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A TRANSKETOLASE-BASED SYNTHESIS OF (+)-*exo*-BREVICOMIN

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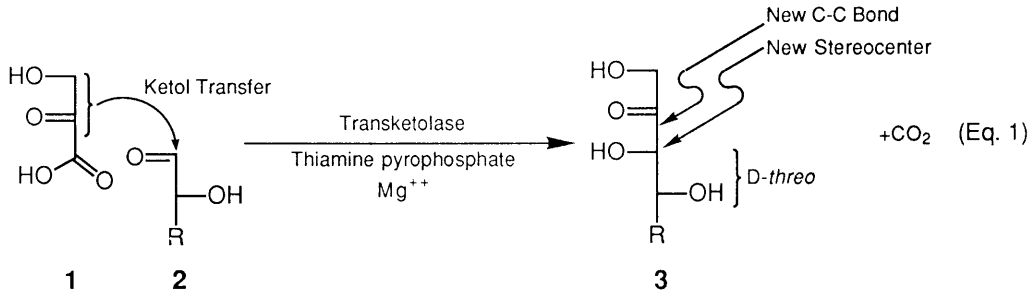
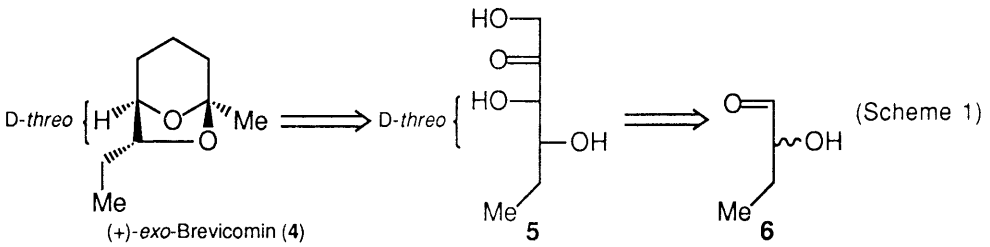
Abstract The naturally occurring beetle pheromone (+)-*exo*-brevicomin was synthesized by a strategy combining chemical and enzymatic steps. The commercially available enzyme transketolase (EC 2.2.1.1) catalyzed the condensation of β-hydroxypyruvic acid and 2-hydroxybutyraldehyde to furnish the central intermediate in the sequence, optically active hydroxyketone **5**. A short sequence converted ketose **5** to protected aldose **8**. Wittig extension of the aldehyde followed by hydrogenation and ketal hydrolysis generated the title compound.

Transketolase (TK) (EC 2.2.1.1) is a readily available enzyme that catalyzes the transfer of a two-carbon ketol unit from a ketose to an aldose.[1] *In vivo*, as part of the pentose cycle, TK reversibly transfers the C1-C2 ketol unit from D-xylulose-5-phosphate to D-ribose-5-phosphate and generates D-sedoheptulose-7-phosphate and D-glyceraldehyde-3-phosphate. Thiamine pyrophosphate (TPP) and magnesium(II) are co-factors for this process. Srere *et al.* demonstrated that β-hydroxypyruvic acid (HPA, **1**) is a substrate for TK and will donate a ketol moiety.[2] The decarboxylation of β-hydroxypyruvate and subsequent loss of carbon dioxide from the reaction mixture render the overall condensation reaction irreversible (Eq. 1). The result of the TK-catalyzed condensation of HPA and 2-hydroxy aldehydes is a vicinal diol possessing the D-*threo* configuration. TK is stereospecific: it accepts only the D-enantiomer of 2-hydroxy aldehydes (aldoses), and produces the *threo* isomer of the product with high diastereoselectivity.[3] These characteristics make transketolase useful for the preparation of chiral synthons.

