Molecular Catalysis 468 (2019) 52–56

Contents lists available at ScienceDirect

Molecular Catalysis

journal homepage: www.elsevier.com/locate/mcat

Multienzymatic cascade synthesis of an enantiopure (2*R*,5*R*)-1,3-oxathiolane anti-HIV agent precursor

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ARTICLE INFO

Keywords:
Enzyme
Subtilisin Carlsberg
Candida antarctica lipase B
HIV
1,3-Oxathiolane

ABSTRACT

An enantiopure (2*R*,5*R*)-1,3-oxathiolane was obtained using a multienzymatic cascade protocol. By employing a combination of surfactant-treated subtilisin Carlsberg and *Candida antarctica* lipase B, the absolute configuration of the resulting 1,3-oxathiolane ring was efficiently controlled, resulting in an excellent enantiomeric excess (> 99%). This enantiopure 1,3-oxathiolane derivative is a key precursor to anti-HIV agents, such as lamivudine, through subsequent *N*-glycosylation.

Introduction

Enzymatic catalysis has drawn considerable attention as an important tool in asymmetric synthesis over the past few decades. As environmentally benign catalysts, enzymes generally exhibit high enantio- and regioselectivity, resulting in economically efficient catalytic processes [1–6]. Of the rich repertoire of useful procedures described, the development of multienzyme-catalyzed cascade reactions is a challenge of particular interest [7–14]. When operating under similar reaction conditions, different enzymes can thus be concurrently or sequentially combined to yield new, efficient synthesis strategies. These methods can circumvent typical drawbacks of multistep synthesis, such as time- and solvent-consumption, as well as yield-reducing isolation and purification schemes. For these reasons, multienzymatic synthesis can be an efficient tool for access to important intermediates with high enantiopurity, *e.g.*, for the synthesis of pharmaceutically active compounds [15–18].

One such group of active compounds is constituted by nucleoside analog reverse-transcriptase inhibitors (NRTIs, Fig. 1), such as lamivudine (**1a**) and emtricitabine (**1c**). Key intermediates in the synthesis of these structures are chiral 1,3-oxathiolane derivatives, which can be obtained through a variety of approaches. Most of these procedures involve kinetic resolution (KR) processes of racemic mixtures, using either selective crystallization mediated by resolving agents, or enzymatic esterification/hydrolysis [19–26]. In these protocols, the low yields caused by the KR process is a major limitation, however potentially circumvented by applying dynamic kinetic resolution (DKR) strategies. In a typical DKR protocol, the starting materials are thus allowed to undergo continuous racemization during the resolution process, leading to the enrichment of one enantiomer and a high overall yield. Nevertheless, reported enzyme-catalyzed DKR processes for the synthesis of 1,3-oxathiolane motifs are limited [17,27].

Herein, we have addressed this challenge, and describe an efficient multienzymatic protocol for the asymmetric synthesis of enantiomerically pure (2*R*, 5*R*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl acetate. Surfactant-treated subtilisin Carlsberg (STS) was thus used in combination with *Candida antarctica* lipase B (CAL B) to yield the enantiopure product in THF and PBS buffer. These enzymes generally show opposite stereoselectivity in catalytic acylation of acyclic secondary alcohols, where the *S*-isomer is typically favored by CAL B and the *R*-isomer by subtilisin Carlsberg [28–30].

Results and discussion

Recently, dynamic hemithioacetal reactions were employed for the asymmetric formation of 1,3-oxathiolan-5-ones by lipase-catalyzed γ-lactonization reactions [31–33]. Following an analogous strategy, the asymmetric synthesis of 1,3-oxathiolane derivatives was undertaken using STS or CAL B (Scheme 1). Both enzyme preparations favored the formation of the *trans*-isomers, although resulting in opposite enantiomers. Thus, in the presence of an acyl donor in THF, glycolaldehyde dimer **2** and 1,4-dithiane-2,5-diol **3** were converted to the

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https://doi.org/10.1016/j.mcat.2019.02.013
Received 9 October 2018; Received in revised form 12 February 2019; Accepted 14 February 2019

