# Kinetic Resolution in the Asymmetric Hydroxylation of Enolates. Stereospecific Synthesis of (2*S*,3*R*)-(−)-Verrucarinolactone

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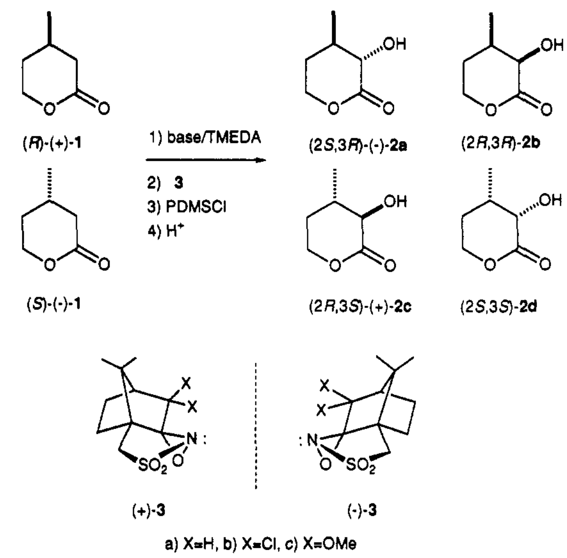
Asymmetric hydroxylation of racemic 3-methylvalerolactone (1) with substoichiometric amounts of the (−)-(camphorylsulfonyl)oxaziridine **3a** affords (2*S*,3*R*)-(−)-verrucarinolactone (**2a**) in 60% ee, which on crystallization is obtained enantiomerically pure. This result not only represents a highly efficient stereospecific synthesis of an important lactone, but also demonstrates the application of kinetic resolution and asymmetric hydroxylation in the synthesis of enantiomerically enriched α-hydroxy carbonyl compounds having multiple stereocenters.

The α-hydroxy carbonyl moiety is commonly featured in many bioactive compounds including sugars, pheromones, antibiotics, terpenes, and alkaloids. Because biological activity is often dependent on the orientation of the hydroxy group attached to the stereogenic carbon, much effort has been focused on the development of efficient methods for the asymmetric synthesis of this structural array. Our recent studies have demonstrated the application of the asymmetric enolate hydroxylation protocol using the (camphorylsulfonyl)oxaziridine derivatives **3** for the synthesis of enantiomerically enriched α-hydroxy carbonyl compounds.[1] High enantioselectivities (>95%) were realized for the hydroxylation of acyclic[2,3] and cyclic ketone enolates with these reagents.[3,4–7] The ee's were dependent not only on the structure of the oxaziridine and enolate, but the reaction conditions as well. As part of our continuing efforts to understand and improve the efficiency of this protocol we describe a simple stereospecific synthesis of (2*S*,3*R*)-(−)- and (2*R*,3*S*)-(+)-verrucarinolactone (**2a** and **2c**) employing kinetic resolution and the asymmetric enolate hydroxylation protocol.

(2*S*,3*R*)-(−)-Verrucarinolactone (**2a**) [(2*S*,3*R*)-(−)-2-hydroxy-3-methylpentanolide] is a structural unit common to the macrocyclic portion of the roridins and verrucarins.[8] These compounds are members of the macrocyclic trichothecane esters, a class of naturally occurring toxins which exhibit a range of significant biological activity including antibiotic, antifungal, and antitumor activity. Several multistep stereoselective syntheses of (2*S*,3*R*)-(−)-**2a** or its acyclic analogue have been described[9] that employ methods which include resolution,[10] Sharpless epoxidation,[11] and asymmetric hydroboration.[11b] MoOPH-mediated hydroxylation of the lithium enolate of (3*R*)-5-((*tert*-butyldimethylsilyl)oxy)-3-methylpentanoate, the protected acyclic analogue of (+)-1, gave a 2:1 mixture of hydroxy lactones favoring the desired 2*S* epimer **2a**.[11b] By using a camphor-derived chiral auxiliary this ratio was improved to 99:1.[12]

