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Highly Enantioselective Acylation of Acyclic *Meso* 1,3-Diols through Synergistic Isothiourea-Catalyzed Desymmetrization/Chiroablative Kinetic Resolution

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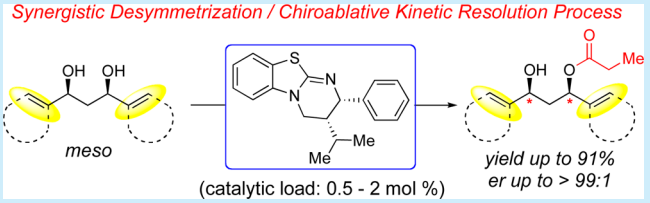
Supporting Information

ABSTRACT: A general and highly efficient organocatalyzed desymmetrization of acyclic meso 1,3-diols through acyl transfer using chiral isothioureas is described. The introduction of π-systems in the acyclic substrates provided new opportunities in terms of reactivity, enantioselectivity and synthetic potential. To reach this high level of enantioselectivity (up to er >99:1), the reaction proceeds through a synergistic mechanism involving a desymmetrization reaction and a chiroablative kinetic resolution process. This methodology was used with success as the sole enantioselective catalytic step (developed on a gram scale) to achieve the total synthesis of the antiosteoporotic diarylheptanoid (−)-diospongin A (7 steps).



Syn 1,3-diol units are ubiquitous in polyketide natural products and analogues thereof. It is the case for many important commercialized drugs such as the antibiotic amphotericin B[1] and the cholesterol-lowering atorvastatin[2] (Lipitor) (Figure 1). Since

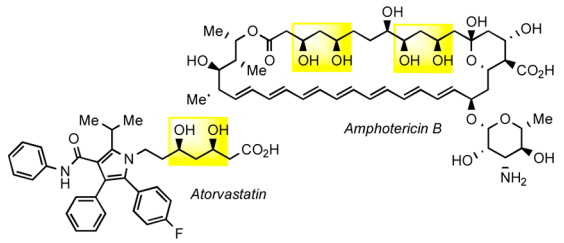


Figure 1. Drugs bearing *syn* 1,3-diol units.

the hydroxylated part of these molecules is fundamental for their biological activity, the stereocontrol of the *syn* 1,3-diol moieties[3] is crucial in their synthesis. In the past, several stereoselective strategies were developed to elaborate this important structural motif mainly by securing the enantiocontrol of a β-hydroxyketones precursor and then ensuring a *syn*-diastereoselective reduction[4] (Scheme 1a). Interestingly, among the numerous possible approaches to prepare the *syn* 1,3-diol motif, the catalytic enantioselective desymmetrization of an acyclic *meso* precursor strategy[5,6] has been undoubtedly underexplored. In contrast to all the classical approaches, attention is first given to the diastereoselective preparation of the achiral *meso* substrates while the enantioselectivity is controlled in a late stage.[7] To the best of our knowledge, only three studies[8] involving an organocatalytic approach have been reported in the literature but two of these afforded only moderate levels of enantioselectivity.[8a,b] The third example reported by Ishihara et al.[8c] led to an excellent enantioselectivity (97:3 er) albeit only with a specific substrate. This limited number of efficient enantioselective catalyzed acyl transfer processes on acyclic *meso* 1,3-diols highlights the difficulty of this transformation, which could be explained by numerous degrees of freedom that do not facilitate the enantiocontrol.[9] More rigidity could be brought by the introduction of π-systems thus providing allylic strains[10] and hence reducing the number of conformations in the transition state.

Moreover π-systems could supply supramolecular stabilizing interactions, such as cation−π[11] and π−π[12] interactions, between the substrate and the catalyst. Finally π-systems, especially double bonds, are particularly convenient for further transformations.

Herein, we report an efficient, general, and highly enantioselective organocatalytic acylative[13] desymmetrization process of acyclic *meso* 1,3-diols. Mechanistically the reaction proceeds through a synergistic process involving a desymmetrization and a *chiroablative* kinetic resolution based on the Horeau principle.[14] Inspired by the concept of stereoablative reactions[15] developed by Stoltz where the enantioselectivity results from the destruction of a stereogenic center (Scheme 1b), *chiroablative* reactions amplify the enantiopurity of a product by transforming the minor enantiomer into a symmetric achiral molecule (without lost of stereogenic centers) (Scheme 1c). Finally, the presence of the double bonds in the desymmetrized products was exploited in various postfunctionalizations and illustrated by the total synthesis of (−)-diospongin A.

