Probing the Abilities of Synthetically Useful Serine Proteases To Discriminate Remote Stereocenters. Chiral Naphthyl Aldehyde Inhibitors

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Abstract: The capacities of subtilisin Carlsberg (SC) and α-chymotrypsin (CT), which are representative of synthetically useful serine proteases, to discriminate between R- and S-configurations of stereocenters remote from the catalytic site have been further explored using chiral naphthyl aldehyde transition state analog inhibitors as probes. The inhibitors evaluated were (3*R*)- and (3*S*)-3-(1-naphthyl and 2-naphthyl)butanal and (4*R*)- and (4*S*)-4-(1-naphthyl and 2-naphthyl)pentanal, for which the methyl groups at the C-3 and C-4 stereocenters, respectively, are significantly removed from the aldehyde functionality that interactswith the catalytic serine residue. Each aldehyde was a competitive inhibitor for both enzymes, with CT being significantly more powerfully inhibited than SC. While only low levels of stereoselectivity were observed with SC, significant stereocenter discrimination was manifest for CT within this series of inhibitors with, encouragingly, the similar degrees of stereoselectivity (up to 3.9-fold) being observed between the enantiomers of the naphthylaldehyde inhibitors bearing both C-3 and C-4 remote methyl substituents. Furthermore, CT consistently favored the *S*-enantiomers within this series of inhibitor structures, which represents a reversal of the stereoselectivity observed previously for inhibition by the analogous phenyl substituted aldehydes. Molecular mechanics and molecular dynamics calculations were performed to identify the binding and orientation differences responsible for the *R*- and *S*-enantiomer binding discriminations observed.

Introduction

Enzymes are highly efficient biocatalysts that are now widely exploited in organic syntheses, largely because of the exceptional asymmetric synthetic advantages that they offer.[1] Among the enzymes that are synthetically useful, hydrolases are currently receiving the most attention because of their ease of use and of their abilities to embrace of a wide range of substrate structures. However, for one-stereocenter, or prochiral, substrates, asymmetric transformations by hydrolases have overwhelmingly focussed on the introduction or selection of stereocenters located adjacent to the site of catalysis.[1] Very few examples have been reported where the stereocenter of interest is three or more bonds removed from the carbonyl group of the ester function undergoing hydrolysis.[2] However, since the whole of an enzyme's active site is chiral, an enzyme has the potential to discriminate of any substrate stereocenter, no matter how remotely it is located from the catalytic site. The asymmetric synthetic promise that enzymic methods offer in this regard is significant, because control of the configurations of stereocenters remote from the chiral auxiliaries or catalysts applied in nonenzymic methodology remains an unsolved problem.[3] However, the meager literature database on this topic does not permit any conclusion to be drawn as to the scope and limitations of the remote stereocenter discriminating potentials of enzymes.

Subtilisin Carlsberg (SC, EC 3.4.21.14) and α-chymotrypsin (CT, EC 3.4.21.1) were selected as representative hydrolases for our initial studies, being commercially available serine proteases that have been applied synthetically[4] and for which high resolution X-ray crystal structures are available.[5] These enzymes have an extended active site binding region composed of several subsites, of which the S_1-pocket[6] dominates, particularly in the binding of hydrophobic groups. Our initial investigations[7] on the remote stereocenter-sensing question

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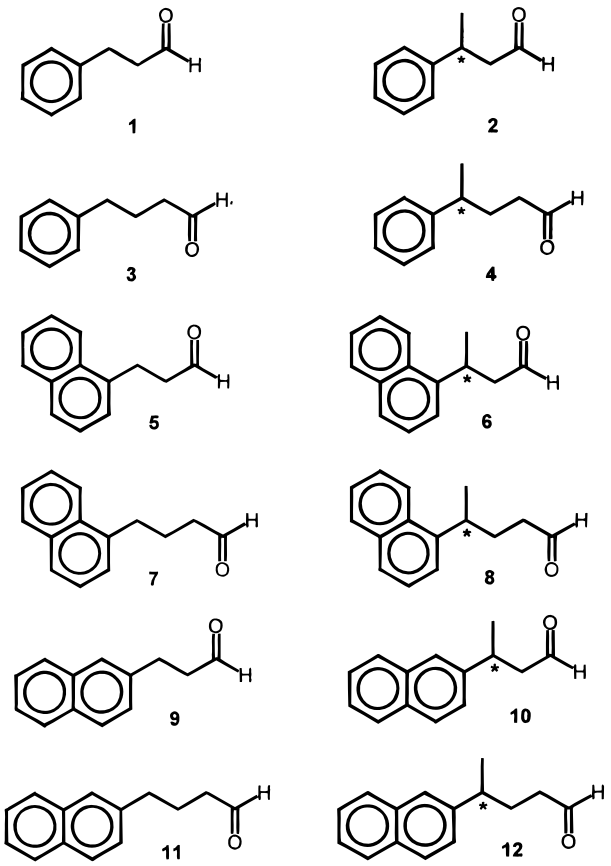
Chart 1



focussed on the interactions of SC and CT with the chiral phenylalkylaldehyde, transition state analog[8] inhibitors **2** and **4** and their achiral parents **1** and **3**. In this paper, the investigation has been extended to the 1- or 2-naphthylalkylaldehyde structures **5**−**12**, selected as suitable probes for S_1-site specificity by graphics analyses based on the X-ray structures of SC and CT.[5] For these naphthyl inhibitors, remote β- or γ-stereocenter and structural specificity selectivities quite different from those of their phenyl analogs **1**−**4** become manifest.

Results and Discussion

Aldehyde structures were selected since they are well-known to be good transition state analog competitive inhibitors of serine proteases[9] and, due to the formation of hydrates,[10] usually have sufficient aqueous solubility for kinetics to be performed in water or with minimal organic cosolvent requirements. The achiral aldehydes **5**, **7**, **9**, and **11** and their respective racemic chiral derivatives **6**, **8**, **10**, and **12** were prepared by unexceptional routes that are fully described in the Experimental Section. Resolutions of the racemates **6**, **8**, **10**, and **12** into their individual enantiomers were accomplished by their conversions into the corresponding diastereomeric imidazolidines with (1*R*,2*R*)-*N*,*N*′-dimethyl-1,2-diphenylethylenediamine.[11] These were chromatographically separable into their individual diastereomers in excellent yields. Moreover, the methyl groups of each pair of diastereomeric imidazolidines exhibited ^{1}H and ^{13}C NMR chemical shifts sufficiently different to permit diastereomeric excess levels of ≥95% to be confirmed in each case.[11]

Each pure imidazolidine diastereomer was then hydrolyzed with wet Si gel of precisely controlled acidity to generate the *R*- and *S*-enantiomers of each of **6**, **8**, **10**, and **12**. In each case, ≥95% *ee* values were reconfirmed by reforming the corresponding imidazolidine diastereomers and repeating the NMR percent *de* analysis. Absolute configurations were assigned on the basis of comparisons of optical rotations with those of literature compounds of established stereochemistry.

The kinetic evaluations of the inhibitory effects of each naphthyl aldehyde on CT and SC were determined by the method of Waley,[12] using suc-Ala-Ala-Pro-Phe-PNA as the standard substrate. The results, which showed competitive inhibition of both enzymes in every case, are recorded in Table 1. For convenient comparison, the K_I values for inhibition of CT and SC by the analogous phenylalkyl aldehydes **1**−**4** obtained previously[7] are also included.

Since the aldehyde inhibitors will be moderately hydrated in the aqueous assay solutions,[13] the observed K_I values, which derive from the free aldehyde concentrations, thus represent maximum values that underestimate the inhibitory power. The true aldehyde K_I's are therefore somewhat lower, which goes part of the way to explain the unexpectedly high, mM rather than μM range, K_I's of many of the Table 1 inhibitors. While the hydrated forms may also be capable of acting as a competitive inhibitors, we were unable to make any predictions in this regard and did not attempt any corrections for hydration effects in our kinetic analyses.

Each of the aldehydes **5**−**12** was a significantly more potent inhibitor of CT than of SC, generally by about an order of magnitude. In view of the similarities of all the SC-K_I's, the following discussion focusses only on CT, for which was observed the strongest inhibition, by the achiral 3-(1-naphthyl)-propanal (**5**) with its K_I of 45 μM. Introduction of a C-3 methyl substituent into **5** is clearly deleterious, with the K_I's of *R*-**6** and *S*-**6** being 10- and 2.7-fold higher, respectively, than that of the achiral parent. Within the 1-naphthyl series, introduction of an extra methylene group, as in **7**, also results in weaker binding, with the K_I of **7** being 5-fold higher than that of its lower homolog **5**. In contrast, creation of a remote stereocenter by inserting a C-4 methyl group now has a beneficial effect on binding, with the K_I's of ***R*-8** and ***S*-8** becoming lower than that of **7** by factors of 4. The CT-binding differences between the inhibitors of the 2-naphthyl series **9**−**12** are somewhat smaller, with the maximum K_I variation being 6-fold between ***R*-10** and ***S*-12**, compared with the 1-naphthyl series with its 10.4-fold K_I difference between **5** and ***R*-6**. However, CT is evidently responsive to minor constitutional isomerism changes in that the achiral 2-naphthylpropanal (**9**) binds 9-fold worse than its 1-naphthyl isomer **5**. Furthermore, the introduction of a C-4 methyl group, as in ***S*-8** and ***R*-8**, now becomes only marginally beneficial. Another contrast between the 1- and 2-naphthyl series is that the achiral 2-naphthyl aldehyde **11**, with its extra methylene group, now binds 3-fold better than its lower homolog **9**.

