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Enantioselective Synthesis of (+)-Nuciferal, (+)-(*E*)-Nuciferol and (+)-α -Curcumene by Chiral Hydrogenesterification Reaction

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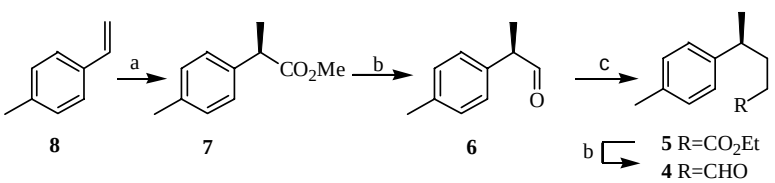
Abstract: Using chiral hydrogenesterification reaction as the key step, the stereoselective synthesis of (+)-nuciferal **1**, (+)-(*E*)-nuciferol **2** and (+)-α-curcumene **3** has been achieved.

Keywords: Nuciferal, nuciferol, α-curcumene, enantioselective synthesis.

The monocyclic aromatic bisabolane type sesquiterpene (+)-nuciferal **1** was isolated from the wood oil of *Torreya nucifera* by Sakai, Nishimura and Hirose in 1965[1]. The structures of (+)-nuciferal **1** and (+)-(*Z*)-nuciferol **2** bear a certain resemblance to those of the two sinensals which promise to become important materials for the creation of orange flavors[2]. Consequently it would be of interest to compare the organoleptic properties of (+)-nuciferal **1** with those of the sinensals. (+)-α-Curcumene **3** had been recognized as odor component of the distantly related gorgonians *Plexaurella dichotoma, P. grisea and P. fusifera*[3]. Although a number of racemic synthesis of them was reported[4], very few asymmetric synthesis of them was described[5]. Herein, we depicted a facile and convenient route to (+)-nuciferal **1**, (+)-(*E*)-nuciferol **2** and (+)-α-curcumene **3** through asymmetric hydrogen-esterification to construct the benzyl chiral carbon with highly stereoselectivity.

Scheme 1



Reagents and conditions:(a) DPPFF, $PdCl_2$, $CuCl_2{\cdot}2H_2O$, 6 MPa CO, MeOH, 1,4-dioxane, 77%, 90% e.e.; (b) i, LAH, 97%; ii, $(COCl)_2$, DMSO, Et_3N, 98%; (c) i, $Ph_3P{=}CHCO_2Et$, benzene, 80 ^{0}C, 97%; ii, Pd/C, H_2, 99%.

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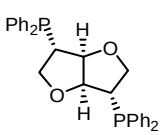
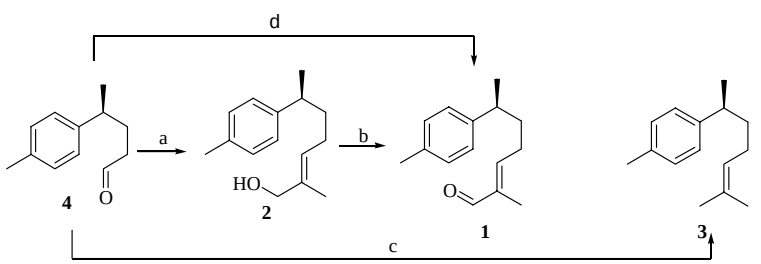
Hydrogenesterification reaction has been researched extensively by Ionue and Chaudhari[6]. Lu and coworkers reported that the complex of DPPFF (1,4: 3,6-dianhydro-2,5-dideoxy-2,5-bis (diphenyl-phosphino)-L-iditol[7a] **Figure 1**) with Pd is a very effect-tively asymmetric homogeneous catalyst in hydrogenesterification of styrene derivatives. Very good enantioselectivity (ee>90%) and regioselectivity have been achieved under the optimized reaction conditions (p_{CO}=6 MPa, 1,4-dioxane, DPPFF (mol): $PdCl_2$ (mol)=3:1, 80 ^{0}C)[7b]. Enlightened by this useful reaction, our strategy is outlined in **Scheme 1**. The commercially available *p*-methyl styrene **8** was used as starting material. Compound **7** was obtained in 77% yield and in 90% e.e. under the optimized condition. Compound **7** was reduced by LAH then subjected to Swern oxidation, compound **6** can be furnished. Wittig olefination of **6** and then hydrogenolysis afforded valeric acid derivative **5**. Compound **5** can be converted into the key intermediate **4** through reduction and oxidation. Takano had synthesized this key intermediate **4** by eight steps in relative laborious manner[5a].

The key intermediate **4** was treated with $Ph_3P{=}C(CH_3)CHO$ to give (+)-nuciferal **1** (**Scheme 2**), or treated with triethyl 2-phosphonopropionate and then reduced with LAH/$AlCl_3$ to give (+)-(*E*)-nuciferol **2**. Further oxidation with MnO_2 in CCl_4 afforded (+)-nuciferal **1**. Compound **4** reacted with isopropylidenetriphenylphosphane in THF to afford (+)-α-curcumene **3**.

Figure 1



Scheme 2



Reagents and conditions: (a) i, NaH, DME, triethyl phosphonopropionate, 24 h, 97%, ii, LAH/$AlCl_3$(1:3), 98%; (b) MnO_2, CCl_4, reflux, 99%; (c) isopropyl triphenylphosphonium iodide, BuLi, THF, 80%; (d) $Ph_3P{=}C(CH_3)CHO$, toluene, reflux for 2 days, 90%.

