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4-ISOPROPYL-2-OXAZOLIN-5-ONE ANION AS MASKED UMPOLED SYNTHON FOR BOTH FORMYL AND HYDROXYCARBONYL ANIONS: GENERATION, REACTIVITY AND SYNTHETIC APPLICATIONS.

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Abstract: The anion of the title compound, simply generated in the presence of catalytic amount of triethylamine, reacts with both common electrophilic olefins and aldehydes to give moderate to good yield of Michael or aldol adducts respectively. Mild acid treatment of these adducts at ambient temperature serves to demask the aldehyde function, allowing one to consider the anion of **1** as a nucleophilic acylating equivalent of formaldehyde. On the other hand, the same anion of **1** may act as a masked umpoled synthon for a hydroxycarbonyl anion since its aldol adducts with aldehydes underwent concomitant isomerization and ring cleavage under mild basic conditions producing dipeptides which could be hydrolyzed to give the corresponding carboxylic acids. Synthetic applications of this chemistry in the area of sugar, aminosugar and non-proteinogenic aminoacid derivatives are discussed.

Introduction

The interaction between carbon atoms of opposite polarity is the fundamental requirement for carbon-carbon bond forming reactions. Consequently, it is not surprising that extensive studies have been directed towards the development of new protocols for temporarily reversing the characteristic reactivity of the carbonyl group,[1] one of the most important functionalities in organic chemistry.

As a continuation of our studies centered on the use of heterocyclic compounds as latent functionalities,[2] we have recently described in preliminary form[3] the use of 4-isopropyl-2-oxazolin-5-one **1**[4] as a masked umpoled synthon for either formyl or hydroxycarbonyl anions.

We describe in this paper the details of our studies and some interesting applications of the synthon **1** to the synthesis of natural compounds.

Results and Discussion

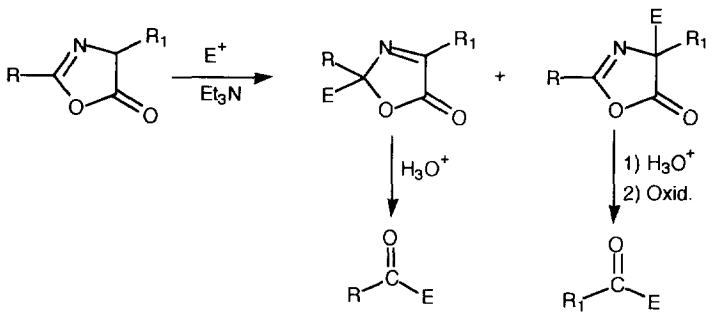
The intramolecular dehydration of acylated aminoacids[5,6] has represented, for more than a century, the most common route to prepare 5(*4H*) oxazolones, archaically referred as azlactones.

In the seventies, the chemistry of this class of compounds has been thoroughly investigated by W. Steglich et al.[7] who demonstrated some important features, namely : 1) they can be easily deprotonated by tertiary amines; 2) the derived ambident anion acts as a nucleophile towards common electrophilic reagents; 3) simple hydrolytic-oxidative steps open the heterocyclic structure yielding carbonyl derivatives. The complete sequence, reported in Scheme I allows consideration of 5(*4H*) oxazolones as acylanions equivalents.[8]

Surprisingly, despite a pertinent accumulation of 5(*4H*) oxazolones, especially of those carrying a C-2 substituent, scant attention has been given to 2-unsubstituted derivatives.

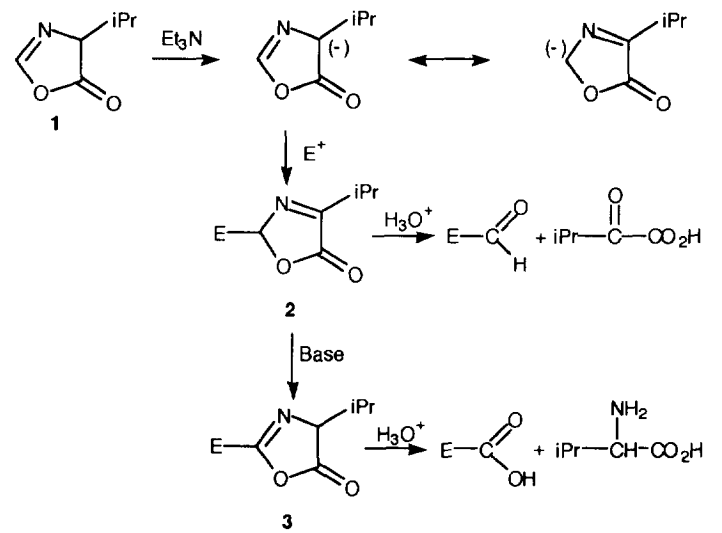
With the aim of developing a new formyl anion equivalent, we were attracted by the possibility of employing the anion of the 4-isopropyl-2-oxazolin-5-one **1** as umpoled reagent. This compound can be easily prepared in multigram quantity by DCC promoted dehydration of *N*-formyl-valine followed by Kugelrohr distillation without aqueous work-up.[4] It is sensitive to moisture and rapidly hydrolyzes in the atmosphere, but it can be stored under nitrogen at room temperature.