Examination of the stereoselectivity differences reveals that for CT, regardless of the 1- or 2-naphthyl substitution or whether

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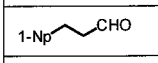
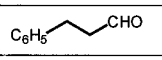
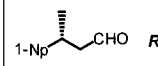
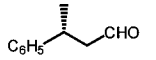
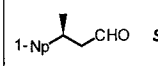
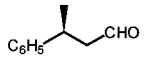
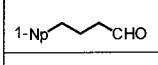
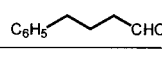
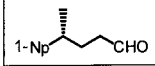
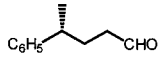
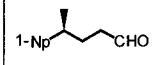
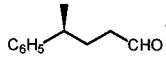
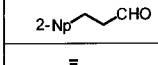
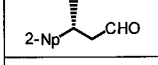
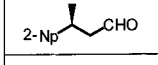
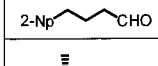
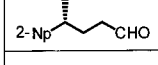
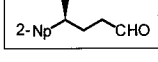
Table 1. Inhibition of α-Chymotrypsin and Subtilisin Carlsberg by the 1- and 2-Naphthyl Aldehydes **5**−**12**, with Their Phenyl Aldehyde Analogs **1**−**4** for Comparison[a]

Inhibitor	CT K_I (mM)	SC K_I (mM)	Inhibitor[b]	CT K_I (mM)[b]	SC K_I (mM)[b]
 **5**	0.045 ± 0.011	3.51 ± 0.33	 **1**	0.51 ± 0.12	8.41 ± 0.67
 ***R*-6**	0.47 ± 0.11	4.90 ± 0.46	 ***R*-2**	0.0084 ± 0.0021	0.53 ± 0.04
 ***S*-6**	0.12 ± 0.029	3.11 ± 0.29	 ***S*-2**	0.74 ± 0.18	9.31 ± 0.74
 **7**	0.22 ± 0.053	1.42 ± 0.13	 **3**	0.15 ± 0.04	5.36 ± 0.43
 ***R*-8**	0.055 ± 0.013	1.33 ± 0.13	 ***R*-4**	0.068 ± 0.017	0.61 ± 0.05
 ***S*-8**	0.059 ± 0.014	1.93 ± 0.18	 ***S*-4**	0.86 ± 0.21	2.95 ± 0.24
 **9**	0.39 ± 0.094	4.42 ± 0.41			
 ***R*-10**	0.51 ± 0.12	1.44 ± 0.14			
 ***S*-10**	0.28 ± 0.067	1.35 ± 0.13			
 **11**	0.13 ± 0.031	2.30 ± 0.22			
 ***R*-12**	0.20 ± 0.048	4.20 ± 0.39			
 ***S*-12**	0.079 ± 0.019	1.73 ± 0.16			

[a] K_I values for both enzymes were determined[7,12] in duplicate at pH 7.5 at 25 °C in 0.1 M NaH_2PO_4, 0.5 M NaCl, 0.25 mM of substrate, 5% DMSO (v/v), and enzyme concentrations of 4.5 nM (SC) and 16 nM (CT). [b] From ref 7.

the remote stereocenter is at the C-3 or C-4 position, the *S*-enantiomers are somewhat preferred over their *R* counterparts. However, even in the best case of inhibitors *R*- and *S*-**6**, where the *S*-enantiomer binds 4-fold better than the *R*, the stereoselectivity difference is well below that required for the effective resolution of a structurally analogous substrate. This contrasts the more favorable stereoselectivity situation with the phenyl aldehydes, where the ***R*-2** over ***S*-2** discrimination by CT is a very healthy 88-fold. In fact, there are several interesting variations in the patterns of CT inhibition between the phenyl aldehydes **1**−**4** and their 1- and 2-naphthyl counterparts **5**−**12**, while for SC the variations between the different inhibitor structures are minor and unremarkable, and with the K_I values in the weakly inhibiting mM range almost throughout. Despite its greater potential for hydrophobic interaction with the S_1-pocket, the naphthyl group evidently does not confer better binding properties, nor does it elicit improved stereorecognition benefits.

The differences in the degree of stereoselectivity between the phenyl and naphthyl inhibitors is not the only interesting observation. In addition, the direction of stereoselectivity is different for the two series. For the phenyl cases studied previously, CT-binding of the *R*- over the *S*-enantiomers was significantly favored for **2** and **4**,[7] whereas for the naphthyl analogs **6**, **10**, and **12**, the *S*-enantiomers now become the preferred inhibitors, albeit to a much lesser degree.

The questions posed by the observed differences and reversals of stereoselectivity for the naphthyl and phenyl inhibitors are intriguing. For the 1-naphthyl probes **5**−**8**, SC appears to be unresponsive to the presence of a methyl substituent that creates a remote stereocenter of either *R*- or *S*-configuration, with the K_I's of ***R*-6**, ***S*-6**, ***R*-8**, and ***S*-8** being very similar to those of their achiral analogs **5** and **7**, respectively. In contrast, for CT, the presence of either an *R*- or *S*-center methyl substituent in ***R*-6** or ***S*-6** exerts a negative influence, with the K_I of the unsubstituted parent **5** being 10.4- and 2.7-fold lower than those of ***R*-6** and ***S*-6**, respectively. On the other hand, the *R*-center methyl substituent of (3*R*)-3-phenylbutanal (***R*-2**) is highly beneficial to good binding, since it binds 61- and 16-fold more strongly than its unsubstituted parent **1** with CT and SC, respectively.[7] In contrast, the presence of similar *R*-center methyl substituent in the 1-naphthyl aldehydes ***R*-6** and ***S*-6** does not bestow a similarly advantageous binding contribution, and this deficiency may well be responsible for the observed stereoselectivity reversal for these inhibitors. Moreover, for the isomeric 2-naphthyl probes **9**−**12**, the reversals of stereoselectivity relative to the phenyl analogs are also attributable to negative contributions binding by *R*-methyl substituents compared with the neutral effect on K_I's of introducing an *S*-configuration methyl group.

Similar reversals of CT stereoselectivity induced by replacing phenyl by naphthyl have also been detected with boronic acid inhibitors.[14] In this case it was suggested that a contributing factor was the fact that the naphthyl groups could be bound in different conformations not available to their C_v-symmetric phenyl analogs. The molecular modeling performed supported this hypothesis, with the caveat that the calculations could not take into account any E1 complexation involving boron−histidine bonds.[15] Fortunately, for aldehyde E1 complexes, there is no corresponding evidence for histidine adducts. Thus the

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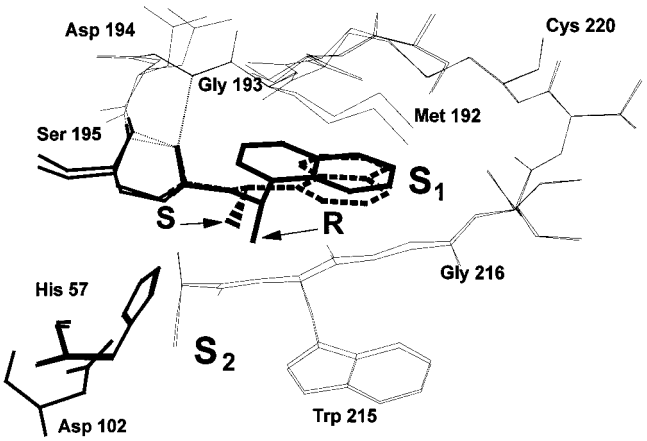

Figure 1. Superimposed energy-minimized E1 complexes of (3*R*)- and (3*S*)-3-(1-naphthyl)butanals, ***R*-6** (boldface —) and ***S*-6** (boldface - -), respectively, in the active site of CT. The oxyanions of the tetrahedral complexes derived from ***R*-6** and ***S*-6** are located in the oxyanion hole, and are stabilized by hydrogen-bonding (···) with the peptide NH's of Ser195 (O^-—N, 3.12 and 3.15 Å respectively for ***R*-6** and ***S*-6**) and Gly193 (O^-—N, 2.89 and 2.88 Å respectively for ***R*-6** and ***S*-6**). The methyl group at the stereocenter of the better inhibitor ***S*-6** is located more deeply inside of the S_2 pocket than that of ***R*-6**, thereby eliciting the better hydrophobic interaction manifest in the lower K_I of ***S*-6**.

search for an explanation of the K_I and stereoselectivity differences *via* molecular modeling based on transition state analog formation by addition of the active site serine nucleophiles is considerably more secure.

Molecular modeling was performed as described previously[7] for the representative pairs of inhibitors ***R*-6**, ***S*-6**, ***R*-10**, and ***S*-10**, using X-ray structures of CT and SC energy-minimized by molecular mechanics. Each inhibitor was individually docked into the active site, with the naphthyl moieties in the S_1-subsite, and with the aldehyde carbonyl carbon covalently bonded to the active site serine-CH_2OH oxygen to form a transition state-like tetrahedral intermediate. Each E1-complex was then subjected to energy-minimization by molecular mechanics calculations, and the optimized conformations and the free energies of each *R*- and *S*-pair of E1 complexes compared. The results are depicted in Figures 1−4.

In each minimized E1 complex, there were strong interactions between the oxyanion of the tetrahedral intermediate and the oxyanion hole H-bonding residues of the peptide backbone N*H*'s of Ser195 and Gly193 of CT and the backbone N*H* of Ser221 and the side chain NH_2 of Asn155 of SC, respectively. Accordingly, it is apparent that the K_I variations manifest in Table 1 reflect the active site differences between the naphthyl and methyl group interactions and orientations of each inhibitor.

Figure 1 shows that the 1-naphthyl moieties of ***R*-6** and ***S*-6** adopt very different orientations in the hydrophobic S_1 pocket of CT. As a result, the methyl group at the stereocenter of the *S*-enantiomer is directed more deeply into the S_2 pocket and thus elicits a stronger hydrophobic interaction than does the corresponding methyl group of ***R*-6**. This accounts for the 3.9-fold lower K_I of ***S*-6** than ***R*-6**. Furthermore, the calculated $\Delta\Delta G$ value (1.8 Kcal/mol) between the two E1 complexes approximates the experimental value[16] of 0.82 kcal/mol.

