New Synthesis of 4,5-Dihydro-1,3-oxazoles and 4,5-Dihydro-1,3-oxazines, Useful Intermediates to Enantiomerically Pure Amino Diols. X-Ray Molecular Structure of (4*S*,5*R*,4'*S*)-1-(4'-Iodomethyl-4'-methyl-4',5'-dihydro-1',3'-oxazol-2'-yl)-3,4-dimethyl-5-phenylimidazolidin-2-one and (4*S*,5*R*,4'*S*,1''*S*)-1-[4'-(1''-Iodobutyl)-4',5'-dihydro-1',3'-oxazol-2'-yl]-3,4-dimethyl-5-phenylimidazolidin-2-one

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The iodocyclization of *O*-alkenyl imidates derived from (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one (**1**) affords diastereoisomeric mixtures of 4,5-dihydro-1,3-oxazoles (**7a** and **b**) and (**9a** and **b**) or 4,5-dihydro-1,3-oxazines (**8a** and **b**) and (**10a** and **b**) which are easily separated by flash chromatography and successively cleaved to enantiomerically pure amino diols. Crystal structures were determined for compounds (**7a**) and (**9a**).

We have developed an approach to enantiomerically pure amino alcohols and amino diols by means of cyclofunctionalization of allylic and homoallylic carbamates containing (*S*)-1-phenylethylamine as a chiral auxiliary group.[1,2] As part of a programme aimed at achieving cyclofunctionalization of the double bonds of allylic and homoallylic alcohols, we investigated the possibility of promoting the halogenocyclization of imidates bonded to a sterically crowded chiral auxiliary. The satisfactory results previously obtained by using imidazolidin-2-ones as chiral auxiliaries[3] prompted us to study the effect of these highly crowded heterocycles on the cyclization of allylic and homoallylic imidates.

The (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one (**1**)[4] has been chosen as the starting material in order to prepare the appropriate allylic and homoallylic imidates. Thus, on addition of a solution of the lithium anion of compound (**1**) in tetrahydrofuran (THF)[3] to a solution of BrCN in THF at −78 °C, the nitrile (**2**) was recovered in 70% yield. Following the standard procedure,[5] the corresponding imidates (**4**)–(**6**) were obtained in very good yield as white solids (Table 1).

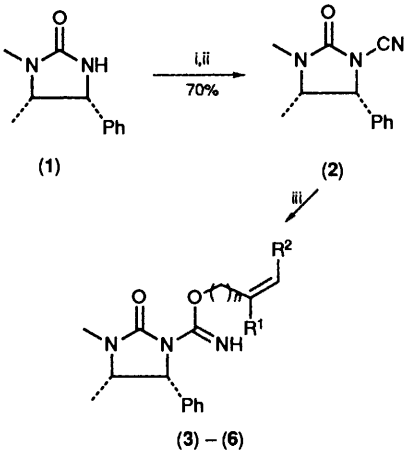
The allylic (**3**) and (**5**) and homoallylic imidates (**4**) and (**6**) were isolated and then cyclized under conditions of kinetic control by treatment with *N*-iodosuccinimide (NIS) in chloroform at room temperature.[6] In agreement with the previously reported results,[7] this iodofunctionalization showed high regioselectivity. Indeed, the cyclization of allylic imidates (**3**) and (**5**) afforded exclusively 4,5-dihydro-1,3-oxazoles (**7a** and **b**) and (**9a** and **b**), respectively, while the homoallylic imidates (**4**) and (**6**) yielded 4,5-dihydro-1,3-oxazines (**8a** and **b**) and (**10a** and **b**), respectively.

Both iodo-4,5-dihydro-1,3-oxazoles (**7a** and **b**) and (**9a** and **b**) and iodo-4,5-dihydro-1,3-oxazines (**8a** and **b**) and (**10a** and **b**) were obtained as diastereoisomeric mixtures and the ratios were determined by ^{13}C NMR spectroscopy. Individual components were easily separated by flash chromatography and characterized (Table 2).

The absolute stereostructure at C-4' of compound (**7a**) was determined to be *S* by X-ray crystallographic analysis. This assignment was consistent with the data obtained from the ^1H NMR spectrum, provided that the conformation in the solution was reversed in respect to the crystalline state (Figure 1).[8]

From an analysis of the ^1H NMR spectra of compounds (**7a**) and (**7b**), the absolute configuration at C-4' was confirmed on the basis of the values of the chemical shifts of the methyl and the iodomethyl group. From inspection of molecular models the conformers of diastereoisomers (**7a**) and (**7b**) account for their respective ^1H NMR patterns. Owing to the shielding effect of the phenyl group present in the chiral auxiliary, the methyl

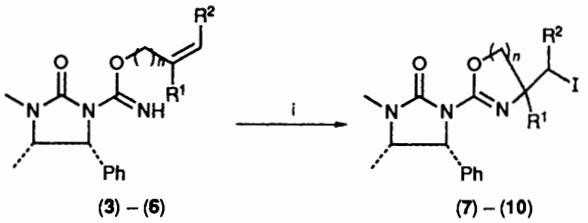
Table 1. Synthesis of allylic and homoallylic imidates.



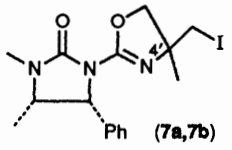
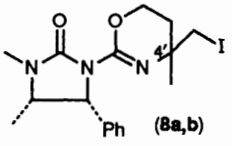
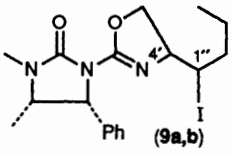
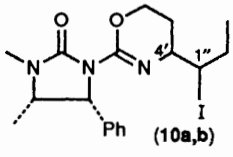
Reagents and conditions: i, BuLi, THF, 0 °C; ii, BrCN, THF, −78 °C; iii, NaH (cat.), $R^2CH{=}CR^1[CH_2]_nOH$, THF, 0 °C.

Product	Yield (%)
(**3**) n = 1; R^1 = Me, R^2 = H	82
(**4**) n = 2; R^1 = Me, R^2 = H	75
(**5**) n = 1; R^1 = H, R^2 = Pr	63
(**6**) n = 2; R^1 = H, R^2 = Et	74

Table 2. Synthesis of diastereoisomeric iodo-4,5-dihydro-1,3-oxazoles and iodo-4,5-dihydro-1,3-oxazines.



Reagents and conditions: i, NIS, $CHCl_3$, room temperature.

