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Synthesis of (+)-*endo*- and (+)-*exo*-Brevicomin *via* Enzyme-Mediated Hydrolysis of an Enol Ester

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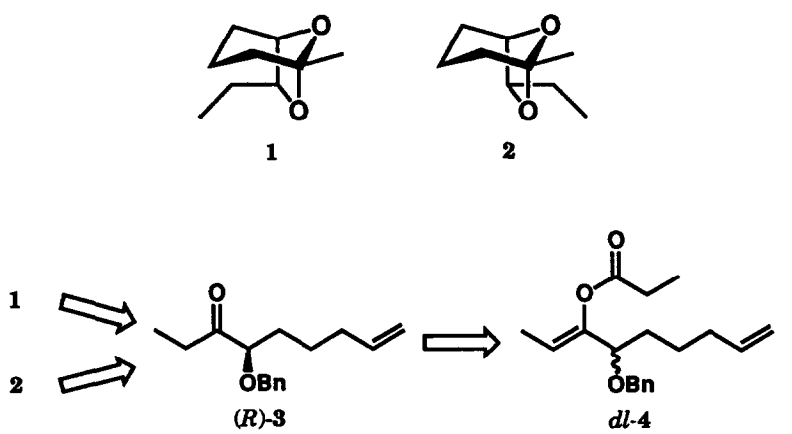
Summary: Optically pure (+)-*endo*- and (+)-*exo*-brevicomin have been synthesized in short steps starting from α-hydroxy ketone derivative, (*R*)-4-benzyloxy-8-nonen-3-one (**3**), which was prepared *via* enzymatic hydrolysis of racemic enol ester **4**..

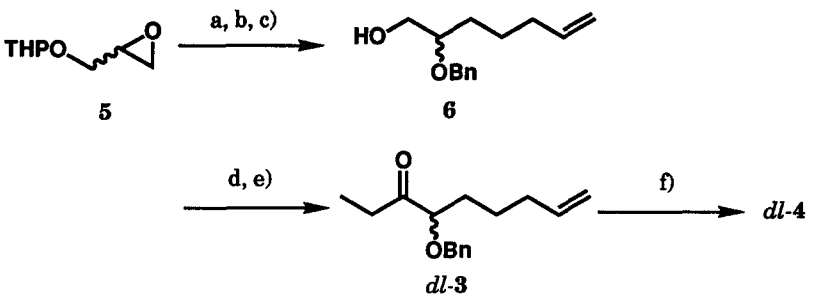
In the preceding paper,[1] we presented a new efficient methodology for the preparation of optically active α-benzyloxy ketones by enzymatic hydrolysis of enol esters. These chiral building blocks are expected to be useful in the synthesis of natural products because the hydroxy group is already protected. As an example of demonstrating the validity of this approach, we planned the synthesis of brevicomin.

(+)-*endo*- and (+)-*exo*-Brevicomins (**1** and **2**, respectively) are components of the attractant pheromone systems found in several bark beetle species belonging to genera *Dendroctonus* and *Dryocetes*.[2] Although a number of asymmetric syntheses of these compounds have been reported,[3] they are not necessarily always satisfactory in their simplicity of the process and the enantimeric and/or diastereomeric excess of the products. Herein, we wish to add a new entry for an efficient synthesis of optically pure **1** nad **2** starting from a common intermediate (*R*)-**3**, which is obtained *via* enzyme-mediated hydrolysis of enol ester *dl*-**4** as the key step (Scheme 1).



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

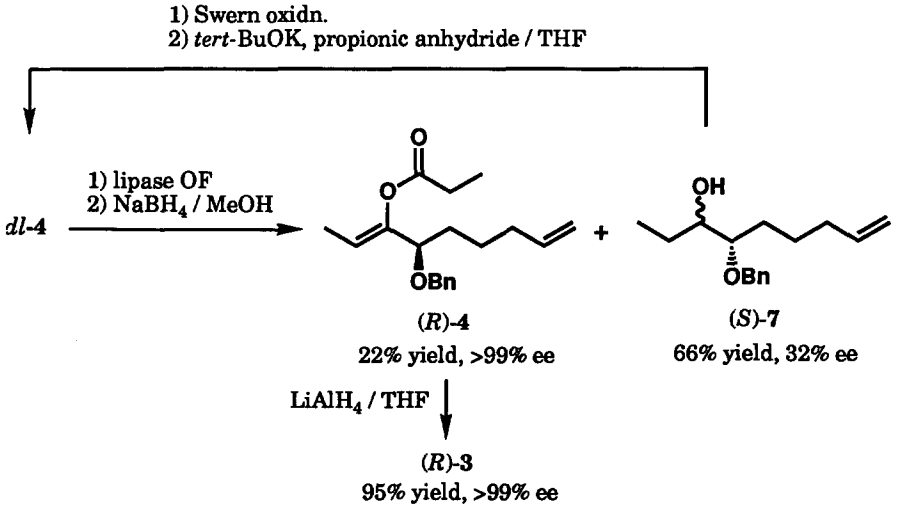
Scheme 1.