Scheme I



We were confident that the sterically hindered isopropyl group at the C-4 and the absence of alkyl substituents at the C-2 on the heterocyclic ring would have assured the regioselective formation of C-2 anion. Its reaction with suitable electrophiles would produce adducts which could be considered immediate precursors of aldehydic compounds through further elaboration according to the protocol developed by Steglich et al.[7]

Scheme II

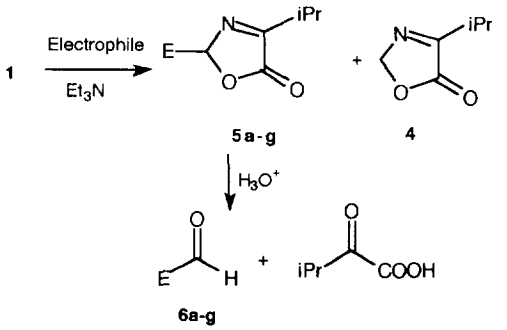


Furthermore, we envisaged the possibility of using the related 2-oxazolin-5-one **3**, the tautomer of 3-oxazolin-5-one **2**, as masked umpoled synthon for hydroxycarbonyl anion. The transformation **2**→**3**, a prerequisite for a successful application of this new concept, could be performed through a base-catalyzed tautomerization. A simple hydrolytic step is eventually required to reveal the carboxylic group. (Scheme II).

Reaction of the anion of 1 with electrophilic olefins

We first studied the behaviour of **2** in Michael type reactions using the following electrophilic olefins as acceptors: a) acrolein; b) 3-buten-2-one; c) methyl acrylate; d) nitroethene; e) methyl 9-cheto-11-undecenoate; f) cyclohexenone; g) cyclopentenone. The addition reactions were performed between -5°C and room temperature in both CH_2Cl_2 or benzene solution. We found that the employment of equimolar quantity of reagents and catalytic Et_3N to generate the nucleophilic anion of **1** are usually satisfactory conditions to obtain moderate to good yields of adducts. Our results (see Experimental) showed that in some cases (entries e-g) the reaction proceeded more slowly and 1.5 equivalents of **1** were required, a competitive base-catalyzed isomerization to 4-isopropyl-3-oxazolin-5-one **4**, the isolable *2H* tautomer, taking place. As expected, the oxazolone **1** undergoes carbon-carbon bond formation with electrophilic olefins exclusively at the carbon attached to two heteroatoms producing the adducts **5a-g**.

Scheme III

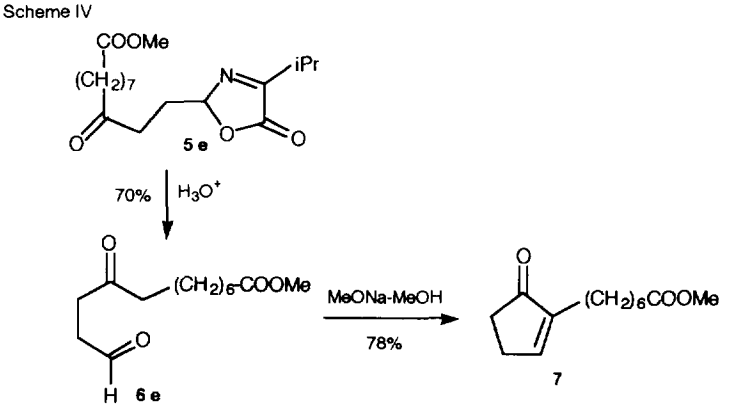


Electrophile:

a = CH_2=CH CHO
b = CH_2=CHCOMe
c = CH_2=CHCO_2Me
d = CH_2=CH NO_2
e = CH_2=CH $CO(CH_2)_7CO_2Me$
f = 2- cyclohexen-1-one
g = 2-cyclopenten-1-one

