Synthesis of Quasienantiomeric Fluorous-Tagged Oxazolidinones and Application in Alkylation and *syn*-Aldol Reactions

by

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Abstract

Evans' oxazolidinones are among the most well-established and extensively used chiral auxiliaries for stoichiometric asymmetric methods in total synthesis. The most common applications are α-alkylation and *syn*-aldol reactions, which build either enantiomers or diastereomers containing flexible function groups for further elaboration. Fluorous quasiracemic synthesis involves synthesis of both enantiomers of a target compound in a single synthesis by implementation of a fluorous tagging strategy. Here, two different fluorous-tagged oxazolidinones were synthesized in an efficientt synthetic strategy. Preliminary alkylation and aldol condensation of the fluorous-tagged imides derived from the corresponding oxazolidinones were carried out and compared with the non fluorous-tagged imide in the aspect of yield and diastereomer ratios. The alkylation and aldol reactions of the quasiracemic mixture were conducted and the resultant crude products were subjected to HPLC analysis.

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Chapter 1 Introduction

1.1 Chiral Auxiliaries

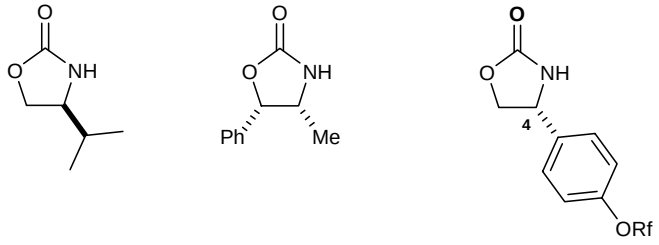
A chiral auxiliary is an optically active chemical compound or unit that is temporarily incorporated into an organic synthesis so that it can transfer chirality, with predictable stereochemistry in newly formed stereocenters. Chiral auxiliaries introduce chirality in otherwise achiral compounds and then in the following reaction step, induce the asymmetric formation of a second stereocenter with steric hindrance as a driving force. After the creation of the second stereocenter, the original auxiliaries can be removed and recycled. Chiral auxiliaries were introduced by E.J. Corey in 1978 with chiral 8-phenylmenthol[1] and by B.M. Trost in 1980 with chiral mandelic acid.[2] The menthol compound is difficult to prepare and an alternative is *trans*-2-phenyl-1-cyclohexanol, introduced by J. K. Whitesell in 1985.[3]

Ideally a stoichiometric chiral auxiliary must be easy to attach efficiently to the substrate, control completely the stereoselectivity in reactions of the attached substrate and be readily removed. If the chiral auxiliary is very inexpensive (e.g. α-methylbenzylamine) it can be destroyed in the cleavage step; however, for most chiral auxiliaries an efficient recycling procedure should be a prerequisite for use.

1.2 Evans' Oxazolidinones

Evans' oxazolidinones (exemplified by **1** and **2**) are among the most well-established and extensively used chiral auxiliaries for stoichiometric asymmetric methods in total synthesis.[4] The most common applications are α-alkylation and *syn*-aldol reactions, which build either enantiomers or diastereomers containing flexible function groups for further elaboration. And the reliable and easily scaleable reaction procedure for these types of transformations contribute to the popularity of Evans' oxazolidinones in organic synthesis.[5] Other applications of Evans' oxazolidinones involving *anti*-aldol reactions, Michael addition, addition to C=O and C=N bonds and cycloaddtion etc. have been also investigated and developed.[5,6] Also a variety of new auxiliaries that evolved from Evans' oxazolidinones, have come forth and been applied in asymmetric synthesis.[5] Removal of the oxazolidinone auxiliaries with no occurrence of racemization or epimerization has been achieved and also the auxiliaries can be efficiently recycled.[5,6]

We designed a pair of derivatives of Evans' oxazolidinones and investigated the reactivity and stereoselection of these derivatives in alkylation and aldol reactions. Compound **3** is one of these derivatives and a perfluorinated group Rf is attached to the oxazolidinone ring by oxyphenyl group. Before the introduction of our studies on these derivatives, I provide an overview of the preparation, *N*-acylation, alkylation, *syn*-aldol reactions and cleavage of Evans' oxazolidinone auxiliaries.



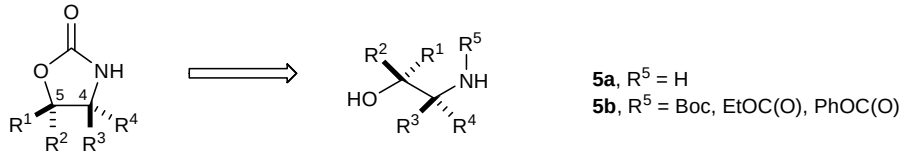
1 2 3

3: Rf group contains perfluorinated groups

1.2.1 Preparation of Oxazolidinones

The general methods to make oxazolidinones **4** with various substituents (R^1, R^2, R^3 and R^4) at C4 and C5 positions start from the corresponding amino alcohols **5** (scheme 1). R^5 can be a proton (**5a**) or an acyl group (**5b**).

Scheme 1 The preparation of oxazolidinones from amino alcohols



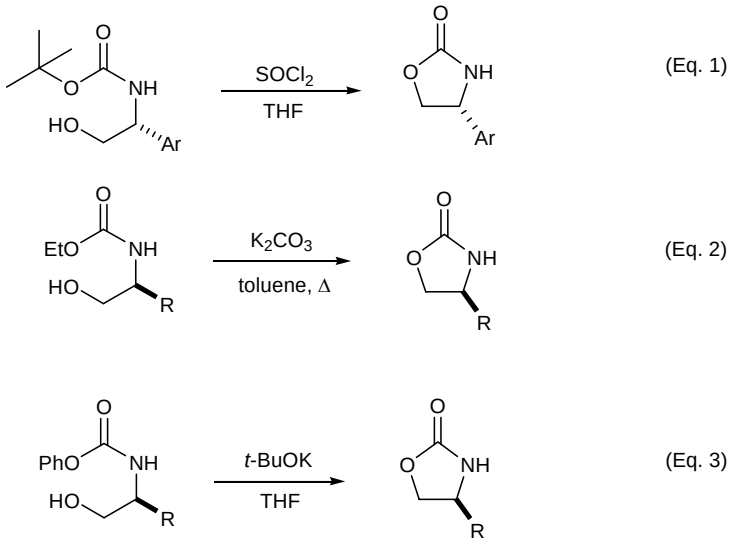
4 5

5a, R^5 = H
5b, R^5 = Boc, EtOC(O), PhOC(O)

In the case of **5a**, phosgene was initially used to combine the amino and alcohol groups by carbonyl group to provide oxazolidinones **4**.[7] Triphosgene often serves as the source of phosgene because it is easier to handle and less dangerous due to its solid state.[8]

The *N*-protected amino alcohol **5b** itself bears the carbonyl group on nitrogen atom, so here an external carbonyl source for the five-membered oxazolidinone ring is unnecessary. The transformation of **5b** into **4** can be conducted in a mild and safe reaction condition by using thionyl chloride ($SOCl_2$, THF, Eq. 1),[9] potassium carboxylate (K_2CO_3, toluene, Eq. 2)[10] or

potassium *t*-butoxide (*t*-BuOK, THF, Eq. 3).[11]



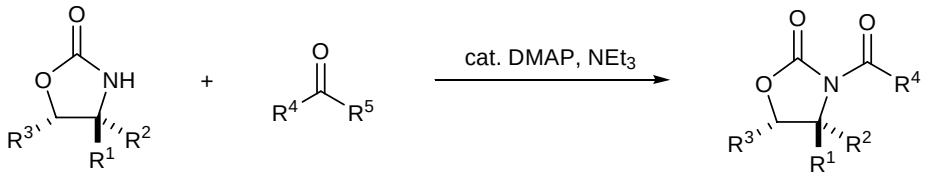
1.2.2 *N*-Acylation Reaction

The first step for oxazolidinone auxiliary to operate in asymmetric synthesis is the attachment of the substrate to the chiral auxiliary, which is typically achieved by an *N*-acylation reaction. Butyllithium and an acid chloride or anhydride (mixed or symmetrical) of the substrate[12] are generally employed, but the excess butyllithium might cause epimerization at the C5 position of the oxazolidinone ring through a dianion intermediate.[13]

A mild, simple and efficient process for the *N*-acylation without inconvenience of epimerization was reported by David Ager and co-workers.[14] This reaction involved treatment of the oxazolidinone with 2-5 mol% DMAP, 1.0 equiv of triethylamine and 1.0-2.0 equiv of acid chloride, mixed or symmetric anhydride of a large variety of substrates at room temperature or at

reflux (scheme 2). This reaction results in a large variety of *N*-acylated oxazolidinone and should extend well to more complex substrates.

Scheme 2 *N-acylation reactions*



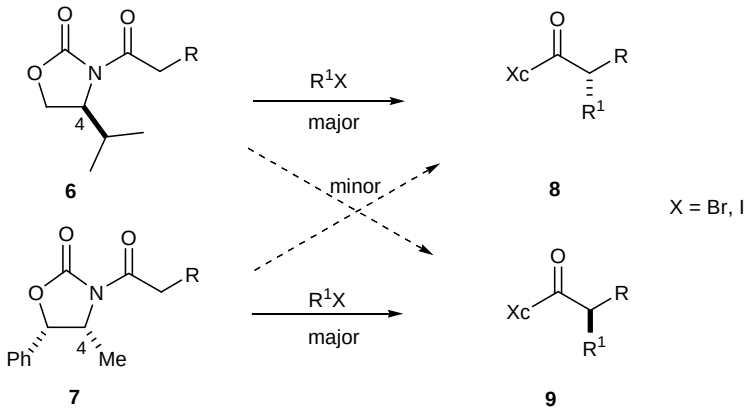
	R^1	R^2	R^3	R^4	R^5
1	Ph	H	H	Me	
2	H	Me	Ph	Et	$OC(O)R^4$,OC(O)Bu-*t*,Cl
3	*t*-Bu	H	H	OBu-*t*	
4	$CH_2C_6H_{11}$-*c*	H	H	C_5H_{11}-*n*	

1.2.3 Alkylation

An intensive investigation of utility of enolates derived from *N*-acylated oxazolidinone in asymmetric alkylation was disclosed in the communication of Evans and co-workers.[15] The general reaction conditions involved treatment of the *N*-acylated oxazolidinone with LDA or NaHMDS in THF at -78 ^oC followed by addition of alkylating agent at 0 ^oC (scheme 3).

As illustrated from their experimental data, the complementary levels of diastereoface selection of alkylation reaction could be deduced from the enolates of **6** and **7** (scheme 3). Less reactive (non-allylic/benzylic) electrophiles require the use of sodium enolates or triflate as leaving group.[15]

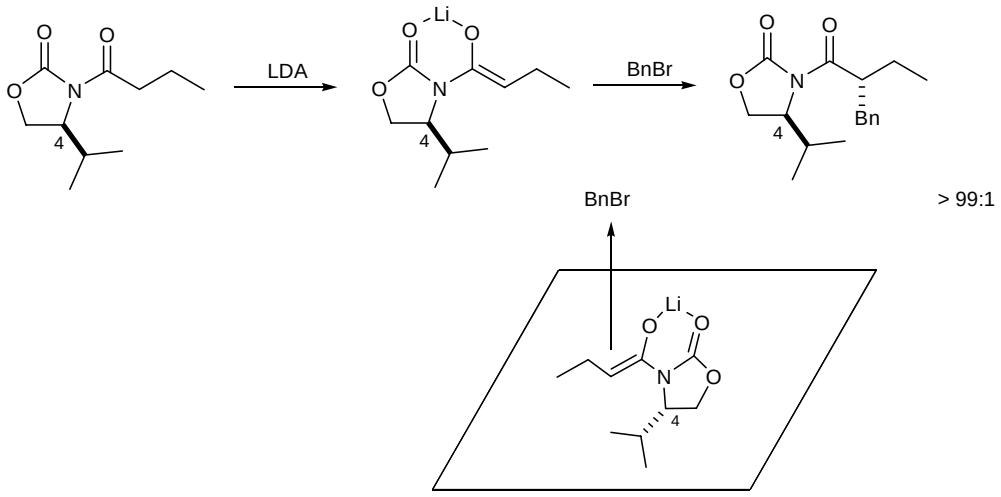
Scheme 3 Alkylation reactions



Evans interpreted that *Z*-enolates were formed with very high selectivity and then the electrophiles tended to attack from the opposite face to the chiral controlling group at C4 position of oxazolidinone ring, which is exemplified in Scheme 4.[15]

The diastereoselection of Evans' oxazolidinone auxiliary in alkylation reactions has been acknowledged in many examples and the stereochemistry of the major product can be reliably assigned by the model in Scheme 4.

