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# Asymmetric Hydrolysis of *cis,cis*-5-Benzyloxy-1,3-diacetoxycyclohexane and Its Application to the Synthesis of Chiral Lactone Moiety in Compactin

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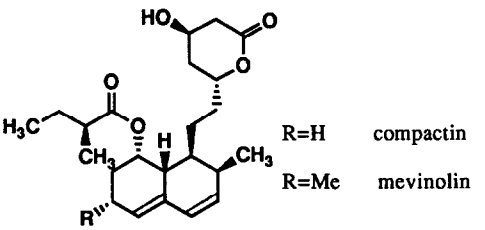
**Abstract:** Asymmetric hydrolysis of *meso* diacetate **3** using pig liver esterase afforded (1*S*,3*R*,5*S*)-(-)-**4**, which was converted into chiral lactone moiety in compactin.

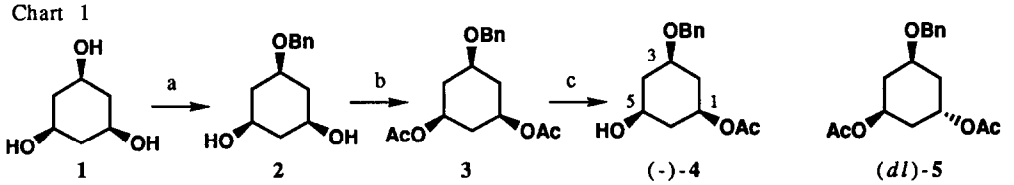
As a part of our studies[1] on asymmetric hydrolysis using biocatalyst, enzymatic hydrolysis of *meso* diacetate **3** is attractive target in connection with the synthesis of compactin and related compounds. Recent paper[2] involving the erroneous assignment for absolute configuration of the hydrolyzed product (-)-**4** prompts us to publish our results.




Compactin and mevinolin[3] are potent competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), the rate-limiting enzyme in cholesterol biosynthesis. We have developed a new synthetic route to the chiral lactone moiety in compactin from (-)-**4**.

Direct benzylation of *cis*-1,3,5-cyclohexanetriol **1**[4] afforded the monobenzylether **2** in 40% yield, accompanied by di- and tri-benzylether in 17% and 13% yields, respectively. Compound **2** was subjected to usual acetylation to give a substrate **3** (91%) (Chart 1). Results of asymmetric hydrolysis of **3** using hydrolytic

Chart 1




**1** **2** **3** (-)-**4** (*dl*)-**5**

a: NaH, BnCl, DMSO, 40%; b: $Ac_2O$, Py, 91%; c: PLE, 62% (87% ee).

Table Asymmetric Hydrolysis of **3** with Enzyme

| Entry | Enzyme | Reaction Time (h) | Yield of **4** (%) | Optical Purity (% ee) | Absolute Configuration | Yield of **2** (%) | Recovery of **3** (%) |
|---|---|---|---|---|---|---|---|
| 1 | *Pseudomonas fluorescens* lipase (PFL) | 22 | 13 | 18 | 1*R*,3*S*,5*R* | 19 | 64 |
| 2 | PFL* | 2.5 | 16 | 84 | 1*R*,3*S*,5*R* | 1 | 79 |
| 3 | *Aspergillus niger* lipase | 18 | 21 | 36 | 1*R*,3*S*,5*R* | 8 | 72 |
| 4 | *Rhizopus delemar* lipase | 41 | 33 | 36 | 1*R*,3*S*,5*R* | 44 | 14 |
| 5 | porcin pancleas lipase | 22 | 25 | 0 | ----- | 12 | 60 |
| 6 | pig liver esterase (PLE) | 10 min | 62 | 87 | 1*S*,3*R*,5*S* | 1 | 32 |

