Aldol Condensation of Evans Chiral Enolates with Acetophenones. Its Application to the Stereoselective Synthesis of Homochiral Antifungal Agents

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The results of the aldol condensation of Evans chiral imide enolates with a series of acetophenones are reported. Activated acetophenones, such as 2,4-difluoroacetophenone, α-chloroacetophenone, and α-chloro- and α-bromo-2,4-difluoroacetophenone, reacted with the lithium enolate of **5** with good levels of enolate facial diastereoselectivity toward the (2*R*)-isomers (>10:1) but with low *anti*:*syn* selectivity (*ca.* 3:2). Sodium and potassium enolates of **5** were also tested. The nature of the solvent influenced the degree of diastereofacial biases. Less activated ketones, such as acetophenone, reacted only to a *ca.* 50% extent without facial or *anti*:*syn* stereoselectivities. Chairlike pericyclic transition states are believed to govern the reaction. When α-bromoacetophenones were used, longer reaction times and higher temperatures resulted in the selective formation of the $\mathbf{S_2}$ epoxide (*syn*-(2*R*,3*R*), **11**) with good levels of selectivity. Equilibration studies performed in THF with the corresponding metal aldolates generated *in situ* by deprotonation of the aldol adducts indicated that an aldol/retroaldol process was first established followed by a slower formation of the epoxide. Stereoselection is thought to originate by a faster oxirane formation of the *syn* bromohydrins as compared to the *anti* due to steric interactions between the α-group and the leaving bromide. Optimum retroaldol–epoxide formation rates were obtained using the sodium enolate in ether at −78 °C. Under these conditions the $\mathbf{S_1}$:$\mathbf{S_2}$:$\mathbf{A_1}$:$\mathbf{A_2}$ ratio of epoxides was 6:83:10:0.3 and the major isomer was isolated by recrystallization in 79% yield. An improved synthesis of amino alcohol **3**, an advanced intermediate in the preparation of orally active antifungal agents, using a tandem of this new ketone–aldol technology and a Curtius rearrangement, is reported. The new sequence proceeds with an overall yield of 53% and does not require chromatographic purifications.

Introduction

In 1981, Evans and co-workers reported the aldol condensation of the boron enolates of homochiral imide **1** with aldehydes as a useful tool for constructing vicinal *syn* stereogenic centers in a highly controlled fashion (Figure 1).[1] Since then, this particular reaction has been widely applied in the synthesis of natural products and pharmaceuticals.[2] More recently, several variations, such as the type of metal, stoichiometry, and presence of Lewis acids, have been introduced as a means of modifying the original diastereoselective biases of the reaction.[3] Meanwhile, other chiral enolates have also been reported to undergo stereoselective aldol condensations with comparable levels of stereoselection.[4] However, whereas optimization of the enolate unit has received a great deal of interest, the same cannot be said about the electrophile moiety, where aldehydes have concentrated all the attention. For example, to the best of our knowledge there is only one paper in which the condensation of an Evans chiral enolate with a ketone has been mentioned, and that was the highly activated hexafluoroacetophenone.[5] Thermodynamically unfavored equilibria, lack of stereoselection, and competing transenolization processes are some of the potential drawbacks that one could predict for such a transformation. Wherever the problem may lie, the truth is that the use of chiral enolates in the diastereoselective aldol reaction with ketones has been surprisingly overlooked.

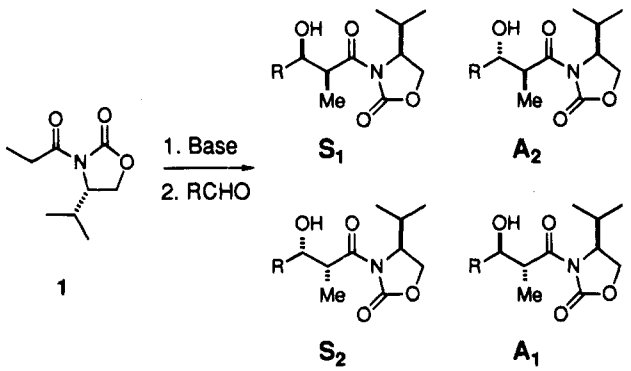

Figure 1. Stereochemistry of aldol adducts.

[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1995.

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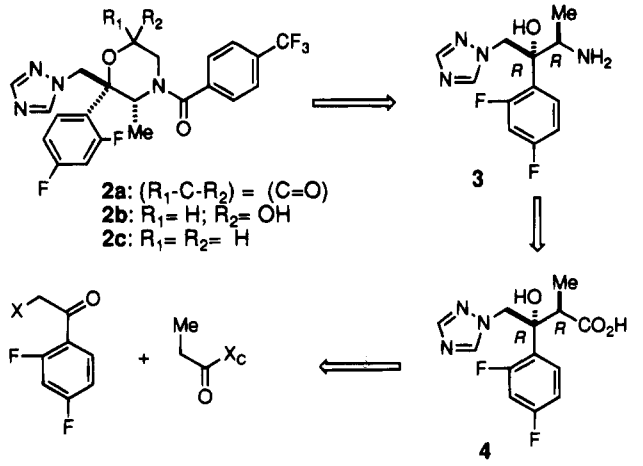
Scheme 1. Retrosynthesis of Antifungal Agent 2



In the search for new, orally active antifungal agents we have recently described compounds of formula **2** (Scheme 1) as having excellent anti *Candida* properties in *in vivo* animal models of systemic and vaginal candidiasis.[6] For large scale preparations of **2** and other related compounds we required an expeditious enantioselective synthesis of amino alcohol **3**. Previously reported preparations of this intermediate are long (10 steps, 15% overall yield), and they involve column chromatography purifications and the use of expensive reactants.[7] Thus, bearing in mind the fact that the Curtius rearrangement constitutes an excellent way of converting acids into amines with retention of configuration at the migrating center,[8] we identified compound **4** as the key intermediate of our synthesis through a retrosynthetic analysis of **2**. The β-hydroxy-α-methylcarboxylic acid unit of **4** automatically suggested an unprecedented, *syn*-selective aldol condensation between a chiral propionyl unit and an acetophenone derivative.

In this paper we report the details of our investigations on the aldol condensation of Evans chiral imide enolates with substituted acetophenones, and we describe the application of this particular reaction to the preparation of compound **3**, an advanced intermediate in the synthesis of the new orally active antifungal agents **2**. The new synthesis of **3** described in this work consists of five steps from propionyl imide **5**, it proceeds with an overall yield of 53% yield, and it requires no chromatography purification.

Results

Aldol Reaction Using α-Chloroacetophenones. Previous work[1,9] has shown that the aldol condensation of the lithium enolate of propionyl imide **1** with aldehydes proceeds only with a certain degree of stereoselectivity. Thus, the reaction with benzaldehyde furnishes a 7:32:59:2 ratio of the $\mathbf{S_1}$:$\mathbf{S_2}$:$\mathbf{A_1}$:$\mathbf{A_2}$ adducts (see Figure 1 for nomenclature). That is to say, the transformation exhibits a good *si* diastereofacial bias ($\mathbf{S_2}+\mathbf{A_1}$:$\mathbf{S_1}+\mathbf{A_2}$ = 10:1) but displays no *syn:anti* selection ($\mathbf{S_1}+\mathbf{S_2}$:$\mathbf{A_2}+\mathbf{A_1}$, *i.e.* *syn:anti* = 1:1.5). Similar (2*R*)-selective trends were found using aliphatic aldehydes, although in this case the *syn* adduct was majority (*syn:anti* = 5.6:1 for isobutyraldehyde and 2.3:1 for *n*-pentanal).[10,11]

The equivalent reaction using ketones as the electrophile has not yet been explored. We first believed that a low reactivity of the ketone may have accounted for the hampering of this type of transformation. In the hope that the use of an α-haloacetophenone could both activate the carbonyl and push the reaction to completion by an *in situ* intramolecular trapping of the β-alkoxy-γ-halo intermediate to form a β,γ-epoxy derivative, we first employed α-chloro-2,4-difluoroacetophenone as the ketone source. However, when the lithium enolate of imide **5**[12] was prepared (LDA, −78 °C, THF)[13] and condensed with α-chloro-2,4-difluoroacetophenone (1.2 equiv, −78 °C, 1 h), chlorohydrins were obtained in good yield (scheme shown in Table 1). We reasoned that the activation of the carbonyl group resulting from the α-halogen or the phenyl substitution, or both, was enough to provide the required electrophilicity (see below for the results obtained with other acetophenones) and that internal trapping was, therefore, not a requisite to push the reaction to completion. Indeed, α-substitution has been reported by Thornton to dramatically accelerate the aldol condensation of certain lithium enolates with ketones.[14]

Table 1 shows the ratios obtained by HPLC analysis of the unpurified reaction mixtures using a wide range of conditions.[15] The results indicate that the overall behavior observed using α-chloro-2,4-difluoroacetophenone is similar to that obtained with benzaldehyde, namely a good chirality transfer at the α-carbon ($\mathbf{S_2}+\mathbf{A_1}$:$\mathbf{S_1}+\mathbf{A_2}$ = 10:1) and a very low, although reversed, *syn:anti* selectivity (1.3:1) (entry 1). Reaction times of 2 min (entry 1) or 1 h (entry 2) as well as the use of LHMDS instead of LDA (entry 8) did not produce significant differences in yield or product ratios, except for the small amounts of $\mathbf{A_2}$. The percentages of this latter diastereomer showed a variability (0.4−6%), the reason for which has not yet been determined. An inverse addition, in which the cooled (−78 °C) preformed lithium enolate was added via cannula to the ketone, was also tested to prove that a deficit or excess of ketone did not modify the product ratio (entry 3). Instead, heating the reaction proved to be detrimental. Thus, stirring at −50 °C for 1 h started to produce both equilibration and increasing amounts of retroaldol products (entry 4). Higher temperatures (−20 °C, 1 h) caused the reaction to revert almost completely to the starting materials (entry 5), indicating that at this temperature the retroaldol process is preferred. The nature of the solvent seemed to play

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(7) (a) Konosu, T.; Miyaoka, T.; Tajima, Y.; Oida, S. *Chem. Pharm. Bull.* **1991**, *39*, 2241−2246. (b) Amino alcohols **3** and **23** were synthesized from (*R*)-methyl lactate according to the method described in: Tasaka, A.; Tamura, N.; Matsushita, Y.; Teranishi, K.; Hayashi, R.; Okonogi, K.; Itoh, K. *Chem. Pharm. Bull.* **1993**, *41*, 1035−1042.

(8) An, B.; Kim, H.; Cha, J. K. *J. Org. Chem.* **1993**, *58*, 1273−1275.

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(10) Nerz-Stormes, M.; Thornton, E. R. *J. Org.Chem.* **1991**, *56*, 2489−2498.

(11) The original ratios reported for diastereomers $\mathbf{A_1}$ and $\mathbf{S_2}$ in the lithium aldol of isobutyraldehyde and *n*-pentanal in refs 1 and 9 have been carefully examined in ref 10 and proved to be inverted. The new corrected values have been used in this work.

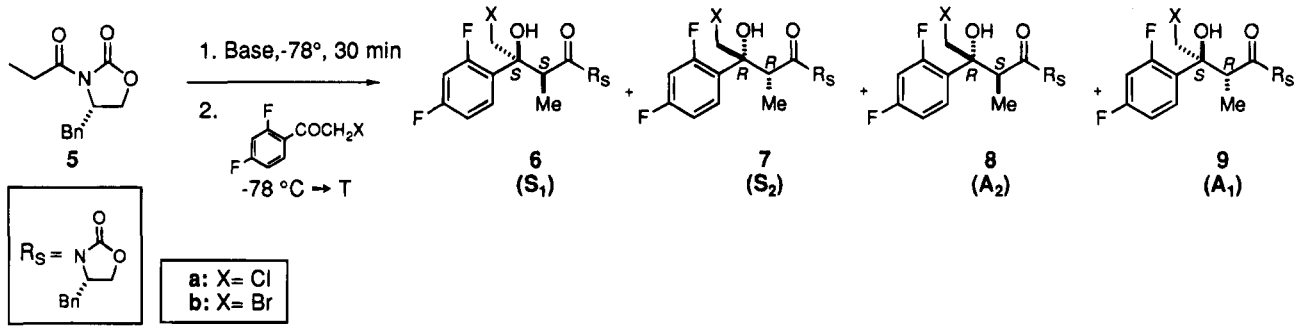
(12) We chose (*S*)-4-benzyl-2-oxazolidinone among the Evans chiral auxiliaries because of the in-house, multikilogram availability of this substance from our fine chemical subsidiary Urquima.

(13) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739.

(14) Das, G.; Thornton, E. D. *J. Am. Chem. Soc.* **1990**, *112*, 5360−5362.

(15) Stereochemical assignments for the halohydrins and epoxides were ultimately made by chemical correlation to amines **3** and **23** (see the Experimental Section for the rationale).