Substrate	Product	Yield (%)	Diastereoisomeric ratio **a**:**b**	Major isomer 4′-configuration
(3)	 (7a,7b)	72	60:40	*S*
(4)	 (8a,b)	80	70:30	*S*
(5)	 (9a,b)	66	60:40	*S*
(6)	 (10a,b)	64	92:8	

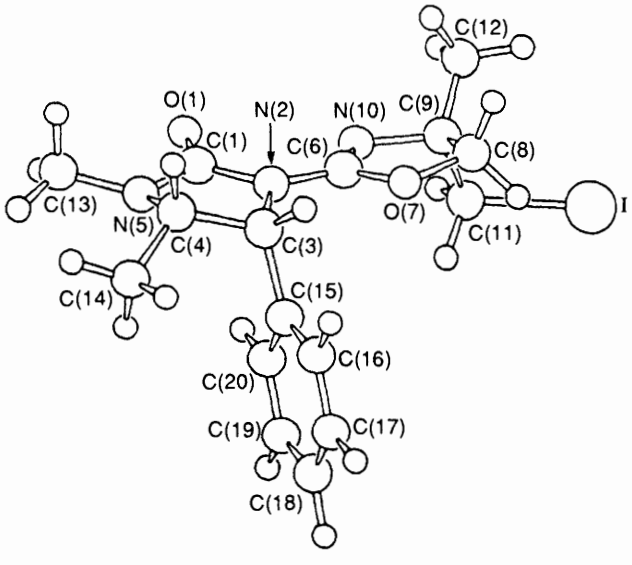


Figure 1. The molecular structure of compound (**7a**), showing the atom-numbering scheme.

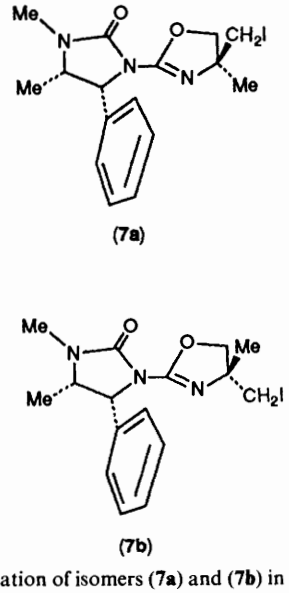


Figure 2. Conformation of isomers (**7a**) and (**7b**) in solution.

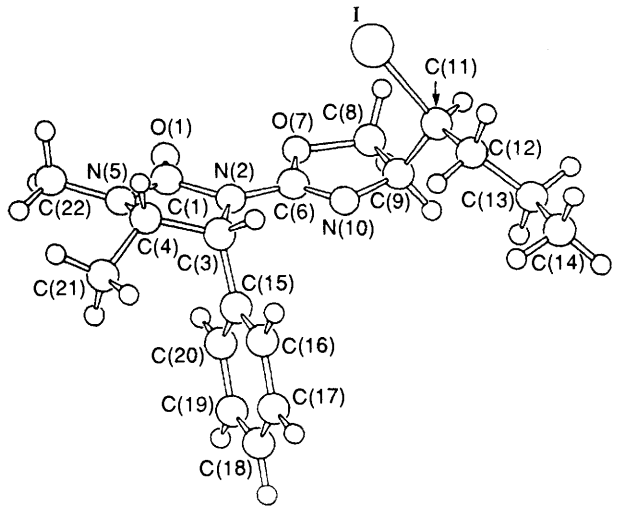


Figure 3. The molecular structure of compound (**9a**), showing the atom-numbering scheme.

Table 3. Relevant torsion angles (°) for compounds (**7a**) and (**9a**).

	(7a)	(9a)
N(2)–C(1)–N(5)–C(4)	16.6	15.5
C(1)–N(2)–C(3)–C(4)	−16.5	−16.5
N(2)–C(3)–C(4)–N(5)	24.1	23.3
C(3)–C(4)–N(5)–C(1)	−26.4	−25.1
N(5)–C(1)–N(2)–C(3)	0.8	2.2
C(1)–N(2)–C(6)–O(7)	171.1	−0.9
C(1)–N(2)–C(6)–N(10)	−5.8	178.7
C(3)–N(2)–C(6)–O(7)	−13.7	−177.2
C(3)–N(2)–C(6)–N(10)	169.3	2.3
C(6)–O(7)–C(8)–C(9)	−10.1	−2.7
O(7)–C(8)–C(9)–N(10)	10.6	4.2
C(8)–C(9)–N(10)–C(6)	−7.4	−4.3
N(10)–C(6)–O(7)–C(8)	6.1	0.0
O(7)–C(6)–N(10)–C(9)	1.2	3.3
C(8)–C(9)–C(11)–I	−67.1	59.6
C(8)–C(9)–C(11)–C(12)		176.3
C(9)–C(10)–C(12)–C(13)		72.5
C(11)–C(12)–C(13)–C(14)		178.6

group of compound (**7a**) resonates at higher field (δ 1.1) relative to the methyl group of its isomer (**7b**) (δ 1.35). Furthermore the iodomethyl groups of compound (**7b**) and (**7a**) resonate at δ 2.9 and 3.2, respectively (Figure 2).

On the basis of ^{1}H NMR spectral data, we reasonably assigned the *S* configuration also to C-4′ of the oxazine (**8a**), since the same pattern as for compound (**7a**) was observed. Absorptions for the methyl and iodomethyl groups in the oxazine (**8a**) appeared at δ 0.85 and 3.15, respectively, while for its isomer (**8b**) the shielding effect of the opposite phenyl group gave rise to absorptions at δ 1.15 and 2.5, respectively.

The stereogenic centre at C-4′ in compound (**9a**) was determined to have the *S* configuration by X-ray crystallographic analysis. In this case the data for the solid state evidenced a conformation in which the dipoles C=O and C=N were opposed.[8] Furthermore this conformation was identical with that in solution, as shown by ^{1}H NMR data. A deshielding effect was observed for the iodomethyl group in the *S* configuration (δ 4.25), while a shielding effect was evidenced in the *R* configuration (δ 3.95), clearly due to the phenyl group of the chiral auxiliary (Figure 3).

