Highly Diastereoselective Alkylation of 1-Benzoyl-2-alkyl-3-(1′-methylbenzyl)imidazolidin-4-ones

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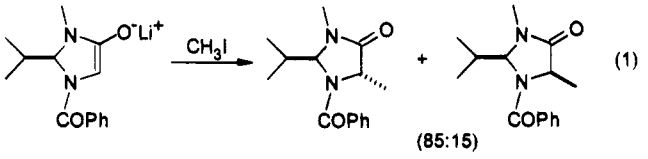
The synthetic utility of 2-alkyl-substituted 1,3-imidazolidinones for the enantioselective preparation of α-amino acids is now well documented in the literature. Incorporation of a *N*(3)-phenethyl group in these heterocycles leads to substantial enhancements in the diastereoselectivity of alkylation of the corresponding lithium enolates, so that stereoselectivities in the order of 19:1 to 49:1 are observed for 2-isopropyl and 2-*tert*-butyl derivatives, respectively. X-ray crystallographic analysis on five *N*(3)-phenethyl-substituted imidazolidinones provided evidence that the long-distance effect of that chiral moiety is the result of conformational changes provoked by steric interactions between the 2-alkyl and the *N*(3)-phenethyl groups. No additivity of the stereodirecting effects by the stereogenic centers at C(2) and C(1′) was noticed. Thus, as it could have been anticipated from basic principles, *intramolecular* combinations of stereogenic centers do not necessarily lead to "matched" and "mismatched" joint stereoinducing effects.

Introduction

Among the various methods available for the preparation of optically active α-amino acids,[3] the use of chiral imidazolidinones derived from glycine is particularly convenient[4] (Scheme 1).

An important attribute of this system is the high diastereoselectivity observed in alkylations of the imidazolidinone lithium enolates: >95% when the electrophile is methyl iodide or benzyl bromide.[4a] The major product of alkylation results from approach of the electrophile *trans* to the *tert*-butyl group, the steric influence of which is a determining factor here. By comparison, methylation of the C(2)-isopropyl analogue affords a *trans*:*cis* = 85:15 product mixture (eq 1).[4b]



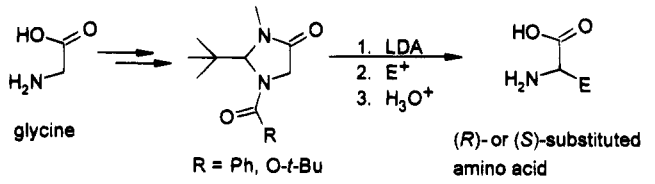
(1)

The following step in this method involves a hydrolytic reaction to afford the desired α-amino acids, and this usually requires heating to temperatures above 100 °C with concentrated (4 N to saturated) aqueous HCl. While these conditions are tolerated by a large variety of substituted amino acids, which are obtained by this method without appreciable racemization,[4,5] it is clear that milder reaction conditions would be desirable for handling more sensitive amino acids.[6]

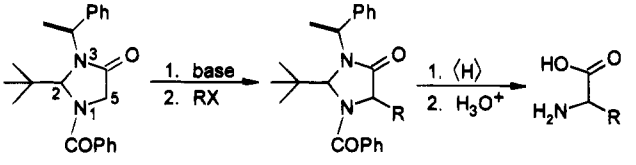
In this regard, we have described recently the preparation of diastereomeric imidazolidinones (*R*,*S*)-**1** and (*S*,*S*)-**1**,[7] containing a labile group at N(3) whose removal (e.g., by catalytic hydrogenolysis) could facilitate (following diazotation) the isolation of the desired α-amino acids (Scheme 2).

In this paper we report the results of a study on the stereoselectivity of the alkylation (RX = CH_3I, $PhCH_2Br$) of the lithium enolates derived from (*R*,*S*)- and (*S*,*S*)-

Scheme 1



Scheme 2



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(1) Instituto Politécnico Nacional.

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(3) (a) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.

(4) (a) Seebach, D.; Miller, D. D.; Müller, S.; Weber, T. *Helv. Chim. Acta* **1985**, *68*, 949. (b) Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237. (c) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277. (d) Seebach, D.; Dziadulewicz, E.; Behrendt, L.; Cantoreggi, S.; Fitzi, R. *Liebigs Ann. Chem.* **1989**, 1215. (e) Seebach, D.; Gees, T.; Schuler, F. *Liebigs Ann. Chem.* **1993**, 785. (f) Plenevaux, A.; Al-Darwich, M. J.; Lemaire, C.; Delefiore, G.; Comar, D. *Appl. Radiat. Isot.* **1994**, *45*, 361. (g) Song, Y.; Niederer, D.; Lane-Bell, P. M.; Lam, L. K. P.; Crawley, S.; Palcic, M. M.; Pickard, M. A.; Pruess, D. L.; Vederas, J. C. *J. Org. Chem.* **1994**, *59*, 5784. (h) Studer, A.; Seebach, D. *Heterocycles* **1995**, *40*, 357. Studer, A.; Seebach, D. *Liebigs Ann.* **1995**, 217.

(5) For extensions to the synthesis of enantiopure β-amino acids, see: (a) Juaristi, E.; Escalante, J.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1992**, *57*, 2396. (b) Juaristi, E.; Quintana, D. *Tetrahedron: Asymmetry* **1992**, *3*, 723. (c) Juaristi, E.; Escalante, J. *J. Org. Chem.* **1993**, *58*, 2282.

(6) See, for example: Blaser, D.; Ko, S. Y.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 6230. Blank, S; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1765.

(7) Juaristi, E.; Rizo, B.; Natal, V.; Escalante, J.; Regla, I. *Tetrahedron: Asymmetry* **1991**, *2*, 821.

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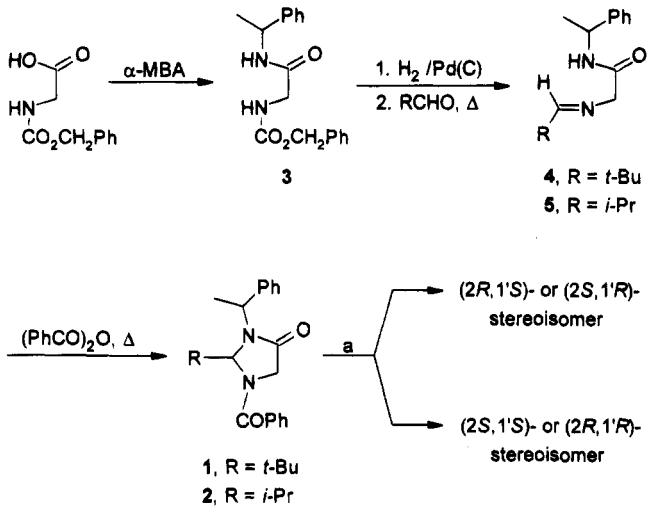
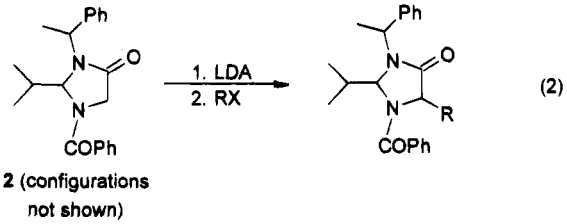
Scheme 3[a]



[a] Key: (a) fractional crystallization and flash column chromatography.

1, as well as those derived from isopropyl analogues (*R*,*S*)- and (*S*,*S*)-**2** (eq 2).