The corresponding picture for SC is depicted in Figure 2. For both E1 complexes of ***R*-6** and ***S*-6**, the naphthyl groups penetrate adequately, and almost equivalently, into S_1 to provide good hydrophobic binding contributions. In addition, now the methyl groups at the stereocenters of both enantiomers are

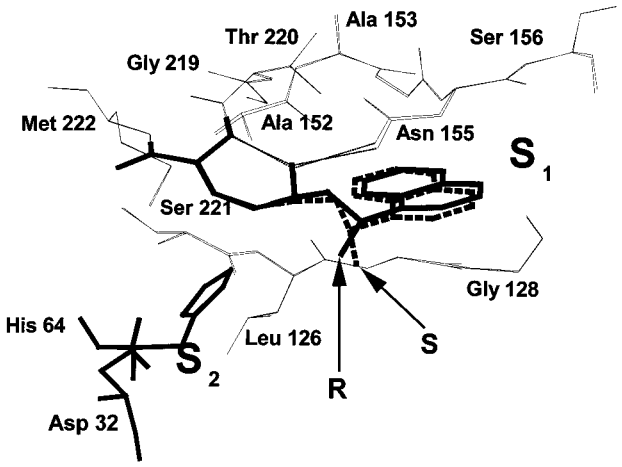

Figure 2. Superimposed energy-minimized E1 complexes of (3*R*)- and (3*S*)-3-(1-naphthyl)butanals, ***R*-6** (boldface —) and ***S*-6** (boldface - -), respectively, in the active site of SC. The negative charges of the oxyanions of the tetrahedral complexes derived from ***R*-6** and ***S*-6** are again stabilized to similar degrees by the oxyanion hole, by hydrogen-bonding (···) with the peptide NH of Ser221 (O^-—N, 2.80 and 2.91 Å, respectively, for ***R*-6** and ***S*-6**) and the side chain $-NH_2$ of Asn155 (O^-—N, 2.81 and 2.82 Å, respectively, for ***R*-6** and ***S*-6**). The methyl groups at the stereocenters of ***R*-6** and ***S*-6** are directed outside of the active site and do not contribute to binding. Furthermore, the naphthyl moieties of both ***R*-6** and ***S*-6** are oriented very similarly in the hydrophobic S_1-pocket. The absence of significant binding differences is in accord with the comparable inhibitory powers of ***R*-6** and ***S*-6** measured experimentally.

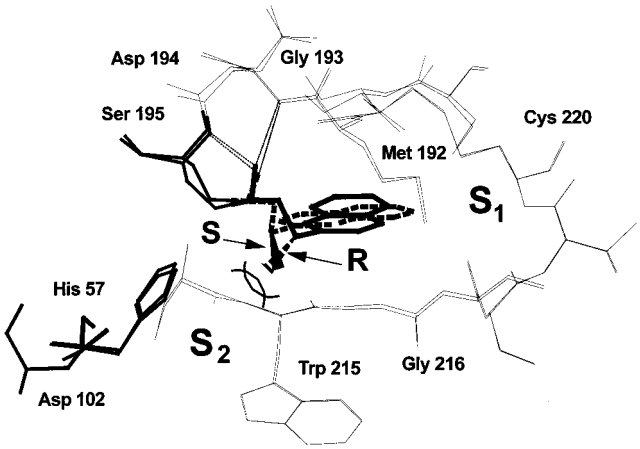

Figure 3. Superimposed energy-minimized E1 complexes of (3*R*)- and (3*S*)-3-(2-naphthyl)butanal, ***R*-10** (boldface —) and ***S*-10** (boldface - -), respectively, in the active site of CT. The oxyanions of the tetrahedral complexes derived from ***R*-10** and ***S*-10** are located in the oxyanion hole, stabilized by hydrogen-bonding (···) with the peptide NH's of Gly193 (O^-—N, 2.75 and 2.79 Å, respectively, for ***R*-10** and ***S*-10**), but having weak interaction with the peptide NH's of Ser195 (O^-—N, 3.45 and 3.85 Å, respectively, for ***R*-10** and ***S*-10**). While the methyl group at the stereocenter of ***R*-10** must occupy a sterically unfavorable location very close to the peptide bond of Trp215, that of ***S*-10** is more agreeably positioned outside of the active site. This factor, together with the deeper penetration of the 2-naphthyl groups of ***S*-10** into the S_1 hydrophobic pocket, explains the lower K_I of the *S*-enantiomer.

oriented toward the outside of the active site and do not make any binding contributions. Thus the overall binding efficiencies of ***R*-6** and ***S*-6** with SC are comparable, as reflected by their almost equivalent K_I's and by the virtually indistinguishable calculated free energy values of the minimized E1 complexes for ***R*-6** (−1285.9 Kcal/mol) and ***S*-6** (−1286.1 Kcal/mol). In

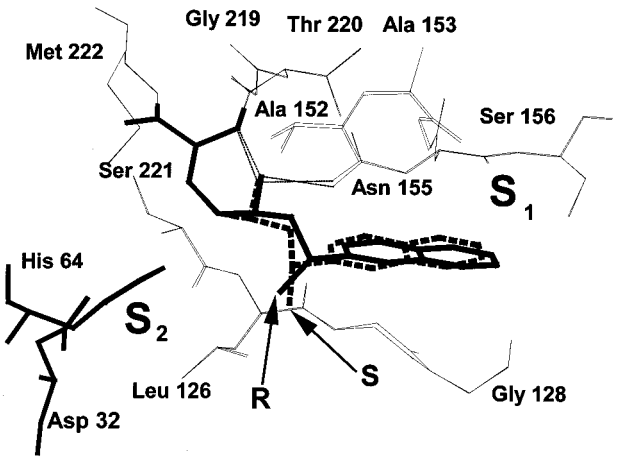

Figure 4. Superimposed energy-minimized E1 complexes of (3*R*)- and (3*S*)-3-(2-naphthyl)butanal, ***R*-10** (boldface —) and ***S*-10** (boldface - -), respectively, in the active site of SC. Again, good oxyanion hole stabilization is seen for both tetrahedral complexes derived from ***R*-10** and ***S*-10**, involving hydrogen-bonding (···) with the peptide NH of Ser221 (O^-—N, 2.82 and 2.99 Å, respectively, for ***R*-10** and ***S*-10**) and the side chain $-NH_2$ of Asn155 (O^-—N, 2.77 and 2.78 Å, respectively, for ***R*-10** and ***S*-10**). The comparable K_I's of ***R*-10** and ***S*-10** are in agreement with the similar orientations of both naphthyl groups in S_1 and the external-to-active-site locations of each methyl group that preclude stereocenter discrimination differences.

the isomeric 2-naphthyl aldehyde series, the interpretations of the molecular modeling results on the E1 complexes of ***R*-10** and ***S*-10** were carried out similarly. In these cases, the K_I-differences for inhibition of CT (1.8-fold) and SC (1.1-fold) by the enantiomers are very small. This is reflected in the molecular modeling results (Figures 3 and 4), which reveal only minor differences in the active site positions and orientations of the ***R*-10** and ***S*-10** in both CT and SC.

While the levels of remote stereocenter stereoselectivity achieved in the present study are modest, the data demonstrate that the use of chiral competitive inhibitors as probes, in conjunction with molecular modeling, is clearly an effective strategy. Our eventual goal is to establish that molecular modeling prior to experimental work can provide an effective filter which will identify the structures with the highest *R*-to-*S* discrimination potential and thereby eliminate the need for more time consuming experimental or kinetic screening. In this regard, the results to date are very encouraging, in that when little positional or free energy differences are seen between the modeled E1 complexes of enantiomeric inhibitors, the K_I variations are small, and there will be little stereocenter configuration discrimination. On the other hand, when there is a large K_I separation, such as the potentially preparatively significant 88-fold factor between ***R*-** and ***S*-2**, clearly discernible differences between the active site orientations of the two enantiomers are evident, particularly with respect to the stereocenter region, with the more favorable position of the lower energy complex clearly identifiable.[7]

Experimental Section

The materials and suppliers, equipment, and analytical methods used were as described previously.[7] When needed, solvents were dried by standard methods.[17]

1-Naphthyl Series. 3-(1-Naphthyl)propanal (5) [General Procedure A]. To a solution of 1-naphthaldehyde (2.2 g, 14.0 mmol, 1.0 mol equiv) in CH_2Cl_2 (18 mL) was added *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidine)acetamide[18] (10.2 g, 28.0 mmol, 2.0 mol equiv) at 20 °C. The reaction mixture was stirred for 2 days at 20 °C and then concentrated *in vacuo*. The crude product was chromatographed on a Si gel column (hexanes/EtOAc, 80/20 elution) to give *N*-methoxy-*N*-methyl-3-(1-naphthyl)prop-2-enamide (3.30 g, 98%) as a white solid: mp 66−67 °C; IR (cm^{-1}) 1656, 1611; ^1H NMR ($CDCl_3$) δ 3.35 (3H, s), 3.78 (3H, s), 7.11 (1H, d, J = 15.5 Hz), 7.45−7.60 (3H, m), 7.76−7.90 (3H, m), 8.20−8.30 (1H, m), 8.57 (1H, d, J = 13.5 Hz).

N-Methoxy-*N*-methyl-3-(1-naphthyl)prop-2-enamide (1.66 g, 6.9 mmol) in EtOAc (24 mL) containing 10% Pd/C (60 mg) was stirred under H_2 (1 atm) at 20 °C for 20 h. The reaction mixture was filtered through Celite and then Si gel and then concentrated *in vacuo* to give *N*-methoxy-*N*-methyl-3-(1-naphthyl)propanamide (1.60 g, 96%) as colorless oil: IR (cm^{-1}) 1737, 1663; ^1H NMR ($CDCl_3$) δ 2.86 (2H, t, J = 7.4 Hz), 3.21 (3H, s), 3.38−3.50 (2H, m), 3.57 (3H, s), 7.35−7.55 (4H, m), 7.70−7.90 (2H, m), 8.06−8.10 (1H, m).

To a solution of *N*-methoxy-*N*-methyl-3-(1-naphthyl)propanamide (243 mg, 1.0 mmol, 1.0 mol equiv) in THF (10 mL) was added $LiAlH_4$ (48 mg, 1.2 mmol, 1.2 mol equiv) at −78 °C under a N_2 atmosphere. Stirring was continued for 20 min at −78 °C, and the mixture then poured into 5% ethanolic HCl (10 mL) at 0 °C and partitioned between brine (10 mL) and ether:CH_2Cl_2 (1:1). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* and 3-(1-naphthyl)-propanal[19] (**5**, 146 mg, 79%) isolated by radial TLC (Chromatotron, hexanes/EtOAc, 90/10) as a colorless oil: IR (cm^{-1}) 1721; ^1H NMR ($CDCl_3$) δ 2.92 (2H, t, J = 7.5 Hz), 3.42 (2H, t, J = 8.1 Hz), 7.30−8.00 (7H, m), 9.88 (1H, t, J = 1.2 Hz).