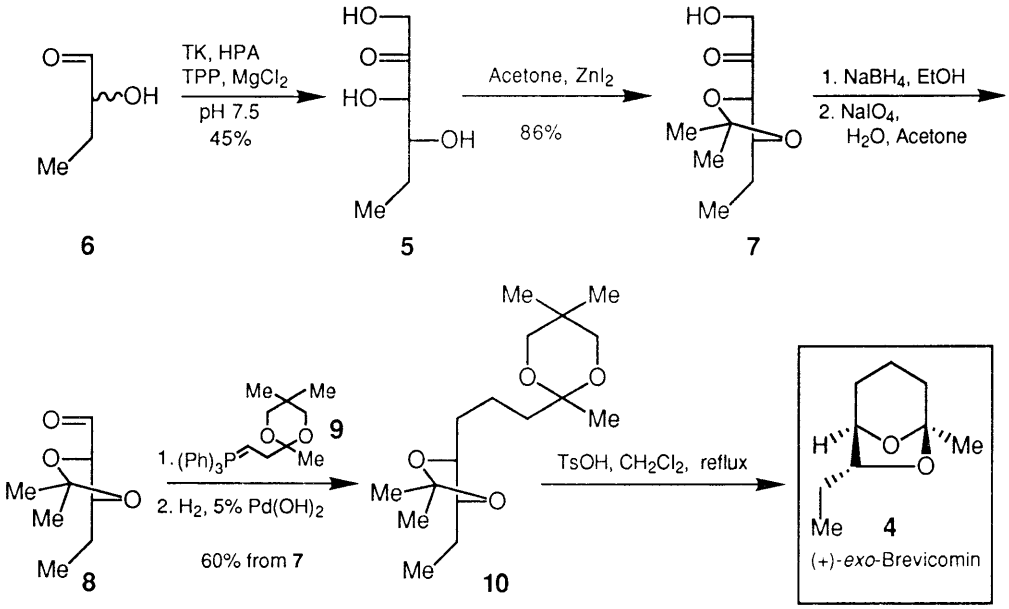


The pheromone (+)-*exo*-brevicomin[4] (**4**) (Scheme 1) provides a simple target with which to test the synthetic utility of transketolase, since its vicinal diol moiety is in the D-*threo* configuration and can be obtained from a stereoselective, TK-catalyzed transformation. We envisioned trihydroxy ketone **5** as the central

intermediate in a synthetic strategy wherein compound **5** is synthesized directly from 2-hydroxy butyraldehyde (**6**) by a stereoselective ketol transfer process catalyzed by TK.



In this letter, we describe a total synthesis of (+)-*exo*-brevicomin that utilizes transketolase from baker's yeast as the sole source of enantioselectivity (Scheme 2). We used racemic 2-hydroxy butyraldehyde as the starting material, taking advantage of the ability of transketolase to effect a kinetic resolution of racemic substrates. We prepared **6** directly by ozonolysis of commercially available (Aldrich) DL-3-hydroxy-1-butene (O_3, CH_2Cl_2; Zn, HOAc). Aldehyde **6** is a good substrate for transketolase ($V_6/V_{glyceraldehyde}$ = 0.42).[5] Treatment of **6** (10-40 mmol) and HPA (1.2 equiv., Sigma) with transketolase (10-25 U) and the required cofactors magnesium(II) chloride (3.0 mM) and TPP (0.1 mM, Sigma) at pH 7.5 effected the smooth conversion of **6** to hydroxy ketone **5** in 45% yield (90% of theoretical yield).[6,7] Without pH control, the medium became more basic as the reaction progressed. We maintained the pH at 7.5 using a pH controller and



(Scheme 2)

0.1 M HCl. Compound **5** was isolated by continuous extraction of the reaction mixture with ethyl acetate and was purified by silica gel chromatography (15% MeOH in ethyl acetate). Selective protection of the secondary hydroxyl groups was accomplished by zinc iodide mediated ketalization of **5** in anhydrous acetone to afford acetonide **7** in 86% yield.[8] We converted hydroxyketone **7** to its corresponding diastereomeric esters using *R* and *S* Mosher's acid and found the enantiomeric excess of **7**, and hence the entire sequence, to be greater than 95%.[9] Having successfully blocked the vicinal diol moiety, we were now ready to excise C-1 converting hydroxy ketone **7** to aldehyde **8**.

We accomplished the conversion of **7** to **8** in two operations without purification of intermediates. The carbonyl moiety of **7** was reduced with $NaBH_4$ to the corresponding 1,2-diol. Oxidative cleavage of the diol with $NaIO_4$ in buffered (pH 7 phosphate buffer) aqueous acetone gave the desired aldehyde **8**. The remaining carbons required for (+)-*exo*-brevicomin were added in a single step via Wittig reagent **9**.[10] Addition of a THF solution of aldehyde **8**, used directly from $NaIO_4$ cleavage without purification, to the freshly prepared solution of **9** resulted in the formation of the corresponding Z-alkene (60% yield from **7**). Hydrogenation (1 atm H_2, hexanes, 20 min) of the alkene over Pearlman's catalyst furnished the saturated compound **10** in ca. 85% yield.[11] In their synthesis of (+)-*exo*-brevicomin, Kotsuki *et al.* had prepared **10**.[12] Analytical data obtained for **10** were compared with published data and unambiguously established the identity of our sample. We converted this material to (+)-*exo*-brevicomin by mild acid catalyzed transketalization with *p*-toluenesulfonic acid in dichloromethane, following the procedure of Kotsuki *et al.*[12] We confirmed the identity of the enzymatically-obtained sample of (+)-*exo*-brevicomin by ^1H NMR, ^{13}C NMR, and GC/HRMS.[13]

In summary, we have demonstrated the synthetic utility of the enzyme transketolase (EC 2.2.1.1) in the enantiospecific synthesis of (+)-*exo*-brevicomin. Starting from racemic 2-hydroxy butyraldehyde the synthesis of the title compound utilized the capacity of TK to effect a kinetic resolution of the DL mixture to dictate the enantiospecificity of the entire sequence. We are currently engaged in further studies concerning the use of transketolase in synthesis.

