ORGANIC LETTERS

2004
Vol. 6, No. 18
3159−3161

Chiral Benzyl Centers through Asymmetric Catalysis. A Three-Step Synthesis of (*R*)-(−)-α-Curcumene via Asymmetric Hydrovinylation

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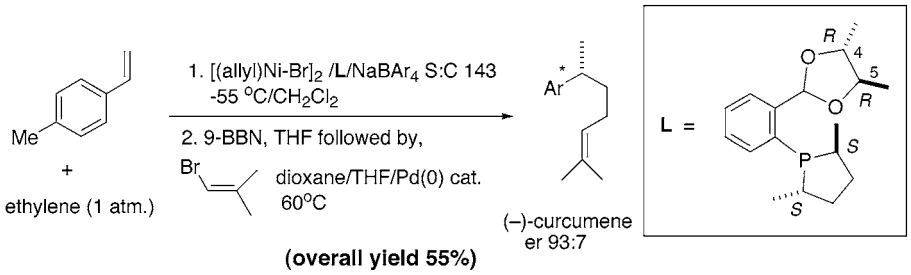
Received June 24, 2004

ABSTRACT



(overall yield 55%)

A three-step, two-pot procedure involving asymmetric hydrovinylation followed by Suzuki–Miyaura reaction represents by far the shortest synthesis of this popular bisabolane. Other applications for the synthesis of similar compounds with chiral benzyl centers can be easily envisioned.

Several important classes of natural products, among them, bisabolanes, heliannanes, serrulatanes, and pseudopterosins (Figure 1), are characterized by a benzylic chiral center, often carrying a methyl group at this position.[1] Diverse biological activities[2] exhibited by these compounds include antiinflammatory, antiviral, and antimycobacterial properties, and they have attracted considerable attention from synthetic chemists. No less than 12 nonracemic syntheses of the simplest member of this class of compounds, (*R*)-(−)-α-curcumene, are known. (*R*)-(−)-α-Curcumene and related (*R*)-(−)-*ar*-turmerone are the consitutents of a large number of essential oils, and it has been amply demonstrated that intermediates for their synthesis could in principle be used for a number of other bisabolane and other related terpenes.[1a]

Despite their rather simple structures, the stereocenter at the benzylic position[3] poses a significant challenge in the asymmetric synthesis of even the simplest of these molecules. Judged by the number of publications (vide infra) dealing

(1) For recent references, see the following and others cited therein. (a) Bisabolanes: Hagiwara, H.; Okabe, T.; Ono, H.; Kamat, V. P.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 895. Vyvyan, J. R.; Loitz, C.; Looper, R. E.; Mattingly, C. S.; Peterson, E. A.; Staben, S. T. *J. Org. Chem.* **2004**, *69*, 2461. (b) Heliannanes: Kishuku, H.; Shindo, M.; Shishido, K. *Chem. Commun.* **2003**, 350. (c) Pseudopterosins: Look, S. A.; Fenical, W.; Jacobs, R. S.; Clardy, J. *Proc. Natl. Acad. Sci.* **1986**, *83*, 6238. Johnson, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 13486. Harrowven, D. C.; Tyte, M. J. *Tetrahedron Lett.* **2004**, *45*, 2089. (d) Serrulatanes: Rodriguez, A.; Ramirez, C. *J. Nat. Prod.* **2001**, *64*, 100. Dehmel, F.; Lex, J.; Schmalz, H.-G. *Org. Lett.* **2002**, *4*, 3915.

(2) (a) Bohlman, F.; Lonitz, M. *Chem. Ber.* **1978**, *111*, 843. (b) McEnroe, F. J.; Fenical, W. *Tetrahedron* **1978**, *34*, 1661. (c) Fusetani, N.; Sugano, M.; Matsunaga, S.; Hashimoto, K. *Experientia* **1987**, *43*, 1234. (d) Wright, A. E.; Pomponi, S. A.; McConnell, O. J.; Kohmoto, S.; McCarthy, P. J. *J. Nat. Prod.* **1987**, *50*, 976. (e) Ohno, M.; Todoriki, R.; Yamamoto, Y.; Akita, H. *Chem. Pharm. Bull.* **1994**, *42*, 1590. (f) Asaoka, M.; Shima, K.; Fujii, N.; Takei, H. *Tetrahedron* **1988**, *44*, 4757. (g) Rucker, G.; Breitmaier, E.; Manns, D.; Maier, W.; Marek, A.; Heinzmann, B.; Heiden, K.; Seggewies, S. *Arch. Pharm.* **1997**, *330*, 12. (h) Mayer, A. M. S.; Jacobson, P. B.; Fenical, W.; Jacobs, R. S.; Glaser, K. B. *Life Sci.* **1998**, *62*, 401.