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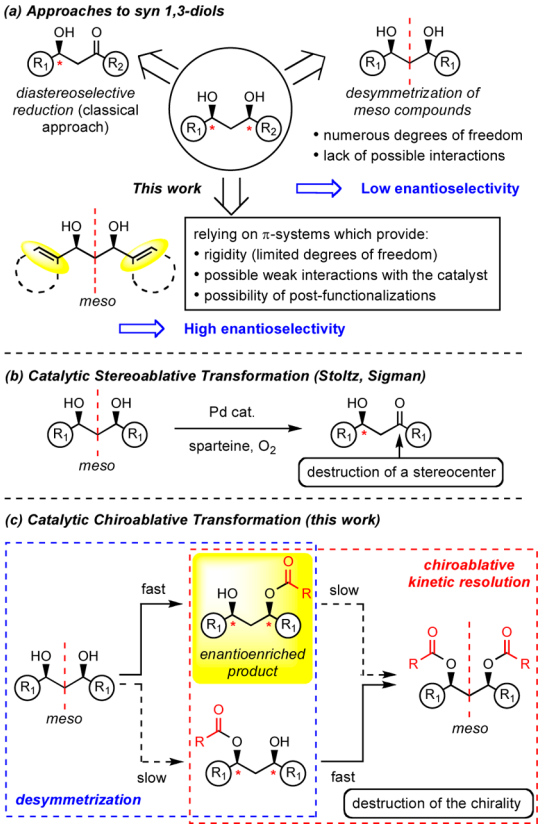
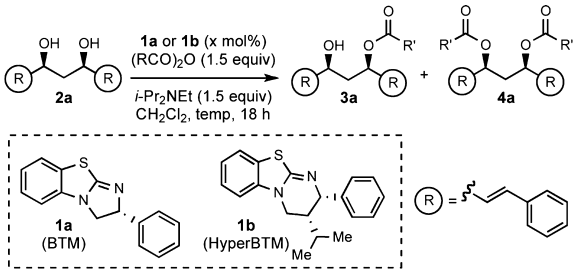
Scheme 1. Approaches to Acyclic *Syn* 1,3-Diols



Birman's isothiourea catalyst (**1a**) was chosen for the first desymmetrization attempts, as it afforded particularly good results in the kinetic resolution of alcohols bearing π-systems.[16,17] The optimization study was conducted on *syn*-1,7-diphenylhepta-1,6-dien-3,5-diol (**2a**), easily prepared following a two-step sequence[18] (Table 1). The screening of the acylating reagent nature revealed the importance of this parameter (Table 1, entries 1−3). Indeed, propionic anhydride (Table 1, entry 2) provided, after 18 h, the best enantioselectivity (88.2:11.8 er) but with low conversion (47%) in the preparation of **3a**. Cooling the reaction to −10 °C (Table 1, entry 4) improved both the yield and selectivity (91:9 er), while switching to Smith's HyperBTM catalyst (**1b**)[19] afforded significantly increased conversion and selectivity (Table 1, entry 5) with a reduced reaction time (98.1:1.9 er in 2.5 h). Full consumption of anhydride led to the formation of a large amount of *meso* diester **4a**. Reduced amounts of base and anhydride improved the yield in **3a** (Table 1, entry 6). Finally cooling to −20 °C and using only 2 mol % of catalyst gave a better yield of the virtually enantiomerically pure monoester **3a** (Table 1, entry 7). The presence of Na_2SO_4 recommended in the Birman's seminal study[16] did not benefit the reaction using catalyst **1b** (Table 1, entries 6 and 7). With these optimized conditions in hand, we then explored the scope of the desymmetrization on various precursors (Scheme 2). In the *syn*-1,7-diarylhepta-1,6-dien-3,5-diol series, the nature of the aryl groups was first examined.

Hence different aromatic substituents were tested such as 2-methoxy (**3b**), 4-methoxy (**3c**), and 4-chloro (**3e**), and all afforded comparable levels of enantioselectivity. Heteroaromatic substituents such as 2-furyl groups (**3d**) could be used without alteration of either the yield or selectivity (98.4:1.6 er). The replacement of aromatic groups by a methyl group had a limited

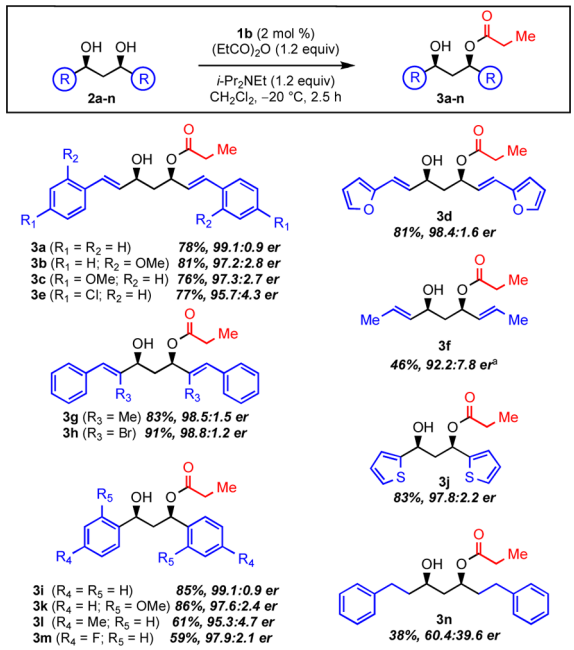
Table 1. Selected Optimization Experiments[a]



