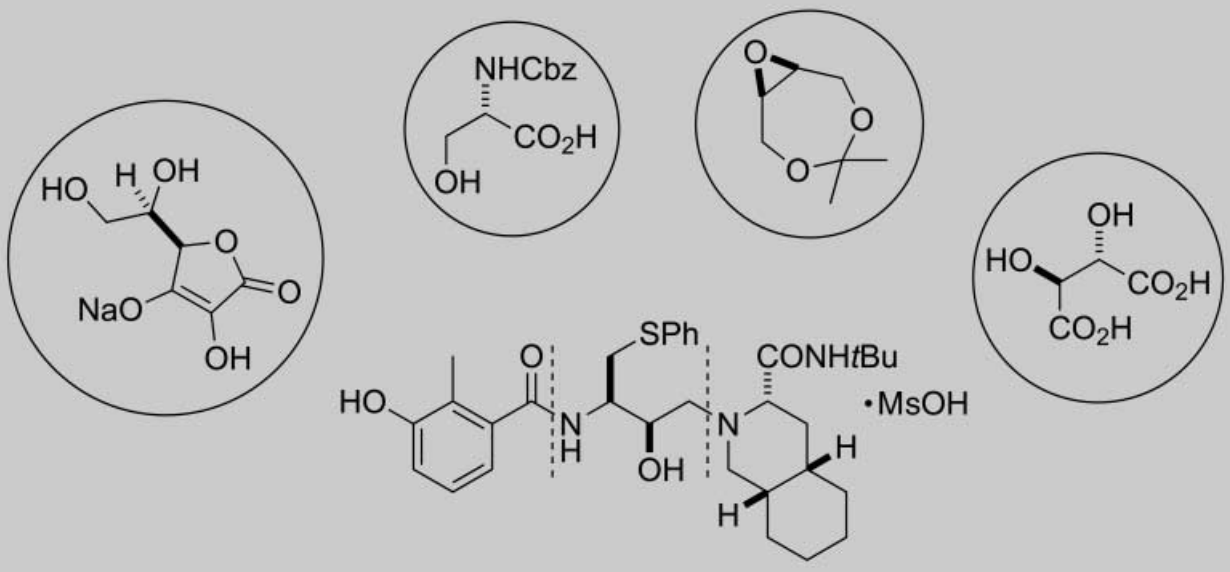
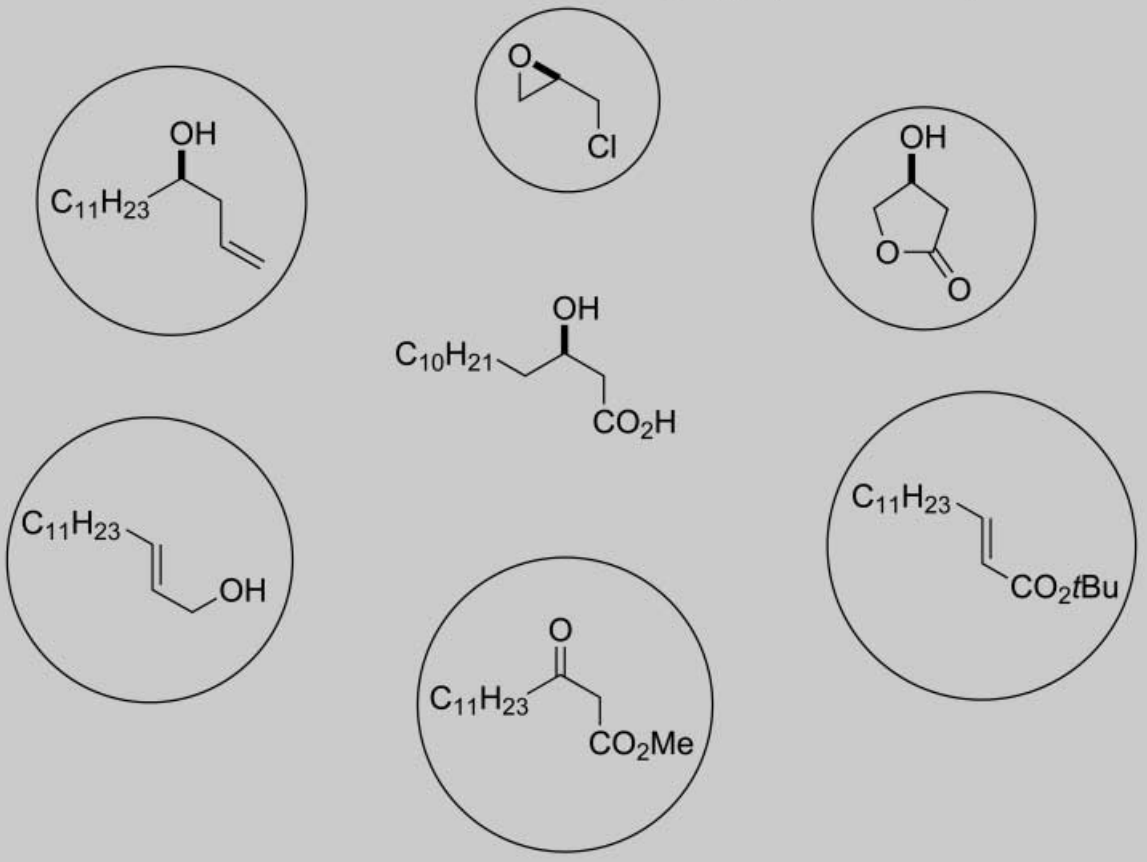
A Process in Need Is a Process Indeed



"Discovery consists of seeing what everybody has seen
and thinking what nobody has thought."

— Albert von Szent-Györgyi (1893–1986)



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A Process in Need Is a Process Indeed: Scalable Enantioselective Synthesis of Chiral Compounds for the Pharmaceutical Industry

Masaya Ikunaka*[a]

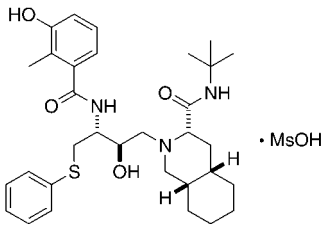
Dedicated to Professor Kenji Mori, The University of Tokyo, who inspired the author to love synthetic organic chemistry

Abstract: This report deals with enantioselective synthesis of viracept **1** (nelfinavir mesylate, AG 1343), a potent HIV protease inhibitor, and 3-hydroxytetradecanoic acid **3**, a component of lipid A comprising lipopolysaccharide embedded in the cell surface of Gram-negative bacteria, from both strategic and practical perspectives. As regards the synthesis of **1**, the synthetic approaches to its central intermediate **2** possessing the common structural motif of 1,4-differentially substituted-2-amino-3-hydroxylbutane are mainly discussed with emphasis on the molecular symmetry that has helped streamline the synthetic strategy. In the discussion of the synthetic strategies to access a single enantiomer of **3**, the chiral methodologies that have been applied so far are assessed for industrial viability; the synthetic alternatives explored include resolution via diastereomeric salt formation, lipase-catalyzed kinetic resolution, asymmetric synthesis, and chiral pool approaches.

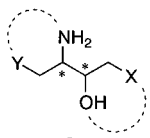
Keywords: asymmetric synthesis · chiral pool · desymmetrization · resolution · scalable synthesis

Introduction

With their increasing molecular complexity,[1] newly developed chemical entities of pharmacological relevance, such as active pharmaceutical ingredients (APIs), and pharmaceutical intermediates, have challenged process chemists of both the fine chemicals and the pharmaceutical industry to supply them in a scalable, industrially viable manner as much as ever did.[2] In view of such industrial requirements, this report will deal with two comparative case studies to see what difference synthetic strategy can make: One case study is on the synthesis of viracept **1** (nelfinavir mesylate, AG 1343), a potent HIV protease inhibitor, with a focal point on how to assemble the central key intermediate of a common 1,4-differentially substituted-2-amino-3-hydroxybutane motif **2**.[3] The other is on the synthesis of a single enantiomer of 3-hydroxytetradecanoic acid (**3**), which would serve the structure activity relationship study around not only lipid A **4**, an active principle of lipopolysaccharide (LPS) eliciting endotoxic reactions of Gram-negative bacteria, but also its truncated analogues in the search for therapeutically efficacious immunostimulants (Figure 1).[4]



Viracept (Nelfinavir mesylate) **1**



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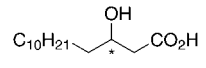

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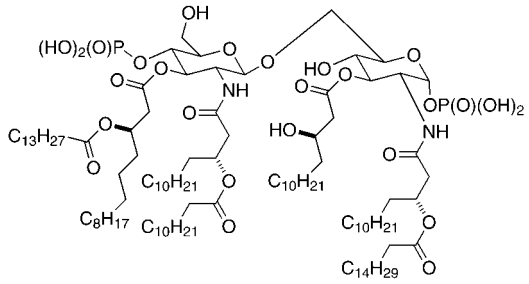

Lipid A from *Salmonella minnesota* **4**

Figure 1. Structures of viracept **1**, its central intermediate **2**, 3-hydroxytetradecanoic acid **3**, and lipid A **4** containing (*S*)-**3**.