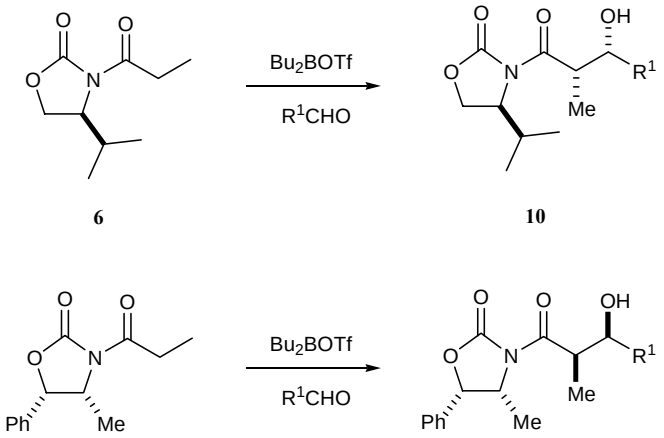
Scheme 4 Diastereoselection of alkylation reactions of Evans' oxazolidinones



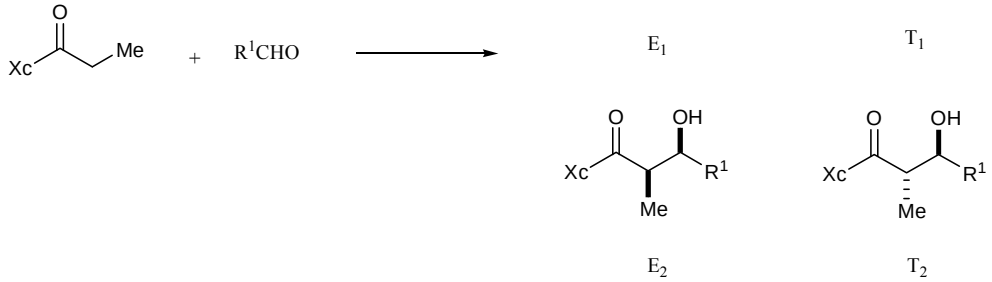
1.2.4 Aldol Condensation

Evans and co-workers used the boron enolates that were derived from the corresponding *N*-propionylimides **6** and **7** in aldol addition (scheme 5). And high enantioselectivity (E_1 vs. E_2 or T_1 vs. T_2) and diastereoselection ($E_1 + E_2$ vs. $T_1 + T_2$) were observed for the aldol reaction (Eq. 4).[16]

Scheme 5 *syn-Aldol reactions of Evans' oxazolidinone*



	R^1	E_1:E_2	yield, %
6	Me_2CH	497:1	**10**, 78
7	Me_2CH	<1:500	**11**, 91
6	C_6H_5CHO	>500:1	**10**, 88
7	C_6H_5CHO	<1:500	**11**, 89

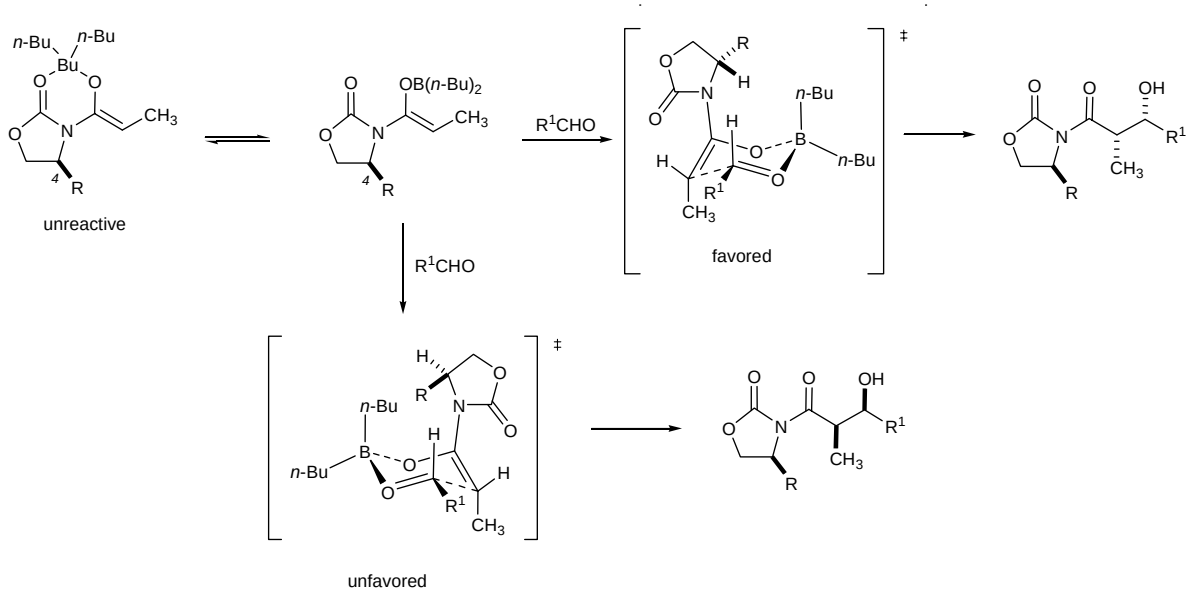


(Eq. 4)

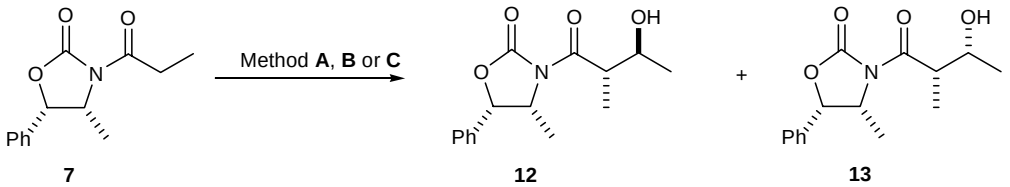
It was observed that both **6** and **7** formed the (*Z*)-enolates (*Z*:*E* ≥ 100) with high

stereoselectivity when treated with either LDA (THF, -78 ^{o}C) or Bu_2BOTf. But high stereoselectivity in the aldol reaction was obtained for boron enolate and low stereoselection was observed for lithium enolate.[13] Evans suggested that boron enolates undergo aldol reactions via a chair-like cyclohexane transition state: R group is apart from the enolate π-face to minimize dipole-dipole interaction within the imide; R^1 group in pseudo-equatorial position to avoid the steric interaction with the butyl ligand on boron (scheme 6).[17] On the contrary, lithium enolates may go through the cyclohexane transition state in either way where R^1 group can be in either pseudo-equatorial or -axial position since lithium metal center does not bear exo-ligands.

Scheme 6 Diastereoselection of *syn*-aldol reactions of Evans' oxazolidinones



The amount of Bu_2BOTf is important to the *syn*-diastereoselectivity of these aldol reactions. Heathcock and co-workers reported their observation of *anti*-dominated product **12** by treatment of **7** with 2 equiv of Bu_2BOTf.[18]



7 **12** **13**

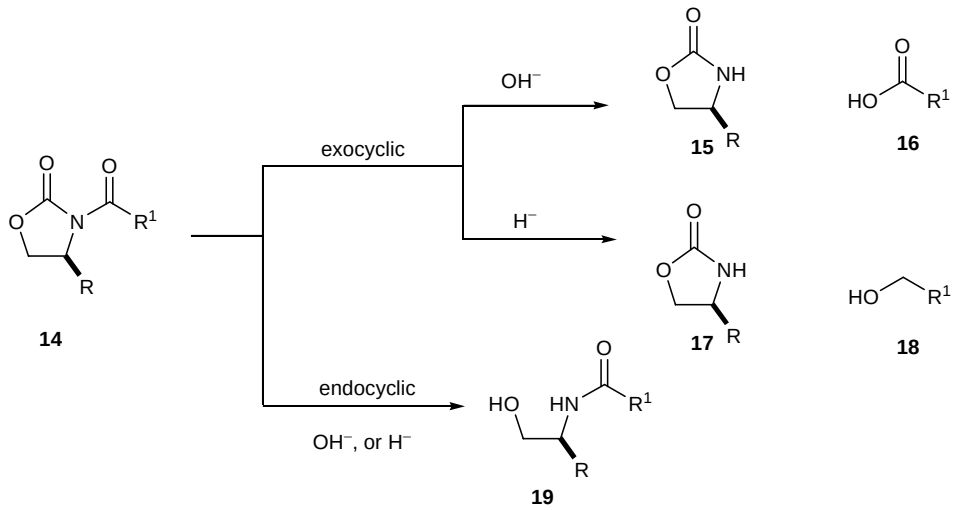
	Bu_2BOTf (equiv)	Hünigs Base (equiv)	CH_3CHO (equiv)	R_2AlCl (equiv)	**12**:**13**	**12** (Yield, %)
A	1.1	1.15	2.0	3.0	2.5:1	60
B	2.0	1.15	1.25	-	7:1	50-70
C	2.0	1.15	1.25	-	7:1	79

There have been many other applications of Evans' oxazolidinones, including highly diastereoselective asymmetric acylation reactions,[19] asymmetric hydroxylation,[20] diastereoselective aldol condensation of β-keto imide,[21] Michael addition,[22] addition to C=O and C=N bonds,[20] cycloaddtion, etc.[23]

1.2.5 Cleavage of the Oxazolidinone Auxiliaries

Two types of cleavage of oxazolidinones have been observed: exocyclic cleavage and endocyclic cleavage. The exocyclic cleavage is usually desired but endocyclic cleavage occurs when the oxazolidinone derived carboximides **14** bear bulky R^1 group (scheme 8).[24]

Scheme 7 Cleavage of Evans' oxazolidinone auxiliaries



Lithium hydroxide is the common reagent for the transformation of **14** into **15** and **16**, but sometimes undesired endocyclic cleavage occurs. This can be avoided by using lithium hydroperoxide instead.[25] The cleavage by using lithium boron (or aluminum) hydride reductively removes the auxiliary to form the alcohol **18**.[26] These two methods are among the most common ones to remove the oxazolidinone **15** with no racemization or epimerization.

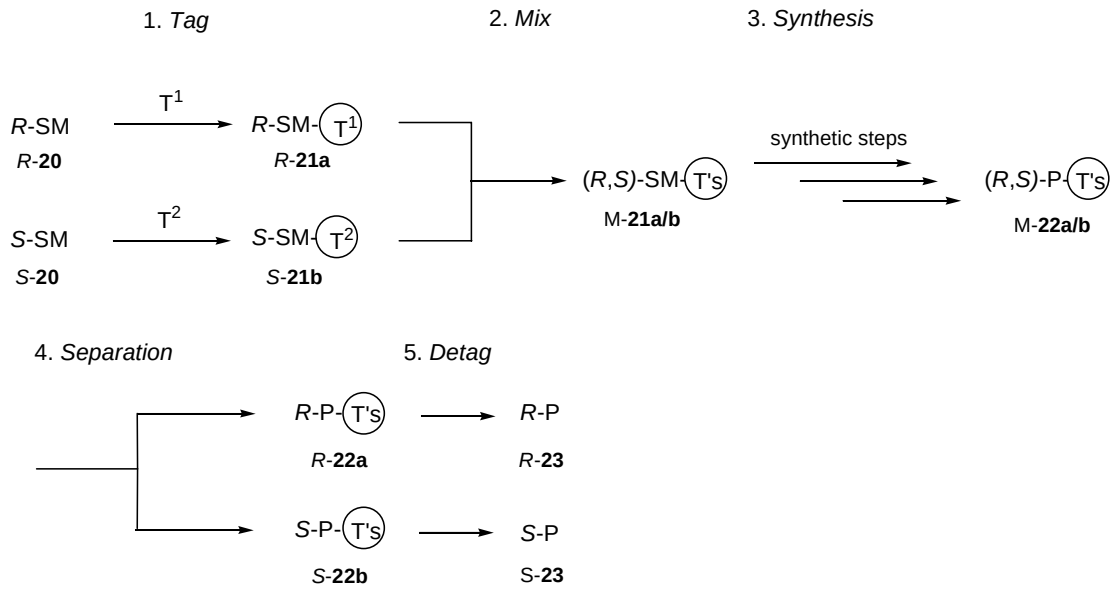
All the above studies concerning Evans' oxazolidinones have already been investigated well, applied widely in organic synthesis and been the basis of the studies on the derivatives of Evans' oxazolidinones, such as superquat auxiliaries,[27] polymer-attached oxazolidinones,[28] and also the perfluorinated oxazolidinone derivatives designed by us. The perfluorinated group plays a crucial role in the application of our oxazolidinone derivatives to quasiracemic synthesis that will be introduced in the following.

1.3 Quasiracemic Synthesis

Fluorous quasiracemic synthesis was introduced by Curran[30] and it involves synthesis of both enantiomers of a target compound in a single synthesis by implementation of a fluorous tagging strategy.