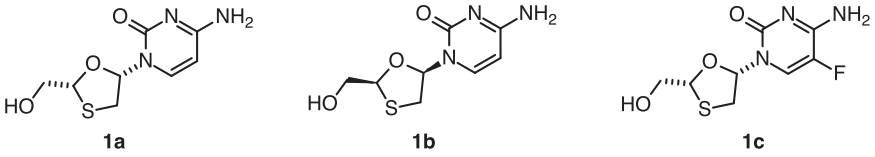
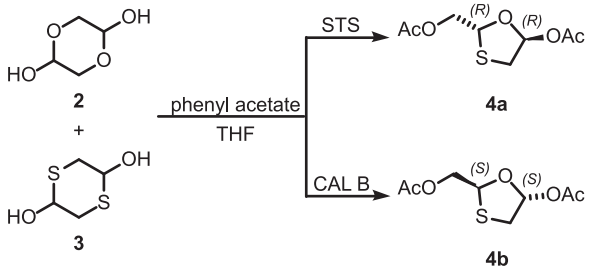


Fig. 1. Structures of lamivudine (**1a**), ent-lamivudine (**1b**) and emtricitabine (**1c**).



Scheme 1. Enzyme-catalyzed asymmetric formation of (2*R*,5*R*)-5-acetoxy-1,3-oxathiolan-2-yl)methyl acetate (**4a**), (2*S*,5*S*)-5-acetoxy-1,3-oxathiolan-2-yl) methyl acetate (**4b**).

enantioenriched (2*R*,5*R*)-1,3-oxathiolane (**4a**) catalyzed by STS, whereas the (2*S*,5*S*)-isomer (**4b**) was the main product in the CAL B-mediated process [17,34]. Furthermore, replacing compound **2** with the benzoyl-protected aldehyde **5** led to a higher enantiomeric excess of (2*R*)-1,3-oxathiolane derivative **5a** (82% *ee*) in the STS-catalyzed DKR process.

For further use in, *e.g.*, NRTI synthesis, the enantiopure (2*R*)-isomer is desired. For this, we envisaged that applying a resolution protocol to the enantioenriched isomer **5a** would result in the enantiomerically pure compound. Since KR processes focus on resolving racemic mixtures involving compounds with single stereocenters, thereby yielding a maximum of 50% yield, expanding the scope to resolve a racemate containing two chiral centers would at most provide 25% overall yield. Therefore, the present resolution design for the enantioenriched isomer was expected to result in better yields compared to the conventional KR process for racemic mixtures. As the most frequently used catalysts for selective hydrolysis of esters [35–38], lipases were chosen in current case.

