JOC Article

Stereoselectivity and Regioselectivity in Nucleophilic Ring Opening in Derivatives of 3-Phenylisoxazolo[2,3-*a*]pyrimidine. Unpredicted Dimerization and Ring Transformation. Syntheses of Derivatives of Pyrimidinylmethylamine, Pyrimidinylmethylamino Acid Amides, and α-Amino-2-pyrimidinylacetamides[1]

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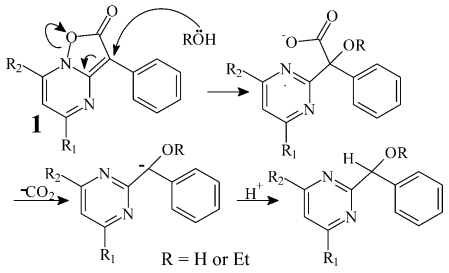
The nucleophilic ring opening of the isoxazolone ring in 2-oxo-3-phenylisoxazolo[2,3-*a*]pyrimidine derivatives by optically active amino acid amides and ephedrine led to pyrimidinylmethylamino acid amides. Using amides of different L-amino acids and (−)-ephedrine resulted in different degrees of stereoselectivity. The degree of streoselectivity depended mostly on the nucleophile used. When applying hydroxy amines such as ephedrine, the attack via the secondary amino group was found as the favored regioselectivity. Upon replacement of the oxo group in position 2 in the phenylisoxazolo[2,3-*a*]pyrimidine system by an imino group, it was expected that the spontaneous decarboxylation that follows the ring opening would not take place, thus achieving amino acid amide derivatives of 2-pyrimidinylacetamide, which are closely related to pyrimidoblamic acid, an important constituent of *Bleomycins*, used in cancer therapy. However, by heating 5,7-dimethyl-2-imino-3-phenylisoxazolo[2,3-*a*]pyrimidine in solution, it underwent an unprecedented dimerization process that involved both the phenyl and the imino group. After protecting the imino group by acetylation, the ring opening by nucleophiles was possible, resulting in the formation of derivatives of 2-pyrimidinylacetamide. 2-Acetylimino-5,7-dimethyl-3-phenylisoxazolo[2,3-*a*]pyrimidine also underwent a ring transformation, yielding an interesting indolone derivative. Selectivity in ring opening and mechanisms of dimerization and ring transformation are discussed.

Introduction

The heterocyclic system 2-oxo-3-phenylisoxazolo[2,3-*a*]pyrimidine (**1**) was previously shown to undergo a nucleophilic ring opening with water and alcohols, followed by decarboxylation to produce pyrimidinyl phenyl methanol derivatives[2](Scheme 1). Therefore, the use of amino acid derivatives as nucleophiles in this reaction seemed a promising method for the preparation of interesting pyrimidine derivatives. Derivatives of amino acids play important roles in many biological systems.[3−8]

SCHEME 1



Pyrimidoblamic acid (**2**) is an important constituent of *Bleomycins*, which are used in cancer therapy.[9,10]

In the present work various optically active amino acid amides were heated with derivatives of 2-oxo-3-phenylisoxazolo[2,3-*a*]pyrimidines (**1**), resulting in ring opening by the amino group and subsequent decarboxylation to produce new pyrimidine amino amides (Scheme 2). A chiral center is produced in this process, and it was observed that by using optically active amino amides, there is a modest stereoinduction to produce different

(1) Portions of this investigation have been presented: Zvilichovsky, G.; Gurvich, V.; Klausner, Y. S.; Gbara, I. *The XVIth International Congress of Heterocyclic Chemistry*; Bozeman MT, August 10−15, 1997; Abstract p POII-302. Zvilichovsky, G.; Gbara, I. *The 63rd Meeting of The Israel Chemical Society*; Tel Aviv, Israel February 9−11, 1998; Abstract p 184. Zvilichovsky, G.; Gbara, I. *XVIIIth European Colloquium on Heterocyclic Chemistry*; Roen, France, October 4−7, 1998; p B-82.

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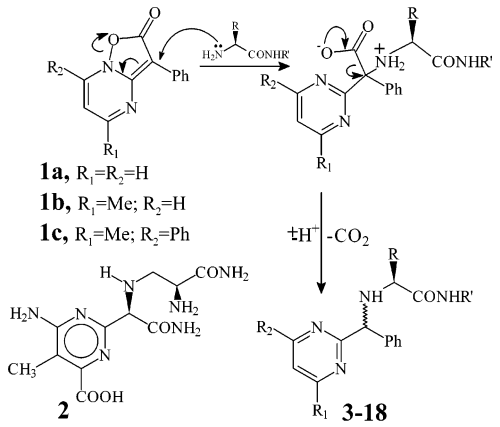
SCHEME 2



[a]For subsituents R and R' see table 1

amounts of the expected diasteromers. Upon replacement of the oxo group in position 2 in the phenylisoxazolo[2,3-*a*]pyrimidine system by an imino group, it was expected that the spontaneous decarboxylation would not take place, thus achieving amino acid amide derivatives of 2-pyrimidinylacetamide, which are closely related to pyrimidoblamic acid (**2**), which is a pyrimidinylacetamide derivative as well. The same as in pyrimidoblamic acid (**2**), the side chain is linked through the amino group on the chiral α carbon at position 2 of the pyrimidine ring. However, by heating 5,7-dimethyl-2-imino-3-phenylisoxazolo[2,3-*a*]pyrimidine (**27**) in solution it underwent an unprecedented dimerization process that involved both the phenyl and the imino group. After protecting the imino group by acetylation, the ring opening by nucleophiles was possible resulting in the formation of derivatives of 2-pyrimidinylacetamide. 2-Acetylimino-5,7-dimethyl-3-phenylisoxazolo[2,3-*a*]pyrimidine (**32**) also underwent a ring transformation, yielding an interesting indolone derivative (**45c**).

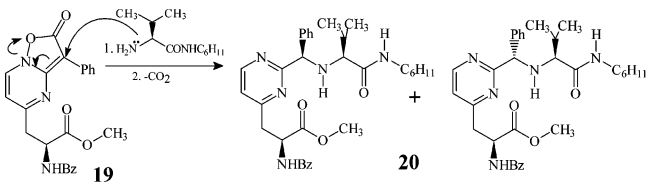
Results and Discussion

Ring Opening of 2-Oxo-3-phenylisoxazolo[2,3-*a*]-pyrimidines (1) with Amino Acid Amides. The reaction between optically active amino acid amides and derivatives of 2-oxo-3-phenylisoxazolo[2,3-*a*]pyrimidines (**1**) were carried out by reflux in dioxane, resulting in ring opening by the amino group and subsequent decarboxylation to produce new pyrimidine amino amides (**3**−**18**, Scheme 2). The diasteromeric excess was determined by NMR of the reaction mixture, e.g., by estimation of the ratio of the NMR signals of the two isomers. In most cases it was possible to separate the two stereoisomers on a silica gel column, using a petroleum ether−ethyl acetate gradient. The driving force for this reaction is probably due to both the aromatization of the pyrimidine ring and the good carboxylate leaving group. The spontaneous decarboxylation occurs because pyrimidinylacetic acid undergoes facile decarboxylation, similarly to *β*-keto acids. The steric induction is probably due to an interaction between the chiral amide side chain and the pyrimidine ring. Pyrimidines are known to interact by both hydrogen bonding and electronic interactions. The reaction is performed in dry solvents and protected from air and light. These conditions are necessary because it was

TABLE 1. Experimental Conditions and Results of the Ring Opening of 2-oxo-3-phenylisoxazolo[2,3-*a*]-pyrimidines by L-amino Acid Amides

no.	amino amide of	R′	R_1	R_2	time (h)	de (%)	overall yield (%)
3	Ala	cyclohexyl	H	H	24	15	66
4	Ala	cyclohexyl	Me	H	36	15	77
5	Phe	cyclohexyl	H	H	36	12	55
6	Phe	cyclohexyl	Me	H	48	9	76
7	Phe	cyclohexyl	Me	Ph	72	15	75
8	Val	cyclohexyl	Me	H	24	33	64
9	Val	cyclohexyl	Me	Ph	36	33	65
10	Pro	cyclohexyl	Me	H	36	67	80
11	Pro	cyclohexyl	Me	Ph	24	82	62
12	Val	H	H	H	48	60	50
13	Val	H	Me	H	36	60	45
14	Val	H	Me	Ph	50	43	50
15	Leu	benzyl	Me	Ph	48	50	61
16	Val	benzyl	Me	H	32	60	55
17	Val	benzyl	Me	Ph	24	55	40
18	N^{α}-Boc Lys	benzyl	Me	Ph	30	∼100	69

SCHEME 3



shown[2,11] that the heterocyclic system (**1**) is sensitive to light and oxygen and may react with water. Conditions of the reaction and results are summarized in Table 1.