The strategy of fluorous quasiracemic synthesis is shown in Scheme 9. Enantiomers *R*-**20** and *S*-**20** are attached with different fluorous groups T^1 and T^2 that contain perfluoroalkyl groups as tags to provide *R*-**21a** and *S*-**21b**. T^1 differs from T^2 only in fluorine content, so *R*-**21a** and *S*-**21b** are quasienantiomers. *R*-**21a** and *S*-**21b** are mixed to make a quasiracemic mixture M-**21a/b**, which is then taken through a series of steps to make a final tagged product mixture M-**22a/b**. All the tagged molecules are typically soluble in common organic solvents.[30]

Scheme 8 Strategy of quasiracemic synthesis

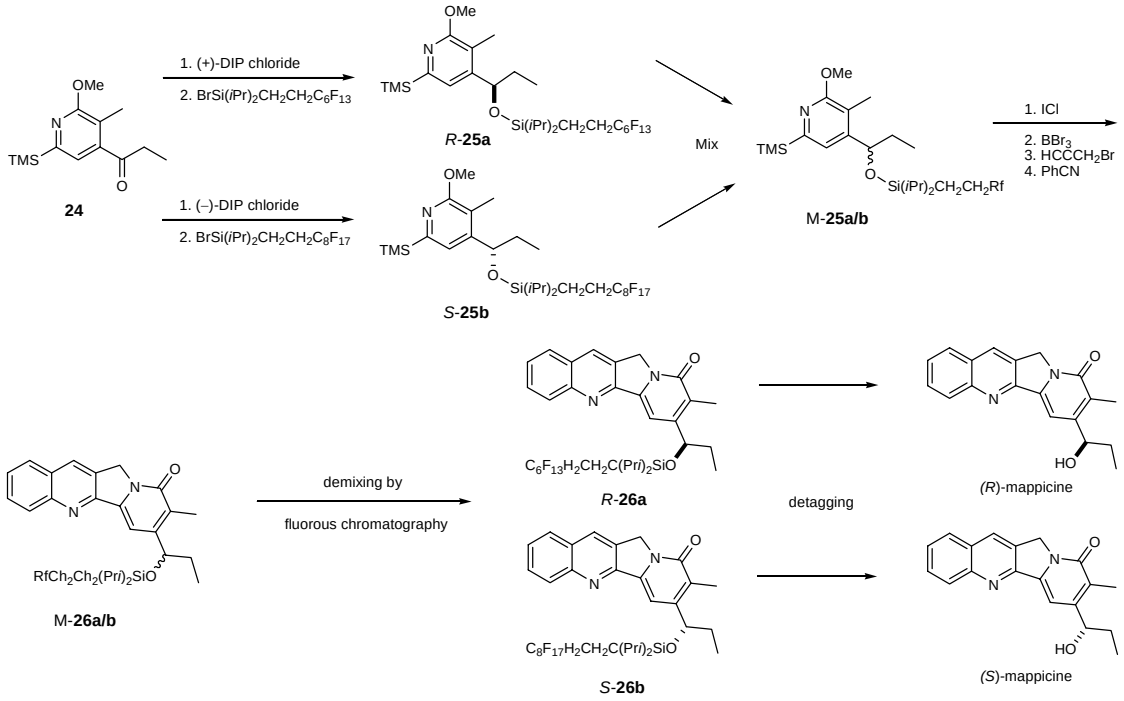


The mixture M-**22a/b** is then separated by fluorous HPLC (F-HPLC) on Fluoro*Flash*^{TM} column that is selective based on the fluorine content to provide the two pure quasienantiomers *R*-**22a** and *S*-**22b**. The tags are finally removed to generate the two true enantiomers *R*-**23** and *S*-**23**.

The F-HPLC column contains a stationary phase of $Si(Me)_2CH_2CH_2C_8F_{17}$ and has a strong and selective retention of fluorous compounds. Molecules with longer fluorinated chains have longer retention times on the column.[31] A typical mobile phase for F-HPLC is a gradient of MeOH-H_2O with increasing MeOH up to 100%. Other solvents such as MeCN or THF can be used to replace MeOH for the gradient elution. Isocratic elution using the above solvents also works well for some samples.

Our group has employed the fluorous quasiracemic synthesis to make both enantiomers of mappicine (scheme 10).[30] Quasienantiomers *R*-**25a** and *S*-**25b** were provided by stereoselective reduction of ketone **24** followed by silylization with silyl bromides bearing $-(CH_2)_2C_6F_{13}$ and $-(CH_2)_2C_8F_{17}$ groups as tags, respectively. The quasienantiomers *R*-**25a** and *S*-**25b** behave like true enantiomers when subjected to the typical spectroscopic analyses (^1H and ^{13}C NMR) and chromatographic techniques (flash chromatography). *R*-**25a** and *S*-**25b** were then mixed in equimolar amounts for the four-step quasiracemic synthesis to provide quasiracemic mixture of protected mappicines M-**26a/b**. This mixture was then separated by fluorous chromatography to provide pure *R*-**26a** and ***S*-26b**. Deprotection of resolved quasienantiomers provided *R*-mappicine and *S*-mappicine, respectively.

Scheme 9 Quasiracemic synthesis of both enantiomers of Mappicine



A fluorous quasiracemic synthesis should be considered when both enantiomers are needed for structure identification, biological testing, or any other aim.

Chapter 2 Synthesis of Quasienantiomeric Fluorous-Tagged Oxazolidinones and Application in Alkylation and *syn*-Aldol Reactions

2.1 Design of Quasienantiomeric Fluorous-Tagged Oxazolidinones

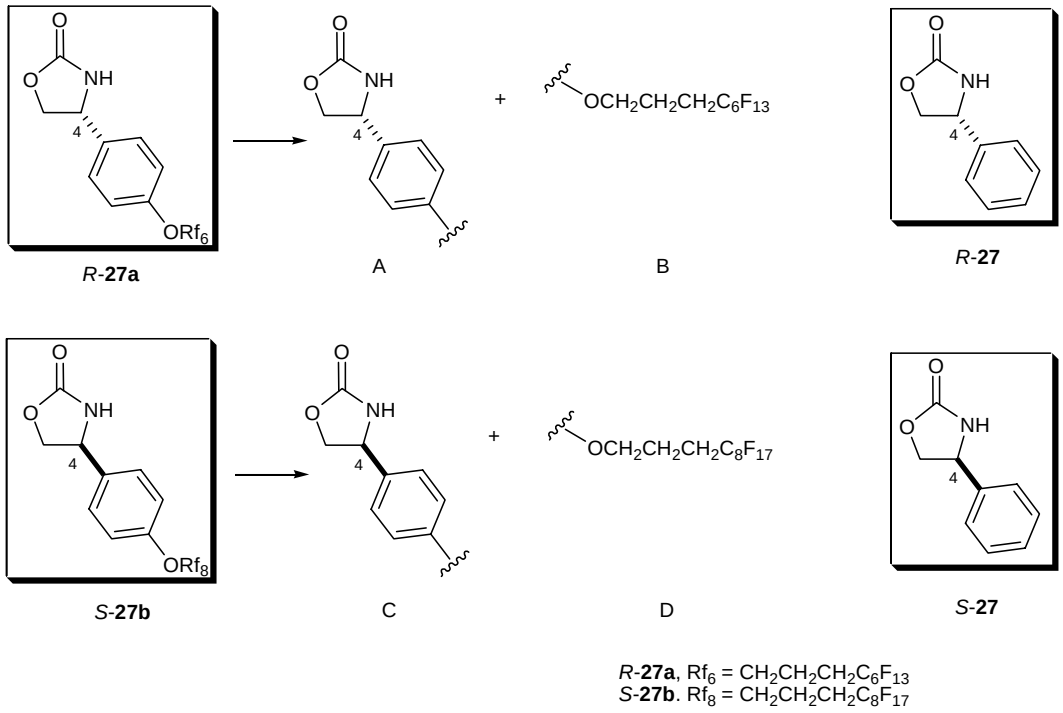


Figure 1 Structure of quasiracemic fluorous-tagged oxazolidinones *R*-**27a** and *S*-**27b**

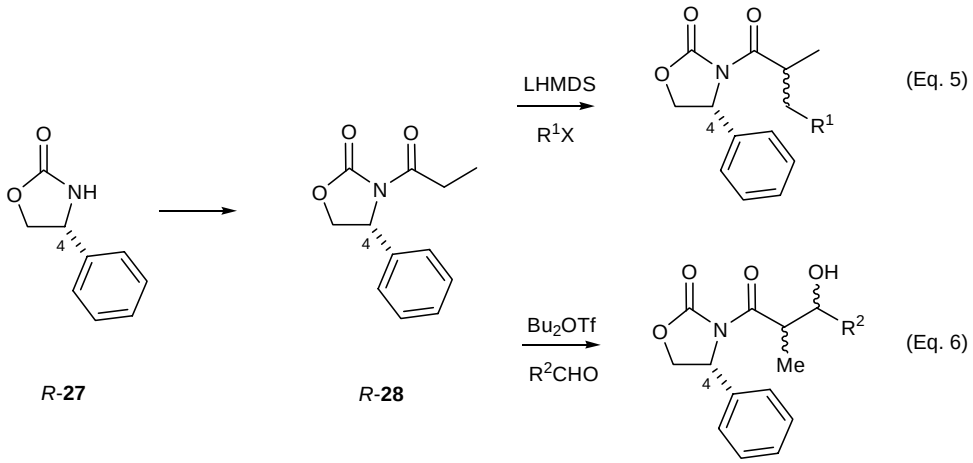
We designed a pair of quasienantiomeric fluorous-tagged oxazolidinones *R*-**27a** and *S*-**27b** (Figure 1), each of which is composed of two parts: One part is phenyloxazolidinone core, which is labeled as A for *R*-**27a** and C for *S*-**27b**; the other part is perfluoroalkylpropyloxy group with B for *R*-**27a** and D for *S*-**27b**. The core structure A of *R*-**27a** is derived from the commonly used

auxiliary 4*R*-phenyloxazolidin-2-one *R*-**27**.[32] Meanwhile, the core structure C of *S*-**27a** is derived from *S*-**27**, the enantiomer of *R*-**27**. The fluorous group B (3-perfluorohexylpropyl-1-oxy) differs from D (3-perfluorooctylpropyl-1-oxy) in fluorine content. Accordingly, while *R*-**27** and *S*-**27** are true enantiomers, *R*-**27a** and *S*-**27b** are quasienantiomers. Based on this structure association, it was expected that *R*-**27a** (*S*-**27b**) would exhibit similar reactivity and stereoselection to *R*-**27** (*S*-**27**) in the same alkylation and *syn*-aldol reactions. The suffixes "**a**" and "**b**" following a compound name designate the fluorous tag group: "**a**" series, perfluorohexylpropyl ($C_6F_{13}CH_2CH_2CH_2$-); "**b**" series, perfluorooctylpropyl ($C_8F_{17}CH_2CH_2CH_2$-). The prefixes *R*- or *S*- before numbers indicate the *R*- or *S*-enriched enantiomer at C4 position of oxazolidinone ring.

The reactivity and stereoselectivity of the fluorous-taged oxazolidinones *R*-**27a** (*S*-**27b**) in alkylation and aldol reactions are compared to those of the non fluorous-tagged counterpart *R*-**27** (*S*-**27**), which is one of our two aims. The other aim is to apply a mixture (a quasiracemate) of quasienantiomers *R*-**27a** and *S*-**27b** (1:1) to the same alkylation and aldol reactions and the resultant mixture is subjected to F-HPLC analysis. Since *S*-**27** is the enantiomer of *R*-**27**, it must have the same reactivity and stereoselection as *R*-**27**. Therefore we chose only *R*-**27** as the substrate for the non-fluorous control reaction.

Imide *R*-**28** is derived from the corresponding oxazolidinones *R*-**27** and it undergoes alkylation reaction with R^1Br (Eq. 5) and aldol condensation with R^2CHO (Eq. 6). Similarly, the imides derived from fluorous-tagged oxazolidinones *R*-**27a** and *S*-**27b** are also employed in the reactions (Eq. 5 and Eq. 6). The yield and the diastereomer ratio of the product for each imide are

compared to another one to reach the first aim.



For the second aim, quasienantiomeric imides *R*-**28a** and *S*-**28b** are prepared from the quasienantiomers *R*-**27a** and *S*-**27b** and then mixed to afford a quasiracemic mixture M-**28a/b** (prefix M means quasiracemic mixture), as shown in Figure 2. M-**28a/b** undergoes alkylation or aldol condensation to afford a mixture M-**29a/b** that involves the crude product *R*-**29a** from *R*-**28a** and *S*-**29b** from *S*-**28b**. Then M-**29a/b** is subjected to analysis by F-HPLC. Since *R*-**29a** and *S*-**29b** have different fluorine content, they elute from the F-HPLC column in different retention time. By F-HPLC analysis of the reaction crude products of quasiracemate M-**28a/b**, individual imides *R*-**28a** and *S*-**28b**, we can see the difference between quasiracemic synthesis and single reaction.