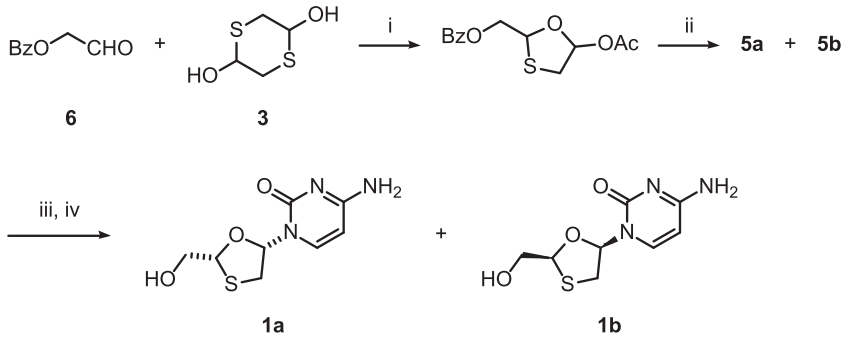
First, racemic mixture **5** was applied to hydrolysis in a biphasic phosphate-buffered saline (PBS)/THF system in the presence of lipases, and the reaction was followed by chiral HPLC chromatography. Lipase preparations from *Candida rugosa* (CRL), *Burkholderia cepacia* (PS-C I) and *Candida antarctica* (CAL B) were evaluated, of which CAL B resulted in formation of isomer **5a**, indicating that selective hydrolysis of either the benzoyl- or the acetyl-groups occurred. Furthermore, the enantioenriched isomer **5a** (C-5-configuration unknown) was prepared [17], and subjected to hydrolysis in the presence of CAL B in a PBS/THF mixture. Chiral HPLC analysis showed that the enantiomer of **5a** was completely eliminated, giving rise to an excellent *ee* of > 99%. However, a diastereomeric ratio (**5a**/**5b**) of 4:1 was recorded (Fig. S1). To identify the configuration of minor isomer **5b**, the **5a**/**5b** mixture was converted to the nucleoside by conventional Vorbrüggen coupling and deprotection (*cf.* Scheme 2). By comparing the chiral HPLC results of the product with lamivudine (reference), it was observed that the product consisted of lamivudine **1a** and *ent*-lamivudine **1b** in a ratio of 4:1. This indicates that isomer **5b** possessed the 2*S* configuration, thereby not being suitable for lamivudine synthesis. According to the results in Scheme 1, the configuration of isomer **5a**, prepared using the STS-system, could be deduced to be the (2*R*,5*R*)-isomer, in which case diastereomer **5b** would have a (2*S*,5*R*) configuration. Therefore, rather than acting upon the primary benzoyl ester in the 1,3-oxathiolane, CAL B appeared to selectively hydrolyze the secondary acetyl ester group in the 5*S*-position [39–43]. This was expected, in part since secondary alcohols have been deemed more favorable products in most enzyme-catalyzed hydrolysis reactions [44,45], but also due to the benzoyl group in the primary position. However, selective formation of primary alcohols can be observed with cyclic substrates, including carbohydrates and nucleosides [46] (Fig. 2).

To potentially achieve higher yields in the second step, we returned to enantioenriched isomer **4a**, obtained in the STS-catalyzed DKR process when the reaction was carried out in the presence of phenyl acetate and triethylamine at 4 °C. Compound **4** was in this case obtained as a mixture, consisting of two pairs of diastereomers, in which the major isomer **4a** exhibited 50% *ee* (Scheme 3). As shown in Fig. S2, the ratio of the *trans*- and *cis*-isomers was 84:16, compared to a ratio of approximately 2:1 in the reaction not catalyzed by enzyme [34]. The enzyme preparation thus further favored formation of the *trans* isomers. CAL B was subsequently used to catalyze the hydrolysis of mixture **4** in a PBS/THF (1:1) system. The results were conspicuous, and selective hydrolysis of the acetate group near the C2 position was observed, resulting in pure primary alcohol **7** (Scheme 3, Fig. S3). According to ^{1}H NMR spectroscopy and chiral HPLC analysis in form of acetylated compound **4a**, an excellent diastereomeric ratio (*dr*) (33:1) and an excellent *ee* (> 99%) were determined for compound **7**. Combined with NOE-NMR spectroscopy and chiral HPLC studies [34], the absolute configuration of compound **7** could be elucidated as 2*R*,5*R*. The results indicate that CAL B catalyzes the regio- and stereoselective hydrolysis of the C-2(*R*)-ester as well as the C-5(*S*)-ester, resulting in the exclusive formation of isomer **7**.

With access to the enantiopure isomer, different parameters were next examined for optimization of the STS-CAL B-mediated enzymatic protocol. In the first step, when toluene was used as solvent, both the *ee* and the yield decreased significantly compared with THF. Moreover, prolonging the reaction time from 2 d to 4 d could slightly improve the yield, however at the cost of reducing the *ee* from 57% to 42%. In addition, increasing the STS loading did not influence the reaction significantly (Table 1). In the cascade hydrolysis step, THF was proven to be the optimal solvent compared with TBME and toluene [34].

From these results, THF was considered the optimal solvent for both processes, establishing the cascade enzyme-mediated synthesis of enantiopure 1,3-oxathiolane derivatives. Compounds **2** and **3** were first allowed to react at 4 °C in the presence of STS for 2 d, at which time the solid was removed by filtration. PBS buffer and CAL B were subsequently added to the filtrate, and the reaction proceeded at ambient condition overnight. Following this procedure, compound **7** could be obtained in 50% yield and > 99% *ee* after purification by column chromatography. This DKR-KR protocol for the formation of enantiomerically pure (2*R*,5*R*)-1,3-oxathiolane derivatives thus display advantages in, for example, reducing the number of synthetic steps and increasing the final yields in comparison to traditional KR processes.