**Scheme I**




Our synthesis of (2*S*,3*R*)-(−)-**2a** is outlined in Scheme I and involves the asymmetric hydroxylation of racemic 3-methylvalerolactone (**1**), available on a multigram scale via the copper chromite oxidation of 3-methyl-1,5-pentanediol[13] with **3**. In principle four products can result on hydroxylation of the enolate of (±)-**1**: trans diastereoisomers **2a** and **2c** and cis diastereoisomers **2b** and **2d**. Unequal amounts of **2a–d** will result if substoichiometric amounts of the oxidant **3** are used. The enantiomeric purity of compounds **2a–d** will be dependent upon stereoselectivity for formation of the cis and trans diastereoisomers and the discrimination of the chiral oxidant for one enantiomer of the racemate, i.e. kinetic resolution.[14]

Typically the enolate of (±)-**1** was generated at −78 °C by treatment with 1.2 equiv of the appropriate base in the presence of 2.5 equiv of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) followed by addition of the oxaziridine **3**. To facilitate isolation of the products, due to similar $R_f$ values with the camphorsulfonimine byproduct, 1.2 equiv of chlorodimethylphenylsilane (PDMSCl) was added

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**Table I. Asymmetric Hydroxylation of (±)-3-Methylvalerolactone (1) in the Presence of TMEDA**

| entry | oxaziridine 3 [equiv] | base | verrucarinolactone (2*S*,3*R*)-2a % isolated yield[a] | % de | % ee[b] |
|---|---|---|---|---|---|
| 1 | (−)-**3a** (X = H) [1.0] | LDA[c] | 10 | | |
| 2 | (−)-**3a** (X = H) [1.0] | LDA | 60 | 90 | |
| 3 | (−)-**3a** (X = H) [0.5] | LDA | 54 | >95 | 56 |
| 4 | (−)-**3a** (X = H) [0.5] | LDA/$BF_3 \cdot OEt_2$[d] | 41 | >95 | 46 |
| 5 | (−)-**3a** (X = H) [0.5] | LDA/LiCl[d] | 46 | >95 | 56 |
| 6 | (−)-**3a** (X = H) [0.5] | LICA[e] | 58 | >95 | 60 |
| 7 | (−)-**3a** (X = H) [0.5] | NaHMDS | 25 | >95 | 39 |
| 8 | (+)-**3a** (X = H) [0.5] | LDA | 53[f] | >95 | 55 |
| 9 | (−)-**3b** (X = Cl) [1.0] | LDA | 54 | 90 | |
| 10 | (−)-**3b** (X = Cl) [0.5] | LDA | 45 | >95 | 37 |
| 11 | (−)-**3b** (X = Cl) [0.5] | NaHMDS | 21 | >95 | 50 |
| 12 | (−)-**3c** (X = OMe) [1.0] | LDA | 45 | 90 | |
| 13 | (−)-**3c** (X = OMe) [0.5] | LDA | 32 | >95 | 31 |
| 14 | (−)-**3c** (X = OMe) [0.5] | NaHMDS | no reaction | | |

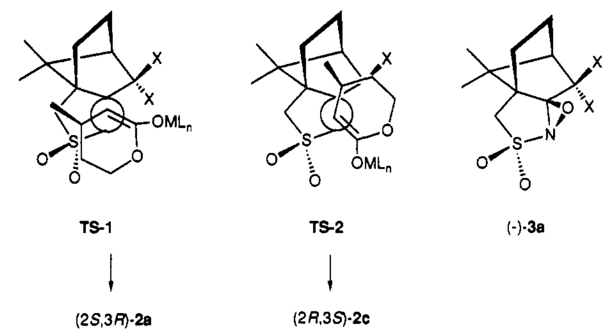
[a] Based on the equalvances of oxaziridine. [b] Determined on the Mosher ester. [c] In the absence of TMEDA. [d] 1.0 equiv of $BF_3 \cdot OEt_2$ or LiCl added. [e] Lithium isopropylcyclohexylamide. [f] (2*R*,3*S*)-**2c** obtained.

to the reaction mixture prior to workup. The silylated alcohols were isolated by flash chromatography, hydrolyzed by treatment with Amberlyst 15 ion exchange resin, and purified by flash chromatography. The cis/trans ratios were determined by $^1$H NMR and the ee's by conversion to the Mosher esters. These results are summarized in Table I.