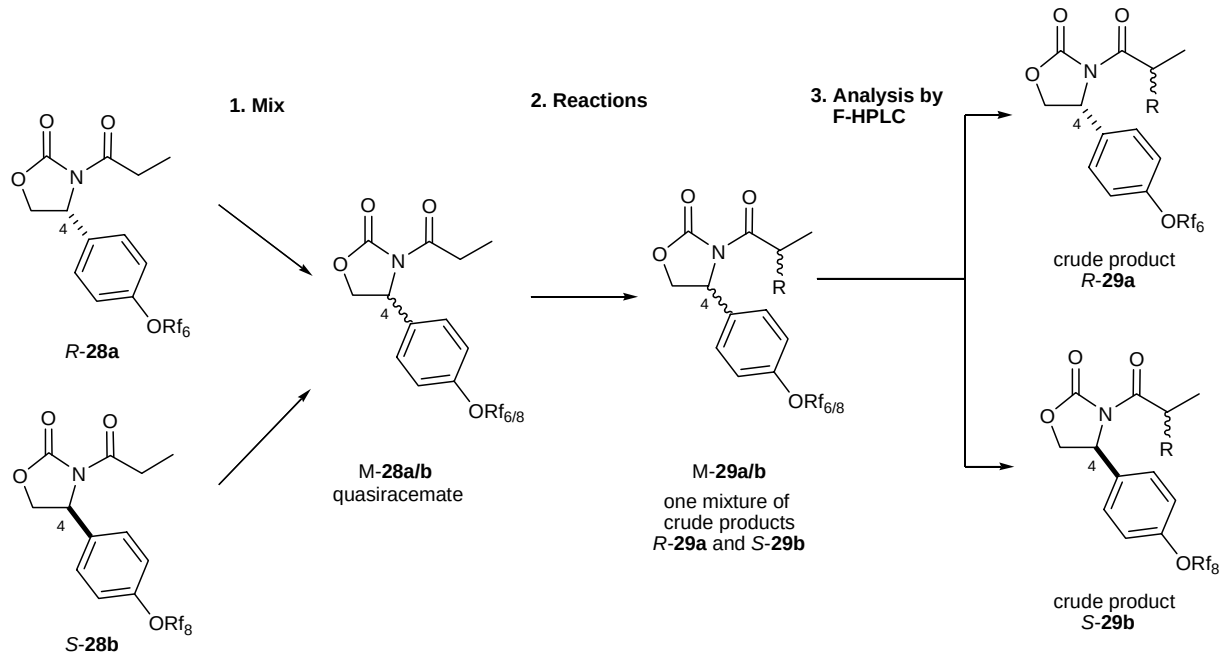
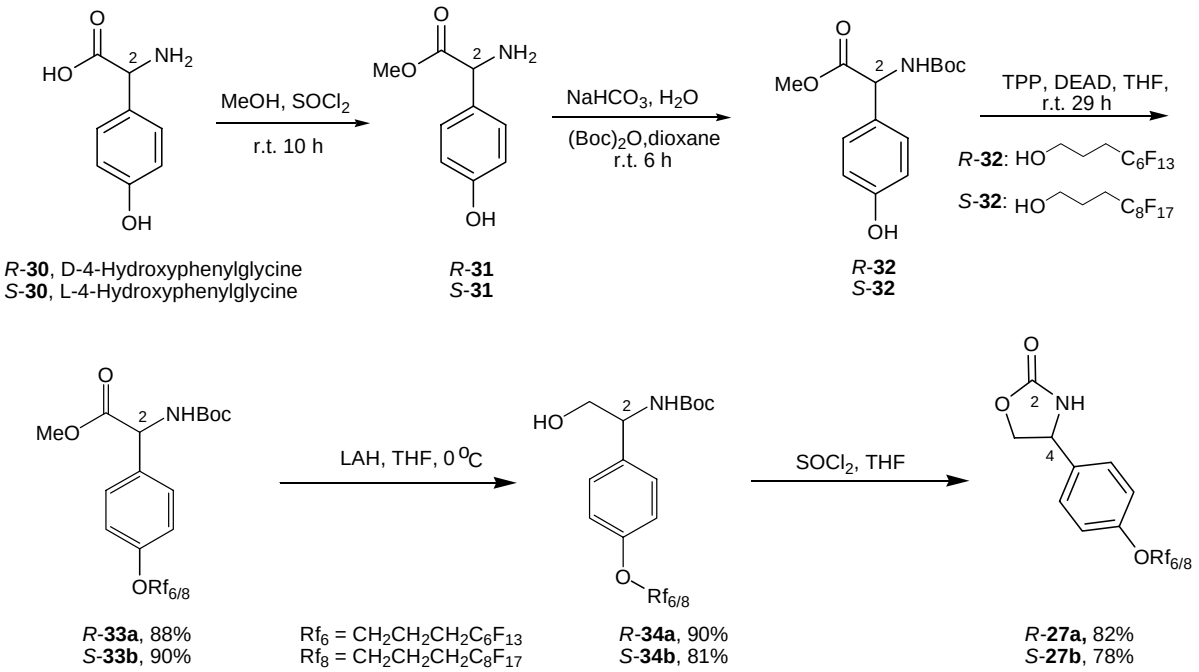


Figure 2 Strategy of the reactions of the quasiracemate M-**28a/b**

2.2 Synthesis of Quasienantiomeric Fluorous-Tagged Oxazolidinones

The synthesis of *R*-**27a** and *S*-**27b** was achieved over five steps, as shown in Scheme 10. Esterification of commercially available D-4-hydroxyphenylglycine *R*-**30** in the presence of thionyl chloride and methanol afforded crude amino ester *R*-**31**. It showed good purity by ^{1}H NMR spectroscopic analysis and so the crude product was directly used for the next step. Treatment of *R*-**31** with Boc anhydride (Boc_2O) and $NaHCO_3$ in dioxane/water provided the crude Boc amino ester *R*-**32**, which was condensed with 3-perfluorohexylpropan-1-ol in Mitsunobu conditions[33] (DEAD and TPP) to provide fluorous-tagged Boc amino acid *R*-**33a** in

Scheme 10 Synthesis of fluorous-tagged oxazolidinones *R*-**27a** and *S*-**27b**



88% isolated yield[34] (85% yield over three steps). Starting from L-4-hydroxyphenylglycine *S*-**30**, esterification, Boc protection and Mitsunobu reaction by using 3-perfluorooctylpropan-1-ol were conducted to afford *S*-**33b** in 86% overall yield.[34]

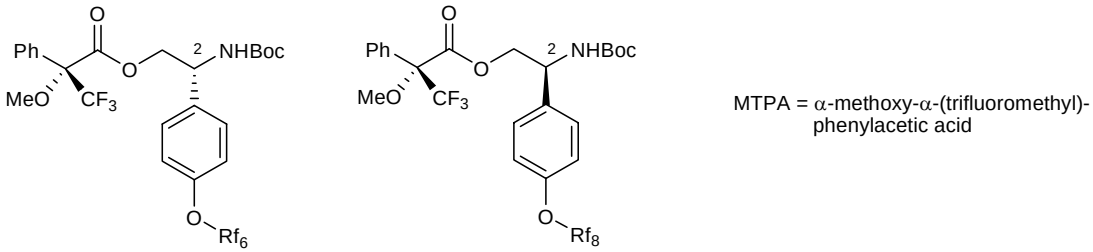
Reduction of *R*-**33a** (*S*-**33b**) by LAH (THF, 0 °C) provided Boc amino alcohol *R*-**34a** (*S*-**34b**) in isolated yield of 90% (81%).[34] Treatment of *R*-**34a** (*S*-**34b**) with thionyl chloride (THF, 0 °C) afforded fluorous-tagged oxazolidinone *R*-**27a** (*S*-**27b**) in isolated yield of 82% (78%).[34] In this reaction, the Boc group of *R*-**34a** (*S*-**34b**) was the source of carbonyl group at C2 position of the five-member oxazolidinone ring of *R*-**27a** (*S*-**27b**).

It was observed that *R*-**27a** and *S*-**27b** had identical ^{1}H NMR and ^{13}C NMR spectra. But the optical rotation values of these two compounds in $CHCl_3$ were opposite in sign and different in magnitude: *R*-**27a**, $[\alpha]_D^{20}$ –6.08 (c = 0.17**);** *S*-**27b**, $[\alpha]_D^{20}$ +16.78 (c = 0.13). The similarity in the properties of ^{1}H NMR and ^{13}C NMR spectroscopy, and different magnitude in optical rotation values were also observed for quasienantiomers *R*-**33a** and *S*-**33b,** *R*-**34a** and *S*-**34b**. Table 1 lists the optical rotation values for these four compounds.

Table 1 Optical rotation values of *R*-**33a**, *S*-**33b**, *R*-**34a** and *S*-**34b** in $CHCl_3$.

compound	$[\alpha]_D^{20}$ (c)
R-33a	-19.12 (0.19)
S-33b	+42.53 (0.87)
R-34a	-16.82 (2.53)
S-34b	+18.10 (2.50)

To ensure that racemization of an amino ester intermediate did not occur prior to reduction of the esters *R*-**33a** and *S*-**33b**, we conducted experiments to measure the enantiopurity of amino alcohols *R*-**34a** and *S*-**34b**. Mosher ester derivatives (*R*)-MTPA-*R*-**35a** and (*R*)-MTPA-*S*-**35b** (Figure 3) were prepared by treatment of *R*-**34a** and *S*-**34b** with (*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetic chloride in the presence of DMAP (CH_2Cl_2).



(*R*)-MTPA-*R*-**35a** (*R*)-MTPA-*S*-**35b**

Figure 3 Mosher esters (*R*)-MTPA-*R*-**35a** and (*R*)-MTPA-*S*-**35b**

While the quasienantimeric amino alcohols *R*-**34a** and *S*-**34b** exhibited identical characteristics of proton NMR spectroscopy, the separation of several proton NMR signals of Mosher esters (*R*)-MTPA-*R*-**35a** and (*R*)-MTPA-*S*-**35b** was observed, as expected for quasidiastereomers. The ^{1}H NMR spectrum of (*R*)-MTPA-*R*-**35a** was compared to

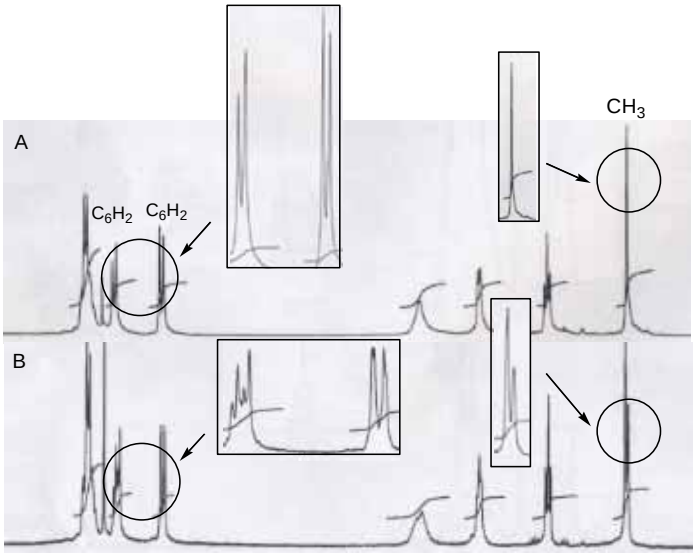


Figure 4 300 MHz ^{1}H NMR spectra: A. (*R*)-MTPA- *R*-**35a**; B. 1:1 mixture of (*R*)-MTPA-*R*-**35a** and (*R*)-MTPA-*S*-**35b**

that of a mixture of these two Mosher esters, as shown in Figure 4. The separation of the proton signals of (*R*)-MTPA-*R*-**35a** and (*R*)-MTPA-*S*-**35b** are obvious in the phenyl protons at C2 position and in the methyl protons.

Correspondingly, the different chemical shifts between these two Mosher esters are listed in Table 2, here Δδ equals to chemical shift δ_{35b} minus δ_{35a}. Proton NMR signals for only one diastereomer were found for (*R*)-MTPA-*R*-**35a** and also for (*R*)-MTPA-*S*-**35b**. So both the amino alcohols *R*-**34a** and *S*-**34b** have 100% ee. The transformation of *R*-**34a** (*S*-**34b**) into oxazolidinone *R*-**27a** (*S*-**27b**) occurred without breaking the bonds connecting to the stereocenter at C2 position, so *R*-**27a** (*S*-**27b**) is assumed to be enantiopure compounds.

Table 2 The different chemical shift between (*R*)-MTPA-*R*-**35a** and (*R*)-MTPA-*S*-**35b**.

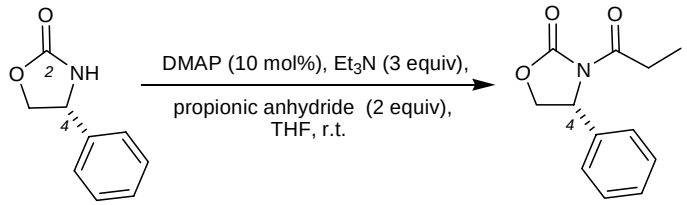
	δ (ppm)			
	2H (meta to ORf)	2H (ortho to ORf)	OMe	ee (%)
(*R*)-MTPA-*R*-35a	6.85, 6.83	7.20, 7.17	3.45	100
(*R*)-MTPA-*S*-35b	6.85, 6.84	7.19, 7.16	3.47	100
Δδ (ppm)	0.00, 0.01	–0.01, –0.01	0.02	

2.3 *N*-Acylation of the Quasienantiomeric Fluorous-Tagged Oxazolidinones

N-Propionyl oxazolidinone *R*-**28** was afforded by treatment with oxazolidinone *R*-**27** with DMAP (10 mol%), 3 equiv of Et_3N and 2 equiv of propionic anhydride (THF, r. t.), followed by purification by flash chromatography in 92% yield[34] (scheme 11). Fluorous-tagged imides *R*-**28a** and *S*-**28b** was formed through the same synthesis and were isolated in 86% and 80% yields.[34] As the former quasienantiomer pairs, *R*-**28a** and *S*-**28b** have identical characteristics of ^{1}H NMR and ^{13}C NMR spectroscopy. The optical rotation values of these two compounds in $CHCl_3$ are shown

in Table 3.

Scheme 11 *N-Acylation reactions of R-**27**, R-**27a** and S-**27b***



R-**27** *R*-**28**, 92%

Table 3 Optical rotation values of *R*-**28a** and *S*-**28b** in $CHCl_3$.

