79:21, respectively.

We recently reported β-diastereoselective radical cyclizations of **1a** with α,β-unsaturated (-)-8-phenylmenthyl ester[1, 2] as a chiral radical acceptor.[3] High selectivity was observed when the reaction was carried out in the presence of Lewis acids, which gave an unsaturated ester with an *s-trans* conformation. We report here our efforts to control the stereochemistry at both the α- and β-position in the cyclization of alkenyl radical **1b**, which has a methyl substituent at the α-position (**Scheme 1**).



Scheme 1

Four possible diastereomers, **3a-d**, can be obtained in the cyclization of **1b** (**Figure 1**). Hence, before the radical reactions were investigated, these diastereomers were synthesized by alternative routes.

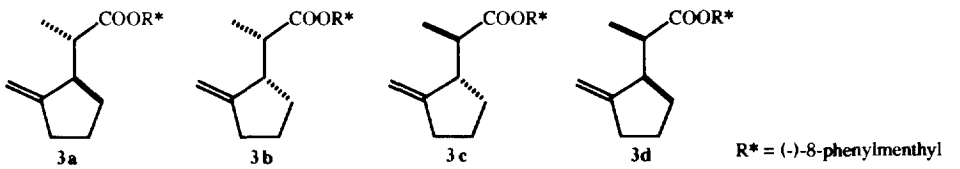
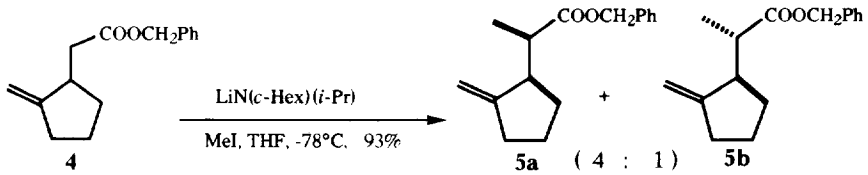
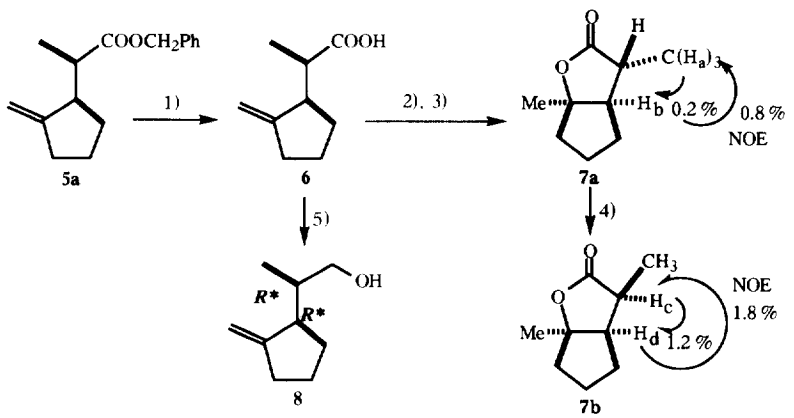


Figure 1 Four possible diastereomers



Scheme 2

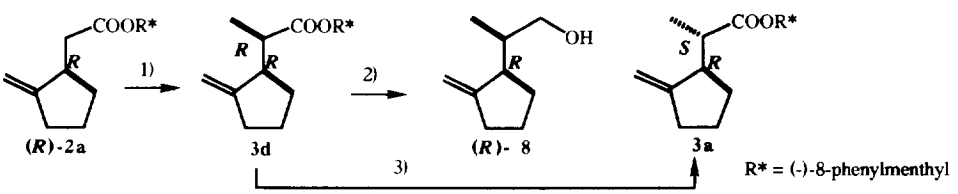
Methylation of racemic ester **4** gave a mixture of **5a** and **5b** at a yield of 93% and with a diastereoselectivity of 4 : 1 (**Scheme 2**). The stereochemistry of the main product **5a** was determined by NOE experiments after conversion to **7a** and then to diastereomer **7b** (**Scheme 3**). In NOE studies of **7a**, irradiation of H_a resulted in a 0.2% NOE to H_b and irradiation of H_b resulted in a 0.8% NOE to H_a. Furthermore, irradiation of H_c in **7b**, resulted in a 1.2% NOE to H_d and irradiation of H_d resulted in a 1.8% NOE to H_c. Thus, the relative stereochemistry of **5a** was determined as shown.