Regardless of the structure of the heterocyclic system (**1**) and the alkyl group on the amidic nitrogen, L-alanine and L-phenylalanine derivatives gave only 12−15% diasteromeric excess. All valine derivatives and L-leucine showed a higher selectivity 33−60%. L-Proline and L-lysine gave the highest selectivity (above 82%).

An example of a further approach to pyrimidoblamic acid analogues was the introduction of chiral functional groups at the pyrimidine ring (Scheme 3). The preparation of **19**, which was reacted with *N*-cyclohexylamide of L-valine to yield the amino acid ester derivative (**20**), has been described earlier.[12]

Ring Opening of 2-Oxo-3-phenylisoxazolo[2,3-*a*]-pyrimidines (1) with *N*-Methyl-2-hydroxyamines. The isoxazolopyrimidine system (**1b**) was heated with (−)-ephedrine (**21**) under the same conditions. Theoretically one could get four isomers: two stereoisomers as a result of interaction through the *N*-methylamino group (**22**, Scheme 4) and two stereoisomers arising from interaction through the hydroxy group (**23**, Scheme 4). In practice only two isomers of ring opening were observed.

The fact that no traces of more isomers were observed could lead to one of two conclusions that either the stereoselectivity is quantitative in both OH and NHMe interaction or a regiospecific course takes place and the two products are strereoisomers. Although the NMR spectra of the two isomers showed significant differences, it was concluded that they are two stereoisomers (**22a**

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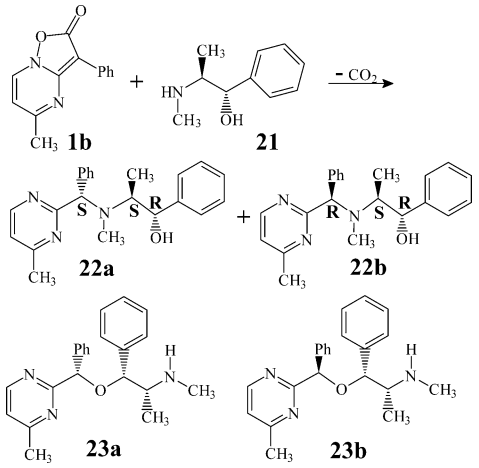
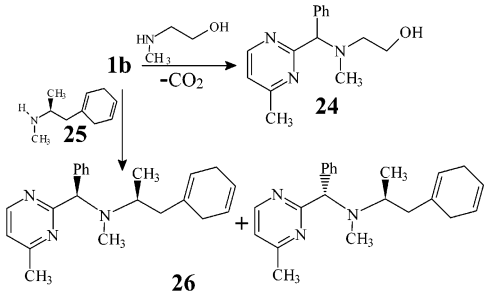
(12) Zvilichovsky, G.; Gurvich. V. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1069.

SCHEME 4



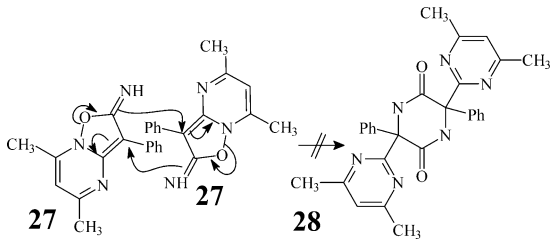
SCHEME 5



and **22b**) in a 3:4 ratio, which are the result of the attack of the amino group. To verify this selectivity it was advisable to react the hetereocyclic system (**1b**) with the achiral 2-(*N*-methylamino)ethanol and see whether only one product is obtained. The latter experiment resulted in one product, presumably by the interaction through the secondary amino group (**24**, Scheme 5). It is also assumed that **22a** has the *S* configuration. This assumption is a result of building a hydrogen-bonded model, showing the influence of the 3D structure on the chemical shift of both the protons of the C-methyl group and the proton at the new chiral center. For comparison the chiral secondary amine (**25**)[13] was used in the reaction with **1b** yielding two stereoisomers **26**, without any stereoselectivity (Scheme 5). However, the isomers could be separated by column chromatography. The chemical shifts in the NMR spectra of the two isomers were not as different from each other as in those derived from ephedrine.

Dimerization of 5,7-Dimethyl-2-imino-3-phenylisoxazolo[2,3-*a*]pyrimidine. Although the ring opening of the heterocyclic system (**1** and **19**) is followed by a spontaneous decrboxylation, in the imino analogue (**27**), which was described earlier,[14] the decarboxylation should not take place. The result of such a ring opening should lead to pyrimidinylacetamide derivatives, structures closely related to pyrimidoblamic (**2**) acid, which is a pyrimidinylacetamide as well. We tried to heat the imino derivative 5,7-dimethyl-2-imino-3-phenylisoxazolo[2,3-*a*]-pyrimidine (**27**), with nucleophiles. Whereas the reaction of **1** or **19** with nucleophiles takes place by heating in

SCHEME 6



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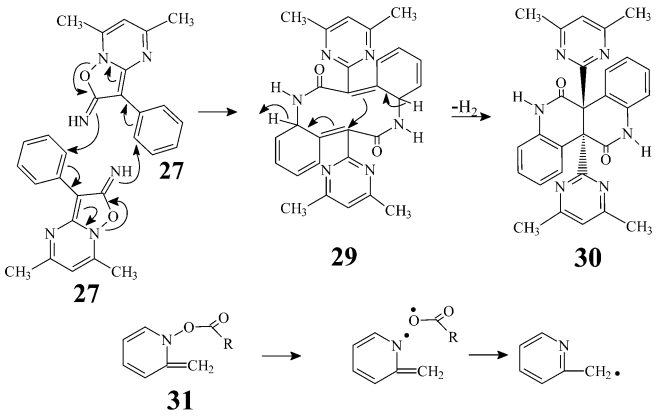

boiling dioxane for periods longer than 18 h, the imino analogue (**27**) underwent a much faster transformation, leaving the nucleophile unchanged. The solution turns red, and two colored products were detected and separated by chromatography: an orange-red product, which was quite unstable, and another yellow-orange solid. Considering the reactivity toward nucleophiles (Scheme 1) and the fact that the imino group may function as a nucleophile, a dimerization was expected leading to the dimer **28**, which was not the case (Scheme 6).

Unexpectedly, upon submission to mass spectrometry the dimer lacked two hydrogens. In addition, the NMR spectrum of this yellow product showed only four hydrogens for each of the phenyl groups. These findings and the fact that the ring transformation, described below, involved an attack of the iminic nitrogen on the phenyl ring and considering the reactivity of position 3 in **1** and **19** (Scheme 1) allowed us to suggest the structure and mechanisms for the formation of the dimerization product (**30**, Scheme 7).

The mechanisms are not necessarily concerted. The ionic mechanism is based on the somewhat unexpected behavior of the phenyl double bond as a vinylog of the reactive site at position 3 toward nucleophiles (see Scheme 1). A radical mechanism is possible as well. The feasibility of a radical mechanism is based on the known homolytic cleavage of *O*-acyl picoline *N*-oxide[15] and the evidence for a free radical cleavage shown[16] for intermediate (**31**). The latter may be looked upon as an open chain analogue of the structure of the oxo and imino isoxazole moieties in the isoxazolopyrimidine systems, **1**, **19**, and **27**. Referring to both the free radical and the ionic mechanisms, it seems that a hydrogen acceptor is necessary for the steps leading from **29** to **30**. This might

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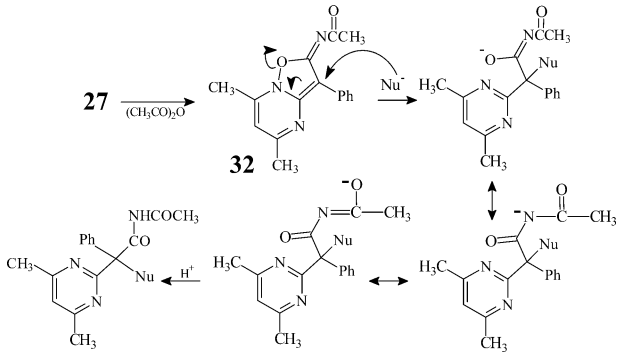
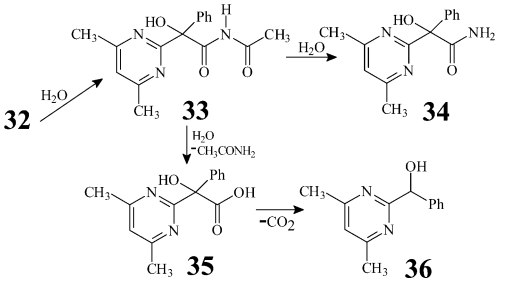
SCHEME 8



SCHEME 9



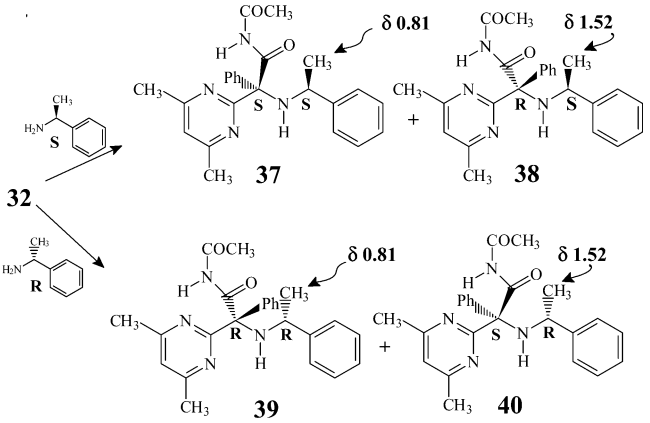
be explained by the formation of the unidentified orange-red product, which could have been involved in acceptance of hydrogens.