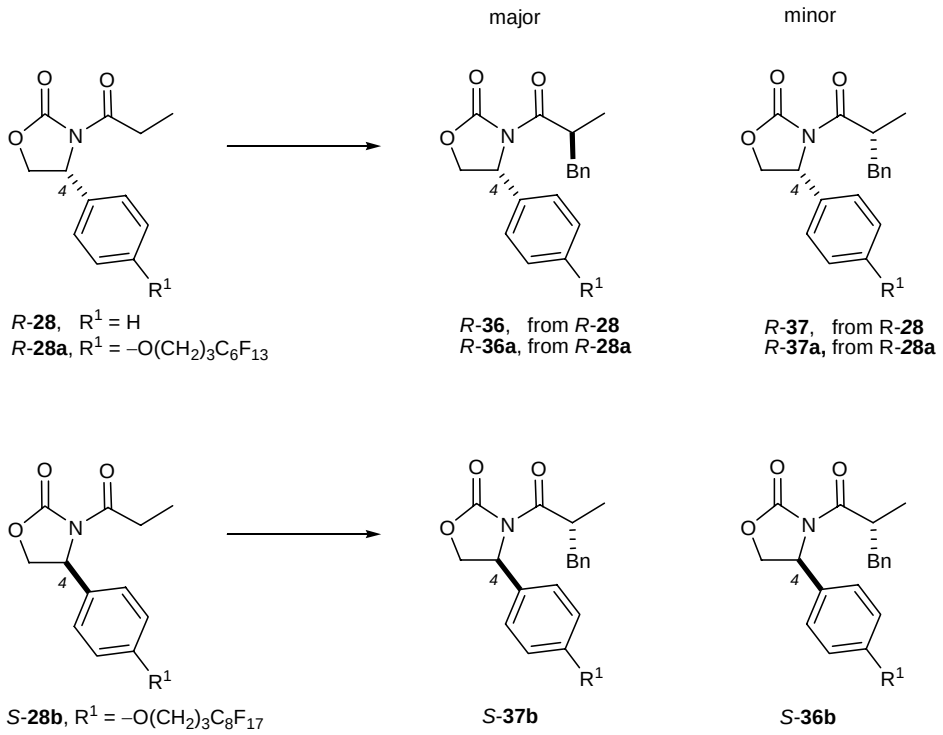
	R-28a	*S*-28b
$[\alpha]_D^{20}$ (c)	-27.00 (0.20)	+18.61 (0.18)

2.4 Alkylations and *syn*-aldol reactions of imides *R*-**28**, *R*-**28a** and *S*-**28b**

The diastereoselective alkylations and *syn*-aldol reactions of the enolates derived from imides *R*-**28**, *R*-**28a** and *S*-**28b** and comparison of the reactivity and stereoselection of the two fluorous-tagged oxazolidinone auxiliaries with the non-fluorous one are disclosed in this section.

Scheme 12 shows the diastereoselective alkylation process. The alkylation involved treatment of the imide *R*-**28** (*R*-**28a**, *S*-**28b**) in THF with 1.5 equiv of lithium bis(trimethylsilyl)amide (LHMDS, 1.0 M in THF) at −78 °C to provide the lithium enolate, followed by treatment with 3 equiv of benzyl bromide at −78 °C. Both of the major and monor diastereomer products were isolated by flash chromatography. The *N*-deacylation of the imide was found to concur with the

Scheme 12[a] Alkylation reactions of *R*-**28**, *R*-**28a** and *S*-**28b** with BnBr



[a] Conditions: (a) LHMDS; (b) BnBr

alkylation reaction and the oxazolidinone *R*-**27** (*R*-**27a,** *S*-**27b**) was obtained. Also there was a small amount of starting material recovered.

For the control alkylation of *R*-**28**, the minor product *R*-**37** has been reported in literature.[35] Since only two diastereomers can be provided, we are sure of the structure of the major product *R*-**36**. These results also accord with the diastereoselection of the alkylation of the imides derived from Evans' oxazolidinones.[15] In the cases of *R*-**28a** and *S*-**28b**, we compared the separation of the proton signals of the major and minor products with that of *R*-**28** and found that they are similar. So *R*-**36a** and *R*-**37a** were assumed as the major and minor products of *R*-**28a** respectively**,** and *S*-**37b** and *S*-**36b** as the major and minor ones of *S*-**28b**.

The alkylation studies are summarized in Table 4. For each imide, diastereomer ratio (entries A-C) was obtained from the ^{1}H NMR spectrum of crude alkylation product. A number of trends are evident from the data in the table. First, the similar yields of major products of *R*-**28** (62%[34]), *R*-**28a** (58%[34]) and *S*-**28b** (60%[34]) indicated that the fluorous-tagged imides *R*-**28a** and *S*-**28b** exhibited similar reactivity to the non fluorous-tagged imide *R*-**28**. Second, *R*-**28** (*R*-**36**:*R*-**37** ≥ 95:5), *R*-**28a** (*R*-**36a**:*R*-**37a** ≥ 93:7) and *S*-**28b** (*S*-**37b**:*S*-**36b** ≥ 92:8) underwent highly diastereoselective alkylation with BnBr. F-HPLC analysis of the crude product of the fluorous-tagged imides *R*-**28a** (*S*-**28b**) via UV light clearly showed the components in the mixture: diastereomeric products (not separable), deacylation product and unreacted imide.

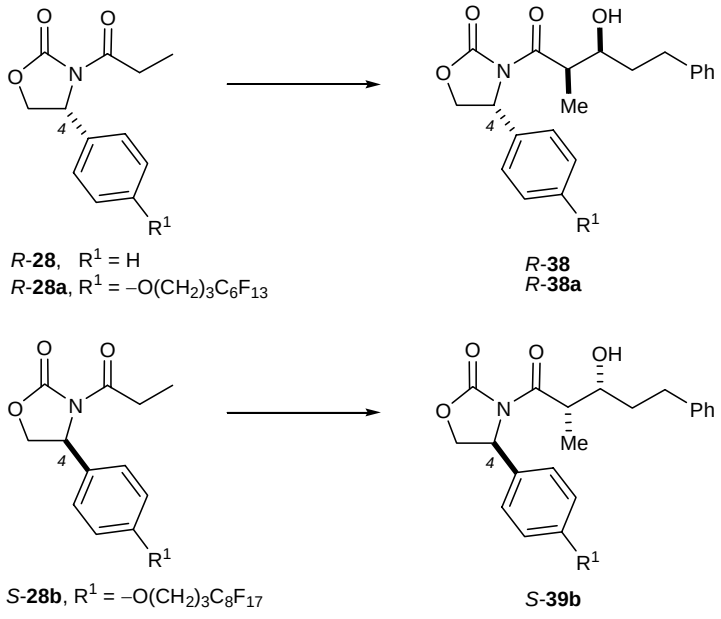
Table 4. Stereoselective alkylation of the enolates derived from imides *R*-**28**, *R*-**28a** and *S*-**28b**.

Imide	diastereomer ratio[a]	main diastereomer isolated yield of, %[b]	isolated compounds ratios [c]	HPLC analysis ratios [d]
R-28	*R*-36:*R*-37 ≥ 95:5	*R*-36, 62%	*R*-36:*R*-27:*R*-28 15:3:1	-
R-28a	*R*-36a:*R*-37a ≥ 93:7	*R*-36a, 58%	*R*-36a:*R*-27a:*R*-28a 13:5:1	*R*-36a:*R*-27a:*R*-28a 14:2:1
S-28b	*S*-37b:*S*-36b ≥ 92:8	*S*-37b, 60%	*S*-37b:*S*-27b:*S*-28b 6:3:1	*S*-37b:*S*-27b:*S*-28b 5:1:1

[a] Diastereomer ratios were determined by integration of the relevant signals in the 300 MHz ^{1}H NMR spectra of crude product corresponding to the C4 protons at the five-membered oxazolidinone rings of major and minor diastereomers; both of the diastereomers were separated by flash chromatography. [b] Yields are calculated after flash chromatography. [c] Ratios were determined by calculation of the weight of main diastereomer, *N*-deacylation product and recovered imide, which were isolated by flash chromatography. [d] Ratios were determined by integration of the area of corresponding peaks in F-HPLC spectra of crude product.

Then we conducted the aldol condensation of the boron enolates of *R*-**28** (*R*-**28a**, *S*-**28b**) (scheme 13). The general condition was enolization of the imide with 1.2 equiv of dibutylboryl triflate (Bu_2OTf, 1.0 M in CH_2Cl_2) in the presence of diisopropylethylamine (DIPEA, 1.3 equiv) at 0 °C, followed by condensation with 1.5 equiv of hydrocinnamaldehyde ($PhCH_2CH_2CHO$) at −78 °C. Only one diastereomer *R*-**38**[34] **(***R*-**38a**[34], *S*-**39b**[34]) and unreacted starting material were obtained after flash chromatography. The ratio of the product and the recovered imide was determined by the isolated weight. The crude aldol reaction products of *R*-**28a** and *S*-**28b** were also subjected to F-HPLC analysis. All these results are summarized in Table 5.

Scheme 13 Aldol reactions of *R*-**28**, *R*-**28a** and *S*-**28b** with hydrocinnamaldehyde



R-**28**, R^1 = H
R-**28a**, R^1 = $-O(CH_2)_3C_6F_{13}$

R-**38**
R-**38a**

S-**28b**, R^1 = $-O(CH_2)_3C_8F_{17}$

S-**39b**

Table 5. Stereoselective aldol condensation of the boron enolates derived from imides *R*-**28**, *R*-**28a** and *S*-**28b**.

imide	*syn*-isomer isolated yield of, %[a]	recovered imide isolated yield of, %[a]	HPLC analysis ratios [b]
R-28	*R*-38, 81%	7%	-
R-28a	*R*-38a, 38%	55%	*R*-28a:*R*-38a 1:1
S-28b	*S*-39b, 53%	40%	*S*-28b: *S*-39b 1:2

[a] Yields were obtained after flash chromatography. [b] Ratios were determined by integration of the area of corresponding peaks in F-HPLC spectrum of crude product.

Surprisingly we observed that both of the aldol condensation of the fluorous substrates *R*-**28a** (38%) and *S*-**28b** (53%) afforded *syn*-products in much lower yields than the non-fluorous substrate *R*-**28** (81%); 55% of *R*-**28a** and 40% of *S*-**28b** were recovered by flash chromatography. The F-HPLC chromatogram of the crude product of *R*-**28a** (*S*-**28b**) showed two main peaks that were identified as the *syn*-product and unreacted imide by co-injection of the pure isolated product and imide with the crude product, respectively.

The optimistic point is that few by-products were generated for the fluorous substrates *R*-**28a** and *S*-**28b** and that the recovered imides can be recycled. The yields of *R*-**38a** (84%) and *S*-**39b** (88%) based on the recovered starting materials were good. Also the diastereoselectivety of *R*-**28a** and *S*-**28b** were not affected by the fluorous tags. So *R*-**28a** and *S*-**28b** can still be applied in aldol reaction. These preliminary studies on alkylation and aldol condensation provided a basis for the subsequent quasiracemic synthesis.

2.5 Alkylation and Aldol Condensation of Quasiracemic Mixture of *R*-28a and *S*-28b

A quasiracemic mixture M-**28a/b** of imides *R*-**28a** and *S*-**28b** (1:1) underwent alkylation with BnBr in the same conditions as we used for the individual imides to provide a mixture of crude products. It has been mentioned that resolution of the fluorous-tagged mixture can be achieved by fluorous chromatography. So the reaction mixture of M-**28a/b** directly eluted from Fluoro*Flash*^{TM} column by an isocratic MeCN:H_2O 9:1 and was analyzed via UV light. We used the same conditions to analyze the crude alkylation product of individual fluorous-tagged imide. The F-HPLC chromatograms of the crude alkylation products of M-**28a/b**, *R*-**28a** and *S*-**28b** are all shown in Figure 5.

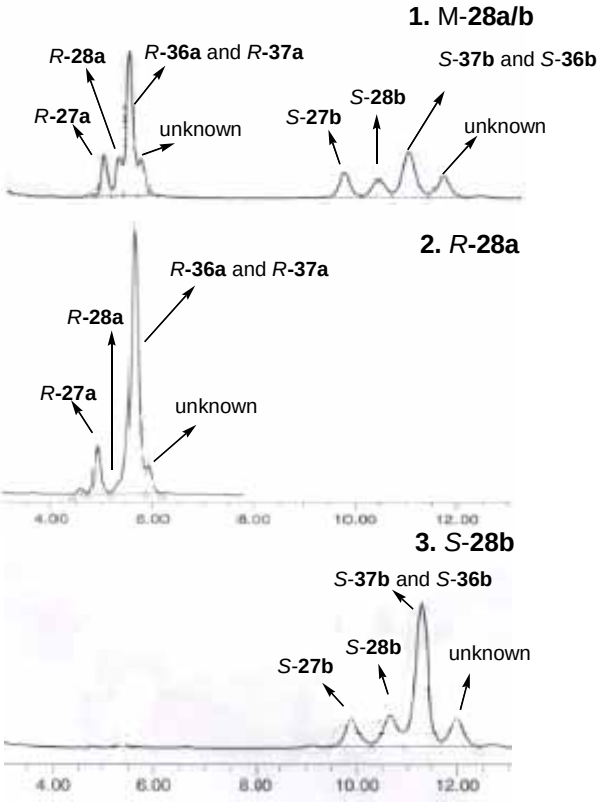


Figure 5 F-HPLC analysis of alkylation reaction: 1. M-**28a/b**; 2. *R*-**28a**; 3.*S*-**28b**.

