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Enzymatic kinetic resolution of 1,1-dioxo-2,3-dihydro-1*H*-1λ⁶-thiophen-3-ol via temporary derivatisation

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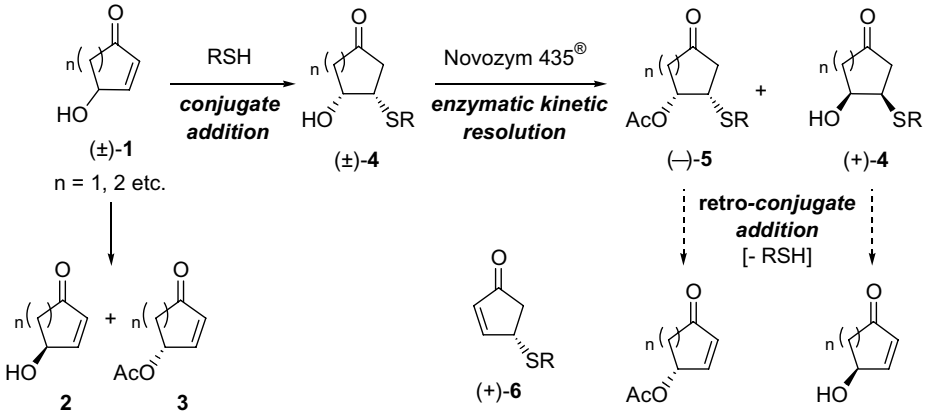
Abstract—Following the thio-conjugate addition of (±)-**9**, its enantiomers were extremely efficiently discriminated using Novozym 435®. The thio-differentiating unit may then be removed either under reductive conditions, using Raney nickel, or following an oxidation–elimination sequence. In this manner enantioenriched derivatives of 1,1-dioxo-2,3-dihydro-1*H*-1λ⁶-thiophen-3-ol **9** may be accessed.

We have recently reported that cyclic conjugated alkenols (of the type **1**, where $n = 1$ or 2) undergo highly efficient enzymatic kinetic resolution once the electron poor alkene has undergone conjugate addition with a thiol.[1] This observation was of interest since reports,[2] corroborated by us,[1] indicated that the direct enzymatic kinetic resolution of this type of cyclic allylic alcohol was not an efficient process, affording **2** and **3** with low levels of enantioselectivity. The likely explanation for this observation is that the sp^2 and sp^3 hybridised carbon units flanking the stereogenic centre possess similar spatial requirements. Thus, following the *syn*-selective conjugate addition of benzyl thiol to 4-hydroxycyclopent-2-enone **1**, extremely efficient resolution ($E >$ 200) of (±)-**4** was realised using Novozym 435® (Scheme 1).[1]



Scheme 1. Temporary derivatisation for the enzymatic kinetic resolution of cyclic alkenols.

Keywords: Enzymatic kinetic resolution; Cyclic sulfone; Temporary derivatisation.
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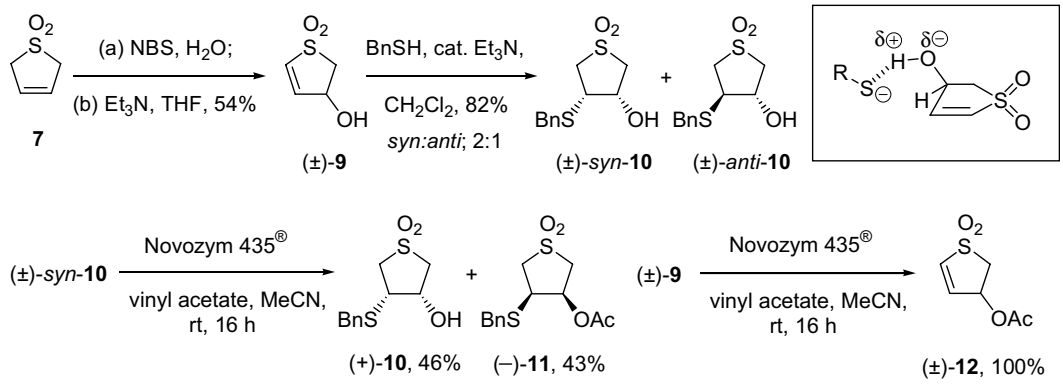