Table 1. The Aldol Condensation of the Enolate of Imide 5 and α-Halo-2,4-difluoroacetophenone[a]



entry	X	base[b]	rxn time, min	T,[c] °C	solv	halohydrins S1 (6)	S2 (7)	A1 (8)	A2 (9)	S2:S1 (7:6)	syn:anti	halohydrin:epoxide	HPLC yield,[d] %
1	Cl	LDA	2	−78	THF	4.5	52	37	6.5	11:1	1.3:1	>100:1	84
2	Cl	LDA	60	−78	THF	4.5	58	37	0.4	13:1	1.7:1	>100:1	88
3	Cl	LDA (inv addn)	60	−78	THF	4.5	53	38	4.5	11:1	1.3:1	>100:1	82
4	Cl	LDA	60	−50	THF	10	49	38	2.6	5:1	1.5:1	>100:1	81
5	Cl	LDA	60	−20	THF	32	20	48[e]	−[l]	0.6:1	1:1[e]	50:50[f]	12
6	Cl	LDA/Ti(iOPr)$_3$Cl	120	−40	THF	53	10	37	−	1:5	1.7:1	>100:1	35
7	Cl	LDA/Et$_2$AlCl	60	−78	THF	3.5	45	50	1	13:1	0.9:1	>100:1	37
8	Cl	LHMDS	60	−78	THF	4	52	41	3	13:1	1.3:1	>100:1	86
9	Cl	LHMDS	2	−78	Et$_2$O	2.3	56	40	2	24:1	1.4:1	>100:1	85
10	Cl	LHMDS/H$_2$O[g]	60	−78	THF	3.7	51	45	0.3	14:1	1.2:1	>100:1	66
11	Cl	NaHMDS	60	−78	THF	10	42	46	2.2[e]	4:1	1.1:1	87:13[h]	25
12	Cl	KHMDS/tol[i]	60	−78	THF	17	32	47	2[e]	2:1	1:1	40:60[j]	6
13	Br	LHMDS	2	−78	THF	3.3	48	33	1	14:1	1.5:1	85:15[k]	73
14	Br	LHMDS	2	−78	Et$_2$O	2.5	54	37	1	22:1	1.5:1	95:5	75

[a] Product ratios are taken directly from the UV response of the HPLC detector. See the Experimetal Section for details. [b] Unless otherwise noted, a THF solution of the base was used. [c] T indicates final temperature; the initial temperature was always −78 °C. [d] Sum of the peak percent areas assigned to the halohydrins as given by the HPLC detector. [e] Nonbaseline resolution of HPLC peaks. [f] The epoxide fraction consisted in a 50:50:<1:<1 mixture of S_1:S_2:A_1:A_2. [g] Reaction performed in the presence of 0.2 equiv of water. [h] The epoxide fraction consisted in a 15:50:35:<1 mixture of S_1:S_2:A_1:A_2. [i] Transenolization products and starting material present in the crude reaction mixture. [j] The epoxide fraction consisted in a 15:70:15:<1 mixture of S_1:S_2:A_1:A_2. [k] The epoxide fraction consisted in a 7:73:20:<1 mixture of S_1:S_2:A_1:A_2; [l] (−) indicates <0.2%.

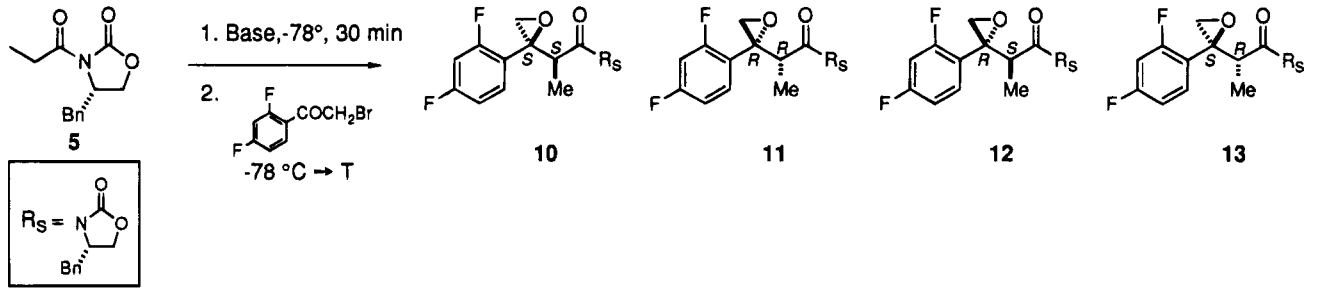
an important role, but only regarding enolate face selection. Thus, the S_2:S_1 ratio was substantially enhanced (24:1) when ether was used, whereas the *syn:anti* ratio remained practically unchanged (entry 9). One trial was performed in the presence of water (20% equiv) to ascertain how traces of humidity could influence product equilibration (entry 10), but comparable ratios were obtained. Except for entry 5, formation of epoxides was negligible in all cases (<1%).

Sodium and potassium enolates of **5** are more reactive than their lithium counterparts.[13] Furthermore, the more ionic sodium and potassium aldolates could afford epoxides more rapidly than lithium aldolates and, in this way, completion of the reaction could be highly favored. But at the same time, the impaired chelating properties of these metals could raise the energy of the aldolates and render the reaction energetically disfavored. Thus, in the attempt to investigate the degree of these antagonistic effects we performed the reaction of the sodium[13] and potassium[16] enolates of **5**, generated using NaHMDS and KHMDS, respectively, with α-chloro-2,4-difluoroacetophenone. Unfortunately, and in spite of numerous attempts, these reactions did not proceed to any large extent (5−20% yield by ^{1}H NMR). To avoid possible retroaldol phenomena associated with the quenching procedure, several approaches were investigated including addition of aqueous phosphate, pH 7, buffer, saturated aqueous NH_4Cl, precooled (−78 °C) glacial AcOH in THF, and *p*-TsOH in THF. Inverse quenching was also tested. In all cases, very little reaction and mostly recovery of the starting materials was observed. Increasing the reaction temperature to −40 °C was also seemingly to no avail. Higher temperatures (−20 to −10 °C) started to cause enolate decomposition, especially with potassium. Interestingly, HPLC analysis of the crude reaction mixtures indicated that the little product formed showed lower S_2:S_1 and *syn:anti* ratios than those obtained with lithium (footnote in entries 11 and 12). As expected, an increasing degree of epoxide formation was seen in the series Li−Na−K (*ca.* <1%, 13%, and 61% of the total product, respectively).

Aldol Condensation with α-Bromo-2,4-difluoroacetophenone. Since the aldol reaction using α-chloro-2,4-difluoroacetophenone displayed poor *syn:anti* stereoselection and did not afford epoxides in a convenient manner, we wondered whether changing the nature of the leaving group in the acetophenone moiety would modify the course of the reaction. Attention was thus focused on the aldol condensation using α-bromo-2,4-difluoroacetophenone, a more suitable candidate to afford epoxides directly. On the basis of the results obtained with the chloro analogue, we did not expect substantial changes in the stereochemical outcome of the aldol process itself. However, if epoxide formation was to be the rate-determining step for the overall transformation, it was possible that new nonbonded interactions imposed by the required *anti*-periplanar OCCBr angle during elimination could arise in the corresponding TS, resulting in a favorable diastereomeric *syn:anti* ratio of epoxides.

(16) Evans, D. A.; Britton, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 6881−6883.

Table 2. The Aldol Condensation of the Enolate of Imide 5 and α-Bromo-2,4-difluoroacetophenone[a]



entry	base[b]	rxn time, min	T,[c] °C	solv	S_1 (10)	epoxides S_2 (11)	A_1 (12)	A_2 (13)	S_2:S_1 (11:10)	*syn:anti*	halohydrin:epoxide	HPLC yield,[d] %
1	LDA	180	−10	THF	11	76	12	1	7:1	7:1	<1:100	85
2	LHMDS	180	−10	THF	11	74	14	1	7:1	6:1	<1:100	80
3	LHMDS	180	−10	Et_2O	28	62	8.5	1.5	2:1	9:1	<1:100	74
4	NaHMDS	2	−78	THF	6	69	25	0.5	11:1	3:1	2:98	81
5	NaHMDS	2	−78	Et_2O	6	85	9	0.2	14:1	9:1	15:85[e]	63
6	NaHMDS	60	−78	Et_2O	6	83	10	0.3	14:1	9:1	1:99	89
7	NaHMDS/solid	60	−78	Et_2O	7	77	16	−[g]	10:1	5:1	6:94	90
8	NaHMDS/tol	60	−78	tol	8	70	21	1	9:1	3.5:1	1:99	72
9	KHMDS/tol[f]	2	−78	THF	6	62	30	2	10:1	2:1	<1:100	69
10	KHMDS/tol[f]	2	−78	Et_2O	5	70	25	−	14:1	3:1	7:93	53

[a] Product ratios are taken directly from the UV response of the HPLC detector. See the Experimetal Section for details. [b] Unless otherwise noted, a THF solution of the base was used. [c] *T* indicates final temperature; the initial temperature was always −78 °C. [d] Sum of the peak percent areas assigned to the epoxides as given by the HPLC detector. [e] The halohydrin fraction consisted in a 6:34:60:<0.2 mixture of S_1:S_2:A_1:A_2. [f] Transenolization products and starting material present in the crude reaction mixture. [g] (−) indicates <0.2%.

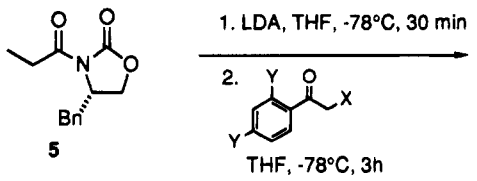
When the reaction was performed under the standard conditions (LHMDS, −78 °C, THF; RBr, −78 °C, THF) and quenched rapidly (2 min) after addition of the bromo derivative, bromohydrins were the main products formed, together with small amounts of epoxides (Table 1, entry 13).[15] Up to this stage, no major differences at the halohydrin level were found between the aldol reaction using α-bromo-2,4-difluoroacetopheone and that using α-chloro-2,4-difluoroacetophenone, since both showed a poor (3:2) *syn:anti* selection and a good diastereofacial selectivity. Overall facial diastereoselection (*i.e.* $\mathbf{S_2}+\mathbf{A_1}$:$\mathbf{S_1}+\mathbf{A_2}$) was improved for bromo (19:1), but this was due to the lower amount of isomer $\mathbf{A_2}$ formed in this case. The significant differences started to appear when the reaction mixture was allowed to react for longer periods of time and at higher temperatures (Table 2), as the TLC spots converged into a new, *major* substance. Product isolation and characterization identified the compound as the *syn*-(2*R*,3*R*)-epoxide (**11**). Separation by silica gel chromatography and HPLC−MS analysis allowed the full characterization of two other minor diastereomers, namely the *syn*-(2*S*,3*S*) (**10**) and the *anti*-(2*R*,3*S*) (**13**) epoxides. The stereochemistries of these three adducts were unambiguously determined by chemical correlation with compounds **3** and **23** as shown in Scheme 6. Finally, the fourth epoxide [*anti*-(2*S*,3*R*) (**12**)] was formed in very small amount, but it could still be detected and identified by HPLC−MS. Its absolute stereochemistry was assigned by default.

Since the absolute and relative rates of epoxide formation could be highly dependent on the type of counterion and the nature of the solvent, several experiments were performed to determine the role of these variables in the outcome of the stereoselectivity. First, the sodium and potassium enolates of **5** were condensed with α-bromo-2,4-difluoroacetophenone, and the reaction was quenched 2 min later. HPLC−MS analysis of the unpurified mixtures revealed that, contrarily to the lithium case, sodium and potassium enolates very rapidly yielded the epoxides at −78 °C (Table 2, entries 4 and 9). Only trace amounts of bromohydrins were detected. Interestingly, the $\mathbf{S_2}$:$\mathbf{S_1}$ ratio of epoxides was higher for sodium and potassium (*ca.* 12:1) than for lithium (*ca.* 7:1), whereas the *syn:anti* ratio showed an opposite trend: 7:1 for lithium, 3:1 for sodium, and 2:1 for potassium. With the potassium enolates, a competing transenolization process was observed, resulting in recovery of part of the starting imide and other self-condensed, non-imide products. This limited its use for potential synthetic purposes.

The effect of the solvent was also investigated. In ether and under bromohydrin-yielding conditions (−78 °C, 2 min) the lithium enolate of **5** (generated with a THF solution of LHMDS and thus still containing that solvent) afforded an improved $\mathbf{S_2}$:$\mathbf{S_1}$ ratio (22:1) as compared to that obtained in THF (14:1) (Table 1, entries 13 and 14). This trend was already observed in the chloro series (see Table 1, entry 9). However, epoxide formation in ether required higher temperatures, and this dramatically reduced the diastereofacial selectivity within these compounds ($\mathbf{S_2}$:$\mathbf{S_1}$ = 2:1) (Table 2, entry 3). This discouraging result prompted the use of sodium, as more reactive aldolates could already eliminate bromide in ether at −78 °C. Indeed, when the reaction was performed with the sodium enolate of **5** (1 *M* NaHMDS in THF) in ether at −78 °C and quenched after 1 h, epoxides were formed cleanly and the diastereomeric ratios were best, with a high diastereofacial selectivity within the *syn* adducts ($\mathbf{S_2}$:$\mathbf{S_1}$ = 14:1) and good *syn:anti* selection (9:1) (Table 2, entry 6). Running the reaction using solid NaHMDS to avoid any source of THF afforded comparable $\mathbf{S_2}$:$\mathbf{S_1}$ ratios and a somewhat lower *syn:anti* selectivity (entry 7). This impairment was more pronounced in toluene, where the *syn:anti* selectivity dropped to 3.5:1 (entry 8).

With these results in hand, we sought to broaden our knowledge in this series by exploring the reaction with other metal enolates (see Table 1). Thus, not surprisingly, the poorly nucleophilic boron enolate of propionyl imide **5** [1 equiv of a 1 M solution of Bu_2BOTf in CH_2Cl_2,

Table 3. Product Distribution of the Aldol Condensation between the Lithium Enolate of Imide 5 and Different Acetophenones[a]



entry	Y	X	aldol adducts S_1	S_2	A_1	A_2	S_2:S_1	*syn:anti*	HPLC yield,[b] %
1[c]	H	H	31	42	24	2.4	0.7:1	2.7:1	62
2	F	H	6[d]	56[d]	32	6	9:1	1.6:1	80
3[c,e]	H	Cl	3.7	41	52	3.3	11:1	0.8:1	88
4[c]	H	OMe	10	48	42	–	5:1	1.4:1	37

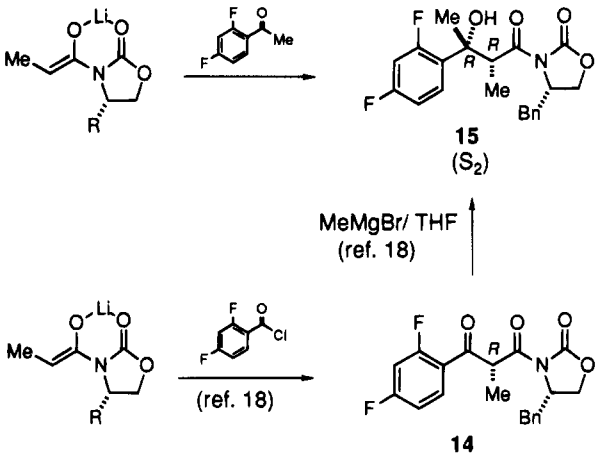
[a] Product ratios are taken directly from the UV response of the HPLC detector. See the Experimetal Section for details. [b] Sum of the peak percent areas assigned to the products as given by the HPLC detector. [c] HPLC peaks assigned by MS and/or by HPLC pattern analogy. [d] Nonbaseline resolution on the HPLC chromatogram. [e] No detectable amounts of epoxide. [f] (–) denotes <0.2%.