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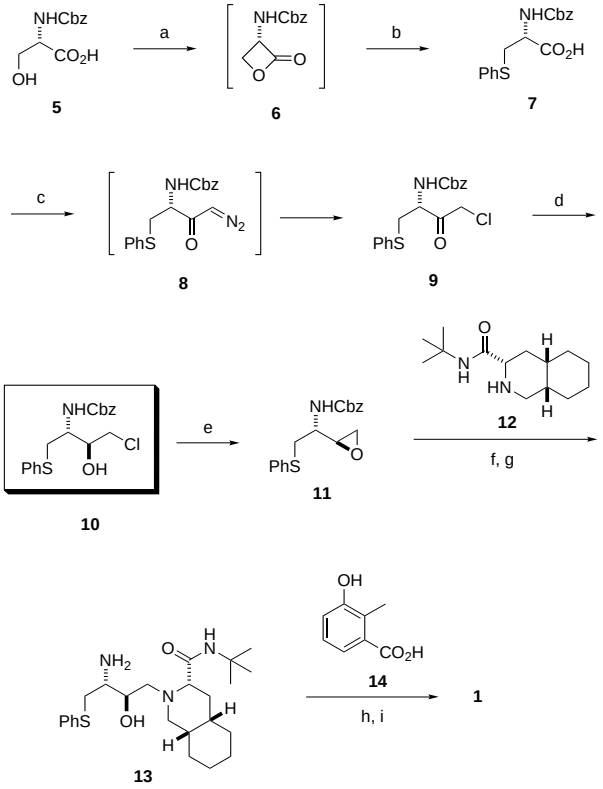
Synthesis of Viracept 1 and Its Central Intermediate 2

The first synthesis of viracept 1 from *N*-Cbz L-serine (5): The discovery synthesis of viracept **1** explored at Agouron Pharmaceuticals employed *erythro*-(2*S*,3*R*)-1-chloro-3-*N*-Cbz-amino-2-hydroxy-4-phenylthiobutane (**10**) as a central intermediate, which, in turn, could be assembled from *N*-Cbz L-serine **5**, a natural α-amino acid derivative (Scheme 1).[5] Once epoxide **11** was formed, nucleophic substitution with octahydro-2(1*H*)-isoquinoline **12** proceeded smoothly, and amide formation with 3-hydroxy-2-methylbenzoic acid **14** afforded **1**.

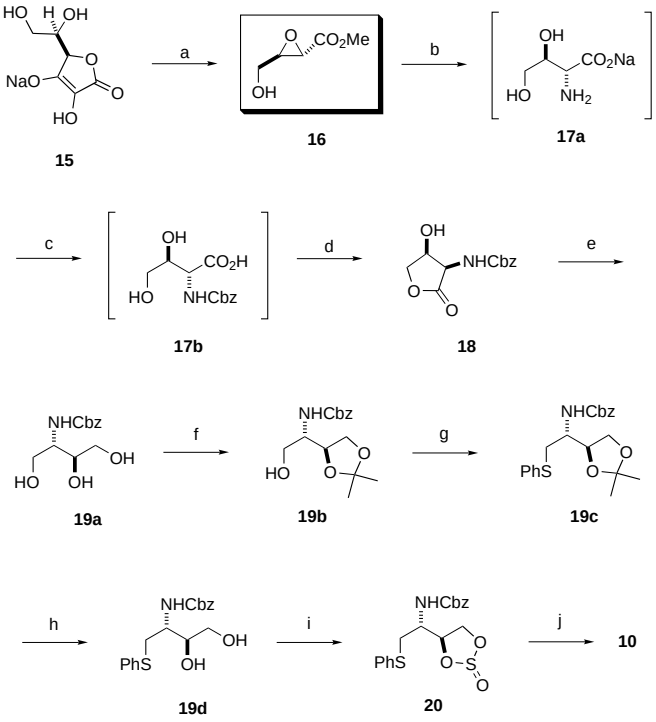


Scheme 1. The first synthesis of viracept **1** starting from N-Cbz L-serine **5**. a) $MeO_2CN{=}NCO_2Me$, Ph_3P, THF, $-55\,^{\circ}C$. b) PhSNa, THF (**7**: 44% yield from **5**). c) 1) *i*BuOCOCl, Et_3N, THF; 2) CH_2N_2; 3) HCl. d) $NaBH_4$, THF, H_2O (**10**: 26% yield from **7**). e) KOH, EtOH (85%). f) **12**, EtOH, $80\,^{\circ}C$ (40%). g) HBr, AcOH (71%). h) **14**, DCC, HOBt, DMF (59%). i) $MeSO_3H$, CH_2Cl_2 (99%).

This seminal synthesis of **10** fully exploited both β-hydroxy and carboxyl groups of L-serine. However, it ended up suffering from three practical drawbacks, which are itemized as follows: 1) a costly set of reagents for intramolecular Mitsunobu reaction to install a phenylthio group to the hydroxy terminal (**5** → **6** → **7**; a three-step overall yield of 44%); 2) use of hazardous and explosive diazomethane to effect one-carbon homologation at the carboxyl terminal leading to α'-chloro ketone (**7** → **8** → **9**); 3) less complete stereo-directing effect of the α-N-Cbz amino group on the $NaBH_4$-mediated reduction in building the *erythro*-disposed amino alcohol (**9** → **10**; a four-step overall yield of 26% from **7**).

To avoid using intractable diazomethane in assembling α'-chloro ketone **9**, an ingenious protocol was devised at Kaneka wherein magnesium enolate of sodium α-chloroacetate served as a chloromethyl anion equivalent.[6] However, even if **9** could be prepared in a safer way, the L-serine-based synthesis would remain less industrially viable, unless **9** were reduced to **10** with much higher diastereoselectivity. The reason is that, to remove the unwanted *threo*-(2*R*,3*R*)-diastereomer of **10** generated as a reduction by-product, the product mixture has to be recrystallized from dichloromethane at $-78\,^{\circ}C$.

Synthesis of *erythro*-(2*S*,3*R*)-3-*N*-Cbz-amino-2-butanol 10 from sodium erythorbate (15): A method to overcome such methodological limitations plaguing the original approach to **10** (Scheme 1) involves installing an amine functionality regio- and stereoselectively in a chiral four-carbon scaffold equipped with differentiated terminals. Its molecular ends being at different oxidation levels, methyl (2*S*,3*R*)-4-hydroxy-2,3-epoxybutanoate **16** was assumed to serve the purpose, and it was actually used to full advantage in assembling **10** at Nagase (see Scheme 2).[3]



Scheme 2. Synthesis of (2*S*,3*R*)-3-*N*-Cbz-amino-2-butanol **10** from sodium erythorbate **15**. a) ref. [7]; 78% overall yield in three steps. b) 1) NaOH, MeOH, ice-cooling; 2) conc. NH_3, $50\,^{\circ}C$. c) 1) CbzCl, aq $NaHCO_3$, $0\,^{\circ}C \rightarrow rt$; 2) aq HCl. d) *p*-$TsOH \cdot H_2O$, H_2O, rt (**18**: 63% yield from **16**). e) $Ca(BH_4)_2$, MeOH (72%). f) PPTS, MeCOMe (quantitative yield). g) 1) MsCl, Et_3N, PhMe; 2) PhSH, K_2CO_3, DMF (79%). h) 0.1M aq HCl, MeOH, $80\,^{\circ}C$ (79%). i) $SOCl_2$, Et_3N, CH_2Cl_2 (quantitative yield). j) 1) LiCl, DMF, $80\,^{\circ}C$; 2) aq HCl (70%).

