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Synthesis and Absolute Configuration of Novel *N*,*O*-Psiconucleosides Using (*R*)-*N*-Phenylpantolactam as a Resolution Agent

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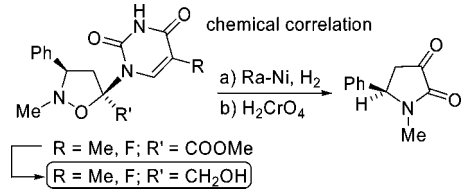

A series of novel *N*,*O*-psiconucleosides has been prepared in both enantiomeric forms by resolution of an advanced racemic synthetic intermediate using (*R*)-*N*-phenylpantolactam as a chiral resolution agent. The absolute configuration of all of these compounds has been unequivocally established by chemical correlation with the novel (*R*)- or (*S*)-1-methyl-5-phenylpyrrolidine-2,3-dione, prepared from the known (*R*)- and (*S*)-1-methyl-5-phenylpyrrolidin-2-one, respectively.

Introduction

Pantolactone is an efficient chiral auxiliary in Diels−Alder reactions.[1] In sharp contrast, only a few examples of the use of (*R*)-pantolactone as chiral auxiliary in 1,3-dipolar cycloadditions have been described,[2–4] and the attained levels of asymmetric induction were low to moderate [10−50% diastereomeric excesses (de)]. Several years ago we described the enantioselective synthesis of (*R*)- and (*S*)-3-hydroxy-4,4-dimethyl-1-phenylpyrrolidin-2-one [(*R*)- and (*S*)-*N*-phenylpantolactam, (*R*)- and (*S*)-**1**, Figure 1] as novel chiral auxiliaries,[5,6] related to pantolactone, and their efficient use in asymmetric Diels−Alder reactions.[7] However, (*R*)- and (*S*)-**1** have never been used in 1,3-dipolar cycloadditions.

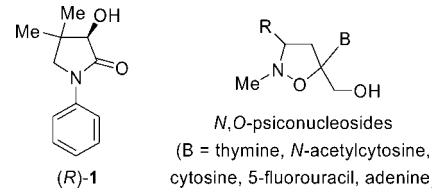

FIGURE 1. Structures of (*R*)-*N*-phenylpantolactam, (*R*)-**1**, and the *N*,*O*-psiconucleosides developed by the groups of Merino, Chiacchio, and Romeo.

This fact, together with our experience in the enantioselective synthesis of isoxazolidines through 1,3-dipolar cycloaddition of (*Z*)-α-phenyl-*N*-methylnitrone with enantiopure allylic fluorides under environmentally friendly conditions (microwave irradiation and metal triflate catalysis)[8] prompted us to consider the use of *N*-phenylpantolactam as a chiral auxiliary in 1,3-dipolar cycloadditions of nitrones with alkenes.

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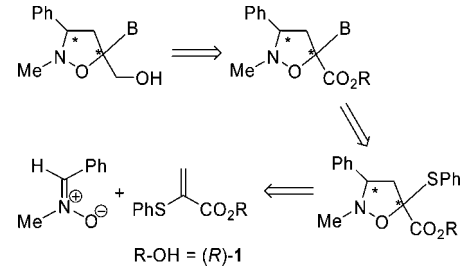
As a continuation of our recent interest on the use of (*R*)- and (*S*)-**1** as chiral auxiliaries for the synthesis of biologically active compounds,[9–11] we focused our attention on the synthesis of a series of *N*,*O*-psiconucleosides (Figure 1) through 1,3-dipolar cycloadditions of nitrones with alkenes. *N*,*O*-Psiconucleosides constitute a particular class of modified nucleosides bearing a heterocyclic system (isoxazolidine) instead of the ribose ring and branched at the anomeric carbon atom with a hydroxymethyl group, which could share the antiviral or anticancer activity observed for other *N*,*O*-nucleosides.[12–15]

To the best of our knowledge, the sole groups that have reported the synthesis of *N*,*O*-psiconucleosides (Figure 1) both in racemic[16–19] and in enantiopure[20] form are those of Chiacchio, Romeo, and Merino, who developed a synthetic procedure based on the 1,3-dipolar cycloaddition of a suitable nitrone with a 2-(acetoxy)acrylate, followed by a Vorbrüggen nucleosidation and $NaBH_4$ reduction of the ester group at the anomeric position to a hydroxymethyl function. The 1,3-dipolar cycloadditions carried out for the synthesis of these compounds proceeded with *cis*/*trans* selectivities ranging from 2.5:1 to 8.6:1. The sole example reported of enantioselective synthesis of *N*,*O*-psiconucleosides, which used a chiral nitrone derived from 2,3-*O*-isopropylidene-D-glyceraldehyde, afforded a moderate diastereofacial selectivity (*anti*/*syn* = 2.6:1). However, the absolute configuration of the isoxazolidine moiety was assumed on the basis of a theoretical study of the cycloaddition reaction[20] but was not unequivocally established by X-ray diffraction analysis of any intermediate or final product or by correlation with compounds of known absolute configuration.

Herein we report (1) a study on the potential use of (*R*)-**1** as a chiral auxiliary for the enantioselective synthesis of a novel series of *N*,*O*-psiconucleosides, which involves as the key step a 1,3-dipolar cycloaddition of a nitrone with an acrylate derived from (*R*)-**1**, according to the retrosynthetic analysis shown in Scheme 1; (2) the preparation of these *N*,*O*-psiconucleosides in enantiopure form by resolution of an advanced precursor using (*R*)-**1** as the resolving agent; and (3) the establishment of the absolute configuration of all of these compounds by correlation of advanced enantiopure intermediates with (*R*)- or (*S*)-1-methyl-5-phenylpyrrolidine-2,3-dione, whose preparation from (*R*)- and (*S*)-1-methyl-5-phenylpyrrolidin-2-one[21] is also herein described.

SCHEME 1. Retrosynthetic Analysis of the Novel *N*,*O*-Psiconucleosides Based on (*R*)-*N*-Phenylpantolactam as a Chiral Auxiliary



Results and Discussion

First, to study the regio- and the *endo*/*exo* stereoselectivity of the 1,3-dipolar cycloaddition we carried out the reaction with the known dipolarophile **8**[22] and the known nitrone **10**.[23] Methyl 2-phenylthioacrylate, **8**, was obtained from racemic methyl 2-bromopropionate, (±)-**2**, by reaction with sodium thiophenoxide, followed by oxidation of the resulting methyl 2-phenylthiopropionate, (±)-**3**, with $NaIO_4$ to give sulfoxide **6**, as a diastereoisomeric mixture of two racemic pairs (Scheme 2). Reaction of the mixture of sulfoxides **6** with an excess (1.9 equiv) of an equimolar mixture of Ac_2O and MsOH gave **8** in good yield, via a Pummerer rearrangement followed by AcOH elimination. Nitrone **10**, whose configuration is known to be (*Z*), was obtained as described[23] by reaction of benzaldehyde with *N*-methylhydroxylamine. Reaction of acrylate **8** and nitrone **10** in the presence of 10% indium(III) triflate under microwave irradiation gave a mixture of (±)-**11** and (±)-**14** in an approximate ratio of 7:3, with a modest 41% yield. The mixture could be separated by silica gel column chromatography, and each stereoisomer was fully characterized by spectroscopic means and HRMS. Compounds (±)-**11** and (±)-**14** correspond to the *exo*- and *endo*-adducts with respect to the ester function, respectively (Scheme 2). Noteworthy, when the cycloaddition reaction was carried out with conventional heating under reflux, yields were lower after much longer reaction times. Indeed, the use of microwave irradiation as an alternative mode of heating reaction mixtures in cycloaddition reactions has been reported to drastically reduce reaction times, increase yields, and modify product ratios.[24]

Cross signals in the NOESY experiment of (±)-**11** among the pairs of signals of 4-H_α/*C*-phenyl H_{ortho}, 4-H_β/3-H, and 4-H_β/*S*-phenyl H_{ortho}, the last one of low intensity, clearly support the *syn*-relationship among 4-H_α and the phenyl group at C3 and among 4-H_β and the phenylthio group at C5. The same conclusion was obtained from NOE difference experiments: (a) on irradiation at δ 2.83 ppm (4-H_β) a positive NOE was observed for the signals of 4-H_α (δ 3.20 ppm) and *S*-phenyl H_{ortho} (δ 7.62−7.65 ppm) and (b) on irradiation at δ 3.20 ppm