In the solid state compounds (**7a**) and (**9a**) have opposite conformations of the oxazole ring with respect to the imidazolidin-2-one ring, in agreement with the flexibility shown by these species in solution around the bond linking the two fragments. Furthermore there is a clear preference for a coplanar arrangement of the two rings. A comparison between the torsion angles of compounds (**7a**) and (**9a**) is reported in Table 3. The torsion angle C(1)–N(2)–C(6)–O(7), which defines the relative positions of C(1) and O(7), is (+)-antiperiplanar and (−)-synperiplanar in compounds (**7a**) and (**9a**), respectively, according to the Klyne and Prelog definitions.[9] The two compounds maintain the same stereochemistry at each stereogenic centre, so that, owing to the conformational difference between the two derivatives, the iodine atoms lie on opposite sides of the oxazole ring relatively to the phenyl substituent on the chiral auxiliary. Thus the orientation of the iodomethyl moiety common to both compounds (**7a**) and (**9a**) is described by the torsion angles C(8)–C(9)–C(11)–I as (−)-synclinal and (+)-synclinal, respectively, although little substitutional disorder of the halogen was detected in compound (**9a**).[10]

Table 4. Relevant bond distances (Å) and angles (°) for compounds (**7a**) and (**9a**), with standard deviations in parentheses.

	(7a)	(9a)
C(1)–O(1)	1.20(1)	1.16(1)
C(1)–N(2)	1.40(1)	1.44(1)
N(2)–C(3)	1.48(1)	1.45(2)
C(3)–C(4)	1.53(1)	1.56(1)
C(4)–N(5)	1.48(1)	1.44(2)
C(1)–N(5)	1.37(1)	1.38(2)
N(2)–C(6)	1.36(1)	1.37(2)
C(6)–O(7)	1.33(1)	1.29(1)
O(7)–C(8)	1.43(1)	1.44(1)
C(8)–C(9)	1.54(1)	1.55(1)
C(9)–N(10)	1.48(1)	1.51(2)
C(6)–N(10)	1.29(1)	1.30(2)
C(9)–C(11)	1.52(1)	1.53(1)
C(11)–I	2.15(1)	2.15(1)
C(11)–Cl		1.70(1)
N(2)–C(1)–N(5)	105.8(9)	104(1)
C(1)–N(2)–C(3)	112.3(7)	112(1)
N(2)–C(3)–C(4)	101.6(7)	103(1)
C(3)–C(4)–N(5)	101.8(7)	100(1)
C(1)–N(5)–C(4)	111.5(8)	115(1)
N(2)–C(6)–O(7)	114.2(8)	119(1)
N(2)–C(6)–N(10)	127.2(8)	119(1)
C(6)–O(7)–C(8)	106.0(7)	105(1)
O(7)–C(8)–C(9)	105.0(8)	107(1)
C(8)–C(9)–N(10)	102.8(8)	101(1)
C(8)–C(9)–C(11)	112.0(9)	110(1)
C(6)–N(10)–(C9)	106.5(8)	105(1)
C(9)–C(11)–I	113.4(7)	112(1)
C(9)–C(11)–C(12)		108(1)
C(11)–C(12)–C(13)		111(1)
C(12)–C(13)–C(14)		107(1)

In both compounds the imidazolidin-2-one and the oxazole rings are approximately planar, but the torsion angles for the imidazolidinone moiety indicate a slight puckering of the ring. In fact, the elevation of the C-4 atom above the least-squares plane passing through the remaining four atoms is *ca.* 0.4 Å in both cases, giving rise to an 'envelope' form.

Bond distances and angles, some of which are reported in Table 4, are comparable within the two species and with those of imidazolidine derivatives, as well as with those of similar molecules.[11] Atomic co-ordinates are given in Tables 5 and 6 for compounds (**7a**) and (**9a**), respectively.

The cyclization of compounds (**6**) to oxazines (**10a** and **b**) led to a 9:1 diastereoisomeric mixture, as shown from the ^{13}C NMR spectrum. Since it was difficult to obtain crystals suitable

Table 5. Fractional atomic co-ordinates for compound (**7a**), with standard deviations in parentheses.

Atom	*x*	*y*	*z*
I	−0.197 42(15)	0.415 72(10)	−0.024 24(2)
O(1)	−0.176 4(10)	0.542 7(9)	0.188 2(2)
C(1)	0.002 7(18)	0.494 2(12)	0.187 5(3)
N(2)	0.132 2(12)	0.477 5(8)	0.153 7(2)
C(3)	0.343 5(14)	0.410 5(11)	0.163 8(2)
C(4)	0.350 8(14)	0.438 1(11)	0.209 1(2)
N(5)	0.122 7(12)	0.442 7(10)	0.219 4(2)
C(6)	0.071 7(15)	0.507 1(11)	0.115 1(2)
O(7)	0.230 0(11)	0.505 3(8)	0.088 7(2)
C(8)	0.142 7(15)	0.563 9(13)	0.051 7(3)
C(9)	−0.097 8(17)	0.568 6(13)	0.058 7(3)
N(10)	−0.115 6(14)	0.542 0(10)	0.102 5(2)
C(11)	−0.208 1(19)	0.418 1(12)	0.040 3(3)
C(12)	−0.194 3(25)	0.729 0(15)	0.048 2(3)
C(13)	0.052 9(18)	0.474 6(15)	0.259 5(3)
C(14)	0.464 4(17)	0.307 7(14)	0.234 2(3)
C(15)	0.366 9(9)	0.225 9(7)	0.150 6(2)
C(16)	0.569 1(9)	0.171 6(7)	0.140 4(2)
C(17)	0.604 5(9)	0.003 4(7)	0.131 4(2)
C(18)	0.437 6(9)	−0.110 4(7)	0.132 8(2)
C(19)	0.235 4(9)	−0.056 1(7)	0.143 0(2)
C(20)	0.200 0(9)	0.112 1(7)	0.152 0(2)

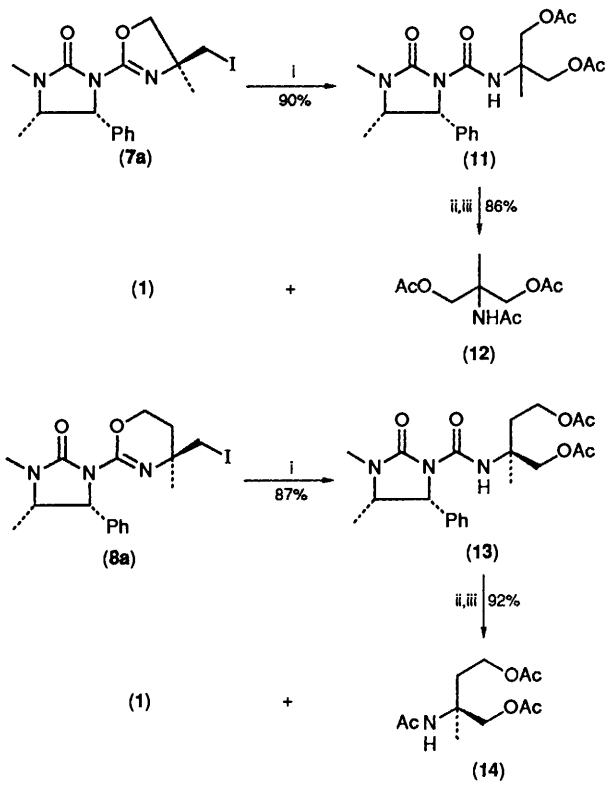
Table 6. Fractional atomic co-ordinates for compound (**9a**), with standard deviations in parentheses.