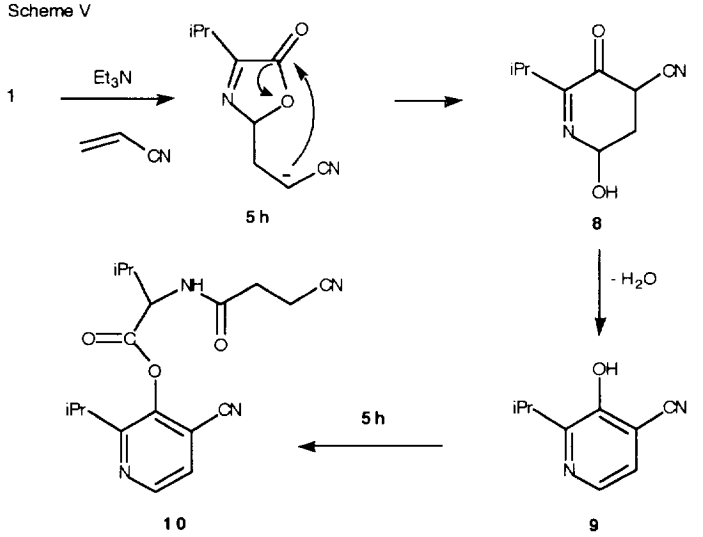
The isolated adducts were subsequently hydrolyzed by treatment with 5% hydrochloric acid in THF solution at room temperature to produce in excellent yield the corresponding aldehydic compounds **6**. The α-ketoacid formed by cleavage of the heterocyclic system was easily separated from aldehydes by washing with aqueous $NaHCO_3$. (Scheme III). A nice application of this convenient methodology is represented by the preparation of the 2-substituted 2-cyclopenten-1-one **7**, an intermediate widely utilized for prostaglandin synthesis[9] through base-promoted cyclization of methyl 9,12-dioxododecanoate **6e**. (Scheme IV).

Scheme IV



Interestingly, a notable exception to the trend of reactivity in the range of the investigated α,β-unsaturated compounds was offered by acrylonitrile. In this case, we were able to isolate, as the sole reaction product, the 2,3,4-trisubstituted-pyridine derivative **10**, as a white crystalline compound. Its unexpected formation formally requires the interaction of two molecules of the usual adduct **5h** which, however, we were unable not only to isolate but also to detect in the reaction mixture (Scheme V).

Scheme V



The formation of **10** can be accounted for by an intramolecular ring enlargement of **5h** to give the heterocycle **8**, followed by dehydration to the substituted 3-hydroxy pyridine **9**, in turn undergoing subsequent *O*-acylation through ring opening of a further molecule of **5h**.

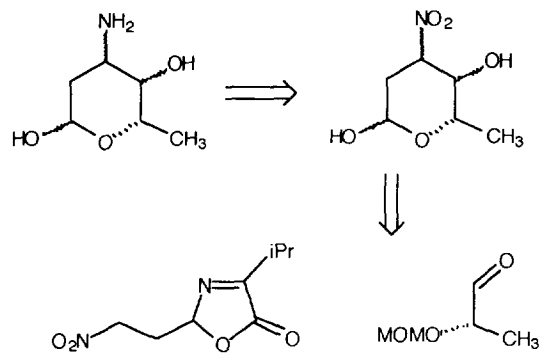
Synthesis of Ristosamine

The 3-aminoesoses *L*-daunosamine, *L*-acosamine and *L*-ristosamine are important structural components of glycosidic antibiotics from which they can be obtained by hydrolysis. Structure-activity relationship studies have demonstrated the crucial importance of the aminosugar moiety in determining not only the intensity but also the variety of biological actions of the antibiotics. As a consequence, their structures became attractive targets for synthetic chemists. The excellent yield found in the conjugate addition of the anion of **1** to nitroethene to give **5d**, the easy release of the aldehydic group from the derived oxazolinone ring system, besides the versatility of the nitro group, prompted us to investigate its application as starting point for aminosugar synthesis.

