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Enantioselective Enzymatic Desymmetrization of Highly Functionalized *Meso* Tetrahydropyranyl Diols†

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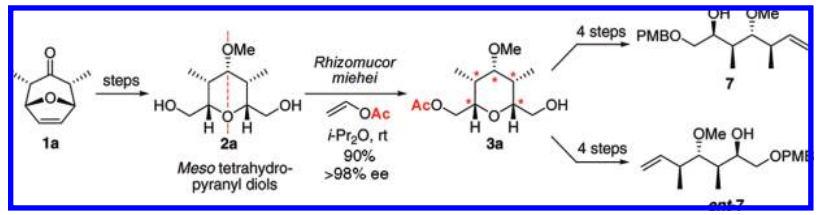
ABSTRACT



The enantioselective enzymatic desymmetrization of several highly substituted *meso*-tetrahydropyranyl diols is described. This transformation leads to valuable building blocks containing up to five stereogenic centers, which are revealed in a single step with both high yields and excellent enantiomeric excesses. Moreover, it was shown that this kind of building blocks could provide an easy access to both enantiomers of highly functionalized stereotetrads.

Many natural products bear a tetrahydropyran (THP) moiety and some, such as kendomycin,[1] phorboxazoles,[2] and ratjadone A,[3] present interesting biological activities (Figure 1). This observation led chemists to develop strategies and new approaches to obtain this particular heterocycle in a stereoselective fashion.[4] Among these, the Prins reaction,[5] the Petasis−Ferrier rearrangement,[6] the intramolecular oxa-Michael additions,[7] and the hetero-Diels−Alder cycloadditions[8] have been widely adopted.

The enantioselective desymmetrization of *meso* compounds has become a powerful strategy in synthesis[9] as it allows to reveal and/or generate multiple stereogenic centers in a single operation. Hence, in the context of total synthesis, the retrosynthetic analysis is based on the detection of *hidden symmetry* within the target molecule. The desymmetrization of *meso* compounds containing functions such as epoxides,[10]

† Dedicated to Professor Mark Lautens on the occasion of his 50th birthday.

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(1) *Isolation*: Funahashi, Y.; Kawamura, N.; Ishimaru, T. Japan Patent 08231551 [A2960910], 1996; *Chem. Abstr.* **1997**, *126*, 6553; Japan Patent 08231552, 1996; *Chem. Abstr.* **1996**, *125*, 326518. *Total syntheses*: (a) Yuan, Y.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 14720–14721. (b) Smith III, A. B.; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2005**, *127*, 6948–6949. (c) Smith III, A. B.; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2006**, *128*, 5292–5299. (d) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2008**, *10*, 3813–3816. (e) Magauer, T.; Martin, H. J.; Mulzer, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6032–6036. *Formal syntheses*: Bahnck, K. B.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2008**, *130*, 13177–13180.

(2) *Isolation*: Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126–8127. *Total syntheses of Phorboxazole A*: (a) Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S *J. Am. Chem. Soc.* **1998**, *120*, 5597–5598. (b) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942–10953. (c) Gonzalez, M. A.; Pattenden, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 1255–1258. (d) Williams, D. R.; Kiryanov, A. A.; Emde, U.; Clark, M. P.; Berliner, M. A.; Reeves, J. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 1258–1262. (e) White, J. D.; Lee, T. H.; Kuntiyong, P. *Org. Lett.* **2006**, *8*, 6039–6042. (f) White, J. D.; Lee, T. H.; Kuntiyong, P. *Org. Lett.* **2006**, *8*, 6043–6046. *Total syntheses of Phorboxazole B*: (aa) Evans, D. A.; Cee, V. J.; Smith, T. E.; Fitch, D. M.; Cho, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2533–2536. (bb) Evans, D. A.; Cee, V. J.; Smith, T. E.; Fitch, D. M.; Cho, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2536–2540. (cc) Li, D.-R.; Zhang, D.-H.; Sun, C.-Y.; Zhang, J.-W.; Yang, L.; Chen, J.; Liu, B.; Su, C.; Zhou, W.-S.; Lin, G.-Q. *Chem.—Eur. J.* **2006**, *12*, 1185–1204. (dd) Lucas, B. S.; Gopalsamuthiram, V.; Burke, S. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 769–772.