Atom	*x*	*y*	*z*
I	−0.395 4(3)	−0.472 8(2)	0.0111 (1)
Cl	−0.478 2(13)	−0.445 9(8)	−0.000 3(8)
O(1)	−0.082 9(22)	−0.811 4(14)	−0.127 1(6)
C(1)	−0.108 2(20)	−0.733 7(16)	−0.161 2(9)
N(2)	−0.261 4(16)	−0.668 8(13)	−0.161 5(7)
C(3)	−0.265 4(18)	−0.585 2(17)	−0.213 4(9)
C(4)	−0.078 8(18)	−0.577 2(16)	−0.233 7(8)
N(5)	−0.018 6(19)	−0.686 6(16)	−0.211 0(8)
C(6)	−0.385 8(28)	−0.679 2(17)	−0.116 5(8)
O(7)	−0.368 8(13)	−0.752 5(9)	−0.070 6(5)
C(8)	−0.517 7(18)	−0.740 2(16)	−0.032 3(8)
C(9)	−0.621 3(24)	−0.641 3(12)	−0.062 8(7)
N(10)	−0.517 7(20)	−0.613 4(15)	−0.121 6(8)
C(11)	−0.635 8(9)	−0.540 4(12)	−0.015 3(8)
C(12)	−0.727 9(17)	−0.441 9(12)	−0.048 2(10)
C(13)	−0.910 8(18)	−0.469 2(20)	−0.055 7(13)
C(14)	−0.993 1(28)	−0.362 8(23)	−0.087 9(16)
C(15)	−0.386 3(19)	−0.614 8(9)	−0.266 1(7)
C(16)	−0.471 9(19)	−0.527 3(9)	−0.298 2(7)
C(17)	−0.575 6(19)	−0.554 5(9)	−0.349 8(7)
C(18)	−0.593 6(19)	−0.669 2(9)	−0.369 2(7)
C(19)	−0.507 9(19)	−0.756 7(9)	−0.337 0(7)
C(20)	−0.404 3(19)	−0.729 5(9)	−0.285 5(7)
C(21)	−0.0476 (29)	−0.571 5(23)	−0.307 8(11)
C(22)	0.160 6(23)	−0.721 0(29)	−0.217 6(13)

for X-ray diffraction analysis, the configuration of this product remained unassigned.

To provide an illustration of the synthetic opportunities presented by diastereomerically pure iodo-oxazoles and iodo-oxazines, a simple sequence was devised to lead to amino diols (Scheme 1).

Cleavage of the heterocyclic ring was first performed by treatment of compound (**7a**) with AgOAc in refluxing AcOH. The corresponding urea (**11**) was obtained in good yield, and successive acidic hydrolysis with HCl allowed us to obtain the amino diol, which was immediately converted into the corresponding triacetate (**12**), along with the unchanged chiral



Scheme 1. *Reagents and conditions:* i, AgOAc, AcOH, reflux; ii, 12M-HCl, reflux; iii, Ac_2O, pyridine.

auxiliary (**1**), recovered in good yield. The same synthetic sequence was applied to compound (**8a**) and the enantiomerically pure amino diol triacetate (**14**) was obtained in good yield, *via* the urea (**13**).

The results reported in this paper demonstrate that the iodocyclization of imidates bonded to a chiral auxiliary can constitute a useful approach to enantiomerically pure amino diols, interesting compounds that could be precursors of 'unnatural' amino acids.

Experimental

Mps were determined in capillary tubes in a Buchi 510 hot-stage apparatus and are uncorrected. IR spectra (Nujol mulls) were recorded on a Perkin-Elmer Model 682 spectrophotometer. ^1H NMR spectra were measured on a Varian EM 390 (90 MHz) or a Varian Gemini 300 (300 MHz) instrument, with $CDCl_3$ as solvent. ^{13}C NMR measurements were obtained using a Varian FT 80 instrument (20 MHz) with $CDCl_3$ as solvent. Chemical shifts are quoted to higher frequency of Me_4Si. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Mass spectra were obtained at 70 eV using a VG-7070E instrument. THF was dried over $LiAlH_4$ and distilled immediately prior to use. $CHCl_3$ was dried over molecular sieves 4 Å. Column chromatography was carried out in Merck Kieselgel H (type 60) or Merck neutral or basic alumina. TLC was performed on precoated Merck Kieselgel 60 F_{254} plates.

(4S,5R)-1-*Cyano*-3,4-*dimethyl*-5-*phenylimidazolidin*-2-*one* (**2**).—To a stirred solution of compound (**1**)[4] (9.5 g, 50 mmol) in dry THF (100 ml) at 0 °C was added BuLi (20 ml; 2.5M solution in a mixture of C_6H_{14} isomers) and the mixture was stirred for 1 h. The yellow solution was then slowly added to a stirred solution of cyanogen bromide (5.75 g, 50 mmol) in dry THF (70

ml) at −78 °C and the mixture was allowed to warm up to 0 °C during 12 h. After addition of water (100 ml) and extraction with CH_2Cl_2, the organic layer was dried and successively evaporated under reduced pressure. The residue was chromatographed on silica gel [cyclohexane–CH_2Cl_2 (2:8) as eluant] to give the title compound (**2**) (7.5 g, 70% yield) as a white solid, m.p. 164–166 °C; ν_{max} 2 220 and 1 730 cm^{-1}; δ_H 0.8 (3 H, d, *J* 6 Hz), 2.85 (3 H, s), 4.05 (1 H, dq *J* 6 and 8 Hz), 5.15 (1 H, d, *J* 8 Hz), and 7.1–7.6 (m, 5 H, Ph); δ_C 14.7, 28.8, 56.2, 62.2, 127.3, 129.1, 129.5, 132.8, and 154.2; *m/z* 215 (M^+), 200, 189, 157, and 77; $[\alpha]_D$ − 234.6° (*c* 0.1, CH_2Cl_2) (Found: C, 66.7; H, 6.1; N, 19.5. $C_{12}H_{13}N_3O$ requires C, 66.96; H, 6.09; N, 19.52%).