According to Weigel's protocol[7] epoxy ester **16** was prepared from sodium erythorbate **15**, an inexpensive food preservative produced by fermentation, in a three-step overall yield of 78%. After alkaline hydrolysis of **16**, the resulting sodium carboxylate was treated with aqueous ammonia; the

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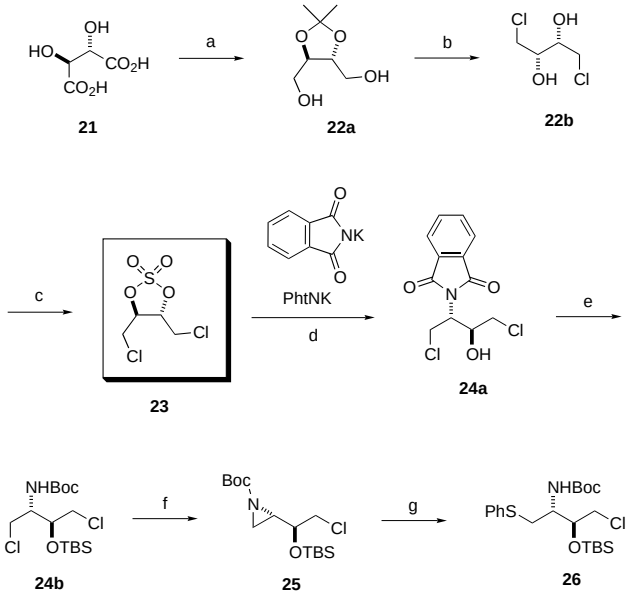
carboxyl group exerted its inductive effect to make the C–O bond located α to it more vulnerable to S_N2 substitution whereby the amine functionality could be installed successfully in a desired sense of regioselectivity. N-Benzyl carbamate formation and lactonization were both effected in aqueous medium without isolating **17a** and **17b**. Being hydrophobic enough to be extracted into an organic solvent, lactone **18** was isolated without difficulty, and then purified by crystallization; the four-step overall yield of **18** from **16** was 63%. When **18** was treated with $NaBH_4$ in the presence of $CaCl_2$, triol **19a** was obtained in 72% yield.

To discriminate between the two primary hydroxy groups in **19a**, the 1,2-diol moiety was temporarily masked as a 1,3-dioxolane ring. The discrete, unaffected primary hydroxyl group in **19b** was then substituted with a phenylthio group to give **19c** in a two-step overall yield of 79%. After the diol functionality was uncovered in 79% yield, **19d** was converted to cyclic sulfite **20**, which, on nucleophilic displacement by LiCl, was converted into **10** in 70% yield, the purity of which was high enough to be used in the ensuing processes that would converge on **1** (Scheme 1). Dispensing with chromatographic purification and cryogenic conditions, this synthetic program allowed **10** to be produced under strict stereocontrol in fourteen-step overall yield of 17%.

Synthesis of *erythro*-(2*S*,3*R*)-3-*N*-Boc-amino-2-butanol O-silyl ether 26 from D-tartaric acid (21): If the symmetry element hidden in the chiral four-carbon intermediates such as **16** and **19a** were recognized, functional group manipulations could be more streamlined in achieving the synthetic goal. To take advantage of such latent symmetrical features, however, the synthesis had to depend on unnatural, more expensive D-tartaric acid (**21**), as explored at Seoul National University and Samchully (Scheme 3).[8]

Concomitant acetalization and methyl ester formation of **21** was followed by $NaBH_4$-mediated reduction to give diol **22a** in a two-step overall yield of 85%. After O-mesylation, substitution with chloride was accompanied by acetal removal to afford bischlorohydrin **22b** in 55% yield, which was converted to cyclic sulfate **23** in 95% yield according to the standarad operations: 1) cyclic sulfite formation with $SOCl_2$; and 2) Ru^{VIII}-catalyzed oxidation. By virtue of the molecular symmetry, nucleophilic attack of potassium phthalimide (PhtNK) at either sulfate end led to the same substitution product **24a** in a quantitative yield with both terminal chlorides being unaffected.

To install a phenylthio group regioselectively, the molecular terminal closer to the amine functionality was activated by aziridine-ring formation. After the nitrogen protection was switched from the N-Pht group to an N-Boc group in a three-step overall yield of 75%, the secondary alcohol was masked as a *tert*-butyldimethylsilyl (TBS) ether **24b**. When it was treated with NaH in THF, *N*-Boc aziridine **25** was obtained quantitatively. Nucleophilic attack by a soft nucleophile, $Et_3NH^+PhS^-$, took place favorably to open the aziridine ring giving **26** in 82% yield with the terminal chloride again untouched. In the event, N,O-doubly protected **26**, a synthetic equivalent of **10**, could be obtained under excellent stereocontrol in an eleven-step overall yield of approximate 27%.



Scheme 3. Synthesis of (2*S*,3*R*)-3-*N*-Boc-amino-2-butanol *O*-silyl ether **26** from D-tartaric acid **21**. a) 1) $Me_2C(OMe)_2$, *p*-TsOH·H_2O, PhH, MeOH (quantitative yield); (2) $NaBH_4$, MeOH (85%). b) MsCl, Et_3N, LiCl, MeCN, 55 °C (55%). c) 1) $SOCl_2$, $CHCl_3$; 2) $RuCl_3$, $NaIO_4$, CCl_4/MeCN/H_2O (95%). d) PhtNK, DMF (quantitative yield). e) 1) H_2NNH_2·H_2O, *i*PrOH; 2) HCl, MeOH; 3) $(Boc)_2O$, Et_3N, THF (75%); 4) *t*Bu(Me)$_2$-SiCl (TBSCl), DMF, imidazole (yield unspecified). f) NaH, THF (quantitative yield). g) PhSH, Et_3N, MeOH (82%).

However, from the practical viewpoint, it seems doubtful that the synthesis of **26** from D-tartaric acid (**21**) was able to benefit from the symmetry-based strategy, because, compromising the starting material cost, it ended up only three steps less than in the synthetic processes via more elaborate chiral intermediate **16** (Scheme 2).

Synthesis of epoxide 11 via *threo*-(2*R*,3*R*)-3-*N*-Cbz-amino-butane-1,2-diol (32b): Indeed, (2*S*,3*R*)-3-*N*-Cbz-amino-1,2-epoxybutane (**11**) served the first synthesis of viracept **1** as outlined in Scheme 1. However, chiral chlorohydrin **10** does not represent the one and only synthetic precursor to **11**, because it could be constructed also from *threo*-(2*R*,3*R*)-3-*N*-Cbz-amino-1,2-diol **32b**, if the epoxide ring were formed with inversion at the secondary alcohol in it (Scheme 4). In fact, such retrosynthetic analysis turned out rewarding enough to reveal another dimension of molecular symmetry whereby the synthesis could start with 3,5,8-trioxabicyclo[5.1.0]octane **27**, a simple, easy-to-prepare *meso* epoxide, as demonstrated at Japan Tobacco[9]

Because of the internal symmetry inherent in the *meso* configuration of **27**, its aminolysis should lead to the same racemic *trans*-amino alcohol regardless of which epoxide terminal would undergo nucleophilic attack by an achiral amine. Interestingly, when **27** was treated with (*R*)-α-phenethylamine **28** in *i*PrOH, more polar diastereomer **29** possessing the desired configuration crystallized consistently from the reaction mixture in >99% *de* and 37–40% yield. On acid treatment to drive acetal migration with **29** in a thermodynamically more stable direction, dioxolane **30** was generated, which was then subjected to catalytic hydrogenolysis in the