(2)

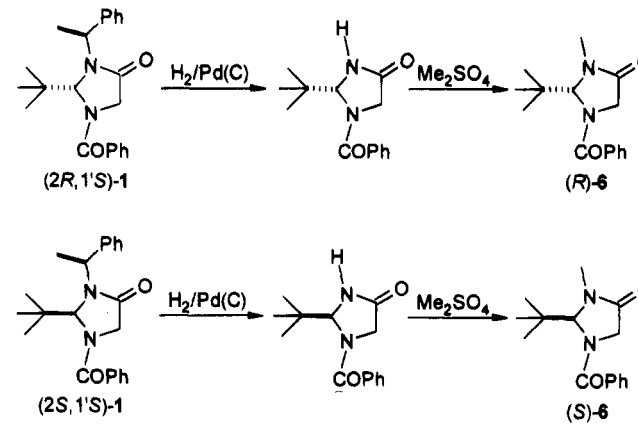
An important issue is whether the stereogenic center at the phenethyl group affects the stereoselectivity of alkylation, relative to that observed in the *N*-methylated derivatives. The consequences of the *N*-phenethyl group on the ease of hydrolysis of the alkylated compounds will be discussed in a separate report.[8]

Results and Discussion

A. Preparation of 1-Benzoyl-2-*tert*-butyl- and 1-Benzoyl-2-isopropyl-3-(1'(*S*)-methylbenzyl)imidazolidin-4-one (1 and 2). As shown in Scheme 3, (carbobenzyloxy)glycine[9] was treated with 1.1 equiv of dicyclohexylcarbodiimide (DCC) and then with 1.1 equiv of (*S*)-α-methylbenzylamine [(*S*)-MBA] to give crystalline amide **3** in 60% yield. Alternatively, the starting Cbz-glycine was converted to the corresponding acid chloride with oxalyl chloride in CH_2Cl_2, in the presence of some DMF,[10] and then treated with (*R*)-MBA to afford (*R*)-**3** in 70% yield[7] (Scheme 3).

Hydrogenolysis of **3** effected the removal of the carbobenzyloxy (Cbz) protective group, and condensation with either pivalaldehyde or isobutyraldehyde (with azeotropic removal of water) provided imines **4** (R = *t*-Bu) or **5** (R = *i*-Pr) in 85% and 65% yields, respectively. Cyclization was then achieved upon treatment with benzoic anhydride[11] to furnish 55:45 diastereoisomer mixtures of imidazolidinones **1** and **2** in 81% and 55% yield, respectively. The slightly prevailing diastereoisomer proved to be that of *unlike* [*u*; i.e., (*R*,*S*) or (*S*,*R*)] relative configuration, whereas the minor product has like [*l*; i.e., (*R*,*R*) or (*S*,*S*)] configuration[12] (see below).

Scheme 4



Separation of the *like* and *unlike* diastereoisomers of **1** and **2** was carried out by fractional crystallization from methanol or chloroform–hexane (5:95) of the *unlike* isomer. Flash chromatography[13] of the mother liquor then afforded the *like* isomer, as well as an additional portion of the *unlike* isomer (see Experimental Section).

The stereoisomeric (2*S*,1'*R*)- and (2*R*,1'*R*)-**1** and -**2** were similarly prepared and separated, employing (*R*)-MBA instead of (*S*)-MBA.

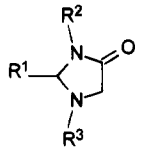
B. Assignment of Configurations. B1. Assignment of Configuration in (2*R*,1'*S*)- and (2*S*,1'*S*)-1-Benzoyl-2-*tert*-butyl-3-(1'-methylbenzyl)imidazolidin-4-one [(2*R*,1'*S*)- and (2*S*,1'*S*)-1]. The assignment of configuration in (2*R*,1'*S*)-**1** and (2*S*,1'*S*)-**1** was carried out by chemical correlation with known (2*R*)- and (2*S*)-1-benzoyl-2-*tert*-butyl-3-methyl-1,3-imidazolidin-4-ones [(*R*)- and (*S*)-**6**;[14] Scheme 4].

Hydrogenolytic removal of the phenethyl group[15] afforded the corresponding NH aminals, which were then methylated to produce imidazolidinones **6**, the $[\alpha]_D$ values of which agreed with those described in the literature for the (*R*) and (*S*) enantiomers.[7,14]

B2. Assignment of Configuration in (2*R*,1'*S*)- and (2*S*,1'*S*)-1-Benzoyl-2-isopropyl-3-(1'-methylbenzyl)-imidazolidin-4-ones [(2*R*,1'*S*)- and (2*S*,1'*S*)-2]. A tentative assignment of the relative configuration in (2*R*,1'*S*)- and (2*S*,1'*S*)-**2** was first proposed on the basis of the apparently consistent trends in physical properties, and in particular melting points, for the diastereoisomeric series collected in Table I. Indeed, it was observed (entries 1–6) that for each pair of *like*/*unlike* isomers, it is the former that has a lower melting point. Thus, the diastereoisomer of **2** with mp 125–126 °C was assigned as (2*S*,1'*S*)-**2** and the one with mp 149–150 °C as (2*R*,1'*S*)-**2**. This assignment of configuration was confirmed by X-ray crystallographic analysis of (2*R*, 1'*S*)-**2** (see below).

(8) García-Barradas, O.; Studer, A.; Juaristi, E.; Seebach, D. Manuscript in preparation.
(9) Purchased from Aldrich Chemical Co.
(10) Cf. Buckley, T. F.; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 6157.
(11) Cf. Juaristi, E.; Quintana, D.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 2553.
(12) For the definition of *like*/*unlike* stereochemical descriptors, see: Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654. Also see: Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis*; Wiley: New York, 1991; Chapter 3.
(13) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(14) Fitzi, R.; Seebach, D. *Angew. Chem.* **1986**, *98*, 363; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 345.
(15) Augustine, R. L. *Catalytic Hydrogenation*; Marcel Dekker: New York, 1965; pp 139–142.
(16) Polt, R.; Seebach, D. *J. Am. Chem. Soc.* **1989**, *111*, 2622.

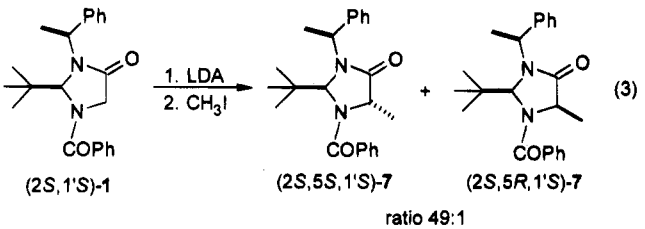
Table 1. Apparent Correlation of Melting Points and Relative Configuration in Diastereoisomeric Imidazolidinones[a]



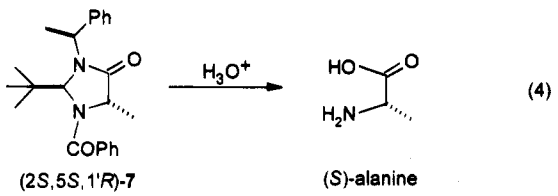
entry	R^1	R^2	R^3	rel config	mp (°C)	ref
1	*t*-Bu	1′-MBA	COPh	*like*	126–7	7
2	*t*-Bu	1′-MBA	COPh	*unlike*	185–6	7
3	*t*-Bu	1′-MBA	CO_2CH_2Ph	*like*	70–3	8
4	*t*-Bu	1′-MBA	CO_2CH_2Ph	*unlike*	125–7	8
5	*t*-Bu	$CH(CH_3)CO_2Me$	COPh	*like*	oil	16
6	*t*-Bu	$CH(CH_3)CO_2Me$	COPh	*unlike*	123–4	16
7	*i*-Pr	1′-MBA	COPh	*like*	125–6	this work
8	*i*-Pr	1′-MBA	COPh	*unlike*	149–50	this work

[a] These melting points correspond to enantiopure materials rather than racemic mixtures.

C. Diastereoselectivity of the Alkylation of 1-Benzoyl-2-alkyl-3-(1′-methylbenzyl)imidazolidin-4-ones. C1. Methylation of (2*S*, 1′*S*)-1 and (2*R*, 1′*R*)-1. Treatment of the title imidazolidinone with lithium diisopropylamide (LDA) afforded the corresponding lithium enolate which was treated with methyl iodide to produce the desired methylated derivatives in 82% yield (eq 3).

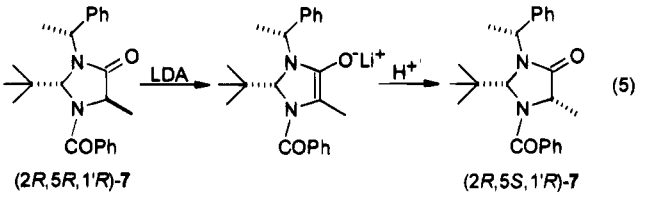


Analysis of the ^1H (270 MHz) and ^{13}C (22.49 MHz) NMR spectra for the crude product showed a 98:2 ratio of diastereoisomeric methylated products. That the major product corresponds to that arising from alkylation *trans* to the *tert*-butyl group was established by hydrolysis to alanine of positive optical rotation; that is, (*S*)-alanine[17] (eq 4).