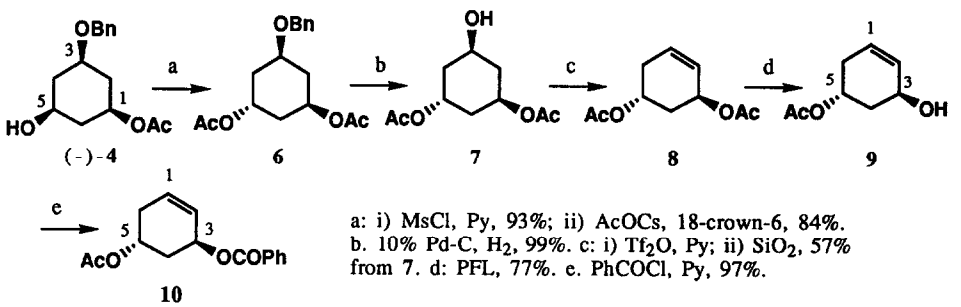
* DMSO was added as additive.

enzymes were summarized in Table. Among the tested enzymes, pig liver esterase (PLE) showed the best result to afford (1*S*,3*R*,5*S*)-**4** (62% isolated yield, 91% conversion yield, 87% ee,[5] entry 6).

*Pseudomonas fluorescens* lipase (PFL) resulted in low optical purity (entry 1), but afforded better results ((1*R*,3*S*,5*R*)-**4**, 16% isolated yield, 78% conversion yield, 84% ee) in the presence of DMSO as additive (entry 2).[6] Enantioselective hydrolysis using PLE, PFL, and acetylcholinesterase (electric eel) of the racemic *r*-1-benzyloxy-*c*-3,*t*-5-diacetoxycyclohexane (*dl*-**5**) resulted in poor yield and low optical purity.

Absolute configuration of the hydrolyzed product (-)-**4** was established by the exciton chirality method[7] as follows (Chart 2). Inversion of $C_5$-hydroxy group of (-)-**4** using Ikegami's procedure[8] afforded diacetate **6** (93%), which was subjected to hydrogenolysis using 10% Pd-C catalyst to give the alcohol **7** (99%). Dehydration of **7** under mild conditions was achieved, in 57% yield, by trifluoromethanesulfonylation and subsequent treatment with silica gel.[9] To differentiate two types of acetates (acetates of allylic alcohol and homoallylic alcohol) of **8**, enzymatic hydrolyses were studied. Among them, PFL afforded regioselectively hydrolyzed product **9** (77%) as a major product (regioselectivity : 30 to 1). The CD spectrum of the benzoate **10** showed negative first Cotton effect, which allows to conclude the absolute configuration of $C_3$-position of **10** to be *S*. This result indicated that the absolute configuration of (-)-**4** should be 1*S*,3*R*,5*S* .[2]

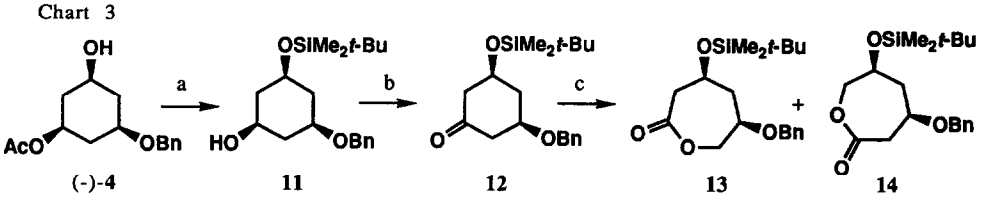
Chart 2




a: i) MsCl, Py, 93%; ii) AcOCs, 18-crown-6, 84%. b. 10% Pd-C, $H_2$, 99%. c: i) $Tf_2O$, Py; ii) $SiO_2$, 57% from 7. d: PFL, 77%. e. PhCOCl, Py, 97%.

Next, diastereoselective synthesis of chiral lactone moiety in compactin from (-)-**4** was studied. As a preliminary attempt, hydroxy group of (-)-**4** was protected as *t*-butyldimethysilyl ether, and subsequent hydrolysis afforded **11** in 61% yield. PCC oxidation of **11** afforded corresponding ketone **12** (86%). Baeyer Villiger oxidation of **12** with mCPBA proceeded in nonregioselective manner to afford a mixture of **13** and desired **14** in ratio of 47 to 53.