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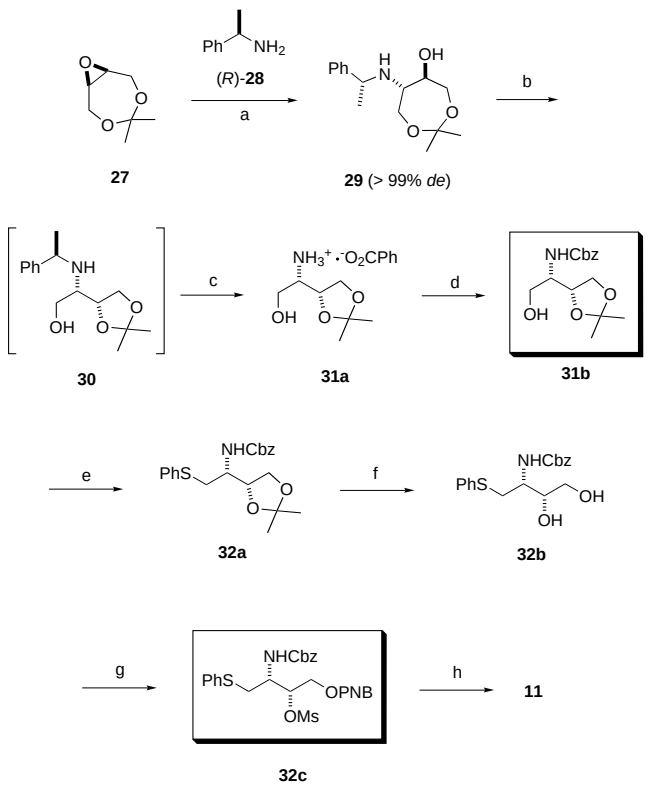


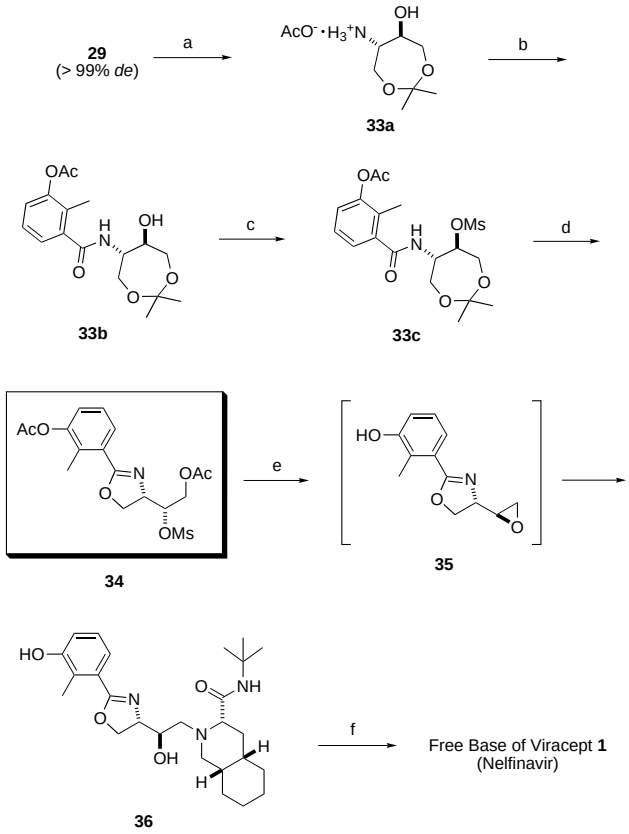
Scheme 4. Synthesis of (2*S*,3*R*)-3-*N*-Cbz-amino-1,2-epoxybutane **11** from *meso* epoxide **27**. a) (*R*)-α-phenethylamine **28**, *i*PrOH (37–40%). b) MsOH (1.25 equiv), $Me_2C(OMe)_2$ (0.1 equiv), MeCOMe (91%). c) H_2, 5% Pd/C, $PhCO_2H$, *i*PrOH (**31a**: 82% yield from **29**). d) CbzCl, K_2CO_3, PhMe, H_2O. e) 1) MsCl, Et_3N, PhMe; 2) PhSH, NaOH, nBu_4NBr, PhMe, H_2O. f) HCl, MeOH, H_2O. g) 1) 4-nitrobenzoyl chloride (PNBCl), 2-picoline, AcOEt; 2) MsCl, Et_3N, AcOEt (**32c**: 80–84% yield from **31a**). h) KOH, 1,4-dioxane, H_2O (98%).

presence of benzoic acid to give both enantiomerically and diastereomerically pure **31a** of high crystallinity in 82% overall yield from **29**. Benzyl carbamate formation gave **31b**, the primary alcohol of which was substituted with a phenylthio group under the standard conditions to provide **32a**. Having served its tactical role to differentiate between the molecular terminals, the acetal protection in **32a** was removed by acidic hydrolysis to give diol **32b**, a (2*R*)-epimer of **19d** (Scheme 2).

To invert the secondary alcohol concomitantly with epoxide formation, 1,2-diol **32b** was treated with 4-nitrobenzoyl chloride (PNBCl) in the presence of 2-picoline to block its primary alcohol selectively. The untouched secondary alcohol was then mesylated to afford **32c** in 84% overall yield from **31a**. Saponification with aqueous KOH was accompanied by in situ intramolecular nucleophilic displacement to provide **11** in 98% yield. Coupled with the stereochemical inversion in the epoxide formation (**32c** → **11**), the desymmetrization of *meso* epoxide (**27** → **29** → **31a**) succeeded in producing **11** in a ten-step overall yield of 25% from **27** without recourse to expensive reagents or chromatographic purification.

The ultimate industrial synthesis of viracept 1 via oxazoline formation: To battle against the recent outbreak of an AIDS epidemic, viracept **1** has to be supplied at the lowest possible manufacturing cost. This ultimate goal of process research and development has been achieved when the three following issues could be further addressed: 1) redundant operations to discriminate between the two primary hydroxyl groups [**29** → **30** → **31a** (Scheme 4)]; 2) surplus protection/deprotection to carry the amine functionality through the synthesis [**31b** → **11** (Scheme 4) → **13** (Scheme 1)]; and 3) no diastereoselectivity for the aminolysis of *meso* epoxide **27** with (*R*)-α-phenethylamine **28** (Scheme 4).

The first two methodological problems were resolved successfully by taking advantage of the electron-delocalized nature of the amide functionality [HN-C=O↔$^+$HN=C-O$^-$] whereby the 2-amino-1-ol moiety could be transformed into its dormant form of oxazoline ring **34** (Scheme 5).[10] On catalytic N-debenzylation on **29**, the resulting primary amine



Scheme 5. Concise synthesis of nelfinavir (free base of **1**) via oxazoline **34**. a) H_2, Pd/C, AcOH (1.0 equiv) (83–90%). b) 3-acetoxy-2-methylbenzoyl chloride, $NaHCO_3$, CH_2Cl_2, H_2O. c) MsCl, Et_3N, CH_2Cl_2. d) 1) $BF_3 \cdot OEt_2$, CH_2Cl_2; 2) Ac_2O. e) **12**, K_2CO_3, MeOH, H_2O (**36**: 62–65% yield from **33a**); f) PhSH (2.0 equiv), $KHCO_3$ (2.0 equiv), MeCO*i*Bu, 115 °C (81–84%).

33a was acylated with 3-acetoxy-2-methylbenzoyl chloride (O-acetyl acid chloride of **14**) to give amide **33b**, which was then O-mesylated to provide **33c**. Under the influence of a Lewis acid catalyst, $BF_3 \cdot OEt_2$, the amide oxygen was allowed to replace one of the two acetal oxygen atoms smoothly to form an oxazoline ring. When the reaction was quenched with acetic anhydride, oxazoline **34** was isolated successfully in 65–71% overall yield from **33a**. On treatment with amine **12** in the presence of K_2CO_3 in aqueous MeOH, double

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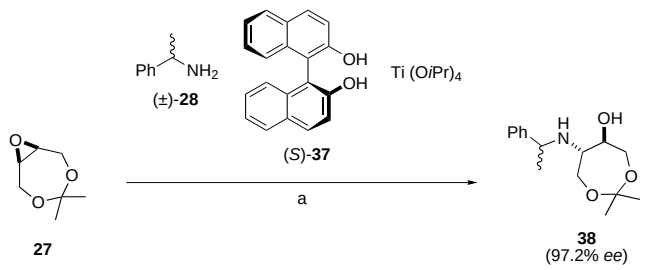
O-deacetylation on **34** was followed by intramolecular substitution to give epoxide **35** with stereochemical inversion, which then underwent an intermolecular nucleophilic attack by **12** in a consecutive fashion. As a result, elaborate oxazoline **36**, a penultimate intermediate with the proper *erythro*-configuration, was obtained in a four-step overall yield of 62–65%. Finally, the oxazoline ring in **36** was opened successfully by potassium thiophenoxide to provide nelfinavir, the free base of **1**, in 81–84% yield, which amounted to a six-step overall yield of 42–49% starting from cyclic amino alcohol **29**.