(3*R*)- and (3*S*)-3-(1-Naphthyl)butanal (*R*-6 and *S*-6) [General Procedure B]. To 1-naphthaldehyde (3.0 g, 19.2 mmol, 1.0 mol equiv) in CH_2Cl_2 (18 mL) was added methyl 2-(triphenylphosphoranylidine)-acetate (7.68 g, 23.1 mmol, 1.2 mol equiv) at 20 °C. The reaction mixture was stirred for 15 h at 20 °C and then concentrated *in vacuo*, and the crude product chromatographed on Si gel column (hexanes/EtOAc, 90/10 elution) to give methyl 3-(1-naphthyl)prop-2-enoate (4.11 g, 99%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 3.85 (3H, s), 6.52 (1H, d, J = 15.8 Hz), 7.45−7.62 (3H, m), 7.73 (1H, d, J = 7.3 Hz), 7.85−7.95 (2H, m), 8.15−8.25 (1H, m), 8.53 (1H, d, J = 15.7 Hz); ^{13}C NMR δ 52.3, 120.9, 123.9, 125.5, 126.0, 126.7, 127.4, 129.2, 131.0, 131.9, 132.2, 134.2, 142.4, 167.8.

To a slurry of CuI (3.77 g, 19.8 mmol, 1.2 mol equiv) in Et_2O (80 mL), ethereal MeLi (1.4 M, 28.3 mL, 39.6 mmol, 2.4 mol equiv) was added dropwise during 5 min at 0 °C under N_2 atmosphere. The reaction mixture was stirred for 10 min at 0 °C then cooled to −25 °C. A solution of methyl 3-(1-naphthyl)prop-2-enoate (3.50 g, 16.5 mmol, 1.0 mol equiv) in Et_2O (20 mL) was injected into the reaction mixture at −25 °C. The reaction mixture was stirred for an additional 1 h at −25 °C and then quenched with saturated aqueous NH_4Cl (50 mL). The resulting mixture was stirred until the solid had dissolved and the aqueous layer had turned deep blue. The organic layer was separated, and the aqueous phase extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*, and the crude product purified by radial TLC (Chromatotron, hexanes/EtOAc, 90/10) to yield methyl (±)-3-(1-naphthyl)butanoate (1.50 g, 40%) as a colorless oil: IR (cm^{-1}) 1740; ^1H NMR δ 1.45 (3H, d, J = 6.8 Hz), 2.63 (1H, d of d J = 15.3, 9.3 Hz), 2.87 (1H, d of d, J = 15.2, 5.3 Hz), 3.67 (3H, s), 4.13−4.28 (1H, m), 7.35−7.60 (4H, m), 7.74 (1H, d, J = 8.1), 7.85−7.92 (1H, m), 8.19 (1H, d, J = 8.4 Hz); ^{13}C NMR δ 21.7, 31.3, 42.8, 52.1, 122.8, 123.5, 126.0, 126.1, 126.6, 127.4, 129.5, 131.6, 134.5, 142.2, 173.5.

To methyl (±)-3-(1-naphthyl)butanoate (1.00 g, 4.38 mmol, 1.0 mol equiv) in Et_2O (5 mL) was added $LiAlH_4$ (116 mg, 2.63 mmol, 2.4 H^- mol equiv) at 0 °C under N_2. The reaction mixture was stirred for 5 min at 0 °C, then warmed to 20 °C, and stirred for an additional 30 min. It was then diluted with EtOAc (5 mL), and the reaction then quenched by the slow addition of brine (5 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated *in vacuo*, and

(16) Calculated from $\Delta\Delta G = -RT \ln[(K_I)_S/(K_I)_R]$.

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(18) Evans, D. E.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

(±)-3-(1-naphthyl)butan-1-ol (820 mg, 94%) was purified by radial TLC (Chromatotron, hexanes/EtOAc, 80/20) as a colorless oil: ^{1}H NMR δ 1.43 (3H, d, J = 6.8 Hz), 1.85−2.20 (2H, m), 3.53−3.73 (2H, m), 3.75−3.90 (2H, m), 7.36−7.55 (4H, m), 7.68−7.75 (1H, m), 7.80−7.90 (1H, m), 8.15−8.23 (1H, m); ^{13}C NMR δ 22.4, 30.5, 41.1, 61.7, 123.1, 123.6, 125.9, 126.1, 126.3, 127.0, 129.5, 132.1, 134.5, 143.6.

DMSO (703 mg, 9.0 mmol, 2.4 mol equiv) in CH_2Cl_2 (2.0 mL) was added dropwise at −60 °C under N_2 atmosphere to a solution of oxalylchloride (571 mg, 4.5 mmol, 1.2 mol equiv) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 3 min then (±)-3-(1-naphthyl)-butan-1-ol (750 mg, 3.75 mmol, 1.0 mol equiv) in CH_2Cl_2 (4.0 mL) was added dropwise at −60 °C. The reaction mixture was stirred for 15 min, and Et_3N (1.82 g, 17.9 mmol, 5.0 mol equiv) was then added at −60 °C. After the reaction mixture was stirred for 5 min at −60 °C, it was warmed to 20 °C, the reaction quenched by the addition of brine (10 mL), the organic layer separated, and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with water (10 mL), then with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by radial TLC (Chromatotron, hexanes/EtOAc, 90/10) to give (±)-3-(1-naphthyl)butanal ((±)-**6**, 722 mg, 97%) as a colorless oil: IR (cm^{-1}) 1724; ^{1}H NMR δ 1.46 (3H, d, J = 6.9 Hz), 2.70−3.00 (2H, m), 4.15−4.32 (1H, m), 7.32−7.60 (4H, m), 7.73 (1H, d, J = 8.0 Hz), 7.85−7.93 (1H, m), 8.10−8.20 (1H, m), 9.77 (1H, t, J = 1.8 Hz); ^{13}C NMR δ 22.1, 29.0, 51.8, 123.2, 123.3, 126.1, 126.2, 126.7, 127.6, 129.6, 131.5, 134.5, 141.8, 202.3.

The above racemate was resolved as follows: To (±)-3-(1-naphthyl)-butanal ((±)-**6**, 6.70 mg, 3.38 mmol, 1.0 mol equiv) in Et_2O (30 mL) was added molecular sieves (7.0 g) followed by (1*R*,2*R*)-*N*,*N*′-dimethyl-1,2-diphenyl-ethylenediamine[11] (812 mg, 3.38 mmol, 1.0 mol equiv) at 20 °C under N_2. The reaction mixture was stirred for 15 h at 20 °C and then filtered through Celite. The filtrate was concentrated *in vacuo*, and the diastereomeric imidazolidines separated by column chromatography on Si gel (hexanes/EtOAc, 90/10 elution) to give diastereomerically pure *R*,*R*,*R*-*N*,*N*′-dimethyl-4,5-diphenyl-2-[2-(1-naphthyl)-propyl]-1,3-imidazolidine (less polar, 600 mg, 85%, >95% *de*): $[\alpha]^{24}_D$ −53.0° (*c* 0.6, $CHCl_3$); IR (cm^{-1}) 3033, 2964, 2792, 1454; ^{1}H NMR δ 1.49 (3H, d, J = 7.0 Hz), 1.95−2.15 (1H, m), 2.11 (3H, s), 2.27 (3H, s), 2.40−2.55 (1H, m), 3.56 (2H, d of d, J = 39.0, 8.4 Hz), 3.85−3.95 (1H, m), 4.05−4.25 (1H, m), 7.10−7.34 (10H, m), 7.43−7.56 (4H, m), 7.70−7.80 (1H, m), 7.85−7.94 (1H, m), 8.29 (1H, d, J = 8.9 Hz); ^{13}C NMR δ 24.4, 29.8, 34.8, 37.2, 41.3, 76.0, 79.6, 83.1, 122.5, 123.2, 125.3, 125.6, 125.8, 126.4, 127.1, 127.3, 127.6, 128.0, 128.1, 128.2, 129.0, 131.6, 134.1, 139.8, 141.0, 143.2, and *R*,*R*,*S*-*N*,*N*′-dimethyl-4,5-diphenyl-2-[2-(1-naphthyl)propyl]-1,3-imidazolidine (more polar, 610 mg, 86%, >95% *de*): $[\alpha]^{24}_D$ −85.2° (*c* 0.5, $CHCl_3$); IR (cm^{-1}) 3030, 2967, 2793, 1452; ^{1}H NMR δ 1.56 (3H, d, J = 6.8 Hz), 1.95−2.30 (2H, m), 2.19 (3H, s), 2.54 (3H, s), 3.54 (2H, d of d, J = 22.9, 8.7 Hz), 4.05−4.20 (2H, m), 7.02−7.10 (2H, m), 7.15−7.30 (8H, m), 7.45−7.65 (4H, m), 7.70−7.80 (1H, m), 7.88−7.96 (1H, m), 8.52 (1H, d, J = 9.1 Hz); ^{13}C NMR δ 20.5, 29.3, 34.6, 40.5, 41.8, 75.4, 80.0, 82.8, 122.6, 123.8, 125.4, 125.6, 125.8, 126.3, 127.2, 128.0, 128.1, 128.9, 131.4, 134.0, 139.6, 140.5, 144.5.

Each diastereomer was converted back to its aldehyde component as follows: To Si gel (1.7 g, Si gel 60, Merck, 70−230 mesh) in CH_2Cl_2 (6 mL) was added 15% H_2SO_4 (170 μL). After 5 min, the water phase disappeared due to absorption on the Si gel surface. A solution of *R*,*R*,*R*-*N*,*N*′-dimethyl-4,5-diphenyl-2-[2-(1-naphthyl)propyl]-1,3-imidazolidine (140 mg, 0.34 mmol) in CH_2Cl_2 (1.5 mL) was then added at 20 °C, and the reaction mixture was stirred for 30 min at 20 °C. The solid phase was separated by suction filtration, and the solid was washed several times with CH_2Cl_2. The filtrate was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give (3*R*)-3-(1-naphthyl)butanal (***R*-6**, 60 mg, 90%, >95% *ee*) as a colorless oil: $[\alpha]^{24}_D$ −21.0° (*c* 0.3, Et_2O); lit.[20] $[\alpha]^{20}_D$ −3.0° (*c* 0.1, EtOH, 55% *ee*), spectroscopically identical to the racemate ((±)-**6**). HRMS, Calcd for M^+ $C_{14}H_{14}O$ *m/e* 198.1045, found *m/e* 198.1041.