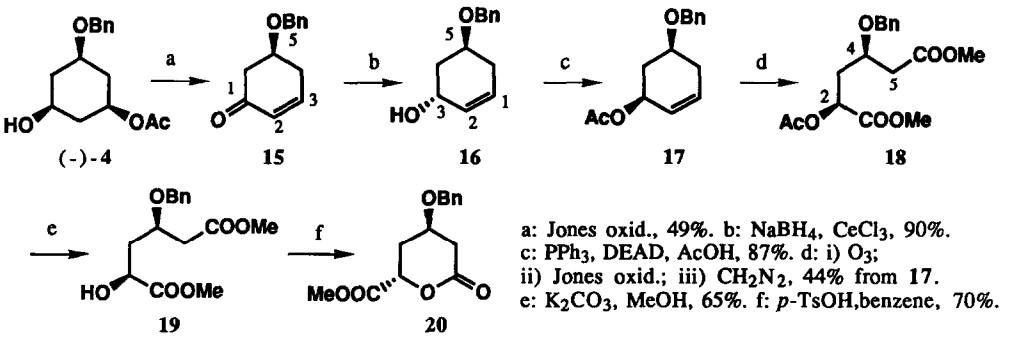
Chart 3




a: i) *t*-$BuMe_2SiCl$, HMPA, poly(4-vinylpyridine); ii) $K_2CO_3$, MeOH, 61% from (-)-**4**. b: PCC, 86%. c: *m*CPBA, **13** (18%), **14** (20%)

Stereoselective synthesis of the lactone moiety could be accomplished as follows (Chart 4). Jones oxidation of (-)-**4** afforded the enone **15** (49%). The diastereoselective reduction of ketone function in **15** was achieved by $NaBH_4$-$CeCl_3$ to afford 3,5-*trans* isomer **16** (90%).[10] Compound **16** was converted to the acetate **17** with desirable configuration by Mitsunobu method.[11] The diester **18** was obtained in 44% yield from **17** *via* ozonolysis, Jones oxidation and subsequent esterification with $CH_2N_2$. After hydrolysis of acetate, lactonization of **19** in the presence of *p*-TsOH afforded the lactone moiety **20** (70%) of compactin.

Chart 4




a: Jones oxid., 49%. b: $NaBH_4$, $CeCl_3$, 90%.
c: $PPh_3$, DEAD, AcOH, 87%. d: i) $O_3$;
ii) Jones oxid.; iii) $CH_2N_2$, 44% from **17**.
e: $K_2CO_3$, MeOH, 65%. f: *p*-TsOH,benzene, 70%.

## References and Notes


1. (a) Z.-F. Xie and K. Sakai, *J. Org. Chem.* **55**, 820 (1990); (b) K. Okano, H. Suemune, and K. Sakai, *Chem. Pharm. Bull.*, **37**, 1995 (1989); (c) Z.-F. Xie and K. Sakai, *ibid*, **37**, 1650 (1989); (d) Z.-F. Xie, I. Nakamura, H. Suemune, and K. Sakai, *J. Chem. Soc., Chem. Commun.*, **1988**, 966.
2. M. Carda, J. Van der Eycken, and M. Vandewalle, *Tetrahedron Asymmetry*, **1**, 17 (1990), in which (-)-**4** was assigned to be 1*R*,3*S*,5*R* by CD spectrum of **15**.
3. (a) A. P. Kozikowski and C.-S. Li, *J. Org. Chem.*, **52**, 3541 (1987), references sited therein; (b) C. R. Johnson, C. H. Senanayake, *ibid*, **54**, 735 (1989); (c) K. Prasad and O. Repic, *Tetrahedron Lett.*, **25**, 2435 (1984).
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5. The enantiomeric excess (% ee) of **4** was determined by 270 MHz $^1$H-NMR after conversion to (+)-MTPA ester; J. A. Dale, D. L. Dulh, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).
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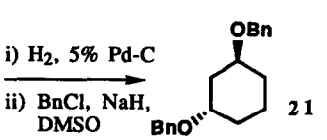
7. N. Harada, Y. Takuma, and H. Ueda, *J. Am. Chem. Soc.*, **100**, 4029 (1978).
8. Y. Torisawa, H. Okabe, and T. Ikegami, *Chem. Lett.*, **1984**, 1555.
9. H. Kashihara, H. Suemune, T. Kawahara, and K. Sakai, *Tetrahedron Lett.*, **28**, 6489 (1987).
10. Stereochemistry of **16** was determined by $^{13}$C-NMR spectrum ($CDCl_3$) of **21** (δ: 75.3 (CH), 68.3 (CH), 39.2 ($CH_2$), 34.2 ($CH_2$), 30.2 ($CH_2$), 18.1 ($CH_2$) for cyclohexane ring), which indicates *trans* configuration of two substituents. Vandewalle *et al.*[2] assigned for **16** to be 3,5-*cis*.