Enzyme reusability is an important aspect when considering practical applications, not only for lowering the costs, but also for avoiding unnecessary environmental impact. In order to examine the reusability of the STS preparation, experiments were performed under the same reaction conditions as used for the results in Table 1 (entry 2). After each cycle, the enzyme was separated by filtration and subsequently added to the new reaction vial for the next cycle. At least five consecutive cycles were carried out, and STS proved highly reusable in the addition-cyclization-acetylation reaction without any significant loss of activity (Fig. 3).



Scheme 2. STS-CAL B-catalyzed synthesis of lamivudine and *ent*-lamivudine from compounds **3** and **6**; (i) phenyl acetate, STS, Et_3N, THF, 4 °C; (ii) CAL B, PBS/THF, rt, **5a**:**5b** (4:1); (iii) silylated N^4-acetylcytosine, TMSI, MeCN, 0 °C; (iv) K_2CO_3, MeOH, rt, 45% for two steps, **1a**:**1b** (4:1).

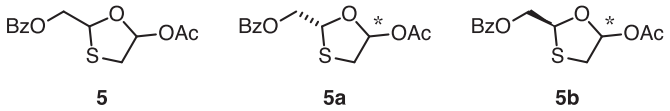
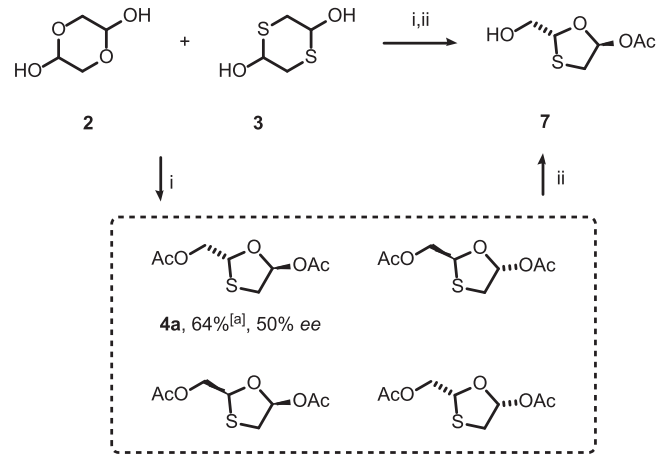


Fig. 2. Structures of (5-acetoxy-1,3-oxathiolan-2-yl)methyl benzoate (**5**), ((2*R*)-5-acetoxy-1,3-oxathiolan-2-yl)methyl benzoate (**5a**) and ((2*S*)-5-acetoxy-1,3-oxathiolan-2-yl)methyl benzoate (**5b**).



Scheme 3. STS-CAL B-catalyzed synthesis of compound **7**; (i) phenyl acetate, STS, Et_3N, THF, 4 °C; (ii) CAL B, PBS/THF, rt. [a]Ratio of four isomers determined by chiral HPLC.

Table 1
Optimization of STS-catalyzed DKR conditions.[a]

Entry	Time	STS (mg)	Solvent	dr[b]	*ee* (%)[c]	Yield (%)[d]
1	2d	15	Toluene	2.6:1	19	7
2	1d	30	THF	3.7:1	57	16
3	2d	15	THF	4.0:1	50	46
4	3d	15	THF	3.5:1	46	49
5	4d	15	THF	4.0:1	42	49
6	2d	30	THF	4.0:1	48	45

[a] Reaction conditions: compound **2** (0.12 mmol), compound **3** (0.16 mmol), Et_3N (0.13 mmol), phenyl acetate (0.71 mmol), 4 °C.
[b] Estimated by ^1H NMR spectroscopy from the isolated racemic mixture.
[c] Estimated by chiral HPLC spectroscopy (Chiral-JM column) using hexane:2-propanol (9:1) as mobile phase.
[d] Isolated yield.

