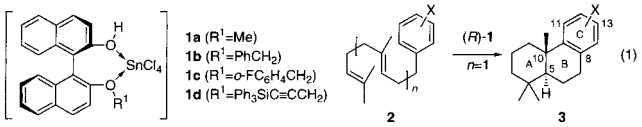
Enantioselective Biomimetic Cyclization of Homo(polyprenyl)arenes. A New Entry to (+)-Podpcarpa-8,11,13-triene Diterpenoids and (−)-Tetracyclic Polyprenoid of Sedimentary Origin

Kazuaki Ishihara,† Hideaki Ishibashi,‡ and Hisashi Yamamoto*,‡

Graduate School of Engineering and Research Center for Advanced Waste and Emission Management Nagoya University, CREST Japan Science and Technology Corporation (JST) Furo-cho, Chikusa, Nagoya 464-8603, Japan

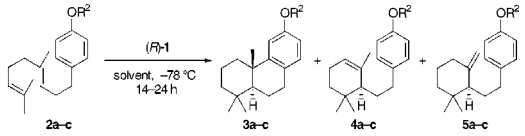
Received September 29, 2000

Acid-induced cyclization of polyprenoids is one of the simplest and most widely used methods for the synthesis of polycyclic terpenoids.[1] We recently reported the first enantioselective cyclization of 2-polyprenylphenols induced by a Lewis acid-assisted chiral Brønsted acid (chiral LBA), **1**.[2] A hydroxy group in polyprenylphenols assists this polyene cyclization as a good nucleophilic internal terminator. We describe here the application of this approach to a more challenging synthetic problem: the first enantioselective cyclization of homo(polyprenyl)arenes **2** possessing an aryl group that serves as a less-nucleophilic terminator than a hydroxy group (eq 1).



Although cyclization via 2-(2-arylethyl)-1,3,3-trimethylcyclohexyl carbocations has been widely used to contruct the B-ring of podocarpa-8,11,13-triene diterpenoids **3**,[3] there have been only a few reports on successive cyclizations of homogeranylbenzene derivatives **2** ($n = 1$) to **3**.[4] We initially studied the enantioselective cyclization of 4-homogeranylphenol (**2a**) and its ether derivatives **2b** and **2c**[5] with (*R*)-**1**. Representative results are summarized in Table 1. Reaction of **2a** in dichloromethane with (*R*)-**1a** at −78 °C for 14 h gave the desired trans tricyclic product **3a** in 87% yield and 38% ee (entry 1). The other products were monocyclization products, **4a** and **5a**. The enantioselectivity of **3a** was improved to 49% ee with toluene in place of dichloromethane, but the yield of **3a** was decreased and the yields of **4a** and **5a** were increased (entry 2). Furthermore, the enantioselectivity increased to 59% ee when **2b** was used in place of **2a** (entry 3). In screening several protective groups, R^1 in (*R*)-**1** and R^2 in **2** ($n = 1$), we found that triphenylsilylpropargyl or *o*-fluorobenzyl group and *tert*-butyldiphenylsilyl group were the most suitable R^1 and R^2, respectively, with regard to enantioselectivity (entries 6 and 7): the reaction of **2c** with (*R*)-**1c** gave *trans*-**3c** in 9% yield and 81% ee (entry 6). The relationship between enantioselectivity and R^1 is not clear. The steric bulkiness of R^2 may impair interaction between tin tetrachloride and the basic oxygen atom of OR^2. The absolute configuration of *trans*-**3** shown in Table 1 was assigned to be 5*S* and 10*S* based on the known optical rotation.[3c] Notably, the tricyclic compounds **3a**−**c** obtained in the cyclization of **2a**−**c** were only trans isomers regardless of the reaction conditions.[3e,f]

Table 1. Enantioselective Cyclization of Homogeranylbenzene Derivatives **2a**−**c**



entry	**2a**−**c** (R^2)	(*R*)-**1** (equiv)	solvent, time (h)	molar ratio[a] **3a**−**c** [ee (%)][b]	**4a**−**c**	**5a**−**c**	**2a**−**c**
1[c]	**2a** (H)	**1a** (1.1)	CH_2Cl_2, 14	87 [38]	6	7	0
2[c]	**2a**	**1a** (1.1)	toluene, 14	28 [49]	40	32	0
3	**2b** (Me)	**1a** (2.0)	toluene, 19	10 [59]	36	36	18
4	**2b**	**1b** (2.0)	toluene, 24	13 [61]	33	32	22
5[d]	**2c** (*t*-$BuPh_2Si$)	**1a** (2.0)	toluene, 24	13 [72]	35	35	17
6[d]	**2c**	**1c** (2.0)	toluene, 48	9 [81]	44	47	0
7[d]	**2c**	**1d** (1.1)	toluene, 96	19 [80]	40	41	0

