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ASYMMETRIC CYCLIZATION OF UNSATURATED ALDEHYDES CATALYZED BY A CHIRAL LEWIS ACID

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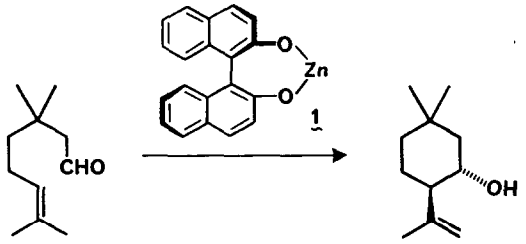
Summary: A highly enantioselective cyclization of prochiral unsaturated aldehydes has been accomplished with a chiral zinc reagent derived from dimethylzinc and (R)-(+)-1,1'-bi-2-naphthol.

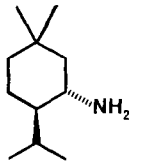
Of the available methods for constructing multicarbocyclic structures, cationic polyolefin cyclization, a synthetic strategy that mimics the key biosynthetic transformation leading to polycyclic triterpenes, seems to have the highest potential.[1] Although these cyclizations proceed stereospecific with respect to the relative configurations of the chiral centers, the products were always racemic. Consequently, the only remaining, formidable problem is to explore an effective method for asymmetric cyclization to create the first chiral center in a substrate. The first and still most spectacular of these are the chiral acetal cyclization by Johnson.[2] A chiral iminium ion cyclization has also been reported.[3,4] Here we wish to disclose a yet unknown example in the asymmetric olefinic cyclization catalyzed by a chiral Lewis acid as illustrated below.



2 3

The chiral zinc reagent 1 was prepared in situ from dimethylzinc[5] and optically pure (R)-(+)-1,1'-bi-2-naphthol (molar ratio, 1:1) in methylene chloride at -78°C for 3 h.[6,7] Cyclization of 3-methylcitronellal (2)[8] with the reagent 1 was effected at -78°C for 20 min and at 0°C for 20 min to furnish the single isomer in 91% yield which was characterized by ^{1}H NMR and GC analysis to be

the pure trans alcohol 3 possessing a methylene double bond. The optical purity of 3, $[\alpha]_D^{27}$ +10.8° (c 1.01, THF), was substantiated by GC on a 25-m PEG-HT capillary column after converting to its (S)-(-)- and (R)-(+)-MTPA esters to be 90% ee. The absolute configuration of the alcohol 3 was deduced from the optical rotation of the known cyclic amine 4.[9] One attractive feature of our chiral reagent 1 is its C_2 symmetry. When the ligand with C_2 symmetry is bound to metal, reactants experience the same chiral environment regardless of the side from which they approach. This principle was beautifully demonstrated by Noyori in his asymmetric reduction of ketones with binaphthol-modified complex aluminum hydride reagent.[10]



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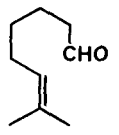

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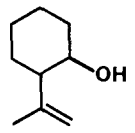

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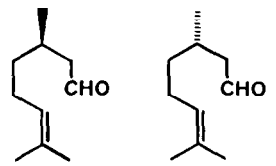
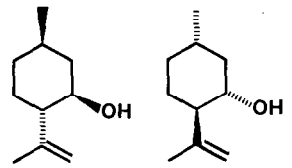
In contrast to the surprisingly high asymmetric induction in the cyclization of 2, exposure of 7-methyl-6-octenal (5) to the reagent 1 afforded the trans alcohol 6 which was shown to be totally racemic. These two striking observations invoked us to further examine the behavior of the chiral zinc reagent 1 toward the cyclizations of optically active citronellal[11] with the object of finding complementary informations about the important influence of 3-methyl group in the asymmetric cyclization of 2. Accordingly, separate treatment of (R)-(+)- and (S)-(-)-citronellal with the reagent 1 under the same conditions gave rise to the exclusive formation of (R)- and (S)-isopulegol, respectively.[12] No rate acceleration was observed in either substrate. The asymmetric induction is therefore totally controlled by the C(3)-chiral center on the substrate and is independent of the chirality of the reagent 1.



(R)-form (S)-form

citronellal

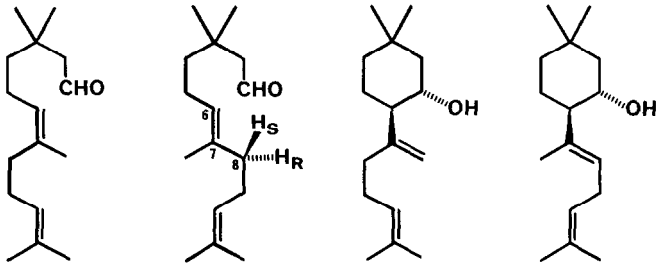


(R)-form (S)-form

isopulegol

Our study was further extended to the asymmetric cyclization of (Z)-3-methylfarnesal (7) and its (E)-isomer 8.[13] Reaction of the (Z)-isomer 7 with the reagent 1 at -78°C for 20 min and at 0°C for 20 min furnished the trans alcohol 9, $[\alpha]_D^{24}$ +25.9° (c 1.01, THF) having a methylene double bond exclusively in 89% yield. Its enantiomeric excess was determined by GC after conversion to its (S)-(-)-MTPA ester to be 91% ee. On the other hand, the (E)-isomer 8 under the similar conditions

gave a major product in 80% yield accompanied by 3% of an unidentified product, from which the major product was successfully separated by preparative TLC on $AgNO_3$-impregnated silica gel (ether-hexane, 1:10 as eluant) to be the pure trans alcohol 10, $[\alpha]_D^{21}$ +5.1° (c 0.95, THF)