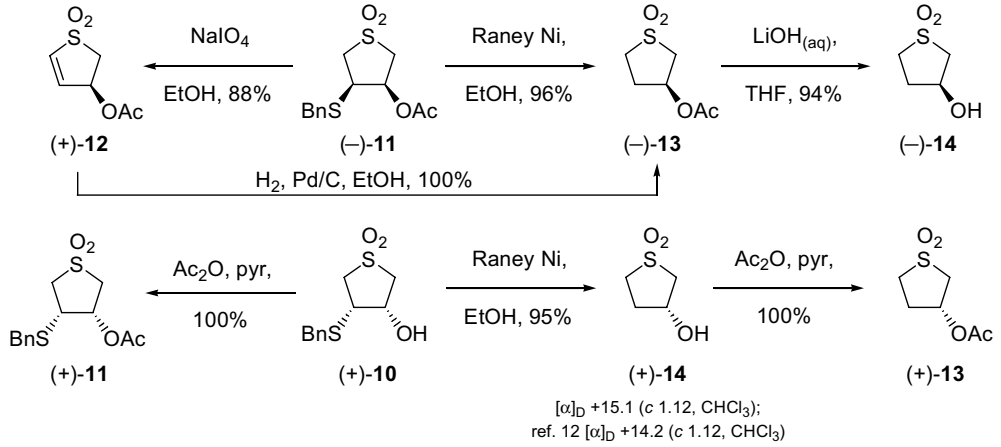
Scheme 2. Enzymatic kinetic resolution of (±)-*syn*-**10**.

In this series ($n = 1$) we were unable to remove the sulfur unit in a retro-conjugate addition sense to regenerate the now enantioenriched 4-substituted cyclic compound, since the elimination of acetic acid, generating (+)-**6**, occurred more readily. However, in the six-membered series ($n = 2$) we managed to perform this transformation embodying our temporary tetrahedralisation-enzymatic resolution concept. The extension of this sequence for the preparation of both enantioenriched cyclic alkenols and alkanols possessing a sulfonyl functional group is the subject of this letter.

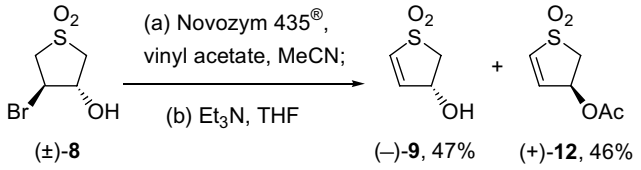
Cyclic five-membered sulfones possessing both unsaturation and saturation have been employed as structural components in target molecules[3] and as synthetic building blocks.[4] In a wider sense, the sulfone unit has found widespread use in the preparation of complex synthetic targets and many methods for the derivatisation of sulfonyl-containing molecules exist.[5]

The synthesis of (±)-**9** was accomplished following a literature method involving the conversion of butadiene sulfone **7** into bromohydrin **8** (see Scheme 4), which was then subjected to base mediated dehydrobromination using triethylamine (Scheme 2).[6] This compound underwent *syn*-selective conjugate addition, albeit with less stereoselectivity than in the corresponding ketone series,[1] affording the diastereomeric conjugate adducts **10**.

The relative stereochemistry of the major diastereoisomer, isolated by flash column chromatography, was confirmed by X-ray crystallography.[7] It seems plausible that the hydroxyl-substituent serves to overcome steric barriers to this addition process by hydrogen bonding. This hypothesis was corroborated by the observation that in polar solvents, capable of perturbing the proposed hydrogen bonding, significantly more of the *anti*-diastereomer was observed. For example, when the reaction was carried out in MeOH/Et_3N, a reversal in stereochemical preference was observed (*syn*-(±)-**10**:*anti*-(±)-**10**; 1:2). The major diastereoisomer (±)-*syn*-**10** was treated with Novozym 435® and vinyl acetate (5 equiv) in acetonitrile and after 16 h, the crude products were separated in good yield following flash column chromatography.[8] Chiral HPLC analysis indicated that both acetate (−)-**11** and the unreacted starting material (+)-**10** were highly enantioenriched (ee > 98%). Acetate (−)-**11** was isolated and proved not to undergo the facile loss of acetic acid (generating the vinyl sulfone) as observed in the corresponding cyclopentanone series (see Scheme 1). As a means of comparison, under the same conditions (±)-**9** underwent complete conversion into the corresponding racemic acetate (±)-**12**. This observation contrasts the behaviour of acyclic hydroxyl-substituted vinyl sulfones, which have been reported to undergo efficient enzymatic kinetic resolution.[9]



Scheme 3. Desulfurisation of the enantioenriched conjugate adducts (+)-**10** and (−)-**11**.



Scheme 4. Kinetic enzymatic resolution of bromohydrin (±)-**8**.

We then sought methods to remove the thiol unit. In this context two strategies were investigated; namely, the reductive Raney nickel cleavage of the sulfide bond in the presence of the sulfonyl moiety,[10] and the oxidative Cope-type elimination of sulfenic acid.[11] For example, (−)-**11** was converted into vinyl sulfone (+)-**12** in one-pot following treatment with $NaIO_4$. Pleasingly, the sulfide unit was also effectively removed using Raney nickel, in this instance generating the saturated sulfone (−)-**13**. The enantiomeric series may be accessed in a similar fashion, and opposite optical rotations were observed (Scheme 3).