[a] Determined by GC and ^{1}H NMR analyses. [b] Determined by chiral HPLC analysis. [c] Product ratio was determined by GC and ^{1}H NMR analyses after acetylation of products. [d] Product ratio was determined by GC and ^{1}H NMR analyses after desilylation and acetylation of products.

The diastereoselective cyclization of **4** and **5** with achiral LBA was explored to increase the chemical yield of **3**. After treating **2b** with (*R*)-**1b** at −78 °C for 3 days to completely consume **2b**, an achiral LBA, tin tetrachloride−trifluoroacetic acid, was added to the reaction solution at the same temperature and the mixture was stirred for an additional 1 day. As expected, the desired product **3b** was obtained in 62% ee and 86% yield from **2b** in a one-pot procedure (cf. entry 4 in Table 1). Furthermore, the desilylation of a crude mixture of **3c**, **4c**, and **5c**, which were obtained in the enantioselective cyclization of **2c** induced by (*R*)-**1c**, with tetrabutylammonium fluoride was highly effective at increasing the reactivity of the subsequent diastereoselective cyclization. Thus, the desired product **3a** was obtained in 78% ee and 94% yield from **2c** in three steps (Scheme 1; cf. entry 6 in Table 1). Since (±)-**3** has already been converted into (±)-ferruginol (**6**) by King[6] and Ghatak,[3d] the present method represents a formal and the first enantioselective total synthesis of (+)-**6**.

The enantioselective cyclization of 1-homogeranyl-3-(*tert*-butyldiphenylsiloxy)benzene (**2d**) was also examined with use of (*R*)-**1c** in toluene at −78 °C (Scheme 2). As expected, tricyclic product **3d** was obtained in 78% ee (trans only), together with the monocyclization products **4d** and **5d**. However, the subsequent cyclization of desilylated compounds **4e** and **5e** with $BF_3{\cdot}Et_2O$ in nitromethane[4c] gave a 37:63 mixture of *trans*- and *cis*-**3e** together with a small amount of *trans*-**7**.[7] *Fortunately, the*

† Graduate School of Engineering.

‡ Research Center for Advanced Waste and Emission Management.

(1) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Part B, pp 341−409.

(2) (a) Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 4906. (b) Nakamura, S.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8131.

(3) (a) Matsumoto, T.; Usui, S. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 212. (b) Matsumoto, T.; Suetsugu, A. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1450. (c) Axon, B. W.; Davis, B. R.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2956. (d) Banik, B. K.; Chakraborti, A. K.; Ghatak, U. R. *J. Chem. Res. (S)* **1986**, 3391. (e) Banik, B. K.; Ghosh, S.; Ghatak, U. R. *Tetrahedron* **1988**, *44*, 6947. (f) Ghosh, S.; Banik, B. K.; Ghatak, U. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3189 and references therein.

(4) For the cationic cyclization of homogeranylbenzene derivatives bearing regioselectivity- and/or diastereoselectivity-inducing auxiliaries, see the following. Tosyl group: (a) Janssen, C. G. M.; Godefroi, E. F. *J. Org. Chem.* **1982**, *47*, 3274. Trimethylsilyl group: (b) Janssen, C. G. M.; Godefroi, E. F. *J. Org. Chem.* **1984**, *49*, 3600. Cyano group: (c) Harring, S. R.; Livinghouse, T. *Tetrahedron* **1994**, *50*, 9229.

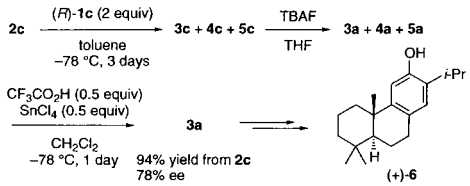
(5) For preparation of **2**, see: Araki, S.; Sato, T.; Butsugan, Y. *J. Chem. Soc., Chem. Commun.* **1982**, 285.