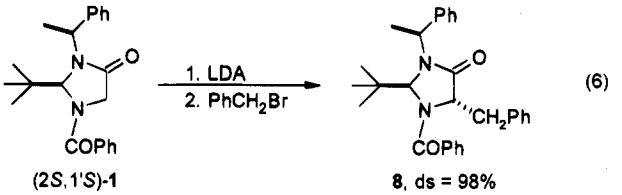


The enantiomeric substrate (2*R*,1′*R*)-**1** was methylated in the same way to give 94% yield of the expected 98:2 mixture of the *trans* and *cis* products. This diastereoisomeric ratio was determined by means of ^1H NMR spectroscopy at 400 MHz. Assignment of the signals corresponding to the minor *cis* product, obtained in only 2%, was secured by epimerization of the major *trans* product via enolate formation and protonation to give the *cis* isomer (eq 5). This result shows that both methyl iodide and a proton exhibit a large preference for approach on the diastereotopic enolate face that is *trans* to the *tert*-butyl group.

(17) Cf. Aldrich Catalog/Handbook 1994–1995; p 38.

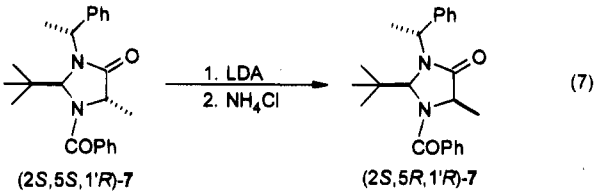


C2. Benzylation of (2*S*,1′*S*)-1. The lithium enolate of (2*S*,1′*S*)-**1** was also treated with benzyl bromide to afford the benzylated derivative **8** in 80% yield and with high diastereoselectivity (eq 6).

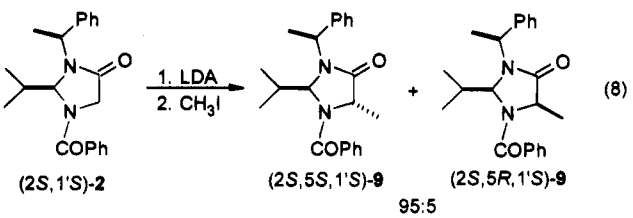


C3. Methylation of the *Unlike* Isomers (2*R*,1′*S*)-1 and (2*S*,1′*R*)-1. Once it was established that alkylation of the *like* isomers (2*S*,1′*S*)-**1** and (2*R*,1′*R*)-**1** proceeds with 98% diastereoselectivity, it was decided to determine the stereoselectivity of the methylation of the *unlike* imidazolidinones. Accordingly, (2*R*,1′*S*)-**1** and (2*S*,1′*R*)-**1** were metalated with LDA and then treated with CH_3I to give the diastereoisomeric products of methylation in 85% yield and in a 98:2 ratio. That the major product has *trans* configuration was established by hydrolysis to (*R*)-alanine (cf. Scheme 5).

Determination of the diastereomer ratio in the methylated products was again (see section C1) facilitated by epimerization at C(5) in the main product, so that all signals (main and minor) in the ^1H NMR spectra of the crude mixtures could be assigned with confidence (eq 7).



C4. Methylation of (2*S*,1′*S*)-2 and (2*R*,1′*R*)-2. The analogous 2-isopropyl-substituted imidazolidinones **2** of relative configuration *like* were methylated as described above for **1** (see sections C1 or C3). The yield for the methylation of (2*S*,1′*S*)-**2** was 87%, and the analysis of ^1H NMR spectra of the crude product indicated a 95:5 ratio of diastereoisomeric products. Assignment of configuration in these products was achieved by comparison of spectroscopic data with those in the *tert*-butyl-substituted system (**7**) and by X-ray crystallographic analysis (see below, Section D). It was concluded that the main product corresponds to the one originating from alkylation on the enolate face opposite to the isopropyl group (eq 8).



Scheme 5

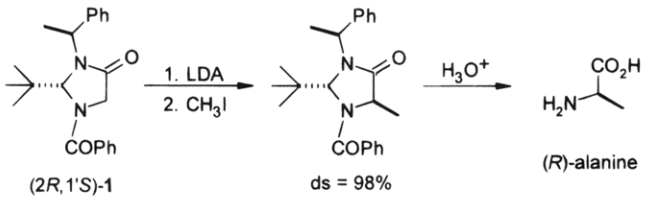
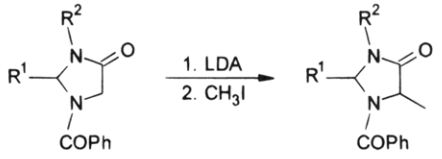


Table 2. Diastereomer Ratios Obtained in the Methylation of Imidazolidinones 1, 2, 6, 11, and 12



compd	R^1	R^2	*trans/cis* ratio
l-**1**	*t*-Bu	α-MBA	98:2
u-**1**	*t*-Bu	α-MBA	98:2
l-**2**	*i*-Pr	α-MBA	95:5
u-**2**	*i*-Pr	α-MBA	95:5
6	*t*-Bu	CH_3	95:5
11	*i*-Pr	CH_3	85:5
12	H	α-MBA	62:38[a]

[a] (*S*)-MBA induces addition on the *Re* face of the enolate; thus, *ul*-1,3 induction.

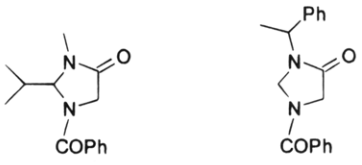
Diastereoisomer (2*S*,5*R*,1′*S*)-**9**, the minor product in this reaction, could also be prepared by epimerization at C(5) of the major product, by means of the metalation–protonation sequence described in sections C1 and C3.

C5. Methylation and Benzylation of (2*R*,1′*S*)-2 and (2*S*,1′*R*)-2. Determination of the stereoselectivity of the methylation of *unlike* imidazolidinones (2*R*,1′*S*)- and (2*S*,1′*R*)-**2** was based on ^{1}H NMR data of the crude reaction products. Diastereoselectivities of 95% were established. That addition of the electrophile takes place predominantly on the enolate face opposite to the isopropyl group was again confirmed by hydrolysis to optically active alanine or by X-ray crystallographic analysis of the benzylated analogue (2*S*,5*S*,1′*R*)-**10** (eq 9 and section D).

(9)

Results and Discussion

Table 2 summarizes the diastereoselectivities observed in the methylation of diastereoisomeric *like*- and *unlike*-**1**, *like*- and *unlike*-**2**, their N(3)-methyl analogues (**6** and **11**), and, finally, the methylenic derivative **12**.



The contrasting influence between a *tert*-butyl and an isopropyl group at C(2) has been reported before:[4b]

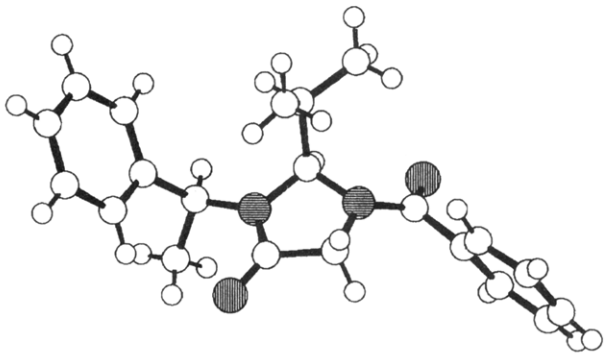


Figure 1. Molecular structure of (2*R*,1′*S*)-**2**.[20]

whereas methylation of **6**-Li takes place with a 95:5 *trans/cis* ratio (95% ds), the diastereoselectivity drops to 85% in the 2-isopropyl analogue **11**. Nevertheless, diastereoselectivities increase when the N(3)-methyl group is replaced by the α-methylbenzyl group. Indeed, the 95:5 *trans/cis* ratio encountered in the methylation of **6** increases to a 98:2 ratio in **1**. Furthermore, the 85:15 *trans/cis* ratio found in the methylation of **11** increases to a 95:5 ratio in **2**.

Reaction always proceeds on the enolate face opposite to the alkyl group at C(2), regardless of the configuration of the phenethyl group. Thus, it is clear that the asymmetric induction by C(2) is dominant over the inducing effect of C(1′). Nevertheless, the 62:38 isomeric ratio observed in the methylation of C(2)-unsubstituted imidazolidinone **12** indicates that the influence of the phenethyl group is not negligible.

