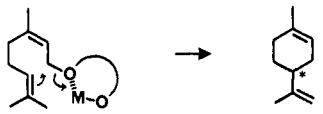
Chiral Leaving Group. Biogenetic-Type Asymmetric Synthesis of Limonene and Bisabolenes

Soichi Sakane, Junya Fujiwara, Keiji Maruoka, and Hisashi Yamamoto*

Department of Applied Chemistry, Nagoya University Chikusa, Nagoya 464, Japan

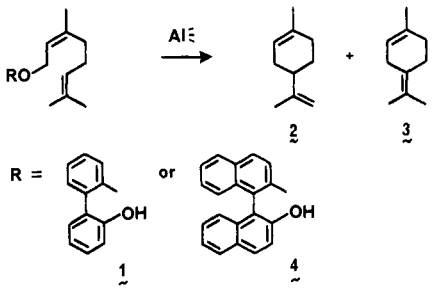
Received April 26, 1983

The structural diversity found in terpene metabolism is mostly elaborated by olefinic cyclizations of five basic acyclic precursors.[1] The biological strategy for construction of new C–C bonds involves intramolecular electrophilic alkylation of remote double bonds to a cationic center generated by the ionization of allylic pyrophosphates,[2] in which the enzyme may require a divalent cation, Mg^{2+} or Mn^{2+}, for catalytic activity.[3] Formation of limonene from neryl precursors is commonly assumed to be a suitable model for related terpene biosynthesis. Although a number of regiochemical features of this simple cyclization have been delineated,[4] the crucial enantioface differentiation taking place at the enzyme active site as well as the important role of a divalent metal to assist with C–O heterolysis of the allylic substrates have received scant attention.[5] For a number of years we have been intrigued in the simulation of such a cyclization in organic chemistry. It is with great pleasure that we record herein the first asymmetric syntheses of monocyclic terpenes limonene and bisabolenes in a biogenetic manner (eq 1).



(1)

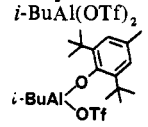
First, the cyclization of biphenol mononeryl ether (**1**) was studied. Treatment of **1** in CH_2Cl_2 with diisobutylaluminum hydride (DIBAH) (1.2 equiv of a 1 M hexane solution) under argon at −78 °C for 30 min and at 20°C for 10 h furnished a mixture of limonene (**2**) and terpinolene (**3**) (81% yield) in a ratio



1 **4** **2** **3**

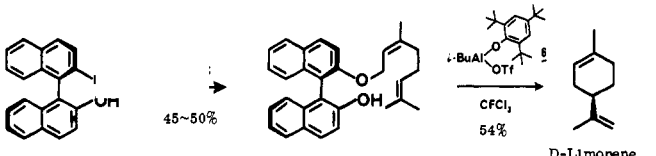
of 8:1.[6] None of the acyclic components were detected in the crude reaction mixture by GLC analysis. The use of Me_3Al or

Table I. Asymmetric Synthesis of D-Limonene[a]

entry	aluminum reagent	condition[b]	chemical yield, %[c] (selectivity)[d]	D-limonene[e,f] $[\alpha]_D$, deg (c)[g]	D-limonene[e,f] optical yield % ee
1	i-Bu_2AlOTf	A	36 (3:1)	+45 (0.96)	39
2	i-$BuAl(OTf)_2$	B	27 (4:1)	+46 (0.46)	40
3		C	29 (5.2:1)	+74 (0.36)	64
4	**6**	D	58[h] (14:1)	+88 (1.44)	77