(*i*-Pr)$_2$NEt, CH_2Cl_2, −78 °C, 0.5 h][1] failed to react with both α-bromo- and α-chloro-2,4-difluoroacetophenone. Addition of 2 equiv of the boron triflate to explore the conditions reported by Heathcock[3d] was also unsuccessful. Chlorotitanium enolates generated according to the protocol previously reported by Evans[17] [$TiCl_4$, (*i*-Pr)$_2$NEt, CH_2Cl_2), 0 °C, 1 h] also failed to react. Triisopropoxytitanium enolates generated by the Thornton procedure[10] [LDA, −78 °C, then Ti(O*i*-Pr)$_3$Cl, THF, −40 °C] gave little reaction but an unexpected switch within the *syn* isomers (S_2:S_1 = 1:5.5). However, the major *anti* isomer was still A_1. Finally, running the lithium reaction with the ketone precomplexed with a Lewis acid (2 equiv of Et_2AlCl)[3d] did not produce major changes except for a slight increase of the *anti* isomer.

Aldol Condensation with Other Acetophenones. To investigate the scope of the present aldol condensation, the LDA-generated lithium enolate of imide **5** was reacted with a series of less activated acetophenones. The diastereomeric ratios are shown in Table 3.

We first tried acetophenone itself (entry 1) and found that the reaction repeatedly went to only *ca.* 60% completion, both at −78 °C and at −20 °C. As with the substituted acetophenones, the *syn:anti* ratios were low, but surprisingly, a complete lack of stereoselectivity was found within the *syn* isomers. Activation of the carbonyl group via phenyl substitution (*i.e.* 2,4-difluoroacetophenone, entry 2) was sufficient to make the reaction go to completion and recover facial diastereoselection. Seemingly, activation of the carbonyl group by an α-heteroatom (α-chloro, entry 3) resulted in reaction completion and comparable stereoselective biases, although a slight shift toward the *anti* products was detected (*ca. syn:anti* = 0.8:1). α-Methoxyacetophenone gave little transformation, with somewhat lower diastereomer ratios (entry 4). Finally, α-(1*H*-1,2,4-triazol-1-yl)-2,4-difluoroacetophenone failed to react under our experimental conditions (Li, Na, and K enolates). We later found out that in this latter process the retroaldol reaction is preferred, as the corresponding products spontaneously revert to the starting materials upon aldolate generation with base. In general, the compounds under the HPLC peaks were identified by their MS spectra, and the absolute stereochemistry was tentatively assigned by analogy with the HPLC patterns of the α-halo-2,4-difluoroacetophenone aldol reactions of Table 1. To establish unambiguously the veracity of one of these assignments, the aldol adduct tentatively assigned as *syn*-(2*R*,3*R*) (**15**) (entry 2) was independently prepared via diastereoselective acylation–methyl Grignard addition, a two-step process known to afford the S_2 stereochemistry.[18] (Scheme 2)

Scheme 2. Stereochemistry Proof of Compound 15



A first attempt using nonaromatic ketones, such as acetone, and the lithium enolate of **5** afforded aldol adducts, although in a nonselective way.

Discussion. The prevalence of the (2*R*)-isomers observed in this study is interpreted as the reaction taking place preferentially via a transition state (TS) in which the electrophile approaches from the *si* face of the chelated lithium (*Z*)-enolate, in the same way as the related alkylations,[13] acylations,[18] and aldol condensations with aldehydes[9,10] using these enolates and opposite and complementary to the diastereofacial selectivity of the corresponding boron enolates[1] (Scheme 3). While this model has found wide acceptance to explain α-induction in chemical transformations of this kind, there is still controversy about the origin of the stereoselection at the β-carbon in the aldol condensation, *i.e.* the factors dictating the *syn:anti* biases. Aggregated or monomeric reacting enolates,[19] open or chelated transition states,[3d] and chairlike or boatlike pericyclic structures[20] have all been invoked in one case or another to explain particular stereoselection outcomes. Since the biases observed in the aldol condensation using lithium enolates and aldehydes have been satisfactorily explained on the basis of the energy analysis of monomeric, Zimmerman–Traxler pericyclic TS,[20] we decided to adopt this working model for the rationale of our results.

The low levels of *syn:anti* selection reported for the lithium aldol reactions with aldehydes have been in part assigned to a concomitant participation of chairlike and boatlike TS leading to different stereochemistries.[20,21]

(17) Evans, D. A.; Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216.

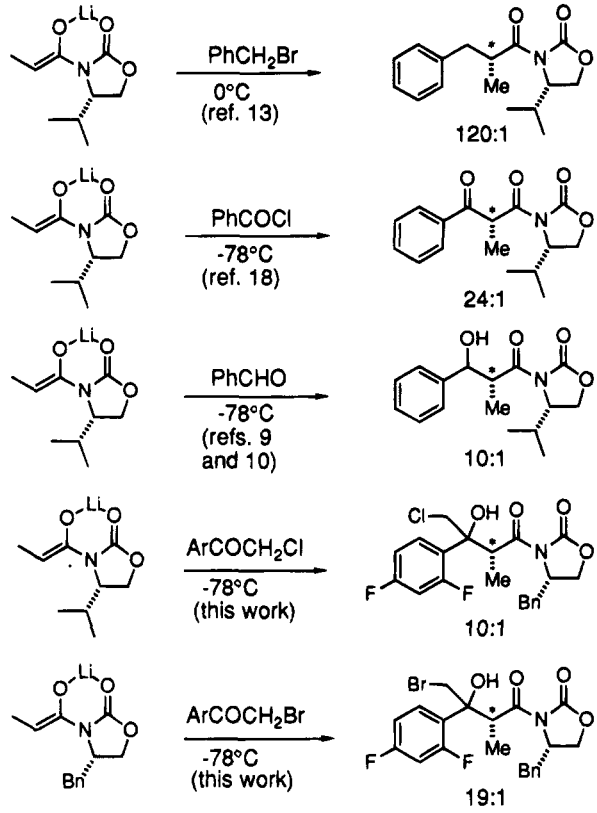
(18) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154–1156.

(19) Arnett, E. M.; Palmer, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 7354–7360 and references cited therein.

(20) Evans, D. A.; Nelson, J. V.; Taber, T. T. *Top. Stereochem.* **1982**, *13*, 1.

(21) Seebach has pointed out that the two long Li–O bonds (*ca.* 2 Å) confer to the presumed pericyclic transition states a rather different shape from that of cyclohexane conformers. Seebach, D.; Amstutz, R.; Dunitz, J. *Helv. Chim. Acta* **1981**, *64*, 2622–2626.

Scheme 3. α-Induction of Chiral Imide Enolates



However, when the electrophile is a ketone, the reaction must proceed only through chairlike TS as boatlike structures would inevitably carry highly energetic 1,2-eclipsing interactions (Figure 2). This means that the low *syn:anti* selectivity observed in the aldol condensation with ketones is most probably a direct consequence of the similar size of the ligands attached to the carbonyl group (Ar *vs* CH_2Cl) in a chairlike TS like the one shown in Figure 3.

The previous rationalizations would account for the high diastereofacial selectivity and the low *syn:anti* ratios observed in the aldol step. Prior to the rationalization of the stereoselection observed during the second step, *i.e.* the epoxide formation, we needed to obtain some insight into the extension and ease of the retroaldol reaction.

It has been stated that lithium aldol reactions are practically instantaneous, even at −80 °C.[22] Indeed, when we quenched the aldol reaction immediately (2 min) after addition of the haloacetophenone at −78 °C, HPLC analysis indicated disappearence of the starting imide **5** and formation of a roughly 3:2 kinetic mixture of the ($\mathbf{S_2}$):($\mathbf{A_1}$) halohydrins together with small amounts of the two other diastereomers (Table 1, entries 1 and 13). To ascertain when and to what extent the retroaldol process started to appear, we generated the metal aldolates of the *anti* adduct **9** *in situ* by treatment with 1 equiv of base at −78 °C and quenched the mixture at different times and temperatures. The results are shown in Table 4.

First, we found that equilibration within the chloro series takes place sluggishly at −78 °C (entries 1 and 2)[23] and that it occurs without significantly increasing the amounts of $\mathbf{S_1}$ or $\mathbf{A_2}$ ($\mathbf{S_2}$:$\mathbf{S_1}$ = 16:1, after both 0.5 and 3 h). Furthermore, under these conditions only trace amounts of retroaldol products (**5** and the acetophenone) are formed. When the temperature was increased (−50 °C), the ratios obtained departing from the *in situ* generated aldolate of **9a** (entry 3) and those registered for the aldol reaction at the same temperature (Table 1, entry 4) started to converge, indicating that the extent of the equilibration was rapidly increasing with temperature. Significantly, the $\mathbf{S_2}$:$\mathbf{S_1}$ ratio dropped to 9:1 and the retroaldol products began to appear. Finally, heating to −20 °C for 1 h gave mostly retroaldol products and a complete loss of the $\mathbf{S_2}$:$\mathbf{S_1}$ selectivity (entry 4). In a similar way, the sodium aldolate of **9a** generated by treatment with NaHMDS produced few retroaldol equilibration products at −78 °C (entry 5) but extensive retroaldol when heated to −40 °C (entry 6). This corroborated our first observations that the sodium enolate aldol addition is a disfavored process.

The equivalent series of experiments was next performed with the bromo derivative **9b**. Although a similar behavior was in principle expected, the extent of equilibration was now harder to monitor as epoxide formation

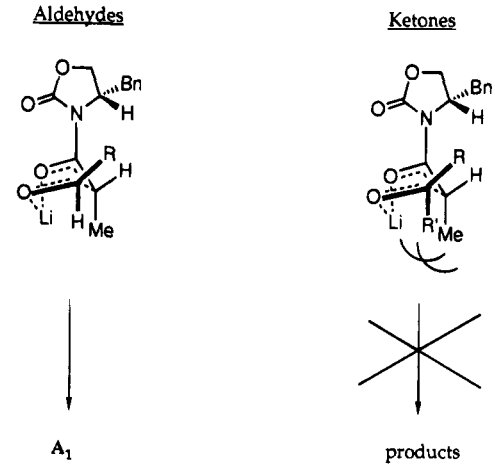


Figure 2. Boatlike transition states.

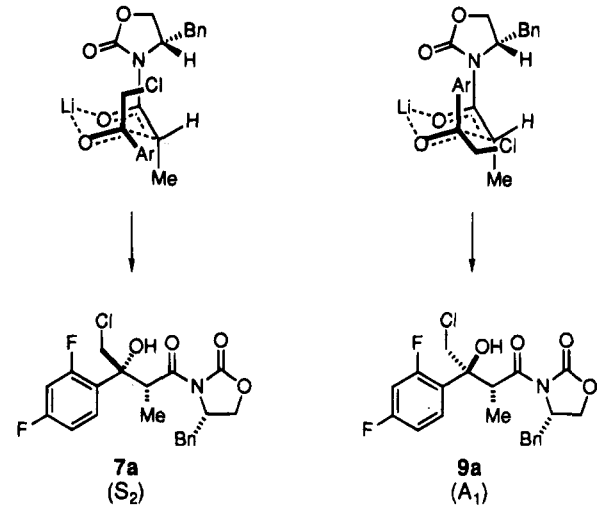
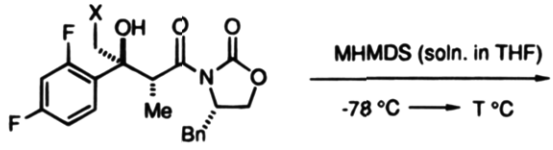


Figure 3. Chairlike transition states.

(22) Arnett, E. M.; Fisher, F. J.; Nichols, M. A.; Ribeiro, A. A. *J. Am. Chem. Soc.* **1990**, *112*, 801−808.

(23) It has been proved that certain aldol reactions experience equilibration already at −78 °C. Heathcock, C. H.; Lample, J. *J. Org. Chem.* **1983**, *48*, 4330−4337.