Nucleophilic Ring Opening of the Isoxazole Ring in 2-Acetylimino-5,7-dimethyl-3-phenylisoxazolo-[2,3-*a*]pyrimidine. Synthesis of Derivatives of α-Amino-2-pyrimidinylacetamide. To continue in our synthetic studies on the nucleophilic opening of the isoxazole ring by nucleophiles and avoid the dimerization reaction, the imino group was acetylated. The driving forces for the isoxazole ring opening in the carbonyl analogue (**1**) are both the good carboxylate ion leaving group and the aromatization of the pyrimidine ring, as shown in Scheme 1. Therefore we thought that an acetyl group should bring about enhanced stabilization of the anion produced in a nucleophilic attack, by extended resonance, as shown in Scheme 8. Indeed it slowed the dimerization and enabled the nucleophilic ring opening of the isoxazolone ring. 2-Acetylimino-5,7-dimethyl-3-phenylisoxazolo[2,3-*a*]pyrimidine (**32**) reacted with nucleophiles the same way as the carbonyl derivative (**1**) and even faster. The absence of the competing fast reaction also served as a clue for the assumption that the free imino group has a role in the competing dimerization process.

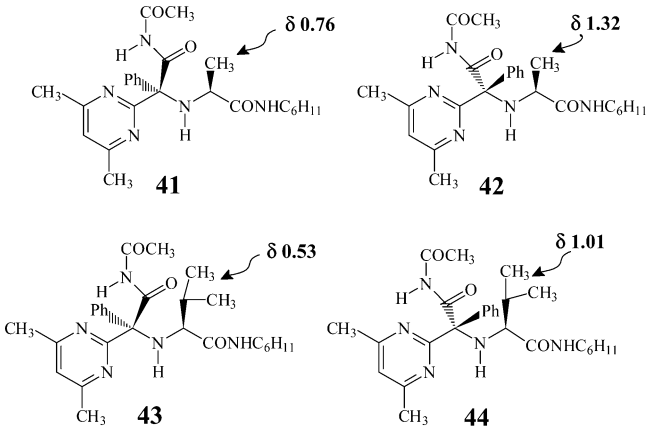
The reaction of **32** with water in wet dioxane resulted in ring opening. The imide group that is formed in the reaction can undergo hydrolysis in two pathways, leading either to the known product (**36**, Scheme 9) by the spontaneous decarcboxylation of the intermediate **35** or directly to the pyrmidinylacetamide derivative (**34**). In the conditions of the experiment, two products were isolated, **33** and **34** (Scheme 9). The pyrimidinylacetamide derivative (**34**) could be crystallized for X-ray diffraction analysis.

The process of the ring opening brings about the formation of a new chiral center, and it was of interest to determine whether this reaction is stereospecific. Thus, 2-acetylimino-5,7-dimethyl-3-phenylisoxazolo[2,3-*a*]pyrimidine (**32**) was heated with (*R*)-1-phenylethylamine and also with (*S*)-1-phenylethylamine. In both cases two stereoisomers were obtained in a ratio of 4:1 (Scheme 10). The diasteromers could be separated by column chromatography. An interesting phenomenon was the pronounced difference in the chemical shifts of the methyl group, near the amino group, in the two diasteromers. Whereas in one isomer the chemical shift of this methyl group was at δ 1.52, in the second isomer it was at δ 0.81. This observed difference could be explained by a "through space" effect, probably due to a relatively rigid structure as a result of hydrogen bonding, keeping this methyl group in a different shielding environment. By building models and looking at the spatial environment of the methyl groups, the steric structures of all four products (**37**−**40**) were proposed (Scheme 10).

SCHEME 10

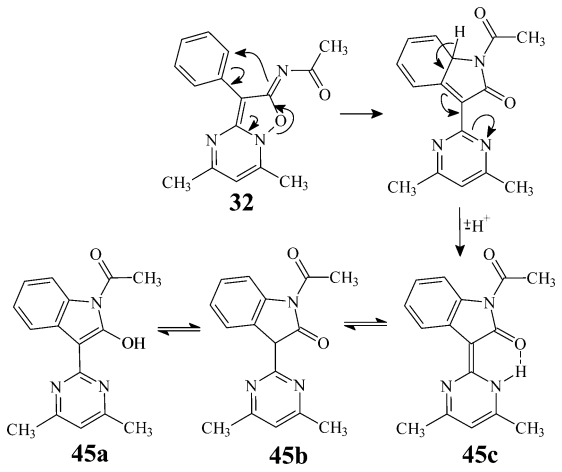


To show the synthetic applicability to pyrimidine derivatives related to pyrimidoblamic acid (**2**), 2-acetylimino-5,7-dimethyl-3-phenylisoxazolo[2,3-*a*]pyrimidine (**32**) was heated with cyclohexylamides of L-alanine and L-valine. The diastereomeric ratios in these reactions were 2:1 and 3:1, respectively. As in the case described above (products **37**−**40**), the alkyl groups of both alanine and valine segments showed considerable chemical shift differences within the pairs of diastereomers. This observation permitted us to try to suggest the spatial structures of these products (**41**−**44**).



Ring Transformation of 2-Acetylimino-5,7-dimethyl-3-phenylisoxazolo[2,3-*a*]pyrimidine. When the nucleophile failed to open the isoxazole ring in 2-acetylimino-5,7-dimethyl-3-phenylisoxazolo[2,3-*a*]py-

SCHEME 11



rimidine (**32**), a new rearrangement product of **32** was observed. It proved to be, by a single-crystal X-ray diffraction, the ring transformation product (3*E*)-1-acetyl-3-(4,6-dimethylpyrimidin-2(1*H*)-ylidene)-1,3-dihydro-2*H*-indol-2-one (**45c**). The product **45c** is one of the tautomeric forms of 4,6-dimethylpyrimidin-2-yl)indol-2-ol (**45a**−**c**), and its stability deserves explanation as the aromaticity of both the pyrimidine and the indole ring are lost. A proposed mechanism for the transformation of **32** to **45** is outlined in Scheme 11. Both ionic and free radical mechanisms may be considered.

Summary. The reactivity of position 3 in both the 2-oxo and 2-imino derivatives of 3-phenylisoxazolo[2,3-*a*]pyrimidine toward nucleophiles was demonstrated. The dimerization of the 2-imino derivative (**27**) and the ring transformation in the acetylimino derivative (**32**) show an extension of this reactivity to the phenyl ring at position 3. The steric induction that occurs in the ring opening of the isoxazole ring in these derivatives of 3-phenylisoxazolo[2,3-*a*]pyrimidine is probably due to an interaction between the chiral nucleophile and the pyrimidine ring. The nature of the interaction is most likely by hydrogen bonding. Pyrimidines are known to interact by both hydrogen bonding and electronic interactions. This interaction could be with either the attacking nucleophilic molecule or with surrounding molecules. The fact that the diasteroselectivity also takes place in the 2-acetylimino derivative (**32**) eliminates the possibility that it occurs at the decarboxylation step. The ratio between the diasteroisomers was determined by the ^{1}H NMR signals in the reaction mixtures. The diasteromeric excess is in most of the cases modest but it was possible to separate the isomers. Where possible, attempts to determine the absolute configuration were done by studying the ^{1}H NMR spectra, because crystals for X-ray diffraction were not available. It is worthy to note that when two enantiomeric amines were used as nucleophiles, the major products (e.g., **37** and **39**) had the same configuration at the newly produced chiral center as the reactants.