[a] Most of these reactions were run on a 1 mmol scale using 3 equiv of the aluminum reagents. [b] Conditions (°C (h)) A: −130 (1), −100 (3), −94 (3), −84 (2.5), −78 (4); B: −130 (4), −100 (5.5), −94 (1), −78 (3); C: −130 (1), −78 (9), −60 (3); D: −130 (3). [c] Isolated by chromatography on silica gel, unless otherwise specified. [d] Selectivity refers to the ratio of limonene and terpinolene, which was determined by capillary GLC analysis (20-m OV-101, 125 °C). [e] D-Limonene was separated from terpinolene by prepacked column chromatography on silica gel (*n*-pentane as eluant). [f] Commercial D-limonene (supplied from Wako Pure Chemical Industries, Ltd.) was found to be >98% enantiomerically pure. Its optical purity was substantiated by NMR analysis after converting to α-terpineol (Brown, H. C.; Geoghegan, P. J., Jr.; Lynch, G. J.; Kurek, J. T. *J. Org. Chem.* 1972, *37*, 1941) and then to the MTPA ester by using (*S*)-(−)-MTPA chloride and 4-(dimethylamino)pyridine (Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* 1969, *34*, 2543). In the presence of Sievers' reagent the MTPA ester of α-terpineol derived from the commercially available D-limonene gave a single methoxy signal, whereas the diastereomeric esters formed from the racemic limonene exhibited two sets of the signals with equal intensities. [g] In *n*-pentane. Commercially available D-limonene exhibited specific rotation $[\alpha]^{20}_D$ + 115° (*c* 0.82, *n*-pentane), which was not concentration dependent in *c* 0.44–1.50. [h] Determined by capillary GLC (20-m OV-101, 125 °C) using veratrole (*o*-dimethoxybenzene) as an internal standard.

Scheme I



(R)-(+)-Binaphthol **5** D-Limonene 77% ee

[a] Me_3SiCl, NEt_3. [b] NaH, neryl bromide. [c] H_3O^+.

dimethylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide as reagent in experiments otherwise comparable to that described above produced **2** and **3** in yields of 76% (ratio, 7:1) and 63% (5:1), respectively. Moreover, the reaction of **4** with aluminum reagents producing **2** and **3** follows: DIBAH, 77% (9:1); Me_3Al, 72% (7.5:1). Notably, the cyclization of neryl phenyl ether has proved to proceed much more slowly than those of **1** and **4** under the similar conditions.[7] The remarkable rate acceleration observed here should be ascribed to the novel *metal-anchimeric assistance* of the aluminum reagents bound with the neighboring hydroxyl group for effecting the ionization of the allylic substrates.

With the demonstration of the anchimeric effect of metal in terpene synthesis accomplished, our attention has been focused on the enantioselective cyclization of neryl precursors, a reaction that would provide access to a variety of terpenes in enantiomeric form. Accordingly, (*R*)-(+)-binaphthol mononeryl ether (**5**) ($[\alpha]^{20}_D$ +39.4° (*c* 0.77, THF)) was prepared in 45–50% yield[8]

(1) Johnson, W. S. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 9. Cane, D. E. *Tetrahedron* **1980**, *36*, 1109.

(2) For the intermolecular version in terpene biosynthesis, see: Coates, R. M. *Fortschr. Chem. Og. Naturst.* **1976**, *33*, 73. Poulter, C. D.; Rilling, H. C. *Acc. Chem. Res.* **1978**, *11*, 307. Poulter, C. D.; Rilling, H. C. In "Biosynthesis of Isoprenoid Compounds"; Porter, J. W., Ed.; Wiley: New York, 1981; Vol. 1, pp 161–224.

(3) For the metal effect to ionize allylic substrates, see: George-Nascimento, C.; Pont-Lezica, R.; Cori, O. *Biochem. Biophys. Res. Commun.* **1971**, *45*, 199. Brems, D. N.; Rilling, H. C. *J. Am. Chem. Soc.* **1977**, *99*, 8351. King, H. L., Jr.; Rilling, H. C. *Biochemistry* **1977**, *16*, 3815.

(4) Previous biogenetic-type limonene syntheses: Haley, R. C.; Miller, J. A.; Wood, H. C. S. *J. Chem. Soc. C* **1969**, 264. Rittersdorf, W.; Cramer, F. *Tetrahedron* **1967**, *23*, 3015, 3023; **1968**, *24*, 43. Valenzuela, P.; Cori, O. *Tetrahedron Lett.* **1967**, 3089. Kitagawa, Y.; Hashimoto, S.; Iemura, S.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1976**, *98*, 5030. Kobayashi, S.; Tsutsui, M.; Mukaiyama, T. *Chem. Lett.* **1976**, 1137.