To overcome the lack of selectivity in the aminolytic desymmetrization step [**27** → **29** (Scheme 4)], a new asymmetric process was developed ingeniously at Japan Tobacco (Scheme 6). When **27** was treated with (±)-α-phenethylamine **28** (1.0 equiv) in the presence of (*S*)-1,1′-bi-2-naphthol **37** (0.5 mol%), Ti(O*i*Pr)$_4$ (0.5 mol%), and water (10 mol%) in *n*heptane/toluene (9:1) at 40 °C,[11] the aminolysis in question took place enantioselectively giving **38** of 97.2% *ee* in 95% yield. Such excellent stereochemical consequence could be ascribed to the (*S*)-1,1′-bi-2-naphthol-titanium complex discriminating between the two prochiral acetal oxygen atoms through bidentate chelation with the epoxide oxygen atom and one of those enantiotopic oxygen atoms. Thus, being tightly chelated, the Lewis acid catalyst could function even in the presence of the basic reactant (±)-**28** without suffering deactivation.[11]

Now that the catalytic asymmetric synthesis of **38** (Scheme 6), and hence **33a** (Scheme 5), was established, it could be integrated into the existing processes that proceeded *via* the oxazoline formation (Scheme 5), which has culminated



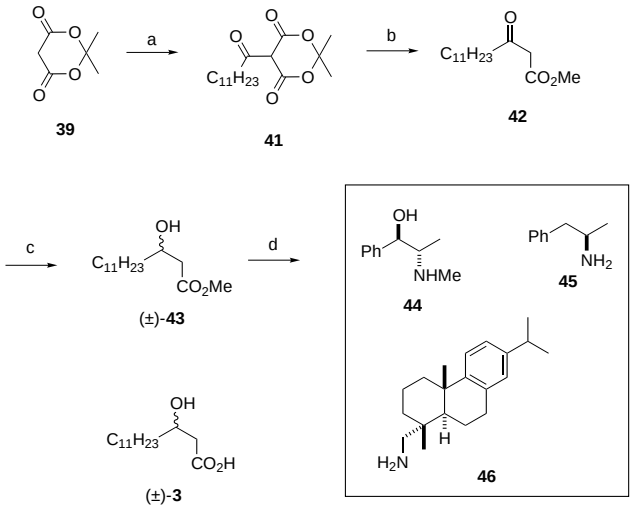
Scheme 6. Asymmetric aminolysis of *meso* epoxide **27** by a chiral Lewis acid catalyst. a) (±)-**28** (1.0 equiv), (*S*)-**37** (0.5 mol%), Ti(O*i*Pr)$_4$ (0.5 mol%), H_2O (10 mol%), *n*heptane/PhMe (9:1), 40 °C, 24 h (95%).

in the ultimate industrial processes to produce viracept **1**. In the meanwhile, a more sophisticated two-fold synthesis of **1** was explored based on the oxazoline-formation tactics at Agouron Pharmaceuticals, while it is not certain whether either approach was actually scaled up or not:[12, 13] One approach commenced with D-tartaric acid (**21**) to construct a chiral four-carbon scaffold on which the oxazoline ring was formed.[12] The other more elegant method employed (3*R*,4*S*)-4-amino-3-hydroxy-tetrahydrofuran as an immediate precursor for the oxazoline formation,[13a] which, in turn, could be prepared from *meso* 3,4-epoxytetrahydrofuran by Jacobsen's chiral (salen)Cr^{III} catalyst.[13b]

Synthesis of (*R*)- and (*S*)-3-Hydroxytetradecanoic acid (3)

Synthesis of a single enantiomer of **3** seems less demanding than that of viracept **1** and its central four-carbon intermediates such as **10** (Schemes 1 and 2), **32c** (Scheme 4), and **34** (Scheme 5), because **3** possesses only one stereogenic center (Figure 1). However, it is ironic that scalable processes to access either (*R*)- or (*S*)-**3** are few notwithstanding various synthetic methodologies explored so far, which actually cover the following alternatives: 1) resolution of (±)-**3**[14–17] via diastereomeric salt formation with basic resolving agents;[14b, 15, 18] 2) kinetic resolution of (±)-**3** and its methyl ester via lipase-catalyzed enantioselective O-acetylation;[14a, 19, 20] 3) asymmetric bioreduction of β-keto acid;[16, 20a] 4) asymmetric reduction of β-keto ester over chiral metal/complex catalysts;[14c, 21–23] 5) stereoselective functionalization through Sharpless' asymmetric epoxidation[24] and dihydroxylation;[25] 6) stereoselective construction of homoallyl alcohol through Brown's asymmetric allyboration;[26] 7) chiral pool synthesis starting from (*S*)-β-hydroxy-γ-butyrolactone[27] or (*S*)-epichlorohydrin.[4] Thus, the scope and limitation intrinsic to each methodology will be discussed from the pragmatic viewpoint in the sections that follow.

Resolution by diastereomeric salt formation: Chiral separation of racemic **3** by diastereomeric salt formation with chiral amine would represent a standard method to access a single enantiomer of **3** if its racemic synthesis could be implemented on scale. The most typical approach to (±)-**3** started with acylation of Meldrum's acid **39** with dodecanoyl chloride **40** to give **41**,[14] which, on methanolysis, was converted to β-keto ester **42** in 72% overall yield from **39** (Scheme 7).[14c] Reduction with $NaBH_4$ gave (±)-**43** in 87% yield.[14b] Saponification eventually provided (±)-**3** in a three-step overall yield of 65% from **39**.[14a] Except for Meldrum's



Scheme 7. Synthesis of (±)-**3** starting from Meldrum's acid **39** and structures of chiral amine used to resolve (±)-**3**. a) 1) $C_{11}H_{23}COCl$ **40**, py, CH_2Cl_2, 0 °C → rt; 2) aq HCl. b) MeOH, reflux (**42**: 72% yield from **39**).[14c] c) $NaBH_4$, EtOH, 0 °C → rt (87%).[14b] d) 1) 10 M aq NaOH; 2) pH 2 (conc HCl); 3) recrystallization (*n*hexane) [(±)-**3**: 65% yield from **39**].[14a]

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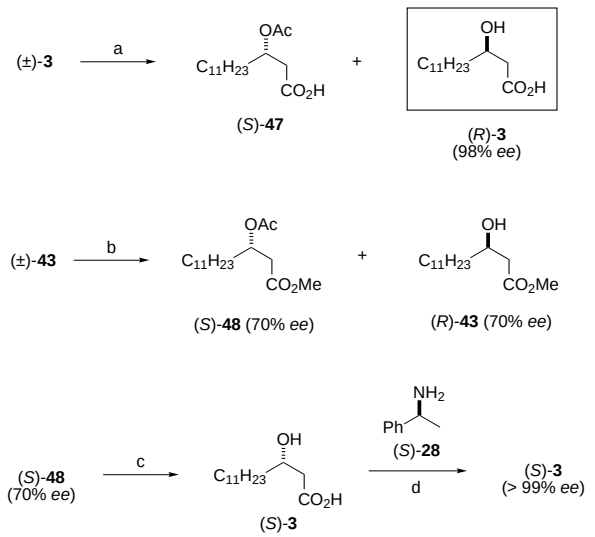
acid-based synthesis, there are other approaches to prepare (±)-**3**, such as the Reformatsky reaction to prepare ethyl ester of (±)-**3** from ethyl bromoacetate and dodecanal,[15] γ-alkylation of a dianion generated from methyl acetoacetate with decyl halide to give **42**,[16] and acylation of a barium chelate complex of methyl acetoacetate with acid chloride.[17]

Resolution of (±)-**3** into (*R*)-**3** by diastereomeric salt formation was effected using chiral amine as the resolving agent, such as (1*S*,2*R*)-L-ephedrine (**44**),[14b] (*R*)-D-α-methyl-β-phenethylamine (**45**),[15] and dehydroabietylamine (**46**).[18] Resolution efficiency reported for each resolving agent is as follows: **44**, 50% *ee* and 25% overall yield after twofold recrystallization; **45**, no data for optical purity or overall yield for a single recrystallization step; **46**, 95% *ee* and 24% overall yield after twofold recrystallization.