Table 4. Product Distribution (Percent) after Metal Aldolate Generation[a]

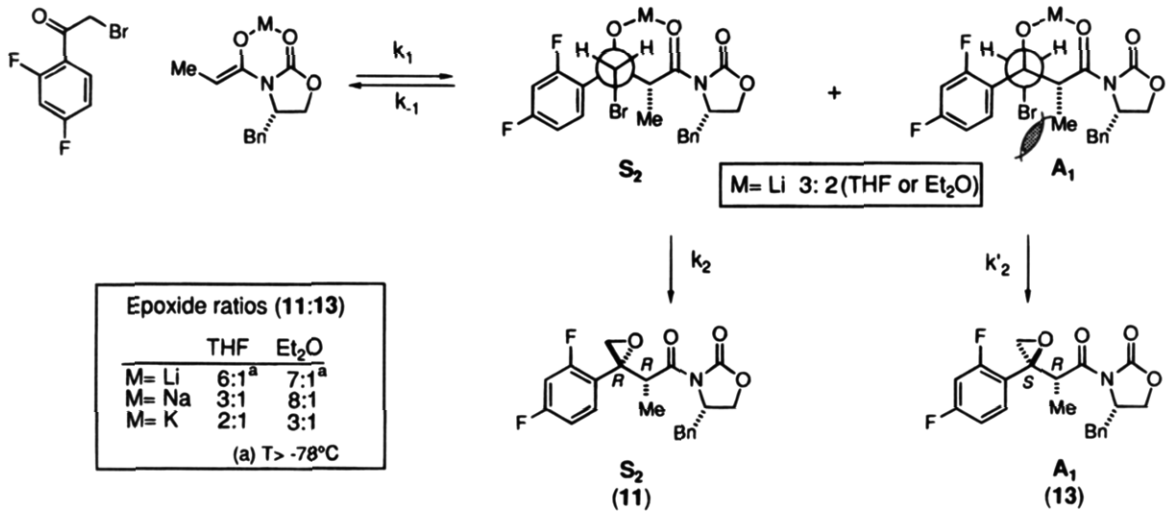


9

						halohydrins						epoxides						
entry	X	M	solv	T, °C	time, min	S_1	S_2	A_1	A_2	S_2:S_1	*syn:anti*	S_1	S_2	A_1	A_2	S_2:S_1	*syn:anti*	halohydrin:epoxide
1	Cl	Li	THF	−78	30	0.4	6.5	92.5	–	16:1	1:100	–	0.3	0.2	–	–	–	99:1
2	Cl	Li	THF	−78	180	1.7	28	69	1.3	16:1	1:2.3 -	–	–	–	–	–	–	>100:1
3	Cl	Li	THF	−50	60	6	57	36	0.8	10:1	1.7:1	–	–	–	–	–	–	>100:1
4[b]	Cl	Li	THF	−20	60	20	30	49	1	1.5:1	1:1	–	–	–	–	–	–	>100:1
5	Cl	Na	THF	−78	30	–	0.7	95	–	–	1:100	–	0.3	4	–	–	–	96:4
6[b]	Cl	Na	THF	−40	60	–	–	9	–	–	–	–	11	80	–	–	1:8	9:91
7	Br	Li	THF	−78	30	0.5	5.5	74	–	10:1	1:12 -	–	5	15	–	–	1:3	80:20
8	Br	Li	Et_2O	−78	30	–	3	88	3	–	1:30 -	–	1.5	5.1	–	–	–	93:7
9	Br	Li	THF	−20	60	–	–	–	–	–	–	6.5	60	33	0.5	9:1	2:1	<1:100
10	Br	Li	Et_2O	−20	60	6	10	8.5	2.5	1.6:1	1.6:1	20	42	11	–	2:1	6:1	27:73
11	Br	Na	THF	−78	30	–	–	2	–	–	–	–	2	96	–	–	1:50	2:98

[a] Product ratios are taken directly from the UV response of the HPLC detector. See the Experimetal Section for details. [b] Mostly retroaldol products.

Scheme 4. Reaction Mechanism



was observed upon aldolate formation. Thus, the *anti*-bromohydrin **9b** led to little equilibration when treated with LHMDS (−78 °C, 30 min) and to 20% of epoxides (entry 7). However, when NaHMDS was used (−78 °C, 30 min), formation of the *anti*-epoxide $\mathbf{A_1}$ was rapid and complete, producing only traces of equilibration adducts (2% of epoxide $\mathbf{S_2}$) (entry 11). This latter result proved also that deprotonation with NaHMDS in THF is fully taking place at −78 °C, something that was not clear *a priori* as kinetic proton removal of tertiary alcohols can be very slow or even nonexistent at that temperature. It seems reasonable to believe that complete deprotonation in that solvent must be attained with LHMDS as well.

Although the previous experiments gave some insight into the retroaldol process, the mechanistically relevant result arrived when the lithium aldolate of the *anti*-adduct **9b** was slowly heated to −20 °C (entry 9). Under these conditions, the *syn*-epoxide **11** was preferentially formed, in similar ratios to those obtained from the direct aldol. This switch from the *anti* to the *syn* stereochemistry during epoxide formation became the basis for our interpretation of the reaction which is summarized in Scheme 4 and explained below.

We have proved that the chlorohydrins and bromohydrins are formed practically with a lack of *syn:anti* selectivity. Furthermore, the stereospecific elimination of bromide from the bromohydrin lithium aldolates occurs rather slowly at −78 °C, and higher temperatures are required to achieve completion. Additionally, we have proved that the retroaldol process starts to take place at −78 °C and readily increases above this temperature. Then, the observed epoxide *syn*-selectivity must be the consequence of the following two factors. First, elimination must be faster for the $\mathbf{S_2}$ aldolate than for the $\mathbf{A_1}$ isomer (*i.e.* $k_2 > k'_2$). Second, the difference in the rate constants between the retroaldol process (k_{-1}) and the epoxide formation (k_2 or k'_2) must be big enough to allow the aldol ratios rapidly to reestablish from the selective elimination of one adduct. Then, under these conditions, and according to the Curtin−Hammet principle,[24] the selectivity of the overall reaction would correlate only with the k_2/k'_2 coefficient and should be independent of the departing bromohydrin ratio. In full accordance with this model are the results obtained with sodium and

(24) Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111−128.

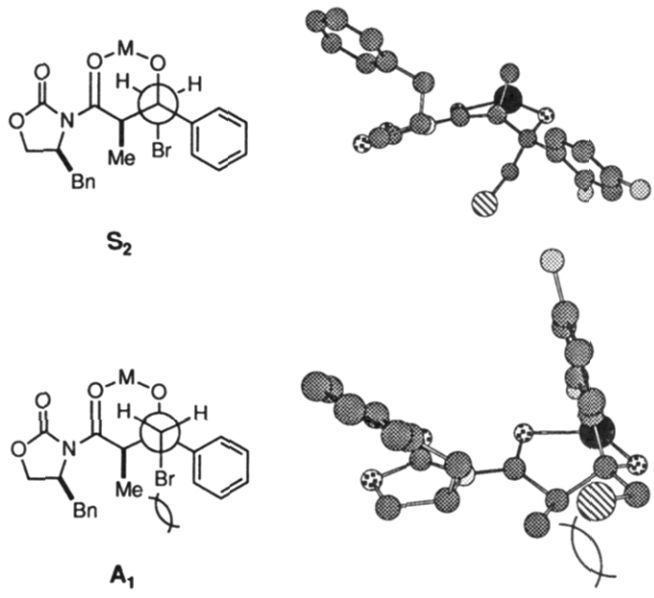
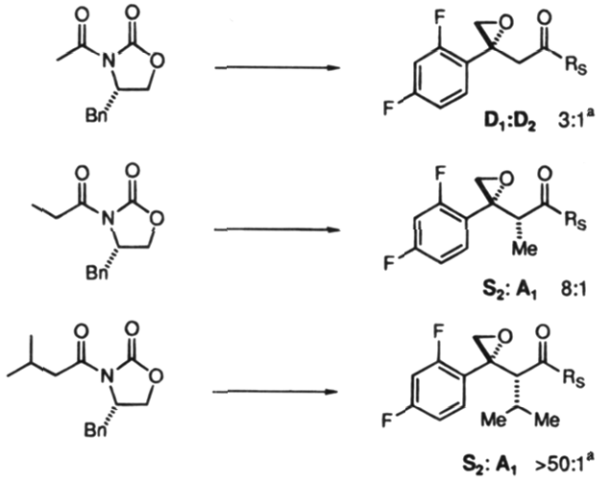


Figure 4. Chem3D-generated representations of the transition states leading to the *syn* and *anti* epoxides.

Scheme 5. Effect of the α-Substituent

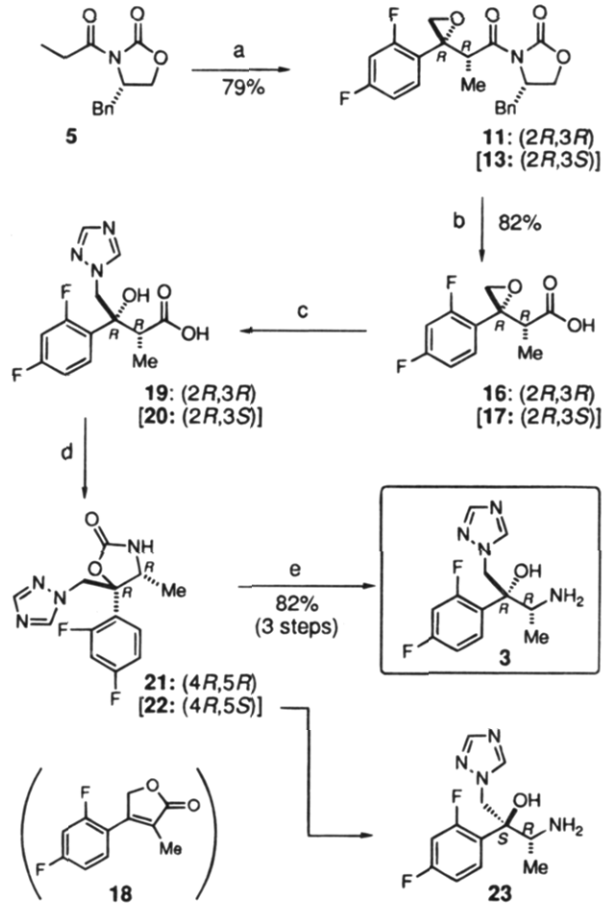


Cond.: (1) NaHMDS, Et_2O, -78°C, 30 min; (2) $ArCOCH_2Br$, -78°C, 1h; [a]The configuration of the major isomer was tentatively assigned as shown

potassium enolates in THF. Indeed, sodium and potassium aldolates eliminate bromide more rapidly than lithium (see above), thus leaving less time for re-equilibration and consequently affording a lower *syn:anti* ratio of epoxides, closer to the original aldol ratios.

Although a myriad of plausible TS conformers can be envisaged, we tentatively assigned the stereoselection observed in this transformation to the differences in energy of the two TS depicted in Figure 4. Thus, the required *anti*-planarity of the OCCBr dihedral angle during epoxide formation generates disfavoring nonbonded interactions between the leaving bromine and the α-methyl in the *anti*-bromohydrin $\mathbf{A_1}$. This repulsion is absent in the *syn*-bromohydrin $\mathbf{S_2}$, where the Me and Br groups lie on opposite sides, thus providing a lower energy path to the course of the reaction. In full accordance with this model are the results obtained with the *N*-acetyl- and *N*-isovaleroyloxazolidinones (Scheme 5). In the first case, where the intermediate bromohydrin has no group tethered to the α-position, the aforementioned nonbonded interaction must be negligible and one would expect a small $\Delta\Delta G^{\ddagger}$ for this transformation. Indeed, when the sodium aldol reaction was performed under the standard conditions (−78 °C, ether, 1 h), the diastereomeric ratio dropped to 3:1 (determined by ^1H NMR). Conversely, a bulky group such as isopropyl enhanced the nonbonded interactions, and one isomer (presumably the $\mathbf{S_2}$ isomer) was formed in ratios >97%, with only traces (Σ <3%) of other isomers.

Scheme 6. Synthesis of Amino Alcohols 3 and 23



(a) (i) NaHMDS, Et_2O, -78°C, 30 min; (ii) 2,4-diF-C_6H_3-$COCH_2Br$, -78°C, 1h; (b) LiOH, H_2O_2, THF, H_2O, 0°C, 30 min; (c) Triazole, NaH, DMF, 60°C, 3h; (d) $(PhO)_2P(=O)N_3$, pyr, 75°C, 20 h; (e) 4*N* HCl, refl, 5 days.

Chemical Correlation and Synthesis of Amino Alcohol 3. The relative and absolute stereochemistries of all the isomers were conclusively established by chemical correlation with the known *syn*-(2*R*,3*R*)-amino alcohol **3** or the *anti*-(2*S*,3*R*)-amino alcohol **23**.[7b]

Scheme 6 summarizes the new process leading to these key intermediates. The sodium enolate of imide **5** was formed under the reported conditions (1 M THF solution of NaHMDS, 1.1 equiv, ether, −78 °C, 30 min)[10] and reacted with 1.05 equiv of α-bromo-2,4-difluoroacetophenone at −78 °C for 1 h. Recrystallization afforded the desired *syn*-(2*R*,3*R*) epoxy imide $\mathbf{S_2}$ (**11**) in 79% yield, accompanied with traces of the other less polar $\mathbf{S_1}$ and $\mathbf{A_1}$ isomers. Best results were obtained by quenching the reaction at once with aqueous NH_4Cl solution at −78 °C. Removal of the chiral auxiliary under the reported standard conditions (LiOH, H_2O_2, THF, 0 °C, then Na_2-

SO_3 and HCl)[25] proved to be quite delicate as the contact of epoxy acid **16** with acid medium for prolonged periods of time produced butenolide **18**. This could be avoided by careful control of the temperature, and acidification of the reducing mixture to pH 3 with $NaHSO_4$ before organic extraction. Under these conditions, epoxy acid **16** could be obtained in 82% yield. The chiral auxiliary was recovered in 81% yield after recrystallization. Epoxide opening with sodium or potassium triazolate (DMF, 60 °C) prior to chiral auxiliary removal was unsuccessful, as free oxazolidinone and a mixture of unidentified products were obtained. This was interpreted as a consequence of a retroaldol process of the unstable sodium and potassium aldolates, which produced an enolate that decomposed to free oxazolidinone and a reactive ketene derivative.[18] Epoxide opening needed thus to be performed after chiral auxiliary liberation. Consequently, epoxy acid **16** was treated with excess sodium triazolate generated *in situ* (triazole, NaH, DMF, 60 °C, 3 h) to afford the highly crystalline triazolo acid **19** in quantitative yield. Curtius rearrangement of the crude reaction mixture (DPPA, pyridine, 75 °C, 20 h) took place smoothly to afford oxazolidinone **21** quantitatively by TLC analysis. Finally, acid hydrolysis of the unpurified reaction mixture (4 N HCl, reflux, 5 days) produced amino alcohol **3** very sluggishly. Column chromatography of an aliquot revealed that the overall yield from epoxy acid **16** was 82%. The spectroscopic data and optical rotation of **3** were identical to those of a sample obtained from (*R*)-methyl lactate following a published procedure.[7b] The equivalent process departing from the *anti*-epoxy imide **13** afforded amino alcohol **23**.