11. O. Mitsunobu, *Synthesis*, **1981**, 1.

12. Selected spectroscopic data. All compounds listed were obtained as colorless oil.
(1*S*,3*R*,5*S*)-(-)-**4**: $[\alpha]_D^{21}$ -4.88 (c=1.85, $CHCl_3$), reported value[2] $[\alpha]_D^{20}$ -5.0 (c=1, $CHCl_3$). $^1$H-NMR ($CDCl_3$) δ: 4.74 (1H, tt, J=10.7, 4.3 Hz, $C_1$-H), 3.71 (1H, m, $C_5$-H), 3.49 (1H, tt, J=10.4, 4.1 Hz, $C_3$-H), 2.04 (3H, s, OAc).
**6**: $[\alpha]_D^{23}$ -7.35 (c=1.53, $CHCl_3$). $^1$H-NMR ($CDCl_3$) δ: 5.30 (1H, tt, J=3.5, 3.5 Hz, $C_3$-H), 5.01 (1H, tt, J=10.6, 4.3 Hz, $C_1$-H), 4.50, 4.59 (1H each, d, J=11.7 Hz, $C\underline{H}_2$Ph), 3.75 (1H, tt, J=10.6, 4.1 Hz, $C_5$-H), 2.03, 2.04 (3H each, s, OAc x 2).
**8**: $[\alpha]_D^{21}$ -189.4 (c=1.03, $CHCl_3$). $^1$H-NMR ($CDCl_3$) δ: 5.85 (1H, m, $C_2$-H), 5.79 (1H, m, $C_1$-H), 5.41 (1H, m, $C_3$-H), 5.16 (1H, tt, J=8.4, 4.9 Hz, $C_5$-H), 2.53 (1H, ddd, J=17.8, 4.8, 4.8 Hz, $C_6$-H), 2.056, 2.059 (3H each, s, OAc x 2).
**9**: $[\alpha]_D^{14}$ -150.2 (c=1.32, $CHCl_3$). $^1$H-NMR ($CDCl_3$) δ: 5.84 (1H, m, $C_2$-H), 5.77 (1H, m, $C_1$-H), 5.17 (1H, m, $C_5$-H), 4.38 (1H, m, $C_3$-H), 2.49 (1H, m, $C_6$-H), 2.05 (3H, s, OAc). The assignments of $C_3$-, and $C_5$-H were established by $^1$H,$^1$H COSY 2D NMR spectrum.
**10**: $[\alpha]_D^{14}$ -253.4 (c=0.50, $CHCl_3$). CD (MeOH): $\Delta\varepsilon$ =-9.09 (226 nm, c=7.25 x $10^{-5}$).
**11**: $[\alpha]_D^{14}$ +1.8 (c=1.0, $CHCl_3$). **12**: $[\alpha]_D^{17}$ -1.36 (c=1.26, $CHCl_3$).
**13**: $[\alpha]_D^{17}$ -5.95 (c=0.47, $CHCl_3$). **14**: $[\alpha]_D^{16}$ +18.9 (c=0.45, $CHCl_3$).
**15**: $[\alpha]_D^{24}$ -4.67 (c=1.20, $CHCl_3$), reported value[2] $[\alpha]_D^{20}$ -3.0 (c=1.8, $CHCl_3$). $^1$H-NMR ($CDCl_3$) δ: 7.32 (5H, m, aromatic H), 6.89 (1H, ddd, J=9.0, 4.6, 3.7 Hz, $C_3$-H), 6.07 (1H, dt, J=9.0, 1.9 Hz, $C_2$-H), 4.56, 4.58 (1H each, d, J=12.2 Hz, $OC\underline{H}_2$Ph), 3.91 (1H, m, $C_5$-H).