Lipase-catalyzed kinetic resolution: Besides diastereomeric salt formation with chiral amine, a chemoenzymatic method was also applied to resolve (±)-**3** in a kinetic manner. When (±)-**3** was treated with vinyl acetate in the presence of *Pseudomonas* lipase (lipase PS-30, Amano) in THF, (*S*)-**3** underwent preferential O-acetylation leaving (*R*)-**3** unaffected (Scheme 8).[14a] Repeated recrystallization of the resolved product mixture from *n*hexane allowed (*R*)-**3** of 98% *ee* to be isolated in 37% overall yield without recourse to chromatographic purification.

Another option to access a single enantiomer of **3** by enzymatic kinetic resolution was to use the methyl ester of (±)-β-hydroxy acid **3** [(±)-**43**] as a substrate (Scheme 8).[19] When O-acetylation of (±)-**43** with vinyl acetate was allowed to proceed halfway in the presence of immobilized lipase



Scheme 8. Kinetic resolution of (±)-**3** and its methyl ester (±)-**43** by lipase-catalyzed enantioselective O-acetylation. a) 1) *Pseudomonas* lipase (lipase PS-30, Amano), CH_2=CHOAc, THF, stream of N_2 to purge MeCHO, 65 °C, 36 h; 2) Recrystallization (*n*hexane) [(*R*)-**3**: 37% yield]. b) 1) immobilized lipase (Amano PS), CH_2=CHOAc, THF, 26–28 °C, 5 d, (50% conversion); 2) silica gel chromatography [(*S*)-**48**: 46% yield; (*R*)-**43**: 49% yield]. c) 1) 6 M HCl/MeOH (1:3), 40 °C, 2 d; 2) NaOH (1.6 equiv), MeOH, 90 °C, 30 min (92%). d) 1) (*S*)-**28** (1.18 equiv), MeOH/MeCN (1:5); 2) recrystallization [MeOH/MeCN (1:5)]; 3) 10% aq citric acid [(*S*)-**3** of > 99% *ee*: 52% yield].

(Amano PS), the O-acetyl product (*S*)-**48** (70% *ee*; 46% yield) was separated from the untouched (*R*)-alcohol **43** (70% *ee*; 49% yield) by silica gel chromatography. Acid-catalyzed deacetylation of (*S*)-**48** followed by alkaline hydrolysis of the methyl ester gave partially resolved (*S*)-**3** in a two-step overall yield of 92%, the optical purity of which could be upgraded *via* diastereomeric salt formation with (*S*)-α-phenethylamine **28** (1.18 equiv). After single recrystallization, (*S*)-**3** of > 99% *ee* was obtained in 22% overall yield from (±)-**3**.

Enantioselestive hydrolysis of *O*-butanoate of (±)-**43** was also attempted using *Geotrichum candium* (GC-4) lipase (Amano) along with enantioselective O-acetylation of (±)-**43** using the same enzyme; in neither case, however, the optical purity of the resolved alcohol exceeded 90% *ee*.[20]

Whether the resolution is conducted kinetically by enzymatic catalysis or by diastereomeric salt formation, it remains less industrially viable in general, unless the unwanted enantiomer could be racemized for another round of resolution. However, enantiomers each of β-hydroxy acid **3** and β-hydroxy ester **43** being highly susceptible to β-elimination, their racemization should be difficult to effect in a simple practical way.

Furthermore, enzyme-catalyzed kinetic resolution of secondary alcohol cannot be conducted on an industrial scale, if the resolved products, alcohol and its ester, were difficult to separate during the extractive work-up. Possessing a long aliphatic chain, neither β-hydroxyl ester (*R*)-**43** nor β-hydroxyl acid (*R*)-**3** would remain in the aqueous phase, while O-acetates each of the respective antipodes, (*S*)-**48** and (*S*)-**47**, were extracted into an organic solvent because of the similar hydrophobicity.[14a, 19a]

Therefore, any chiral separation method should not be employed outside the laboratory to obtain single enantiomers of **3** on a larger scale.

Asymmetric reduction of β-keto ester: Asymmetric reduction of prochiral β-keto ester **42** (Scheme 7) and its parent acid would represent a logical method to access a single enantiomer of **3**. When β-keto tertradecanoic acid and its potassium salt were treated with fermenting bakers' yeast[16] and *Saccharomyces cerevisiae* Hansen,[20a] respectively, asymmetric reduction proceeded with high enantioselectivity to give (*R*)-**3** in > 97% *ee*. Treatment with diazomethane gave methyl ester (*R*)-**43**, which was then purified by silica gel chromatography; however, the isolation yield was too low for either bioreduction to be run in industry: 22% yield for the bakers' yeast reduction;[16] and 10% yield for the *S. cerevisiae* Hansen reduction.[20a]

If β-keto ester **42** were reduced in organic medium using a chiral metal/complex catalyst, product isolation could be facilitated enough to increase the isolation yield. When β-keto ester **42** (10 g) was hydrogenated over an (*R*,*R*)-tartaric acid-NaBr-modified Raney Ni catalyst (prepared from 1.9 g of Raney alloy) at hydrogen pressure of 96.8 atm in methyl propanoate (30 mL) doped with AcOH (0.1 mL) at 100 °C, (*R*)-**43** of 86% *ee* was isolated quantitatively (Scheme 9).[14c, 21] Saponification followed by salt formation with dicyclohexylamine (DCHA) produced salt (*R*)-**49** of high crystallinity,

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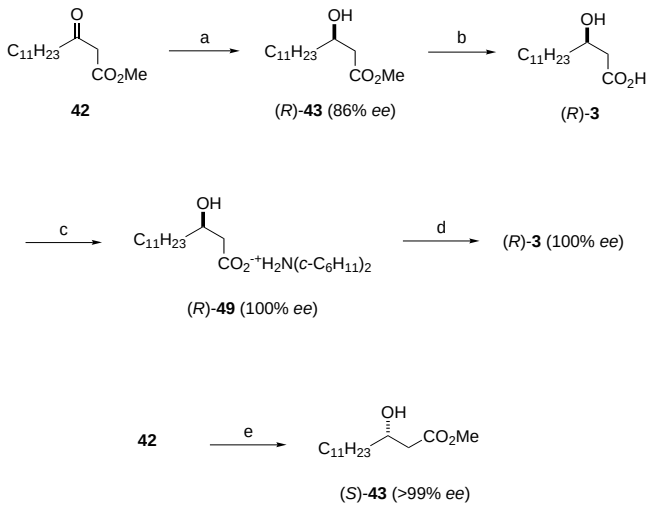


Scheme 9. Asymmetric reduction of β-keto ester **42** over chiral metal-complex catalysts. a) H_2 (96.8 atm), (*R*,*R*)-tartaric acid/NaBr/Raney Ni, *n*$PrCO_2Me$, 100 °C (quantitative yield). b) 1) aq NaOH; 2) acid (79.7 %). c) 1) (*c*-$C_6H_{11})_2NH$, MeCN; 2) recrystallization from MeCN (×3). d) 10 % aq HCl [(*R*)-**3** of 100 % *ee*: 72.1 % yield from crude (*R*)-**3**]. e) H_2 (100 atm), $RuCl_2$[(*R*)-BINAP], MeOH, rt (91 %).

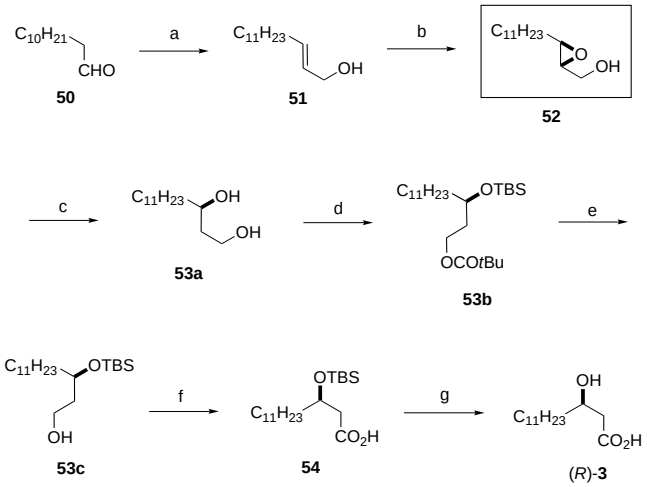
which, on three-fold recrystallization from MeCN, provided (*R*)-**3** of 100 % *ee* in 57 % overall yield from **42**.