Conclusion. We have demonstrated that the lithium enolates of Evans chiral imides react with activated acetophenones with good facial diastereoselection but negligible *syn:anti* selectivity. Different experiments using *in situ*-generated pure aldolates have proved that the aldol/retroaldol equilibrium is already present at −78 °C and that it rapidly progresses with increasing temperature. When acetophenones bearing good leaving groups in the α-position are used, oxirane formation irreversibly pulls the equilibria toward the products in a stereoselective manner due to a difference in nonbonded interactions in the transition states during the stereospecific elimination of bromide. The use of lithium enolates in THF or sodium enolates in ether confers a slow, selective epoxide formation that allows a rapid reestablishment of the aldol equilibrium, resulting in the preferential formation of one isomer, independently of the original *syn:anti* ratio. These results are readily applied to the synthesis of amino alcohol **3**, an advanced intermediate in the obtention of new, orally active antifungal agents, which proceeds in five steps from propionyl imide **5** in 53% overall yield and requires no chromatographic purifications.

Experimental Section

General. Tetrahydrofuran (THF) and ether were dried by distillation under argon from sodium metal/benzophenone ketyl. Diisopropylamine was distilled under argon from calcium hydride. Lithium, sodium, and potassium hexamethyldisilazanes were purchased from Aldrich Chemical Co. and were used as received. Flash chromatography was performed on SDS silica gel 60 (230–400 mesh). ^1H (80 MHz) and ^{13}C NMR (20 MHz) spectra were recorded on a Bruker AC-80 spectrometer. Coupling constants are reported in hertz. Melting points were recorded on Mettler FP-80, FP-81, and FP-82 apparatuses heating a capillary tube containing the sample at a rate of 3 °C/min. IR spectra were recorded on a Perkin-Elmer 983 instrument. Optical rotations were determined with a Perkin-Elmer 241 polarimeter at room temperature and at 589 nm using a sodium lamp. Data are reported as follows: $[\alpha]_D$ (concentration g/100 mL, solvent). Elemental analysis was performed with a Carlo Erba EA-1108 instrument. Water-sensitive reactions were performed under an argon atmosphere using oven-dried glassware.

(*S*)-3-Acyl-4-benzyl-2-oxazolidinones were obtained from (*S*)-4-benzyl-2-oxazolidinone following the Evans protocol.[1] (*S*)-4-Benzyl-2-oxazolidinone was purchased from Urquima S.A. (Sant Fost de Capcentelles, Spain).

HPLC Analysis. Analytical HPLC was performed on a Hewlett-Packard HP 1050 chromatograph equipped with a 4 mm × 25 cm Lichrospher 100RP18e 5 μm silica gel column coupled to a UV detector (210 nm) using an acetonitrile/water mixture of 64:36 as the eluent. HPLC–MS analyses were performed using the same HPLC system coupled through a Hewlett-Packard Particle-Beam Interface 59980 to a Hewlett-Packard 5988 mass spectometer. Known amounts of *syn*-epoxide **11** and *syn*-bromohydrin **7b** were injected onto the HPLC to determine the accuracy of the detector. Linearity was obtained for each of the two compounds (50–5500 ng). Regresion data were as follows:

11: $y = 1714.0x + 908.76$, $r^2 = 1.000$ ($n = 5$)

7b: $y = 1584.6x + 252.28$, $r^2 = 1.000$ ($n = 5$)

For routine analysis over this entire range, diastereomer ratios within a given family were taken directly from the UV response (peak area). For different families (epoxides and halohydrins), we proved that both types of compounds gave a comparable UV response (response of **11**/response of **7b** = 1.08).

α-Chloro-2,4-difluoroacetophenone. To cooled (0 °C) 1,3-difluorobenzene (50 g, 43 mL, 0.44 mol) was added dropwise chloroacetyl chloride (49.5 g, 35 mL, 0.44 mol, 1 equiv), and the reaction mixture was stirred at that temperature for 15 min. Following, $AlCl_3$ (58.5 g, 0.44 mol, 1 equiv) was added in portions, resulting in gas evolution, and the mixture was stirred for 1.5 h at 10 °C and for 0.5 h at 40 °C. The reaction was poured carefully to a cooled (0 °C) solution containing concentrated HCl (100 mL) in ice (300 mL) and then stirred at that temperature for a few minutes. Ether was added and the aqueous phase discarded. The organic phase was washed (3×) with saturated aqueous $NaHCO_3$, then with water, and finally with brine. The organic fraction was dried over anhydrous Na_2SO_4, the drying agent was filtered, and the filtrate was concentrated under reduced pressure to a white solid (72.5 g, 87%): mp 47–48 °C; IR (KBr) ν 1693, 1603, 548 cm^{-1}; ^1H NMR ($CDCl_3$) δ (TMS) 8.02 (dt, $J_d = 6.5$, $J_t = 9$, 1H), 7.2–6.7 (m, 5H), 4.67 (d, $J = 2.7$, 2H); ^{13}C NMR ($CDCl_3$) δ ($CDCl_3$) 187.99 and 187.75 (C=O), 173.27, 172.66, 169.42, 168.79, 160.42, 159.80, 156.67, and 156.05 (CFs), 133.75, 133.55, 133.23, and 133.01 (CH), 119.88, 119.37, and 119.20 (C), 113.51, 113.35, 112.44, and 112.27 (CH), 106.21, 104.93, 104.84, and 103.56 (CH), 49.94 and 49.37 (CH_2Cl). Anal. Calcd for $C_8H_5ClF_2O$: C, 50.42; H, 2.67. Found: C, 50.24; H, 2.67.

α-Bromo-2,4-difluoroacetophenone. Following a similar procedure but using bromoacetyl bromide, α-bromo-2,4-difluoroacetophenone was obtained in 91% yield as a white, low-melting solid that was recrystallized from ether/hexane: mp 32–33 °C; IR (film) ν 1678, 1604, 1264 cm^{-1}; ^1H NMR ($CDCl_3$) δ (TMS) 7.99 (dt, $J_d = 6.5$, $J_t = 9$, 1H), 7.2–6.7 (m, 5H), 4.46 (d, $J = 2.4$, 2H); ^{13}C NMR ($CDCl_3$) δ ($CDCl_3$) 187.75 and 187.54 (C=O), 173.14, 172.53, 169.19, 168.55, 160.31, 159.70, 156.40, and 155.79 (CFs), 133.89, 133.70, 133.37, and 133.17 (CH), 119.81, 119.64, 119.15, and 118.97 (C), 113.32, 113.16, 112.25, and 112.09 (CH), 106.14, 104.87, 104.77, and 103.49 (CH),

(25) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *49*, 6141–6144.

35.51, and 35.03 (CH_2Br). Anal. Calcd for $C_8H_5BrF_2O$: C, 40.88; H, 2.14. Found: C, 40.73; H, 2.20.

Stereochemical Assignment of Chlorohydrins 6a, 7a, 8a, and 9a. TLC analysis of the reaction mixture resulting from the aldol condensation of the lithium enolate of **5** and α-chloro-2,4-difluoroacetophenone (see below) indicated formation of two main spots. The slower running spot (EtOAc/hexane) was isolated by flash chromatography, chemically characterized, and determined to be formed of a *ca.* 100:1 mixture of adducts by HPLC. The identical mass spectra of these peaks (EI and CI-CH_4, particle beam) revealed their isomeric relationship. The relative stereochemistry was assigned *anti* on the basis of the lower field Me signal in the ^1H NMR spectrum ($\delta_{anti} - \delta_{syn} = 0.4$ ppm).[26] The stereochemistry of carbons 2 and 3 was tentatively assigned as (2*R*,3*S*) (**9a**) for the major isomer and (2*S*,3*R*) (**8a**) for the minor isomer based upon the identical HPLC pattern of the related bromohydrins, whose stereochemistries were unambiguously assigned (see below). The faster running spot was identified by ^1H NMR and HPLC–MS as a 9:1 mixture of the *syn* chlorohydrins (**7a** + **6a**). The major isomer was obtained as a single diastereomer by recrystallization and its absolute stereochemistry was assigned *syn*-(2*R*,3*R*) (**7a**) by a similar reasoning. The absolute stereochemistry of the minor *syn* isomer was assigned (2*S*,3*S*) (**6a**) by elimination. Two chlorohydrins, **7a** and **9a**, were fully characterized:

[3(2*R*,3*R*),4*S*]-4-Benzyl-3-[4-chloro-3-(2,4-difluorophenyl)-3-hydroxy-2-methyl-1-oxobutyl]-2-oxazolidinone (7a) and [3(2*R*,3*S*),4*S*]-4-Benzyl-3-[4-chloro-3-(2,4-difluorophenyl)-2-methyl-1-oxobutyl]-2-oxazolidinone (9a). To a cooled (−78 °C) solution containing diisopropylamine (1.8 mL, 12.9 mmol, 1.2 equiv) in THF (25 mL) was added a 1.6 N solution of *n*-BuLi in hexane (7.4 mL, 11.8 mmol, 1.1 equiv) and the reaction mixture was stirred at this temperature for 10 min. Then, the flask was cooled to −78 °C and a solution of propionyl imide **5** (2.5 g, 10.7 mmol) in dry THF (10 mL) was added dropwise, and the mixture was stirred at this temperature for 30 min. Next, a solution containing α-chloro-2,4-difluoroacetophenone (2.45 g, 12.9 mmol, 1.2 equiv) in THF (10 mL) was added dropwise (1 min), and the mixture was quenched 1 h later by the addition of a saturated aqueous NH_4Cl solution (50 mL) in one portion. The volatiles were removed *in vacuo*, and the aqueous residue was then partitioned between dichloromethane and water. The aqueous phase was discarded, and the organic phase was washed with 5% aqueous $NaHCO_3$ and brine and then dried over anhydrous Na_2SO_4; the drying agent was filtered off, and the filtrate was concentrated to a cream-colored oil containing all four chlorohydrins (6.66 g).

HPLC–UV analysis of the unpurified reaction mixture [*anti*-(2*S*,3*R*) (**8a**) t_R 7.0 min; *anti*-(2*R*,3*S*) (**9a**) t_R 7.5 min; *syn*-(2*R*,3*R*) (**7a**) t_R 10.6 min; *syn*-(2*S*,3*S*) (**6a**) t_R 11.8 min] indicated an area relationship for these products of 0.4:37:58:4.5, respectively.

The crude reaction mixture was purified by flash chromatography (EtOAc/hexane 1:5) to afford two fractions, the faster running one containing the *syn*-isomers together with traces of starting propionyl imide **5** (2.8 g, 66%) and a more polar fraction containing the *anti*-isomers (1.5 g, 35%). The semicrystalline mixture of *syn*-chlorohydrins was washed with a 1:1 mixture of ether/hexane, and the remaining solid was recrystallized from ether/hexane to afford the pure *syn*-(2*R*,3*R*)-isomer (**7a**) [**7a**:**6a** = 99.4:0.6 by HPLC].

7a: mp 109–110 °C; IR (KBr) ν 3459, 1785, 1662, 1612, 1494, 1384 cm^{-1}; ^1H NMR ($CDCl_3$) δ (TMS) 7.78 (dt, J_d = 6.5, J_t = 9.5, 1H), 7.5–7.1 (m, 5H), 7.1–6.6 (m, 2H), 4.97 (s, 1H, OH), 4.77 (q, J = 7, 1H), 4.9–4.5 (m, 1H), 4.20 (d, J = 5, 2H), 4.00 (s, 2H), 3.48 (dd, J = 3.5, J = 13.2, 1H), 2.72 (dd, J = 10, J = 13.2, 1H), 1.04 (d, J = 7, 3H); ^{13}C NMR ($CDCl_3$) δ ($CDCl_3$) 177.57 (C=O), 169.23, 168.65, 165.15, 164.63, 156.87, 156.30, 152.80, and 152.36 (CFs), 152.80 (C=O), 135.13 (C), 131.29, 131.01, 130.82, and 130.55 (CH), 129.34 (CH), 129.07 (CH), 127.50 (CH), 124.11, 123.92, 123.52, and 123.33 (C), 111.85, 111.68, 110.83, and 110.66 (CH), 105.47, 104.20, 104.10, and 102.82 (CH), 77.53 and 77.27 (COH), 66.22 (CH_2O), 55.67 (CHN), 51.95 and 51.64 (CH_2Cl), 41.14 and 40.89 (CHMe), 37.75 (CH_2Bn), 14.57 (Me); $[\alpha]_D$ −2.1° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{21}H_{20}ClF_2NO_4$: C, 59.51; H, 4.76; N, 3.30. Found: C, 59.90; H, 4.79; N, 3.37.

The fraction containing the *anti*-chlorohydrins was recrystallized from ether/hexane to afford the pure *anti*-(2*R*,3*S*)-isomer (**9a**) [**9a**:**8a** = 99.8:0.2 by HPLC]:

9a: mp 114–115 °C; IR (KBr) ν 3477, 1759, 1666, 1492, 1385, 1363 cm^{-1}; ^1H NMR ($CDCl_3$) δ (TMS) 7.66 (dt, J_d = 6.5, J_t = 9.5, 1H), 7.4–7.1 (m, 3H), 7.1–6.5 (m), 4.88 (s, 1H, OH), 4.84 (q, J = 7, 1H), 4.7–4.3 (m, 1H), 4.3–3.8 (m, 4H), 2.68 (dd, J = 3.3, J = 13.4, 1H), 2.08 (dd, J = 9.6, J = 13.4, 1H), 1.41 (d, J = 7, 3H); ^{13}C NMR ($CDCl_3$) δ ($CDCl_3$) 177.21 (C=O), 169.28, 168.68, 165.52, 164.67, 156.89, 156.29, 153.20, and 152.40 (CFs), 152.40 (C=O), 134.72 (C), 131.53, 131.24, 131.06, and 130.78 (CH), 129.11 (CH), 129.05 (CH), 127.51 (CH), 126.24, 126.05, 125.60, and 125.41 (C), 111.83, 111.66, 110.81, and 110.63 (CH), 105.52, 104.27, 104.13, and 102.88 (CH), 76.86 and 76.61 (COH), 65.92 (CH_2O), 54.72 (CHN), 49.68 and 49.41 (CH_2Cl), 42.76 and 42.52 (CHMe), 37.28 (CH_2Bn), 12.21 (Me); $[\alpha]_D$ +28.2° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{21}H_{20}ClF_2NO_4$: C, 59.51; H, 4.76; N, 3.30. Found: C, 59.58; H, 4.69; N, 3.36.