The F-HPLC analysis of crude alkylation products of *R*-**28a** (*S*-**28b**) shows four peaks which are corresponding to deacylation product, starting material (imide), two unseparable diastereomeric products and a small unkown peak in the sequence of increasing retention time. Each of the former three peaks was identified by co-injection of the pure compound corresponding to this peak with the crude product to the F-HPLC column. The area ratios of the four peaks in the sequence of increasing retention time are 11:4:74:11 for *R*-**28a** and 13:13:61:13 for *S*-**28b**. The two fluorous parts (Rf_6 and Rf_8) were separated by about 4 min. The F-HPLC analysis of the crude alkylation product of M-**28a/b** shows two pairs of four peaks in two separable ranges of retention time. The crude product of *R*-**28a** was co-injected with that of M-**28a/b** and the resultant chromatogram shows that the four peaks of *R*-**28a** overlap with the four peaks (retention time: 4-6 min; area ratios: 14:14:58:14 in the sequence of increasing retention time) of M-**28a/b**. Meanwhile, the four peaks of *S*-**28b** overlap with the other four peaks (retention time: 10-12 min; area ratios: 17:17:49:17) of M-**28a/b**. So the two pairs of four peaks of M-**28a/b** are corresponding to the alkylation product of *R*-**28a** and that of *S*-**28b**, respectively.

These F-HPLC analyses elucidate that the alkylation reaction of the quasiracemic mixture M-**28a/b** with benzyl bromide is similar to that of the individual quasienantiomer imide. *R*-**28a** and *S*-**28b** show more similarity to each other in the alkylation of the quasiracemate than in that of the individual quasienantiomer. The separation of two fluorous parts (Rf_6 and Rf_8) of the crude product of M-**28a/b** on F-HPLC column by about 4 min is enough to resolve the two parts.

The boron enolate of M-**28a/b** was condensed with hydrocinnamaldehyde and the crude product was directly subjected to F-HPLC chromatography analysis via UV light (MeCN:H_2O 90:10, isocratic). The F-HPLC analysis of the crude product of individual quasienantiomer imide was conducted in the same condition. Figure 6 shows the resultant three chromatograms of the crude products of M-**28a/b**, *R*-**28a** and *S*-**28b**. The chromatogram for *R*-**28a** (*S*-**28b**) shows two major peaks that were identified as the aldol product and the remained imide by co-injection. The aldol product eluted faster than the imide on the fluorous column. The area ratios of these two peaks are 50:50 for *R*-**28a** and 67:33 for *S*-**28b** in the sequence of increasing retention time. The

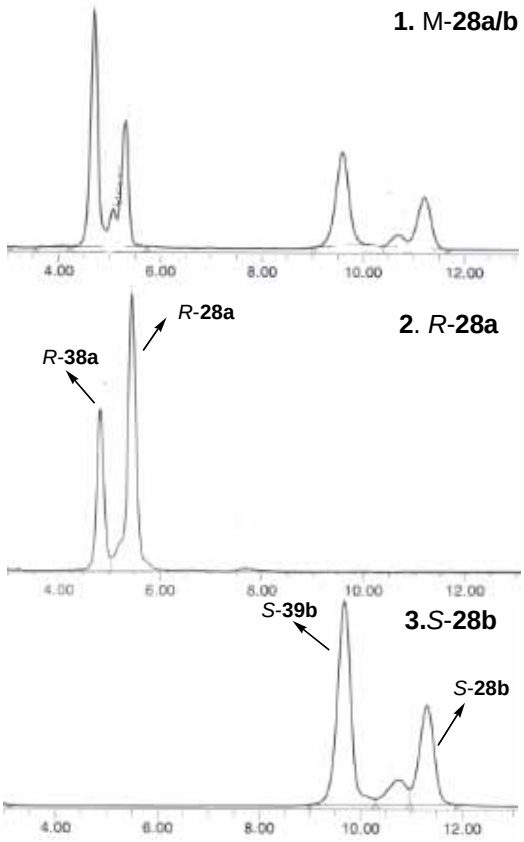


Figure 6 F-HPLC analysis of aldol reaction: 1. M-**28a/b**; 2. *R*-**28a**; 3. *S*-**28b**.

chromatogram of M-**28a/b** shows two pairs of two peaks. The pair (retention time: 4-6 min; area ratio: 67:33 in the sequence of increasing retention time) corresponds to the crude product of *R*-**28a** and the other pair ((retention time: 10-12 min; area ratio: 67:33) is the crude product of *S*-**28b**. As the alkylation with BnBr, the aldol condensation of the quasiracemate M-**28a/b** with hyrdrocinnamaldehyde is similar to that of the individual quasienantiomer imide. *R*-**28a** and *S*-**28b** show more similarity to each other in the aldol reaction of the quasiracemate than in that of the individual imide. The separation of the two fluorous parts (Rf_6 and Rf_8) of the crude aldol product of M-**28a/b** on F-HPLC column is about 4 min, which is similar to the alkylation reaction.

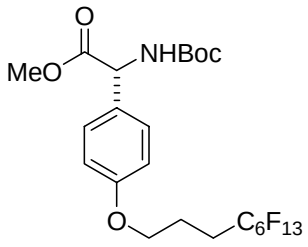
These studies indicate that the reactivity and stereoseletion of the quasiracemic mixture of *R*-**28a** and *S*-**28b** is similar to the individual imide. The advantage of the quasiracemic synthesis is: It can provide both of the enantiomers in a single reaction.

2.6 Conclusion

In summary, two different fluorous-tagged oxazolidinones were synthesized in an efficientt synthetic strategy. Preliminary alkylation and aldol condensation of the fluorous-tagged imides derived from the corresponding oxazolidinones were carried out and exhibited as good diastereoselectivety as the non fluorous-tagged imide. In the case of yield of aldol reaction, the fluorous-tagged imides showed big difference with the non-fluorous tagged one. The alkylation and aldol reactions of the quasiracemic mixture were conducted and showed similar reactivity and diastereoselection to the same reactions of individual imide.

Chapter 3 Experimental

General. Toluene, THF, dichloromethane and diethyl ether were purified by filtration through activated alumina under an nitrogen atmosphere. Other reagents were used as they were received from Aldrich. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance DPX 300 (300 MHz), Avance DRX 500 (500 MHz) and Avance 600 (600 MHz) spectrometers. $CDCl_3$ was used as the NMR solvent unless otherwise noted. Infrared spectra were taken on a Mattson Genesis Series FTIR using thin film deposition on NaCl plates. Low resolution mass spectra were obtained on a Fision Autospec and reported in *m*/*e* units. High resolution mass spectra were obtained on a VG 70-G or VG-Autospec double focusing instrument under EI mode. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at the Na D-line (λ = 589 nm) using a 1 dm cell at 20 ºC. HPLC analyses were conducted by using Waters 600 controller and Waters 2487 dual λ absorbance detector. Thin layer chromatography (TLC) was performed on silica gel 60 F254 glass backed plates with a layer thickness of 0.25 mm manufactured by E. Merck. Flash chromatography was performed on silica gel (230-400 mesh ASTM) purchased from Sorbtech or Bodman.



R-**33a**

(***R*)-*N*-(*t*-Butoxycarbonyl)-4-hydroxyphenylglycine methyl ester (32):** D-4-Hydroxyphenylglycine *R*-**30** (3.00 g, 17.96 mmol) was suspended in methanol (60 mL) and thionyl chloride (2.4 ml, 32.89 mmol) was added dropwise via syringe over 10 min. The mixture was stirred for about 12 h at room temperature and the solvent was evapored under vacuum. The residue was washed twice with ether and the organic layer was dried ($MgSO_4$) and concentrated to yield crude white solid D-4-hydroxyphenylglycine methyl ester *R*-**31** (3.25 g) as a hydrochloride salt that was used in the next step without purification (see ref. 36).

^{1}H NMR (300 MHz, DMSO) δ 9.86 (s, 1H), 8.79 (s, 3H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 5.15 (s, 1H), 3.71 (s, 3H).

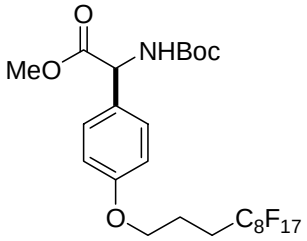
To a mixture of crude D-4-hydroxyphenylglycine methyl ester *R*-**31** (3.25g, 17.00 mmol) and $NaHCO_3$ (2.268 g, 27 mmol) in H_2O (38 mL) was added Boc anhydride (4.70 g, 21.53 mmol) in dioxane (38 mL) at 0 ºC. The mixture was stirred for 1 h at 0 °C and then 6 h at room temperature. After it was acidified with 1N HCl to approximately pH 2, the mixture was extracted with ethyl acetate (3 x 75 mL). The organic layer was combined, washed with H_2O and brine and dried ($MgSO_4$). The solvent was removed by rotary evaporation to yield crude (*R*)-*N*-(*t*-butoxycarbonyl)-4-hydroxylphenylglycine *R*-**32** (4.98 g) which was used directly without further

purification (see ref. 36).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, *J* = 7.8 Hz, 2H), 6.75 (d, *J* = 8.2 Hz, 2H), 5.63 (d, *J* = 6.8 Hz, 1H), 5.24 (d, *J* = 6.8 Hz, 1H), 3.71 (s, 3H), 1.44 (s, 9H).

(*R*)-*N*-(*t*-Butoxycarbonyl)-4-[(3-perfluorohexyl)propyl-1-oxy]phenylglycine methyl ester (*R*-33a): To a solution of crude *R*-**32** (1.30 g, 4.63 mmol), 3-(perfluorohexyl)propanol (2.63 g, 6.96 mmol) and triphenyphosphine (1.84 g, 7.02 mmol) in THF (13 mL) was added a solution of DEAD (1.35 g, 6.98 mmol) in THF (13 mL) dropwise over 30 min and the mixture was stirred at room temperature for about 16 h. The mixture was concentrated and the residues were purified by column chromatography (4:1 hexanes/EtOAc) to yield the product *R*-**33a** (2.65 g, 90%) as colorless oil:

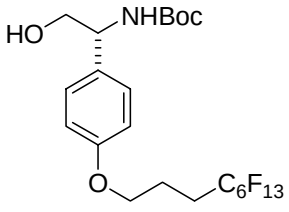
$[\alpha]_D^{20}$ -19.12 (c = 0.19, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.53 (d, *J* = 6.0 Hz, 1H), 5.28 (d, *J* = 7.1 Hz, 1H), 4.05 (t, *J* = 5.8 Hz, 2H), 3.72 (s, 3H), 2.34 (m, 2H), 2.13 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 158.6, 154.8, 129.5, 128.4 (2C), 114.8 (2C), 80.1, 66.3, 57.0, 52.6, 28.3 (3C), 27.9, 20.5; IR (NaCl) 3434, 2928, 2930, 1747, 1715, 1613, 1513, 1209, 1055, 1028; LRMS (ES^+) 664 (M + Na^+); HRMS (ES^+) Calcd. for $C_{23}H_{24}NNaO_5F_{13}$ (M + Na^+) 664.1345. Found 664.135.



S-**33b**

(*S*)-*N*-(*t*-Butoxycarbonyl)-4-[(3-perfluorooctyl)propyl-1-oxy]phenylglycine methyl ester (*S*-33b): The procedure to make *S*-**32b** (overall yield in three steps, 86%) is the same as *R*-**32a**, starting from L-4-hydroxy-phenyl- glycine and perfluorooctylpropanol.

$[\alpha]_D^{20}$ +42.53 (c = 0.87, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.52 (d, *J* = 6.3 Hz, 1H), 5.21 (d, *J* = 7.1 Hz, 1H), 4.05 (t, *J* = 5.8 Hz, 2H), 3.72 (s, 3H), 2.34 (m, 2H), 2.14 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 158.6, 154.8, 129.5, 128.4 (2C), 114.8 (2C), 80.1, 66.3, 57.0, 52.6, 28.3 (3C), 27.9, 20.5; IR (NaCl) 3380, 2980, 1715, 1612, 1587, 1369, 1055, 1028, 834, 721, 704, 655; LRMS (ES^+) 764 (M + Na^+); HRMS (ES^+) Calcd. for $C_{25}H_{24}NNaO_5F_{17}$ (M + Na^+) 764.1281. Found 764.127.

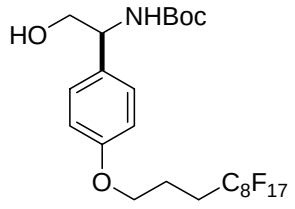


R-**34a**

(*R*)-*N*-(*t*-Butoxycarbonyl)-4-[(3-perfluorohexyl)propyl-1-oxy]phenylglycinol (*R*-34a): To a solution of *R*-**33a** (2.00 g, 3.12 mmol) in THF (20 mL) was added LAH (0.36 g, 9.36 mmol) in 5

portions at 0 ºC and the mixture was stirred for 2 h. The reaction was quenched by careful addition of sat. aq. NH_4Cl at 0 °C. 0.3M HCl (3.5 mL) was added and the mixture was filtered through celite. The filtered residue was rinsed with ether and the filtrate was extracted with ether (3 x 10 ml). The organic layer was combined, washed with brine and dried ($MgSO_4$) and concentrated. Purification by column chromatography (1:1 hexanes/EtOAc) provided *R*-**34a** (1.70 g, 90 %) as pale yellow oil:

$[\alpha]_D^{20}$ -16.82 (c = 2.53, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.37 (bs, 1H), 4.70 (bs, 1H), 4.03 (t, *J* = 5.8 Hz, 2H), 3.76 (bs, 2H), 2.36 (m, 2H), 2.13 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 156.2, 132.1, 127.8 (2C), 114.6 (2C), 79.9, 66.7, 66.3, 56.3, 28.3 (3C), 27.9, 20.5; IR (NaCl) 3367, 2979,, 2935, 2876, 1693, 1613, 1513, 1478, 1454, 1392, 1367, 1243, 1205, 1145, 1052, 1028, 696; LRMS (ES^+) 636 (M + Na^+); HRMS (ES^+) Calcd. for $C_{22}H_{24}NNaO_4F_{13}$ (M + Na^+) 636.1395. Found 636.140.