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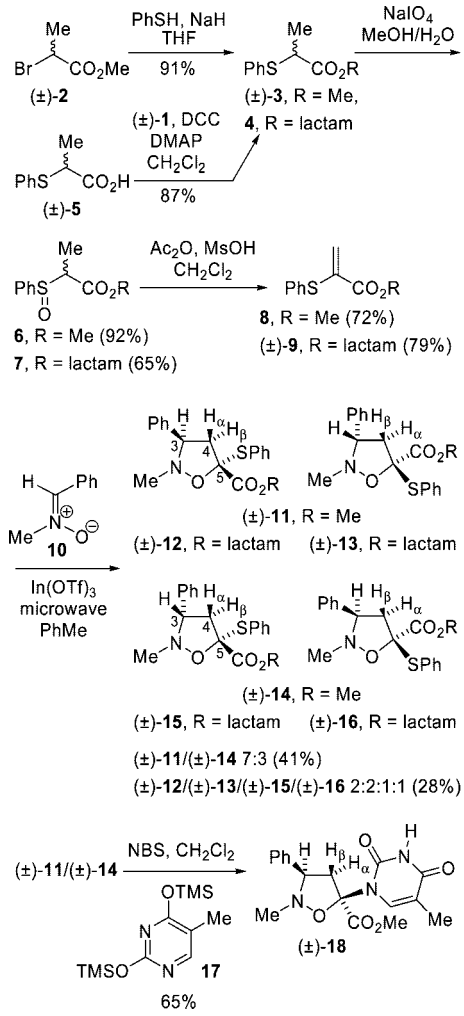
SCHEME 2. Study of the Diastereoselectivity of the 1,3-Dipolar Cycloaddition of Nitrone 10 and Acrylates 8 and (±)-9



(4-H_α) a positive NOE was observed for the signals of 4-H_β (δ 2.83 ppm) and *C*-phenyl H_{ortho} (δ 7.24−7.32 ppm).

In the case of (±)-**14**, cross signals in the NOESY experiment among the pairs of signals of 4-H_β/*C*-phenyl H_{ortho} and 4-H_α/3-H were observed, among others. In this case, cross signals between 4-H_β or 4-H_α and *S*-phenyl H_{ortho} were not observed. However, the NOE difference experiments were conclusive: (a) on irradiation at δ 2.65 ppm (4-H_β) a positive NOE was observed for the signals of 4-H_α (δ 3.41 ppm), *C*-phenyl H_{ortho} (δ 7.40−7.44 ppm) and *S*-phenyl H_{ortho} (δ 7.61−7.65 ppm), and (b) on irradiation at δ 3.41 ppm (4-H_α) a positive NOE was observed for the signal of 4-H_β (δ 2.65 ppm), but not for the signals of *C*-phenyl H_{ortho} and *S*-phenyl H_{ortho}.

Worthy of note, reaction of the mixture of (±)-**11** and (±)-**14** with the commercially available *O*,*O*-bis(trimethylsilyl)thymine, **17**, and NBS gave a crude product from which *N*,*O*-nucleoside (±)-**18** was isolated by silica gel column chromatography in 65% yield. The relative configuration of (±)-**18** was established as before through NOE experiments and corresponded to the β-anomer (nucleobase and phenyl group in a *cis*-relationship). In the NOESY experiment, cross signals among the pairs of protons 4-H_β/*C*-phenyl H_{ortho} and 3-H/4-H_α were observed among others. As in the case of (±)-**14**, the NOE difference experiments on (±)-**18** were conclusive: (a) on irradiation at δ 2.62 ppm (4-H_β) a positive NOE was observed for the signals of 4-H_α (δ 4.13 ppm), *C*-phenyl H_{ortho} (δ 7.03 ppm) and pyrimidinedione 6-H (δ 7.63 ppm), and (b) on irradiation at δ 4.13 ppm (4-H_α) a positive NOE was only observed for the signals of 4-H_β (δ 2.62 ppm) and 3-H (δ 3.75 ppm). The preferential formation of (±)-**18** is in agreement with reported results in closely related cases.[17] β-Anomers of nucleosides derived from pyrimidine bases are preferentially formed at room temperature, and these were the sole stereoisomers observed under equilibration conditions at 45 °C.[17]

To study the effect of the chiral auxiliary on the facial selectivity of the 1,3-dipolar cycloaddition, we synthesized the α-phenylthioacrylate derived from racemic *N*-phenylpantolactam, (±)-**9**, as the dipolarophile (Scheme 2). Racemic 2-phenylthiopropionic acid, (±)-**5**, prepared by reaction of racemic ethyl 2-bromopropionate with sodium thiophenoxide[25] followed by saponification,[26] was esterified with (±)-**1** in the presence of DCC under DMAP catalysis to give in high yield the corresponding ester **4**, as a diastereomeric mixture of two racemic pairs in an approximate ratio of about 7:3 (^{1}H NMR), which indicates partial epimerization of the α-ester stereogenic center during the esterification. This mixture was oxidized as such with $NaIO_4$ to give in good yield sulfoxide **7**, as a diastereomeric mixture of four racemic pairs. Reaction of the mixture of sulfoxides **7** with an excess (1.6 equiv) of an equimolar mixture of Ac_2O and MsOH in CH_2Cl_2 under reflux gave (±)-**9** in high yield. Reaction of nitrone **10** and acrylate (±)-**9** was carried out as before in toluene solution using indium(III) triflate as the catalyst under microwave irradiation. From this reaction, a stereoisomeric mixture of racemic cycloadducts **12**, **13**, **15**, and **16** was isolated in only 28% yield, after column chromatography. Substantial amounts of (±)-**1** (41%) were also isolated, arising from hydrolysis of the ester function either in the starting (±)-**9** or in the products formed in the cycloaddition process. In the ^{1}H NMR spectrum of the mixture of racemic cycloadducts **12**, **13**, **15**, and **16**, four singlets were observed in the range 5.25−5.40 ppm corresponding to the 3-H proton of the pantolactam moiety of the four diastereomeric racemic pairs. From the integral of these signals, an approximate ratio for these cycloadducts (±)-**12**/(±)-**13**/(±)-**15**/(±)-**16** = 2:2:1:1 was obtained. Taking into account the regio- and stereoselectivity observed in the cycloaddition of **8** and **10** and the configuration of one of the minor cycloadducts derived from (*R*)-**1**, which was obtained in pure form by a different procedure (compound **26** or **27**, see below), the main diastereomers of the above mixture must be the *exo*-adducts with respect to the ester function (±)-**12** and (±)-**13**.

Since *N*-phenylpantolactam did not influence the facial diastereoselectivity of the 1,3-dipolar cycloaddition of nitrone **10** and acrylate (±)-**9**, we planned the use of (*R*)-**1** as a resolution agent for the preparation of enantiopure *N*,*O*-psiconucleosides as shown in Scheme 3. The resolution agent would be introduced in a late stage of the synthetic sequence, just prior to the separation of the diastereomeric esters **20** and **21**, to improve its recovery. However, although saponification of (±)-**18** gave the corresponding carboxylic acid, (±)-**19**, attempted esterification of this acid with (*R*)-**1**, using DCC and DMAP as catalyst, failed (Scheme 3).

Taking into account that this result could be due to the steric hindrance of the carboxylic acid (±)-**19**, we decided to introduce

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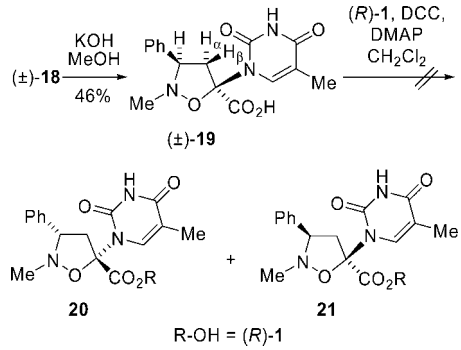
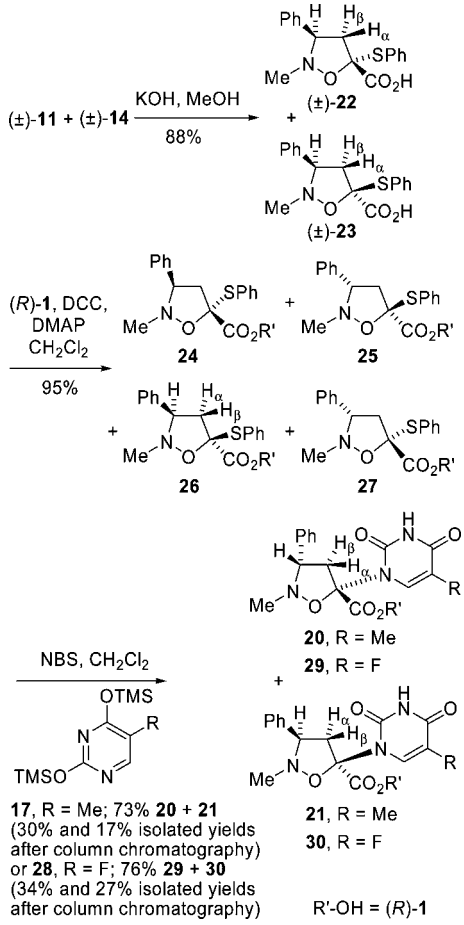
SCHEME 3. Attempted Esterification of Acid (±)-19 with (*R*)-1



SCHEME 4. Preparation of Enantiopure Precursors of *N*,*O*-Psiconucleosides



the resolution agent in the precursor of (±)-**18**, i.e., the diastereomeric mixture (±)-**11** and (±)-**14**, since the phenylthio group at the α-carboxylic position is less bulky than the thymine substituent. Saponification of the diastereomeric mixture of (±)-**11** and (±)-**14** gave the corresponding mixture of acids, (±)-**22** and (±)-**23**, which was reacted as such with the resolution agent (*R*)-**1** to give in good yield the corresponding mixture of diastereomeric esters **24**−**27** (Scheme 4). Upon purification of this mixture by silica gel column chromatography, most of the product (94% yield) eluted as a diastereomeric mixture of **24**/**25**/**26**/**27** in an approximate ratio of 3:3:1:1. The main components of the mixture, **24** and **25**, corresponded to the *exo*-adducts with respect to the ester function. A small amount of the product (about 1% yield) eluted as one of the minor diastereomers **26** or **27** and was fully characterized, except for the absolute configuration of the two stereogenic centers of the isoxazolidine ring.