In this regard, it is perhaps surprising that both the *like* and *unlike* isomers of **1** and **2** afford the same ratios of isomeric products at C(5). One could have anticipated a best combination of stereocenters leading to better stereoselectivities when compared to the less optimal combination.[18] Therefore, it is evident that no additivity of stereodirecting effects must be expected among diastereoisomeric substrates.

An explanation for the effect that the phenethyl group has on the stereoselectivity of alkylation in **11**-Li (85% ds) *vis à vis* **2**-Li (95% ds) may be found in the X-ray crystallographic structure of (2*R*,1′*S*)-**2** (Figure 1). Indeed, steric congestion between the phenethyl and isopropyl group forces the latter into a conformation in which one of its methyl groups points into the imidazolidinone ring. As a consequence, the *effective* size of the isopropyl group is similar to that of a more bulky *tert*-butyl group, so that the observed diastereoselectivity is comparable to that exhibited by **6**-Li (see Table 2).

Support for the "methyl-inside" conformation of **11** in solution comes from ^{1}H NMR data. In particular, the coupling constant between the isopropyl C-H proton and C(2)-H, $^3J \leq 2.0$ Hz, suggests a dihedral angle closer to 60° rather than 180°. Furthermore, molecular mechanics calculations (PCMODEL 4.0[19]) give a global minimum which corresponds to a methyl-inside conformer; $\tau_{H-C(i\text{-}Pr)-C(2)-H} = 60.2°$.

(18) For the proposal of "matched/mismatched" combinations of intermolecular reactions between chiral reagents, see: Masamune, S.; Choy, W.; Petersen, J. S.; Siota, L. W. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(19) Gilbert, K. E. *PCMODEL 4.0*; Serena Software: Bloomington, IN, 1991.

(20) The author has deposited atomic coordinates for this structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Figure 2 (supporting information) contains the X-ray crystal structures of four additional *N*(3)-phenethyl imidazolidinones: (2*S*,5*S*,1′*R*)-**7**, (2*R*,5*R*,1′*R*)-**9**, (2*S*,5*S*,1′*R*)-**10**, and (*S*)-**12**. Space groups, cell constants, number of reflections measured, and final *R* values for the X-ray analyses are collected in Table 3 (supporting information).

Summary and Conclusions

The results presented in this paper demostrate that the diastereoselectivity of the alkylation of imidazolidin-4-ones is enhanced by incorporation of a phenethyl substituent at N(3). In heterocycles containing a *tert*-butyl group at C(2), diastereoselectivities in the order of 49:1 are achieved, whereas in 2-isopropyl analogues, 19:1 selectivities are observed.

Imidazolidinones containing an isopropyl group at C(2) and the phenethyl group at N(3), i.e., **2**, are alkylated with as high diastereoselectivity as that exhibited by the derivative with *tert*-butyl at C(2) and methyl at N(3). X-ray crystallographic and ^{1}H NMR data indicate that the phenethyl group fixes the conformation of the isopropyl substituent, so that one of its methyl groups is situated above the five membered ring, hindering addition of the electrophile to the enolate face *syn* to the isopropyl group of reference.

Both *like* and *unlike* isomers of **1** and **2** are alkylated with similar stereoselectivity. Thus, no additivity of the stereodirecting centers at C(2) and C(1′) is observed in this system.

Experimental Section

General Information. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, CCl_4, $(CD_3)_2CO$, or D_2O solution with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given as δ values (ppm) and coupling constants J are given in Hz. Optical rotations $[\alpha]_D$ were measured at ambient temperature in 1 or 0.1 dm cells, concentration c in g/100 mL.

THF was initially distilled over KOH and then heated to reflux over K/benzophenone (under argon) until the blue color of the benzophenone ketyl persisted; at this point the THF was distilled and handled by means of syringes and cannulas.[21] The *n*-BuLi employed (ca. 1.6M in *n*-hexane) was titrated prior to its use.[22] Flasks, stirring bars, and hypodermic needles used for the generation of organometallic compounds were dried for ca. 12 h at 120 °C and allowed to cool in a desiccator over anhydrous calcium sulfate.

Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, and by the microanalytical laboratories at ETH-Zürich.

General Procedure for the Alkylation of Imidazolidinones. In a dry two-necked round-bottom flask, provided with addition funnel, rubber septa, and thermometer, was placed under argon diisopropylamine (1.65 mmol) in 20 mL of THF, which was then cooled to −20 °C before the slow addition of 1.8 mmol of *n*-BuLi (ca. 1.6 M in *n*-hexane). The resulting solution was stirred at −20 °C for 20 min and then cooled to −78 °C before the dropwise addition of 1.5 mmol of the heterocycle in 30 mL of THF. Stirring was continued for 45 min at −78 °C in order to secure the complete formation of the enolate. The alkylating agent (3 mmol, 100% excess) was then added dropwise via syringe, and the reaction mixture was stirred at −78 °C until no further changes were detected by TLC (2−3 h). At this point the reaction was quenched by the addition of saturated aqueous NH_4Cl solution, allowed to warm to ambient temperature, and extracted with three portions of Et_2O. The combined ethereal extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in a rotary evaporator.

2-[*N*-(Benzyloxycarbonyl)amino]-*N*′-[(*R*)-α-methylbenzyl]acetamide [(*R*)-3]. In a 500-mL three-necked flask provided with magnetic stirrer was placed 15.1 g (72 mmol) of *N*-(benzyloxycarbonyl)glycine in 100 mL of CH_2Cl_2 and 0.43 mL (5.6 mmol) of DMF. The resulting solution was cooled to 0 °C before the dropwise addition of 6 mL (79 mmol) of oxalyl chloride. The reaction mixture was stirred at rt for 2 h before the addition of additional 100 mL of CH_2Cl_2 and was then cooled to −15 °C, treated with 10.2 mL (79 mmol) of (*R*)-methylbenzylamine, and stirred overnight at rt. The workup procedure involved extraction with 100 mL of 1 M HCl solution, 100 mL of water, and two 70-mL portions of saturated aqueous $NaHCO_3$ solution. Concentration in a rotary evaporator afforded the crude product which was crystallized from hexane−ethyl acetate to give 16.6 g (73% yield) of the desired product as a white solid with mp 89−90 °C (lit.[7] mp 91−92 °C for the (*S*) enantiomer): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 (d, J = 7.0 Hz, 3 H), 3.83 (d, J = 5.6 Hz, 2 H), 5.09 (m, 3 H), 5.4−5.5 (br), 6.25−6.35 (br), 7.2−7.4 (m, 10 H).

2-[*N*-(Benzyloxycarbonyl)amino]-*N*′-[(*S*)-α-methylbenzyl]acetamide [(*S*)-3]. In a 500 mL three-necked flask provided with two addition funnels was placed 10 g (47 mmol) of *N*-(benzyloxycarbonyl)glycine in 150 mL of ethyl acetate. The flask was submerged in an ice−water bath (0 °C) before the addition of a solution containing 11 g (52 mmol) of dicyclohexylcarbodiimide in 50 mL of ethyl acetate. The reaction mixture was stirred at 0 °C for 1 h, treated with 6.66 mL (51 mmol) of (*S*)-methylbenzylamine, and then stirred for 4 additional h. Filtration of the precipitated dicyclohexylurea and concentration afforded 9.8 g (65% yield) of the desired product: mp 91−92 °C (lit.[7] mp 91−92 °C); $[\alpha]^{28}_D$ = −75.2 (c = 1, absolute ethanol); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.4 (d, 3 H, J = 7.2 Hz), 3.78 (d, 2 H, J = 6 Hz), 5.05 (q, 1 H, J = 7.2 Hz), 5.05 (s, 2 H), 5.88 (t, 1 H, J = 7.2 Hz), 7.0 (br, 1 H), 7.3 (s, 5 H), 7.35 (s, 5H); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 21.7, 44.3, 48.7, 66.8, 125.9, 127.1, 127.8, 128.0, 128.4, 128.4, 136.0, 142.9, 156.5, 168.1.