**16**: $[\alpha]_D^{20}$-41.1 (c=1.03, $CHCl_3$), reported value[2] $[\alpha]_D^{20}$ -39.3 (c=0.6, $CHCl_3$). $^1$H-NMR ($CDCl_3$) δ: 7.32 (5H, m, aromatic H), 5.71, 5.89 (1H each, m, $C_{1,2}$-H), 4.53, 4.59 (1H each, d, J=12.0 Hz, $OC\underline{H}_2$Ph), 4.13 (1H, m, $C_3$-H), 3.87 (1H, ddd, J=9.2, 4.6, 4.6 Hz, $C_5$-H), 2.71 (1H, d, J=9.2 Hz, $C_3$-OH).
**17**: $[\alpha]_D^{20}$+61.7 (c=1.03, $CHCl_3$). $^1$H-NMR ($CDCl_3$) δ: 7.34 (5H, m, aromatic H), 5.88 (1H, m, $C_2$-H), 5.75 (1H, m, $C_1$-H), 5.42 (1H, m, $C_3$-H), 4.56, 4.61 (1H each, d, J=11.9 Hz, $OC\underline{H}_2$Ph), 3.84 (1H, m, $C_5$-H).
**18**: $[\alpha]_D^{20}$+21.0 (c=4.29, $CHCl_3$). $^1$H-NMR ($CDCl_3$) δ: 7.31 (5H, m, aromatic H), 5.19 (1H, dd, J=10.4, 3.1 Hz, $C_2$-H), 4.41, 4.61 (1H each, d, J=11.2 Hz, $OC\underline{H}_2$Ph), 3.70, 3.71 (3H each, s, COOMe x 2), 2.72 (1H, dd, J=15.2, 5.6 Hz, $C_5$-H), 2.54 (1H, dd, J=15.2, 6.3 Hz, $C_5$-H), 2.15 (2H, m, $C_2$-H), 2.04 (3H, s, OAc).
**19**: $[\alpha]_D^{20}$+4.61 (c=4.29, $CHCl_3$).$^1$H-NMR ($CDCl_3$) δ: 7.33 (5H, m, aromatic H), 4.56, 4.64 (1H each, d, J=11.0 Hz, $OC\underline{H}_2$Ph), 4.41 (1H, m, $C_2$-H), 4.18 (1H, m, $C_4$-H), 3.68, 3.76 (3H each, s, COOMe x 2), 3.02 (1H, d, J=6.02, OH), 2.71 (1H, dd, J=15.2, 5.9 Hz, $C_5$-H), 2.57 (1H, dd, J=15.2, 6.3 Hz, $C_5$-H), 2.11 (1H, ddd, J=14.4, 9.4, 2.8 Hz, $C_3$-H), 1.83 (1H, ddd, J=14.4, 9.6, 3.3 Hz, $C_3$-H).
**20**: $[\alpha]_D^{20}$-11.5 (c=0.46, $CHCl_3$). $^1$H-NMR ($CDCl_3$) δ: 7.33 (5H, m, aromatic H), 4.93 (1H, dd, J=5.6, 4.9 Hz, $C_6$-H), 4.45, 4.52 (1H each, d, J=11.7 Hz, $OC\underline{H}_2$Ph), 4.00 (1H, m, $C_4$-H), 3.62 (3H, s, COOMe), 2.81 (1H, d, J=5.3 Hz, $C_3$-H), 2.80 (1H, d, J=3.6 Hz, $C_3$-H), 2.52 (1H, ddd, J=14.4, 4.9, 4.9 Hz, $C_5$-H), 2.31 (1H, ddd, J=14.4, 5.6, 3.5 Hz, $C_5$-H). MS *m/z*: 264 ($M^+$), 205, 158. High MS: Calcd for $C_{14}H_{16}O_5$ 264.0997; Found 264.1001.