(5) Enantioselective syntheses of α-terpineol from neryl and linalyl precursors were reported previously. See: Stephan, W. *J. Prakt. Chem.* **1898**, *58*, 109. Winstein, S.; Valkanas, G.; Wilcox, C. F. *J. Am. Chem. Soc.* **1972**, *94*, 2286. Godtfredsen, S.; Obrecht, J. P.; Arigoni, D. *Chimia* **1977**, 31, 62. Poulter, C. D.; King, C.-H. R. *J. Am. Chem. Soc.* **1982**, *104*, 1420, 1422.

(6) The ratio of **2** and **3** was determined by capillary GLC (20-m OV-101, 125 °C) using 1-dodecene as an internal standard. The ether **1** was prepared in 45–50% yield by treatment of biphenol in *i*-PrOH with neryl bromide (1.1 equiv) in the presence of *t*-BuOK (1.1 equiv) at 20 °C for 1 day.

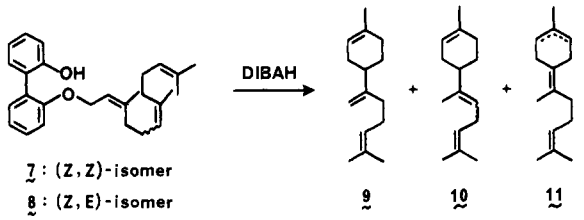
(7) Attempted cyclization of neryl phenyl ether with diisobutylaluminum phenoxide (1.2 equiv) in CH_2Cl_2 at 20 °C for 1 day resulted in 50% recovery of the starting material.

(8) Preparation of **5** is as follows: (*R*)-(+)-Binaphthol in THF was treated with trimethylsilyl chloride (1.1 equiv) and triethylamine (1.5 equiv) at 0 °C for 3 h to afford (*R*)-(+)-binaphthol monosilyl ether exclusively, which was alkylated with neryl bromide (1.1 equiv) and NaH (1.1 equiv) in THF–HMPA at 20 °C for 1 day, producing **5** (45–50% overall yield) after aq HCl workup. Direct alkylation of (*R*)-(+)-binaphthol resulted in formation of its dineryl ether with recovered (*R*)-(+)-binaphthol.

0002-7863/83/1505-6154$01.50/0

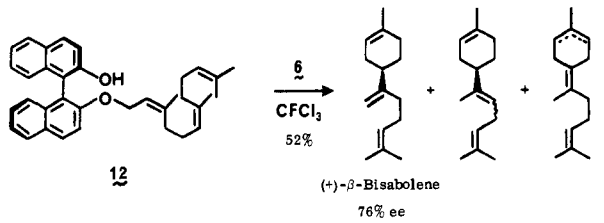
by the monosilylation and alkylation of (*R*)-(+)-binaphthol as the chiral auxiliary.[9] Reaction of **5** with DIBAH (1.2 equiv) under the standard conditions gave naturally occurring D-limonene and **3** (ratio, 5:1) in 58% yield with only moderate optical yield (~12% ee). Surprisingly, a dramatic enhancement in both regio- and enantioselectivity was observed when **5** was treated with modified organoaluminum reagents at low temperature as revealed in Table I. The highest enantioface differentiation was finally achieved by the use of (2,4,6-tri-*tert*-butylphenoxy)isobutylaluminum trifluoromethanesulfonate (**6**)[10] (3 equiv)[11] in $CFCl_3$ at −130 °C (*n*-pentane–liquid N_2 bath) for 3 h, producing D-limonene (54% yield) almost exclusively in 77% ee (Scheme I).