2-[*N*-(2,2′-Dimethylpropylidene)amino]-*N*′-[(*R*)-α-methylbenzyl]acetamide [(*R*)-4]. In a hydrogenation flask was placed under argon 600 mg of 10% Pd(C), and then 3.6 g (11.4 mmol) of (*R*)-**3** in 40 mL of methanol. The flask was pressured to 10 atm of H_2 and shaken overnight at 35 °C. The reaction mixture was filtered through Celite and concentrated to afford 2.1 g (*ca.* 100% yield) of the deprotected amine as a yellow-brownish oil. Two grams (11.2 mmol) of this product was redissolved in 140 mL of CH_2Cl_2 and treated with 1.6 mL (11.2 mmol) of Et_3N and 2.5 mL (22.4 mmol) of pivalaldehyde. The resulting solution was placed in a flask provided with an inverted Dean−Stark trap, heated to reflux for 5 h, and then allowed to cool to rt to be washed with two 30-mL portions of H_2O and dried over anhydrous Na_2SO_4. Concentration in a rotary evaporator afforded 2.3 g (83% yield) of (*R*)-**4** as a brownish oil: $[\alpha]^{28}_D$ = +70 (c = 1.05, CH_2Cl_2) [lit.[7] for the (*S*)-enantiomer $[\alpha]^{29}_D$ = −73.8 (c = 1, ethanol)]. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.08 (s, 9 H), 1.50 (d, J = 6.9 Hz, 3 H), 4.04 (dd, J = 4.7 Hz, 2 H), 5.18 (q, $J \simeq$ 7 Hz, 1 H), 7.25−7.40 (m, 5 H), 7.59 (t, J = 1.4 Hz, 1 H).

2-[*N*-(2,2′-Dimethylpropylidene)amino]-*N*′-[(*S*)-α-methylbenzyl]acetamide [(*S*)-4] was prepared in similar fashion (see also ref 7) in 85% yield.

2-[*N*-(2-Methylpropylidene)amino]-*N*′-[(*R*)-α-methylbenzyl]acetamide [(*R*)-5]. The same procedure described above for the preparation of (*R*)-**4** was followed, with 12.3 g (41.8 mmol) of (*R*)-**3** (i.e., 7.4 g of free amine) and 7.6 mL (83.6 mmol) of isobutyraldehyde. The desired imine (*R*)-**5** was obtained in 65% yield (6.3 g) as a yellowish oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95−1.15 (m, 6 H), 1.49 (d, J = 7.0 Hz, 3 H), 2.3−2.6 (m, 1 H), 4.04 (dd, J = 4.7 Hz, 2 H), 5.17 (dq, $J \simeq$ 7.0 Hz, 1 H), 7.15 (brd, 1H), 7.2−7.4 (m, 5 H), 7.61 (dt, J = 1.4 Hz, 1 H).

(2*R*,1′*R*)- and (2*S*,1′*R*)-1-Benzoyl-2-*tert*-butyl-3-(α-methylbenzyl)-1,3-imidazolidin-4-one [(2*R*,1′*R*)- and (2*S*,1′*R*)-

(21) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley: New York, 1975; p 256.
(22) Juaristi, E.; Martínez-Richa, A.; García-Rivera, A.; Cruz-Sánchez, J. S. *J. Org. Chem.* **1983**, *48*, 2603.

1]. In a 100-mL round-bottom flask, provided with stirring bar and condenser, was placed 2.2 g (8.9 mmol) of (*R*)-**4** and the mixture treated with 50 mL of toluene containing 2.2 g (9.8 mmol) of benzoic anhydride. The resulting solution was heated to reflux for 7 h and then concentrated to give a yellow semisolid, which was redissolved in CH_2Cl_2, washed twice with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated to provide the crude product. Recrystallization from hexane–ethyl acetate followed by flash chromatography afforded 2.5 g (81% yield) of the desired mixture of products.

Separation of (2*R*,1′*R*)- and (2*S*,1′*R*)-1. The *unlike* diastereoisomer was separated by recrystallization from hexane–ethyl acetate. The remaining mixture (mother liquors) was then passed through a flash column (hexane–ethyl ether–CH_2Cl_2, 18:1:1) to provide both individual isomers.

(2*R*,1′*R*)-1: isolated yield, 0.5 g (17%); R_f = 0.07 (hexane–ethyl ether–CH_2Cl_2, 18:1:1); melting point, 129 °C (lit.[7] mp 126–127 °C for the (*S*,*S*) enantiomer; $[\alpha]^{29}_D = -66.3$ (*c* = 1, $CHCl_3$) [lit.[7] $[\alpha]^{29}_D = +60.5$ (*c* = 1, CH_2Cl_2) for the (*S*,*S*) enantiomer]; IR 3000 (m), 2970 (m), 1700 (s), 1650 (s), 1600 (w), 1450 (m), 1430 (m), 1390 (s), 1375 (s), 1300 (m), 1275 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 9 H), 1.97 (d, *J* = 7.3 Hz, 3 H), 3.77 (AB, *J* = 15.7 Hz, 1 H), 4.13 (A*B*, *J* = 15.7 Hz, 1 H), 4.80 (q, *J* = 7.2 Hz, 1 H), 5.85 (s, 1 H), 7.2–7.6 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3, 26.1, 39.9, 54.0, 55.8, 80.2, 127.0, 127.7, 128.1, 128.6, 131.5, 134.2, 140.7, 170.3, 171.2; MS *m/z* 351.3 (M^+, 0.2), 335.2 (0.3), 293.2 (53), 189.1 (35), 105.1 (100), 77.1 (21).

Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.31; H, 7.44; N, 8.07.

(2*S*,1′*R*)-1: isolated yield, 0.6 g (20%); R_f = 0.06 (hexane–ethyl ether–CH_2Cl_2, 18:1:1); melting point 185–186 °C (lit.[7] mp 185–186 °C) for the (*R*,*S*) enantiomer; $[\alpha]^{28}_D = -42.5$ (*c* = 1.06, $CHCl_3$) [lit.[7] $[\alpha]^{29}_D = +45.5$ (*c* = 1, CH_2Cl_2) for the (*R*,*S*) enantiomer]; IR 3006 (m), 2980 (m), 1710 (s), 1670 (s), 1450 (m), 1430 (m), 1390 (s), 1360 (m), 1305 (m), 1285 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 9 H), 1.76 (d, *J* = 7.1 Hz, 3 H), 3.94 (AB, *J* = 15.7 Hz, 1 H), 4.23 (A*B*, J = 15.7 Hz, 1 H), 4.66 (q, *J* = 7.1 Hz, 1 H), 5.74 (s, 1 H,), 7.2–7.6 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 25.8, 39.6, 54.3, 59.1, 82.0, 127.0, 127.1, 128.2, 128.5, 128.6, 131.6, 134.2, 141.2, 170.5, 171.3; MS *m/z* 351.2 (M^+, 0.2), 335.2 (0.3), 293.2 (52), 189.1 (34), 105.1 (100), 77.1 (22).

(2*S*,1′*S*)- and (2*R*,1′*S*)-1 were prepared and separated as described in ref 7.

(2*R*,1′*R*)- and (2*S*,1′*R*)-1-Benzoyl-2-isopropyl-3-(α-methylbenzyl)-1,3-imidazolidin-4-one [(2*R*,1′*R*)- and (2*S*,1′*R*)-2]. Following the same procedure described for the conversion of (*R*)-**4** into **1**, 4.5 g (19.2 mmol) of (*R*)-**5** was treated with 4.8 g (21.1 mmol) of benzoic anhydride. The crude product was purified by flash chromatography (hexane–ethyl acetate, 1:1) to afford 2.4 g (37% yield) of the diastereoisomeric mixture of products, in a ca. 1:1 ratio. Fractional crystallization (hexane–ethyl acetate or hexane–chloroform) provided pure (2*S*,1′*R*)-**2**, whereas flash chromatography of the mother liquor (eluent: CH_2Cl_2–hexane–ethyl acetate, 18:1:1) allowed for the isolation of (2*R*,1′*R*)-**2**.