1) 3*N* NaOH, MeOH, THF, 84%, 2) I_2, $NaHCO_3$, THF, 0°C, 89%, 3) *n*-Bu_3SnH, AIBN, benzene, reflux, 92%, 4) LDA, THF, then isopropanol, -78°C, 86%, 5) LAH, ether, 0°C, 91%.

Scheme 3

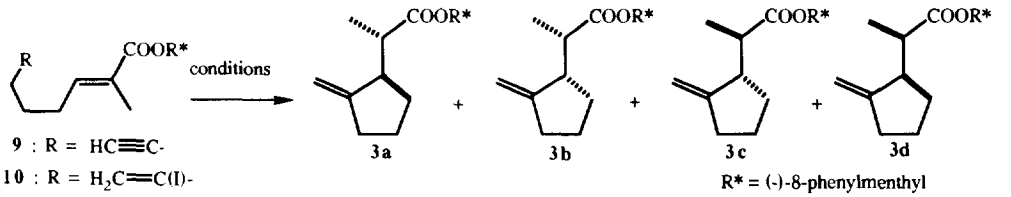
Methylation of (***R***)-**2a**[3a] and subsequent reduction gave the optically active alcohol (***R***)-**8** as a single diastereomer (**Scheme 4**)[4]. Since the relative configuration of (***R***)-**8** was comparable to that of racemic alcohol **8**, which was prepared from **6**, **3d** was determined to be (-)-8-phenylmenthyl (*R*)-2-[(*R*)-2-methylenecyclopentyl]propionate. Under basic conditions, **3d** gave **3a**. The other diastereomers, **3b** and **3c**, were synthesized by the same method using (***S***)-**2a**.[3a,4]



1) Lithium *N*-isopropylcyclohexylamide, MeI, THF, -78°C, 97%, 2) LAH, ether, 0°C, 91%,
3) Lithium *N*-isopropylcyclohexylamide, then isopropanol, THF, -78°C, 86%.

Scheme 4

Table 1 Intramolecular radical cyclizations of **9** and **10**

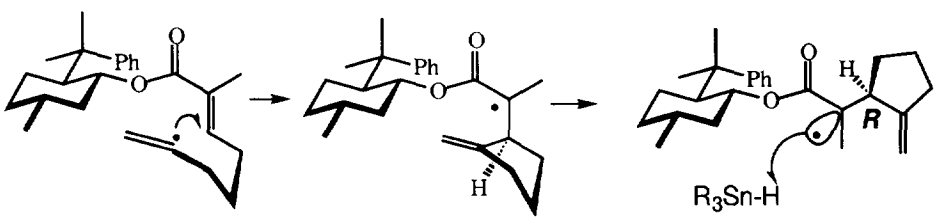


conditions : **A)** *n*-Bu_3SnH (1.5 eq.), AIBN (cat.), benzene.
B) *n*-Bu_3SnH (1.5 eq.), Et_3B (1.05 eq.), toluene.

run	substrate **9** or **10**	conditions	temp. (°C)	yield (%)	ratio[a] **3a** : **3b** : **3c** : **3d**	selectivity α **(3a+3b)** : **(3c+3d)**	selectivity β **(3a+3d)** : **(3b+3c)**
1	**9**	**A**	80	82[b]	66 : 18 : 9 : 7	84 : 16	73 : 27
2	**9**	**B**	0	77[b]	67 : 18 : 9 : 6	85 : 15	73 : 27
3	**10**	**A**	80	76	60 : 20 : 10 : 10	80 : 20	70 : 30
4	**10**	**B**	0	73[c]	71 : 12 : 11 : 6	83 : 17	77 : 23
5	**10**	**B**	-98	72[c]	78 : 12 : 9 : 1	90 : 10	79 : 21

a) The product ratio was determined by ^{1}H-NMR. b) A tributylstannyl group in the initial products was removed by a treatment with BF_3•OEt_2. c) (-)-8-Phenylmenthyl 2-methyl-2,7-octadienoate was also obtained at a yield of 7%.