entry	catalyst (*x* mol %)	anhydride	temp (°C)	yield **3a**[b] (**4a**) (%)	er[d]
1	**1a** (8)	$(MeCO)_2O$	0	53 (4)	83.1:16.9
2	**1a** (8)	$(EtCO)_2O$	0	42 (5)	88.2:11.8
3	**1a** (8)	$(i\text{-}PrCO)_2O$	0	42 (18)	61.4:38.6
4	**1a** (8)	$(EtCO)_2O$	−10	56 (8)	91.1:8.9
5	**1b** (8)	$(EtCO)_2O$	−10	50 (50)	98.1:1.9
6[e,f,g]	**1b** (8)	$(EtCO)_2O$	−10	62 (29)	96.6:3.4
7[e,f,g]	***1b*** *(2)*	*$(EtCO)_2O$*	−20	*78*[c] *(18)*	*99.1:0.9*

[a]Typical experiment: **2a** (50 mg, 0.18 mmol), *i*-Pr_2NEt (45 μL, 0.27 mmol), Na_2SO_4 (100 mg), and catalyst (8 mol %) in CH_2Cl_2 (760 μL) was cooled before addition of anhydride (34 μL, 0.27 mmol). [b]Determined by ^1H NMR. [c]Isolated yield. [d]Determined by HPLC column Lux-Cellulose-2, hexane/ethanol 80/20, 1 mL/min. [e]Performed in 2.5 h. [f]Without Na_2SO_4. [g]1.2 equiv of anhydride and 1.2 equiv of *i*-Pr_2NEt.

Scheme 2. Scope of the Desymmetrization



[a]er determined after acylation with 4-bromobenzoic anhydride.

impact on the selectivity (**3f**), while additional substituents on the double bonds (**3g** and **3h**) could be added leading also to excellent results. Then we examined the influence of the aromatic groups on a series of *syn*-1,3-diarylpropane-1,3-diols (**3i**−**m**). Hence, the desymmetrization of diol **2i** using isothiourea **1b** led to monoester **3i** in high yield and with an er up to 99.1:0.9 thus demonstrating the generality of the method. Various substitution patterns with electron-donating substituents (**3k** and **3l**) or electron-withdrawing atoms (**3m**) were examined, and all gave

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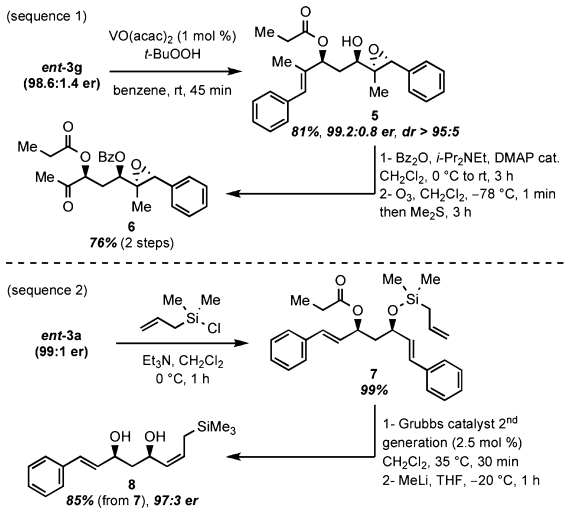
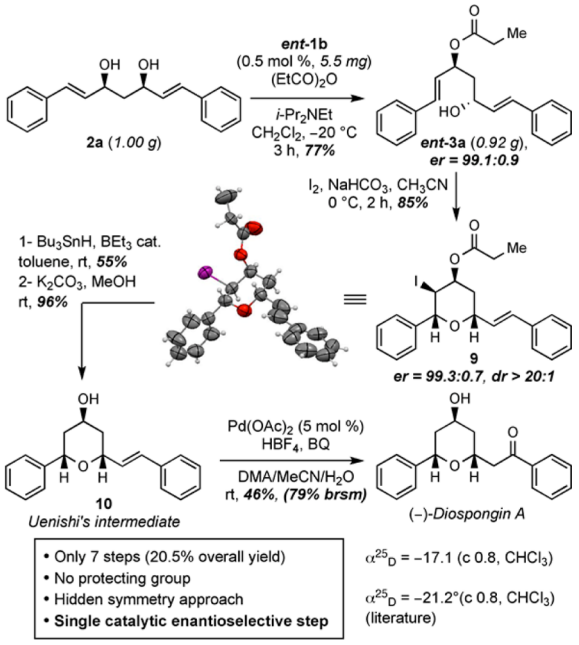
excellent results. The enantioselective acyl transfer was also successfully performed on substrates bearing heteroaromatic groups such as thiophenes (**3j**). In order to evaluate the influence of the double bonds on the enantioselectivity, the reaction was performed on yashabushidiol A (**2n**). The reaction rate drastically slowed down (incomplete conversion after 2.5 h) and the enantiomeric ratio of **3n** dropped to 60.4:39.6, highlighting the importance of the unsaturations.