(2*R*,1′*R*)-2: isolated yield, ca. 0.52 g (ca. 8% yield); R_f = 0.06 (hexane–ethyl acetate–CH_2Cl_2, 18:1:1); melting point, 125–126 °C; $[\alpha]^{28}_D = -48.3$ (*c* = 1.04, $CHCl_3$); IR 3040 (w), 2995 (m), 2960 (m), 1685 (s), 1645 (s), 1600 (w), 1570 (m), 1490 (m), 1440 (m), 1385 (s), 1370 (s), 1320 (m), 1300 (m), 1270 (s), 1170 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65 (d, *J* = 6.7 Hz, 3 H), 0.94 (d, *J* = 6.7 Hz, 3 H), 1.68 (m, 1 H), 1.77 (d, *J* = 7.3 Hz, 3 H), 3.91 (AB, *J* = 15.5 Hz, 1 H), 4.13 (A*B*, *J* = 15.5 Hz, 1 H), 5.34 (q, *J* = 7.3 Hz, 1 H), 5.97 (br, 1 H), 7.3–7.6 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 16.3, 18.9, 33.6, 50.5, 53.7, 74.9, 127.5, 128.0, 128.0, 128.5, 128.6, 131.4, 134.5, 140.3, 168.0, 171.3; MS (*m/z*) 337.2 (M^+ + 1, 0.1), 293.1 (47), 189.0 (34), 105.0 (100), 77.0 (20).

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.70; H, 7.00; N, 8.32.

(2*S*,1′*R*)-2: isolated yield, ca. 0.65 g (ca. 10%); R_f = 0.04 (hexane–ethyl acetate–CH_2Cl_2, 18:1:1); melting point, 149–150 °C; $[\alpha]^{28}_D = +183.2$ (*c* = 1.03, $CHCl_3$); IR 3040 (w), 2995 (m), 2960 (m), 1685 (s), 1660 (s), 1600 (w), 1490 (m), 1450 (w), 1380 (s), 1320 (m), 1300 (m), 1270 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, *J* = 6.7 Hz, 6 H), 1.73 (d, *J* = 7.2 Hz, 3 H), 2.1 (br, 1 H), 3.93 (AB, *J* = 15.6 Hz, 1 H), 4.13 (A*B*, *J* = 15.6 Hz, 1 H), 5.2 (br, 1 H), 5.55 (br, 1 H), 7.3–7.6 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 18.2, 19.0, 34.6, 52.6, 53.9, 76.0, 127.7, 127.9, 128.2, 128.4, 128.6, 128.9, 131.4, 134.6, 138.7, 167.9, 171.1; MS (*m/z*) 337.2 (M^+ + 1, 0.1), 293.1 (48), 189.0 (34), 105.0 (100), 77.0 (19).

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.70; H, 7.32; N, 8.29.

(*R*)- and (*S*)-6 and (*R*)- and (*S*)-11. The preparation of these *N*(3)-methyl imidazolidinones is described in references 4b and 14.

(2*S*,5*S*,1′*R*)-1-Benzoyl-2-*tert*-butyl-5-methyl-3-(α-methylbenzyl)-1,3-imidazolidin-4-one [(2*S*,5*S*,1′*R*)-7]. According to the general alkylation procedure described above, 0.55 g (1.6 mmol) of (2*S*,1′*R*)-**1** was methylated with CH_3I to give after flash chromatography (hexane–ethyl acetate, 3:1) 0.49 g (83% yield) of (2*S*,5*S*,1′*R*)-**7** as a white solid, mp: 235–237 °C; R_f = 0.24 (hexane-ethyl acetate, 3:1); $[\alpha]^{28}_D = -132.1$ (*c* = 1.08, $CHCl_3$); IR, 3060 (w), 3000 (m), 2975 (m), 1705 (s), 1642 (s), 1449 (m), 1398 (s), 1351 (m), 1310 (m), 1289 (s), 1178 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 9 H), 1.02 (d, *J* = 4.7 Hz, 3 H), 1.74 (d, *J* = 7.1 Hz, 3 H), 4.32 (q, *J* = 6.7 Hz, 1 H), 4.67 (q, *J* = 6.9 Hz, 1 H), 5.76 (br, 1 H), 7.2–7.7 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 20.7, 26.0, 40.7, 58.3, 59.8, 81.2, 127.0, 127.2, 127.7, 128.2, 128.5, 128.9, 131.5, 137.0, 141.5, 170.9, 173.6; MS (*m/z*) 365.2 (M^+, 0.2), 307.1 (71), 203.1 (30), 105 (100).

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 75.79; H, 7.74; N, 7.69. Found: C, 75.59; H, 7.57; N, 7.67.

(2*R*,5*R*,1′*R*)-1-Benzoyl-2-*tert*-butyl-5-methyl-3-(α-methylbenzyl)-1,3-imidazolidin-4-one [(2*R*,5*R*,1′*R*)-7]. According to the general alkylation procedure described above, 0.6 g (1.8 mmol) of (2*R*,1′*R*)-**1** was methylated with CH_3I to give after flash chromatography (hexane–ethyl acetate, 2:1) 0.6 g (94% yield) of (2*R*,5*R*,1′*R*)-**7** as a colorless oil; R_f = 0.34 (hexane–ethyl acetate, 2:1); $[\alpha]^{28}_D = +5.1$ (c = 1.16, $CHCl_3$); IR 3060 (w), 3008 (m), 2971 (m), 1703 (s), 1642 (s), 1605 (w), 1581 (m), 1493 (m), 1482 (m), 1449 (m), 1377 (s), 1330 (m), 1310 (m), 1288 (s), 1082 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (br, 3 H), 1.11 (s, 9 H), 2.03 (d, *J* = 7.2 Hz, 3 H), 4.23 (q, *J* = 6.6 Hz, 1 H), 4.72 (q, *J* = 6.9 Hz, 1 H), 5.88 (br, 1 H), 7.2–7.7 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 19.2, 26.3, 41.2, 56.8, 58.2, 79.7, 126.6, 127.0 127.7, 128.5, 128.6, 128.8, 131.4, 137.0, 141.2, 170.7, 173.4; MS (*m/z*) 365.2 (M^+, 0.2), 307.1 (68), 203.0 (44), 105.0 (100), 77.0 (20).

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 75.79; H, 7.74; N, 7.69. Found: C, 75.56; H, 7.57; N, 7.69.

(2*S*,5*R*,1′*R*)-1-Benzoyl-2-*tert*-butyl-5-methyl-3-(α-methylbenzyl)-1,3-imidazolidin-4-one [2*S*,5*R*,1′*R*)-7]. Epimerization of 0.3 g (0.9 mmol) of (2*S*,5*S*,1′*R*)-**7** was achieved according to the same procedure described for alkylation, with saturated ammonium chloride aqueous solution instead of alkylating agent. Purification of the crude product was accomplished by flash chromatography (pentane–ethyl ether, 2:1) to give 0.2 g (63% yield of (2*S*,5*R*,1′*R*)-**7** as a white solid: mp 136–137 °C; R_f = 0.29 (pentane-ethyl ether, 2:1); $[\alpha]^{28}_D = -96.4$ (*c* = 1.26, $CHCl_3$); IR 3060 (w), 3008 (s), 2977 (m), 2875 (w), 1701 (s), 1655 (s), 1605 (w), 1493 (m), 1483 (m), 1446 (m), 1400 (w), 1372 (s), 1330 (m), 1290 (s), 1177 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (s, 9 H), 1.52 (d, *J* = 7.0 Hz, 3 H), 1.78 (d, *J* = 7.1 Hz, 3 H), 3.94 (q, *J* = 6.3 Hz, 1 H), 4.66 (q, *J* = 7.0 Hz, 1 H), 5.75 (br, 1 H), 7.2–7.5 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.7, 20.5, 26.7, 37.4, 58.3, 59.0, 81.9, 127.1, 127.1, 127.1, 128.3, 128.5, 128.5, 130.6, 136.0, 141.4, 173.3; MS (*m/z*) 365.2 (M^+, 0.1), 307.1 (56), 203.0 (37), 105.0 (100), 77.0 (19).

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 75.79; H, 7.74; N, 7.69. Found: C, 75.48; H, 7.64; N, 7.69.