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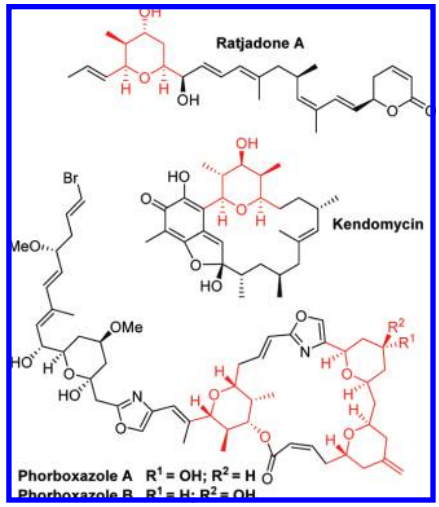


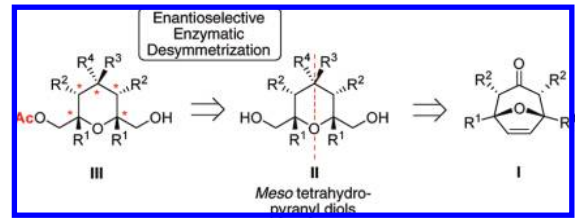
Figure 1. Natural products containing a highly substituted THP subunit.

anhydrides,[11] diols[12] and polyols,[13] dienes,[14] ketones,[15] or oxabicycles[16] has been successfully applied to the total synthesis of various challenging natural products.[17] However, as highlighted by Hoffmann in a recent review,[18] the use of *meso* compounds in asymmetric synthesis is greatly dependent on how easy these *meso* building blocks are built.

Syntheses of THP subunits through enantioselective desymmetrization using a preformed THP ring are rare. Indeed, to our knowledge, only two methods have been described so far: (1) the enzyme-mediated hydrolysis of diesters[19] or mono-transesterification of diols which, when applied to 2,4,6-substitued *meso*-THP, lead to the generation of up to three new stereogenic centers, and (2) the asymmetric ring-opening cross-metathesis involving chiral catalysts.[20]

In this paper, we report the synthesis of a new class of *meso* compounds **II** bearing a 2,3,4,5,6-substituted tetrahydropyranyl diol motif easily obtained from oxabicycles of type **I** and their enantioselective enzymatic desymmetrization, which reveals and creates up to five new stereogenic centers[21] in a one-pot fashion (Scheme 1).

Scheme 1. Synthetic Strategy toward THP Containing up to Five Stereogenic Centers



The synthesis of the *meso* compounds relied on the oxabicycles of type **I** easily available through a highly diastereoselective [4 + 3] cycloaddition between furan derivatives and oxyallyl cation precursors following the procedure developed by Lubineau and Bouchain[22] (Scheme

(3) *Isolation*: Schummer, D.; Gerth, K.; Reichenbach, H.; Höfle, G. *Liebigs Ann.* **1995**, 685–688. *Total Syntheses*: (a) Williams, D. R.; Ihle, D. C.; Plummer, S. V. *Org. Lett.* **2001**, *3*, 1383–1386. (b) Bhatt, U.; Christmann, M.; Quitschalle, M.; Claus, E.; Kalesse, M. *J. Org. Chem.* **2001**, *66*, 1885–1893.

(4) For a review on THP, see: (a) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045–2053. (b) Larrosa, I.; Romea, P.; Urpi, F. *Tetrahedron* **2008**, *64*, 2683–2723.

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(10) For selected examples on catalytic enantioselective desymmetrization of *meso* epoxides *by ring opening of a nucleophile*, see: (a) Arai, K.; Salter, M. M.; Yamashita, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 955–957. (b) Matsunaga, S.; Das, J.; Roels, J.; Vogl, E. M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 2252–2260. (c) Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001–1004. *By based-induced rearrangement, see*: Södergren, M. J.; Bertilsson, S. K.; Andersson, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 6610–6618, and references therein.