The present study has been successfully extended to the synthesis of bisabolenes[12] from biphenol (*Z,Z*)-monofarnesyl ether (**7**) and its *Z,E* isomer **8**.[13] Reaction of the *Z,Z* isomer **7** with DIBAH (1.2 equiv) at −78 °C for 30 min and at 20 °C for 4.5 h furnished β-bisabolene (**9**) preferentially in 60% yield accompanied by 16% of α-bisabolene (**10**) (*E/Z*, 2.7:1) and 9% of γ-bisabolene (**11**) (*E/Z*, 1:3).[14] On the other hand, the *Z;E* isomer **8** under the similar conditions transformed to an equal mixture of **9** (34%) and **10** (30%; *E/Z*, 2.6:1) along with **11** (7%; *E/Z*, 1:1).[15] Noteworthy is the preferential formation of **9** from



the *Z,Z* isomer **7** vs. **8**, since it implies that during deprotonation the aluminum reagent may be responsible for the discrimination of the stereochemistry of the farnesyl moiety.

Furthermore, by switching the biphenol moiety to a chiral auxiliary and manipulating the modified organoaluminum reagents, asymmetric synthesis of bisabolenes appears feasible. Thus, exposure of (*R*)-(+)-binaphthol (*Z,Z*)-monofarnesyl ether (**12**)[16] ($[\alpha]^{20}_D$ +28.6° (*c* 1.02, THF)) to the aluminum reagent **6** (3 equiv) in $CFCl_3$ at −130 °C for 3 h led to the formation of bisabolenes (ratio of *Z*-α/β/*Z*-γ/*E*-γ/*E*-α = 1:90:4:1:25) in 52% yield, from which (+)-β-bisabolene was separated by preparative TLC on $AgNO_3$-impregnated silica gel (ether/hexane, 1:10 as eluant).[17] This product was 76% enantiomerically pure, as determined by the comparison of the magnitude of the optical rotation, $[\alpha]^{20}_D$ +56° (*c* 2.94, EtOH), with that of authentic sample.[18,19]



The terpene syntheses disclosed above provide a new body of results that, coupled with certain other considerations, (1) indicate that the six-membered ring is formed with a high degree of neighboring π-bond participation during C–O heterolysis of **5** and **12**, thus allowing the remote chiral transfer efficiently and (2) suggest that the overall process may involve conformationally rigid cationic structures. The origin of the high enantioselection arising from the rigid, unique conformation of the chiral acyclic precursor must await further research.

Acknowledgment. Support for this research from the Ministry of Education, Japanese Government (Grand-in-aid 57102008), and Kuraray Co., Ltd., is gratefully acknowledged. We thank Professor R. Noyori for valuable discussions.

Registry No. (*Z*)-**1**, 86803-76-1; (±)-**2**, 7705-14-8; **3**, 586-62-9; (*Z*)-**4**, 86803-77-2; (*R*)-(*Z*)-**5**, 86851-45-8; **6**, 86822-06-2; (*Z,Z*)-**7**, 86803-78-3; (*Z,E*)-**8**, 86803-79-4; (±)-**9**, 4891-79-6; (±)-(*E*)-**10**, 70286-16-7; (±)-(*Z*)-**10**, 70332-15-9; (*E*)-**11**, 53585-13-0; (*Z*)-**11**, 13062-00-5; (*R*)(*Z,Z*)-**12**, 86803-80-7; *i*-Bu_2AlOTf, 86803-81-8; *i*-$BuAl(OTf)_2$, 86803-82-9; D-limonene, 5989-27-5; (+)-β-bisabolene, 20377-48-4; 2,6-bis(*tert*-butyl)-4-methylphenoxyisobutylaluminum trifluoromethanesulfonate, 86803-83-0; (*R*)-(*Z*)-α-bisabolene, 70286-33-8; (*R*)-(*E*)-α-bisabolene, 70286-31-6; (*R*)-(+)-binaphthol, 18531-94-7; (*R*)-(+)-binaphthol monosilyl ether, 86803-84-1; dimethylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide, 86803-85-2; (*Z*)-neryl bromide, 25996-10-5.

(9) Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1978**, *11*, 8. Recently a highly enantioselective reducing agent using chiral binaphthol was reported: Noyori, R. *Pure Appl. Chem.* **1981**, *53*, 2315.