(2*R*,5*S*,1′*R*)-1-Benzoyl-2-*tert*-butyl-5-methyl-3-(α-methylbenzyl)-1,3-imidazolidin-4-one [(2*R*,5*S*,1′*R*)-7]. Partial epimerization of 0.55 g (1.5 mmol) of (2*R*,5*R*,1′*R*)-**7** was accomplished according to the same general procedure described above for alkylation reactions, employing saturated aqueous ammonium chloride solution instead of alkyl halide. Purification of the crude product by flash chromatography

(pentane–ethyl ether, 2:1) afforded 0.48 g of a mixture containing a 20:80 mixture of the desired product and starting material. The epimerized material presented R_f = 0.48 (hexane–ethyl ether, 2:1) and some individual ^{1}H NMR (300 MHz, $CDCl_3$) signals: 1.96 (d, J = 7.2 Hz, 3 H), 4.12 (q, J = 7.1 Hz, 1 H), 4.81 (q, J = 6.9 Hz, 1 H), 5.75 (br, 1 H), 7.2–7.7 (m, 10 H).

(2*R*,5*R*,1′*S*)-1-Benzoyl-2-*tert*-butyl-5-benzyl-3-(α-methylbenzyl)-1,3-imidazolidin-4-one [(2*R*,5*R*,1′*S*)-8]. According to the general alkylation procedure described above, 0.35 g (1 mmol) of (2*R*,1′*S*)-**1** was benzylated with benzyl bromide to give after flash chromatography (hexane–ethyl acetate, 3:2) 0.33 g (87% yield) of (2*R*,5*R*,1′*S*)-**8** as a white solid: mp 240–240.5 °C; $[\alpha]^{28}_D$ = −11.0 (*c* = 1, CH_2Cl_2); ^{1}H NMR (270 MHz, $CDCl_3$, 60 °C) δ 0.78 (s, 9 H), 1.45 (d, J = 7.25 Hz, 3 H), 3.2 (AB, 2H), 4.71 (q, J = 6.6 Hz, 1H), 4.73 (dd, J = 3.9 Hz, 1 H), 5.10 (br, 1 H), 7.00–7.50 (m, 15 H); ^{13}C NMR (67.80 MHz, $CDCl_3$, 60 °C) δ 19.5, 26.6, 35.1, 41.2, 58.1, 62.8, 81.7, 126.9, 127.4, 127.9, 128.1, 128.2, 128.6, 128.7, 131.0, 131.4, 135.6, 136.9, 140.2, 170.6, 172.3.

(2*S*,5*S*,1′*S*)-1-Benzoyl-2-*tert*-butyl-5-benzyl-3-(α-methylbenzyl)-1,3-imidazolidin-4-one [(2*S*,5*S*,1′*S*)-8]. According to the general alkylation procedure described above, 0.35 g (1.0 mmol) of (2*S*,1′*S*)-**1** was benzylated with benzyl bromide to give after flash chromatography (hexane–ethyl acetate, 7:3) 0.30 g (80% yield) of (2*S*,5*S*,1′*S*)-**8** as a colorless semisolid; $[\alpha]^{28}_D$ = +44.0 (*c* = 1, CH_2Cl_2); ^{1}H NMR (270 MHz, $CDCl_3$, 60 °C) δ 0.91 (s, 9 H), 1.83 (d, J = 7.2 Hz, 3 H), 3.1 (AB, 2H), 4.60 (dd, J = 3.9 Hz, 1 H), 4.72 (q, J = 7.26 Hz, 1H), 5.35 (br, 1H), 6.65–7.5 (m, 15 H); ^{13}C NMR (67.80 MHz, $CDCl_3$, 60 °C) δ 17.7, 26.8, 35.1, 41.8, 57.0, 62.2, 80.2, 126.4, 127.6, 127.7, 127.9, 128.4, 128.6, 130.1, 131.2, 135.3, 136.6, 140.9, 170.3, 172.2.

(2*S*,5*S*,1′*R*)-1-Benzoyl-2-isopropyl-5-methyl-3-(α-methylbenzyl)-1,3-imidazolidin-4-one [(2*S*,5*S*,1′*R*)-9]. According to the general alkylation procedure described above, 0.44 g (1.3 mmol) of (2*S*,1′*R*)-**2** was methylated with CH_3I to give after flash chromatography (pentane–ethyl ether, 2:1) and recrystallization from hexane–ethyl acetate 0.28 g (62% yield) of (2*S*,5*S*,1′*R*)-**9** as a white solid, mp 119–120 °C; R_f = 0.12 (pentane–ethyl ether, 2:1); $[\alpha]^{28}_D$ = +89.2 (*c* = 1.16, $CHCl_3$); IR 3070 (w), 3008 (m), 2972 (m), 2926 (w), 1698 (s), 1643 (s), 1581 (m), 1495 (m), 1449 (s), 1428 (w), 1391 (s), 1310 (m), 1285 (m), 1177 (w), 1096 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, J = 6.2 Hz, 6 H), 1.03 (br, 3 H), 1.75 (d, J = 7.2 Hz, 3 H), 2.15 (br, 1 H), 4.32 (q, J = 6.0 Hz, 1 H), 5.18 (br, 1 H), 5.58 (br, 1 H), 7.3–7.6 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.1, 18.3, 19.2, 19.5, 34.9, 53.2, 58.0, 75.9, 127.4, 127.6, 127.9, 128.1, 128.9, 131.2, 136.9, 138.9, 170.4, 171.2; MS (*m*/*z*) 351.3 (M^+ +1, 1), 307.2 (73), 203.1 (49), 105.0 (100), 77.0 (23).

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.60, H, 7.60; N, 7.84.

(2*R*,5*R*,1′*R*)-1-Benzoyl-2-isopropyl-5-methyl-3-(α-methylbenzyl)-1,3-imidazolidin-4-one [(2*R*,5*R*,1′*R*)-9]. According to the general alkylation procedure described above, 0.37 g (1.1 mmol) of (2*R*,1′*R*)-**2** was methylated with CH_3I to give after flash chromatography (pentane–ethyl ether, 2:1) and recrystallization from hexane–ethyl acetate 0.24 g (62% yield) of (2*R*,5*R*,1′*R*)-**9** as a white solid: mp 153–153.5 °C; R_f = 0.12 (pentane–ethyl ether, 2:1); $[\alpha]^{28}_D$ = −17 (*c* = 1.06, $CHCl_3$); IR, 3070 (w), 3008 (s), 2971 (m), 2875 (w), 1698 (s), 1640 (s), 1605 (w), 1580 (m), 1495 (m), 1454 (m), 1391 (s), 1310 (m), 1285 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (d, J = 6.8 Hz, 3 H), 0.95 (br, 6 H), 1.85 (d, J = 7.3 Hz, 3 H), 1.92 (br, 1 H), 4.30 (q, J = 6.5 Hz, 1 H), 5.16 (q, J = 7.3 Hz, 1 H), 5.88 (br, 1 H), 7.2–7.6 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4, 16.8, 18.9, 19.3, 34.0, 51.8, 57.8, 75.2, 127.2, 127.3, 127.9, 128.5, 128.9, 131.3, 136.8, 140.5, 170.4, 171.3; MS (*m*/*z*) 351.3 (M^+ + 1, 0.3), 307.2 (80), 203.1 (48), 105.1 (100), 77.1 (23).

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.47; H, 7.57; N, 7.84.

(2*S*,5*R*,1′*R*)-1-Benzoyl-2-isopropyl-5-methyl-3-(α-methylbenzyl)-1,3-imidazolidin-4-one [(2*S*,5*R*,1′*R*)-9]. Epimerization of 0.18 g (0.5 mmol) of (2*S*,5*S*,1′*R*)-**9** was achieved by means of its metalation, following the general procedure for alkylation described above, and protonation of the corresponding enolate with saturated aqueous ammonium chloride solution. Purification of the crude product was accomplished by means of flash chromatography (pentane–ethyl ether, 2:1) to afford 0.15 g (83% yield) of (2*S*,5*R*,1′*R*)-**9** as a colorless oil: R_f = 0.06 (pentane-ethyl ether, 2:1); $[\alpha]^{28}_D$ = +77.6 (*c* = 1.25, $CHCl_3$); IR 3070 (w), 3007 (s), 2973 (m), 2875 (w), 1687 (s), 1654 (s), 1603 (m), 1495 (m), 1427 (m), 1372 (s), 1334 (m), 1286 (s), 1178 (w), 1099 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J = 6.8 Hz, 6 H), 1.42 (d, J = 7.0 Hz, 3 H), 1.72 (d, J = 7.2 Hz, 3 H), 2.01 (m, 1 H), 4.03 (br, 1 H), 5.17 (q, J = 7.2 Hz, 1 H), 5.47 (br, 1 H), 7.3–7.5 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 18.4, 19.2, 19.3, 32.8, 53.1, 57.5, 76.8, 126.8, 127.6, 128.0, 128.5, 128.8, 130.1, 136.3, 139.0, 171.1, 173.3; MS (*m*/*z*) 350.2 (M^+, 0.8), 307.1 (52), 203.0 (39), 105.0 (100), 77.0 (21).