Preparation of Imidates (**3**)–(**6**).—To a suspension of NaH (50% dispersion in oil; 0.24 g, 5 mmol; previously washed with n-pentane) in dry THF (30 ml) at 0 °C was added a solution of the appropriate allylic or homoallylic alcholic (20 mmol) in dry THF (30 ml) and the mixture was stirred for 1 h. The clear solution was slowly dropped into a solution of compound (**2**) (4.3 g; 20 mmol) in dry THF (40 ml) at 0 °C. After 1 h MeOH (1 ml) was added, the mixture was poured into cold water and extracted with CH_2Cl_2, and the extract was dried and evaporated to dryness; the residue was purified by chromatography over neutral alumina [cyclohexane–ethyl acetate (1:1) as eluant] to give the imidates (**3**)–(**6**) in good yield.

(4S,5R)-O-(2-*Methylprop*-2-*enyl*) 3,4,-*Dimethyl*-2-*oxo*-5-*phenylimidazolidine*-1-*carboximidate* (**3**). This *compound* was obtained in 82% yield as a low melting solid; ν_{max} 3 320, 1 740, and 1 640 cm^{-1}; δ_H 0.8 (3 H, d, *J* 6 Hz), 1.35 (3 H, s), 2.80 (3 H, s), 3.9 (1 H, dq, *J* 6 and 8 Hz), 4.40 (2 H, s), 4.65 (2 H, m), 5.25 (1 H, d, *J* 8 Hz), 7.0–7.5 (5 H, m, Ph), and 8.3 (1 H, br s, =NH); δ_C 14.8, 19.0, 28.1, 54.2, 60.5, 69.2, 112.1, 126.7, 128.8, 128.5, 137.0, 152.8, and 158.3; *m/z* 287 (M^+), 272, 216, 189, 132, and 77; $[\alpha]_D$ −23.7° (*c* 0.1, CH_2Cl_2) (Found: C, 66.8; H, 7.4; N, 14.65. $C_{16}H_{21}N_3O_2$ requires C, 66.88; H, 7.37; N, 14.62%).

(4S,5R)-O-(3-*Methylbut*-3-*enyl*) 3,4-*Dimethyl*-2-*oxo*-5-*phenylimidazolidine*-1-*carboximidate* (**4**). This *compound* was obtained in 75% yield as a crystalline solid, m.p. 95–96 °C; ν_{max} 3 300, 1 720, and 1 620 cm^{-1}; δ_H 0.8 (3 H, d, *J* 6 Hz), 1.55 (3 H, s), 2.0 (2 H, t, *J* 6 Hz), 2.8 (3 H, s), 3.8–4.3 (3 H, m), 4.6 (2 H, m), 5.15 (1 H, d, *J* 8 Hz), 7.0–7.4 (5 H, m, Ph), and 8.2 (1 H, br s, =NH); δ_C 14.8, 22.0, 28.1, 36.3, 54.2, 60.5, 63.7, 111.8, 126.8, 127.9, 128.3, 129.1, 137.1, 141.7, and 153.0; *m/z* 301 (M^+), 286, 217, 175, 132, 117, 91, and 77; $[\alpha]_D$ −42.1° (*c* 0.1, CH_2Cl_2) (Found: C, 67.6; H, 7.7; N, 13.9. $C_{17}H_{23}N_3O_2$ requires C, 67.75; H, 7.69; N, 13.94%).

(4S,5R)-O-[(*Z*)-*Hex*-2-*enyl*] 3,4-*Dimethyl*-2-*oxo*-5-*phenylimidazolidine*-1-*carboximidate* (**5**). This *compound* was obtained in 63% yield as a crystalline solid, m.p. 50–51 °C; ν_{max} 3 320, 1 730, and 1 630 cm^{-1}; δ_H 0.75 (3 H, d, *J* 6 Hz), 0.8 (3 H, t, *J* 7 Hz), 1.25 (2 H, m), 1.8 (2 H, m), 2.75 (3 H, s), 3.8 (1 H, dq, *J* 6 and 7 Hz), 4.45 (2 H, m), 5.1 (1 H, d, *J* 7 Hz), 5.1–5.8 (2 H, m), 6.9–7.4 (5 H, m, Ph), and 8.2 (1 H, br s, =NH); δ_C 13.6, 14.6, 22.5, 28.1, 29.4, 54.2, 60.6, 61.8, 123.7, 126.9, 127.9, 128.4, 134.2, and 137.1; *m/z* 315 (M^+), 286, 217, 189, 132, and 77; $[\alpha]_D$ −25.3° (*c* 0.1, CH_2Cl_2) (Found: C, 68.8; H, 8.0; N, 13.35. $C_{18}H_{25}N_3O_2$ requires C, 68.54; H, 7.99; N, 13.32%).

(4S,5R)-*O*-[(*Z*)-*Hex*-3-*enyl*] 3,4-*Dimethyl*-2-*oxo*-5-*phenylimidazolidine*-1-*carboximidate* (**6**). This *compound* was obtained in 74% yield as a crystalline solid, m.p. 98–99 °C; ν_{max} 3 300, 1 720, and 1 650 cm^{-1}; δ_H 0.8 (3 H, d, *J* 6 Hz), 0.9 (3 H, t, *J* 6 Hz), 1.8 (3 H, s), 1.95 (4 H, m), 3.6–4.2 (3 H, m), 4.8–5.5 (2 H, m), 5.15 (1 H, d, *J* 7 Hz), 7.0–7.5 (5 H, m, Ph), and 8.2 (1 H, br s, =NH); δ_C 14.2, 14.8, 20.5, 26.2, 28.1, 54.2, 60.6, 65.5, 124.2, 126.9, 127.3, 128.4, 129.1, and 133.6; *m/z* 315 (M^+), 300, 234, 217, 175, 149, 117, 91, and 77; $[\alpha]_D$ −63.7° (*c* 0.1, CH_2Cl_2) (Found: C, 68.4; H, 8.0; N, 13.3. $C_{18}H_{25}N_3O_2$ requires C, 68.54; H, 7.99; N, 13.32%).

Preparation of 4,5-*Dihydro*-1,3-*oxazoles* (**7**) *and* (**9**) *and of* 4,5-*Dihydro*-1,3-*oxazines* (**8**) *and* (**10**).—To a stirred solution of an imidate (**3**)–(**6**) (10 mmol) in dry $CHCl_3$ (100 ml) was added NIS (2.5 g, 11 mmol), and the mixture was stirred for 3 h at room temperature. After work-up with saturated aq. $Na_2S_2O_8$, the organic layer was dried and the solvent was removed under reduced pressure. The residue was then purified by chromatography over silica gel [cyclohexane–ethyl acetate (1:1) as eluant] to give the corresponding cyclic compounds (**7**)–(**10**) in good yield and by this method the pure diastereoisomers were obtained as white solids. Crystals suitable for X-ray analysis were obtained by slow crystallization from propan-2-ol.