The asymmetric reduction of **42** should be effected more efficiently over a chiral homogeneous catalyst than over the asymmetrically modified heterogeneous Ni catalyst. In fact, catalytic hydrogenation proceeded smoothly over commercially available $\{RuCl_2[(R)\text{-BINAP}]\}_2NEt_3$ (0.05 mol %) in the presence of catalytic HCl (0.1 mol %) in MeOH at hydrogen pressure of 4.1 atm (gauge pressure; Parr apparatus) at 45 °C. The resulting (*R*)-**43** was subjected to saponification (aq LiOH, THF; 1M aq HCl) to give free acid (*R*)-**3**, which was combined with DCHA in MeCN to form crystalline salt (*R*)-**49**. After single recrystallization from MeCN, (*R*)-**49** of 97 % *ee* was obtained in 91 % overall yield from **42**.[22] In contrast, when asymmetric hydrogenation was run at higher hydrogen pressure of 100 atm over $RuCl_2$[(*S*)-BINAP], prepared in situ from $Ru(OAc)_2$[(*S*)-BINAP], (*S*)-**43** of > 99 % *ee* could be obtained in 91 % yield (Scheme 9).[23]

Indeed, asymmetric hydrogenation over a chiral BINAP-Ru^{II} complex catalyst may seem to be a scalable method to produce a single enantiomer of **3**. However, this state-of-the art methodology has suffered from two technical issues that would both detract from its industrial viability: For one thing, enantioselectivity remains mediocre unless hydrogen pressures as high as 100 atm could be applied. In addition, because of its homogeneous nature, the precious asymmetric catalyst is difficult to separate from the product; in fact, long-chained β-hydroxy ester **43** being less volatile, the catalyst would not be recovered in industry without high vacuum distillation facilities.

Asymmetric oxidation and C–C bond formation: Except for β-keto ester **42**, allylic alcohol and α,β-unsaturated ester would comprise prochiral precursors to single enantiomers of **3** if they were oxygenated by asymmetric epoxidation[24] and dihydroxylation,[25] respectively. Whichever asymmetric oxidation method is employed, both olefinic ends are supposed to be involved in the oxidative functionalization; hence, an extra C–O bond should be reductively removed afterwards. It is such functional group manipulations needed to adjust the oxidation state that have rendered those synthetic processes lengthy and, as such, less viable in industry.

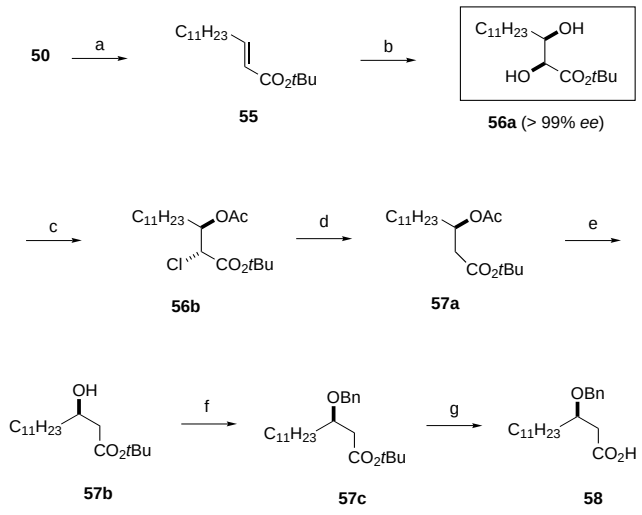
Sharpless' asymmetric epoxidation of allylic alcohol **51**, prepared from dodecanal **50** in a two-step overall yield of 79 %, gave (2*S*,3*R*)-2,3-epoxy-1-ol **52** (Scheme 10).[24] When



Scheme 10. Synthesis of (*R*)-**3** using Sharpless' asymmetric epoxidation. a) 1) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, rt (86 %); 2) *i*Bu_2AlH (DIBAL-H), CH_2Cl_2, −78 °C (92 %). b) (−)-diethyl-D-tartrate (DET), $Ti(OiPr)_4$, *t*BuO_2H, CH_2Cl_2, −20 °C (81 %). c) $NaAl(OCH_2CH_2OMe)_2H$ (Red-Al), THF, −20 °C → rt (89 %). d) 1) *t*BuCOCl, DMAP, CH_2Cl_2 (83 %); 2) *t*Bu-$(Me)_2SiCl$ (TBSCl), imidazole, DMF (84 %). e) DIBAL-H, PhMe, CH_2Cl_2, −78 °C (76 %). f) Jones reagent, MeCOMe, 0 °C (54 %). g) HF/Py, THF, −20 °C (70 %).

it was treated with $NaAl(OCH_2CH_2OMe)_2H$ (Red-Al) in THF, reductive epoxide opening took place regioselectively at the C-2 position to give (*R*)-1,3-diol **53a** in 72 % overall yield from **51**. After masking the secondary hydroxy group *via* three-step functional group manipulations [53 % overall yield: 1) protection of the primary alcohol as a pivaloyl ester; 2) protection of the secondary alcohol as a *tert*-butyldimethylsily (TBS) ether; 3) reductive removal of the pivaloyl ester], primary alcohol **53c** was oxidized under Jones' conditions. Finally, deprotection of the silyl ether furnished (*R*)-**3** in a two-step overall yield of 38 %, the overall yield from **50** being 11 % in nine steps.

Instead of being reduced to allylic alcohol, α,β-unsaturated ester **55** was subjected to Sharpless' asymmetric dihydroxylation to give (2*S*,3*R*)-2,3-dihydroxy ester **56a** of > 99 % *ee* in a two-step overall yield of 91 % (Scheme 11).[25] To remove the hydroxy group at the C-2 position selectively, **56a** was converted to (2*R*,3*S*)-2-chloro-3-acetoxy ester **56b** in 63 % yield via cyclic ortho ester. Radical reduction with tributyltin hydride initiated by thermolysis of AIBN removed the chloride to give **57a** in 99 % yield. After NaOMe-catalyzed methanolysis, *tert*-butyl ester of (*R*)-**3**, **57b**, was obtained in 75 % yield, which was subjected to acid-catalyzed mild

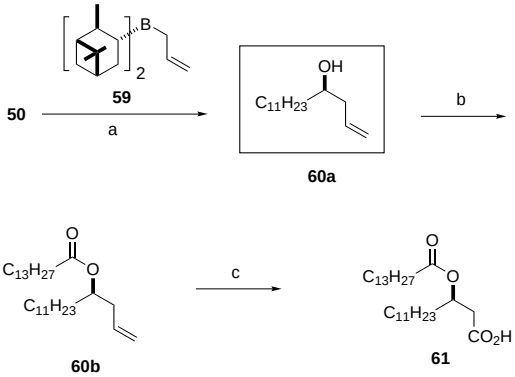


Scheme 11. Synthesis of *O*-benzyl ether of (*R*)-**3**, **58**, using Sharpless' asymmetric dihydroxylation. a) $Ph_3P{=}CHCO_2tBu$, CH_2Cl_2, 23 °C (92 %). b) AD-mix-β [$(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_4 \cdot 2H_2O$], $MeSO_2NH_2$, *t*BuOH, H_2O, 10 °C (99 %). c) $MeC(OMe)_3$, TMSCl, CH_2Cl_2, 23 °C (**56b**: 66 % yield; unreacted **56a**: 23 % yield). d) nBu_3SnH, AIBN, PhH, reflux (99 %). e) NaOMe, MeOH, 0 °C (**57b**: 75 % yield; unreacted **57a**: 17 %). f) $PhCH_2OC(=NH)CCl_3$, CF_3SO_3H, *c*-C_6H_{12}/CH_2Cl_2, 23 °C. g) TFA, CH_2Cl_2, 23 °C (**58**: 65 % yield from **57b**).