The diastereomeric mixture of **24**−**27** was reacted as such with *O*,*O*-bis(trimethylsilyl)thymine, **17**, and NBS, as before, to give a mixture of only two diastereomeric *N*,*O*-nucleosides, the β-anomers **20** and **21** in a ratio of 1:1 (Scheme 4), which could be separated by silica gel column chromatography. At this stage, their absolute configuration being unknown, each anomer was merely distinguished by the elution time and by the $[\alpha]^{20}_D$ value. Thus in the case of **20** and **21**, the first eluted product (R_f 0.18, CH_2Cl_2/MeOH 6:1) had an $[\alpha]^{20}_D$ −67.0 (*c* 0.25, AcOEt) and the second eluted product (R_f 0.12) had an $[\alpha]^{20}_D$ +1.1 (*c* 0.19, AcOEt).

Similarly, the mixture of **24**−**27** was reacted with *O*,*O*-bis(trimethylsilyl)-5-fluorouracil, **28**, prepared as described previously,[27] and NBS to give a mixture of the β-anomers of the corresponding *N*,*O*-nucleosides **29** and **30** in a ratio of 1:1, which was efficiently separated by silica gel column chromatography (Scheme 4). As before, at this stage, anomers **29** and **30** were distinguished by the elution time and by the $[\alpha]^{20}_D$ value. The first eluted product (R_f 0.31, CH_2Cl_2/MeOH 6:1) had an $[\alpha]^{20}_D$ −48.0 (*c* 0.39, AcOEt) and the second eluted product (R_f 0.21) had an $[\alpha]^{20}_D$ −18.1 (*c* 0.22, AcOEt).

Attempts to carry out the reduction of the ester function of **20** with $NaBH_4$ in MeOH at 0 °C for 30 min, as described in a related case,[19,20] left the starting compound unchanged. When this reaction was carried out at 50 °C for 48 h, transesterification took place, the methyl ester (−)-**18** being formed. Consequently, we decided to carry out first the transesterification of compounds **20**, **21**, **29**, and **30** with K_2CO_3 in MeOH. In this way we obtained in good yields the corresponding methyl esters (−)-**18**, (+)-**18**, (−)-**31**, and (+)-**31**, respectively, with complete recovery of the resolution agent (*R*)-**1**. Reduction of the ester function of compounds (−)-**18**, (+)-**18**, (−)-**31**, and (+)-**31**, was carried out cleanly in moderate yields by reaction with a 65% toluene solution of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al), thus obtaining the corresponding *N*,*O*-psiconucleosides (−)-**32**, (+)-**32**, (−)-**33**, and (+)-**33**, respectively (Scheme 5).

All attempts to obtain a single crystal for X-ray diffraction analysis of the foamy esters **20**, **21**, **29**, and **30** were fruitless. Consequently, to establish the absolute configuration of the esters **20**, **21**, **29**, **30**, (−)- and (+)-**18**, and (−)- and (+)-**31**, we planned the correlation study shown in Scheme 6.

Hydrogenation of pantolactam esters **20**, **21**, **29**, or **30** or methyl esters **18** or **31** could give alcohols **34** and **35** through the shown intermediates,[28] which imply (1) reduction of the isoxazolidine N−O bond, (2) thymine or 5-fluorouracil elimination to give the corresponding ketone, (3) hydrogenation of the ketone function to alcohol, and (4) condensation of the secondary amine formed in the first step with the ester function leading to the lactam ring. Throughout this transformation, the configuration of C3 of the initial isoxazolidine derivative is retained, while the configuration of C5 is lost. On the other hand, the closely related lactams (+)- and (−)-**37** are known oily compounds,[21] what allows a correlation between these known compounds and those obtained by hydrogenation of the enan-

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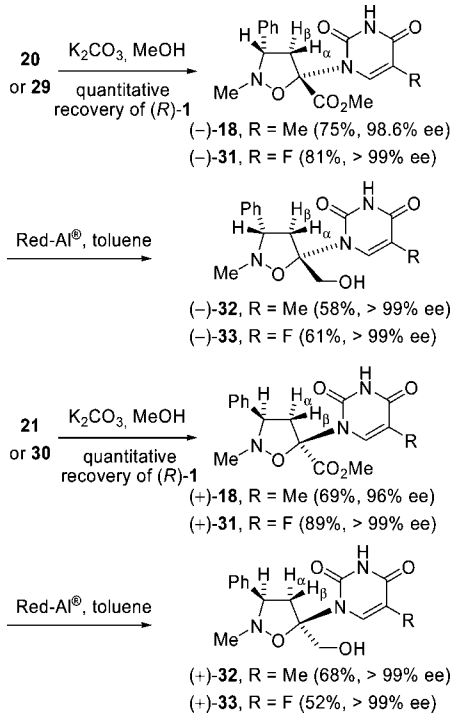
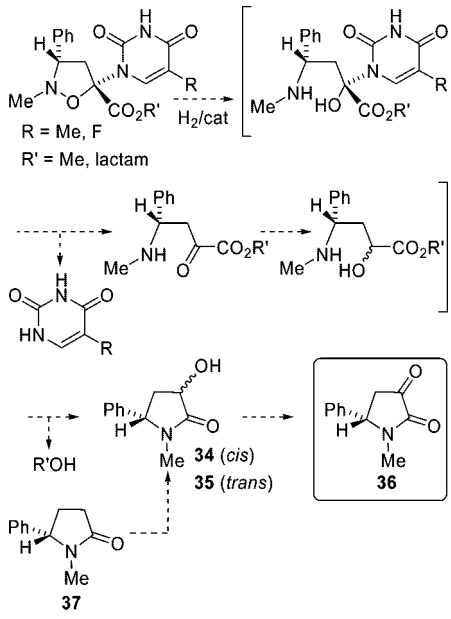
SCHEME 5. Preparation of Enantiopure *N,O*-Psiconucleosides



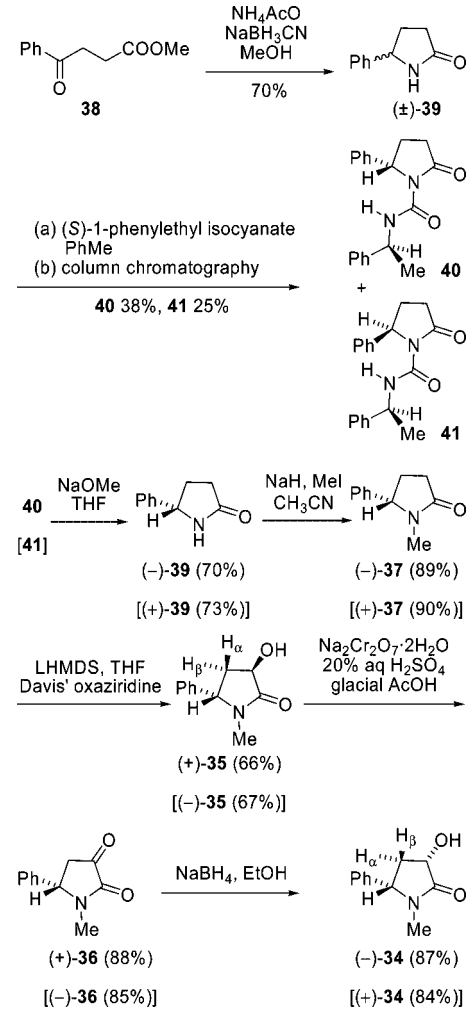
SCHEME 6. Proposed Correlation among the Ester Precursors of *N,O*-Psiconucleosides and Known Lactams (+)- and (−)-37, through their Conversion into New Ketolactams 36



tiopure isoxazolidine esters. For strategic reasons, we decided to carry out the correlation at the level of the pyrrolidine-2,3-dione **36**, which (1) contains only one stereogenic center, the one corresponding to C3 in the starting isoxazolidine ester, and (2) could be a solid compound, as it is the case for the known racemic mixture.[29] Conversion of **37** to the pyrrolidine-2,3-dione **36** could be carried out by α-hydroxylation of the lactam α-position followed by chromic acid oxidation.[29]

(29) Dagne, E.; Castagnoli, N., Jr. *J. Med. Chem.* **1972**, *15*, 356–360.