(3) For a recent approach in which an asymmetric Cu-catalyzed conjugate addition of Me_2Zn was used in synthesis of the serrulatane diterpene erogorgiaene, see: Cesati, R. R.; de Armas, J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 96.

10.1021/ol048790v CCC: $27.50
Published on Web 08/03/2004

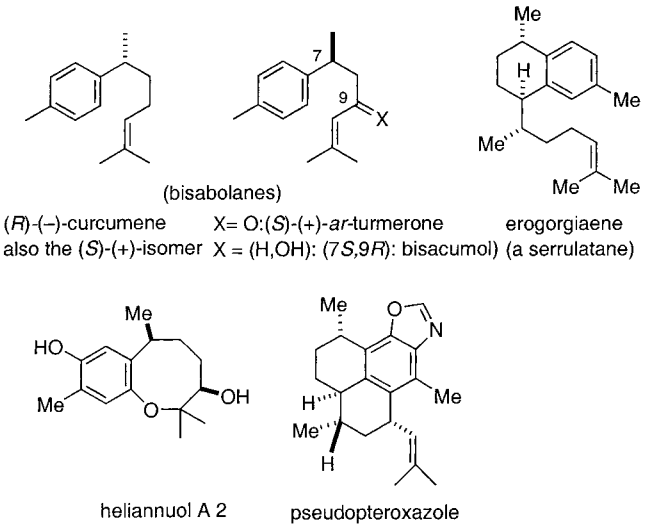


Figure 1. Prototypical natural products with chiral benzyl centers.

with the synthesis of curcumene, this molecule has evolved as a test target for demonstrating new asymmetric processes. The nonenzymatic methods[4] employed include stoichiometric chirality transfer via diastereoselective synthesis starting from a *t*-leucinol-derived oxazoline (8 steps, 31% yield),[5] citronellal (6 steps, 28% yield),[6] and (−)-phenyl methyl sufoximine (>9 steps, ~13% yield).[7] More practical catalytic procedures to install the asymmetric center have used Itsuno−Corey ketone reduction (~6 steps, 14% yield),[8] Sharpless asymmetric epoxidation (8 steps, 7% yield),[9] and Ni-catalyzed cross-coupling of benzyl Grignard reagents (5 steps, 34% yield).[10] Selectivity in the key step[11] and ease of synthesis vary considerably among these methods, and most involve chromatographic separations. For example, the ee of the final product from the cross-coupling approach is only 66%, whereas it approaches ~100% in the *t*-leucine-derived material. Arguably the "shortest (incidentally, also the most recent) route" starts with citronellal and involves six steps and multiple chromatographic separations to produce curcumene in 28% overall yield.[6] α-Curcumene (**1**) has been

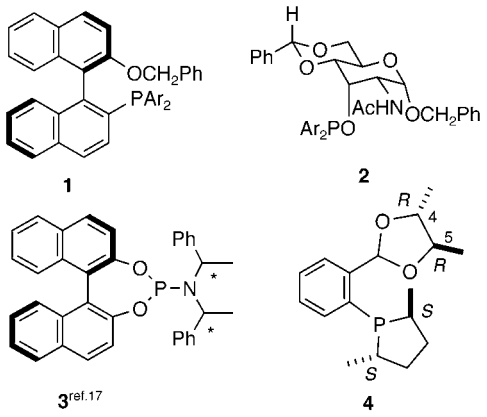
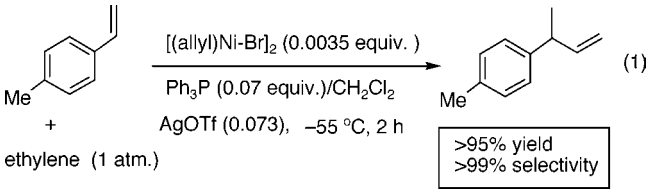


Figure 2. Ligands for asymmetric hydrovinylation.

isolated from many natural sources in both enantiomerically pure forms, where as *ar*-turmerone (**2**), isolated from the rhizomes of *Curcuma longa Linn* exists only in the (*S*)-(+)-form. Since biological activities of the two bisabolane enantiomers vary considerably,[2a−c] any practical synthesis should deliver both enantiomers in high stereochemical purity. We recently achieved[12] significant improvements in the Ni-catalyzed asymmetric hydrovinylation of various vinylarene derivatives, and in this note we document an application of this reaction for a *three-step* enantioselective synthesis of (*R*)-(−)-α-curcumene starting from commercially available 4-methylstyrene and ethylene. The intermediates generated for this synthesis can also be used for a number of bisabolane sesquiterpenes. As an example, a new five-step synthesis (26% yield from 4-methylstyrene, $[\alpha]_D = -58$) of (*R*)-(−)-*ar*-turmerone is presented. The current best synthesis of this compound uses a low-yielding baker's yeast reduction to install the asymmetric center and involves six steps (11% yield, $[\alpha]_D = +62$).[4b] Bisacumol, which carries an additional chiral center at C_9, can also be prepared by this route from *ar*-tumerone by using already established reduction protocols.[13] Synthesis of α-curcumene starts with



hydrovinylation of 4-methylstyrene. In the racemic series, the hydrovinylation of 4-methylstyrene can be achieved in