(11) For a general review on enantioselective stereoselective ring opening of *meso* anhydrides, see: Atodiresei, L.; Schiffers, I.; Bolm, C. *Chem. Rev.* **2007**, *107*, 5683–5712.

(12) For recent examples of enantioselective catalytic desymmetrization of *meso* diols, see: (a) Kündig, E. P.; Enriquez Garcia, A.; Lomberget, T.; Perez Garcia, P.; Romanens, P. *Chem. Commun.* **2008**, 3519–3521. (b) Birman, V. B.; Jiang, H.; Li, X. *Org. Lett.* **2007**, *9*, 3237–3240. (c) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67–70. (d) Shimizu, H.; Onitsuka, S.; Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2005**, *127*, 5396–5413.

(13) For recent examples of enantioselective catalytic desymmetrization of *meso* polyols, see: (a) Lucas, B. S.; Burke, S. D. *Org. Lett.* **2003**, *5*, 3915–3918. (b) Harada, T.; Egusa, T.; Igarashi, Y.; Kinugasa, M.; Oku, A. *J. Org. Chem.* **2002**, *67*, 7080–7090. (c) Chênevert, R.; Rose, Y. S. *J. Org. Chem.* **2000**, *65*, 1707–1709.

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(15) For recent examples of catalytic desymmetrization of *meso* ketones, see: (a) Chandler, C. L.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6737–6739. (b) Ramachary, D. B.; Barbas, C. F. *Org. Lett.* **2005**, *7*, 1577–1580.

(16) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48–58.

(17) Some significant examples: *Vannusal B*: Nicolaou, K. C.; Zhang, H.; Ortiz, A.; Dagneau, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8605–8610. *Tamiflu*: Zutter, U.; Iding, H.; Spurr, P.; Wirz, B. *J. Org. Chem.* **2008**, *73*, 4895–4902. *Ionomycin*: Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. *Org. Lett.* **2002**, *4*, 1879–1882. *Quadrigemine C and Psycholeine*: Lebsack, A. D.; Link, J. T.; Overman, L. E.; Stearns, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 9008–9009.

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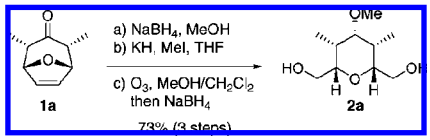
(19) (a) Lampe, T. F. J.; Hoffmann, H. M. R.; Bornsheuer, U. T. *Tetrahedron: Asymmetry* **1996**, *7*, 2889–2900. (b) Chênevert, R.; Goupil, D.; Rose, Y. S.; Bédard, E. *Tetrahedron: Asymmetry* **1998**, *9*, 4285–4288.

(20) (a) Gillingham, D. G.; Kataoka, O.; Garber, S. B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 12288–12290. (b) Gillingham, D. G.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 3860–3864. (c) Ibrahem, I.; Yu, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3844–3845.

(21) We use the term "reveal" because the stereogenic centers pre-exist before the operation of desymmetrization and "create" because in our case one carbon is prochiral (C4).

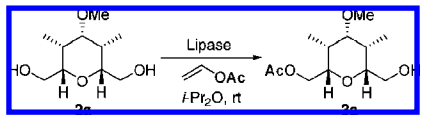
2). Hence, multigram amounts of *meso* oxabicycle **1a** could be obtained by simple crystallization of the crude material. The synthetic sequence toward diol **2a** from oxabicycle **1a** required three steps: first, a highly stereoselective reduction of the ketone using sodium borohydride followed by an alkylation of the free hydroxyl group mediated by KH and an ozonolysis [MeOH/CH_2Cl_2 (1.5/2), −60 °C] terminated by a reduction with an excess of sodium borohydride. Based on this strategy, a variety of *meso*-tetrahydropyranyl diols **2a**−**i** was synthesized.[23]