SCHEME 7. Preparation of the Enantiopure Ketolactams (+)- and (−)-36



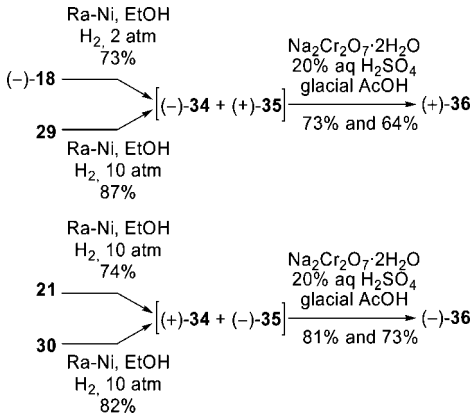
(*R*)- and (*S*)-1-methyl-5-phenylpyrrolidine-2,3-dione, (−)- and (+)-**36**, were prepared as shown in Scheme 7. Methyl 4-oxo-4-phenylbutanoate, **38**, prepared by reaction of the corresponding acid with MeOH under acidic catalysis,[30] was subjected to reductive amination by reaction with ammonium acetate in MeOH using $NaBH_3CN$ as the reducing agent. From this reaction, the known[31] racemic 5-phenyl-γ-butyrolactam, (±)-**39**, was directly isolated in 70% yield. This compound had been previously prepared by a tedious procedure involving reductive amination of 4-oxo-4-phenylbutyric acid followed by cyclization of the obtained 4-amino-4-phenylbutyric acid using 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent) to activate the carboxylic group.[31] Resolution of (±)-**39** was carried out as previously described,[21] by (1) conversion into a mixture of diastereoisomeric derivatives **40** and **41** on reaction with (*S*)-1-phenylethyl isocyanate, (2) silica gel column chromatography separation of the diastereoisomers, and (3) methanolysis. The absolute configuration of **40** had been previously established as (5*S*,1′*S*) on the basis of NMR and chromatographic parameters.[21,32] In the present work, we have confirmed the

(30) Hilborn, J. W.; Jurgens, A. R.; Senanayake, C. H. U.S. patent 5936124, 1999.

(31) Nilsson, B. M.; Vargas, H. M.; Ringdahl, B.; Hacksell, U. *J. Med. Chem.* **1992**, *35*, 285–294.

(32) Pirkle, W. H.; Robertson, M. R.; Hyun, M. H. *J. Org. Chem.* **1984**, *49*, 2433–2437.

SCHEME 8. Chemical Correlation among Esters 18, 21, 29, and 30 with Ketolactams (+)- or (−)-36



previous assignment by X-ray diffraction analysis of a single crystal of the solid derivative **40** (Figure 1 of Supporting Information). Thus, its methanolysis product (−)-**39** should be (5*S*)-5-phenylpyrrolidin-2-one. Consequently, the oily derivative **41** and its methanolysis product (+)-**39** should have (5*R*)-configuration. Methylation of (−)- and (+)-**39** as described gave the corresponding compounds (−)- and (+)-**37**.[21] The α-hydroxylation of (−)-**37** was carried out with the Davis oxaziridine (*trans*-3-phenyl-2-phenylsulfonyloxaziridine).[33,34] Thus, reaction of (−)-**37** with LHMDS followed by reaction of the resulting lithium enolate with the Davis oxaziridine gave, after column chromatography, a solid product containing mainly (3*R*,5*S*)-*trans*-3-hydroxy-1-methyl-5-phenylpyrrolidin-2-one, (+)-**35**, together with a small amount of the corresponding *cis*-stereoisomer (^{1}H NMR). An analytically pure sample of (+)-**35** was obtained by crystallization of the crude product from Et_2O/AcOEt. Chromic acid oxidation[29] of a mixture of alcohols, from the oxidation of (−)-**37** with the Davis oxaziridine, gave in good yield the corresponding (5*S*)-1-methyl-5-phenylpyrrolidine-2,3-dione, (+)-**36**. Reduction of (+)-**36** with $NaBH_4$ in MeOH gave a solid mixture containing mainly the (3*S*,5*S*)-*cis*-3-hydroxy-1-methyl-5-phenylpyrrolidin-2-one, (−)-**34**, which was obtained in pure form by crystallization from Et_2O/AcOEt. Although, the ^{1}H NMR data of the *cis*-alcohol (−)-**34** coincided with those described for (±)-**34**,[29] the *cis*-configuration of (−)-**34** was clearly established by NOESY experiments, thus confirming the relative stereochemistry of both alcohols **34** and **35**.

Similarly, oxidation of (+)-**37** with the Davis oxaziridine gave mainly *trans*-alcohol (−)-**35**, which on oxidation with chromic acid gave dione (−)-**36** from which *cis*-alcohol (+)-**34** was obtained on reduction with $NaBH_4$ in MeOH. Compounds (−)- and (+)-**34**, (+)- and (−)-**35**, and (+)- and (−)-**36** are all new compounds that have been fully characterized.

Knowing the absolute configuration of ketones (+)- and (−)-**36**, we carried out the correlation study shown in Scheme 8. Thus, Ra-Ni hydrogenation of methyl ester (−)-**18** gave a diastereomeric mixture of alcohols, containing mainly a *cis*-alcohol, which after oxidation with chromic acid gave ketone (*S*)-(+)-**36**. Since the configuration of the isoxazolidine C3 carbon atom of (−)-**18** is not modified during its transformation into ketone (+)-**36**, the configuration of C3 in (−)-**18** should be (*S*). Moreover, since the relative configuration in (−)-**18** was previously known (phenyl and thymine groups in a *cis*-relationship), its absolute configuration should be (3*S*,5*S*).

Also, Ra-Ni reduction of pantolactam ester **21** followed by column chromatography gave a mixture of alcohols, which after chromic acid oxidation gave ketone (*R*)-(−)-**36**. Consequently, the absolute configuration of **21** should be (3*R*,5*R*,3′*R*). In a similar way, in the 5-fluorouracil series, from pantolactam ester **29**, ketone (+)-**36** was obtained. Thus, the absolute configuration of **29** should be (3*S*,5*S*,3′*R*). Similarly, from pantolactam ester **30**, ketone (−)-**36** was obtained. Consequently, the absolute configuration of **30** should be (3*R*,5*R*,3′*R*). Knowing the absolute configuration of the above esters [(3*S*,5*S*)-(−)-**18**, (3*R*,5*R*,3′*R*)-(+)-**21**, (3*S*,5*S*,3′*R*)-(−)-**29**, and (3*R*,5*R*,3′*R*)-(−)-**30**], the absolute configuration of the rest of enantiopure compounds herein described could be easily deduced as follows: (3*R*,5*R*)-(+)-**18**, (3*S*,5*S*,3′*R*)-(−)-**20**, (3*S*,5*S*)-(−)-**31**, (3*R*,5*R*)-(+)-**31**, (3*S*,5*S*)-(−)-**32**, (3*R*,5*R*)-(+)-**32**, (3*S*,5*S*)-(−)-**33**, and (3*R*,5*R*)-(+)-**33**.

Antiviral Activity. Compounds (+)-**32**, (−)-**32**, and (−)-**33** were evaluated for antiviral activity against a wide variety of RNA and DNA viruses, including influenza (subtypes A/H1N1, A/H3N2 and B) in Madin Darby Canine Kidney (MDCK) cells; parainfluenza-3, reovirus-1, Sindbis virus, Coxsackie virus B4, Punta Toro virus in Vero cells; herpes simplex virus-1 (KOS), herpex simplex virus-2 (G), herpex simplex virus-1 (TK- KOS ACV^r), vaccinia virus, and vesicular stomatitis virus in human embryonic lung (HEL) fibroblast cells; vesicular stomatitis virus, Coxsackie virus B4, and respiratory syncytial virus in HeLa cells; and feline corona virus (FIPV) and feline herpes virus in Crandell-Rees Feline Kidney (CRFK) cells. None of these compounds showed activity against any of the above viruses at the highest concentration tested (100 μM).