Experimental Section

General Procedure for Reaction of 2-oxo-3-phenylisoxazolo[2,3-*a*]pyrimidines (1) with Amides of Amino Acids. An amino acid amide (1.1 mmol) and a derivative of 2-oxo-3-phenylisoxazolo[2,3-*a*]pyrimidine derivative (**1**)[10] (1.0 mmol) were refluxed in 1,4-dioxane (25 mL) under dry nitrogen or argon, protected from light. The progress of the reaction was monitored by TLC and NMR of aliquots. The period of heating is reported in Table 1. The solvent was evaporated in a vacuum. The ratio of diasteroisomers was determined by ^{1}H NMR of the residue. The residue was subjected to silica gel column chromatography, and the isomers eluted with ethyl acetate−petroleum ether gradient. The isomer that came out first from the column was labeled **a** and the second as **b**. Overall yields and diasteromeric excess are given in Table 1. Rotations, which are given below, are for products with purity as shown by NMR. The overall yields include fractions that consisted of a mixture of diasteromers. All products were hygroscopic oils or semisolids. Elementary analyses were not always reliable, so the high-resolution MS is reported in most of the ring opening products.

Data for **3a**: yield of isolated isomer 23%. ^{1}H NMR ($CDCl_3$): δ 8.70 (d, J = 5.0 Hz, 2H), 7.5−7.3(m, 5H), 7.20(t, J = 5.0 Hz, 1H), 5.0 (s, 1H), 3.8 (m, 1H), 3.2 (m, 1H), 1.9−0.9 (m, 10H), 1.36 (d, J = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 173.8, 170.6, 157.3, 141.7, 130.9, 128.8, 127.6, 127.2, 119.4, 67.4, 57.5, 47.3, 33.0, 25.4, 24.7, 20.2. $[\alpha]^{25}_D$ = +12.9° ($CHCl_3$, c = 2). ESI-HRMS (MH^+/z): 339.2164 (calcd for $C_{20}H_{26}N_4O$ + H 339.2184). Data for **3b**: yield of isolated isomer 18%. ^{1}H NMR ($CDCl_3$): δ 8.69 (d, J = 5.0 Hz, 2H), 7.4−7.2 (m, 5H), 7.1 (d, J = 5.0 Hz, 1H), 4.96 (s, 1H), 3.7 (m, 1H), 3.2 (m, 1H), 1.8−0.9 (m, 10H), 1.32 (d, J = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 173.7, 170.0, 157.3, 140.6, 128.8, 127.9, 127.5, 119.4, 66.8, 55.2, 47.5, 33.2, 33.1, 25.5, 24.80, 20.2. $[\alpha]^{25}_D$ = −90.1° ($CHCl_3$, c = 2). ESI-HRMS (MH^+/z): 339.2186 (calcd for $C_{20}H_{26}N_4O$ + H 339.2184).

Data for **4a**: yield of isolated isomer 30%. ^{1}H NMR ($CDCl_3$): δ 8.52 (d, J = 5.1 Hz, 1H), 7.43−7.20 (m, 5H), 7.00 (d, J = 5.1 Hz, 1H), 4.96 (s, 1H) 3.8 (m, 1H), 3.2 (m, 1H), 2.46 (s, 3H), 1.87−0.84 (m, 10H), 1.3 (d, J = 6.9 Hz, 3H). $[\alpha]^{25}_D$ = +14.1° ($CHCl_3$, c = 4). Anal. Calcd for $C_{21}H_{28}N_4O$·0.5HOH: C, 69.78; H, 8.09. Found: C, 69.53; H, 7.87. Data for **4b**: yield of isolated isomer 25%. ^{1}H NMR ($CDCl_3$): δ 8.54 (d, J = 5.1 Hz, 1H), 7.48−7.22 (m, 5H), 7.02 (d, J = 5.1 Hz, 1H), 4.93 (s, 1H) 3.7 (m, 1H), 3.1 (m, 1H), 2.48 (s, 3H), 0.9−1.9 (m, 10H), 1.36 (d, J = 6.9 Hz, 3H). $[\alpha]^{25}_D$ = −81.8° ($CHCl_3$, c = 2). Anal. Calcd for $C_{21}H_{28}N_4O$·HOH: C, 68.08; H, 8.16. Found: C, 68.23; H, 7.88.

Data for **5a**: yield of isolated isomer 20%. ^{1}H NMR ($CDCl_3$): δ 8.40 (d, J = 4.8 Hz, 2H), 7.3−7.04(m, 10H), 6.9 (t, J = 4.8, Hz, 1H) 4.82 (s, 1H), 3.9 (m, 1H), 3.2 (m, 1H), 3.21 (m, 2H), 1.7−1.0 (m, 10H). $[\alpha]^{25}_D$ = +149°. Anal. Calcd for $C_{26}H_{30}N_4O$·HOH: C, 72.19; H, 7.46. Found: C, 72.17; H, 7.43. Data for **5b**: yield of isolated isomer 30%. ^{1}H NMR ($CDCl_3$): δ 8.47 (d, J = 4.9 Hz), 7.51−7.10 (m, 10H), 7.02 (t, J = 4.9 Hz, 1H), 4.85 (s, 1H), 3.70 (m, 1H), 3.38 (m, 1H), 3.19 (dd, J_1 = 13.7 Hz, J_2 = 3.8 Hz, 2H), 1.77−1.02 (m). $[\alpha]^{25}_D$ = +10.2° ($CHCl_3$, c = 2). Anal. Calcd for $C_{26}H_{30}N_4O$·HOH: C, 72.19; H, 7.46. Found: C, 71.99; H, 7.68.

Data for **6a**: yield of isolated isomer 29%. ^{1}H NMR ($CDCl_3$): δ 8.45 (d, J = 5.2 Hz, 1H), 7.45−7.11 (m, 10H), 6.95 (d, J = 5.2 Hz, 1H), 4.85 (s, 1H), 3.83−3.72 (m, 1H), 2.75−2.66 (m, 1H), 3.22−3.10 (m, 2H), 2.46 (s, 3H), 1.93−1.10 (m, 10H). $[\alpha]^{25}_D$ = −47.4° ($CHCl_3$, c = 3). ESI-HRMS (MH^+/z): 429.2662 (calcd for $C_{27}H_{32}N_4O$ + H 429.2654). Anal. Calcd for $C_{27}H_{32}N_4O$: C, 75.67; H, 7.53. Found: C, 75.61; H, 7.82. Data for **6b**: yield of isolated isomer 36%. ^{1}H NMR ($CDCl_3$): δ 8.29 (d, J = 5.1 Hz, 1H), 7.34−7.17 (m, 10H), 6.89 (d, J = 5.1 Hz, 1H), 4.76 (s, 1H), 3.78−3.72 (m, 1H), 3.29−3.27 (m, 1H), 3.18 (dd, J_1 = 13.7 Hz, J_2 = 3.8 Hz, 2H), 2.33 (s, 3H), 1.79−0.88 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 172.4, 169.5, 167.1, 156.5, 141.8, 137.5, 129.4, 128.5, 128.4, 127.3, 127.15, 126.6, 118.6, 67.1, 63.2, 47.3, 39.9, 32.9, 32.8, 25.4, 24.6, 24.1. $[\alpha]^{25}_D$ = +91.2° ($CHCl_3$, c = 2). ESI-HRMS (MH^+/z): 429.2620 (calcd for $C_{27}H_{32}N_4O$ + H 429.2654).

Data for **7a**: yield of isolated isomer 41%. ^{1}H NMR ($CDCl_3$): δ 8.02−7.98 (m, 2H), 7.54−6.95 (m, 14H), 4.87 (s, 1H), 3.84−3.80 (m, 1H), 3.27−3.2 (m, 2H), 2.75−2.66 (m, 1H), 2.4 (s, 3H), 1.6−1.0 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 172.4, 169.2, 167.9, 163.3, 139.9, 137.7, 136.6, 130.8, 129.6, 128.8, 128.6, 128.3, 127.8, 127.4, 127.1, 126.8, 114.1, 66.3, 60.1, 47.6, 39.9, 33.2, 33.0, 25.5, 24.8, 24.4. $[\alpha]^{25}_D = -22.1°$ ($CHCl_3$, $c = 4$). ESI-HRMS (MH^+/z): 505.2959 (calcd for $C_{33}H_{36}N_4O$ + H 505.2967). Data for **7b**: yield of isolated isomer 41%. ^{1}H NMR ($CDCl_3$): δ 7.82−7.80 (m, 2H), 7.5−7.0 (m, 14H), 4.79 (s, 1H), 3.7 (m, 1H), 3.1 (m, 1H), 2.65 (m, 2H), 2.42 (s, 3H), 1.7−0.9 (m, 10H). $[\alpha]^{25}_D = -86.7°$ ($CHCl_3$, $c = 2$). ESI-HRMS (MH^+/z): 505.2913 (calcd for $C_{33}H_{36}N_4O$ + H 505.2967).