Similarly, *R*,*R*,*S*-*N*,*N*′-dimethyl-4,5-diphenyl-2-[2-(1-naphthyl)propyl]-1,3-imidazolidine (210 mg, 0.50 mmol), Si gel (2.5 g), and 15% H_2SO_4 (250 μL) gave (3*S*)-3-(1-naphthyl)butanal (***S*-6**, 88 mg, 89%, >95% *ee*) as a colorless oil: $[\alpha]^{24}_D$ +21.0° (*c* 0.3, Et_2O); lit.[20] $[\alpha]^{20}_D$ +2.0° (*c* 0.1, EtOH, 35% *ee*); HRMS, calcd for M^+ $C_{14}H_{14}O$ *m/e* 198.1045, found *m/e* 198.1046, spectroscopically identical to the racemate ((±)-**6**).

4-(1-Naphthyl)butanal (7) [General Procedure C]. Jones oxidation[21] of 3-(1-naphthyl)propanal (**5**, 130 mg, 0.71 mmol) in acetone (3 mL) gave 3-(1-naphthyl)propanoic acid (124 mg, 88%) as a light yellow solid: ^{1}H NMR δ 2.83 (2H, t, J = 7.7 Hz), 3.45 (2H, t, J = 8.3 Hz), 7.35−7.60 (4H, m), 7.70−7.80 (1H, m), 7.85−7.92 (1H, m), 8.02−8.10 (1H, m), 10.8−11.1 (1H, br).

3-(1-Naphthyl)propanoic acid (95 mg, 0.48 mmol) in $SOCl_2$ (283 mg, 5.0 mmol) was refluxed for 2 h under an N_2 atmosphere, the excess $SOCl_2$ was then removed under reduced pressure, and the crude product Kugelrohr-distilled to give 3-(1-naphthyl)propanoyl chloride as a colorless oil. This was dissolved immediately in Et_2O (1.0 mL) and added dropwise at 0 °C to a solution of CH_2N_2 prepared from Diazald (520 mg, 2.4 mmol, 5.0 mol equiv) in Et_2O (6.5 mL), and the reaction mixture was then stirred at 20 °C for 3 h. The reaction mixture was then concentrated under reduced pressure, and the crude product purified by radial TLC (Chromatotron, hexanes/EtOAc, 90/10) to give 1-diazo-4-(1-naphthyl)butan-2-one (78 mg, 73% from acid) as a yellow oil: IR (cm^{-1}) 1645; ^{1}H NMR δ 2.71 (2H, 7, J = 7.0 Hz), 3.40 (2H, t, J = 8.1 Hz), 5.11 (1H, s), 7.25−7.55 (4H, m), 7.65−7.89 (2H, m), 7.99 (1H, d, J = 7.2 Hz); ^{13}C NMR δ 27.8, 41.4, 54.6, 123.3, 125.3, 125.5, 125.8, 126.0, 127.0, 128.8, 131.5, 133.8, 136.6, 193.8.

To 1-diazo-4-(1-naphthyl)butan-2-one (75 mg, 0.33 mmol) in MeOH (2.5 mL) at 60 °C was added a catalytic amount of Ag_2O. After N_2 evolution ceased (5 min), the reaction mixture was stirred for an additional 30 min at 60 °C, Norit added, and the reaction mixture filtered, concentrated under reduced pressure, and purified by radial TLC (Chromatotron, hexanes) to give methyl 4-(1-naphthyl)butanoate (67 mg, 89%) as a colorless oil: IR (cm^{-1}) 1736; ^{1}H NMR δ 2.07 (2H, q, J = 7.6 Hz), 2.40 (2H, t, J = 7.3 Hz), 3.10 (2H, t, J = 7.3 Hz), 3.66 (3H, s), 7.31−7.55 (4H, m), 7.71 (1H, d, J = 8.4 Hz), 7.80−7.89 (1H, m), 8.06 (1H, d, J = 9.0 Hz); ^{13}C NMR δ 25.7, 32.2, 33.6, 51.4, 123.7, 125.4, 125.5, 125.8, 126.1, 126.8, 128.7, 131.8, 133.9, 137.4, 173.8.

Using general procedure B above, methyl 4-(1-naphthyl)butanoate (63 mg, 0.28 mmol, 1.0 mol equiv) and $LiAlH_4$ (6.7 mg, 0.15 mmol, 2.2 H^- mol equiv) gave 4-(1-naphthyl)butan-1-ol (50 mg, 91%) as a colorless oil: IR (cm^{-1}) 3600−3200 (br); ^{1}H NMR δ 1.25 (1H, s), 1.65−1.95 (4H, m), 3.12 (2H, t, J = 7.0 Hz), 3.65−3.75 (2H, m), 7.30−7.55 (4H, m), 7.72 (1H, d, J = 8.1 Hz), 7.82−7.90 (1H, m), 8.01−8.10 (1H, m).

4-(1-Naphthyl)butan-1-ol (49 mg, 0.25 mmol, 1.0 mol equiv), oxalyl chloride (37 mg, 0.29 mmol, 1.2 mol equiv), DMSO (46 mg, 0.59 mmol, 2.4 mol equiv) and Et_3N (124 mg, 1.23 mmol, 5.0 mol equiv) gave 4-(1-naphthyl)butanal[19] (**7**, 37 mg, 77%) as a colorless oil: IR (cm^{-1}) 1726; ^{1}H NMR δ 2.11 (2H, q, J = 7.6 Hz), 2.55 (2H, t, J = 7.1 Hz), 3.13 (2H, t, J = 7.3 Hz), 7.30−7.55 (4H, m), 7.74 (1H, d, J = 8.8 Hz), 7.82−7.89 (1H, m), 8.02−8.11 (1H, m), 9.79 (1H, t, J = 1.5 Hz).

The preparations of aldehydes ***R*-8** and ***S*-8** were carried out in the same manner, as follows.

(4*R*)-4-(1-Naphthyl)pentanal (*R*-8). (3*R*)-3-(1-Naphthyl)butanal (***R*-6**, 105 mg, 0.53 mmol), Jones reagent, and acetone (2 mL) gave (3*R*)-3-(1-naphthyl)butanoic acid (103 mg, 91%) as a light yellow solid: mp 64−67 °C; $[\alpha]^{25}_D$ −4.5° (*c* 0.27, $CHCl_3$); IR (cm^{-1}) 3540−3046 (br), 1707; ^{1}H NMR δ 1.46 (3H, d, J = 6.8 Hz), 2.58−2.75 (1H, m), 2.85−2.98 (1H, m), 4.05−4.25 (1H, m), 7.33−7.60 (4H, m), 7.73 (1H, d, J = 7.7 Hz), 7.82−7.91 (1H, m), 8.16 (1H, d, J = 9.1 Hz), 10.23−11.48 (1H, br); ^{13}C NMR δ 21.1, 30.5, 42.1, 122.3, 122.9, 125.5, 125.6 126.1, 127.0, 129.0, 131.0, 134.0, 141.3, 179.0.

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(3*R*)-3-(1-Naphthyl)butanoic acid (41 mg, 0.19 mmol, 1.0 mol equiv) and $SOCl_2$ (164 mg, 1.38 mmol, 7.3 mol equiv) gave (3*R*)-3-(1-naphthyl)butanoyl chloride as a colorless oil, which on treatment with ethereal CH_2N_2 (large excess) gave (4*R*)-1-diazo-4-(1-naphthyl)pentan-2-one (34 mg, 76% from acid) as a yellow oil: $[\alpha]^{23}_D$ +1.5° (*c* 0.20, CH_2Cl_2); IR (cm^{-1}) 1635; ^1H NMR δ 1.44 (3H, d, J = 6.8 Hz), 2.52−2.68 (1H, m), 2.82 (1H, d of d J = 15.0, 5.1 Hz), 4.22 (1H, se, J = 7.2 Hz), 5.15 (1H, s), 7.33−7.60 (4H, m), 7.72 (1H, d, J = 7.4 Hz), 7.82−7.90 (1H, m), 8.18 (1H, d, J = 7.7 Hz); ^{13}C NMR δ 21.0, 30.7, 48.8, 55.1, 122.4, 123.0, 125.4, 125.5, 126.1, 126.9, 128.9, 131.1, 133.9, 141.8, 193.6.

(4*R*)-1-Diazo-4-(1-naphthyl)pentan-2-one (30 mg, 0.126 mmol), Ag_2O (catalytic amount), and MeOH (1.0 mL) gave methyl (4*R*)-4-(1-naphthyl)pentanoate[22,23] (26 mg, 87%) as a colorless oil: $[\alpha]^{25}_D$ +20.5° (*c* 0.34, CH_2Cl_2); IR (cm^{-1}) 1736; ^1H NMR δ 1.40 (3H, d, J = 6.9 Hz), 2.00−2.37 (4H, m), 3.62 (3H, s), 3.68 (1H, se, J = 7.0 Hz), 7.38−7.55 (4H, m), 7.72 (1H, d, J = 7.3 Hz), 7.84−7.91 (1H, m), 8.10−8.16 (1H, m); ^{13}C NMR δ 21.5, 32.1, 32.6, 32.9, 51.4, 122.5, 123.0, 125.3, 125.6, 125.8, 126.6, 128.9, 131.7, 134.0, 142.3, 174.1.