Conclusions

In summary, we have implemented a multienzyme-catalyzed cascade DKR-KR protocol for the synthesis of enantiopure (2*R*,5*R*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl acetate. The enantioenriched 1,3-oxathiolane intermediate was generated by STS-catalyzed addition-cyclization-acetylation and subsequently resolved by adding CAL B to selectively hydrolyze the desired isomer. By employing a protease (STS) and a lipase (CAL B) as catalysts, straightforward control of the absolute configuration of the product formed could be achieved. Two achiral starting materials were used for the formation of 1,3-oxathiolane ring and consecutively selecting correct isomer. Furthermore, STS displayed high reusability properties, which is crucial for practical applications. Compared with previous lamivudine syntheses carried out in multiple steps and involving repeated purifications, the key, enantiomerically pure compound could be readily obtained by just one column chromatography step, which is time- and solvent-saving. This straightforward approach represents obvious advantages with respect to both high catalytic efficiency and environmental friendliness. In addition, since 1,3-oxathiolane derivatives can be converted to lamivudine through *N*-glycosylation reactions, our study provides efficient access to compounds that can be smoothly converted to enantiopure lamivudine as well as other nucleosides, for instance emtricitabine and apricitabine

Experimental

General methods

All commercially available starting materials were of reagent grade and used as received. Subtilisin Carlsberg (Art. No: P5380) and *Candida antarctica* lipase B (Art. No: L4777) were purchased from Sigma-Aldrich. ^1H NMR and ^{13}C NMR data were recorded on a Bruker Avance DMX 400 instrumentation at 400 MHz. Chemical shifts are reported as δ values (ppm) with $CHCl_3/CDCl_3$ (^1H NMR δ 7.26, ^{13}C NMR δ 77.16) as internal references. Thin layer chromatography (TLC) was performed on precoated Cromatofolios AL Silica gel 60 F254 (Merck, Darmstadt, Germany). Detection was performed using UV light, $KMnO_4$ staining, or PMA stain, and subsequent heating. Flash column chromatography was performed on silica gel 60, 0.040 - 0.063 mm (SDS). Analytical high performance liquid chromatography (HPLC) with chiral stationary phases was performed using an HP-Agilent 1100 series controller, equipped with Daicel chiralpak OJ (4.6 × 250 mm, 20 μm) and Reprosil Chiral-JM (4.6 × 250 mm, 10 μm) columns. Solvents for HPLC use were of spectrometric grade.

Immobilization of subtilisin Carlsberg

To a solution of octyl β-D-glucopyranoside (15 mg) and Brij 56 (15 mg) in phosphate buffer (0.5 M, pH 7.2, 6 mL) was added subtilisin Carlsberg (60 mg). The mixture was rapidly frozen with liquid nitrogen and lyophilized overnight.

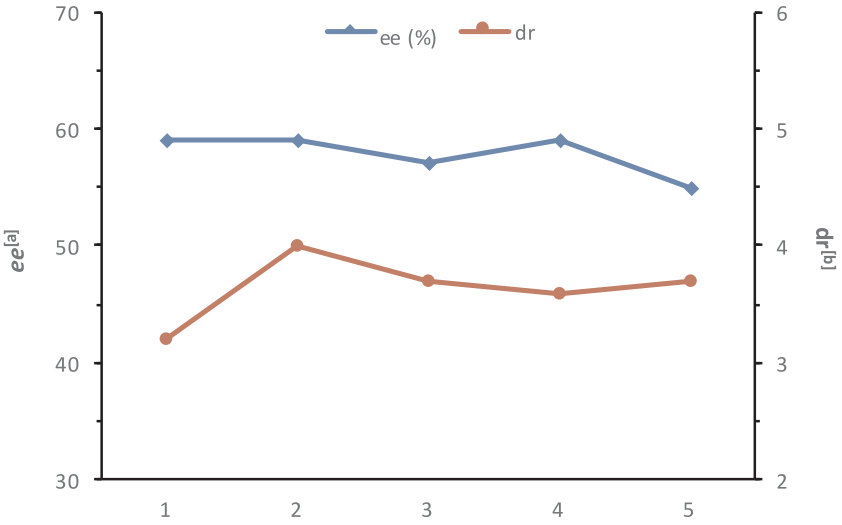


Fig. 3. STS reusability. Reaction conditions: compound **2** (0.12 mmol), compound **3** (0.16 mmol), Et_3N (0.13 mmol), phenyl acetate (0.71 mmol), 4 °C, 1 d; [a] Estimated by ^{1}H NMR spectroscopy from isolated mixture; [b] Estimated by chiral HPLC.