Anal. calcd for $C_{21}H_{24}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 74.65; H, 7.70; N, 7.80.

(2*R*,5*S*,1′*R*)-1-Benzoyl-2-isopropyl-5-methyl-3-(α-methylbenzyl)-1,3-imidazolidin-4-one [(2*R*,5*S*,1′*R*)-9]. Epimerization of 0.16 g (0.5 mmol) of (2*R*,5*R*,1′*R*)-**9** was accomplished by metalation according to the general procedure, followed by protonation with saturated aqueous ammonium chloride solution. Purification of the crude product was accomplished by flash chromatrography (pentane–ethyl ether, 2:1) to give 0.04 g (25% yield) of (2*R*,5*S*,1′*R*)-**9** as a colorless oil: R_f = 0.07 (pentane-ethyl ether, 2:1); $[\alpha]^{28}_D$ = +20.6 (*c* = 1.40, $CHCl_3$); IR 3060 (w), 3008 (s), 2970 (m), 2880 (w), 1694 (s), 1654 (s), 1602 (m), 1496 (m), 1446 (m), 1373 (s), 1334 (m), 1286 (s), 1178 (w), 1099 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.63 (d, J = 6.8 Hz, 3 H), 0.97 (d, J = 6.9 Hz, 3 H), 1.39 (d, J = 6.9 Hz, 3 H), 1.81 (d, J = 6.9 Hz, 3 H), *ca.* 1.8 (m, 1 H), 3.97 (q, J = 6.9 Hz, 1 H), 5.29 (q, J = 7.2 Hz, 1 H), 5.89 (d, J = 2.5 Hz, 1 H), 7.25–7.5 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2, 16.4, 19.3, 32.2, 51.0, 57.4, 75.7, 126.8, 127.4, 127.6, 127.8, 128.0, 128.5, 128.8, 130.2, 136.2, 140.6, 171.2, 173.6; MS (*m*/*z*) 350.2 (M^+, 0.7), 307.1 (54), 203.0 (37), 105.0 (100), 77.0 (20).

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.15; H, 7.43; N, 7.88.

(2*R*,5*R*,1′*R*)- and (2*S*,5*S*,1′*R*)-1-Benzoyl-2-isopropyl-5-benzyl-3-(α-methylbenzyl)-1,3-imidazolidin-4-one [(2*R*,5*R*,1′*R*)- and (2*S*,5*S*,1′*R*)-10]. A mixture of (2*R*,1′*R*)- and (2*S*,1′*R*)-**2** (0.47 g, 1.4 mmol; 5:4 ratio) was benzylated with benzyl bromide according to the general procedure for alkylation described above. Separation and purification of the diastereoisomeric products was accomplished by flash chromatography (pentane–ethyl ether, 2:1) to provide 0.25 g (75% of theoretical yield) of (2*R*,5*R*,1′*R*)-**10** and 0.09 g (33% of theoretical yield).

(2*R*,5*R*,1′*R*)-10: R_f = 0.18 (pentane–ethyl ether, 2:1); mp 141–142 °C; $[\alpha]^{48}_D$ = −89.9 (*c* = 1.06, $CHCl_3$); IR, 3055 (w), 3008 (m), 2980 (m), 2925 (m), 1698 (s), 1635 (s), 1600 (w), 1580 (m), 1495 (m), 1454 (m), 1390 (s), 1331 (w), 1277 (w); ^{1}H NMR (300 MHz, DMSO-d_6, at 100 °C) δ 0.66 (d, 6 H), 1.50 (d, J = 6.4 Hz, 3 H), 1.82 (br, 1 H), ca. 3.0 (AB, 2 H), 4.77 (br, 1 H), 4.89 (q, J = 7.1 Hz, 1 H), 5.19 (br, 1 H), 6.8–7.6 (m, 15 H); ^{13}C NMR (75 MHz, DMSO-d_6, at 100 °C) δ 15.7, 16.4, 17.8, 33.4, 51.9, 61.0, 76.6, 126.5, 127.2, 127.4, 127.6, 127.9, 128.2, 128.6, 129.6, 131.1, 135.2, 136.2, 140.6, 168.8, 169.4; MS (*m*/*z*) 427.3 (M^+ + 1, 0.1), 383.2 (43), 279.1 (25), 105.0 (100), 91.0 (7), 77.0 (19).

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.71; H, 7.30; N, 6.48.

(2*S*,5*S*,1′*R*)-10: R_f = 0.13 (pentane–ethyl ether, 2:1); colorless oil; ^{1}H NMR (300 MHz, DMSO-d_6, at 100 °C) δ 0.55 (br, 3 H), 0.69 (d, J = 6.6 Hz, 3 H), 1.48 (d, J = 7.1 Hz, 3 H), 1.90 (br, 1 H), ca. 3.1 (AB, 2 H), 4.78 (br, 1 H), 4.85 (q, J = 7.4 Hz, 1 H), 5.86 (br, 1 H), 7.0–7.6 (m, 15 H); MS (*m*/*z*), 427.3 (M^+ + 1, 1.1), 383.2 (74), 279.2 (42), 105.1 (100), 77.0 (22).

(*S*)-1-Benzoyl-3-(α-methylbenzyl)-1,3-imidazolidin-4-one [(*S*)-12]. In a 250-mL round bottom flask provided with magnetic stirrer and rubber septa was placed 150 mL of dry CH_2Cl_2. The flask was cooled to 0 °C, and then 2.64 g (23.4 mmol) of chloroacetyl chloride was added under nitrogen, followed by the slow addition of 3.04 g (7.8 mmol) of 1,3,5-tris((*S*)-α-methylbenzyl)hexahydrotriazine[23] in 20 mL of dry

(23) Amoroso, R.; Cardillo, G.; Tomasini, C.; Tortoreto, P. *J. Org. Chem.* **1992**, *57*, 1082.

CH_2Cl_2. The resulting solution was stirred at ambient temperature for 1 h, and then ammonia was bubbled into the reaction mixture for 2–3 min (NH_4Cl precipitates as a white solid). The reaction mixture was stirred overnight at ambient temperature, the precipitate was filtered, and the filtrate was treated with 2 g (23.8 mmol) of $NaHCO_3$ and 50 mL of ethanol. Stirring was continued for 3 h before the addition of 2 more g of $NaHCO_3$ in 10 mL of H_2O and 3.34 g (23.4 mmol) of benzoyl chloride. The resulting mixture was stirred for 4 h at rt, washed with H_2O, dried over Na_2SO_4, and concentrated. Purification was achieved by flash chromatography (CH_2Cl_2–acetone, 16:1) followed by recrystallization from ethyl ether. The desired product was obtained as a white solid, mp 123–125 °C, in 34% yield (0.78 g): $[\alpha]^{28}_D = +122$ ($c = 1$, $CHCl_3$); ^1H NMR (60 MHz, $CDCl_3$) δ 1.65 (d, $J = 7.0$ Hz, 3 H), 4.1 (s, 2 H), 4.6 (AB, $J = 7.0$ Hz, 1 H), 5.0 (AB, $J = 7.0$ Hz, 1 H), 5.5 (q, $J = 7.0$ Hz, 1 H), 7.29 (s, 5 H), 7.4 (s, 5 H); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 16.2, 49.0, 51.1, 59.3, 126.9, 128.0, 128.0, 128.7, 130.8, 134.3, 138.4, 166.2, 169.0; MS (*m/z*) 294.3 (M^+), 189, 162, 134, 105, 77.

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.44; H, 6.12. Found: C, 73.33; H, 6.31.

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Supporting Information Available: ^1H NMR data of compounds (*R*)-**5**, (2*R*,5*R*,1′*S*)-**8**, (2*S*,5*S*,1′*S*)-**8**, and (2*S*,5*S*,1′*R*)-**10**, Figure 2, and Table 3 (8 pages). This material is contained in libraries on microfiche, inmediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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