Scheme 2. Synthesis of the *meso*-Tetrahydropyranyl Diol **2a**



Five commercially available lipases were screened.[24] A typical experiment was conducted at room temperature with a mixture of *meso* diol **2a** (0.245 mmol, 50 mg) and lipase (30 mg) in the presence of vinyl acetate[25] (2 mL) and diisopropyl ether (2 mL). The outcome of this initial screening indicated that *Rhizomucor miehei* lipase (RML) was the enzyme of choice for the transesterification of **2a** (Table 1, entry 3) leading to the corresponding monoacetate in high yield (90%) and excellent molecular recognition (ee >98%) within 24 h. *Pseudomonas fluorescens* lipase (PFL) also exhibited an interesting activity (Table 1, entry 2); however, the yield and ee were slightly lower.

Table 1. Screening of Lipases for the Enantioselective Enzymatic Desymmetrization of Tetrahydropyranyl Diols

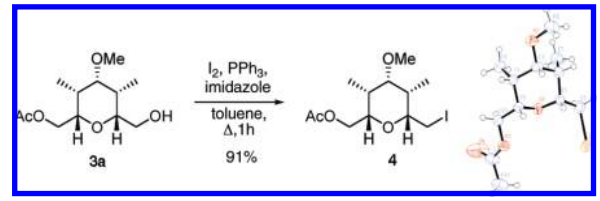


entry	lipase	reaction time (h)	yield[a] (%)	ee[b] (%)
1	PPL	48	0	
2	PFL	24	81	>94
3	RML	24	90	>98
4	CAL-B	20	100[c]	
5	CRL	20	100[c]	

[a] Isolated yields after column chromatography. [b] Determined by chiral HPLC (Sepapak-2-HR) after purification by column chromatography. [c] Formation of the *meso*-diacetate.

The absolute configuration of alcohol **3a**, obtained through RML-promoted transesterification was determined unambiguously by X-ray analysis of its corresponding iodide derivative **4**[26] (Scheme 3).

Scheme 3. Synthesis of the Iodide Derivative **4** from the Desymmetrized Compound **3a** and Its ORTEP View



We then examined the scope of the RML-promoted desymmetrization using the variously substituted *meso* THP diols **2a**−**i**. The modification of the substituent at C4 on the THP ring (R^4) was first tested: the hydroxyl group in this position can be protected by several groups with different hindrances without effect on the yields or the selectivities (Table 2, entries 1−4). Even more interestingly, it appeared that the inversion of configuration on C4 (Table 2, entry 5) or the total reduction of this position (Table 2, entry 6) had no significant effect on ee. Increasing the steric hindrance at C3 positions (R^2) resulted only in a very slight decrease of the enantioselectivity when a methyl was changed for an ethyl group (96% ee) (Table 2, entry 7), but a dramatic fall of reactivity and enantioselectivity of the reaction was observed when a methyl group was changed for a phenyl group (Table 2, entry 8). Finally, desymmetrized THP **3i** bearing three quaternary centers could be obtained in 72% yield and 94% ee from *meso*-triol **2i** bearing a free tertiary alcohol in C4 position.

We then explored the synthetic potential of the transformation and showed that the desymmetrized building block **3a**[27] could easily be converted into both enantiomers **7** and ***ent*-7** of a *syn-anti-anti* stereotetrad just by changing the order of the synthetic sequence (Scheme 4). Iodination of the free primary alcohol of **3a** followed by saponification, protection of the alcohol as its *p*-methoxybenzyl ether using PMB-trichloroacetimidate (PMBTCA) in the presence of $Yb(OTf)_3$,[28] and a Zn-mediated ring-opening of the THP ring furnished the valuable polyfunctionalized tetrad **7** in 64% overall yield.

Its enantiomer ***ent*-7** could be obtained by starting with the PMB protection, then saponification, followed by iodination and Zn-mediated ring-opening in a similar 69% overall yield. In this non-aldol strategy to polypropionate fragments,

(22) (a) Lubineau, A.; Bouchain, G. *Tetrahedron Lett.* **1997**, *38*, 8031–8032. (b) Lautens, M.; Bouchain, G. *Org. Synth.* **2002**, *79*, 251–253.