Synthesis

(5-acetoxy-1,3-oxathiolan-2-yl)methyl acetate (4a)

Glycolaldehyde dimer **2** (15 mg, 0.12 mmol), 1,4-dithiane-2,5-diol **3** (24 mg, 0.16 mmol), triethylamine (17 µL, 0.13 mmol), and phenyl acetate (90 µL, 0.71 mmol) in dry THF (1 mL) were added to a sealed-cap vial containing surfactant-treated subtilisin Carlsberg (15 mg) together with 4 Å molecular sieves (30 mg). The reaction mixture was cooled to 4 °C. After 2 d, the mixture was filtered and washed with saturated NH_4Cl and brine, after which the mixture was dried over $MgSO_4$ and the solvent removed under vacuum. The crude product was purified by column chromatography (Hex:EtOAc = 11:1) affording compound **4a** as a clear oil (25 mg, 46%). 50% *ee*, determined by HPLC analysis (Chiral JM column, λ = 210 nm, Hex:iPrOH = 9:1, 0.5 mL/min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.68 (d, J = 4.1 Hz, 1 H), 5.54 (dd, J = 6.1, 4.0 Hz, 1 H), 4.33–4.21 (m, 2 H), 3.32 (dd, J = 11.5, 4.2 Hz, 1 H), 3.14 (d, J = 11.5 Hz, 1 H), 2.10 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.6, 169.9, 99.3, 83.3, 66.0, 37.7, 21.3, 20.9.

(2R,5R)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl acetate (7)

Glycolaldehyde dimer **2** (45 mg, 0.38 mmol), 1,4-dithiane-2,5-diol **3** (72 mg, 0.47 mmol), triethylamine (51 µL, 0.37 mmol), and phenyl acetate (270 µL, 2.03 mmol) in dry THF (3 mL) were added to a sealed-cap vial containing surfactant-treated subtilisin Carlsberg (60 mg) together with 4 Å molecular sieves (120 mg). The reaction mixture was cooled to 4 °C. After 2 d, the solid was removed by filtration, and CAL B preparation (40 mg) and PBS buffer (pH 8.0, 3 mL) were added to the filtrate. The biphasic mixture was slowly stirred overnight, after which time the mixture was diluted with EtOAc (20 mL) and washed with saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (20 mL) twice. The combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was concentrated and the crude product was purified by column chromatography (Hex:EtOAc = 6:1), yielding compound **7** (66 mg, 50%) as a clear oil. 99% *ee*, determined in the form of compound **4a** by chiral HPLC analysis (Chiral JM column, λ = 210 nm, Hex:iPrOH = 9:1, 0.5 mL/min) [34]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.68 (d, J = 4.2 Hz, 1 H), 5.54–5.46 (m, 1 H), 3.85 (ddd, J = 11.5, 8.2, 3.1 Hz, 1 H), 3.79–3.71 (m, 1 H), 3.32 (dd, J = 11.5, 4.2 Hz, 1 H), 3.15 (d, J = 11.5 Hz, 1 H), 2.10 (s, 3 H). ^{13}C NMR (101 Hz, $CDCl_3$) δ = 169.4, 98.5, 85.7, 63.9, 37.2, 20.6. HRMS (ESI-TOF): m/z $[M + 1]^+$ calcd for $C_6H_{11}O_4S$: 179.0378; found: 179.0373. $[\alpha]_D^{25}$ −65.3 (c = 0.3, $CHCl_3$).

Acknowledgments

This work was in part supported by the Swedish Research Council. YR and LH thank the China Scholarship Council for special scholarship awards.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.mcat.2019.02.013.

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