(4S,5R,4′S)-1-(4′-*Iodomethyl*-4′-*methyl*-4′,5′-*dihydro*-1′,3′-*oxazol*-2′-*yl*)-3,4-*dimethyl*-5-*phenylimidazolidin*-2-*one* (**7a**) *and* 4S,5R,4′R)-1-(4′-*Iodomethyl*-4′-*methyl*-4′,5′-*dihydro*-1′,3′-*oxazol*-2′*yl*)-3,4-*dimethyl*-5-*phenylimidazolidin*-2-*one* (**7b**). The diastereoisomeric mixture was obtained in 72% yield [diastereoisomeric ratio (**7a**):(**7b**) 60:40]; ν_{max} 1 730 and 1 630 cm^{-1}; *m/z* 413 (M^+), 286, 272, 215, 132, 117, 91, and 77.

Isomer (**7a**): R_f 0.6 (EtOAc); m.p. 162 °C (decomp); δ_H 0.8 (3 H, d, *J* 6 Hz), 1.2 (3 H, s), 2.85 (3 H, s), 3.25 (2 H, ABq, *J* 13.5 Hz), 3.9 (1 H, dq, *J* 6 and 8 Hz), 4.05 (2 H, ABq, *J* 7 Hz), 5.2 (1 H, d, *J* 8 Hz), and 7.0–7.5 (5 H, m, Ph); δ_C 14.7, 16.9, 25.9, 28.1, 54.5, 61.1, 67.1, 78.0, 126.3, 127.2, 128.0, and 135.8; $[\alpha]_D$ −139.6° (*c* 0.1, CH_2Cl_2).

Isomer (**7b**): R_f 0.5 (EtOAc); δ_H 0.8 (3 H, d, *J* 6 Hz), 1.35 (3 H, s), 2.8 (3 H, s), 2.85 (2 H, ABq, *J* 9 Hz), 3.9 (1 H, dq, *J* 6 and 8 Hz), 4.1 (2 H, ABq, *J* 8 Hz), 5.25 (1 H, d, *J* 8 Hz), and 7.1–7.5 (5 H, m, Ph); δ_C 14.6, 17.5, 25.7, 28.1, 54.6, 61.1, 78.2, 126.3, 127.2, 128.0, and 135.8 (Found: C, 35.7; H, 3.73; N, 7.8. $C_{16}H_{20}IN_3O_2$ requires C, 35.58; H, 3.73; N, 7.78%).

(4S,5R,4′S)-1-(4′-*Iodomethyl*-4′-*methyl*-5′,6′-*dihydro*-4′H-1′,3′-*oxazin*-2′-*yl*)-3,4-*dimethyl*-5-*phenylimidazolidin*-2-*one* (**8a**) *and* (4S,5R,4·R)-1-(4′-*Iodomethyl*-4′-*methyl*-5′,6′-*dihydro*-4′H-1′,3′-*oxazin*-2′-*yl*)-3,4-*dimethyl*-5-*phenylimidazolidin*-2-*one* (**8b**). The diastereoisomeric mixture was obtained in 80% yield [diastereoisomeric ratio (**8a**):(**8b**) 70:30]; ν_{max} 1 730 and 1 645 cm^{-1}; *m/z* 427(M^+), 412, 300, 286, 272, 175, 132, 91, and 77.

Isomer (**8a**): R_f 0.6 (EtOAc); m.p. 109–111 °C; δ_H 0.75 (3 H, d, *J* 6 Hz), 0.85 (3 H, s), 1.3–1.7 (2 H, m), 2.8 (3 H, s), 3.15 (2 H, ABq, *J* 10 Hz), 3.85 (1 H, dq, *J* 6 and 8 Hz), 4.2 (2 H, m), 5.3 (1 H, d, *J* 8 Hz), and 7.0–7.4 (5 H, m, Ph); δ_C 15.6, 21.1, 28.2, 28.8, 32.9, 51.0, 54.9, 61.4, 63.9, 127.4, 128.0, 128.6, and 138.0; $[\alpha]_D$ +8.5° (*c* 0.1, CH_2Cl_2).

Isomer (**8b**): R_f 0.5 (EtOAc); δ_H 0.75 (3 H, d, *J* 6 Hz), 1.25 (3 H, s), 1.45–1.7 (2 H, m), 2.5 (2 H, ABq, *J* 10 Hz), 2.8 (3 H, s), 3.8 (1 H, dq, *J* 6 and 8 Hz), 4.15 (2 H, m), 5.25 (1 H, d, *J* 8 Hz), and 7.0–7.4 (5 H, m, Ph); δ_C 15.5, 20.8, 28.3, 28.8, 32.0, 50.8, 54.9, 61.6, 63.7, 127.4, 128.0, 128.6, and 138.0 (Found: C, 36.7; H, 4.0; N, 7.6. $C_{17}H_{22}IN_3O_2$ requires C, 36.84; H, 4.00; N, 7.58%).

(4S,5R,4′S,1″S)-1-[4′-(1″-*Iodobutyl*)-4′,5′-*dihydro*-1′,3′-*oxazol*-2′-*yl*]-3,4-*dimethyl*-5-*phenylimidazolidin*-2-*one* (**9a**) *and* (4S,5R,4′R,1″R)-1-[4′-(1″-*Iodobutyl*)-4′,5′-*dihydro*-1′,3′-*oxazol*-2′-*yl*]-3,4-*dimethyl*-5-*phenylimidazolidin*-2-*one* (**9b**). The diastereoisomeric mixture was obtained in 66% yield as a white solid [diastereoisomeric ratio (**9a**):(**9b**) 60:40]; ν_{max} 1 720 and 1 640 cm^{-1}; *m/z* 441 (M^+), 386, 314, 258, 233, 189, 175, 132, 91, and 77.

Isomer (**9a**): R_f 0.65 (EtOAc); m.p. 119–121 °C; δ_H 0.75 (3 H, d, *J* 6 Hz), 0.9 (3 H, t, *J* 7 Hz), 1.2–1.7 (4 H, m) 2.8 (3 H, s), 3.8 (1 H, dq, *J* 6 and 8 Hz), 4.25 (1 H, m), 4.6 (3 H, m), 5.2 (1 H, d, *J* 8 Hz), and 7.1–7.4 (5 H, m, Ph); δ_C 12.7, 13.1, 14.8, 22.9, 34.9, 41.5, 54.8, 61.2, 69.7, 71.5, 120.9, 121.3, 122.2, and 130.1; $[\alpha]_D$ −95.3° (*c* 0.1, CH_2Cl_2).