Stereochemical Assignment of Bromohydrins 6b, 7b, 8b, and 9b. All four diastereomeric bromohydrins coming from the aldol condensation of the lithium enolate of **5** and α-bromo-2,4-difluoroacetophenone (see below) were chemically identified by HPLC–MS analysis of the chromatographed fractions. The assignment of the relative *syn*/*anti* stereochemistry for these compounds was again founded upon the different chemical shifts of the methyl signals in the ^1H NMR spectrum[26] and further corroborated by chemical correlation (see Scheme 6). The configurations of carbons 2 and 3 of the major bromohydrins were assigned *syn*-(2*R*,3*R*) (**7b**) and *anti*-(2*R*,3*S*) (**9b**) by transformation into the corresponding epoxy imides **11** and **13**, respectively, upon treatment with NaHMDS (a process that occurs without retroaldol/aldol equilibria) and further correlation of those with compounds **3** and **23**, respectively. The C_2 and C_3 stereochemistries of the remaining minor bromohydrins were assigned *syn*-(2*S*,3*S*) (**6b**) and *anti*-(2*S*,3*R*) (**8b**) by default. Two bromohydrins, **7b** and **9b**, were fully characterized.

[3(2*R*,3*R*),4*S*]-4-Benzyl-3-[4-bromo-3-(2,4-difluorophenyl)-3-hydroxy-2-methyl-1-oxobutyl]-2-oxazolidinone (7b) and [3(2*R*,3*S*),4*S*]-4-Benzyl-3-[4-bromo-3-(2,4-difluorophenyl)-2-methyl-1-oxobutyl]-2-oxazolidinone (9b). Following an identical procedure to that described in the previous example but using α-bromo-2,4-difluoroacetophenone (3.02 g, 12.9 mmol, 1.2 equiv) as the electrophile and quenching the reaction 2 min after the end of the ketone addition, a mixture of bromohydrins, accompanied with small amounts (*ca.* 15%) of the corresponding epoxides, was obtained (7.88 g).

HPLC–UV analysis of the unpurified crude reaction mixture [epox-*syn*-(2*R*,3*R*) (**11**) t_R 9.3 min; epox-*syn*-(2*S*,3*S*) (**10**) t_R 10.9 min; bromh-*anti*-(2*S*,3*R*) (**8b**) t_R 11.2 min; bromh-*anti*-(2*R*,3*S*) (**9b**) t_R 11.7 min; epox-*anti*-(2*R*,3*S*) (**13**) t_R 12.2 min; epox-*anti*-(2*S*,3*R*) (**12**) t_R 13.6 min; bromh-*syn*-(2*R*,3*R*) (**7b**) t_R 17.0 min; bromh-*syn*-(2*S*,3*S*) (**6b**) t_R 19.8 min] indicated an area relationship for these products of 12:1.3:1.3:28:4:<0.1:49:4.7, respectively.

Column chromatography (silica gel, EtOAc/hexane 1:9) afforded a less polar fraction consisting in an unresolved 10:1 mixture of *syn*-bromohydrins, contaminated with traces of the *anti*-epoxide **13**, and a more polar fraction containing a 100:1 mixture of *anti*-bromohydrins and traces of the *syn*-epoxide **11**. The mixture of *syn*-bromohydrins was recrystallized from ether/hexane to afford the pure *syn*-(2*R*,3*R*)-isomer (**7b**) [**7b**:**6b** > 99.9:0.1 by HPLC].

7b: mp 129–131 °C; IR (KBr) ν 3427, 1777, 1657, 1611, 1494, 1381 cm^{-1}; ^1H NMR ($CDCl_3$) δ (TMS) 7.74 (dt, J_d = 6.5,

(26) In a series of related α-methyl-β-carbinols, Tanaka *et al.* have found that the *syn* isomers invariably showed their methyl doublets at higher fields than their *anti* analogues. Tanaka, T.; Takeda, N.; Konosu, T.; Yasuda, H.; Oida, S. *Chem. Pharm. Bull.* **1992**, *40*, 661–665.

J_t = 9.5, 1H), 7.5–7.1 (m, 5H), 7.1–6.6 (m, 2H), 4.81 (s, 1H, OH), 4.77 (q, J = 7, 1H), 4.9–4.5 (m, 1H), 4.21 (d, J = 5, 2H), 4.07 (d, J = 10.5, 1H), 3.74 (dd, J_{CF} = 0.8, J = 10.5, 1H), 3.46 (dd, J = 3.5, J = 13.2, 1H), 2.75 (dd, J = 10, J = 13.2, 1H), 1.05 (d, J = 7, 3H); ^{13}C NMR ($CDCl_3$) δ ($CDCl_3$) 177.60 (C=O), 169.49, 168.68, 165.25, 164.61, 156.91, 156.30, 152.76, and 152.23 (CFs), 152.76 (C=O), 135.02 (C), 131.43, 131.15, 130.96, and 130.68 (CH), 129.38 (CH), 129.015 (CH), 127.63 (CH), 124.59, 124.41, 124.02, and 123.91 (C), 111.77, 111.60, 110.75, and 110.59 (CH), 105.52, 104.26, 104.16, and 102.88 (CH), 76.80 and 76.56 (COH), 66.33 (CH_2O), 55.67 (CHN), 41.82 and 41.59 (CHMe), 41.20 and 40.87 (CH_2Br), 38.10 (CH_2Bn), 14.93 (Me); $[\alpha]_D$ +5.1° (c 1 , $CHCl_3$). Anal. Calcd for $C_{21}H_{20}BrF_2NO_4$: C, 53.86; H, 4.30; N, 2.99. Found: C, 54.08; H, 4.32; N, 3.03.

The fraction containing the *anti*-bromohydrins was recrystallized from ether/hexane to afford the pure *anti*-(2*R*,3*S*)-isomer (**9b**) [**9b**:**8b** = 99:1]:

9b: mp 133–135 °C; IR (KBr) ν 3475, 1765, 1669, 1606, 1491, 1390 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (TMS) 7.64 (dt, J_d = 6.5, J_t = 9.5, 1H), 7.4–7.2 (m, 3H), 7.1–6.6 (m, 4H), 4.96 (d, J = 1.5, 1H, OH), 4.87 (q, J = 7, 1H), 4.7–4.3 (m, 1H), 4.3–3.8 (m, 4H), 2.66 (dd, J = 3.4, J = 13.4, 1H), 2.06 (dd, J = 9.5, J = 13.4, 1H), 1.41 (d, J = 7, 3H); ^{13}C NMR ($CDCl_3$) δ ($CDCl_3$) 177.23 (C=O), 169.27, 168.68, 165.45, 164.68, 156.87, 156.27, 153.13, and 152.56 (CFs), 152.39 (C=O), 134.69 (C), 131.44, 131.16, 130.97, and 130.69 (CH), 129.10 (CH), 129.05 (CH), 127.51 (CH), 126.97, 126.78, 126.34, and 126.14 (C), 111.72, 111.55, 110.70, and 110.53 (CH), 105.54, 104.28, 104.16, and 102.89 (CH), 76.19, and 75.93 (COH), 65.92 (CH_2O), 54.69 (CHN), 42.82 and 42.60 (CHMe), 38.86 and 38.57 (CH_2Br), 37.25 (CH_2Bn), 12.22 (Me); $[\alpha]_D$ +27.0° (c 1 , $CHCl_3$). Anal. Calcd for $C_{21}H_{20}BrF_2NO_4$: C, 53.86; H, 4.30; N, 2.99. Found: C, 53.96; H, 4.32; N, 3.02.

[3(2*R*,3*R*),4*S*]-4-Benzyl-3-[3-(2,4-difluorophenyl)-3,4-epoxy-2-methyl-1-oxobutyl]-2-oxazolidinone (11), [3(2*R*,-3*S*),4*S*]-4-Benzyl-3-[3-(2,4-difluorophenyl)-3,4-epoxy-2-methyl-1-oxobutyl]-2-oxazolidinone (13), and [3(2*S*,3*S*)-4*S*]-4-benzyl-3-[3-(2,4-difluorophenyl)-3,4-epoxy-2-methyl-1-oxobutyl]-2-oxazolidinone (10). To a cooled (−78 °C) solution containing a 1 M solution of sodium hexamethyldisilazane (NaHMDS) in THF (0.22 L, 0.22 mol, 1.05 equiv) in dry ether (1 L) was added a solution of propionyl imide **5** (50 g, 0.214 mol) in dry ether (0.22 L), and the mixture was stirred at this temperature for 30 min. Then, α-bromo-2,4-difluoroacetophenone (53 g, 0.22 mol, 1.05 equiv) was added solid in portions while the temperature was maintained below −70°C. The reaction was quenched 1 h after the addition of a saturated aqueous NH_4Cl solution (1.4 L) in one portion. The mixture was warmed to room temperature, and the aqueous phase was separated and extracted (2×) with ether. The combined organic phases were successively washed with 0.5 N aqueous HCl until acid pH remained, with 5% aqueous $NaHCO_3$, and with brine and then dried over anhydrous Na_2SO_4; the drying agent was filtered off, and the filtrate was concentrated to a cream-colored oil that crystallized (130 g).

Diastereomeric analysis of the unpurified reaction mixture before crystallization [epox-*syn*-(2*R*,3*R*) (**11**) t_R 9.3 min; epox-*syn*-(2*S*,3*S*) (**10**) t_R 10.9 min; bromh-*anti*-(2*R*,3*S*) (**9b**) t_R 11.7 min; epox-*anti*-(2*R*,3*S*) (**13**) t_R 12.2 min; epox-*anti*-(2*S*,3*R*) (**12**) t_R 13.6 min] indicated an area relationship for these products of 83:6:1:10:0.3, respectively. The bulk of the reaction mixture was recrystallized from ether/hexane 1:2 to afford the crystalline epoxide (66 g, 79% yield) with a product distribution of 94:1:0.3:5:<0.1.

For characterization purposes, another run containing 10.21 g of unpurified reaction mixture was flash chromatographed (silica gel, EtOAc/hexane 1:4) to afford a first, faster running fraction containing a mixture of starting propionyl imide **5** and the *syn*-(2*S*,3*S*)-epoxide (**10**) in very small amounts. (For characterization purposes, isomer **10** was obtained in larger amounts by performing the reaction with LHMDS in ether, as this solvent produces larger proportions of that adduct: see Table 2, entry 3.) A second, more polar fraction contained the *anti*-(2*R*,3*S*)-epoxide (**13**), and a last, slower running fraction contained the *syn*-(2*R*,3*R*)-epoxide (**11**).

10: mp 68–69 °C (ether/hexane); IR (KBr) ν 1764, 1693, 1610, 1503, 1359, 1218 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (TMS) 7.6–7.0 (complex signal, 6H), 7.0–6.6 (m, 2H), 4.8–4.4 (m, 1H), 4.47 (q, J = 7, 1H), 4.13 (br d, J = 4.4, 2H), 3.19 (dd, J = 3.5, J = 13.2, 1H), 3.15 (d, J = 4.6, 1H), 2.86 (d, J = 4.6, 1H), 2.74 (dd, J = 9.1, J = 13.2, 1H), 1.23 (d, J = 7, 3H); ^{13}C NMR ($CDCl_3$) δ ($CDCl_3$) 173.37 (C=O), 169.36, 168.76, 167.57, and 166.94 (CF), 156.94, 156.33, 155.11, and 154.49 (CF), 152.97 (C=O), 135.16 (C), 132.07, 131.80, 131.59, and 131.32 (CH), 129.46 (CH), 128.97 (CH), 127.44 (CH), 122.47, 122.27, 121.74, and 121.56 (C), 111.79, 111.60, 110.73, and 110.56 (CH), 105.04, 103.77, and 102.51 (CH), 66.10 (NCH*C*H$_2$O), 57.73 (CO epox), 55.53 (CHN), 51.85 (CH_2O epox), 42.15 (*C*HMe), 37.83 (*C*H$_2$Bn), 12.73 (Me); $[\alpha]_D$ +101.8° (c 1, $CHCl_3$). Anal. Calcd for $C_{21}H_{19}F_2NO_4$: C, 65.11; H, 4.94; N, 3.62. Found: C, 65.02; H, 4.96; N, 3.67.

13: oil; IR (film) ν 1766, 1690, 1611, 1380, 1208 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (TMS) 7.81 (dt, J_d = 6.7, J_t = 8, 1H), 7.28 (s, 5H, Ph), 7.1–6.6 (m, 2H), 4.8–4.4 (m, 1H), 4.58 (q, J = 6.7, 1H), 4.13 (d, J = 4.9, 2H), 3.29 (dd, J = 3.5, J = 14.2, 1H), 3.20 (d, J = 3.2, 1H), 2.83 (d, J = 3.2, 1H), 2.65 (dd, J = 9.9, J = 14.2, 1H), 1.26 (dd, J_{CF} = 1.3, J_d = 6.7, 3H); ^{13}C NMR ($CDCl_3$) δ ($CDCl_3$) 171.85 (C=O), 169.34, 168.74, 166.73, and 166.13 (CF), 156.90, 156.28, 154.38, and 153.31 (CF), 153.31 (C=O), 135.65 (C), 132.54, 132.29, 132.05, and 131.80 (CH), 129.42 (CH), 128.96 (CH), 127.26 (CH), 122.99, 122.81, 122.27, and 122.07 (C), 112.39, 112.22, 1121.34, 111.16 (CH), 104.67, 103.40, and 102.12 (CH), 65.97 (NCH*C*H$_2$O), 57.38 (CO epox), 55.74 (CHN), 49.65 and 49.50 (CH_2O epox), 42.11 (*C*HMe), 37.46 (*C*H$_2$Bn), 12.74 (Me); $[\alpha]_D$ −30.1° (c 1, $CHCl_3$). Anal. Calcd for $C_{21}H_{19}F_2NO_4$: C, 65.11; H, 4.94; N, 3.62. Found: C, 65.17; H, 4.92; N, 3.65.