Conclusion

We have developed a synthetic entry into enantiopure *N*,*O*-psiconucleosides using (*R*)-*N*-phenylpantolactam as a resolution agent, which is efficiently recovered. The absolute configuration of these *N*,*O*-psiconucleosides was unambiguously established through the conversion of significant intermediate esters into the new ketones (+)- and (−)-**36**. These ketones were independently synthesized in enantiopure form from the known lactams (−)- and (+)-**37**, by α-hydroxylation with the Davis oxaziridine followed by chromic acid oxidation. The absolute configuration of (−)-**37** was clearly established by X-ray diffraction analysis of its precursor **40**, thus confirming a previous assignment based on NMR and chromatographic parameters.[21,32]

Experimental Section

Diastereoisomeric Mixture of Methyl (3*R,5*R**)- and (3*R**,5*S**)-2-Methyl-3-phenyl-5-(phenylthio)isoxazolidine-5-carboxylate (±)-11 and (±)-14.** A solution of acrylate **8** (6.00 g, 30.9 mmol) in anhydrous toluene (24 mL) was placed in a microwave tube, nitrone **10** (4.60 g, 34.0 mmol, 1.1 equiv) and $In(OTf)_3$ (1.73 g, 3.12 mmol, 0.1 equiv) were added, the tube was closed and the reaction mixture was subjected to microwave irradiation at 110 °C (infrared detection) for 5 min. After evaporation of the toluene in vacuo, water (200 mL) was added and the mixture was extracted with AcOEt (3 × 200 mL). The combined organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a residue (9.1 g), which was subjected to column chromatography [silica gel (230 g), hexane/AcOEt mixtures]. On elution with a

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(34) Davis, F. A.; Chattopadhyay, S.; Towson, J. C.; Lal, S.; Reddy, T. *J. Org. Chem.* **1988**, *53*, 2087–2089.

mixture of hexane/AcOEt 90:10, a diastereomeric mixture of cycloadducts (±)-**11** and (±)-**14** in an approximate ratio of 7:3 (4.12 g, 41% yield) was isolated as a yellow oil. A part of the above mixture (220 mg) was subjected to column chromatography [silica gel (10 g), hexane/AcOEt mixtures]. On elution with hexane/AcOEt 94:6, (±)-**11** (21 mg, 5% yield) and a mixture of (±)-**11** and (±)-**14** (156 mg) were isolated as yellow oils. The last mixture was subjected to a new column chromatography [silica gel (10 g), hexane/AcOEt mixtures]. On elution with hexane/AcOEt 95:5, (±)-**14** (106 mg, 20% yield) was isolated as a yellow oil.

(±)-**11**: R_f 0.33 (hexane/AcOEt 4:1); IR (NaCl) ν 3061, 3031, 2996, 2952, 2920, 2850, 1734 (C=O st), 1603, 1584, 1495, 1474, 1439, 1276, 1257, 1199, 1137, 1113, 1089, 1050, 1016, 961, 918, 864, 829, 753, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.68 (s, 3H, *N*-CH_3), 2.83 (dd, $J_{4\text{-H}\alpha/4\text{-H}\beta}$ = 13.8 Hz, $J_{3\text{-H}/4\text{-H}\beta}$ = 7.5 Hz, 1H, 4-H$_\beta$), 3.20 (dd, $J_{4\text{-H}\alpha/4\text{-H}\beta}$ = 13.8 Hz, $J_{3\text{-H}/4\text{-H}\alpha}$ = 9.6 Hz, 1H, 4-H$_\alpha$), 3.54 (br signal, 1H, 3-H), 3.64 (s, 3H, OCH_3), 7.24−7.32 (complex signal, 5H, Ar-H *C*-phenyl), 7.32−7.43 (complex signal, 3H, Ar-H$_{meta}$ and Ar-H$_{para}$ *S*-phenyl), 7.62−7.65 (m, 2H, Ar-H$_{ortho}$ *S*-phenyl); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 43.6 (CH_3, *N*-CH_3), 49.1 (CH_2, C4), 52.8 (CH_3, OCH_3), 73.0 (CH, C3), 90.3 (C, C5), 127.8 (CH, Ar-C$_{ortho}$ *C*-phenyl), 128.2 (CH, Ar-C$_{para}$ *C*-phenyl), 128.6 (CH) and 128.8 (CH) (Ar-C$_{meta}$ *C*-phenyl and Ar-H$_{meta}$ *S*-phenyl), 129.7 (CH, Ar-C$_{para}$ *S*-phenyl), 129.9 (C, Ar-C$_{ipso}$ *C*-phenyl), 136.3 (CH, Ar-C$_{ortho}$ *S*-phenyl), 137.1 (C, Ar-C$_{ipso}$ *S*-phenyl), 170.3 (C, COO); HRMS calcd for $[C_{18}H_{19}NO_3S + H]^+$ 330.1164, found 330.1151.

(±)-**14**: R_f 0.37 (hexane/AcOEt 4:1); IR (NaCl) ν 3061, 3036, 2999, 2953, 2918, 2875, 2850, 1738 (C=O st), 1476, 1455, 1439, 1289, 1265, 1198, 1178, 1137, 1116, 1079, 1063, 1026, 986, 956, 854, 751, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.65 (dd, $J_{4\text{-H}\alpha/4\text{-H}\beta}$ = 13.8 Hz, $J_{3-\text{H}/4\text{-H}\beta}$ = 9.9 Hz, 1H, 4-H$_\beta$), 2.72 (s, 3H, *N*-CH_3), 3.41 (dd, $J_{4\text{-H}\alpha/4\text{-H}\beta}$ = 13.8 Hz, $J_{3\text{-H}/4\text{-H}\alpha}$ = 7.5 Hz, 1H, 4-H$_\alpha$), 3.51 (s, 3H, OCH_3), 3.59 (dd, $J_{3\text{-H}/4\text{-H}\beta}$ = 9.9 Hz, $J_{3\text{-H}/4\text{-H}\alpha}$ = 7.5 Hz, 1H, 3-H), 7.31−7.40 (complex signal, 6H, Ar-H$_{meta}$ and Ar-H$_{para}$ *S*-phenyl, Ar-H$_{meta}$ and Ar-H$_{para}$ *C*-phenyl), 7.40−7.44 (m, 2H, Ar-H$_{ortho}$ *C*-phenyl), 7.61−7.65 (m, 2H, Ar-H$_{ortho}$ *S*-phenyl); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 43.0 (CH_3, *N*-CH_3), 50.5 (CH_2, C4), 52.6 (CH_3, OCH_3), 72.9 (CH, C3), 92.0 (C, C5), 128.0 (CH, Ar-C$_{ortho}$ *C*-phenyl), 128.4 (CH, Ar-C$_{para}$ *C*-phenyl), 128.7 (CH) and 128.8 (CH) (Ar-C$_{meta}$ *S*-phenyl and Ar-H$_{meta}$ *C*-phenyl), 129.3 (CH, Ar-C$_{para}$ *S*-phenyl), 131.5 (C, Ar-C$_{ipso}$ *C*-phenyl), 135.7 (CH, Ar-C$_{ortho}$ *S*-phenyl), 136.8 (C, Ar-C$_{ipso}$ *S*-phenyl), 168.5 (C, COO); HRMS calcd for $[C_{18}H_{19}NO_3S + H]^+$ 330.1164, found 330.1169.

Mixture of (3*R,5*R**)- and (3*R**,5*S**)-2-Methyl-3-phenyl-5-(phenylthio)isoxazolidine-5-carboxylic Acid (±)-22 and (±)-23.** To a solution of the above mixture of (±)-**11** and (±)-**14** (3.70 g, 11.3 mmol) in MeOH (50 mL) was added 85% KOH (1.49 g, 22.6 mmol, 2 equiv), and the mixture was heated under reflux for 3 h. The organic solvent was evaporated in vacuo, water (100 mL) was added and the mixture was washed with AcOEt (100 mL). The aqueous phase was made acidic with aqueous 1 N HCl (20 mL) till pH 4 and was extracted with AcOEt (3 × 100 mL). The combined organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a mixture of (±)-**22** and (±)-**23** (3.10 g, 88% yield) as a yellow oil, which was used in the next step without further purification; R_f 0.08 (hexane/AcOEt 1:2); IR (NaCl) ν 3700−2100 (max at 3288, 3060, 3031, 2958, 2850), 1651, 1614 (C=O st), 1581, 1495, 1478, 1455, 1439, 1407, 1374, 1306, 1194, 1158, 1024, 979, 746, 700 cm^{-1}.