Methyl (4*R*)-4-(1-naphthyl)pentanoate (25 mg, 0.103 mmol, 1.0 mol equiv), $LiAlH_4$ (3.0 mg, 0.071 mmol, 2.7 H^- mol equiv), and Et_2O (0.5 mL) gave (4*R*)-4-(1-naphthyl)pentan-1-ol (18 mg, 82%) as a colorless oil: $[\alpha]^{24}_D$ +20.4° (*c* 0.25, $CHCl_3$); IR (cm^{-1}) 3600−3150 (br); ^1H NMR δ 1.32 (1H, s), 1.39 (3H, d, J = 6.9 Hz), 1.50−1.95 (4H, m), 3.53−3.70 (3H, m), 7.38−7.55 (4H, m), 7.68−7.72 (1H, m), 7.82−7.89 (1H, m), 8.07−8.16 (1H, m); ^{13}C NMR δ 21.9, 30.9, 33.4, 33.8, 63.1, 122.5, 123.0, 125.2, 125.6, 125.7, 126.3, 128.9, 131.6, 133.9, 143.3.

(4*R*)-4-(1-Naphthyl)pentan-1-ol (18 mg, 0.084 mmol, 1.0 mol equiv), oxalyl chloride (12.8 mg, 0.101 mmol, 1.2 mol equiv), DMSO (15.4 mg, 0.20 mmol, 2.4 mol equiv), Et_3N (425 mg, 0.42 mmol, 5.0 mol equiv), and CH_2Cl_2 (0.7 mL) gave (4*R*)-4-(1-naphthyl)pentanal (***R*-8**, 16 mg, 89%) as a colorless oil: $[\alpha]^{24}_D$ +25.5° (*c* 0.24, Et_2O); IR (cm^{-1}) 1717; ^1H NMR δ 1.37 (3H, d, J = 6.9 Hz), 1.95−2.15 (2H, m), 2.30−2.41 (2H, m), 3.64 (1H, se, J = 7.0 Hz), 7.30−7.55 (4H, m), 7.70 (1H, d, J = 8.0 Hz), 7.78−7.89 (1H, m), 8.07 (1H, d, J = 7.6 Hz), 9.64 (1H, t, J = 1.4 Hz); ^{13}C NMR δ 21.7, 29.6, 32.7, 41.9, 122.5, 122.9, 125.3, 125.5, 125.8, 126.6, 128.9, 131.6, 133.9, 142.1, 202.1; HRMS, calcd for $M^+C_{15}H_{16}O$ *m/e* 212.1201, found *m/e* 212.1194.

(4*S*)-4-(1-Naphthyl)pentanal (*S*-8). (3*S*)-3-(1-Naphthyl)butanal (***S*-6**, 160 mg, 0.81 mmol), Jones reagent, and acetone (1.2 mL) gave (3*S*)-3-(1-naphthyl)butanoic acid (165 mg, 95%) as a light yellow solid: mp 65−68.5 °C; lit.[24] mp 63−68 °C; $[\alpha]^{25}_D$ +4.7° (*c* 0.27, $CHCl_3$); lit.[25] $[\alpha]^{25}_{365}$ +16.6° (*c* 11.0, Me_2CO), spectroscopically identical to the *R*-enantiomer.

(3*S*)-3-(1-Naphthyl)butanoic acid (160 mg, 0.75 mmol, 1.0 mol equiv) and $SOCl_2$ (656 mg, 5.51 mmol, 7.4 mol equiv) gave (3*S*)-3-(1-naphthyl)butanoyl chloride as a colorless oil which on treatment with ethereal CH_2N_2 (large excess) gave (4*S*)-1-diazo-4-(1-naphthyl)pentan-2-one (143 mg, 81% from acid) as a yellow oil: $[\alpha]^{25}_D$ −2.4° (*c* 0.20, CH_2Cl_2), spectroscopically identical to the *R*-enantiomer.

(4*S*)-1-Diazo-4-(1-naphthyl)pentan-2-one (140 mg, 0.59 mmol, Ag_2O (catalytic amount), and MeOH (4.0 mL) gave methyl (4*S*)-4-(1-naphthyl)pentanoate (134 mg, 94%) as a colorless oil: $[\alpha]^{25}_D$ −19.6° (*c* 0.45, CH_2Cl_2), spectroscopically identical to the *R*-enantiomer.

Methyl (4*S*)-4-(1-naphthyl)pentanoate (130 mg, 0.54 mmol, 1.0 mol equiv), $LiAlH_4$ (13.0 mg, 0.30 mmol, 2.3 H^- mol equiv), and Et_2O (1.0 mL) gave (4*S*)-4-(1-naphthyl)pentan-1-ol (102 mg, 89%) as a colorless oil: $[\alpha]^{24}_D$ −20.9° (*c* 0.46, $CHCl_3$), spectroscopically identical to the *R*-enantiomer.

(4*S*)-4-(1-Naphthyl)pentan-1-ol (95 mg, 0.44 mmol, 1.0 mol equiv), oxalyl chloride (68 mg, 0.53 mmol, 1.2 mol equiv), DMSO (84 mg, 1.07 mmol, 2.4 mol equiv), Et_3N (225 mg, 2.2 mmol, 5.0 mol equiv), and CH_2Cl_2 (3.5 mL) gave (4*S*)-4-(1-naphthyl)pentanal (***S*-8**, 86 mg, 91%) as a colorless oil: $[\alpha]^{25}_D$ −24.7° (*c* 0.30, Et_2O), spectroscopically identical to the *R*-enantiomer. HRMS, calcd for M^+ $C_{15}H_{16}O$ *m/e* 212.1201, found *m/e* 212.1206.

2-Naphthyl Series. 3-(2-Naphthyl)propanal (9). Using general procedure A, 2-naphthaldehyde (3.60 g, 23 mmol, 1.0 mol equiv), and *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidine)acetamide (16.8 g, 46.0 mmol, 2.0 mol equiv) gave *N*-methoxy-*N*-methyl-3-(2-naphthyl)-prop-2-enamide (5.25 g, 95%) as a white solid: mp 85−86 °C; IR (cm^{-1}) 1654, 1613; ^1H NMR ($CDCl_3$) δ 3.34 (3H, s), 3.81 (3H, s), 7.15 (1H, d, J = 14.5 Hz), 7.45−7.55 (2H, m), 7.70−8.00 (6H, m).

N-Methoxy-*N*-methyl-3-(2-naphthyl)prop-2-enamide (564 mg, 2.34 mmol) and 10% Pd/C (20 mg) gave *N*-methoxy-*N*-methyl-3-(2-naphthyl)propanamide (544 mg, 96%) as a colorless oil: IR (cm^{-1}) 1662, 1603; ^1H NMR ($CDCl_3$) δ 2.83 (2H, t, J = 8.1 Hz), 3.13 (2H, t, J = 8.4 Hz), 3.19 (3H, s), 3.61 (3H, s), 7.35−7.50 (3H, m), 7.68 (1H, s), 7.75−7.85 (3H, m).

N-Methoxy-*N*-methyl-3-(2-naphthyl)propanamide (237 mg, 0.97 mmol, 1.0 mol equiv) and $LiAlH_4$ (47 mg, 1,17 mmol, 1.2 mol equiv) gave 3-(2-naphthyl)propanal[25] (**9**, 158 mg, 89%) as white crystals, mp 41.5−42.3 °C; IR (cm^{-1}) 1722; ^1H NMR ($CDCl_3$) δ 2.87 (2H, t, J = 7.9 Hz), 3.13 (2H, t, J = 7.7 Hz), 7.28−7.50 (3H, m), 7.63 (1H, s), 7.73−7.85 (3H, m), 9.86 (1H, t, J = 1.4 Hz).

(3*R*)- and (3*S*)-3-(2-Naphthyl)butanal (*R*-10 and *S*-10). To a slurry of NaH (0.50 g, 20.8 mmol, 1.04 mol equiv) in 1,2-dimethoxyethane (35 mL) was added dropwise triethyl phosphonoacetate (4.5 g, 20.0 mmol, 1.0 mol equiv) at 20 °C under N_2. The reaction mixture was stirred for 1 h until gas evolution had ceased. To this yellow solution was added dropwise a solution of 2-acetonaphthone (3.4 g, 20.0 mmol, 1.0 mol equiv) in 1,2-dimethoxyethane (5 mL), during the addition the temperature at <25 °C. The reaction mixture was then stirred for 30 min at 20 °C and then quenched with water (50 mL), the organic layer separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*, and the crude product purified by column chromatography on Si gel (hexanes/EtOAc, 90/10 elution) to give ethyl-3-(2-naphthyl)but-2-enoate (3.5 g, 73%) as a colorless oil: IR (cm^{-1}) 1709; ^1H NMR δ 1.33 (3H, t, J = 7.2 Hz), 2.68 (3H, s), 4.24 (2H, q, J = 7.1 Hz), 6.28 (1H, s), 7.40−7.60 (3H, m), 7.75−7.95 (4H, m); ^{13}C NMR δ 14.3, 17.8, 59.8, 117.5, 123.9, 125.9, 126.4, 126.6, 127.5, 128.1, 128.4, 133.1, 133.4, 139.3, 155.1, 166.8.

To ethyl-3-(2-naphthyl)but-2-enoate (1.36 g, 2.1 mmol) in EtOAc (21 mL) was added 10% Pd/C (52 mg), and the reaction mixture stirred under H_2 (1atm) for 15 h at 20 °C. The reaction mixture was filtered through Celite and then concentrated *in vacuo* to give (±)-ethyl-3-(2-naphthyl)butanoate (1.36 g, 99%) as a colorless oil: IR (cm^{-1}) 1736; ^1H NMR δ 1.16 (3H, t, J = 7.1 Hz), 1.39 (3H, d, J = 7.0 Hz), 2.56−2.78 (2H, m), 3.46 (1H, hex, J = 7.3 Hz), 4.07 (2H, q, J = 7.2 Hz), 7.35−7.50 (3H, m), 7.66 (1H, s), 7.75−7.85 (3H, m); ^{13}C NMR δ 14.1, 21.7, 36.6, 42.8, 60.2, 124.9, 125.3, 125.4, 125.9, 127.5, 127.6, 128.1, 132.3, 133.5, 143.1, 172.2.