11: mp 104–105 °C (ether/hexane); IR (KBr) ν 1758, 1684, 1609, 1365, 1206 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (TMS) 7.6–6.6 (complex signal, 8H), 4.8–4.4 (m, 1H), 4.62 (q, J = 7, 1H), 4.12 (d, J = 5, 2H), 3.24 (dd, J = 3.5, J = 13.3, 1H), 3.24 (d, J = 4.7, 1H), 2.95 (d, J = 4.7, 1H), 2.57 (dd, J = 9.5, J = 13.3, 1H), 1.19 (d, J = 7, 3H); ^{13}C NMR ($CDCl_3$) δ ($CDCl_3$) 173.24 (C=O), 169.13, 168.52, 167.46, and 166.85 (CF), 156.71, 156.11, 154.98, and 154.36 (CF), 152.71 (C=O), 134.99 (C), 131.90, 131.63, 131.43, and 131.14 (CH), 129.16 (CH), 128.74 (CH), 127.14 (CH), 122.72, 122.51, 121.99, and 121.80 (C), 111.50, 111.30, 110.47, and 110.27 (CH), 104.93, 103.66, and 102.40 (CH), 65.64 (NCH*C*H$_2$O), 57.61 (CO epox), 55.04 (CHN), 50.93 (CH_2O epox), 41.68 (*C*HMe), 37.37 (*C*H$_2$Bn), 12.45 (Me); $[\alpha]_D$ −7.6° (c 1, $CHCl_3$). Anal. Calcd for $C_{21}H_{19}F_2NO_4$: C, 65.11; H, 4.94; N, 3.62. Found: C, 65.42; H, 5.14; N, 3.78.

Equilibration Studies. (Table 4, Entry 9). To a cooled (−78 °C) solution containing diastereomerically pure bromohydrin **9b** (150 mg, 0.32 mmol) in THF (5 mL) was added a 1 M solution of LHMDS in THF (0.337 mL, 1.05 equiv). The mixture was stirred at −78 °C for 2.5 h, then slowly warmed to −20 °C and stirred at this temperature for an additional hour, and finally quenched by the addition of a saturated aqueous NH_4Cl solution (5 mL) in one portion. Usual aldol workup and product isolation afforded a mixture of epoxides. Diastereomeric analysis of the unpurified reaction mixture by HPLC–UV [*syn*-(2*R*,3*R*) (**11**) t_R 9.3 min; *syn*-(2*S*,3*S*) (**10**) t_R 10.9 min; *anti*-(2*R*,3*S*) (**13**) t_R 12.2 min; *anti*-(2*S*,3*R*) (**12**) t_R 13.6 min] indicated an area relationship for these epoxides of 60:6.5:33:0.5, respectively.

(Table 4, Entry 3). Similarly, a cooled (−78 °C) solution containing diastereomerically pure chlorohydrin **9a** was treated with a 1 M solution of LHMDS in THF at −78 °C. The mixture was stirred at −78 °C for 2.5 h, then slowly warmed to −50 °C and stirred at this temperature for an additional hour, and finally quenched by the addition of a saturated aqueous NH_4Cl solution (5 mL) in one portion. Usual aldol workup and product isolation afforded a *ca.* 90:10 mixture of equilibrated chlorohydrins and retroaldol products (*i.e.* propionyl imide **5** and α-chloro-2,4-difluoroacetophenone). Diastereomeric analysis of the unpurified equilibrium mixture by HPLC–UV [*anti*-(2*S*,3*R*) (**8a**) t_R 7.0 min; *anti*-(2*R*,3*S*) (**9a**) t_R 7.5 min; *syn*-(2*R*,3*R*) (**6a**) t_R 10.6 min; *syn*-(2*S*,3*S*) (**7a**) t_R 11.8 min] indicated an area relationship for these products of 0.8:36:57:6, respectively.

Correlation Studies. [3(2*R*),4*S*]-4-Benzyl-3-[3-(2,4-difluorophenyl)-1,3-dioxo-2-methylpropyl]-2-oxazolidinone (14). To a cooled (−78 °C) solution containing diisopropylamine (10.8 mL, 77 mmol, 1.2 equiv) in THF (150 mL) was added a 1.6 N solution of *n*-BuLi in hexane (45 mL, 72 mmol, 1.1 equiv), and the reaction mixture was stirred at this temperature for 10 min. Then, the flask was cooled to −78 °C, and a solution of propionyl imide **5** (15 g, 64.5 mmol) in dry THF (75 mL) was added dropwise; the mixture was stirred at this temperature for 30 min. Following, 2,4-difluorobenzoyl chloride (9.5 mL, 77 mmol, 1.2 equiv) was added, and the mixture was stirred for 2 h at −78 °C and for 30 min at −4 °C and then quenched by the quick addition of a saturated NH_4Cl aqueous solution (60 mL) in one portion. The volatiles were removed *in vacuo*, and the aqueous residue was then partitioned between dichloromethane and water. The aqueous phase was discarded and the organic phase was washed with 5% aqueous $NaHCO_3$ and brine and then dried over anhydrous Na_2SO_4; the drying agent was filtered, and the filtrate was concentrated to an oil that was purified by flash chromatography (EtOAc/hexane 1:4) to afford compound **14** as a white solid (9.85 g, 41%): mp 82−92 °C; IR (KBr) ν 1771, 1756, 1692, 1670, 1601 cm^{-1}; ^1H NMR ($CDCl_3$) δ (TMS) 8.05 (dt, J_d = 6.5, J_t = 9.5, 1H), 7.30 (s, 5H, arom), 7.2−6.7 (m, 2H), 5.22 (q, J = 7.2, 1H), 4.69 (m, 1H), 4.18 (d, J = 5, 2H), 3.52 (dd, J = 3.2, J = 13.5, 1H), 2.77 (dd, J = 10, J = 13.5, 1H), 1.49 (d, J = 7.2, 3H); ^{13}C NMR ($CDCl_3$) δ 193.14 and 192.92 (C=O), 172.93, 172.35, 169.42, 168.87, 160.14, 159.59, 156.50, and 156.00 (CFs), 170.07 (C=O), 153.61 (C=O), 135.56 (C), 133.74, 133.55, 133.21, and 133.02 (CH), 129.52 (CH), 129.00 (CH), 127.30 (CH), 120.69, 120.48, 120.11, and 119.91 (C), 113.10, 112.92, 112.04, and 111.67 (CH), 106.28, 105.00, 104.88, and 103.62 (CH), 66.43 (CH_2O), 55.50 (CHN), 52.46 and 52.09 (CH_2), 37.45 (CH_2Bn), 12.58 (Me); $[\alpha]_D$ −37° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{20}H_{17}F_2NO_4$: C, 64.34; H, 4.59; N, 3.75. Found: C, 64.01; H, 4.63; N, 3.84.

[3(2*R*,3*R*],4*S*)-4-Benzyl-3-[3-(2,4-difluorophenyl)-3-hydroxy-2-methyl-1-oxobutyl]-2-oxazolidinone (15). To a cooled (−78 °C) solution consisting in 1 M solution of MeMgBr in THF (Aldrich, 0.67 mL, 2 mmol, 3 equiv) in a 2:1 mixture of CH_2Cl_2/ether (3 mL) was added a solution of compound **14** (250 mg, 0.67 mmol) in CH_2Cl_2 (3 mL), and the reaction mixture was stirred at −78 °C for 4 h. The reaction mixture was quenched by the quick addition of a 0.5 N HCl aqueous solution (10 mL) in one portion. The mixture was extracted with CH_2Cl_2 (3×) and the combined organic fractions were washed with 5% aqueous $NaHCO_3$ and brine and then dried over anhydrous Na_2SO_4; the drying agent was filtered, and the filtrate was concentrated and purified by column chromatography (EtOAc/hexane 1:4) to furnish a colorless oil (120 mg, 46 %): IR (film) ν 3477, 1778, 1663, 1609, 1492 cm^{-1}; ^1H NMR ($CDCl_3$) δ (TMS) 7.71 (dt, J_d = 6.5, J_t = 9.5, 1H), 7.3−7.2 (m, 5H), 7.0−6.6 (m, 2H), 4.66 (q, J = 7, 1H), 4.9−4.5 (m, 1H), 4.19 (d, J = 5, 2H), 3.45 (dd, J = 3.3, J = 13.3, 1H), 2.75 (dd, J = 10, J = 13.3, 1H), 1.69 (d, J = 1.3, 3H), 0.95 (d, J = 7, 3H); ^{13}C NMR ($CDCl_3$) δ ($CDCl_3$) 178.65 (C=O), 168.65, 168.05, 165.39, 164.82, 156.35, 155.75, 153.04, and 152.45 (CFs), 152.73 (C=O), 135.13 (C), 129.91, 129.61, 129.37, 129.07, 128.23, 128.05, 127.64, and 127.51 (CHs), 111.37, 111.20, 110.36, and 110.19 (CH), 105.48, 104.22, 104.11, and 102.85 (CH), 74.21, and 73.97 (COH), 66.01 (CH_2O), 55.44 (CHN), 43.49 and 43.25 (CHMe), 38.15 (CH_2Bn), 28.27 and 28.05 (CMe), 13.51 (Me); $[\alpha]_D$ +7.1° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{21}H_{21}F_2NO_4$: C, 64.77; H, 5.44; N, 3.60. Found: C, 63.92; H, 5.95; N, 3.43.

The aldol reaction of the lithium enolate of **5** (LDA, −78 °C, THF) with 2,4-difluoroacetophenone (1.2 equiv, −78 °C, 3 h) followed by the usual workup afforded an unpurified reaction mixture consisting mainly of two isomers as indicated by TLC and ^1H NMR. This latter technique indicated a 3:2 ratio of *syn*:*anti* isomers according to the chemical shifts of the representative Me doublets[26] (0.95 and 1.42 ppm, respectively). HPLC−MS analysis [*anti*-(2*S*,3*R*) t_R 8.4 min; *anti*-(2*R*,3*S*) t_R 9.2 min; *syn*-(2*R*,3*R*) (**15**) t_R 13.98 min; *syn*-(2*S*,3*S*) t_R 14.51 min] indicated a ratio of isomers of 6:32:56:6.

The retention time and MS spectra of the compound obtained by methyl Grignard addition (**15**) and that of the previously assigned as the *syn*-(2*R*,3*R*) isomer from the aldol addition were identical, thus corroborating our stereochemical assignment by HPLC analogy.

Synthesis of Amino Alcohols 3 and 23. (2*R*,3*R*)-3-[3-(2,4-Difluorophenyl)-3,4-epoxy-2-methylbutanoic Acid (16) and Its Enantiomer (2*S*,3*S*)-3-[3-(2,4-Difluorophenyl)-3,4-epoxy-2-methylbutanoic Acid. To a cooled (-5 °C) solution containing epoxy imide **11** (30 g, 77.4 mmol) in THF (750 mL) was added dropwise a 35% aqueous solution of H_2O_2 (20 mL, 233 mmol) in water (8 mL), maintaining the reaction temperature between −3 and −4 °C. Next, a solution containing LiOH (4.22 g, 100 mmol) in water (180 mL) was added dropwise while the reaction temperature was maintained between −3 and −1 °C. Once the addition was finished, the reaction was stirred at 0 °C for 30 min. Then, a solution containing Na_2SO_3 (29.3 g, 233 mmol) in water (190 mL) was added dropwise while the temperature was maintained between −3 and +1 °C, and the mixture was stirred for 15 min at 0 °C. Water was added (750 mL), and the alkaline mixture (pH 11) was acidified to pH 3 with a saturated aqueous solution of $NaHSO_4$. NaCl was added, and the aqueous mixture was extracted with chloroform (4×). The mixture was extracted with a 0.5 M aqueous solution of $NaHCO_3$. The organic phase was dried and concentrated to afford the unpurified oxazolidinone (17 g), which was recrystallized from EtOAc/hexane to afford pure crystals (11.1 g, 81%). The alkaline aqueous phase was acidified to pH 3 with saturated $NaHSO_4$, saturated with NaCl, and extracted with chloroform (3×). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to afford a colorless oil (14.5 g, 82%), pure by TLC and NMR analyses, that was used in the next step without further purification. An analytical sample was obtained by flash chromatography (EtOAc): IR (film) ν 3600−2550, 1704, 1610, 1500, 1268 cm^{-1}; ^1H NMR ($CDCl_3$) δ (TMS) 10−8 (br s, 1H, CO_2H), 7.43 (dt, J_d = 6.4, J_t = 9, 1H), 7.1−6.6 (complex signal, 2H), 3.15 (d, J = 4.7, 1H), 3.02 (q, J = 7.3, 1H), 2.89 (d, J = 4.7, 1H), 1.20 (dd, J_{CF} = 0.8, J_d = 7.3, 3H); ^{13}C NMR ($CDCl_3$) δ ($CDCl_3$) 178.37 (C=O), 169.42, 168.79, 167.31, and 166.67 (CF), 156.97, 156.34, 154.85, and 154.20 (CF), 131.49, 131.22, 131.00, and 130.73 (CH), 122.14, 121.94, 121.40, and 121.21 (C), 111.87, 111.69, 110.81, and 110.63 (CH), 105.03, 103.76, and 102.49 (CH), 57.45 (CO epox), 51.58 (CH_2O epox), 45.03 (*C*HMe), 12.26 (Me); $[\alpha]_D$ −48.2° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{11}H_{10}F_2O_3$: C, 57.90; H, 4.42. Found: C, 57.62; H, 4.56.

Following an identical procedure but departing from isomer **10**, the enantiomer of compound **16** was obtained as a colorless oil, showing identical IR and ^1H NMR spectra: $[\alpha]_D$ +45.9° (*c* 1, $CHCl_3$). This proved the absolute stereochemistry of isomer **10**.