Data for **8a**: yield of isolated isomer 18%. ^{1}H NMR ($CDCl_3$): δ 8.44 (d, $J = 5.1$ Hz, 1H), 7.33−7.13(m, 5H), 6.92 (d, $J = 5.1$ Hz, 1H) 4.74 (s, 1H), 3.8 (m, 1H), 2.8 (d, $J = 4.0$ Hz, 1H), 2.35 (s, 3H), 2.1−0.8 (m, 11H), 0.91 (d, $J = 7.0$ Hz, 3H), 0.87 (d, $J = 7.0$ Hz, 3H). ESI-HRMS (MH^+/z): 381.2651 (calcd for $C_{21}H_{28}N_4O$ + H 381.2654). Anal. Calcd for $C_{23}H_{32}N_4O$·0.5HOH: C, 70.92; H, 8.54. Found: C, 71.07; H, 8.48. Data for **8b**: yield of isolated isomer 37%. ^{1}H NMR ($CDCl_3$): δ 8.52 (d, $J = 5.1$ Hz, 1H), 7.40−7.21 (m, 5H), 7.00 (d, $J = 5.1$ Hz, 1H) 4.81 (s, 1H), 3.83−3.71 (m, 1H), 2.87 (d, $J = 3.9$ Hz, 1H), 2.50 (s, 3H), 2.1−0. 99 (m, 11H), 0.98 (d, $J = 7.0$ Hz, 3H), 0.94 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 172.3, 170.0, 167.2, 156.7, 142.1, 128.6, 127.3, 127.2, 118.9, 67.1, 67.1, 47.2, 33.3, 32.8, 31.4, 25.5, 24.7, 24.6, 24.1, 19.8, 17.4. $[\alpha]^{26}_D = -75.4°$ ($CHCl_3$, $c = 1$). ESI-HRMS (MH^+/z): 381.2622 (calcd for $C_{23}H_{32}N_4O$ + H 381.2654).

Data for **9a**: yield of isolated isomer 28%. ^{1}H NMR ($CDCl_3$): δ 8.1 (m, 2H), 7.5−7.2 (m, 9H), 4.83 (s, 1H), 3.9 (m, 1H), 2.9 (m, 1H), 2.5 (s, 3H), 2.2−0.9 (m, 17H), $[\alpha]^{25}_D = -208°$ ($CHCl_3$, $c = 2$). Anal. Calcd for $C_{29}H_{36}N_4O$·0.5HOH: C, 74.80; H, 8.01. Found: C, 74.82; H, 8.33. ESI-HRMS (MH^+/z): 457.2955 (calcd for $C_{29}H_{36}N_4O$ + H 457.2967). Data for **9b**: yield of isolated isomer 16%. ^{1}H NMR ($CDCl_3$): δ 8.0 (m, 2H), 7.4−7.1 (m, 9H), 4.88 (s, 1H), 3.8 (m, 1H), 2.8 (m, 1H), 2.48 (s, 3H), 2.12−0.80 (m, 17H). $[\alpha]^{25}_D = +10.3°$ ($CHCl_3$, $c = 2$). Anal. Calcd for $C_{29}H_{36}N_4O$·0.5HOH: C, 74.80; H, 8.01. Found: C, 74.50; H, 7.94. ESI-HRMS (MH^+/z): 457.2943 (calcd for $C_{29}H_{36}N_4O$ + H 457.2967).

Data for **10a**: yield of isolated isomer 43%. ^{1}H NMR ($CDCl_3$): δ 8.47 (d, $J = 5.0$ Hz, 1H), 7.5−7.2 (m, 5H), 6.95 (d, $J = 5.0$ Hz, 1H), 5.04 (s, 1H), 3.61−3.57 (m, 2H), 3.01 (m, 1H), 2.4 (m, 4H), 2.1−0.9 (m, 14H). $[\alpha]^{25}_D = -207°$ ($CHCl_3$, $c = 2$). ESI-HRMS (MH^+/z): 379.2491 (calcd for $C_{23}H_{30}N_4O$ + H 379.2497). Data for **10b**: yield of isolated isomer 12%. ^{1}H NMR ($CDCl_3$): δ 8.59 (d, $J = 5.0$ Hz, 1H), 7.44−7.24 (m, 5H), 7.04 (d, $J = 5.0$ Hz, 1H) 5.09 (s, 1H), 3.8 (m, 1H), 3.8 (m, 1H), 3.0 (m, 2H), 2.4 (s, 3H), 2.2−0.9 (m, 14H). $[\alpha]^{25}_D = -62.4°$ ($CHCl_3$, $c = 1$).

Data for **11a**: yield of isolated isomer 11%. ^{1}H NMR ($CDCl_3$): δ 8.01−6.80 (m, 10H), 7.34 (s, 1H), 5.14 (s, 1H), 3.7 (dd, $J_1 = 8.8$ Hz, $J_2 = 2.9$ Hz, 1H), 3.53−3.40 (m, 1H), 3.1−3.04 (m, 1H), 2.5 (s, 3H), 2.56−2.53 (m, 1H), 2.1−0.9 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 174.0, 169.6, 167.4, 163.8, 139.9, 136.9, 130.5, 129.3, 128.7, 128.0, 127.5, 127.2, 114.4, 74.6, 64.2, 52.98, 47.3, 32.9, 32.2, 30.5, 25.3, 24.6, 24.5, 24.4, 24.3. ESI-HRMS (MH^+/z): 455.2782 (calcd for $C_{29}H_{34}N_4O$ + H 455.2810). Data for **11b**: yield of isolated isomer 39%. ^{1}H NMR ($CDCl_3$): δ 8.02−7.23 (m, 10H), 7.36 (s, 1H), 5.13 (s, 1H), 3.8 (dd, $J_1 = 8.8$ Hz, $J_2 = 3.0$ Hz, 1H), 3.51−3.39 (m, 1H), 3.11−3.04 (m, 1H), 2.61−2.53 (m, 1H), 2.52 (s, 3H), 2.1−1.09 (m, 14H). ^{13}C NMR ($CDCl_3$): δ 174.1, 169.7, 167.5, 163.9, 140.0, 137.1, 130.6, 129.4, 128.7, 128.1, 127.5, 127.3, 114.5, 74.7, 64.3, 53.1, 47.4, 33.0, 32.3, 30.5, 25.4, 24.6, 24.6, 24.5, 24.4. $[\alpha]^{25}_D = -91.55$ ($CHCl_3$, $c = 4$). ESI-HRMS (MH^+/z): 455.2806 (calcd for $C_{29}H_{34}N_4O$ + H 455.2810).

Data for **12a**: yield of isolated isomer 62%. ^{1}H NMR ($CDCl_3$): δ 8.70 (d, $J = 4.9$ Hz, 2H), 7.39 (d, $J = 7.1$ Hz, 2H), 7.29 (t, $J = 7.1$ Hz, 2H), 7.26−7.12 (m, 4H), 5.64 (br s, 1H), 4.97 (s, 1H), 2.89 (d, $J = 4.4$ Hz, 1H), 2.21−2.09 (m, 1H), 1.00 (d, $J = 6.9$ Hz, 3H), 0.99 (d, $J = 6.9$ Hz, 3H). Anal. Calcd for $C_{16}H_{20}N_4O$·0.5HOH: C, 65.51; H, 7.22. Found: C, 65.23; H, 7.05.

Data for **13a**: yield of isolated isomer 25%. ^{1}H NMR ($CDCl_3$): δ 8.43 (d, $J = 5.0$ Hz, 1H), 7.33 (d, $J = 7.8$ Hz, 2H), 7.24−7.08 (m, 3H), 6.92 (d, $J = 5.0$ Hz, 1H), 5.82 (br s, 1H), 4.84 (s, 1H), 2.78 (d, $J = 3.9$ Hz, 1H), 2.42 (s, 3H), 2.09−2.01 (m, 1H), 0.91 (d, $J = 6.9$ Hz, 6H). $[\alpha]^{25}_D = -10.8°$ ($CHCl_3$, $c = 3$). Anal. Calcd for $C_{17}H_{22}N_4O$·HOH: C, 64.53; H, 7.65. Found: C, 74.79; H, 7.70.

Data for **14a**: yield of isolated isomer 20%. ^{1}H NMR ($CDCl_3$): δ 8.1−8.07 (m, 2H), 7.73−7.14 (m, 8H), 7.41 (s, 1H), 5.88 (d, $J = 4.4$ Hz, 1H), 5.00 (s, 1H), 2.94 (d, $J = 4.4$ Hz, 1H), 2.54 (s, 3H), 2.03 (m, 1H), 0.92 (d, $J = 6.9$ Hz, 6H). $[\alpha]^{25}_D = +7.39^o$ ($CHCl_3$, $c = 2$). Anal. Calcd for $C_{23}H_{25}N_4O$·HOH: C, 70.38; H, 7.19. Found: C, 71.00; H, 7.16.