Isomer (**9b**): R_f 0.55 (EtOAc); δ_H 0.75 (3 H, d, *J* 6 Hz), 0.95 (3 H, t, *J* 7 Hz), 1.25–1.75 (4 H, m), 2.8 (3 H, s), 3.8 (1 H, dq, *J* 6 and 8 Hz), 3.95 (1 H, m, *J* 8 Hz), 4.2 (3 H, m), 5.3 (1 H, d, *J* 8 Hz), 7.1–7.4 (5 H, m, Ph); δ_C 12.1, 13.1, 15.0, 22.5, 33.6, 40.3, 54.5, 61.2, 69.1, 72.2, 120.9, 121.3, 122.2, and 130.1 (Found: C, 37.9; H, 4.25; N, 7.35. $C_{18}H_{24}IN_3O_2$ requires C, 38.05; H, 4.26; N, 7.40%).

(4S,5R)-1-[4′-(1″-*Iodopropyl*)-5′,6′-*dihydro*-4′H-1′,3′-*oxazin*-2′-*yl*]-3,4-*dimethyl*-5-*phenylimidazolidin*-2-*one* (**10**). The diastereoisomeric mixture was obtained in 64% yield as a white solid (diastereoisomeric ratio 92:8); ν_{max} 1 730 and 1 645 cm^{-1}; *m/z* 441 (M^+), 314, 235, 214, 132, 91, and 77.

Major isomer: m.p. 126–128 °C; δ_H 0.7 (3 H, d, *J* 6 Hz), 0.80 (3 H, t, *J* 6 Hz), 1.0–1.8 (3 H, m), 1.95 (1 H, m), 2.8 (1 H, s), 3.45 (1 H, m, CHN), 3.8 (1 H, m, *J* 6 and 8 Hz), 4.8 (1 H, m, CHI), 4.05–4.60 (2 H, m, CH_2O), 5.25 (1 H, d, *J* 8 Hz), and 7.0–7.5 (5 H, m, Ph); δ_C 14.9, 15.2, 24.8, 26.8, 28.4, 45.4, 54.3, 57.4, 60.8, 66.0, 127.3, 127.6, 128.3, 129.1, 137.4, 147.4, and 156.0; $[\alpha]_D$ −6.9° (*c* 0.1, CH_2Cl_2).

Minor isomer: δ_C 14.9, 15.2, 24.8, 26.8, 28.8, 45.4, 54.3, 57.4, 60.5, 65.6, 127.3, 127.6, 128.3, 129.1, 137.4, 147.4, and 156.0 (Found C, 37.95; H, 4.25; N, 7.38. $C_{18}H_{24}IN_3O_2$ requires C, 38.05; H, 4.26; N, 7.40%).

Ring Cleavage of Iodo-4,5-*dihydro*-1,3-*oxazoles and Iodo*-4,5-*dihydro*-1,3-*oxazines*.—Compound (**7a**) or (**8a**) (1 mmol) was dissolved in glacial AcOH (20 ml), AgOAc (1.8 g, 1.1 mmol) was added, and the suspension was refluxed until the starting material completely disappeared (TLC analysis). After filtration of the precipitate, the solvent was removed under reduced pressure and the residue was chromatographed on basic alumina (CH_2Cl_2 as eluant) to give, in good yield, the cleavage product (**11**) or (**13**) respectively, as a crystalline solid.

(4S,5R)-1-[(2-*Acetoxy*-1-*acetoxymethyl*-1-*methylethyl*)*carbamoyl*]-3,4-*dimethyl*-5-*phenylimidazolidin*-2-*one* (**11**). This *compound* was obtained in 90% yield as a crystalline solid, m.p. 62–64 °C; ν_{max} 3 300, 1 740, 1 720, 1 680, and 1 550 cm^{-1}; δ_H 0.74 (3 H, d, *J* 6.7 Hz), 1.33 (3 H, s), 2.00 (3 H, s), 2.01 (3 H, s), 2.74 (3 H, s), 3.86 (1 H, dq, *J* 6.7 and 7 Hz), 4.17 (4 H, m), 5.20 (1 H, d, *J* 7 Hz), 7.2–7.4 (5 H, m, Ph), 8.58 (1 H, br s, NH); δ_C 15.0, 20.0, 21.1, 28.4, 54.8, 55.1, 59.5, 66.3, 66.4, 127.3, 128.7, 129.2, 137.6, 152.3, 158.8, and 171.3; *m/z* 332 (M^+ −73), 272, 291, 218, 190, 161, 142, and 118; $[\alpha]_D$ −7.4° (*c* 0.1, $CHCl_3$) (Found: C, 70.4; H, 8.0; N, 12.3. $C_{20}H_{27}N_3O_6$ requires C, 70.35; H, 7.97; N, 12.31%).

(4S,5R,1′S)-1-[(3′-*Acetoxy*-1′-*acetoxymethyl*-1′-*methylethyl*)*carbamoyl*]-3,4-*dimethyl*-5-*phenylimidazolidin*-2-*one* (**13**). This *compound* was obtained in 87% yield as a crystalline solid, m.p. 78–80 °C; ν_{max} 3 300, 1 730, 1 710, 1 670 and 1 500 cm^{-1}; δ_H 0.73 (3 H, d, *J* 6.6 Hz), 1.29 (3 H, s), 1.90 (1 H, m), 1.95 (3 H, s), 2.02 (3 H, s), 2.15 (1 H, m), 2.74 (3 H, s), 3.86 (1 H, dq, *J* 6.6 and 7.0 Hz), 4.10 (2 H, m), 4.14 (2 H, ABq, *J* 11.0 Hz), 5.20 (1 H, d, *J* 7.0 Hz), 7.10–7.25 (5 H, m, Ph), and 8.47 (1 H, br s, NH); δ_C 14.2, 20.3, 20.4, 22.1, 27.6, 34.0, 58.7, 60.1, 67.8, 126.4, 127.8, 128.4, 136.9, 151.4, 158.0, 170.5, and 170.8; *m/z* 346 (M^+ − 73), 286, 271, 217, 189, 160, 142, and 91; $[\alpha]_D$ −5.6° (*c* 0.1, $CHCl_3$) (Found: C, 60.2; H, 6.95; N, 10.0. $C_{21}H_{29}N_3O_6$ requires C, 60.13; H, 6.97; N, 10.02%).