NMR Data of the Main Diastereoisomer (±)-22. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.69 (s, 3H, *N*-CH_3), 2.89 (dd, $J_{4\text{-H}\alpha/4\text{-H}\beta}$ = 14.1 Hz, $J_{3\text{-H}/4\text{-H}\beta}$ = 8.1 Hz, 1H, 4-H$_\beta$), 3.05 (dd, $J_{4\text{-H}\alpha/4\text{-H}\beta}$ = 14.1 Hz, $J_{3\text{-H}/4\text{-H}\alpha}$ = 9.6 Hz, 1H, 4-H$_\alpha$), 3.46 (m, 1H, 3-H), 7.21−7.45 (complex signal, 8H, Ar-H$_{meta}$, Ar-H$_{para}$ *S*-phenyl and Ar-H *C*-phenyl), 7.66−7.70 (m, 2H, Ar-H$_{ortho}$ *S*-phenyl), 8.1−8.6 (broad signal, 1H, COOH); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 42.7 (CH_3, *N*-CH_3), 48.8 (CH_2, C4), 73.3 (CH, C3), 90.5 (C, C5), 127.7 (CH, Ar-C$_{meta}$ *C*-phenyl), 128.7 (CH, Ar-C$_{meta}$ *S*-phenyl), 128.8 (CH, Ar-C$_{para}$ *C*-phenyl), 128.9 (CH, Ar-H$_{ortho}$ *C*-phenyl), 129.8 (CH, Ar-C$_{para}$ *S*-phenyl), 135.4 (C, Ar-C$_{ipso}$ *C*-phenyl), 135.5 (C, Ar-C$_{ipso}$ *S*-phenyl), 136.2 (CH, Ar-C$_{ortho}$ *S*-phenyl), 171.6 (C, COO).

Diastereoisomeric Mixture of (*R*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 2-Methyl-3-phenyl-5-(phenylthio)isoxazolidine-5-carboxylate 24, 25, 26, and 27. To a cold (0 °C) solution of the diastereoisomeric mixture (±)-**22** and (±)-**23** (3.00 g, 9.5 mmol, 1.05 equiv) in anhydrous CH_2Cl_2 (15 mL) was added DCC (3.75 g, 18 mmol, 2 equiv) portionwise under an argon atmosphere, and the mixture was stirred for 20 min at this temperature. A solution of (*R*)-**1** (1.85 g, 9.0 mmol) in anhydrous CH_2Cl_2 (25 mL) and DMAP (148 mg, 1.2 mmol, 0.13 equiv) were added and the reaction mixture was stirred at room temperature for 16 h. The precipitated dicyclohexylurea (DCU) was filtered off through Celite, and the filtrate was concentrated in vacuo to give a residue (7.5 g) that was subjected to column chromatography [silica gel (220 g), hexane/Et_2O mixtures]. On elution with hexane/Et_2O 4:1, in order of elution a diastereoisomeric mixture of **24**−**27** (4.43 g, 94% yield, approximate dr 3:3:1:1) and a pure *endo* -cycloadduct **26** or **27** (54 mg, 1% yield, dr >98:2) were isolated as a yellow oil and as a white solid, respectively.

26 or **27**: mp 172−174 °C (hexane/Et_2O 3:2); R_f 0.77 (hexane/AcOEt 1:1); $[\alpha]^{20}_D$ −129.7 (*c* 0.13, AcOEt); IR (KBr) ν 3064, 3031, 2970, 2942, 2872, 1742 (C=O st ester), 1704 (C=O st lactam), 1598, 1499, 1475, 1412, 1387, 1324, 1264, 1211, 1178, 1140, 1104, 1058, 966, 758, 693 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98 (s, 3H, 4′α-CH_3), 1.07 (s, 3H, 4′β-CH_3), 2.75 (s, 3H, *N*-CH_3), 2.76 (dd, $J_{4\text{-H}\alpha/4\text{-H}\beta} \approx$ 13.5 Hz, $J_{3\text{-H}/4\text{-H}\beta}$ = 10.2 Hz, 1H, 4-H$_\beta$), 3.42 (dd, $J_{4\text{-H}\alpha/4\text{-H}\beta}$ = 13.5 Hz, $J_{3\text{-H}/4\text{-H}\alpha} \approx$ 7.5 Hz, 1H, 4-H$_\alpha$), 3.45 (d, $J_{5'\alpha\text{-H}/5'\beta\text{-H}}$ = 9.6 Hz, 1H, 5′α-H), 3.54 (d, $J_{5'\alpha\text{-H}/5'\beta\text{-H}}$ = 9.6 Hz, 1H, 5′β-H), 3.77 (dd, $J_{3\text{-H}/4\text{-H}\beta}$ = 10.2 Hz, $J_{3\text{-H}/4\text{-H}\alpha}$ = 7.5 Hz, 1H, 3-H), 5.28 (s, 1H, 3′-H), 7.17 (tm, $J_{\text{Hpara/Hmeta}} \approx$ 7.2 Hz, $J_{\text{Hpara/Hortho}}$ = 1.2 Hz, 1H, Ar-H$_{para}$ *N*-phenyl), 7.28−7.46 (complex signal, 10H, Ar-H$_{meta}$ *N*-phenyl, Ar-H$_{meta}$ *S*-phenyl, Ar-H$_{para}$ *S*-phenyl and Ar-H *C*-phenyl), 7.61 (m, 2H, Ar-H$_{ortho}$ *N*-phenyl), 7.78 (m, 2H, Ar-H$_{ortho}$ *S*-phenyl); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 21.0 (CH_3, 4′α-CH_3), 24.5 (CH_3, 4′β-CH_3), 37.3 (C, C4′), 43.2 (CH_3, *N*-CH_3), 51.1 (CH_2, C4), 57.7 (CH_2, C5′), 72.5 (CH, C3), 79.4 (CH, C3′), 91.5 (C, C5), 119.5 (CH, Ar-C$_{ortho}$ *N*-phenyl), 124.9 (CH, Ar-C$_{para}$ *N*-phenyl), 128.0 (CH, Ar-C$_{meta}$ *C*-phenyl), 128.3 (CH, Ar-C$_{para}$ *C*-phenyl), 128.6 (CH, Ar-C$_{meta}$ *N*-phenyl), 128.7 (CH, Ar-C$_{meta}$ *S*-phenyl), 128.9 (CH, Ar-C$_{ortho}$ *C*-phenyl), 129.0 (CH, Ar-C$_{para}$ *S*-phenyl), 131.5 (C, Ar-C$_{ipso}$ *S*-phenyl), 135.6 (CH, Ar-C$_{ortho}$ *S*-phenyl), 136.8 (C, Ar-C$_{ipso}$ *C*-phenyl), 138.9 (C, Ar-C$_{ipso}$ *N*-phenyl), 167.9 (C) and 168.0 (C) (COO and C2′). Anal. Calcd for $C_{29}H_{30}N_2O_4S$: C, 69.30; H, 6.02; N, 5.57; S 6.38. Found: C, 69.14; H, 6.07; N, 5.55; S 6.11.

(3*S*,5*S*,3′*R*)- and (3*R*,5*R*,3′*R*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 2-Methyl-5-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)-3-phenylisoxazolidine-5-carboxylate 20 and 21. To a solution of the diastereomeric mixture of esters **24**−**27** (6.00 g, 11.9 mmol) in anhydrous CH_2Cl_2 (110 mL) were added **17** (6.50 g, 23.9 mmol, 2 equiv) and 4 Å molecular sieves (5 g) under argon and the reaction mixture was stirred at room temperature for 20 min. Then, NBS (2.32 g, 13.1 mmol, 1.1 equiv) was added and the reaction mixture was stirred at room temperature for 1 h. The resulting mixture was treated with 10% aqueous $Na_2S_2O_3$ (250 mL), the organic phase was separated and the aqueous one was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a residue (8.2 g), which was subjected to column chromatography [silica gel (250 g), hexane/AcOEt mixtures]. On elution with a mixture of hexane/AcOEt 1:1, a diastereomeric mixture of **20** and **21** at an approximate ratio of 1:1 (4.50 g, 73% yield) was obtained as a white foam. Column chromatography of this mixture [silica gel (250 g), CH_2Cl_2/AcOEt mixtures] gave **20** (320 mg, dr >98:2, by ^{1}H NMR) and a mixture of **20** and **21** (2.68 g), on elution with a mixture CH_2Cl_2/AcOEt 13:1; and **21** (640 mg, dr >98:2, by ^{1}H NMR), on elution with a mixture CH_2Cl_2/AcOEt 6:1. The fraction mixture of **20** and **21** was subjected to a

new column chromatography [silica gel (250 g), hexane/AcOEt 6:1)] to give **20** (1.52 g, dr >98:2), a mixture of **20** and **21** (0.61 g), and **21** (400 mg, dr >98:2). Altogether, **20** (1.84 g, 30% total yield, dr >98:2) and **21** (1.04 g, 17% total yield, dr >98:2) were obtained as white foams.