Data for **15a**: yield of purified mixture of two isomers 39%. ^{1}H NMR ($CDCl_3$): δ 8.11−7.24 (m, 15H), 7.42 (s, 1H), 4.90 (s, 1H), 4.35 (m, 2H), 3.2 (m, 1H), 2.55 (s, 3H), 1.8−1.4 (m, 3H), 0.94 (d, $J = 6.5$ Hz, 3H), 0.90 (d, $J = 6.5$ Hz, 3H). Anal. Calcd for $C_{31}H_{34}N_4O$: C, 77.79; H, 7.16; N, 11.71. Found: C, 77.42; H, 7.41; N, 11.37. Data for **15b**: as seen in the mixture. ^{1}H NMR ($CDCl_3$): δ 8.11−7.24 (m, 15H), 7.42 (s, 1H), 5.0 (s, 1H), 4.35 (m, 2H), 3.2 (m, 1H), 2.52 (s, 3H), 1.8−1.4 (m, 3H), 0.69 (d, $J = 6.4$ Hz, 3H), 0.65 (d, $J = 6.4$ Hz, 3H).

Data for **16a**: yield of isolated isomer 11%. ^{1}H NMR ($CDCl_3$): δ 8.52 (d, $J = 5.1$ Hz, 1H), 7.68 (t, $J = 5.7$ Hz, 2H), 7.32−7.21 (m, 10H), 7.00 (d, $J = 5.1$ Hz, 1H), 4.83 (s, 1H), 4.43 (A of double AB system, $J = 14.7$, 5.7 Hz, 1H), 4.36 (B of double AB system, $J = 14.7$, 5.7 Hz, 1H), 2.97 (d, $J = 4.15$ Hz, 1H), 2.50 (s, 3H), 2.18 (m, 1H), 1.00 (d, $J = 7.0$ Hz, 3H), 0.96 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 173.4, 169.9, 167.2, 156.7, 141.9, 138.5, 128.6, 128.5, 127.8, 127.5, 127.3, 127.2, 118.9, 67.4, 67.3, 42.9, 31.6, 24.1, 19.8, 17.8. $[\alpha]^{25}_D = -50.91°$ ($CHCl_3$, $c = 2$). Anal. Calcd for $C_{30}H_{32}N_4$·0.5HOH: C, 76.11; H, 6.98; Found: C, 76.38; H, 7.23.

Data for **17a**: yield of isolated isomer 39%. ^{1}H NMR ($CDCl_3$): δ 8.09 (dd, $J_1 = 6.4$ Hz, $J_2 = 2.8$ Hz, 2H), 7.74 (t, $J = 5.7$ Hz, 1H), 7.52−7.21(m, 11H), 7.46 (s, 1H), 4.95 (s, 1H), 4.49 (A of double AB system, $J = 14.7$, 5.7 Hz, 1H), 4.40 (B of double AB system, $J = 14.7$, 5.7 Hz, 1H), 3.08 (d, $J = 4.2$ Hz, 1H), 2.59 (s, 3H), 2.39 (m, 1H), 1.00 (d, $J = 6.9$ Hz, 3H), 0.99 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 173.5, 169.9, 167.7, 163.6, 142.0, 138.43, 136.6, 130.8, 128.8, 128.6, 128.5, 127.8, 127.3, 127.2, 127.1, 127.1, 114.3, 67.4, 67.3, 43.0, 31.6, 24.3, 19.8, 17.9. ESI-HRMS (MH^+/z): 465.2645 (calcd for $C_{30}H_{32}N_4$-O + H 465.2654). Data for **17b**: Only traces of isolated isomer.

Data for **18**: overall yield, one isomer 69%. ^{1}H NMR ($CDCl_3$): δ 8.06 (m, 2H), 7.61−7.16 (m, 13H), 7.34 (s, 1H), 6.82 (br s, 1H), 5.23 (t, $J = 5.7$ Hz, 1H), 5.06 (s, 1H), 4.34−4.29 (m, 2H), 4.11−4.06 (m, 1H), 2.70−2.54 (m, 3H), 2.51 (s, 3H), 1.81−1.52 (m, 5H), 1.38 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 172.0, 169.8, 167.8, 163.7, 163.7, 141.0, 138.0, 136.8, 130.9, 128.8, 128.5, 128.4, 127.7, 127.4, 127.4, 127.2, 127.1, 114.3, 68.1, 68.0, 47.0, 43.2, 32.3, 29.14, 28.2, 24.3, 23.1. $[\alpha]^{25}_D = +8.11°$ (CHCl3, $c = 4$). ESI-HRMS (MH^+/z): 594.3398 (calcd for $C_{36}H_{43}N_5O_3$ + H 594.3444).

Reaction between Methyl (*S*)-*N*-Benzoyl-2-(5-methyl-2-oxo-3-phenylisoxazolo[2,3-*a*]pyrimidin-7-yl)alaninate (19) and L-*N*-Cyclohexylvalinamide. Methyl (*S*)-*N*-benzoyl-2-(5-methyl-2-oxo-3-phenylisoxazolo[2,3-*a*]pyrimidin-7-yl)alaninate[12] (**19**) (0.08 g, 0.19 mmol) was dissolved in dioxane (10 mL). L-*N*-Cyclohexylvalinamide (0.042 g, 0.21 mmol) was added, and the mixture was refluxed in the conditions described above for 18 h. The reaction was monitored by TLC and NMR of aliquots. The solvent was removed by evaporation in a vacuum. The ratio of isomers was determined by NMR (3:2), and the residue was loaded on silica gel column and eluted with ethyl acetate−petroleum ether gradient (40−100%). First eluted isomer, **20a** (0.2 g of isolated isomer, 43% isolated yield). ^{1}H NMR ($CDCl_3$): δ 8.54 (d, $J = 5.1$ Hz, 1H), 7.63 (dd, $J_1 = 6.99$ Hz, $J_2 = 1.41$ Hz, 2H), 7.48−

7.19 (m, 8H), 7.00 (d, J = 5.1 Hz, 1H), 6.89 (d, J = 8.1 Hz, 1H), 5.20 (dt, J_1 = 8.1 Hz, J_2 = 4.6 Hz, 1H), 4.85 (s, 1H), 3.70 (m, 1H), 3.68 (s, 3H), 3.57 (A of double AB system, J = 16.6, 4.6 Hz, 1H), 3.57 (B of double AB system, J = 16.6, 4.6 Hz, 1H), 2.79 (d, J = 4.9 Hz, 1H), 1.8−0.9 (m, 11H, 10H), 0.92 (d, J = 6.0 Hz, 3H), 0.91 (d, J = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 172.0, 171.7, 170.1, 166.7, 166.2, 157.2, 133.4, 131.7, 128.7, 128.5, 127.5, 127.2, 126.9, 119.4, 67.6, 67.42, 4.99, 33.2, 32.8, 31.5, 25.5, 24.7, 19.6, 17.7. $[\alpha]^{25}_D$= +11.2° ($CHCl_3$, c = 1) ESI-HRMS (MH^+/z): 594.3022 (calcd for $C_{33}H_{40}N_5O_4$ + Na 594.3056). Second isomer, **20b** (37% isolated yield). ^{1}H NMR ($CDCl_3$): δ 8.57 (d, J = 5.1 Hz, 1H), 7.48 (dd, J_1 = 8.3 Hz, J_2 = 1.32 Hz, 2H), 7.48−7.22 (m, 9H), 7.01 (d, J = 5.1 Hz, 1H), 5.15 (dt, J_1 = 7.5 Hz, J_2 = 4.9 Hz, 1H), 4.76 (s, 1H), 3.70 (m, 1H), 3.66 (s, 3H), 3.50 (A of double AB system, J = 16.2, 4.9 Hz, 1H), 3.40 (B of double AB system, J = 16.2, 4.9 Hz, 1H), 2.81 (d, J = 4.2 Hz, 1H), 2.0−0.89 (m, 11H), 0.93 (d, J = 7.0 Hz, 3H), 0.89 (d, J = 7.0, Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 172.1, 171.9, 169.7, 166.9, 166.4, 157.1, 140.5, 133.6, 131.8, 128.7, 128.6, 127.8, 127.7, 127.1, 119.3, 67.2, 65.2, 52.6, 50.4, 47.45, 37.9, 33.4, 33.2, 31.4, 25.5, 24.8, 19.5, 18.1. $[\alpha]^{25}_D$ = +26.06° ($CHCl_3$, c = 2) ESI-HRMS (MH^+/z): 594.3029 (calcd for $C_{33}H_{40}N_5O_4$ + Na 594.3056).