(2*R*,3*S*)-3-[3-(2,4-Difluorophenyl)-3,4-epoxy-2-methylbutanoic Acid (17). Following the previous procedure, epoxy acid **17** was obtained from epoxy imide **13** as a colorless oil: IR (film) ν 3600−2550, 1704, 1610, 1498, 1267 cm^{-1}; ^1H NMR ($CDCl_3$) δ (TMS) 11−10 (br, 1H, CO_2H), 7.42 (dt, J_d = 6.4, J_t = 9, 1H), 7.1−6.6 (complex signal, 2H), 3.27 (d, J = 4.8, 1H), 2.87 (q, J = 7.3, 1H), 2.83 (d, J = 4.8, 1H), 1.22 (d, J = 7.3, 3H); ^{13}C NMR ($CDCl_3$) δ ($CDCl_3$) 178.22 (C=O), 169.43, 168.82, 167.17, 166.56, 157.00, 156.40, 154.76, and 154.14 (CF), 131.30, 131.02, 130.82, and 130.55 (CH), 121.80, 121.60, 121.06, and 120.86 (C), 111.91, 111.74, 110.86, and 110.68 (CH), 105.07, 103.80, and 102.53 (CH), 57.86 (CO epox), 52.38 (CH_2O epox), 45.57 (*C*HMe), 12.23 (Me); $[\alpha]_D$ +8.8° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{11}H_{10}F_2O_3$: C, 57.90; H, 4.42. Found: C, 57.78; H, 4.44.

(2*R*,3*R*)-3-[3-(2,4-Difluorophenyl)-3-hydroxy-2-methyl-3-(1*H*-1,2,4-triazol-1-yl)butanoic Acid (19). To a cooled (0 °C) solution containing NaH (55% mineral oil dispersion, 52 g, 1.2 mol, washed with hexane) in DMF (850 mL) was added 1,2,4-triazole (91.4 g, 1.32 mmol, 4.4 equiv) in portions, and the mixture was stirred at 25 °C until hydrogen gas ceased to evolve (15 min). Then, a solution of epoxy acid **16** (68.7 g, 0.3 mol) in DMF (40 + 20 mL) was added at 10 °C, and the mixture was heated to 60 °C during 3 h. The mixture was

cooled to 0 °C, and a solution of 1 N HCl was added until the pH reached 4. The precipitate formed was filtered, and the filtrate was concentrated *in vacuo*. To the residue was added water, and the pH was adjusted to 4 with 1 N HCl. The precipitate was filtered, and the aqueous filtrate was saturated with NaCl, readjusted to pH 4, and extracted with EtOAc (3×). The collected organic fractions were washed with a pH 4 aqueous solution to remove the triazole and traces of DMF and then dried over anhydrous Na_2SO_4; the drying agent was filtered, and the filtrate was concentrated under reduced pressure to a white solid pure by TLC and containing some triazole by ^1H NMR analysis (overall weight 94 g, 105% mass recovery) that was used in the next step without further purification. An analytical sample was obtained by flash chromatography (EtOAc): mp 214 °C; IR (KBr) ν 3341, 3099, 3000–2200, 1662, 1492, 1128 cm^{-1}; ^1H NMR (DMSO-d_6) δ (central peak of DMSO-d_6) 8.29 (s, 1H), 7.59 (s, 1H), 7.4–6.7 (complex signal, 3H), 4.74 (s, 2H), 3.10 (br q, J = 7.1, 1H), 0.84 (d, J = 7.1, 3H); ^{13}C NMR (DMSO-d_6) δ (DMSO) 174.84 (C=O), 168.17, 167.53, 164.87, and 164.27 (CF), 155.95, 155.34, 152.62, and 152.02 (CF), 150.16 (CH triazole), 144.68 (CH triazole), 130.35, 130.04, 129.87, and 129.57 (CH), 124.85, 124.67, 124.22, and 124.04 (C), 111.20, 111.04, 110.16, and 110.02 (CH), 105.03, 103.74, 103.64, and 102.34 (CH), 75.65 and 75.41 (C), 56.03 and 55.81 (CH_2), 45.01 and 44.79 (CH), 12.46 (Me); $[\alpha]_D$ − 49.2° (*c* 1, MeOH). Anal. Calcd for $C_{13}H_{13}F_2N_3O_3$: C, 52.53; H, 4.41; N, 14.14. Found: C, 52.77; H, 4.62; N, 14.09.

(2*R*,3*S*)-3-[3-(2,4-Difluorophenyl)-3-hydroxy-2-methyl-3-(1*H*-1,2,4-triazol-1-yl)butanoic Acid (20). Compound **20** was obtained from epoxy acid **17** following an identical procedure: mp 153–154 °C; IR (KBr) ν 3401, 3200–2200, 1678, 1610, 1491, 1126 cm^{-1}; ^1H NMR (DMSO-d_6) δ (central peak DMSO-d_6) 8.20 (s, 1H), 7.63 (s, 1H), 7.4–6.7 (complex signal, 3H), 4.67 (AB quartet, $\Delta\nu$ = 0.16, J = 14.5, 2H), 4.0 (br, 2H, CO_2H, OH), 3.16 (br q, J = 7.0, 1H), 1.23 (d, J = 7.0, 3H); ^{13}C NMR (DMSO-d_6) δ (DMSO-d_6) 174.80 (C=O), 168.12, 167.50, 165.45, and 164.83 (CF), 155.93, 155.31, 153.16, and 152.55 (CF), 150.36 (CH triazole), 144.71 (CH triazole), 130.60, 130.30, 130.13, and 129.19 (CH), 125.50, 125.32, 124.85, and 124.66 (C), 110.95, 110.79, 109.93, and 109.77 (CH), 104.88, 103.47, and 102.18 (CH), 74.85 and 74.60 (C), 55.34 and 55.10 (CH_2), 45.80 and 45.61 (CH), 11.60 (Me); $[\alpha]_D$ +59.5° (*c* 1, MeOH). Anal. Calcd for $C_{13}H_{13}F_2N_3O_3$: C, 52.53; H, 4.41; N, 14.14. Found: C, 52.65; H, 4.51; N, 14.22.

(4*R*,5*R*)-4-(2,4-Difluorophenyl)-5-methyl-4-[(1*H*-1,2,4-triazol-1-yl)methyl]-2-oxazolidinone (21). A solution of compound **19** (94 g, 0.316 mol) in pyridine (0.9 L) was treated with diphenylphosphorylazide (DPPA, 104 g, 0.38 mol, 1.2 equiv), and the reaction mixture was heated at 75 °C for 20 h. Water was added, and the volatiles were removed under reduced pressure to afford a residue that was partitioned between chloroform and a pH 9 $NaHCO_3/Na_2CO_3$ aqueous solution. The organic phase was separated and washed (3×) with 10% $NaHCO_3$ aqueous solution until disappearence of diphenylphosphoric acid as monitored by TLC. The organic solution was dried over anhydrous Na_2SO_4 and filtered, and the filtrate was concentrated *in vacuo* to a white solid pure by TLC and ^1H NMR analyses (97 g, 104% mass recovery) that was used in the next step without further purification. An analytical sample was obtained by column chromatography purification ($CHCl_3$:MeOH 9:1) and recrystallization from EtOAc:ether: mp 190–191 °C; IR (KBr) ν 3237, 1766, 1611, 1497, 1271 cm^{-1}; ^1H NMR ($CDCl_3$) δ (TMS) 8.15 (s, 1H), 7.79 (s, 1H), 7.5–7.1 (m, 1H), 7.1–6.7 (m, 2H), 6.30 (br s, 1H, NH), 4.76 (AB quartet, $\Delta\nu$ = 0.15, J = 14.7, 2H), 4.30 (dq, J_{CF} = 2.2, J_q = 6.3, 1H), 0.97 (dd, J_{CF} = 0.8, J_d = 6.4, 3H); ^{13}C NMR ($CDCl_3$) δ (TMS) 170.09 and 169.46 (CF), 164.97 and 164.35 (CF), 157.54 and 156.93 (CF), 156.30 (C=O), 152.69 and 152.06 (CF), 151.59 (CH triazole), 144.50 (CH triazole), 129.28, 129.00, 128.80,, and 128.53 (CH), 119.05, 118.86, 118.39, and 118.20 (C), 112.76, 112.59, 111.71, and 111.255 (CH), 105.75, 104.47, and 103.20 (CH), 85.42 and 85.25 (C), 55.64 and 55.39 (CH_2), 54.08 and 54.00 (CH), 16.70 (Me); $[\alpha]_D$ +85.9° (*c* 1, MeOH). Anal. Calcd for $C_{13}H_{12}F_2N_4O_2$: C, 53.06; H, 4.11; N, 19.04. Found: C, 53.05; H, 4.00; N, 18.91.

(4*R*,5*S*)-4-(2,4-Difluorophenyl)-5-methyl-4-[(1*H*-1,2,4-triazol-1-yl)methyl]-2-oxazolidinone, Hydrate (22). Following an identical procedure, oxazolidinone **22** was obtained from **20**. Water of crystallization could not be removed by drying a solution of the compound over anhydrous Na_2SO_4 nor by concentrating a toluene solution containing the product: mp 110–111 °C; IR (KBr) ν 3470, 3400–2900, 1759, 1611, 1500, 1278 cm^{-1}; ^1H NMR ($CDCl_3$) δ (TMS) 8.13 (s, 1H), 7.62 (s, 1H), 7.8–6.6 (m, 3H), 6.2 (br s, 1H, NH), 4.85 (AB quartet, $\Delta\nu$ = 0.20, J = 14.7, 2H), 4.20 (br q, J = 6.6, 1H), 1.87 (s, H_2O), 1.57 (d, J = 6.6, 3H); ^{13}C NMR ($CDCl_3$) δ (TMS) 170.00 and 169.32 (CF), 165.50 and 164.80 (CF), 157.44 and 156.77 (CF), 156.34 (C=O), 153.14 and 151.28 (CF), 153.14 (CH triazole), 144.29 (CH triazole), 128.19, 127.93, 127.70, and 127.45 (CH), 123.07, 122.88, 122.46, and 122.27 (C), 112.41, 112.25, 111.37, and 111.20 (CH), 106.07, 104.79 and 103.51 (CH), 83.80 and 83.63 (C), 57.40 and 57.23 (CH_2), 52.76 and 52.53 (CH), 16.82 (Me); $[\alpha]_D$ +24.3° (*c* 1, MeOH). Anal. Calcd for $C_{13}H_{12}F_2N_4O_2 \cdot H_2O$: C, 50.00; H, 4.52; N, 17.94. Found: C, 50.18; H, 4.57; N, 18.01.

(2*R*,3*R*)-3-Amino-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (3). A mixture of oxazolidinone **21** (97 g) and 4 N aqueous HCl (0.9 L) was heated at reflux during 5 days. The mixture was cooled to room temperature, alkalinized with 4 N aqueous NaOH, and extracted with chloroform (3×). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4; the drying agent was filtered, and the filtrate was concentrated to afford amino alcohol **3** (116 g) as an oil containing chloroform. To obtain an analytical sample and a value of the yield for the three last steps, an aliquot of 6.0 g was chromatographed on silica gel ($CHCl_3$:MeOH 5:1) to furnish the pure material (3.4 g, 82% overall yield from epoxy acid **16**). The rest of the material was recrystallized from EtOAc/ether: mp 156–157 °C [lit.[7a] 154–155 °C]; IR (KBr) ν 3500–3000, 1611, 1492 cm^{-1}; ^1H NMR ($CDCl_3$) δ (TMS) 7.96 (s), 7.78 (s), 7.7–7.3 (m, 1H), 7.0–6.6 (m, 2H), 4.67 (s, 2H), 3.61 (dq, J_{CF} = 2.8, J_q = 6.5, 1H), 0.85 (d, J = 6.5, 3H); ^{13}C NMR ($CDCl_3$) δ ($CDCl_3$) 168.75, 168.15, 164.88, and 164.32 (CF), 156.39, 155.79, 152.67, and 152.10 (CF), 151.09 (CH triazole), 144.04 (CH triazole), 130.29, 129.95, 129.83, and 129.50 (CH), 124.28, 124.08, 123.59, and 123.41 (C), 111.69, 111.53, 110.68, and 110.51 (CH), 104.90, 103.64, 103.54, and 102.26 (CH), 76.81 and 76.52 (C), 56.54 and 56.28 (CH_2), 50.28 and 50.09 (CH), 19.07 (Me); $[\alpha]_D$ −74.5° (*c* 1.06, $CHCl_3$) [lit.[7a] $[\alpha]_D$ −73° (*c* 1.06 , $CHCl_3$); value from (*R*)-methyl lactate: $[\alpha]_D$ −73.7° (*c* 1.06, $CHCl_3$)]. Anal. Calcd for $C_{12}H_{14}F_2N_4O$: C, 53.73; H, 5.26; N, 20.88. Found: C, 53.69; H, 5.28; N, 20.89.

(2*S*,3*R*)-3-Amino-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (23). Following a similar procedure, amino alcohol **23** was obtained from oxazolidinone **22**: mp 90–91 °C (EtOAc:ether); [value from (*R*)-methyl lactate: mp 92–93 °C)]; IR (KBr) ν 3500–3000, 1609, 1492 cm^{-1}; ^1H NMR ($CDCl_3$) δ (TMS) 8.00 (s, 1H), 7.67 (s, 1H), 7.6–7.3 (m, 1H), 6.9–6.6 (m, 2H), 4.87 (dd, J_{CF} = 1.7, J_d = 13.9, 1H), 4.48 (d, J = 13.9, 1H), 3.54 (dq, J_{CF} = 1.3, J_q = 6.5, 1H), 1.24 (d, J = 6.5, 3H); ^{13}C NMR ($CDCl_3$) δ ($CDCl_3$) 169.09, 168.49, 165.00, and 164.43 (CF), 156.70, 156.10, 152.79, and 152.20 (CF), 151.08 (CH triazole), 143.99 (CH triazole), 130.92, 130.62, 130.45, and 130.15 (CH), 124.94, 124.76, 124.29, and 124.12 (C), 111.81, 111.65, 110.79, and 110.63 (CH), 105.34, 104.06, 103.94, and 102.68 (CH), 77.13 and 76.85 (C), 54.87 and 54.56 (CH_2), 51.58 and 51.40 (CH), 16.92 (Me); $[\alpha]_D$ +99.1° (*c* 1, $CHCl_3$) [value from (*R*)-methyl lactate: $[\alpha]_D$ +98.2° (*c* 1, $CHCl_3$)]. Anal. Calcd for $C_{12}H_{14}F_2N_4O$: C, 53.73; H, 5.26; N, 20.88. Found: C, 53.49; H, 5.27; N, 20.89.

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