(4) Enzymatic or microbial methods: (a) Fuganti, C.; Serra, S. *Synlett* **1998**, 1252. (b) Fuganti, C.; Serra, S.; Dulio, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 279.

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(6) Hagiwara, H.; Okabe, T.; Ono, H.; Kamat, V. P.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 895.

(7) Harmata, M.; Hong, X.; Barnes, C. L. *Tetrahedron Lett.* **2003**, *44*, 7261.

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(9) Takano, S.; Yanase, M.; Sugihara, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1538.

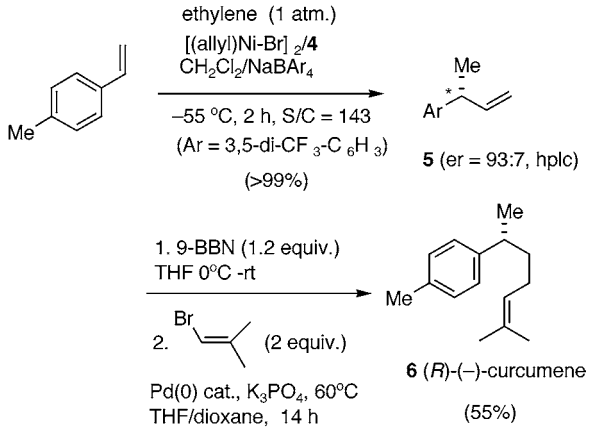
(10) Tamao, K.; Hayashi, T.; Matsumoto, H.; Yamamato, H.; Kumada, M. *Tetrahedron Lett.* **1979**, *20*, 2155.

(11) Since optical rotation ($[\alpha]_D$) was primarily used in estimating enantioselectivities, the values reported in many of the publications are prone to error. For example: Uhde, G.; Ohloff, G. *Helv. Chim. Acta* **1972**, *55*, 262 reports $[\alpha]_D$ values between 34.3 and 37.7. Schmalz reports[8] a specific rotation of +31 (*c* 0.9, $CHCl_3$) for material of 90% ee as determined by HPLC. For a compilation of various values, see ref 7. In this paper we report values based on HPLC of key intermediates, which are further corroborated by optical rotations.

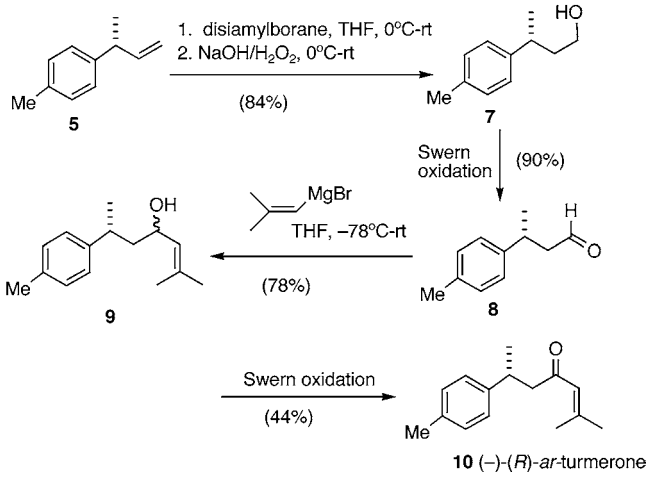
(12) (a) RajanBabu, T. V. *Chem. Rev.* **2003**, *103*, 2845. (b) Nandi, M.; Jin, J.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1999**, *121*, 9899. (c) Park, H.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2002**, *124*, 734. (d) Zhang, A.; RajanBabu, T. V. *Org. Lett.* **2004**, *6*, 1515. (e) For review of classical work on hydrovinylation, see also: Jolly, P. W.; Wilke, G. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; VCH: New York, 1996; Vol. 2, p. 1024.

(13) Li, A.; Yue, G.; Li, Y.; Pan, X.; Yang, T.-K. *Tetrahedron: Asymmetry* **2003**, *14*, 75.