(10) For preparation of the reagent **6**, see: Yamamura, Y.; Umeyama, K.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1982**, *23*, 1933.

(11) The use of 1.2 equiv of **6** gave the unreproducible results.

(12) Recent bisabolene syntheses: (a) Crawford, R. J.; Erman, W. F.; Broaddus, C. D. *J. Am. Chem. Soc.* **1972**, *94*, 4298. (b) Faulkner, D. J.; Wolinsky, L. E. *J. Org. Chem.* **1975**, *40*, 389. (c) Wolinsky, L. E.; Faulkner, D. J.; Finer, J.; Clardy, J. *Ibid.* 1976, *41*, 697. (d) Larkin, J. P.; Nonhebel, D. C.; Wood, H. C. S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2524. (e) Kobayashi, S.; Tsutsui, M.; Mukaiyama, T. *Chem. Lett.* **1977**, 1169. (f) Delay, F.; Ohloff, G. *Helv. Chim. Acta* **1979**, *62*, 369. (g) Becker, M.; Weyerstahl, P. *Ibid.* **1979**, *62*, 2724.

(13) The ethers **7** and **8** were obtained in 50–55% yield by the procedure similar to that described in ref 6. (*Z,Z*)-Farnesol and its *Z,E* isomer were kindly provided from Kuraray Co., Ltd.

(14) The structures **9**–**11** were confirmed by the capillary GLC comparison (20-m OV-101, 150 °C) with the authentic samples: t_r((*Z*)-**10**) = 18.37 min; t_r(**9**) = 19.05 min; t_r((*Z*)-**11**) = 19.53 min; t_r((*E*)-**11**) = 20.72 min; t_r((*E*)-**10**) = 21.49 min. The authentic **9** and **11** were prepared according to ref 12, a and c, respectively. The synthesis of authentic **10** was made by the analogous method as in ref 12c.

(15) Cyclization of **7** and **8** by using dimethylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide showed a similar tendency. The yields and ratios of bisabolenes thus obtained are as follows: **7**: 64% ((*Z*)-**10**/**9**/(*Z*)-**11**/(*E*)-**11**/(*E*)-**10** = 1:18:2.3:1:3.3); **8**: 79% (1.3:6.5:1:1.1:4.3).

(16) The ether **12** was synthesized in 50–52% yield in a like manner as described in ref 8.

(17) Attempted isolation of chiral (+)-(*E*)-α-bisabolene was unsuccessful.

(18) See ref 12a.

(19) The *Z,E* isomer of **12** was subjected to the analogous cyclization conditions providing (+)-β-bisabolene in lower optical yield (62% ee).

In Situ Trapping of Ortho-Lithiated Benzenes Containing Electrophilic Directing Groups[1]

Timothy D. Krizan and J. C. Martin*

Roger Adams Laboratory, Department of Chemistry
University of Illinois, Urbana, Illinois 61801

Received April 26, 1983

The directed ortho lithiation of substituted benzenes is a powerful method for the preparation of synthetically useful aryllithium intermediates.[2] It is used with benzene rings containing kinetically acidic C–H bonds ortho to nonelectrophilic directing groups, such as the methoxyl substituent. It can be used with electrophilic directing groups if the electrophilic center reacts sufficiently slowly with the nucleophilic base (usually *n*-butyllithium) or with the product aryllithium. Two methods have been used to slow this reaction sufficiently to allow the accumulation of synthetically useful concentrations of the aryllithium before addition of the external electrophile to give the desired product: (a) the use of low temperatures (usually −78 °C or lower) and/or (b) the use of electronically deactivated electrophiles, such as amides,[2b] or sterically deactivated electrophiles, such as the 4,4-dimethyl-2-oxazolines.[3] We here report a third stratagem to minimize

(1) Krizan, T. D.; Martin, J. C. "Abstracts of Papers", 185th National Meeting of the American Chemical Society, Seattle, WA, March 20–25, 1983; American Chemical Society: Washington, D.C., 1983; ORGN 116.

(2) For recent reviews, see: (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (b) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306.

0002-7863/83/1505-6155$01.50/0