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ASYMMETRIC TOTAL SYNTHESIS OF OPTICALLY ACTIVE α-CURCUMENE

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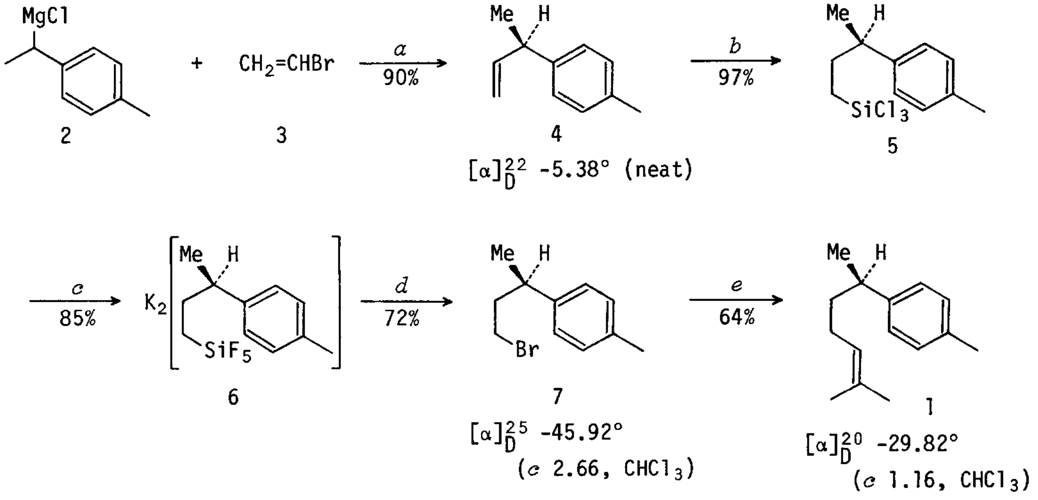
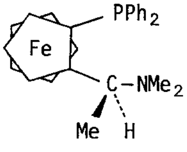
Summary: (*R*)-(-)-α-Curcumene has been prepared in 66% optical yield and in 34% overall yield in five steps by means of asymmetric Grignard cross-coupling reaction catalyzed by a nickel complex of chiral (aminoalkylferrocenyl)phosphine as a key carbon-carbon bond forming step.

We report here the first successful case of a transition metal complex catalyzed asymmetric synthesis of sesquiterpenes,^{1} that is, our initial results on the application of the nickel-catalyzed asymmetric Grignard cross-coupling reaction^2 to the preparation of optically active terpenes. The following Scheme outlines the synthetic route to the title compound, (*R*)-(-)-α-curcumene (1).^{3}





(*S*)-(*R*)-PPFA

[a] 2 : 3 ≃ 2 : 1. (*S*)-(*R*)-PPFA/$NiCl_2$ (0.5 mol%), Et_2O/benzene, -78°C ∿ 0°C, 2 days. The yield is based on 3.

[b] $HSiCl_3$ (1.2 equiv), $H_2PtCl_6 \cdot 6H_2O$ in *i*-PrOH (ca. 0.02 mol%), 60°C, 2 hr.

[c] KF (25 equiv), EtOH, r.t., 1 day.

[d] NBS (1.2 equiv), benzene, 50°C, 8 hr.

[e] (1) Mg, Et_2O, 0°C; (2) Me_2C=CHBr (ca. 3 equiv), Ni(dppp)Cl_2 (0.5 mol%), Et_2O/benzene, 0°C ∿ r.t., 15 hr.

The first key step is the catalytic asymmetric cross-coupling between racemic Grignard reagent 2 and vinyl bromide 3 in the presence of nickel catalyst containing a chiral ferrocenylphosphine, *(S)*-*(R)*-PPFA, which we have recently prepared[4] and found to be one of the most effective chiral ligands for the high asymmetric induction.[2] The anti-Markownikoff hydrobromination of 4 could be accomplished by our new method: a sequence of hydrosilylation, organopentafluorosilicate formation, and the NBS-cleavage of the silicon-carbon bond.[5] The final carbon-carbon bond formation was achieved by the cross-coupling of the Grignard reagent derived from bromide 7 with 1-bromo-2-methylpropene in the presence of Ni(dppp)Cl_2, dppp = $Ph_2P(CH_2)_3PPh_2$, as a catalyst[6] to give *(R)*-(-)-α-curcumene in 66% e.e., based on the published maximum rotation.[3a,7]

The observed optical purity and the predominant formation of the *R* enantiomer both are consistent with the previous results[2] obtained from the reaction between the 1-phenylethyl Grignard reagent (*p*-methyl group lacking) with vinyl bromide.

The availability of α-curcumene of high optical purity in 34% overall yield in five steps from readily available materials demonstrates the efficiency of this approach to asymmetric synthesis of terpenes. Further application and improvements of the present procedure are now in progress.[8]

REFERENCES AND NOTES

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2. T. Hayashi, M. Tajika, K. Tamao, and M. Kumada, *J. Am. Chem. Soc.*, 98, 3718 (1976).
3. (-)-α-Curcumene has been separated from, *e.g.*, the essential oil occurring in rhizomes of *Curcuma aromatica* Salisb. (a) N. P. Damodaran and S. Dev, *Tetrahedron*, 24, 4113 (1968), observed $[\alpha]_D$ 45.1° (*c* 0.75, $CHCl_3$) for (+)-α-curcumene and claimed that "α-curcumene" had not so far been isolated in a pure state. Other reported values lie between 34.3° and 37.7°; (b) G. Uhde and G. Ohloff, *Helv. Chim. Acta*, 55, 262 (1972), and references cited therein. The absolute configuration of *(S)*-(+)-α-curcumene has been determined; (c) V. K. Honwad and A. S. Rao, *Tetrahedron*, 21, 2593 (1965).
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6. K. Tamao, K. Sumitani, Y. Kiso, M. Zembayashi, A. Fujioka, S. Kodama, I. Nakajima, A. Minato, and M. Kumada, *Bull. Chem. Soc. Japan*, 49, 1958 (1976), and references cited therein.
7. The maximum rotation of bromide 7 has been reported to be $[\alpha]_D$ +109° (*c* 2.27, $CHCl_3$).[3c] Based on this value, the optical purity of 7 in our study should be 42%, being inconsistent with the optical purity of 1. This problem remains to be solved.

8. We thank the Grant-in-Aid for Scientific Research of the Ministry of Education (No. 355370, 303523), Asahi Glass Foundation for the Contribution to Industrial Technology and Shin-etsu Chemical Co., Ltd. for support of the work, and Mr. M. Zembayashi and Mr. T. Kotoku for experimental assistance in early stages of the work.

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