20: mp 121−123 °C (CH_2Cl_2/AcOEt 6:1); R_f 0.18 (CH_2Cl_2/AcOEt 6:1); $[\alpha]^{20}_D$ −67.0 (*c* 0.25, AcOEt); IR (KBr) ν 3184 (N−H st), 3063, 2966, 2929, 2876, 1767 and 1706 and 1690 (C=O st), 1598, 1500, 1458, 1410, 1386, 1372, 1325, 1270, 1188, 1122, 1087, 1071, 991, 762, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.00 (s, 3H, 4′α-CH_3), 1.28 (s, 3H, 4′β-CH_3), 2.02 (d, $J_{5\text{-CH3/6-H}}$ = 1.2 Hz, 3H, pyrimidinedione 5-CH_3), 2.65 (dd, $J_{4\text{-Hα/4-Hβ}}$ = 12.6 Hz, $J_{3\text{-H/4-Hβ}}$ = 9.0 Hz, 1H, 4-H_β), 2.79 (s, 3H, *N*-CH_3), 3.47 (d, $J_{5'\alpha\text{-H/5'}\beta\text{-H}}$ = 9.6 Hz, 1H, 5′α-H), 3.61 (d, $J_{5'\alpha\text{-H/5'}\beta\text{-H}}$ = 9.6 Hz, 1H, 5′β-H), 3.96 (dd, $J_{3\text{-H/4-Hβ}}$ = 9.0 Hz, $J_{3\text{-H/4-Hα}}$ = 7.2 Hz, 1H, 3-H), 4.03 (dd, $J_{4\text{-Hα/4-Hβ}}$ = 12.6 Hz, $J_{3\text{-H/4-Hα}}$ = 7.2 Hz, 1H, 4-H_α), 5.45 (s, 1H, 3′-H), 7.17 (tm, $J_{Hpara/Hmeta} \approx$ 7.2 Hz, 1H, Ar-H_{para} *N*-phenyl), 7.28−7.40 (complex signal, 7H, Ar-H_{meta} *N*-phenyl and Ar-H *C*-phenyl), 7.62 (m, 2H, Ar-H_{ortho} *N*-phenyl), 7.79 (q, $J_{5\text{-CH3/6-H}}$ = 1.2 Hz, 1H, pyrimidinedione 6-H), 8.3−8.4 (broad signal, 1H, NH); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 12.8 (CH_3, pyrimidinedione 5-CH_3), 20.9 (CH_3, 4′α-CH_3), 24.4 (CH_3, 4′β-CH_3), 37.5 (C, C4′), 43.4 (CH_3, *N*-CH_3), 51.9 (CH_2, C4), 57.4 (CH_2, C5′), 73.9 (CH, C3), 79.8 (CH, C3′), 92.9 (C, C5), 109.5 (C, pyrimidinedione C5), 119.3 (CH, Ar-C_{ortho} *N*-phenyl), 124.9 (CH, Ar-C_{para} *N*-phenyl), 127.6 (CH, Ar-C_{meta} *C*-phenyl), 128.6 (CH, Ar-C_{para} *C*-phenyl), 128.8 (CH, Ar-C_{meta} *N*-phenyl and Ar-H_{ortho} *C*-phenyl), 134.8 (CH, pyrimidinedione C6), 135.7 (C, Ar-C_{ipso} *C*-phenyl), 138.8 (C, Ar-C_{ipso} *N*-phenyl), 150.4 (C, pyrimidinedione C2), 164.1 (C, pyrimidinedione C4), 164.8 (C, COO), 167.6 (C, C2′). Anal. Calcd for $C_{28}H_{30}N_4O_6 \cdot 0.3H_2O$: C, 64.18; H, 5.89; N, 10.69. Found: C, 64.17; H, 5.72; N, 10.63.

21: mp 121−123 °C (CH_2Cl_2/AcOEt 6:1); R_f 0.12 (CH_2Cl_2/AcOEt 6:1); $[\alpha]^{20}_D$ +1.1 (*c* 0.19, AcOEt); IR (KBr) ν 3185 (N−H st), 3064, 2966, 2929, 2877, 1764 and 1702 and 1686 (C=O st), 1598, 1500, 1458, 1411, 1386, 1373, 1325, 1279, 1190, 1143, 1120, 1087, 1070, 991, 788, 761, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (s, 3H, 4′α-CH_3), 1.35 (s, 3H, 4′β-CH_3), 2.02 (d, $J_{5\text{-CH3/6-H}}$ = 1.2 Hz, 3H, pyrimidinedione 5-CH_3), 2.69 (dd, $J_{4\text{-Hα/4-Hβ}}$ = 13.8 Hz, $J_{3\text{-H/4-Hβ}}$ = 10.2 Hz, 1H, 4-H_β), 2.79 (s, 3H, *N*-CH_3), 3.56 (d, $J_{5'\alpha\text{-H/5'}\beta\text{-H}}$ = 9.9 Hz, 1H, 5′α-H), 3.64 (d, $J_{5'\alpha\text{-H/5'}\beta\text{-H}}$ = 9.9 Hz, 1H, 5′β-H), 3.93 (dd, $J_{4\text{-Hα/4-Hβ}}$ = 13.8 Hz, $J_{3\text{-H/4-Hα}}$ = 6.9 Hz, 1H, 4-H_α), 4.04 (dd, $J_{3\text{-H/4-Hβ}}$ = 10.2 Hz, $J_{3\text{-H/4-Hα}}$ = 6.9 Hz, 1H, 3-H), 5.42 (s, 1H, 3′-H), 7.19 (tm, $J_{Hpara/Hmeta} \approx$ 7.2 Hz, 1H, Ar-H_{para} *N*-phenyl), 7.26−7.43 (complex signal, 7H, Ar-H_{meta} *N*-phenyl and Ar-H *C*-phenyl), 7.64 (m, 2H, Ar-H_{ortho} *N*-phenyl), 7.71 (q, $J_{5\text{-CH3/6-H}}$ = 1.2 Hz, 1H, pyrimidinedione 6-H), 8.46 (br signal, 1H, NH); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 12.8 (CH_3, pyrimidinedione 5-CH_3), 21.1 (CH_3, 4′α-CH_3), 24.8 (CH_3, 4′β-CH_3), 37.9 (C, C4′), 43.4 (CH_3, *N*-CH_3), 51.3 (CH_2, C4), 57.7 (CH_2, C5′), 73.9 (CH, C3), 80.2 (CH, C3′), 92.8 (C, C5), 109.5 (C, pyrimidinedione C5), 119.5 (CH, Ar-C_{ortho} *N*-phenyl), 125.0 (CH, Ar-C_{para} *N*-phenyl), 127.7 (CH, Ar-C_{meta} *C*-phenyl), 128.6 (CH, Ar-C_{para} *C*-phenyl), 128.8 (CH) and 128.9 (CH) (Ar-C_{meta} *N*-phenyl and Ar-H_{ortho} *C*-phenyl), 134.4 (CH, pyrimidinedione C6), 135.5 (C, Ar-C_{ipso} *C*-phenyl), 138.8 (C, Ar-C_{ipso} *N*-phenyl), 150.5 (C, pyrimidinedione C2), 164.0 (C, pyrimidinedione C4), 164.9 (C, COO), 167.6 (C, C2′). Anal. Calcd for $C_{28}H_{30}N_4O_6 \cdot 0.2H_2O$: C, 64.41; H, 5.87; N, 10.73. Found: C, 64.41; H, 5.96; N 10.64.

Methyl (3*S*,5*S*)-(−)-2-Methyl-5-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)-3-phenylisoxazolidine-5-carboxylate (−)-18. To a solution of **20** (125 mg, 0.24 mmol, dr >98:2) in MeOH (3 mL) was added K_2CO_3 (66 mg, 0.47 mmol, 2 equiv) and the mixture was stirred under argon at room temperature for 3 h. The organic solvent was eliminated in vacuo and the residue (196 mg) was subjected to column chromatography [silica gel (10 g), hexane/AcOEt 7:3]. In order of elution, (*R*)-**1**, (49 mg, quantitative yield, >99% ee, by chiral HPLC) as a white solid and (−)-**18** (62 mg, 75% yield, 98.6% ee, by chiral HPLC) as a white foam were isolated.

(−)-**18**: R_f 0.48 (hexane/AcOEt 1:1); $[\alpha]^{20}_D$ −43.1 (*c* 0.26, AcOEt); chiral HPLC (conditions A) t_R 16.99 min, k_2' = 2.19, α = 1.18, Res = 1.28; IR (NaCl) ν 3178, 3035, 2962, 2927, 2854, 1758 and 1690 (C=O st), 1457, 1437, 1365, 1320, 1283, 1201, 1121, 1085, 1068, 996, 850, 790, 767, 700 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 1.77 (d, $J_{5\text{-CH3/6-H}}$ = 1.2 Hz, 3H, pyrimidinedione 5-CH_3), 2.38 (s, 3H, *N*-CH_3), 2.62 (dd, $J_{4\text{-Hα/4-Hβ}}$ = 13.8 Hz, $J_{3\text{-H/4-Hβ}}$ = 10.2 Hz, 1H, 4-H_β), 3.38 (s, 3H, CO_2CH_3), 3.75 (dd, $J_{3\text{-H/4-Hβ}}$ = 10.2 Hz, $J_{3\text{-H/4-Hα}}$ = 7.2 Hz, 1H, 3-H), 4.13 (dd, $J_{4\text{-Hα/4-Hβ}}$ = 13.8 Hz, $J_{3\text{-H/4-Hα}}$ = 7.2 Hz, 1H, 4-H_α), 7.03 (s, 5H, Ar-H), 7.63 (q, $J_{5\text{-CH3/6-H}} \approx$ 1.2 Hz, 1H, pyrimidinedione 6-H), 10.7 (broad signal, 1H, NH); ^{13}C NMR (C_6D_6, 75.4 MHz) δ 12.8 (CH_3, pyrimidinedione 5-CH_3), 42.9 (CH_3, *N*-CH_3), 52.1 (CH_2, C4), 53.3 (CH_3, CO_2CH_3), 74.3 (CH, C3), 93.2 (C, C5), 109.7 (C, pyrimidinedione C5), 127.8 (CH, Ar-C_{meta} phenyl), 128.5 (CH, Ar-C_{para} phenyl), 128.9 (CH, Ar-H_{ortho} phenyl), 134.2 (CH, pyrimidinedione C6), 136.3 (C, Ar-C_{ipso} phenyl), 151.2 (C, pyrimidinedione C2), 164.7 (C, pyrimidinedione C4), 166.3 (C, COO); HRMS calcd for $[C_{17}H_{19}N_3O_5]^{\bullet+}$ 345.1325, found 345.1337. Anal. Calcd for $C_{17}H_{19}N_3O_5 \cdot 0.6H_2O$: C, 57.33; H, 5.72; N, 11.80. Found: C, 57.59; H, 5.68; N, 11.31.