(23) See Supporting Information.

(24) PPL: Pig Pancreatic Lipase; PFL: *Pseudomonas fluorescens*; RML: *Rhizomucor miehei* Lipase; CAL-B: *Candida antarctica B* Lipase; CRL: *Candida rugosa* Lipase type VII.

(25) Vinyl acetate was used here as reagent and co-solvent to solubilize the *meso* diol during the desymmetrization reaction.

(26) CCDC 739869 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(27) The desymmetrization of **2a** was performed on 2 grams scale in 87% and identical ee.

(28) Rai, A. N.; Basu, A. *Tetrahedron Lett.* **2003**, *44*, 2267–2269.

Table 2. Enantioselective Enzymatic Desymmetrization of Tetrahydropyranyl Diols **2a**−**i**[a]

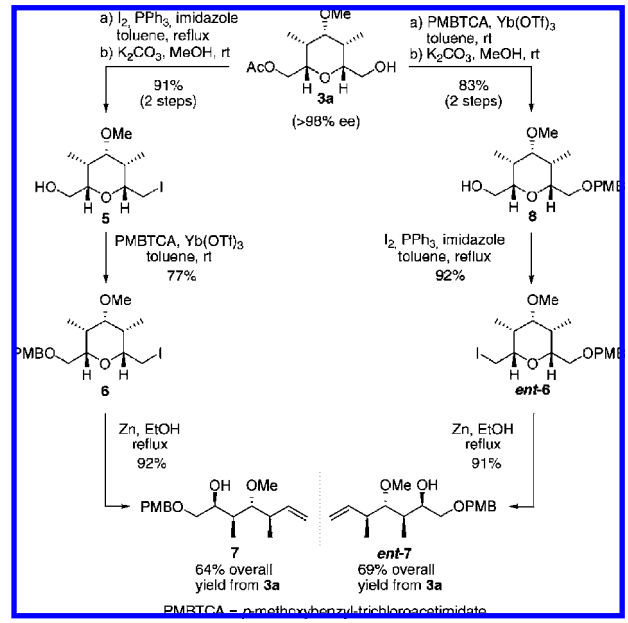
entry	R^1	R^2	R^3	R^4	*meso* diol	product	yield (%)[b]	ee (%)[c]
1	H	Me	H	OMe	**2a**	**3a**	90	>98
2	H	Me	H	OTBS	**2b**	**3b**	89	>98
3	H	Me	H	OBn	**2c**	**3c**	88	>98
4	H	Me	H	OBz	**2d**	**3d**	89	>98
5	H	Me	OMe	H	**2e**	**3e**	58	95
6	H	Me	H	H	**2f**	**3f**	67[d]	96
7	H	Et	H	OMe	**2g**	**3g**	82	96
8	H	Ph	H	OMe	**2h**	**3h**	21[e]	13
9	Me	Me	Me	OH	**2i**	**3i**	72	94

[a] Typical experiment: diol **2a** (0.245 mmol, 50 mg) and *R. miehei* lipase (30 mg) in *i*-Pr_2O (2 mL) and vinyl acetate (2 mL), 24 h. [b] Isolated yields after column chromatography. [c] Determined by chiral HPLC. [d] Reaction over 3 h, 27% of *meso*-diacetate was isolated. [e] Reaction over 72 h, 75% of diol was recovered.

it is important to note that the stereochemistry of the four stereogenic centers of the tetrad is controlled in a single step.

In conclusion, a new class of *meso*-tetrahydropyranyl diols **2a**−**i** were synthesized that underwent efficient *R. miehei* lipase-catalyzed transesterification to afford tetrahydropyrans with up to five stereogenic centers.

Scheme 4. Synthesis of Both Enantiomers **7** and ***ent*-7** of the *syn-anti-anti*-Tetrade from the Desymmetrized Monoacetate **3a**



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Supporting Information Available: Full characterization data and copies of ^{1}H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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