Despite the small size of the methyl group in **1**, hydroxylation with **3** affords much better cis/trans diastereoselectivity than that reported previously for MoOPH, i.e. >90 vs 33%, respectively (entries 2, 9, and 12). With substoichiometric amounts of **3** the cis diastereoisomers, **2b** and **2d**, were not detectable. This is consistent with earlier results establishing that the bulky oxaziridine oxidant preferentially attacks enolates from the sterically least hindered face.[1]

The enantioselectivity reached a maximum of 56–60% ee for the lithium enolate of **1** with the (−)-(camphorylsulfonyl)oxaziridine **3a** (entries 3 and 6). Addition of additives such as $BF_3 \cdot OEt_2$ or LiCl had relatively little effect on the ee's but did result in lower yields (entries 4 and 5). Reduced ee's were observed for the dichloro- and dimethoxy-oxaziridines (−)-**3b** and (−)-**3c** (entries 9–14). While the stereoselectivities were only modest, two crystallizations from diethyl ether afforded (2*S*,3*R*)-(−)-verrucarinolactone (**2a**) enantiomerically pure in about 30% overall yield from **1**. Similar results were observed for the synthesis of unnatural isomer (2*R*,3*S*)-**2c** using oxaziridine (+)-**3a** (entry 8). In terms of yields and simplicity our results are better than previous syntheses of **2a** and/or its acyclic analogue.[9–12]

The molecular recognition for the asymmetric hydroxylation of enolates by the (camphorylsulfonyl)oxaziridine derivatives **3** has generally been interpreted in terms of steric factors. However, recent experimental[1,3–7] and theoretical[15] studies suggest the possibility that metal chelation between enolate and oxaziridine may also have a role in determining the stereoselectivity. Indeed, transition-state structures were calculated in which the metal of the enolate was not only coordinated to the enolate oxygen but to the oxaziridine oxygen and nitrogen atoms as well.[15] Since the ee's were only 60%, both transition-state structure **TS-1** and **TS-2** contributed to the stereoselectivity with **TS-1** lower in energy favoring (2*S*,3*R*)-**2a**. In **TS-1** the geometry is such that there are fewer nonbonded interactions and chelation of the metal enolate with the oxygen and nitrogen atoms of the oxaziridine is more favorable than in **TS-2**.




In summary, a simple enantioselective synthesis of (2*S*,3*R*)-(−)-verrucarinolactone (**2a**) using the asymmetric enolate hydroxylation protocol and kinetic resolution is described. Although inherently inefficient, kinetic resolution has merit if the rate differences for conversion of the enantiomers in the racemate are very different and/or, as in this example, the target is otherwise difficult to prepare.

## Experimental Section

Details concerning the recording of spectra, the analytical instruments used, the determination of melting points and elemental analysis have been previously described.[2] Capillary GLC was performed using a Supelcoport SPB-35 (30 m × 0.75 mm) borosilicate glass column. Glassware, syringes, needles, etc. were oven-dried overnight and cooled in a vacuum desiccator. Oxaziridines **3a**,[16] **3b**,[3] and **3c**[5] were prepared as previously described or purchased from Aldrich.

**(2*S*,3*R*)-(−)-Verrucarinolactone (2a).** A 100-mL two-necked flask fitted with a three-way stopcock, rubber septum, and a magnetic stirring bar was evacuated and filled with dry argon. The flask was cooled to 0 °C, 0.84 mL (6 mmol) of diisopropylamine in 10 mL of THF was introduced followed by addition of 2.2 mL (5.5 mmol) of 2.5 M *n*-butyllithium in hexanes, and the solution was stirred for 30 min. The LDA solution was cooled to −78 °C, and 1.9 mL (12.5 mmol) of TMEDA was added followed by 0.57 g (5.0 mmol) of 3-methylvalerolactone[13] in 10 mL of THF. After the mixture was stirred for 30 min at this temperature, 0.5 or 0.25 mmol of the appropriate (camphorsulfonyl)oxaziridine derivative **3** in 10 mL of THF was added. Stirring was continued for 4 h at −78 °C, at which time 0.94 g (5.5 mmol) of chlorodimethylphenylsilane was added. The reaction mixture was warmed to room temperature, stirred for 12 h, and diluted with 100 mL

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of ether, and the precipitated imine was removed by passage through a pad of 20 g of silica gel in a sintered-glass funnel. The filtrate was stirred with 1.0 g of Amberlyst 15 ion-exchange resin for 30 min and filtered and the solvent removed under vacuum. Flash chromatography (silica gel G) of the residue eluting with 1:1 ethyl acetate/*n*-hexane (1:1) gave 0.19 g (58% based on the amount of **3**) of (2*S*,3*R*)-**2a**: mp 99–100 °C (lit.[11a] mp 103 °C); $[\alpha]^{23}_D$ −6.24° (*c* 4.0, $CHCl_3$) [lit.[11a] $[\alpha]^{23}_D$ −10.7° (*c* 1.0, $CHCl_3$)]. Two crystallizations from ethyl ether improved the ee to >95%: $[\alpha]^{23}_D$ −10.03° (*c* 2.6, $CHCl_3$). Spectroscopic properties were identical with reported values.