The subsequent reduction and oxidation reactions were carried by general procedure B as follows: (±)-Ethyl-3-(2-naphthyl)butanoate (1.0 g, 4.13 mmol, 1.0 mol equiv) and $LiAlH_4$ (100 mg, 2.27 mmol, 2.2 H^- mol equiv) gave (±)-3-(2-naphthyl)butan-1-ol (808 mg, 98%) as a colorless oil: ^1H NMR δ 1.32 (3H, d, J = 7.0 Hz), 1.65 (1H, s), 1.90 (2H, q, J = 6.8 Hz), 3.02 (1H, se, J = 7.1 Hz), 3.45−3.60 (2H, m), 7.30−7.50 (3H, m), 7.60 (1H, s), 7.70−7.85 (3H, m); ^{13}C NMR δ 22.3, 36.5, 40.7, 61.0, 125.1, 125.2, 125.5, 125.9, 127.4, 127.5, 128.0, 132.2, 133.6, 144.2.

(±)-3-(2-Naphthyl)butan-1-ol (700 mg, 3.5 mmol, 1.0 mol equiv), oxalyl chloride (533 mg, 4.2 mmol, 1.2 mol equiv), DMSO (656 mg, 8.4 mmol, 2.4 mol equiv) and Et_3N (1.77 g, 17.5 mmol, 5.0 mol equiv) gave (±)-3-(2-naphthyl)butanal ((±)-**10**, 606 mg, 87%) as a colorless oil: IR (cm^{-1}) 1719; ^1H NMR δ 1.40 (3H, d, J = 7.0 Hz), 2.65−2.95 (2H, m), 3.52 (1H, se, J = 7.3 Hz), 7.35−7.50 (3H, m), 7.64 (1H, s), 7.75−7.85 (3H, m), 9.73 (1H, t, J = 1.9 Hz); ^{13}C NMR δ 22.1, 34.4, 51.6, 125.0, 125.4, 125.5, 126.1, 127.5, 127.6, 128.4, 132.3, 133.5, 142.8, 201.7.

(22) Since the analogous homologation method, which applied to the chiral aldehydes with phenyl groups, proceeded without any racemizations,[7,23] the enantiomeric excesses of the homologated chiral aldehydes ***R*-4**, ***S*-4**, ***R*-8**, and ***S*-8** were deemed to be >95% *ee*. This assumption was supported by the absolute values of optical rotation of each chiral aldehyde pair ***R*-4**, ***S*-4** and ***R*-8**, ***S*-8** being identical, within experimental error.

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The resolution of 3-(2-naphthyl)butanal ((±)-**10**) was carried out by using general procedure C as follows: (±)-3-(2-Naphthyl)butanal ((±)-**10**, 576 mg, 2.91 mmol, 1.0 mol equiv), (1*R*,2*R*)-*N*,*N*′-dimethyl-1,2-diphenylethylenediamine (698 mg, 2.91 mmol, 1.0 mol equiv) and molecular sieves gave *R*,*R*,*R*-*N*,*N*′-dimethyl-4,5-diphenyl-2-[2-(2-naphthyl)propyl]-1,3-imidazolidine (less polar, 560 mg, 92%, >95% *de*) [[α]$^{25}_{D}$ −43.0° (*c* 0.44, $CHCl_3$); IR (cm^{-1}) 3043, 2956, 2787, 1451; ^{1}H NMR δ 1.46 (3H, d, *J* = 7.0 Hz), 1.85−2.00 (1H, m), 2.22 (3H, s), 2.25−2.40 (1H, m), 2.32 (3H, s), 3.33−3.50 (1H, m), 3.55 (2H, d of d, *J* = 29.3, 8.4 Hz), 3.75−3.85 (1H, m), 7.10−7.30 (10H, m), 7.40−7.53 (3H, m), 7.73 (1H, s), 7.78−7.89 (3H, m); ^{13}C NMR δ 24.6, 34.8, 36.2, 38.1, 41.5, 76.1, 79.9, 83.2, 125.2, 125.4, 125.9, 127.1, 127.4, 127.6, 127.9, 128.0, 128.2, 132.3, 133.8, 140.1, 141.1, 145.0] and *R*,*R*,*S*-*N*,*N*′-dimethyl-4,5-diphenyl-2-[2-(2-naphthyl)propyl]-1,3-imidazolidine (more polar, 560 mg, 92%, >95% *de*) as a viscous oil: [[α]$^{25}_{D}$ +20.0° (*c* 0.44, $CHCl_3$); IR (cm^{-1}) 3041, 2962, 2780, 1456; ^{1}H NMR δ 1.47 (3H, d, *J* = 6.9 Hz), 2.01−2.11 (2H, m), 2.28 (3H, s), 2.32 (3H, s), 3.30−3.45 (1H, m), 3.56 (2H, d of d, *J* = 58.9, 8.1 Hz), 3.75 (1H, t, *J* = 6.2), 7.05−7.30 (10H, m), 7.40−7.55 (3H, m), 7.75−7.90 (4H, m); ^{13}C NMR δ 22.3, 35.5, 36.2, 39.3, 40.2, 76.2, 79.6, 83.2, 125.2, 125.4, 125.8, 125.9, 127.2, 127.5, 127.6, 127.8, 128.0, 132.3, 133.8, 140.4, 140.9, 145.5].

R,*R*,*R*-*N*,*N*′-Dimethyl-4,5-diphenyl-2-[2-(2-naphthyl)propyl]-1,3-imidazolidine (378 mg, 0.93 mmol), Si gel (4.6 g), and 15% H_2SO_4 (460 μL) gave (3*R*)-3-(2-naphthyl)butanal (***R*-10**, 162 mg, 89%, >95% *ee*) as a colorless oil: [α]$^{25}_{D}$ −41.8° (*c* 0.3, Et_2O), spectroscopically identical to the racemate ((±)-**10**). HRMS, calcd for M^+ $C_{14}H_{14}O$ *m/e* 198.1044, found *m/e* 198.1043.

R,*R*,*S*-*N*,*N*′-dimethyl-4,5-diphenyl-2-[2-(2-naphthyl)propyl]-1,3-imidazolidine (390 mg, 0.93 mmol), Si gel (4.6 g) and 15% H_2SO_4 (460 μL) yielded (3*S*)-3-(2-naphthyl)butanal (***S*-10**, 162 mg, 88%, >95% *ee*) as a colorless oil: [α]$^{25}_{D}$ +40.4° (*c* 0.2, Et_2O), spectroscopically identical to the racemate ((±)-**10**); HRMS, calcd for M^+ $C_{14}H_{14}O$ *m/e* 198.1044, found *m/e* 198.1037.

4-(2-Naphthyl)butanal (11). Using general procedure C, 3-(2-naphthyl)propanal (**9**, 133 mg, 0.72 mmol), Jones reagent, and acetone (3 mL) gave 3-(2-naphthyl)propanoic acid (132 mg, 92%) as a light yellow solid: ^{1}H NMR δ 2.78 (2H, t, *J* = 7.2 Hz), 3.14 (2H, t, *J* = 7.1 Hz), 7.30−7.60 (3H, m), 7.66 (1H, s), 7.73−7.85 (3H, m), 9.83−10.41 (1H, br).

3-(2-Naphthyl)propanoic acid (97 mg, 0.48 mmol, 1.0 mol equiv) and $SOCl_2$ (490 mg, 4.13 mmol, 8.5 mol equiv) gave 3-(2-naphthyl)-propanoyl chloride as a colorless oil which with ethereal CH_2N_2 (large excess) gave 1-diazo-4-(2-naphthyl)butan-2-one (52 mg, 48% from acid) as a yellow solid: IR (cm^{-1}) 1638; ^{1}H NMR δ 2.70 (2H, t, *J* = 7.5 Hz), 3.11 (2H, t, *J* = 7.3 Hz), 5.15 (1H, s), 7.30−7.57 (3H, m), 7.62 (1H, s), 7.70−7.91 (3H, m); ^{13}C NMR δ 31.6, 42.6, 55.2, 125.9, 126.6, 127.0, 127.5, 128.0, 128.1, 128.7, 132.6, 134.1, 138.6, 194.4.

1-Diazo-4-(2-naphthyl)butan-2-one (30 mg, 0.13 mmol), Ag_2O (catalytic amount) and MeOH (1.0 mL) yielded methyl 4-(2-naphthyl)-butanoate (25 mg, 83%) as a colorless oil: IR (cm^{-1}) 1731; ^{1}H NMR δ 2.05 (2H, q, *J* = 7.2 Hz), 2.37 (2H, t, *J* = 7.1 Hz), 2.82 (2H, t, *J* = 7.3 Hz), 3.66 (3H, s), 7.30−7.90 (7H, m).

Methyl 4-(2-naphthyl)butanoate (22 mg, 0.096 mmol, 1.0 mol equiv) and $LiAlH_4$ (3.0 mg, 0.072 mmol, 3.0 H^- mol equiv) gave 4-(2-naphthyl)butan-1-ol (19 mg, 94%): IR (cm^{-1}) 3600−3200 (br); ^{1}H NMR δ 1.32 (1H, s), 1.60−1.87 (4H, m), 2.81 (2H, t, *J* = 7.2 Hz), 3.67 (2H, t, *J* = 6.3 Hz), 7.30−7.50 (3H, m), 7.62 (1H, s), 7.73−7.85 (3H, m).

4-(2-Naphthyl)butan-1-ol (18 mg, 0.090 mmol, 1.0 mol equiv), oxalyl chloride (18 mg, 0.14 mmol, 1.5 mol equiv), DMSO (21 mg, 0.27 mmol, 3.0 mol equiv), Et_3N (46 mg, 0.45 mmol, 5.0 mol equiv), and CH_2Cl_2 (0.7 mL) gave 4-(2-naphthyl)butanal[25] (**11**, 16 mg, 89%) as a colorless oil: IR (cm^{-1}) 1721; ^{1}H NMR δ 2.05 (2H, q, *J* = 7.4 Hz), 2.49 (2H, t, *J* = 7.3 Hz), 2.82 (2H, t, *J* = 7.3 Hz), 7.30−7.52 (3H, m), 7.61 (1H, s), 7.72−7.88 (3H, m), 9.77 (1H, t, *J* = 1.5 Hz).