The absolute configuration of (+)-**14** was confirmed by comparison of the optical rotation value with that of the identical compound accessed from the chiral pool.[12] This also served to prove the sense of stereoselectivity for the enzymatic step—which, gratifyingly, is the same as that observed for the cyclopentanone series using Novozym 435®.[1]

Following these successful studies, a more expedient method, utilising the same concept, was investigated for the two-step preparation of enantioenriched (−)-**9** and (+)-**12** (Scheme 4). Thus, (±)-**8** was treated with the lipase enzyme under identical conditions described.[8] After 16 h, NMR spectroscopic analysis indicated approximately 50% conversion (this value did not alter significantly after five days). The crude materials were then filtered and MeCN was exchanged for THF before treatment with base to effect dehydrobromination. Thus, the enantioenriched vinyl sulfones were separated following flash column chromatography.

In summary, using our temporary-tetrahedralisation concept, we have accessed efficiently both enantiomers of a group of interesting sulfonyl-containing heterocycles that have been used as building blocks and structural components of pharmacologically useful molecules. For example, (+)-**14** has been used as a structural component in a nanomolar HIV-protease inhibitor related to amprenavir.[3a] Previous syntheses of this type of enantioenriched compound have followed lengthy synthetic sequences from the chiral pool,[12,13] or from a novel desymmetrisation.[14] The latter approach, however, currently suffers from low enantiomeric excesses.

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8. In a 100 mL conical flask a mixture of (±)-*syn*-**10** (0.234 g, 0.85 mmol, 1 equiv), Novozym 435® (0.234 g, 1:1 *w*/*w* enzyme:substrate), vinyl acetate (0.39 mL, 4.23 mmol, 5 equiv) and acetonitrile (25 mL) was shaken for 16 h (200 rpm, 30 °C). The reaction was decanted and the enzyme rinsed with acetonitrile (6 × 20 mL). The combined MeCN washings were concentrated under reduced pressure and the residue purified by column chromatography (1% MeOH in CH_2Cl_2) to give (−)-**11** (0.11 g, 43%, $R_f = 0.4$) and (+)-**10** (0.105 g, 46%, $R_f = 0.1$). Data for compound (+)-**10** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (1H, s, OH), 3.09–3.20 (3H, m, 3 × CH_AH_B), 3.38 (1H, d, $J = 14.0$ Hz, CH_AH_B), 3.46 (1H, ddd, $J = 2.75$, 7.5, 12.5 Hz, C*H*S), 3.80 (1H, d, $J = 13.75$ Hz, CH_AH_B), 3.85 (1H, d, $J = 13.75$ Hz, CH_AH_B), 4.19–4.24 (1H, m, C*H*OH), 7.29–7.39 (5H, m, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) 137.2 (C), 129.2 (CH), 128.9 (CH), 128.5 (CH), 68.9 (CHOH), 59.9 (CH_2), 53.0 (CH_2), 46.9 (CHS), 36.2 (CH_2). IR ν_{max} (neat/cm^{-1}) 3454, 1453, 1311, 1123, 906, 731. HRMS calcd for: $C_{11}H_{18}O_3S_2N$ (CI, $M + NH_4^+$) requires 276.07281: found 276.07253. $[\alpha]_D$ +25.5 *c* 1.12, $CHCl_3$. Data for compound (−)-**11** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (3H, s, CH_3), 3.16 (2H, d, $J = 10.0$ Hz, CH_ACH_B), 3.32 (2H, m, CH_ACH_B), 3.43 (1H, ddd, $J = 3.5$, 10.0, 13.5 Hz, C*H*S), 3.78 (1H, d, $J = 13.5$ Hz, CH_AH_B), 3.83 (1H, d, $J = 13.5$ Hz, CH_ACH_B), 5.50–5.54 (1H, m, C*H*OAc), 7.28–7.37 (5H, m, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) 170.0 (CO), 137.1 (C), 129.4 (CH), 129.1 (CH), 128.3 (CH), 71.4 (CHOAc), 59.2 (CH_2), 54.8 (CH_2), 44.1 (CHS), 36.7 (CH_2), 21.1 (CH_3). IR ν_{max} (neat/cm^{-1}) 3054, 1749, 1421, 1265, 1125, 896, 738, 704. HRMS calcd for: $C_{13}H_{20}O_4S_2N$ (CI, $M + NH_4^+$) requires 318.08337: found 318.08356. $[\alpha]_D$ −41.1 *c* 1.12, $CHCl_3$. HPLC analysis; Daicel AD (∅ 0.46 cm × 0.25 cm, UV 254 nm), 100% EtOH, 0.3 mL/min; (−)-**11** $t_r = 20.59$ min (>98% ee); (+)-**10** $t_r = 41.7$ min (>98% ee).
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