Preparation of Amino diol Triacetates (**12**) and (**14**).—The diacetate (**11**) or (**13**) (1 mmol) was dissolved in MeOH–12M–HCl (1:1; 30 ml) and the solution was heated at reflux for 6 h, until starting material had disappeared (TLC analysis). After removal of the solvent under reduced pressure, the residue was directly acetylated by being dissolved in 1:1 pyridine–Ac_2O (15 ml) at room temperature. After 2 h the solution was poured in 3M-HCl and extracted with CH_2Cl_2. The extract was dried, the solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (ethyl acetate as eluant). The imidazolidin-2-one (**1**) was eluted first in good yield. By further elution, the triacetates (**12**) or (**14**) were obtained in good yield as crystalline solids.

2-*Acetamido*-1,3-*diacetoxy*-2-*methylpropane* (**12**). This *compound* was obtained in 86% yield, m.p. 87–89 °C; ν_{max} 3 400, 1 750, 1 690, and 1 660 cm^{-1}; δ_H 1.39 (3 H, s), 1.93 (3 H, s), 2.07 (6 H, s), 4.25 (4 H, ABq, *J* 10.3 Hz), and 5.90 (1 H, br s, NH); δ_C 18.7, 20.5, 23.9, 55.6, 65.8, 170.4, and 171.1; *m/z* 171 (M^+ −AcOH), 158, 129, 116, 111, 98, and 74 (Found: C, 52.1; H, 7.4; N, 6.05. $C_{10}H_{17}NO_5$ requires C, 51.94; H, 7.41; N, 6.06%).

(2S)-2-*Acetamido*-1,4-*diacetoxy*-2-*methylbutane* (**14**). This *compound* was obtained in 92% yield, m.p. 98–100 °C; ν_{max} 3 500, 1 740, 1 650, and 1 500 cm^{-1}; δ_H 1.31 (3 H, s), 1.91 (3 H, s), 1.95 (1 H, m), 2.0 (3 H, s), 2.05 (3 H, s), 2.23 (1 H, m), 4.11 (2 H, t, *J* 6.8 Hz), 4.19 (2 H, ABq, *J* 11.2 Hz), and 5.90 (1 H, br s, NH); δ_C 20.5, 20.6, 21.7, 23.9, 33.9, 54.8, 60.4, 68.1, 170.3, 171.1, and 171.2; *m/z* 185 (M^+ −AcOH), 172, 112, and 69; $[\alpha]_D$ −14.29° (*c* 0.1, $CHCl_3$) (Found: C, 53.8; H, 7.8; N, 5.7. $C_{11}H_{19}NO_5$ requires C, 53.87; H, 7.81; N, 5.71%).

Crystal Data for Compound (**7a**).—$C_{16}H_{20}IN_3O_2$, M_r = 413.2, orthorhombic, *a* = 6.332(2), *b* = 7.993(1), *c* = 33.376(6) Å, *V* = 1 689.2 Å^3, space group $P2_12_12_1$, *Z* = 4, D_X = 1.63 g cm^{-3}, μ = 1.93 cm^{-1} for Mo-K_α radiation (λ = 0.710 69 Å), crystal dimensions 0.2 × 0.1 × 0.1 mm.

Crystal Data for Compound (**9a**).—$C_{18}H_{24}Cl_{0.3}I_{0.7}N_3O_2$, M_r = 413.9, orthorhombic, *a* = 8.015(3), *b* = 11.571(2), *c* = 20.861(4) Å, *V* = 1 934.7 Å^3, space group $P2_12_12_1$, *Z* = 4, D_X = 1.43 g cm^{-3}, μ = 1.25 cm^{-1} for Mo-K_α radiation, crystal dimensions 0.4 × 0.15 × 0.05 mm.

Data Collection and Processing.—Enraf-Nonius CAD-4 diffractometer, ω/2θ mode with ω-scan width 0.8 + 0.35 tanθ for (**7a**) and 0.9 + 0.35 tanθ for (**9a**), prescan speed 5 deg min^{-1}, graphite-monochromatized Mo-K_α radiation. For compound (**7a**), 1 792 reflections were measured ($2.5 \leqslant \theta \leqslant 25°$; *h,k,l*), 1 614 unique reflections, 1 228 of which with $I > 2.5\sigma(I)$. For compound (**9a**), 1 981 reflections were measured ($2.5 \leqslant \theta \leqslant 25°$; *h,k,l*), 1 589 unique reflections, 1 247 of which had $I > 2.5\sigma(I)$. Absorption correction by the Walker and Stuart method for both compounds [max and min transmission factors = 1.0–0.29 and 1.0–0.26 for compounds (**7a**) and (**9a**), respectively].[12]

Structure Analysis and Refinement.—Both structures were solved by direct methods followed by normal heavy-atom procedures. Full-matrix least-squares refinement was used, the minimizing function being $\Sigma\ w(|F_o| - |F_c|)^2$. The weighting scheme employed was $w = k/[\sigma^2(F_o) + |g|F_o^2]$, where *g* was refined [final value 0.000 14 and 0.008 for (**7a**) and (**9a**), respectively].

The SHELX86 and SHELX76 packages of crystallographic programs[13] were used for all computations with the analytical scattering factors, corrected for the real and imaginary parts of anomalous dispersions, taken from ref. 13*c*. Thermal vibrations were treated anisotropically for all non-hydrogen atoms of the oxazole and imidazolidin-2-one ring substituents, except for the phenyl rings which were treated as 'rigid bodies' (C–C 1.40 Å, C–C–C 120°). Hydrogen atoms were added in calculated positions (C–H 1.08 Å) and were refined as 'riding' on their corresponding C-atoms. For compound (**7a**) final *R*- and R_w-values were 0.041 and 0.044 for 119 parameters refined; an inversed set of co-ordinates was refined to check the absolute configuration. The rejected enantiomer gave agreement indices of 0.046 and 0.049, respectively. In the case of compound (**9a**), after all atoms were located, a peak of *ca.* 5 e A^{-3} was detected at a distance of 1.7 Å from (C11) and 0.8 Å from I. The occurrence of disorder was suspected and, on the basis of the distance from the C-atom, the presence of a small fraction of chlorine was assumed. The final *R*- and R_w-values were 0.065 and 0.071, respectively, for 147 parameters refined. Also for compound (**9a**)

an inversed set of co-ordinates was refined to test the absolute configuration. The rejected enantiomer yielded agreement indices of 0.074 and 0.082, respectively.*

* *Supplementary data* (see section 5.6.3 of the Instructions for Authors, in the January issue). Complete listings of the bond lengths and bond angles, together with atom co-ordinates and thermal parameters, are available on request from the Cambridge Crystallographic Data Centre.

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