(4*R*)-4-(2-Naphthyl)pentanal (*R*-12). (3*R*)-3-(2-Naphthyl)butanal (***R*-10**, 130 mg, 0.66 mmol), Jones reagent, and acetone (2.5 mL) gave (3*R*)-3-(2-naphthyl)butanoic acid (130 mg, 93%) as a light yellow solid: mp 68.0−69.5 °C; lit.[25] 67−69 °C; [α]$^{25}_{D}$ −37.5° (*c* 0.30, EtOH); lit.[25] [α]$^{25}_{D}$ −35.0° (*c* 0.93, EtOH); IR (cm^{-1}) 3540−3020 (br), 1697; ^{1}H NMR δ 1.45 (3H, d, *J* = 6.9 Hz), 2.55−2.82 (2H, m), 3.50 (1H, se, *J* = 7.7 Hz), 7.30−7.50 (3H, m), 7.52 (1H, s), 7.72−7.85 (3H, m), 10.00−10.50 (1H, br); ^{13}C NMR δ 21.8, 36.2, 42.4, 124.9, 125.3, 125.4, 126.0, 127.5, 127.6, 128.2, 132.3, 133.5, 142.8, 178.7.

(3*R*)-3-(2-Naphthyl)butanoic acid (120 mg, 0.56 mmol, 1.0 mol equiv) and $SOCl_2$ (490 mg, 4.13 mmol, 7.4 mol equiv) gave (3*R*)-3-(2-naphthyl)butanoyl chloride as a colorless oil which with ethereal CH_2N_2 (large excess) gave (4*R*)-1-diazo-4-(2-naphthyl)pentan-2-one (100 mg, 75% from acid) as a yellow solid: mp 82.0−83.3 °C; [α]$^{23}_{D}$ −153.4° (*c* 0.37, CH_2Cl_2); IR (cm^{-1}) 1645; ^{1}H NMR δ 1.35 (3H, d, *J* = 7.0 Hz), 2.50−2.80 (2H, m), 3.46 (1H, se, *J* = 7.0 Hz), 5.03 (1H, s), 7.30−7.50 (3H, m), 7.63 (1H, s), 7.72−7.83 (3H, m); ^{13}C NMR δ 21.7, 36.6, 49.0, 55.0, 124.9, 125.2, 125.3, 125.9, 127.5, 127.6, 128.2, 132.2, 133.4, 143.1, 193.5.

(4*R*)-1-Diazo-4-(2-naphthyl)pentan-2-one (93 mg, 0.39 mmol), Ag_2O (catalytic amount), and MeOH (3.0 mL) gave methyl (4*R*)-4-(2-naphthyl)pentanoate (84 mg, 89%) as a colorless oil: [α]$^{25}_{D}$ −27.1° (*c* 0.33, CH_2Cl_2); IR (cm^{-1}) 1731; ^{1}H NMR δ 1.34 (3H, d, *J* = 6.9 Hz), 1.92−2.10 (2H, m), 2.17−2.30 (2H, m), 2.87 (1H, se, *J* = 7.2 Hz), 3.58 (3H, m), 7.30−7.50 (3H, m), 7.59 (1H, s), 7.75−7.87 (3H, m); ^{13}C NMR δ 22.0, 32.2, 33.0, 39.5, 51.3, 125.2, 125.3, 125.4, 125.8, 127.5, 127.6, 128.1, 132.3, 133.6, 143.6, 173.9.

Methyl (4*R*)-4-(2-naphthyl)pentanoate (82 mg, 0.34 mmol, 1.0 mol equiv), $LiAlH_4$ (11.0 mg, 0.26 mmol, 3.0 H^- mol equiv), and Et_2O (1.5 mL) gave (4*R*)-4-(2-naphthyl)pentan-1-ol (70 mg, 95%) as a colorless oil: [α]$^{24}_{D}$ −19.4° (*c* 0.31, $CHCl_3$); IR (cm^{-1}) 3600−3150 (br); ^{1}H NMR δ 1.32 (2H, d, *J* = 6.9 Hz), 1.40−1.80 (5H, m), 2.84 (1H, se, *J* = 7.0 Hz), 3.53 (2H, t, *J* = 7.1 Hz), 7.28−7.45 (3H, m), 7.59 (1H, s), 7.72−7.82 (3H, m), ^{13}C NMR δ 22.3, 30.9, 34.2, 39.9, 62.9, 125.1, 125.2, 125.6, 125.8, 127.5, 127.6, 127.9, 132.2, 133.6, 144.7.

(4*R*)-4-(2-Naphthyl)pentan-1-ol (67 mg, 0.31 mmol, 1.0 mol equiv), oxalyl chloride (48 mg, 0.38 mmol, 1.2 mol equiv), DMSO (59 mg, 0.75 mmol, 2.4 mol equiv), Et_3N (158 mg, 1.57 mmol, 5.0 mol equiv), and CH_2Cl_2 (0.7 mL) gave (4*R*)-4-(2-naphthyl)pentanal (***R*-12**, 59 mg, 89%) as a colorless oil: [α]$^{24}_{D}$ −20.7° (*c* 0.57, Et_2O); IR (cm^{-1}) 1712; ^{1}H NMR δ 1.35 (3H, d, *J* = 6.9 Hz), 1.90−2.10 (2H, m), 2.27−2.40 (2H, m), 2.88 (1H, se, *J* = 6.8 Hz), 7.28−7.50 (3H, m), 7.58 (1H, s), 7.75−7.85 (3H, m), 9.66 (1H, t, *J* = 1.5 Hz); ^{13}C NMR δ 22.2, 30.1, 39.4, 42.1, 125.2, 125.3, 125.4, 126.0, 127.5, 127.6, 128.2, 132.3, 133.5, 143.4, 202.2; HRMS, calcd for M^+ $C_{15}H_{16}O$ *m/e* 212.1201, found *m/e* 212.1198.

(4*S*)-4-(2-Naphthyl)pentanal (S-12). (3*S*)-3-(2-Naphthyl)butanal (***S*-10**, 127 mg, 0.64 mmol), Jones reagent, and acetone (2.5 mL) gave (3*S*)-3-(2-naphthyl)butanoic acid (125 mg, 91%) as a light yellow solid: mp 67.0−69.0 °C; [α]$^{25}_{D}$ +38.0° (*c* 0.30, EtOH), spectroscopically identical to the *R*-enantiomer.

(3*S*)-3-(2-Naphthyl)butanoic acid (121 mg, 0.59 mmol, 1.0 mol equiv) and $SOCl_2$ (490 mg, 4.13 mmol, 7.0 mol equiv) gave (3*S*)-3-(2-naphthyl)butanoyl chloride as a colorless oil which with ethereal CH_2N_2 (large excess) gave (4*S*)-1-diazo-4-(2-naphthyl)pentan-2-one (94 mg, 67% from acid) as a yellow solid: mp 81.5−82.5 °C; [α]$^{25}_{D}$ +154.0° (*c* 0.32, CH_2Cl_2), spectroscopically identical to the *R*-enantiomer.

(4*S*)-1-Diazo-4-(2-naphthyl)pentan-2-one (90 mg, 0.38 mmol), Ag_2O (catalytic amount), and MeOH (3.0 mL) gave methyl (4*S*)-4-(2-naphthyl)pentanoate (85 mg, 93%) as a colorless oil: [α]$^{25}_{D}$ +25.8° (*c* 0.33, CH_2Cl_2), spectroscopically identical to the *R*-enantiomer.

Methyl (4*S*)-4-(1-naphthyl)pentanoate (80 mg, 0.33 mmol, 1.0 mol equiv), $LiAlH_4$ (10.3 mg, 0.25 mmol, 3.0 H^- mol equiv), and Et_2O (1.5 mL) gave (4*S*)-4-(2-naphthyl)pentan-1-ol (70 mg, 98%) as a colorless oil: [α]$^{24}_{D}$ +19.1° (*c* 0.32, $CHCl_3$), spectroscopically identical to the *R*-enantiomer.

(4*S*)-4-(2-Naphthyl)pentan-1-ol (68 mg, 0.32 mmol, 1.0 mol equiv), oxalyl chloride (53 mg, 0.42 mmol, 1.3 mol equiv), DMSO (65 mg, 0.83 mmol, 2.6 mol equiv), Et_3N (175 mg, 1.73 mmol, 5.0 mol equiv), and CH_2Cl_2 (2.5 mL) gave (4*S*)-4-(2-naphthyl)pentanal (***S*-12**, 63 mg, 93%) as a colorless oil: [α]$^{25}_{D}$ +19.6° (*c* 0.57, Et_2O), spectroscopically identical to the *R*-enantiomer; HRMS, calcd for M^+ $C_{15}H_{16}O$ *m/e* 212.1201, found *m/e* 212.1202.

Enantiomeric Excess Determinations of *R*- and *S*-6, 8, 10, and 12. The same general procedure was applied in each case, as follows: To a solution of *R*- or *S*-aldehyde (1.0 mol equiv) in Et_2O was added

molecular sieves followed by (1*R*,2*R*)-*N*,*N*′-dimethyl-1,2-diphenylethylenediamine (1.3 mol equiv) at 20 °C under N_2. The reaction mixture was stirred for 5 h at 20 °C and then filtered through Celite. The filtrate was concentrated *in vacuo*, and the ^{13}C NMR spectrum of the residue was taken. The integrations of the peaks for the methyl groups at the stereocenters of each aldehyde (e.g., 24.4 ppm for ***R*-6**, 20.5 ppm for ***S*-6**) were used to determine the enantiomeric excesses. In each case, the materials were seen to be enantiomerically pure, within the ±5% confidence limits of the NMR method.

Kinetic Measurements. The enzyme kinetic procedures applied were exactly as described previously,[7] except that 10−40 μL of the inhibitor solutions (0.03−0.08 M in DMSO) were employed. The inhibition constants are recorded in Table 1.

Computational Methods. The protocols for the system setup, docking, and energy minimization of E1 complexes were exactly as described previously.[7] The minimized complexes of CT and SC with ***R*-** and ***S*-6** and **-12** are depicted in Figures 1−4.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of ***R*-6**, ***S*-6**, ***R*-8**, ***S*-8**, ***R*-10**, ***S*-10**, ***R*-12**, and ***S*-12**. (16 pages). See any current masthead page for ordering and Internet access instructions.

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