In summary, we have developed a synthetic route to the class of sesquiterpene from cheap starting materials. The present route may be applicable to other members of the bisabolane family.

Spectral data:(S)-(+)-Nuciferal **1**: $[\alpha]_D^{20}$ +51 (c 1.0, $CHCl_3$) (Natural[1], $[\alpha]_D^{20}$ + 62.07 (c 16.55, $CHCl_3$)), IR (film/cm^{-1}): ν 2958, 1689, 1515, 1454, 1285, 818; ^{1}H-NMR: 1.27 (d, 3H, *J* = 7Hz), 1.65 (s, 3 H), 1.70-1.81 (m, 2H), 2.16-2.28 (m, 2H), 2.64 (s, 3H), 2.64-2.74 (m, 1H), 6.42 (t, 1H, *J* = 7.2Hz) 7.06 (d, 2H, *J* =7.8Hz), 7.12 (d, 2H, *J* =7.8Hz), 9.35 (s, 1H); MS: *m/z* 216 (M^+, 3).

(S, *E*)-(+)-Nuciferol **2**: $[\alpha]_D^{20}$ +30 (c 0.9, $CHCl_3$), IR (film/cm^{-1}): ν 3380, 1515, 1444, 1283, 817. ^{1}H-NMR: 1.18 (d, 3H, *J* = 7Hz), 1.53~1.59 (m, 2H), 1.70 (s, 3H), 1.85~1.92 (m, 2H), 2.29 (s, 3H), 2.59~2.61 (m, 1H), 3.85 (s, 2H), 5.14 (t, 1H, *J* = 7Hz), 6.94 (s, 4H). MS: *m/z* 218 (M^+, 22).

(S)-(+)-Curcumene **3**: $[\alpha]_D^{20}$ +40 (c 1.15, $CHCl_3$) (Natural[8], $[\alpha]_D^{20}$ +45.10 (c 0.75, $CHCl_3$)), IR (film/cm^{-1}): ν 2962, 2923, 2857, 1515, 1516, 1453, 1376, 816; ^{1}H-NMR: 1.21 (d, 3H, *J* = 7Hz), 1.53 (s, 3H), 1.60~1.67 (m, 2H), 1.68 (s, 3H) 1.80~1.95 (m, 2H), 2.32 (s, 3H), 2.55~2.65 (m, 1H), 5.10 (t, 1H, *J* = 6.9Hz), 7.09 (s, 4H). MS: *m/z* 202 (M^+, 15).

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References

1. T. Sakai, K. Nishimura, Y. Hirose, *Bull. Chem. Soc. Jpn.*, **1965**, *38*, 381.
2. (a) K. L. Stevens, R. E. Lundin, R. Teranishi, *J. Org. Chem.*, **1965,** *30*, 381. (b) R. A. Flath, R. E. Lundin, R. Teranishi, *Tetrahedron. Lett.*, **1966**, 295. (c) A. F. Thomas, *Chem. Commun.*, **1967**, 947. (d) E. Bertele, P. Schudei, *Helv. Chim. Acta*, **1967**, *50*, 2445.
3. F. J. McEnroe, W. Fenical *Tetrahedron*, **1978**, *34*, 1661.
4. (a) O. P. Vig, B. Vig, I. Raj, *J. Indian Chem. Soc.*, **1965**, *42*, 673. (b) G. Buchi, H. Wuest, *J. Org. Chem.*, **1969**, *34*, 1122. (c) G. Gost, Y. R. Naves, *Helv. Chim. Acta*, **1971**, *54*, 1369. (d) D. A. Evans, G. C. Andrews, G. T. Fujimoto, D. Wells *Tetrahedron Lett.*, **1973**, 1389.
5. (a) S. Takano, E. Goto, K. Ogasawara *Tetrahedron Lett.*, **1982**, 5567. (b) C. Fuganti, S. Serra, A. Dulio *J. Chem. Soc., Perkin 1*, **1999**, 279. (c) S. Takano, T. Sugihara, K. Samizu, *et al.*, *Chem. Lett.*, **1989**, 1781.
6. (a) A. Seayad, A. A. Kelkar, L. Toniolo, R. V. Chaudhari *J. Mol. Catal.*, **2000**, *151*, 47. (b) A. Vavasori, L. Toniolo, G. Cavinato *J. Mol. Catal. A: Chemical*, **2003**, *191*, 9. (c) D. Zim, R. F. Souza, J. Dupont, A. L. Moterio *Tetrahedron Lett.*, **1998**, *39*, 7071. (d) S. Oi, M. Nomura, T. Aiko, Y. Inoue *J. Mol. Catal. A: Chemical*, **1997**, *115*, 289.
7. (a) J. Bakos, B. Heil, L. Marko *J. Organomet. Chem.*, **1983**, *253*, 249. (b) H. Y. Zhou, J. G. Hou, J. Cheng, *et al.*, *J. Organomet. Chem.*, **1997**, *543*, 227.
8. N. P. Damodaran, S. Dev, *Tetrahedron*, **1968**, *24*, 4113.

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