Reaction between 5-Methyl-2-oxo-3-phenylisoxazolo-[2,3-*a*]pyrimidines (1b) and (−)-Ephedrine. (−)-Ephedrine (0.16 g, 0.97 mmol was dissolved in dry dioxane (15 mL). 5-Methyl-2-oxo-3-phenylisoxazolo[2,3-*a*]pyrimidines (**1b**) (0.2 g, 0.87 mmol) was added, and the mixture was refluxed in the conditions described above for 24 h. The solvent was removed by evaporation in a vacuum. The ratio of isomers was determined by NMR, and the residue was loaded on a silica gel column and eluted with ethyl acetate−petroleum ether gradient. The two isomers came too close to one another and could not be separated. However, because of the different amounts, the ^{1}H NMR could be assigned for each of the two isomers. Data for isomer **22a**. ^{1}H NMR ($CDCl_3$): δ 8.57 (d, J = 5.1 Hz, 1H), 7.61 (d, J = 7.1 Hz, 2H), 7.39−7.21 (m, 6H), 7.00 (d, J = 5.1 Hz, 1H), 4.99 (s, 1H), 4.58 (d, J = 3.7 Hz, 1H), 3.19 (m, 1H), 2.57 (s, 3H), 1.72 (s, 3H), 1.07 (d, J = 7.0 Hz, 3H). Data for **22b**. ^{1}H NMR ($CDCl_3$): δ 8.60 (d, J = 5.1 Hz, 1H), 7.45 (d, J = 7.4 Hz, 2H), 7.39−7.21 (m, 6H), 7.10 (d, J = 5.1 Hz, 1H), 5.41 (s, 1H), 4.93 (d, J = 3.1, 1H), 3.20 (m, 1H), 2.57 (s, 3H), 2.30 (s, 3H) 0.88 (d, J = 7.0 Hz, 3H). ESI-HRMS (MH^+/z): 370.1875 (calcd for $C_{22}H_{25}N_3O$ + Na 370.1895).

Reaction between 5-Methyl-2-oxo-3-phenylisoxazolo-[2,3-*a*]pyrimidines (1b) and 2-(Methylamino)ethanol. 2-(Methylamino)ethanol (0.08 g, 0.96 mmol) was dissolved in dioxane (10 mL). 5-Methyl-2-oxo-3-phenylisoxazolo[2,3-*a*]pyrimidines (**1b**) (0.2 g, 0.87 mmol) was added, and the mixture was refluxed in conditions described above for 18 h. The solvent was removed by evaporation in a vacuum. The residue was purified on silica gel column, eluted with ethyl acetate−petroleum ether gradient, yield 0.13 g of **24** (oil, 57%). ^{1}H NMR ($CDCl_3$): δ 8.53 (d, J = 5.1 Hz, 1H), 7.49 (dd, J_1 = 8.3 Hz, J_2 = 1.4 Hz, 2H), 7.32−7.23 (m, 3H), 6.99 (d, J = 5.1 Hz, 1H), 4.83 (s, 1H), 3.70−3.54 (m, 2H), 2.66−2.48 (m, 2H), 2.55 (s, 3H), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 170.1, 167.5, 156.9, 139.89, 129.0, 128.3, 127.6, 118.8, 59.1, 56.5, 40.2, 24.1. ESI-HRMS (MH^+/z): 280.1411 (calc for $C_{15}H_{19}N_3O$ + Na 280.1425).

Reaction between 5-Methyl-2-oxo-3-phenylisoxazolo-[2,3-*a*]pyrimidines (1b) and (*S*)-2-(Cyclohexadien-1-yl)-*N*-methyl-2-propanamine. (*S*)-2-(Cyclohexadien-1-yl)-*N*-methyl-2-propanamine[13] (0.21 g, 1.39 mmol) was dissolved in dioxane (15 mL). 5-Methyl-2-oxo-3-phenylisoxazolo[2,3-*a*]pyrimidines (**1b**) (0.28 g, 1.24 mmol) was added, and the mixture was refluxed in the conditions described above for 18 h. The solvent was removed by evaporation in a vacuum. The ratio of isomers was determined by NMR, and the residue was loaded on a silica gel column and eluted with ethyl acetate−petroleum ether gradient (20−60%). First eluted isomer, **26a** (0.2 g of isolated isomer, 43% yield). ^{1}H NMR ($CDCl_3$): δ 8.51 (d, J = 5.1 Hz, 1H), 7.61 (dd, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 2H), 7.23−7.15 (m, 3H), 6.86 (d, J = 5.1 Hz, 1H), 5.57 (br s, 2H), 5.29 (br s, 1H), 4.89 (s, 1H), 2.82 (m, 1H), 2.58 (m, 2H), 2.43 (s, 3H), 2.33 (m, 4H), 2.08 (s, 3H), 0.96 (d, J = 6.6 Hz, 3H). Anal. Calcd for $C_{22}H_{27}N_3$: C, 79.24; H, 8.16; N, 12.60. Found: C, 79.39; H, 7.91; N, 12.51. Second isomer, **26b** (0.084 g of isolated isomer, hygroscopic oil, 18% yield). ^{1}H NMR ($CDCl_3$): δ 8.53 (d, J = 5.1 Hz, 1H), 7.61 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 2H), 7.28−7.18 (m, 3H), 6.92 (d, J = 5.1 Hz, 1H), 5.60 (br s, 2H), 5.31 (br s, 1H), 4.89 (s, 1H), 2.89−2.84 (m, 1H), 2.64−2.59 (m, 2H), 2.47 (s, 3H), 2.37−2.32 (m, 4H), 2.10 (s, 3H), 0.87 (d, J = 6.3 Hz, 3H). Anal. Calcd for $C_{22}H_{27}N_3$·0.5HOH: C, 77.15; H, 8.24; N, 12.27. Found: C, 77.38; H, 7.97; N, 12.49.

Dimerization of 5,7-Dimethyl-2-imino-3-phenylisoxazolo[2,3-*a*]pyrimidine (27). Formation of 30. 5,7-Dimethyl-2-imino-3-phenylisoxazolo[2,3-*a*]pyrimidine (**27**)[14] (0.22 g, 0.78 mmol) was dissolved in dry dioxane (10 mL). The solution was refluxed for 2 h. After sitting overnight at room temperature an orange solid precipitated. The solid proved to be by TLC a mixture of two products. Separation by silica gel column resulted in a red product (0.08 g, dec 260−265°), which came first out of the column. ^{1}H NMR of the red product (300 MHz, DMSO-d_6): δ 11.42 (br s, 1H, NH), 7.96 (d, J = 7.5 Hz, 2H, *o*-Ph), 7.35 (t, J = 7.5 Hz, 2H, *m*-Ph), 7.12 (t, J = 7.5 Hz, 1H, *p*-Ph), 5.85 (s, 1H), 2.59 (s, 3H), 2.20 (s, 3H). Also eluted was a yellow product (**30**, 0.09 g, mp 283°). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.48 (s, 2H), 7.84 (m, 2H), 6.93−6.88 (m, 6H, Ph), 6.54 (s, 2H, pyrimidine), 2.43 (s, 12H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 169.2, 154.7, 134.0, 124.9, 120.6, 119.7, 118.6, 108.4, 107.7, 86.4. ESI-HRMS (MH^+/z): 477.2030 (calcd for $C_{28}H_{24}N_6O_2$ + H 477.2038).

2-Acetylimino-5,7-dimethyl-3-phenylisoxazolo[2,3-*a*]-pyrimidine (32). 5,7-Dimethyl-2-imino-3-phenylisoxazolo[2,3-*a*]pyrimidine[14] (**27**, 0.3 g, 1.25 mmol) was dissolved in acetic anhydride (1 mL). After 10 min a yellow precipitate appeared. The mixture was stirred for additional 1 h at room temperature, the precipitate collected and washed with ether, mp 138° (0.31 g, 88%). ^{1}H NMR ($CDCl_3$): δ 8.31 (d, J = 7.6 Hz, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.21 (t, J = 7.6 Hz, 1H), 6.34 (s, 1H), 2.59 (s, 3H), 2.51 (s, 3H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 178.9, 169.7, 161.9, 151.2, 145.7, 129.3, 128.0, 126.7, 126.1, 107.6, 88.6, 27.8, 25.2, 15.4. Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.33; H, 5.42; N, 14.57.

Reaction of 2-Acetylimino-5,7-dimethyl-3-phenylisoxazolo[2,3-*a*]pyrimidine (32) with Water. 2-Acetylimino-5,7-dimethyl-3-phenylisoxazolo[2,3-*a*]pyrimidine (**32**, 0.2 g, 0.7 mmol) was dissolved in dioxane (9 mL), water was added (0.5 mL), and the solution was refluxed for 3 h. The solvent was evaporated, and the residue was loaded on a silica gel column. The column was eluted with petroleum ether−ethyl acetate gradient. Two products were isolated, the ring opening product (**33**) and its hydrolysis product (**34**). Ring opening product (**33**): mp 116° (0.1 g, 50%). ^{1}H NMR ($CDCl_3$): δ 7.88 (d, J = 8.1 Hz, 2H), 7.39−7.31 (m, 3H), 7.02 (s, 1H), 6.65 (br s, 1H), 2.54 (s, 6H), 2.46 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 172.2, 169.7, 167.0, 164.6, 138.9, 128.0, 127.7, 126.7, 119.3, 79.7, 24.9, 23.7. Anal. Calcd for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 63.98; H, 5.79; N, 13.96. Data for **34**: mp 132° (0.05 g, 27%). ^{1}H NMR ($CDCl_3$): δ 7.77 (dd, J_1 = 6.60 Hz, J_2 = 1.75 Hz, 2H), 7.32−7.26 (m, 3H), 6.97 (s, 1H), 6.45 (br s, 1H), 2.51 (s, 6H). Structure determined by single-crystal X-ray diffraction. Crystallographic protocol and data are included in Supporting Information.