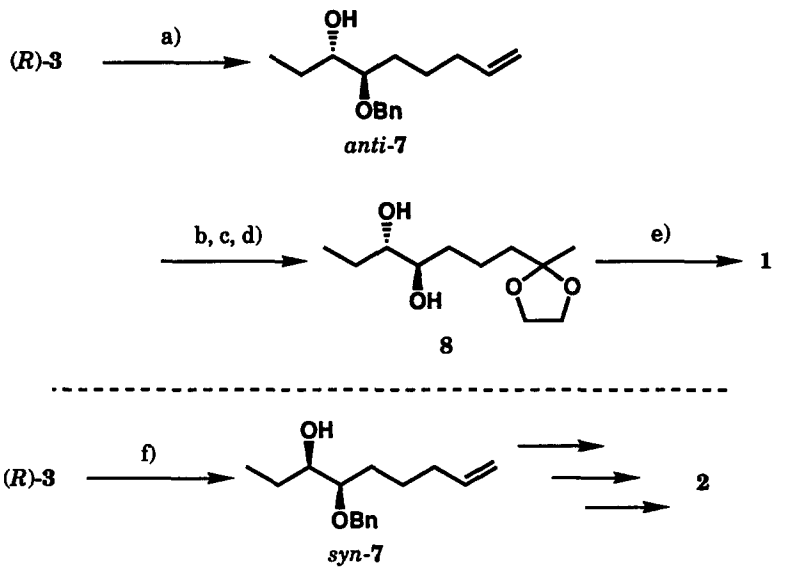
a) CH_2=$CHCH_2CH_2MgBr$, Cu_2Br_2 / THF, -10 °C (90%); b) BnBr, NaH, cat. Bu_4NI / THF, reflux (89%); c) cat. TsOH / MeOH, r.t. (97%); d) Swern oxidn., -78 °C → 0 °C, then EtMgBr / THF, 0 °C (87%); e) Swern oxidn., -78 °C → 0 °C (97%); f) *tert*-BuOK, propionic anhydride / THF, 0 °C (70%).

Scheme 2.

Enol propionate *dl*-**4**, the substrate for enzymatic hydrolysis, was readilly prepared according to Scheme 2. Ring opening of epoxide **5** with Grignard reagent in the presence of cuprous bromide, followed by protection and deprotection of the hydroxy groups afforded alcohol **6**. Monoprotected diol **6** was transformed to *dl*-**3** *via* the sequence of oxidation, Grignard reaction and oxidation. Resulting *dl*-**3** was treated with *tert*-BuOK and propionic anhydride in THF to give exclusively the (*Z*)-isomer *dl*-**4** in 70% yield. The stereochemistry of *dl*-**4** was determined by NOE experiment with 400MHz ^{1}H NMR.



Scheme 3.



a) $Zn(BH_4)_2$ / Et_2O, -30 °C (70%, *syn* : *anti* = 4 : 96); b) O_2, $PdCl_2$, $CuCl_2$ / DME-H_2O, r.t. (85%); c) ethyleneglycol, cat. PPTS / PhH. Dean-Stark trap (97%); d) H_2, 10% Pd-C / EtOH (97%); e) 2 N aq HCl, r.t. (78%); f) L-Selectride® / THF, -100 °C (98%, *syn* : *anti* = 90 : 10).

Scheme 4.

Enzymatic hydrolysis of *dl*-**4** was carried out as follows (Scheme 3). Four grams of *dl*-**4** and 4 g of lipase OF (from Candida cylindracea, Meito Sangyo Co., Ltd.) were added to 400 ml of 0.2 M phosphate buffer (pH 6.5) and incubated for 72 hr at 30 °C. As separation of recovered enol propionate and resulting ketone was somewhat difficult, the reaction mixture was directly treated with $NaBH_4$ in MeOH, in that only the ketone was reduced to monobenzylated diol (*S*)-**7**, the enol ester remaining intact. Then, optically pure enol propionate (*R*)-**4**[4] was easily isolated by choromatography in 22% yield. The corresponding ketone (*R*)-**3**[5] was obtained from (*R*)-**4** by reduction with $LiAlH_4$ in THF without any racemization. The ee's of (*R*)-**3** and **4** were determined by HPLC analysis using CHIRALCEL OJ (Daicel Chemical Industries, Ltd.). The resulting alcohol (*S*)-**7** of low ee was easily converted to the racemic substrate *dl*-**4** through oxidation, enolization with base and esterification (Scheme 2, e) and f)).