(6) King, F. E.; King, T. J.; Topliss, J. G. *J. Chem. Soc.* **1957**, 573.

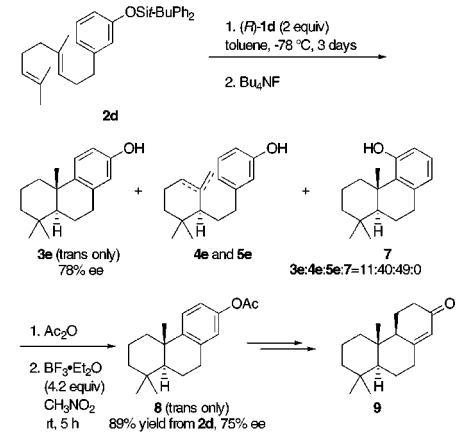
(7) Although several ethers of **4e** and **5e** were examined regarding the second cyclization induced by $SnCl_4{\cdot}CF_3CO_2H$ or $BF_3{\cdot}Et_2O$, cis tricyclic compounds were produced as major products in all cases.

10.1021/ja003541x CCC: $20.00
Published on Web 01/27/2001

Scheme 1. Enantioselective Synthesis of (5*S*,10*S*)-**3a**

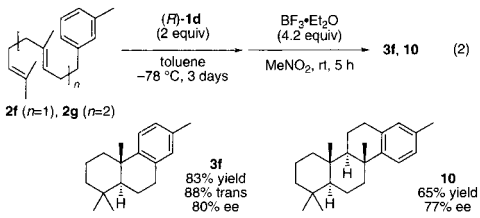


Scheme 2. Enantioselective Synthesis of (5*S*,10*S*)-**8**



*cyclization of acetates of **4e** and **5e** under the same conditions gave (+)-13-acetoxypodocarpa-8,11,13-triene (**8**) with high diastereoselectivity (trans only) and high regioselectivity (no detectable amount of **7**).* Thus, the desired product **8** was obtained in 75% ee and 89% yield from **2d**. This compound **8** can be easily converted into (+)-podocarpa-8(14)-en-13-one (**9**),[3a,8] a versatile intermediate for synthesis of naturally occurring diterpenes, e.g. isophyllocladene,[9a] phyllocladene,[9a] hibaone,[9b] manool,[9c] sclareol,[9c] manoyl oxide,[9c] isoabienol,[9d] *trans*-abienol,[9d] and anticopalic acid.[9e,f] Therefore, the present work can be regarded as the enantioselective total syntheses of the above natural diterpenes.

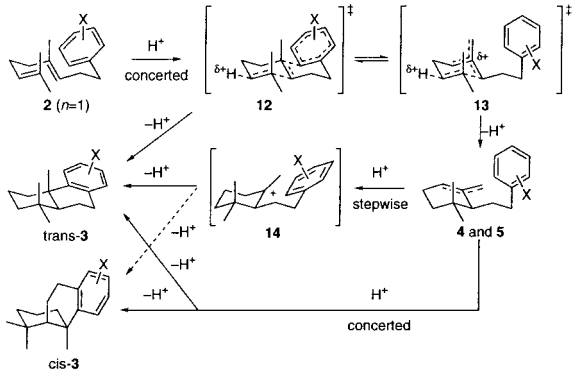
In 1990, Azevedo's group found 13-methylpodocarpa-8,11,-13-triene (**3f**) in a Tasmanian tasmanite sediment.[10] Four years later, Albrecht's group reported the isolation of a series of chiral tetracyclic (**10**), pentacyclic, hexacyclic (**11**), heptacyclic, and octacyclic homologues, from Eocene Messel shale (Germany), which appear to be the remnants of an ancient family of cyclopolyprenoids.[11] Very recently, Corey's group achieved the asymmetric synthesis of **10** and **11** using the diastereoselective Lewis acid-catalyzed polycyclization of polyunsaturated oxiranes.[12] To demonstrate the generality of our synthetic strategy, polycyclic terpenes **3f** and **10** were concisely synthesized by using the LBA **1d**-induced enantioselective cyclization of 3-homo(polyprenyl)toluenes as a key step (eq 2). An achiral LBA,



$SnCl_4$•CF_3CO_2H/CH_2Cl_2, as well as BF_3•Et_2O/$MeNO_2$, was effective for the second step.