Methyl (3*R*,5*R*)-(+)-2-Methyl-5-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)-3-phenylisoxazolidine-5-carboxylate (+)-18. To a solution of **21** (820 mg, 1.55 mmol, >98:2 dr) in MeOH (16.5 mL) was added K_2CO_3 (433 mg, 3.12 mmol, 2 equiv) and the mixture was stirred under argon at room temperature for 3 h. The organic solvent was eliminated in vacuo and the residue (1.3 g) was subjected to column chromatography [silica gel (5 g), hexane/AcOEt 7:3]. In order of elution, (*R*)-**1** (320 mg, quantitative yield, >99% ee, by chiral HPLC) as a white solid and (+)-**18** (370 mg, 69% yield, 96% ee, by chiral HPLC) as a white foam were isolated.

(+)-**18**: R_f 0.48 (hexane/AcOEt 1:1); $[\alpha]^{20}_D$ +44.3 (*c* 0.30, AcOEt); chiral HPLC (conditions A) t_R 15.36 min, k_1' = 1.86); the IR and NMR data coincide with those described before for (−)-**18**; HRMS calcd for $[C_{17}H_{19}N_3O_5]^{\bullet+}$ 345.1325, found 345.1334. Anal. Calcd for $C_{17}H_{19}N_3O_5 \cdot 0.15H_2O$: C, 58.66; H, 5.59; N, 12.07. Found: C, 58.90; H, 5.75; N, 11.71.

(3*S*,5*S*)-(−)-[2-Methyl-5-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)-3-phenylisoxazolidin-5-yl]methanol (−)-32. To a cold (0 °C) solution of (−)-**18** (377 mg, 1.09 mmol) in anhydrous toluene (12 mL) was added Red-Al (1.1 mL, 1.06 g, 3.27 mmol, 3 equiv) dropwise and the mixture was stirred at room temperature for 1 h. The mixture was cooled to 0 °C, water (5 mL) was added dropwise, and then the mixture was made acidic till pH 6 with aqueous 1 N HCl (10 mL). The precipitated solid was filtered off and washed with CH_2Cl_2 (3 × 15 mL) and the combined filtrate and washings were concentrated in vacuo to give alcohol (−)-**32** (201 mg, 58% yield) as a white solid. Part of this solid (168 mg) was crystallized from AcOEt (5 mL) to give the analytical sample of (−)-**32** (94 mg, >99% ee) as a white solid; the mp, R_f, IR and NMR data of this compound coincide with those of (+)-**32**; $[\alpha]^{20}_D$ −132.6 (*c* 0.94, CH_2Cl_2); chiral HPLC (conditions A) t_R 18.97 min, k_1' = 1.24, α = 1.18, Res = 1.39). Anal. Calcd for $C_{16}H_{19}N_3O_4 \cdot 0.1H_2O$: C, 60.22; H, 6.06; N, 13.17. Found: C, 60.07; H, 6.14; N, 13.04.

(3*R*,5*R*)-(+)-[2-Methyl-5-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)-3-phenylisoxazolidin-5-yl]methanol (+)-32. To a cold (0 °C) solution of (+)-**18** (292 mg, 0.85 mmol) in anhydrous toluene (10 mL) was added dropwise Red-Al (0.8 mL, 0.77 g, 2.55 mmol, 3 equiv) and the mixture was stirred at room temperature for 1 h. The mixture was cooled to 0 °C, water (5 mL) was added dropwise, and then the mixture was made acidic till pH 6 with aqueous 1 N HCl. The precipitated solid was filtered off and washed with CH_2Cl_2 (3 × 15 mL) and the combined filtrate and washings were concentrated in vacuo to give alcohol (+)-**32** (184 mg, 68%

yield) as a white solid. Part of this solid (165 mg) was crystallized from AcOEt (5 mL) to give the analytical sample of (+)-**32** (96 mg, >99% ee) as a white solid; mp 194−195 °C (AcOEt); R_f 0.53 (AcOEt/MeOH 10:1); $[\alpha]^{20}_D$ +131.1 (*c* 0.64, CH_2Cl_2); chiral HPLC (conditions A) t_R 21.47 min, $k_2' = 2.93$); IR (KBr) ν 3700−2800 (max at 3523, 3312, 3182, 3085, 3060, 3039, 2961, 2925 and 2877), 1706, 1685, 1670, and 1647 (C=O st), 1467, 1455, 1306, 1293, 1276, 1124, 1114, 1084, 1058, 766, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.86 (d, $J_{5\text{-}CH3/6\text{-}H} \approx 1.2$ Hz, 3H, pyrimidinedione 5-CH_3), 2.69 (s, 3H, *N*-CH_3), 2.89 (dd, $J_{4\text{-}H\alpha/4\text{-}H\beta} = 14.4$ Hz, $J_{3\text{-}H/4\text{-}H\beta} = 9.9$ Hz, 1H, 4-H_β), 3.05 (dd, $J_{4\text{-}H\alpha/4\text{-}H\beta} = 14.4$ Hz, $J_{3\text{-}H/4\text{-}H\alpha} = 7.5$ Hz, 1H, 4-H_α), 3.67 (dd, $J_{3\text{-}H/4\text{-}H\beta} = 9.9$ Hz, $J_{3\text{-}H/4\text{-}H\alpha} = 7.5$ Hz, 1H, 3-H), 3.84 (dd, 1H, $J_{Ha/Hb} = 12.3$ Hz, $J_{Ha/OH} = 7.8$ Hz, CH_a-O), 4.37 (br signal, 1H, OH), 4.49 (dd, 1H, $J_{Ha/Hb} = 12.3$ Hz, $J_{Hb/OH} = 5.4$ Hz, CH_b-O), 7.21−7.30 (complex signal, 5H, Ar-H), 7.78 (q, $J_{5\text{-}CH3/6\text{-}H} = 1.2$ Hz, 1H, pyrimidinedione 6-H), 10.37 (br signal, 1H, NH); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 12.8 (CH_3, pyrimidinedione 5-CH_3), 43.1 (CH_3, *N*-CH_3), 49.0 (CH_2, C4), 64.6 (CH_2, CH_2OH), 73.8 (CH, C3), 97.0 (C, C5), 107.8 (C, pyrimidinedione C5), 127.6 (CH, Ar-C_{meta} phenyl), 128.3 (CH, Ar-C_{para} phenyl), 128.7 (CH, Ar-H_{ortho} phenyl), 136.7 (C, Ar-C_{ipso} phenyl), 138.2 (CH, pyrimidinedione C6), 150.8 (C, pyrimidinedione C2), 165.9 (C, pyrimidinedione C4). Anal. Calcd for $C_{16}H_{19}N_3O_4$: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.72; H, 6.09; N 13.30.

Antiviral Activity Assays. Antiviral activity was determined on the basis of inhibition of virus-induced cytopathic effects (CPE), essentially as described previously.[35,36]

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Supporting Information Available: Experimental details for compounds **4**, **7**, (±)-**9**, (±)-**12**/(±)-**13**/(±)-**15**/(±)-**16**, (±)-**18**, (±)-**19**, **29**, **30**, (−)-**31**, (+)-**31**, (−)-**33**, (+)-**33**, (±)-**39**, **40**, **41**, (−)-**39**, (+)-**39**, (−)-**37**, (+)-**37**, (−)-**35**, (+)-**35**, (−)-**36**, (+)-**36**, (+)-**34**, (−)-**34**, and complementary procedures for (+)-**36** from (−)-**18** and **29**, and (−)-**36** from **21** and **30**. Crystallographic data and CIF file for compound **40**. ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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