7 8 9 10

possessing the (E)-olefinic bond as characterized by ^1H NMR. GC analysis of its (S)-(-)-MTPA ester indicated the optical purity of 32%. As a consequence, the chiral zinc reagent 1 is responsible both for exhibiting a high enantiomeric recognition and for the discrimination of the stereochemistry of the substrate 7 and 8 during deprotonation. In particular, the stereochemical result arising from 8 implies a sort of similarity on the role of enzyme in terpene biosynthesis,[14] since the trans alcohol 10 is thought to generate from 8 by attachment of C(6) to the carbonyl carbon C(1) on the si face of the C(6)-C(7) double bond, and subsequent removal of the pro-R hydrogen from C(8) stereospecifically with formation of the new C(7)-C(8) trans double bond.[15]

In conclusion, the present communication demonstrates a preliminary report of our basic study in the asymmetric olefinic cyclization, which showed the feasibility and some limitations of our approach. Further work will be continued on the refinement of the chiral Lewis acid, and its application to biomimetic polyene cyclizations.

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3. Demailly, G.; Solladie, G. J. Org. Chem. 1981, 46, 3102.
4. For other terpene cyclizations using chiral substrates, see: Yamada, S.; Shibasaki, M.; Terashima, S. Tetrahedron Lett. 1973, 381. Sakane, S.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. J. Am. Chem. Soc. 1983, 105, 6154.

5. We appreciate Toyo Stauffer Chemical Co., Ltd. for generous gift samples of zinc reagents.

6. During this operation, the theoretical amounts of methane gas were evolved.

7. The use of low temperature is essential for obtaining the chiral zinc reagent 1 as a clear solution. This solution upon warming to room temperature turned to a white suspension gradually. A similar result was obtained when dimethylzinc was treated with (R)-(+)-1,1'-bi-2-naphthol at 0~25°C for several hours. Attempted cyclization of the aldehyde 2 with this white suspension under the comparable conditions as described in text gave rise to the trans alcohol 3 in 75% yield with much lower optical purity (~30% ee).

8. Prepared from citral and lithium dimethylcuprate in ether. See: Clive, D. L. J.; Farina, V.; Beaulieu, P. J. Chem. Soc., Chem. Commun. 1981, 643.

9. The amine 4, $[\alpha]_D^{26}$ +58.5° (c 1.93, $CHCl_3$) was obtained according to ref 3. Transformation of 4 to the corresponding trans alcohol 11, $[\alpha]_D^{19}$ +33.0° (c 0.32, $CHCl_3$), was effected by using $NaNO_2$-AcOH in dioxane-water (Shoppee, C. W.; Sly, J. C. P. J. Chem. Soc. 1959, 345). The sign of the optical rotation of 11 was identical with that of the hydrogenation product, $[\alpha]_D^{27}$ +42.4° (c 0.99, $CHCl_3$), of 3.

10. Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. J. Am. Chem. Soc. 1984, 106, 6709. Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. Ibid. 1984, 106, 6717.

11. Optically pure (R)-(+)- and (S)-(-)-citronellal were kindly supplied from Takasago Perfumery Co., Ltd.

12. The zinc reagent 1 is far superior to other Lewis acids for obtaining isopulegol selectively from citronellal. For the effect of Lewis acids in citronellal cyclization, see: Nakatani, Y.; Kawashima, K. Synthesis 1978, 147.

13. The aldehydes 7 and 8 were synthesized from 6(Z)- and 6(E)-farnesol (provided from Takasago Perfumery Co., Ltd.), respectively, by the Swern oxidation (Mancuso, A. J.; Swern, D. Synthesis 1981, 165) and subsequent methylation with Me_2CuLi.

14. Coates, R. M. Fortschr. Chem. Org. Naturst. 1976, 33, 73. Hanson, J. R. In "Comprehensive Organic Chemistry"; Haslam, E., Ed.; Pergamon Press: New York, 1979; Vol 5, p 989. Cane, D. E. Tetrahedron 1980, 36, 1109. Poulter, C. D.; Rilling, H. C. In "Biosynthesis of Isoprenoid Compounds"; Porter, J. W., Ed.; Wiley: New York, 1981; Vol 1, p 161.

15. The similar syn-elimination of an allylic hydrogen is observed in the head-to-tail condensation between isopentenyl pyrophosphate and dimethylallyl pyrophosphate. See: Poulter, C. D.; Rilling, H. C. Acc. Chem. Res. 1978, 11, 307. Overton, K. H. Chem. Soc. Rev. 1980, 447.

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