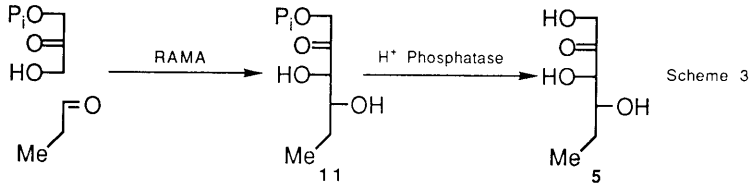
Acknowledgement The National Institutes of Health supported this research (NIH GM 30367, NIH GM 13250). We thank Prof. H. Waldmann (University of Mainz, Germany) for providing a sample of (+)-*exo*-brevicomin. Mass spectrometric analyses were performed by Dr. A. Tyler, Harvard University, Department of Chemistry.

References and Notes

1. Transketolase has been isolated in large quantities from fresh spinach leaves (Villafranca, J. and Axelrod, B. *J. Biol. Chem.*, **246** (1971) 3126) and baker's yeast (Datta, A. and Racker, E. *J. Biol. Chem.*, **236** (1961) 617). The yeast derived enzyme is commercially available from Sigma Chem. Co. The experiments described in this letter were conducted with the commercially available yeast enzyme.
2. Srere, P.; Cooper, J. R.; Tabachnick, M.; and Racker, E. *Arch. Biochim. Biophys.*, **74** (1958) 295.
3. Wood, T. *Prep. Biochem.*, **3** (1973) 509.
4. Isolation: Silverstein, R. M.; Brownlee, R. G.; Bellas, T. E.; Wood, D. L.; and Browne, L. E. *Science*, **159** (1968) 889. Recent previous syntheses of (+)-*exo*-brevicomin: Schultz, M.; Waldman,

W.; Kunz, H. *Tetrahedron Lett*, **31**, (1990) 867. Kotsuki, H.; Kadota, I.; Ochi, M., *Tetrahedron Lett.*, **30** (1989) 3999. Review articles: Singh, S. M.; Ohlschlager, A. C., *Can. J. Chem.*, **66**, (1988) 209. Mori, K., *Tetrahedron*, **45**, (1989) 3233.

5. D. Myles, Y. Kobori, these laboratories, unpublished results.
6. The unreacted hydroxy aldehyde can be isolated in modest yield from the reaction mixture and has been shown by ^1H NMR shift studies to have high (ca. 95%) enantiomeric excess (Y. Kobori, these laboratories, unpublished results).
7. Ketone **5** can also be obtained by a two step procedure from propionaldehyde. The fructose-1,6-diphosphate aldolase-catalyzed (RAMA, EC 4.1.2.13) condensation of propionaldehyde and dihydroxy acetone phosphate furnishes ketophosphate **11** (see Scheme 3 below). This material can be dephosphorylated *in situ* by treatment with acid phosphatase (EC 3.1.3.2). For additional information on this procedure see Bednarski, M. D.; Simon, E. S.; Waldman, H.; Whitesides, G. M. *J. Am. Chem. Soc.* **111** (1989) 627.



Scheme 3

8. Standard ketalization conditions gave unsatisfactory results. For example, catalytic *p*-toluene sulfonic acid (TsOH) in anhydrous acetone with anhydrous copper sulfate as desiccant led to incomplete reaction and several side products. Catalytic TsOH in 2,2-dimethoxy propane afforded the dimethyl ketal of acetonide **7** as the major product.
9. Mosher's acid: α-methoxy-α-trifluoromethylphenylacetic acid. At 300 MHz in $CDCl_3$, the ^1H NMR spectra for the diastereomeric *R* and *S* Mosher's esters of **7** gave readily distinguished AB_q resonances for the C(1) methylene moieties: *R*-Mosher's ester of **7**; 5.16 ppm AB_q (J_{ab} = 18.33 Hz, $\Delta\nu$ = 100.83 Hz). *S*-Mosher's ester of **7**; 5.11 ppm ABq (J_{ab} = 17.91 Hz, $\Delta\nu$ = 95.64 Hz). For preparation of the esters. see: Dale, J. A.; Duli, D. L.; Mosher, H. S. *J. Org. Chem.* **34**, (1969), 2543.
10. Phosphorane **9** was prepared from methyl vinyl ketone as describe by Stowell and Keith (Stowell, J. C. and Keith, D. R. *Synthesis*, **1979**, 132). Treatment of the phosphonium bromide precursor in hexanes with butyllithium furnished **9**.
11. Pearlman's catalyst: Palladium hydroxide on carbon. See P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals," Academic Press, New York, NY, 1967, p. 464.
12. H. Kotsuki, I. Kadota, and M. Ochi, *Tetrahedron Lett.*, **30** (1989) 3999. $[\alpha]^{20}_D$ +15.84 (c, 0.80, $CHCl_3$) lit $[\alpha]^{17}_D$ +16.8 (c, 0.80, $CHCl_3$).
13. ^1H- and ^{13}C NMR spectral data of (+)-*exo*-brevicomin obtained from the transketolase-based strategy were compaired to published data (see reference 4). GC/HRMS for $C_9H_{16}O_2$ expected 156.0115, found 156.1146.

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