**(2*R*,3*S*)-(+)-Verrucarinolactone (2c).** This material was prepared in a similar manner from oxaziridine (+)-**3a** to give 0.15 g (55%) of **2c**: mp 98–99 °C; $[\alpha]^{23}_D$ = +6.07° (*c* 2.6, $CHCl_3$).

**Addition of $BF_3 \cdot OEt_2$ or LiCl.** Enolate oxidations were carried out as described above except that 1.0 equiv of $BF_3 \cdot OEt_2$ or LiCl was added to the preformed enolate of (±)-**1** at −78 °C prior to addition of the oxaziridine.

**Determination of the Enantiomeric Purity of 2a and 2c.** The enantiomeric purity was determined by integration of the OMe group of the Mosher ester of **2**. The Mosher ester was prepared by stirring 26 mg (0.2 mmol) of **2** with 70.2 mg (0.3 mmol) of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, 82.5 mg (0.4 mmol) of 1,3-dicyclohexylcarbodiimide, and 10 mg (0.08 mmol) of 4-(dimethylamino)pyridine in 3 mL of dry dichloromethane for 2 days. The product was purified by preparative chromatography eluting with 1:1 ethyl acetate/*n*-hexane.

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# Cobaloxime-Catalyzed Hydroperfluoroalkylation of Electron-Deficient Alkenes with Perfluoroalkyl Halides: Reaction and Mechanism

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Direct hydroperfluoroalkylation of electron-deficient alkenes—ethyl acrylates **4**, **7**, and **8**, acrylonitrile (**5**), and methyl vinyl ketone (**6**)—with perfluoroalkyl halides $R_fX$ (**1**, X = I; **2**, X = Br) in the presence of cobaloxime(III) (**3**) and zinc gives 1:1 hydroperfluoroalkylation adducts in good yields. This reaction provides a convenient synthesis of β-(perfluoroalkyl)carboxylic esters **9**, **12**, and **13**, nitriles **10**, and ketones **11**. Details of the reaction including effect of solvent, temperature, and ratio of reagents were examined. The reaction is proposed to proceed via a radical mechanism initiated by low-valent cobalt.

Numerous reports have been focused on introduction of per(poly)fluoroalkyl groups into organic molecules via either radical or carbanion route by reduction, photolysis, or thermolysis of perfluoroalkyl halides or under catalysis of transition-metal complexes.[1] C–C multiple bonds are used extensively as acceptors for this purpose. However, the addition of perfluoroalkyl radical $R_f^{\bullet}$ to alkenes connected with a electron-withdrawing group like acrylates is inefficient by routine heat,[2] light,[3] and electrochemical methods[4] because (a) the electrophilic $R_f^{\bullet}$[5] has to attack the electron-deficient C–C multiple bonds, (b) the reaction can not be controlled to a 1:1 addition stage, and (c) certain substrates are not stable enough under such reaction conditions. Therefore, searching for more efficient synthetic methods has been the subject of much interest. Radical reactions of perfluoroalkanesulfonyl halides (iodide,[6] bromide,[7] and chloride[8]) with acrylates initiated by thermal, peroxide, or Ru(II)-complex catalysts were reported, but the procedures were rather tedious. Thus, an alternative route to the synthesis of β-(perfluoroalkyl)carboxylic ester has been just appeared.[9]

We have reported that a bimetal redox couple, cobaloxime(III)/Zn, promoted hydroperfluoroalkylation of acrylate **4** in a preliminary paper.[10] Here a full account of this reaction system, its further application to hydroperfluoroalkylation of other electron-deficient alkenes, and a possible mechanism are described.

## Results and Discussion

The cobaloxime(III) **3**, a well-studied model compound of coenzyme vitamin $B_{12}$[11] can be reduced electrochemically or chemically to low-valent cobalt species,[12] which exhibit powerful nucleophilic reactivity in the carbon–carbon bond formation via several pathways ranging from $S_N2$ to single-electron transfer mechanisms.[13] We hypothesize that

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