Scheme 1. Synthesis of α-Curcumene from 4-Methylstyrene



Scheme 2. Synthesis of (−)-(R)-*ar*-Turmerone



nearly quantitative yield and >99% selectivity for the desired 3-arylbutene using ethylene at 1 atm and catalytic amounts of $[(allyl)NiBr]_2$, Ph_3P, and AgOTf (eq 1).[14] Chiral ligands such as MOP derivatives (**1**),[15,14b] sugar-derived diarylphosphinites (**2**),[16] and binaphthol-derived phosphoramidites (**3**),[17] which gave high ees for other styrene derivatives, gave unacceptably low ees for 4-alkylstyrenes, and until recently, practical levels of asymmetric induction were not feasible for these substrates. We recently described a series of 1-aryl-2,5-dialkylphospholane ligands (e.g., **4**) which carry a dioxolane moiety at the ortho position of the *P*-aryl group that gave outstanding selectivity for a variety of styrene derivatives.[18] In the event, when hydrovinylation of 4-methylstyrene was carried out under our new protocol, 3-(4-methylphenyl)but-1-ene was obtained in greater than 99% yield.[19] Gas chromatographic analysis indicate >99% conversion and >99% selectivity for the olefin isomer shown. No trace of products of styrene dimerization or of isomerization of the double bond was observed (Scheme 1). The enantiomers undergo clean separation on a chiracel-OJ column, and the enantiomeric ratio was estimated as 93:7 (*R*:*S*), which is consistent with optical rotation data in the literature.[20]

The terminal olefin in **5** is ideally suited for further elaboration of the curcumene side-chain.[21] Thus, treatment of compound **5** with 9-BBN in THF, followed by the addition of $Pd(PPh_3)_4$ (5 mol %), K_3PO_4 (1.5 equiv), 2-methyl-1-bromopropene (2 equiv), and dioxane and stirring at 60 °C afforded (−)-α-curcumene **6** as a colorless oil {$[\alpha]_D$ −38 (*c* 2.93, $CHCl_3$; for literature value, see ref 11} in 55% overall yield in three steps from 4-methylstyrene (Scheme 1).

Synthesis of (*R*)-(−)-*ar*-turmerone is accomplished starting with the 3-arylbutene **5**. The olefin **5** is subjected to hydroboration with disiamylborane in THF, followed by oxidation with hydrogen peroxide to give alcohol **7** {$[\alpha]_D$ −24 (*c* 4.11, $CHCl_3$)} in 84% isolated yield in two steps (Scheme 2). Swern oxidation of alcohol **7** gives aldehyde **8** {$[\alpha]_D$ −31 (*c* 3.70, $CHCl_3$)} in 90% yield. Treatment of aldehyde **8** with 2-methyl-1-propenylmagnesium bromide in THF at −78 °C to get a diastereomeric mixture (at C_9 = 6:5) of alcohol(s) **9** in 78% isolated yield. Swern oxidation[22] of alcohol **9** gave (*R*)-(−)-*ar*-turmerone **2** {$[\alpha]_D$ −58 (*c* 0.84, $CHCl_3$); lit.[4b] 62 (*c* 1.25, hexane)} in 44% yield.

In summary, starting with commercially available 4-methylstyrene, *shortest* asymmetric syntheses of bisabolanes (*R*)-(−)-α-curcumene and (*R*)-(−)-*ar*-turmerone have been completed in 52 and 26% yields, respectively. A highly efficient Ni-catalyzed asymmetric hydrovinylation was used as the key step to install the benzylic asymmetric center. Depending on the configuration of the ligand employed, either enantiomer of the product could be produced. Further applications of this chemistry for the synthesis of more complex, structurally related compounds listed in Figure 1 are under investigation.

Acknowledgment. Financial assistance for this research by U.S. National Science Foundation (CHE-0308378) and the donors of the Petroleum Research Fund, administered by the American Chemical Society (36617-AC1), is gratefully acknowledged. We thank Dr. Jian Jin for some of the early experiments.

Supporting Information Available: Full experimental details spectroscopic and chromatographic data for characterization of compounds listed. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Park, H.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2002**, *124*, 734.

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(18) Zhang, A.; RajanBabu, T. V. *Org. Lett.* **2004**, *6*, 1515.

(19) See Supporting Information for procedures and chromatographic and spectroscopic data.

(20) See ref 11.

(21) For another multistep procedure (hydroboration, tosylation, iodide formation, Cu-catalyzed Grignard addition) for this conversion, see ref 4b. Repeated attempts to do the S_N2-diaplacement on the tosylate of **7** with various copper reagents failed in our hands. The Cu-catalyzed reaction of the corresponding iodide with 2-methyl-1-propenylmagnesium bromide was also capricious.

(22) Several other oxidation procedures using PCC, MnO_2, CrO_3/H^+/acetone, Dess−Martin reagent gave unacceptable yields.