In the cyclization of **9** under thermal condition **A**, **3a** was obtained as a major product. The diastereoselectivities at the α- and β-positions were 84:16 and 73:27, respectively (**Table 1**, run 1). Cyclization at 0 °C (condition **B**)[5] did not improve the diastereoselectivity (run 2).[6] The reactivity of stannyl radical toward an acetylenic moiety was low below 0°C.[2a] We then used **10** as a substrate, which easily produces an alkenyl radical even at -98°C. The cyclization of **10** at -98°C gave a modest increase in the diastereoselectivity at both the α- and β-positions. A mixture of the cyclized products was obtained in 72% yield. The selectivity at the α-position was 90 : 10 and that at the β-position was 79 : 21.



Scheme 5 Transition-state model

The stereochemical outcome observed in these radical reactions suggests a working hypothesis for the transition states (**Scheme 5**). The phenyl group shields a π-face of the alkene, and the α-methyl-α,β-unsaturated ester exists in an *s-trans* conformation. The alkenyl radical attacked the β-position of the α-methyl-α,β-unsaturated ester from a less-hindered face of the alkene. The resulting α-radical is planar, since it is

conjugated with carboxylic ester and appears to favor the conformation with the larger cyclopentyl group *anti* to the alkoxy group.[2b] Hydrogen abstraction occurs predominantly from the *Si*-face of the α-radical.

In conclusion, we have reported the intramolecular cyclization of alkenyl radicals using α-methyl-α,β-unsaturated (-)-8-phenylmenthyl ester as a chiral radical acceptor, through which we can control the diastereoselectivities at the α- and β-position. A moderate temperature dependence was observed and the highest diastereoselectivity was observed in the reaction at -98°C.

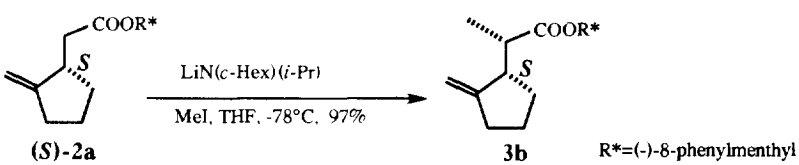
REFERENCES AND NOTES

1 Review of diastereoselective reactions using the 8-phenylmenthyl group as a chiral auxiliary: Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953-964.

2 Diastereoselective radical reaction review: (a) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296-304. ρ-Selective radical reactions using the 8-phenylmenthyl group as a chiral auxiliary: (b) Chen, M.-Y.; Fang, J.-M.; Tsai, Y.-M.; Yeh, R.-L. *J. Chem. Soc., Chem. Commun.* **1991**, 1603. (c) Hamon, D. P. G.; Razzino, P.; Massy-Westropp, R. A. *J. Chem. Soc., Chem. Commun.* **1991**, 332. (d) Hamon, D. P. G.; Massy-Westropp, R. A.; Razzino, P. *J. Chem. Soc., Chem. Commun.* **1991**, 722. (e) Crich, D.; Davies, J. W. *Tetrahedron Lett.* **1987**, *28*, 4205. (f) Snider, B. B.; Zhang, Q. *Tetrahedron Lett.* **1992**, *33*, 5921. (h) Vaβen, R.; Runsink, J.; Scharf, H. -D. *Chem. Ber.* **1986**, *119*, 3492.

3 (a) Nishida, M.; Ueyama, E.; Hayashi, H.; Ohtake, Y.; Yamaura, Y.; Yanaginuma, E.; Yonemitsu, O.; Nishida, A.; Kawahara, N. *J. Am. Chem. Soc.*, **1994**, *116*, 6455. (b) Nishida, M.; Hayashi, H.; Yamaura, Y.; Yanaginuma, E.; Yonemitsu, O.; Nishida, A.; Kawahara, N. *Tetrahedron Lett.*, **1995**, *36*, 269.

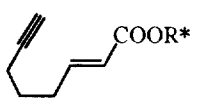
4 The stereochemistry of the methylation of **(*R*)-2a** did not appear to be controlled by (-)-8-phenylmenthyl as a chiral auxiliary. Instead, it was controlled by the adjacent stereogenic carbon. The methylation of **(*S*)-2a** proceeded stereoselectively.



(*S*)-2a **3b** R*=(-)-8-phenylmenthyl

5 Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.*, **1987**, *109*, 2547.

6 In the reaction of **11**, the presence of Lewis acids was essential to achieve high diastereoselectivity.[3a] However, the cyclization of **9** in the presence of BF_3•Et_2O (2 or 32 eq) at 0°C was inefficient.



11 R*=(-)-8-phenylmenthyl

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