O-benzylation with benzyl 2,2,2-trichloroacetimidate to give orthogonally protected **57c**. Finally, acid-catalyzed deprotection of the *tert*-butyl ester provided *O*-benzyl (*R*)-**3**, **58**, in a two-step overall yield of 65 %; a seven-step overall yield of **58** was 28 % from **50**.

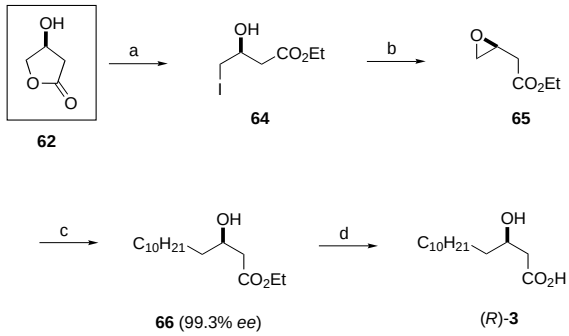
If the secondary alcohol in question was built stereoselectively with concomitant C–C bond formation, aldehyde **50** would serve the asymmetric synthesis of **3** as a more immediate prochiral precursor than **51** (Scheme 10) and **55** (Scheme 11). When Brown's asymmetric allylboration was applied to **50**, homoallylc alcohol **60a** was obtained in > 95 % *ee* and 75 % yield (Scheme 12).[26] O-Acylation followed by permanganate oxidation provided O-tetradecanoate of (*R*)-**3**, **61**, successfully in a two-step overall yield of 88 %.

In spite of its high overall yield of 66 % from **50**, the asymmetric allylboration approach has suffered from both strategic and tactical concerns. From the strategic viewpoint, it has detracted from the atom economy;[28] since introduction of an ally group (C_3) to **50** (C_{12}) gave rise to the C_{15}-skeleton **60a**, the one extra carbon had to be excised in the last stage of the synthesis. The tactical drawbacks plaguing the asymmetric process are two-fold: 1) the cryogenic conditions (−78 °C) needed to achieve high enantioselectivity; and 2) inevitable use of highly flammable diethyl ether as a reaction medium.

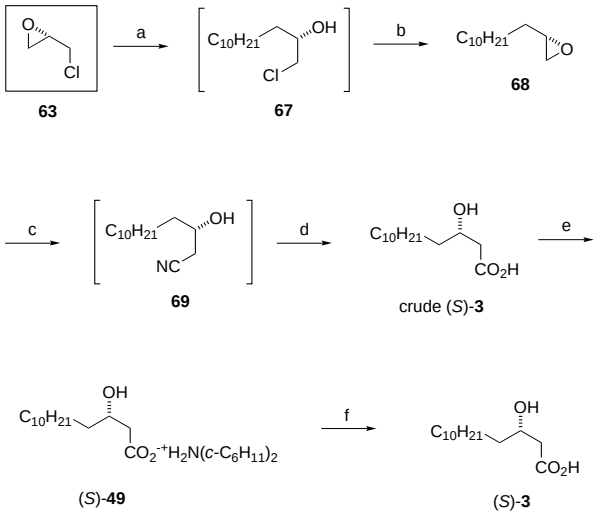


Scheme 12. Synthesis of *O*-tetradecanoate of (*R*)-**3**, **61**, using Brown's asymmetric allylboration. a) 1) allyl-$B(^dIpc)_2$ **59**, Et_2O, −78 °C; 2) MeCHO; 3) 3 M aq AcONa, 30 % aq H_2O_2 [**60a** (b.p. 96 °C at 0.05 mmHg): 75 % yield]. b) $C_{13}H_{27}COCl$, py, CH_2Cl_2, 25 °C, (94 %). c) 1) $KMnO_4$, Aliquat 336, *n*hexane, AcOH, 0 °C; 2) Na_2SO_3 (94 %).

Chiral pool synthesis: Commercially available chiral building blocks could be elaborated to a single enantiomer of **3** if they were suited for building β-hydroxy acid functionality and for homologation as well. In fact, such approaches have been explored successfully using two kinds of bifunctional chiral starting materials: one was (*S*)-β-hydroxy-γ-butyrolactone **62**, available from cheese-manufacturing waste (Scheme 13);[27] and the other was (*S*)-epichlorohydrin **63**,[4] available by Jacobsen's hydrolytic kinetic resolution method (Scheme 14).[29]



Scheme 13. Synthesis of (*R*)-**3** from (*S*)-β-hydroxy-γ-butyrolactone **62**. a) 1) NaI, TMSI, MeCN; 2) EtOH (63 %). b) Ag_2O, MeCN (94 %). c) 1) $C_{10}H_{21}MgBr$, CuI, THF, −30 °C; 2) silica gel chromatography (93 %). d) KOH, EtOH (76 %).



Scheme 14. Synthesis of (*S*)-**3** from (*S*)-epichlorohydrin **63**. a) $C_{10}H_{21}MgBr$ (1.1 equiv), CuI (0.9 mol %), PhMe/THF (29:18), 3–15 °C. b) 48 % aq NaOH, MeOH-PhMe (19:39), rt (**68**: 55 % yield from **63**). c) NaCN (1.2 equiv), MeOH, H_2O, pH 10.8–12.2 (H_2SO_4), 47–52 °C. d) NaOH, H_2O_2, MeOH, H_2O, reflux [crude (*S*)-**3**: 74 % yield from **68**]. e) (*c*-$C_6H_{11})_2NH$, MeCN/MeOH 6:1, 0 °C (68 %). f) aq. H_2SO_4 (98 %).

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Before entering into the C-C bond formation, the lactone ring of **62** was opened with TMSI to give iodohydrin **64**, which, on treatment with silver oxide, was elaborated to ethyl (*S*)-3,4-epoxybutanoate (**65**) (a C_4 intermediate) in a two-step overall yield of 59% (Scheme 13). When **65** was treated with decylmagnesium bromide ($C_{10}H_{21}MgBr$) in the presence of catalytic CuI in THF at $-30\,^{\circ}C$, the epoxide-ring opening took place chemo- and regioselectively to give **66** of 99.3% *ee* in 93% yield after silica gel chromatography. Finally, saponification provided (*R*)-**3** in 76% yield, its four-step overall yield from **62** being 42%.

When commencing with **63** (a C_3 chiral unit), C_{10} and C_1 homologation should be effected in tandem at both electrophilic ends of it (Scheme 14). The first homologation employed chemo- and regioselective epoxide-ring opening of **63** with $C_{10}H_{21}MgBr$ in the presence of catalytic CuI in PhMe/THF (29:18) at temperatures between 3 and $15\,^{\circ}C$. On alkaline treatment to complete the epoxide-ring closure with **67**, (*S*)-1,2-epoxytridecane (**68**) was isolated in a pure state by simple distillation, and it was then subjected to the second homologation with NaCN to give β-hydroxy nitrile **69**. Hydrolysis with basic hydrogen peroxide gave crude acid (*S*)-**3**, which was purified by crystalline salt formation with DCHA. Single crystallization of salt (*S*)-**49** followed by acid treatment liberated purified free acid (*S*)-**3** of 99.5% *ee* in a six-step overall yield of 27% from **63**.

As regards the synthesis of a single enantiomer of **3**, the chiral pool synthesis, especially, that which has employed (*S*)-epichlorohydrin **63** as the starting material,[4] seems to compare favorably with the asymmetric reduction of β-keo ester **42** over a chiral BINAP-Ru^{II} catalyst in terms of industrial viability, because it could dispense with high-pressure equipment, special care to handle the sensitive catalyst, chromatographic purification, and expensive reagents.

Conclusion

Apparently, there seems to be no royal road to process chemistry aimed at developing industrially viable synthetic processes. However, with expertise in total synthesis,[30] the issues inherent in process chemistry should be addressed elegantly as demonstrated by the ultimate industrial synthesis of viracept **1**[10] (Scheme 5). In addition, knowledge in modern synthetic chemistry including asymmetric catalysis and versatile products thereof should help devise a practical enantioselective route to chiral compounds, even if they were as deceptively simple as 3-hydroxytetradecaoic acid **3**[4] (Scheme 14).[31]

In conclusion, suffice it to quote a great European scientist's words: "Discovery consists of seeing what everybody has seen and thinking what nobody has thought." Albert von Szent-Györgyi (1893–1986).

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