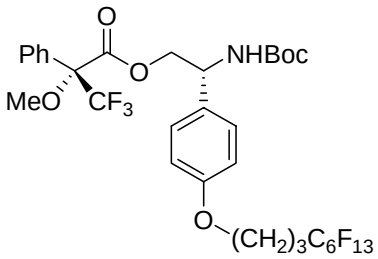


S-**34b**

(*S*)-*N*-(*t*-Butoxycarbonyl)-4-[(3-perfluorooctyl)propyl-1-oxy]phenylglycinol (*S*-34b):

$[\alpha]_D^{20}$ +18.10 (c = 2.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.29 (bs, 1H), 4.71 (bs, 1H), 4.04 (t, *J* = 5.8 Hz, 2H), 3.79 (bs, 2H), 2.34 (m, 2H),

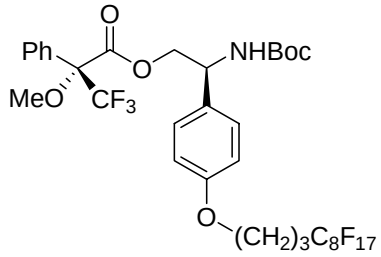
2.14 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 156.2, 132.1, 127.8 (2C), 114.6 (2C), 79.9, 66.7, 66.3, 56.3, 28.3 (3C), 27.9, 20.5; IR (NaCl) 3374, 2979, 2873, 1688, 1614, 1514, 1369, 1244, 1205, 1150, 1057, 1027, 991, 640; LRMS (ES^+) 736 ($M + Na^+$); HRMS (ES^+) Calcd. for $C_{24}H_{24}NNaO_4F_{17}$ ($M + Na^+$) 736.1332. Found 736.134.



(*R*)-MTPA-*R*-**35a**

(*R*)-*N*-(*t*-Butoxycarbonyl)-4-[(3-perfluorohexyl)propyl-1-oxy]phenylglycinyl (*R*)-α-methoxy -α-(trifluoromethyl)phenyl acetate ester ((*R***)-MTPA-*R*-35a):** To a mixture of *R*-**34a** (0.025 g, 0.041 mmol), DMAP (0.010 g, 0.084 mmol) in CH_2Cl_2 (1 mL) was added a solution of (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic chloride (0.026 g, 0.092 mmol) in CH_2Cl_2 (1 mL) dropwise at room temperature. The reaction mixture was stirred overnight and then concentrated. Purification by column chromatography (4:1 hexanes/EtOAc) provided (*R*)-MTPA-*R*-**35a** (0.025mg, 76%) as white solid:

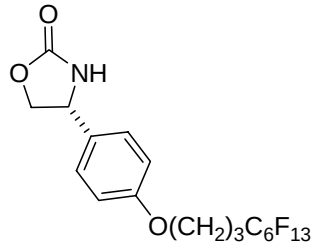
^{1}HNMR (600 MHz, $CDCl_3$) δ 7.42-7.34 (m, 5H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.98 (bs, 1H), 4.94 (bs, 1H), 4.53 (d, *J* = 8.4, 2H), 4.04 (t, *J* = 5.9 Hz, 2H), 3.45 (s, 3H), 2.35-2.28 (m, 2H), 2.13-2.09 (m, 2H), 1.42 (s, 9H).



(*R*)-MTPA-*S*-**35b**

(*S*)-*N*-(*t*-Butoxycarbonyl)-4-[(3-perfluorooctyl)propyl-1-oxy]phenylglycinyl (*R*)-α-Methoxy-α-(trifluoromethyl)phenyl acetate ester ((*R*)-MTPA-*S*-**35b):**

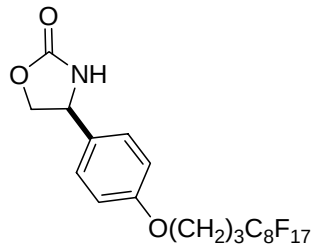
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42-7.34 (m, 5H), 7.18 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.01 (bs, 1H), 4.94 (bs, 1H), 4.56 (d, *J* = 8.4, 2H), 4.04 (t, *J* = 5.8 Hz, 2H), 3.47 (s, 3H), 2.37-2.28 (m, 2H), 2.14-2.09 (m, 2H), 1.42 (s, 9H).



R-**27a**

4(*R*)-{4-[(3-Perfluorohexyl)propyl-1-oxy]phenyl}oxazolidinone (*R*-27a): To a solution of *R*-**34a** (2.10 g, 3.43 mmol) in THF (10 mL) was added $SOCl_2$ (1.0 mL, 13.04 mmol) dropwise via syringe over 10 min at 0 °C and the mixture was stirred at room temperature for 15 h. Excess $SOCl_2$ was removed by rotary evaporation and the residue was dissolved in EtOAc and washed with water, sat. NH_4Cl and brine. The organics were dried over $MgSO_4$ and concentrated. Purification through column chromatography (1:1 hexanes/EtOAc) provided *R*-**27a** (1.48 g, 80%) as white solid:

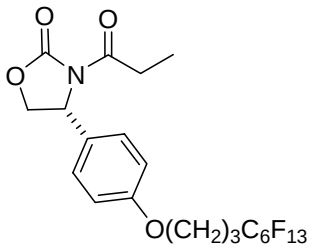
mp 116-118°; $[\alpha]_D^{20}$ -6.08 (c = 0.17, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 5.34 (bs, 1H), 4.95 (t, *J* = 7.8 Hz, 1H), 4.75 (t, *J* = 8.6 Hz, 1H), 4.20 (dd, *J* = 7.0, 8.6 Hz, 1H), 4.08 (t, *J* = 5.8 Hz, 2H), 2.41 (m, 2H), 2.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 159.0, 131.7, 127.5 (2C), 115.1 (2C), 72.7, 66.5, 55.9, 27.9, 20.5; IR (NaCl) 3294, 3054, 2987, 2306, 1747, 1713, 1614, 1515, 1479, 1423, 1261, 1142, 1031, 896, 745, 692; LRMS (EI^+) 539 (M^+); HRMS (EI^+) Calcd. for $C_{18}H_{14}NO_3F_{13}$ (M^+) 539.0766. Found 539.077.



S-**27b**

4(*S*)-{4-[(3-Perfluorooctyl)propyl-1-oxy]phenyl}oxazolidinone (*S*-27b):

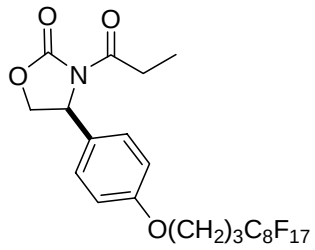
mp 126-129°; $[\alpha]_D^{20}$ +16.78 (c = 0.13, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.6 Hz, 2H), 6.94 (d, *J* = 8.6 Hz, 2H), 5.33 (s, 1H), 4.95 (t, *J* = 7.7 Hz, 1H), 4.75 (t, *J* = 8.6 Hz, 1H), 4.20 (dd, *J* = 7.2, 8.3 Hz, 1H), 4.08 (t, *J* = 5.8 Hz, 2H), 2.41 (m, 2H), 2.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 159.0, 131.7, 127.5 (2C), 115.1 (2C), 72.7, 66.5, 55.9, 27.9, 20.5; IR (NaCl) 3295, 3054, 2987, 2305, 1745, 1713, 1615, 1588, 1515, 1479, 1423, 1402, 1265, 1167, 1031, 896, 744, 704; LRMS (EI^+) 639 (M^+); HRMS (EI^+) Calcd. for $C_{20}H_{14}NO_3F_{17}$ (M^+) 639.0702. Found 639.068.



R-**28a**

4(*R*)-{4-[(3-Perfluorohexyl)propyl-1-oxy]phenyl}-3-propionyloxazolidinone (*R*-28a): To a solution of *R*-**27a** (0.50g, 0.93 mmol) in THF (0.9 mL) was added DMAP (11.3 mg, 0.093 mmol, 10 mol%) and Et_3N (0.13 mL, 0.94 mmol) dropwise. The mixture was kept at 0-10 °C and propionic anhydride (0.25 mL, 1.89 mmol) was added dropwise over 5 min. The reaction mixture was stirred at room temperature for 12 h and the volatiles were removed by rotary evaporation. The residue was washed with water, brine and dried ($MgSO_4$). Purification through chromatography (1:1 hexanes/EtOAc) provided *R*-**28a** (0.48 g, 87%) as a white solid.

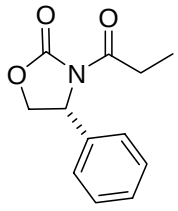
mp 90-93°; $[\alpha]_D^{20}$ -27.00 (c = 0.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.41 (dd, *J* = 3.5, 8.6 Hz, 1H), 4.71 (t, *J* = 8.8 Hz, 1H), 4.31 (dd, *J* = 3.6, 8.9 Hz, 1H), 4.06 (t, *J* = 5.8 Hz, 2H), 3.05 (m, 2H), 2.40 (m, 2H), 2.15 (m, 2H), 1.13 (t, *J* = 7.3, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 158.7, 153.7, 131.7, 127.5 (2C), 114.9 (2C), 70.1, 66.3, 57.1, 29.2, 27.8 (t, 1C), 20.5, 8.1; IR (NaCl) 2985, 2926, 2877, 2305, 1795, 1700, 1613, 1521, 1470, 1454, 1390, 1368, 1323, 1244, 1208, 1188, 1122, 1067, 1021, 941, 836, 757, 700; LRMS (EI^+) 595 (M^+); HRMS (EI^+) Calcd. for $C_{21}H_{18}NO_4F_{13}$ (M^+) 595.1028. Found 595.102.



S-**28b**

4(*S*)-{4-[(3-Perfluorooctyl)propyl-1-oxy]phenyl}-3-propionyloxazolidinone (*S*-28b):

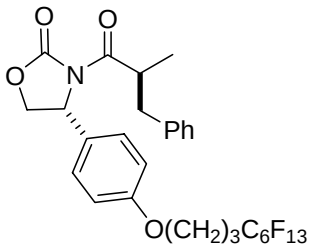
mp 103-107°; $[\alpha]_D^{20}$ +18.61 (c = 0.18, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 5.41 (dd, *J* = 3.5, 8.6 Hz, 1H), 4.71 (t, *J* = 8.8 Hz, 1H), 4.31 (dd, *J* = 3.5, 8.9 Hz, 1H), 4.06 (t, *J* = 5.8 Hz, 2H), 3.05 (m, 2H), 2.40 (m, 2H), 2.15 (m, 2H), 1.13 (t, *J* = 7.3, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 159.1, 154.0, 132.0, 127.8 (2C), 114.9 (2C), 70.4, 66.7, 57.4, 29.5, 28.5 (t, 1C), 20.9, 8.4; IR (NaCl) 3055, 2986, 2879, 2411, 2305, 1783, 1699, 1613, 1587, 1515, 1453, 1383, 1322, 1243, 1200, 1147, 1066, 1023, 975, 896, 831, 806, 746; LRMS (EI^+) 695 (M^+); HRMS (EI^+) Calcd. for $C_{23}H_{18}NO_4F_{17}$ (M^+) 695.0964. Found 695.091.

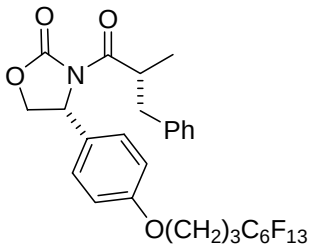


R-**28**

4(*R*)-Phenyl-3-propionyloxazolidinone (*R*-28): See ref. 14.

^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.27 (m, 5H), 5.46 (dd, *J* = 3.6, 8.7 Hz, 1H), 4.73 (t, *J* = 8.8 Hz, 1H), 4.32 (dd, *J* = 3.6, 8.9 Hz, 1H), 2.97 (m, 2H), 1.15 (t, *J* = 7.3, 3H).





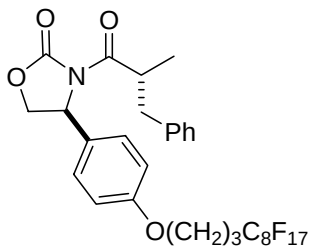
R-**36a** *R*-**37a**

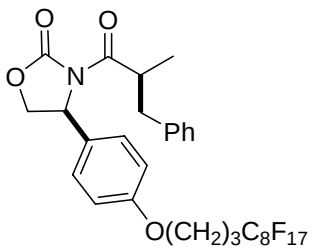
4(*R*)-{4-[(3-Perfluorohexyl)propyl-1-oxy]phenyl}-3-(2*S*-methyl-3-phenylpropionyl)oxazolidinone (*R*-36a): To a mixture of *R*-**28a** (0.05 g, 0.084 mmol) in THF (1.3 mL) was added lithium bis(trimethylsilyl)amide (1.0 M in THF, 0.126 mL, 0.126 mmol) dropwise at -78 °C under an argon atmosphere via syringe and the mixture was allowed to stir for 30 min. Benzyl bromide (0.031 mL, 0.252 mmol) was added at -78 °C and the reaction solution was stirred at this temperature for 2 h. Then the mixture was warmed to room temperature over a further 24 h. Sat. NH_4Cl was added to quench the reaction and the mixture was extracted with ethyl acetate (3 x 10 mL). The organics were combined and washed with brine, dried ($MgSO_4$) and concentrated. Purification through column chromatography (7:3 hexanes/EtOAc) provided major product *R*-**36a** (0.034 g, 59%) as white solid, minor product *R*-**37a** (0.003 g, 5%) also as a white solid, deacylation product *R*-**27a** (0.009g, 23%) and recovered imde *R*-**28a** (0.003 g, 6%). *R*-**36a** is a little polar than *R*-**37a**.