Reaction of 2-Acetylimino-5,7-dimethyl-3-phenylisoxazolo[2,3-*a*]pyrimidine (32) with Amines and Amino Amides. 2-acetylimino-5,7-dimethyl-3-phenylisoxazolo[2,3-*a*]-pyrimidine (**32**, 0.2 g, 0.7 mmol) was dissolved in dioxane (10 mL), the amine or amino amide (0.77 mmol) was added, and the solution was refluxed for 2−4 h. The disappearance of **32** was monitored by TLC. The solvent was removed, and the residue was loaded on a silica gel column and eluted with petroleum ether−ethyl acetate gradient.

Data for **37**: oil (45%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.06 (br d, J = 6.7 Hz, 1H), 7.09−7.34 (m, 10H), 6.99 (s, 1H), 4.63−4.60 (m, 1H), 2.31 (s, 6H), 2.29 (s, 3H), 0.81 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 171.6, 168.1, 167.7, 154.2, 143.3, 137.7, 129.1, 128.9, 128.8, 128.3, 127.9, 126.7, 119.5, 63.4, 50.9, 24.3, 24.1, 20.5. ESI-HRMS (MH^+/z): 403.2131 (calcd for $C_{24}H_{26}N_4O_2$ + H 403.2133).

Data for **38**: oil (22%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.09 (br d, J = 6.4 Hz, 1H), 7.26−7.05 (m, 10H), 6.97 (s, 1H), 4.60−4.53 (m, 1H), 2.44 (s, 6H), 2.29 (s, 3H), 1.52 (d, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 171.1, 167.7, 167.1, 154.1, 142.0, 136.5, 128.5, 128.4, 128.3, 127.7, 127.1, 126.4, 118.93, 62.8, 50.8, 23.8, 23.7, 21.7. ESI-HRMS (MH^+/z): 403.2133 (calcd for $C_{24}H_{26}N_4O_2$ + H 403.2133).

Data for **39**: hygroscopic oil (50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.10 (br d, J = 6.6 Hz, 1H), 7.35−7.09 (m, 10H), 6.99 (s, 1H), 4.62 (m, 1H), 2.32 (s, 6H), 2.30 (s, 3H), 0.81 (d, J = 6.6 Hz, 3H). Anal. Calcd for $C_{24}H_{26}N_4O_2 \cdot 1.5\ H_2O$: C, 67.11; H, 6.81; N, 13.05. Found: C, 66.85; H, 6.91; N, 12.88.

Data for **40**: mp 188° (33%). ^{1}H NMR (300 NHz, $CDCl_3$): δ 10.10 (br d, J = 6.3 Hz, 1H), 7.26−7.05 (m, 10H), 6.97 (s, 1H), 4.56 (m, 1H), 2.44 (s, 6H), 2.32 (s, 3H), 1.52 (d, J = 6.9 Hz, 3H). Anal. Calcd for $C_{24}H_{26}N_4O_2$: C, 71.62; H, 6.51; N, 13.92. Found: C, 71.53; H, 6.49; N, 13.76.

Data for **41** and **42**: oil (72%). Major isomer in the inseparable mixture ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.52 (br d, J = 6.9 Hz, 1H), 7.24−7.16 (m, 5H), 6.98 (s, 1H), 5.50 (d, J = 7.5 Hz, 1H), 4.08 (q, J = 7.0 Hz, 1H), 3.53−3.48 (m, 1H**)**, 2.53 **(**s, 6H), 2.25 (s, 3H), 1.81−1.14 (m, 11H), 0.76 (d, J = 7.0 Hz). Minor isomer in the inseparable mixture ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.32 (br d, J = 7.2 Hz, 1H), 7.04−6.9 (m, 5H), 6.95 (s, 1H), 6.17 (br d, J = 8.1 Hz, 1H), 3.76 (q, J = 7.0 Hz, 1H), 3.74−3.67 (m, 1H), 2.52 **(**s, 6H), 2.25 (s, 3H), 1.81−1.14 (m, 11H), 1.32 (d, J = 7.0 Hz, 3H). Anal. Calcd for $C_{25}H_{33}N_5O_3 \cdot 2H_2O$ C, 61.58; H, 7.65; N, 14.34. Found: C, 61.31; H, 7.36; N, 14.64.

Data for **43**: hygroscopic solid (45%). $[\alpha]^{25}_D$ = −116.04° ($CHCl_3$, c = 2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.31 (br d, J = 8.4 Hz, 1H), 7.26−7.17 (m, 5H), 6.95 (s, 1H), 5.73 (br d, J = 8.1 Hz, 1H), 3.70−3.65 (m, 2H), 2.58 (s, 6H), 2.28 (s, 3H), 1.78−1.13 (m, 11H), 0.53 (d, J = 6.9 Hz, 6H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.5, 168.4, 167.3, 167.2, 154.7, 136.0, 129.5, 128.1, 127.7, 119.0, 62.8, 60.5, 48.0, 33.0, 32.6, 32.2, 25.4, 24.7, 24.5, 23.8, 23.3, 19.0, 18.7. ESI-HRMS (MH^+/z): 502.2777 (calcd for $C_{27}H_{37}N_5O_3$ + Na 502.2794).

Data for **44**: mp 138° (27%). $[\alpha]^{25}_D$ = +20.76° ($CHCl_3$, c = 2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.62 (br d, 1H), 7.26−7.17 (m, 5H), 6.99 (s, 1H), 5.74 (br d, J = 8.1 Hz), 3.62−3.56 (m, 2H), 2.55 (s, 6H), 2.29 (s, 3H), 1.74−1.25 (m, 11H), 1.01 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 171.2, 169.5, 167.5, 167.4, 155.4, 136.9, 128.4, 128.1, 127.8, 119.1, 62.8, 61.0, 48.1, 33.1, 33.0, 30.3, 25.4, 24.7, 23.9, 23.9, 18.8, 18.3. ESI-HRMS (MH^+/z): 502.2787 (calcd for $C_{27}H_{37}N_5O_3$ + Na 502.2794).

(3*E*)-1-Acetyl-3-(4,6-dimethylpyrimidin-2(1*H*)-ylidene)-1,3-dihydro-2*H*-indol-2-one (45c). This product was obtained upon heating of 2-acetylimino-5,7-dimethyl-3-phenylisoxazolo[2,3-*a*]pyrimidine (**32**) with (−)-ephedrine as a nucleophile; 0.13 g of **32** (0.45 mmol) was heated in boiling dioxane (10 mL) with (−)-ephedrine (0.08 g, 0.45 mmol) for 10 h. The solvent was evaporated. Upon silica gel column chromatography (as above), ephedrine was recovered unchanged. In one of the fractions, red crystal separated upon concentration: mp 185° (0.05 g). ^{1}H NMR ($CDCl_3$): δ 8.31 (d, J = 7.5 Hz, 1H), 8.16 (d, J = 7.50 Hz, 1H), 7.22 (t, J = 7.5 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 6.35 (s, 1H), 2.8 (s, 3H), 2.56 (s, 3H), 2.46 (s, 3H).

Single-Crystal X-ray Diffraction Analysis of 45c. A single crystal was coated with vaseline, attached to a glass fiber, and transferred to a Bruker SMART APEX CCD X-ray diffractometer system controlled by a pentium-based PC running the SMART software package.[1] The crystal was mounted on the three-circle goniometer with χ fixed at +54.72° and was rapidly cooled to −150 °C with a Bruker KRYOFLEX nitrogen cryostat. The diffracted graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) was detected on a phosphor screen held at a distance of 6.0 cm from the crystal operating at −44 °C. A detector array of 512 × 512 pixels, with a pixel size of approximately 120 μm, was employed for data collection. The detector centroid and crystal-to-detector distance were calibrated from a least-squares analysis of the unit cell parameters of a carefully centered YLID reference crystal. Empirical formula $C_{16}H_{15}N_3O_2$. Further steps, crystal data, and structure refinements are given in Supporting Information. Bond lengths, angles, discrepancy indices, standard calibrations, data formats, positional parameters, and structure factors, and U values are also included in Supporting Information.

Supporting Information Available: General experimental data, general procedure for the preparation of amino acid amides, copies of ^{1}H NMR spectra of reaction mixtures of ring opening products; ^{1}H NMR, ^{13}C NMR, and high-resolution MS of most of the products; and protocols, data, and Ortep of single-crystal X-ray diffraction of compounds **34** and **45c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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