The next problem to be overcome is diastereoselective preparation of alcohol **7**. Chelation controlled reduction of (*R*)-**3** with $Zn(BH_4)_2$[6] afforded *anti*-**7** with high stereoselectivity (*syn* : *anti* = 4 : 96, Scheme 4).[7] Because the minor isomer *syn*-**7** was easily removed by column chromatography, *anti*-**7** could be isolated as a single isomer. Wacker oxidation of *anti*-**7** followed by protection of resulting carbonyl group and removal of benzyl group afforded diol **8**. HPLC analysis of di-(+)-MTPA ester of **8** using ZORBAX SIL (Du pont Instruments) revealed that this diol was enantiomerically pure. Finally, deprotection of **8** and spontaneous cyclization with 2 N aq HCl in Et_2O yielded (+)-*endo*-brevicomin (**1**) in 62 % yield based on *anti*-**7**; $[\alpha]_D^{23}$ +77.2° (c 1.14, Et_2O), lit.[3f] $[\alpha]_D^{20}$ +80.0° (c 1.3, Et_2O). The

spectral data of **1** are identical with those reported in lit.[3f] The product **1** was confirmed to be solely *endo*-isomer by NMR experiment and capillary GLC analysis.

On the other hand, synthesis of enantio- and diastereomerically pure (+)-*exo*-brevicomin (**2**) was achieved *via* highly stereoselective reduction of (*R*)-**3** with LiBH(*sec*-Bu)$_3$ (L-Selectride®)[6b] to *syn*-**7** (*syn* : *anti* = 90 : 10), followed by the same procedure as the synthesis of **1** (58% yielded from *syn*-**7** in 4 steps); $[\alpha]_D^{25}$ +66.7° (c 1.40, Et_2O), lit.[3f] $[\alpha]_D^{20}$ +69.3° (c 2.5, Et_2O).

In conclusion, the synthesis of pure (+)-*endo*- and (+)-*exo*-brevicomin has been efficiently accomplished in short steps from a common chiral ketone (*R*)-**3** which was obtained by enzyme-mediated kinetic resolution of enol ester *dl*-**4**.

References and Notes

1) K. Matsumoto, N. Suzuki and H Ohta, *Tetrahedron Lett.*, **31**, 0000 (1990).

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4) $[\alpha]_D^{26}$ +73.0° (c 1.03, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.21 (t, J = 7.20 Hz, 3H), 1.31 - 1.72 (m, 4H), 1.55 (d, J = 6.98 Hz, 3H), 1.97 - 2.06 (m, 2H), 2.48 (q, J = 7.20 Hz, 2H), 3.70 (dd, J_1 = 7.48 Hz, J_2 = 4.79 Hz, 1H), 4.38 (d, J = 12.1 Hz, 1H), 4.69 (d, J = 12.1 Hz, 1H), 4.90 - 5.02 (m, 2H), 5.38 (q, J = 6.98 Hz, 1H), 5.77 (tdd, J_1 = 6.73 Hz, J_2 = 13.2 Hz, J_3 = 15.2 Hz, 1H), 7.22 - 7.38 (m , 5H); ^{13}C NMR ($CDCl_3$) δ 9.3, 10.9, 24.9, 27.3, 32.8, 33.5, 70.4, 79.1, 114.1, 114.6, 127.4, 128.0, 128.2, 138.6, 138.7, 147.0, 171.3; IR (neat) 2990, 2950, 2860, 1760, 1640, 1450, 1350, 1260, 1145, 1080, 1000, 905, 810, 730, 695 cm^{-1}; Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.71; H, 8.53%.

5) $[\alpha]_D^{25}$ +63.8° (c 1.01, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.02 (t, J = 7.5 Hz, 3H), 1.2 - 1.8 (m, 4H), 1.8 - 2.2 (m, 2H), 2.55 (q, J = 7.5 Hz, 2H), 3.81 (t, J = 5.5 Hz, 1H), 4.49 (dd, J_1 = 11 Hz, J_2 = 17 Hz, 2H), 4.8 - 5.1 (m, 2H), 5.77 (tdd, J_1 = 6.5 Hz, J_2 = 13 Hz, J_3 = 15 Hz, 1H), 7.2 - 7.4 (m, 5H); IR (neat) 3080, 3050, 2990, 2950, 2870, 1715, 1640, 1500, 1450, 1340, 1205, 1100, 1025, 990, 910, 740, 700 cm^{-1}; Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: 77.82; H, 8.89 %.

6) a) W. J. Gensler, F. Johnson and A. D. B. Sloan, *J. Am. Chem. Soc.*, **82**, 6074 (1960); b) T. Takahashi, M. Miyazawa and J. Tsuji, *Tetrahedron Lett.*, **26**, 5139 (1985).

7) Diastereomeric excess of **7** was determined by capillary GLC analysis.

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