The present investigation on the stereochemistry of the acid-induced polyene cyclization of **2** provide some important gener-

Scheme 3. Possible Reaction Paths for the Acid-Induced Cyclization of **2** ($n = 1$)



alizations.[3,13] The possible reaction paths are shown in Scheme 3. Initial cyclization of **2** ($n = 1$) induced by (*R*)-**1d** should take place through a concerted pathway involving transition states (TSs) **12** and **13** enantioselectively: TS-**12** stereospecifically leads to *trans*-**3**, while TS-**13** leads to a mixture of **4** and **5**. 4-Homogeranylphenol **2a** was completely consumed in toluene in the presence of 1.1 equiv of (*R*)-**1b** (Table 1, entry 2), while the corresponding ethers **2b** and **2c** were obtained in ca. 20% yield even in the presence of 2 equiv of (*R*)-**1** (Table 1, entries 3−5). These experimental results indicate that protection of a hydroxy group in **2a** suppresses not only the second cyclization to form the B-ring but also the initial cyclization to form the A-ring. *Thus, an aryl moiety in **2** ($n = 1$) serves not only as a nucleophilic internal terminator to form the B-ring but also as a remote promoter of cyclization to form the A-ring (a secondary effect) via TS-**12**.* Furthermore, the stereochemistry in the subsequent cyclization of **4** and **5** strongly depends on the nucleophilicity of their terminal benzene ring. Benzene rings without an electron-donating substituent, *para* to the site of electrophilic attack, are not sufficiently nucleophilic to react through the concerted pathways; rather, they require complete protonation to a carbocation **14** which reacts with high stereoselectivity by a stepwise pathway due to the minimum steric effects giving *trans*-**3**: e.g. the second cyclization of **4a**−**c**, **5a**−**c**, and acetates of **4e** and **5e** leads only to *trans*-**3**. With an electron-donating substituent, the concerted pathways that give a mixture of *trans*- and *cis*-**3** predominate over the stepwise pathway.

Nonenzymatic enantioselective polyene cyclization of **2** is a very attractive alternative to multistep synthesis from naturally occurring chiral synthons. We have demonstrated the effectiveness of chiral LBAs for absolute stereocontrol in the initial cyclization step of **2** to form an A-ring and the importance of the nucleophilicity of the internal terminator in **2** for the relative stereocontrol in the subsequent cyclization step.

Supporting Information Available: Experimental details and characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA003541X

(8) (a) Bartltrop, J. A.; Rogers, N. A. *J. Chem. Soc.* **1958**, 2566. (b) Church, R. F.; Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1966**, *31*, 2526.

(9) (a) Duc, D. K. M.; Fetizon, M.; Lazare, S. *J. Chem. Soc., Chem. Commun.* **1975**, 282. (b) Duc, D. K. M.; Fetizon, M.; Flament, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 886. Duc, D. K. M.; Fetizon, M.; Flament, J. P. *Tetrahedron* **1975**, *31*, 1897. (c) Wenkert, E.; Mahajan, J. R.; Nussim, M.; Schenker, F. *Can. J. Chem.* **1966**, *44*, 2575. (d) Vlad, P. F.; Russo, A. G.; Kuang-fang, C. *Zh. Obsch. Chim. (Engl. Ed.)* **1969**, *39*, 423. (e) Manh, D. D. K.; Fetizon, M.; Kone, M. *Tetrahedron* **1975**, *31*, 1903. (f) Ohloff, G. *Justus Liebigs Ann. Chem.* **1958**, *615*, 134.

(10) Azevedo, D. A.; Aquino Neto, F. R.; Simoneit, B. R. T. *Org. Mass Spectrom.* **1990**, *25*, 475 and references therein.

(11) Schaeffer, P.; Poinsot, J.; Hauke, V.; Adam, P.; Wehrung, P.; Trendel, J.-M.; Albrecht, P.; Dessort, D.; Connan, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1166.

(12) Corey, E. J.; Luo, G.; Shouzhong, L. *Angew. Chem., Int. Ed.* **1998**, *37*, 1126.

(13) Corey, E. J.; Staas, D. D. *J. Am. Chem. Soc.* **1998**, *120*, 3526.