The presence of a significant amount of diester **4a** suggested that the observed enantioselectivity could result from a synergistic combination of two highly enantioselective steps,[20] a desymmetrization followed by a *chiroablative* kinetic resolution both catalyzed by isothiourea **1b** as also observed by Birman in a single case.[20b] To corroborate this hypothesis, the enantiomeric excess of **3a** was monitored during the course of transformation. Interestingly, an amplification of the enantioselectivity was observed at higher conversion, validating our initial assumption. This increase correlates also with the concomitant formation of diester **4a**.[18] Several postfunctionalizations based on the rich chemistry pertaining to allylic alcohols[21] were examined as depicted in Scheme 3. First, a highly diastereoselective (dr >95:5) and completely chemoselective epoxidation of ***ent*-3g** directed by the free hydroxyl group was performed using $VO(acac)_2$ as the catalyst,[22] leading to monoepoxide **5**. This intermediate was submitted to a benzoylation followed by an ozonolysis to give the complex ketone **5** bearing four stereogenic centers in only five steps (Scheme 3, sequence 1). Then, the carbon skeleton of monoester ***ent*-3a** was reorganized in dihydroxyallylsilane **8**. After silylation of monoester **3a** with allylchlorodimethylsilane, the resulting silylether **7** was transformed through ring-closing metathesis furnishing an unstable siloxane,[23] which was opened by addition of MeLi (Scheme 3, sequence 2). All these transformations led to interesting chiral building blocks bearing *syn* 1,3-diols diversely functionalized without significant alteration of the enantiomeric ratio compared to the ones of their precursors ***ent*-3a** and ***ent*-3g**, respectively. With this methodology, the total synthesis of a diarylheptanoid natural product was next investigated (Scheme 4), focusing our efforts on the antiosteoporotic (−)-diospongin A[24,25] which bears a tetrahydropyran ring. The desymmetrization of *meso* diol **2a**[26] was performed on a preparative scale (1.00 g)[27] with a highly reproducible yield and selectivity (77%, 99.1:0.9 er) using a catalyst loading lowered to 0.5 mol %.[28] The iodocyclization of ***ent*-3a** afforded iodopyran **9** in a complete regioselective fashion, with excellent diastereoselectivity (up to >20:1 dr) and complete conservation of the initial enantiomeric ratio. The relative and absolute configuration of tetrahydropyran **9** was confirmed by X-ray diffraction.[29] The reduction of the C−I bond under radical conditions followed by a mild hydrolysis led to Uenishi's intermediate **10**.[25f] Wacker oxidation on the styrenyl moiety of pyran **10** under the modified conditions described by Grubbs[30] led to the natural product in only 7 steps, without the requirement of a single protecting group[31] and, most importantly, involving only one catalytic enantioselective step as the synthesis relies on a hidden symmetry approach.[32]

Scheme 3. Postfunctionalizations



Scheme 4. Scalability of the Desymmetrization and Application to the Enantioselective Total Synthesis of (−)-Diospongin A



In conclusion we developed a general, scalable method to desymmetrize easily available acyclic *meso* 1,3-diol substrates through nucleophilic organocatalysis. The high substrate tolerance and excellent level of enantioselectivity of this methodology (up to >99:1 er) contrast with previous approaches. The π-systems are fundamental for the efficiency of the desymmetrization and also synthetically useful for subsequent post-transformations. This was demonstrated through an efficient total synthesis of (−)-diospongin A[33] involving a unique enantioselective step with a low catalytic load below 1 mol %. Also we have shown that a synergistic combination of a desymmetrization and chiroablative kinetic resolution steps catalyzed by a chiral isothiourea resulted in an amplification of the level of enantioselectivity. We think that this synergistic process between two consecutive enantioselective steps catalyzed by the same entity could be generalized for the preparation of valuable chiral building blocks useful in total synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data for all new compounds are provided including the CIF file of molecule **9**.

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Notes

The authors declare no competing financial interest.

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