R-**36a:** mp 129-134°; $[\alpha]_D^{20}$ −14.00 (c = 0.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.05 (m, 7H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.42 (dd, *J* = 4.1, 8.7 Hz, 1H), 4.69 (t, *J* = 8.8 Hz, 1H), 4.24 (dd, *J* = 4.1, 8.9 Hz, 1H), 4.17 (m, 1H), 4.06 (t, *J* = 5.8 Hz, 2H), 3.07 (dd, *J* = 6.7, 13.2 Hz, 1H), 2.53 (dd, *J* = 7.8, 13.4 Hz, 1H), 2.40 (m, 2H), 2.17 (m, 2H), 1.14 (d, *J* = 6.7, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 176.3, 158.9, 153.6, 139.2, 131.7, 129.5 (2C), 128.6 (2C), 127.6 (2C), 126.5, 115.3 (2C), 70.1, 66.7, 57.6, 40.0, 39.8, 28.5, 20.9, 16.5; IR (NaCl) 2924, 1759, 1704, 1514, 1455, 1387, 1308, 1230, 1181, 1142, 1041, 1032, 993, 831, 747, 700; LRMS (ES^+) 708 ($M + Na^+$); HRMS (ES^+) Calcd. for $C_{28}H_{24}NNaO_4F_{13}$ ($M + Na^+$) 708.1395. Found 708.142.

R-**37a:** ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.17 (m, 7H), 6.90 (d, *J* = 8.8 Hz, 2H), 5.29 (dd, *J* = 3.4, 8.5 Hz, 1H), 4.51 (t, *J* = 8.7 Hz, 1H), 4.21 (dd, *J* = 3.6, 8.9 Hz, 1H), 4.17 (m, 1H), 4.05 (t, *J* = 5.8 Hz, 2H), 3.05 (dd, *J* = 7.6, 13.4 Hz, 1H), 2.68 (dd, *J* = 7.2, 13.4 Hz, 1H), 2.32 (m, 2H), 2.15 (m, 2H), 1.14 (d, *J* = 6.8, 3H).





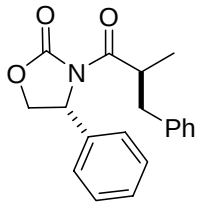
S-**37b** *S*-**36b**

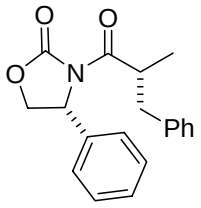
4(*S*)-{4-[(3-Perfluorooctyl)propyl-1-oxy]phenyl}-3-(2*R*-methyl-3-phenylpropionyl) oxazolidinone (*S*-37b): Purification through column chromatography (7:3 hexanes/EtOAc) provided major product *S*-**37b** (60%) as white solid, minor product *S*-**36b** (4%) also as a white solid, deacylation product *S*-**27b** (28%) and recovered imde *S*-**28b** (9%). *S*-**37b** is a little polar than *S*-**36b**.

S-**37b:** mp 138-143°; $[\alpha]_D^{20}$ +2.08 (c = 0.12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.21-7.05 (m, 7H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.42 (dd, *J* = 3.9, 8.7 Hz, 1H), 4.69 (t, *J* = 8.9 Hz, 1H), 4.24 (dd, *J* = 4.1, 8.9 Hz, 1H), 4.17 (m, 1H), 4.06 (t, *J* = 5.8 Hz, 2H), 3.07 (dd, *J* = 6.7, 13.3 Hz, 1H), 2.53

(dd, J = 7.7, 13.3 Hz, 1H), 2.41 (m, 2H), 2.16 (m, 2H), 1.13 (d, J = 6.7, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 158.6, 153.4, 138.9, 131.4, 129.2 (2C), 128.3 (2C), 127.3 (2C), 126.2, 115.0 (2C), 69.8, 66.4, 57.3, 39.7, 39.5, 28.0, 20.6, 16.2; IR (NaCl) 2923, 1758, 1704, 1514, 1387, 1308, 1205, 1180, 1147, 1032, 993, 831, 747, 701; LRMS (ES^+) 808 ($M + Na^+$); HRMS (EI^+) Calcd. for $C_{30}H_{24}NO_4F_{17}$ (M^+) 785.1434. Found 785.144.

S-**36b:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.17 (m, 7H), 6.91 (d, J = 8.7 Hz, 2H), 5.29 (dd, J = 3.4, 8.5 Hz, 1H), 4.51 (t, J = 8.7 Hz, 1H), 4.21 (dd, J = 3.5, 8.9 Hz, 1H), 4.17 (m, 1H), 4.06 (t, J = 5.8 Hz, 2H), 3.05 (dd, J = 7.2, 13.5 Hz, 1H), 2.68 (dd, J = 7.2, 13.4 Hz, 1H), 2.34 (m, 2H), 2.15 (m, 2H), 1.14 (d, J = 6.8, 3H).





R-**36** *R*-**37**

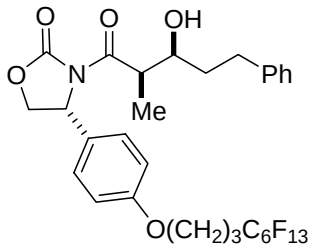
4(*R*)-Phenyl-3-(2*S*-methyl-3-phenylpropionyl)oxazolidinone (*R*-36): Purification through column chromatography (7:3 hexanes/EtOAc) provided major product *R*-**36** (62%) as white solid, minor product *R*-**37** (3%) also as a white solid, deacylation product *R*-**27** (13%) and recovered imide *R*-**28** (4%). *R*-**36** is a little polar than *R*-**37**.

R-**36:** mp 110-113°; $[\alpha]_D^{20}$ –8.33(c = 0.27, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.08 (m, 10H), 5.46 (dd, J = 4.1, 8.8 Hz, 1H), 4.71 (t, J = 8.8 Hz, 1H), 4.25 (dd, J = 4.1, 8.9 Hz, 1H), 4.20 (m, 1H), 3.09 (dd, J = 6.9, 13.3 Hz, 1H), 2.56 (dd, J = 7.7, 13.3 Hz, 1H), 1.15 (d, J = 6.7, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 153.3, 138.8, 129.1 (3C), 129.0 (2C), 128.6, 128.4 (2C), 126.2, 125.7 (2C), 69.7, 57.6, 40.2, 39.6, 16.2; IR (NaCl) 2923, 1758, 1704, 1514, 1455, 1387, 1308, 1205, 1180, 1147, 1032, 993, 831, 747, 701; LRMS (EI^+) 309 (M^+); HRMS (EI^+) Calcd. for $C_{19}H_{19}NO_3$ (M^+) 309.1365. Found 309.136.

R-**37:** See ref. 35.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.21 (m, 10H), 5.33 (dd, *J* = 3.6, 8.8 Hz, 1H), 4.53 (t, *J* = 8.7 Hz, 1H), 4.21-4.16 (m, 2H), 3.05 (dd, *J* = 7.8, 13.4 Hz, 1H), 2.69 (dd, *J* = 7.2, 13.5 Hz, 1H), 1.16 (d, *J* = 6.8, 3H).

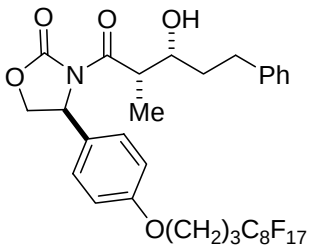


R-**38a**

4(*R*)-{4-[(3-Perfluorohexyl)propyl-1-oxy]phenyl}-3-(2*R*-methyl-3*S*-hydroxy-5-phenyl-propionyl)oxazolidinone (*R*-38a): To a solution of *R*-**28a** (0.10g, 0.168 mmol) in CH_2Cl_2 at 0 °C was added dropwise Bu_2BOTf (1.0 M in CH_2Cl_2, 0.20 mL, 0.200 mmol) followed by the dropwise addition of DIPEA (0.04 mL, 0.22 mL). The reaction mixture was stirred for 1 h at 0 °C and then cooled to −78 °C. Thereafter, freshly distilled hydrocinnamaldehyde (0.04 mL, 0.252 mmol) was added dropwise and the reaction mixture was stirred at −78 °C for 1 h. The reaction mixture was warmed to room temperature over 1 h and stirred at the same temperature for 2 h. Then it was cooled to 0 °C and 0.8 mL of the mixture of pH 7 phosphate buffer and methanol

(1:3) was added. The resulting cloudy solution was then treated with 0.6 mL of a mixture of methanol and 30% H_2O_2 (2:1) via syringe at such a rate so as to keep the temperature below 10 °C. The solution was stirred for 1 h and the volatile material was removed with a rotary evaporator. The resulting mixture was diluted with EtOAc and the organic layer was washed with 5% aq. HCl solution, aq. $NaHCO_3$ solution, brine, dried ($MgSO_4$), filtered and concentrated to give the crude product. Purification by flash chromatography (7:3 hexanes/EtOAc) provided *R*-**38a** (0.050g, 38%) as white solid and recovered starting imide (0.055 g, 55%).

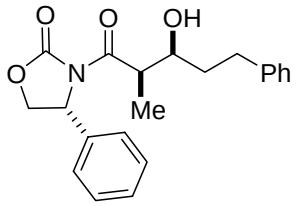
mp 79-84°; $[\alpha]_D^{20}$ –3.86 (c = 0.43, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.15 (m, 7H), 6.92 (d, *J* = 8.5 Hz, 2H), 5.40 (dd, *J* = 3.8, 8.7 Hz, 1H), 4.69 (t, *J* = 8.8 Hz, 1H), 4.27 (dd, *J* = 3.8, 8.9 Hz, 1H), 4.05 (t, *J* = 5.8, 2H), 3.96 (m, 1H), 3.80 (m, 1H), 2.86-2.80 (m, 2H), 2.71-2.67 (m, 1H), 2.33-2.28 (m, 2H), 2.14-2.10 (m, 2H), 1.91-1.86 (m, 1H), 1.68-1.66 (m, 1H), 1.17 (d, *J* = 7.1, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 158.9, 153.2, 141.8, 131.3, 128.5 (2C), 128.3 (2C), 127.2 (2C), 125.8, 115.1 (2C), 70.3, 70.0, 66.4, 57.1, 42.3, 35.4, 32.1, 27.9, 20.6, 10.4; IR (NaCl) 3512, 3063, 3028, 2944, 2880, 1782, 1705, 1613, 1587, 1516, 1497, 1454, 1385, 1319, 1247, 1204, 1145, 1122, 1030, 953, 835, 812, 747, 733, 699, 653; LRMS (EI^+) 729 (M^+); HRMS (EI^+) Calcd. for $C_{30}H_{28}NO_5F_{13}$ (M^+) 729.1760. Found 729.172.



S-**39b**

4(*S*)-{4-[(3-Perfluorooctyl)propyl-1-oxy]phenyl}-3-(2*S*-methyl-3*R*-hydroxy-5-phenyl-propionyl)oxazolidinone (*S*-39b): 53 % yield of *S*-**39b** was and 40% of starting material was recovered.

mp 105-109°; $[\alpha]_D^{20}$ +34.61 (c = 0.38, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.21 (m, 7H), 6.92 (d, *J* = 8.6 Hz, 2H), 5.41 (dd, *J* = 3.8, 8.7 Hz, 1H), 4.70 (t, *J* = 8.9 Hz, 1H), 4.27 (dd, *J* = 3.9, 8.9 Hz, 1H), 4.06 (t, *J* = 5.8, 2H), 3.97 (m, 1H), 3.80 (m, 1H), 2.88-2.80 (m, 2H), 2.73-2.63 (m, 1H), 2.35-2.26 (m, 2H), 2.14-2.09 (m, 2H), 1.92-1.86 (m, 1H), 1.73-1.66 (m, 1H), 1.18 (d, *J* = 7.1, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 158.9, 153.2, 141.9, 131.3, 128.5 (2C), 128.4 (2C), 127.2 (2C), 125.8, 115.1 (2C), 70.3, 70.0, 66.4, 57.1, 42.3, 35.4, 32.1, 28.0, 20.6, 10.4; IR (NaCl) 3521, 3027, 2922, 1782, 1705, 1614, 1515, 1454, 1385, 1248, 1152, 1031, 983, 834, 812, 738, 703, 656; LRMS (ES^+) 852 ($M + Na^+$); HRMS (ES^+) Calcd. for $C_{32}H_{28}NNaO_5F_{17}$ ($M + Na^+$) 852.1594. Found 852.160.



R-**38**

(*R*)-Phenyl-3-(2*R*-methyl-3*S*-hydroxy-5-phenylpropionyl)oxazolidinone (*R*-38): 81% of *R*-**38** was isolated and 7% of starting material was recovered.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.12 (m, 10H), 5.39 (dd, *J* = 4.0, 8.7 Hz, 1H), 4.66 (t, *J* = 8.9 Hz, 1H), 4.21 (dd, *J* = 4.0, 8.9 Hz, 1H), 3.92-3.86 (m, 1H), 3.77-3.69 (m, 1H), 2.83-2.80 (m, 1H), 2.78-2.73 (m, 1H), 2.66-2.56 (m, 1H), 1.89-1.76 (m, 2H), 1.13 (d, *J* = 7.1, 3H);

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