Our own retrosynthetic analysis for an approach to ristosamine depicted in Scheme VI traced us back to the *O*-protected lactaldehyde **11**[10] and the adduct **5d** as the easily available starting materials; the two key steps of the synthesis were a) a classical nitroaldol Henry reaction as a way to make the carbon-carbon bond between the two fragments; b) subsequent aldehyde demasking from the oxazolinone ring system.

The preparation of the nitroderivative **5d** was accomplished in excellent yield performing the reaction at - 5°C and using the 2-nitro-1-benzoyl ethanol / Et3N system as the "*in situ*" nitroethene precursor, in order to minimize nitroolefin polymerization. The ready availability of both starting materials allowed us to put into practice the synthetic project shown in Scheme VII. The natural amino sugars belonging to the L steric series compelled us to employ, as electrophilic partner of **5d**, the known[10] (S)-aldehyde **11**, easily obtained from ethyl (S)-lactate.

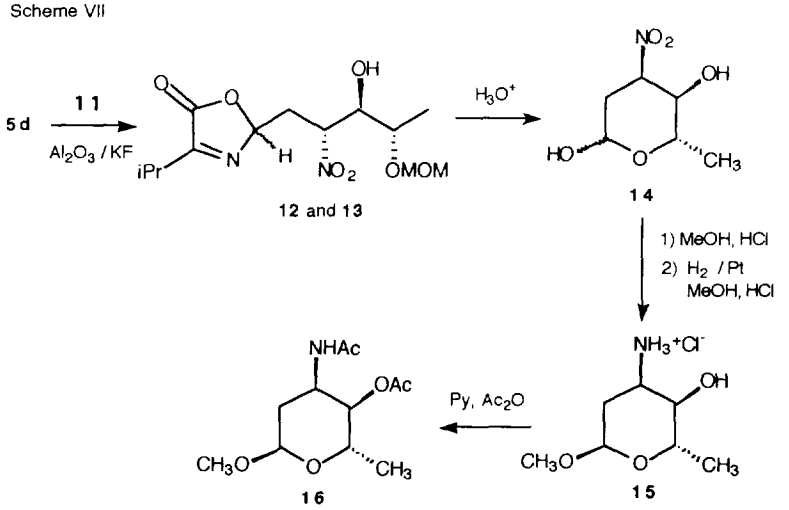
Scheme VI



5 d 11

Among the variety of catalysts and reaction conditions we tried in an attempt to effect the Henry condensation between the nitroderivative **5d** and the *O*-protected aldehyde **11**, the use of KF supported on neutral alumina at room temperature for 24 hours without solvent proved to be the most efficient protocol. Purification of the crude reaction mixture by column chromatography on silica gel allowed the isolation of the diastereomers **12** and **13**, having different configuration at the C-2 asymmetric center. In fact, both compounds were separately hydrolyzed with dilute HCl giving rise to the exclusive formation of the nitrosugar **14**, the aldehydic release from the oxazolinone ring and deprotection of the hydroxyl group taking place simultaneously in this operation. The configuration of the anomeric center of the pure nitroderivative **14** cannot firmly established but only tentatively assigned as that of the corresponding methyl glycoside, which, on hydrogenation in the presence of PtO_2 in methanol-HCl solution, produced the known[11] ristosamine methyl glycoside hydrochloride **15**, the white crystals of which were obtained simply by adding acetone to the ethanolic solution of the reaction mixture.

Scheme VII



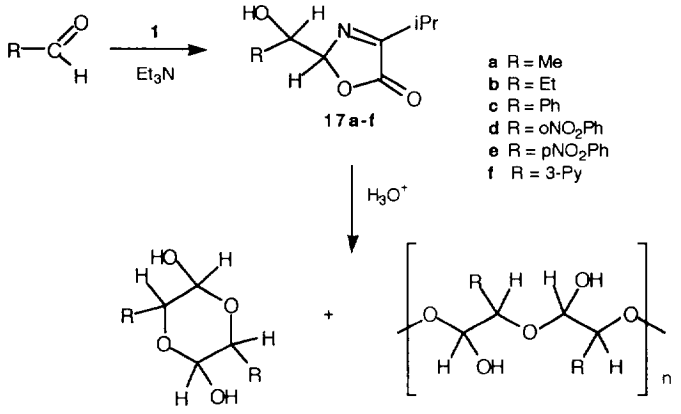
12 and 13

The salt was also transformed into the known[11] bis acetyl derivative **16** by treatment with pyridine and acetic anhydride. The complete diastereo- and enantioselectivity of the sequence, in addition to the facile preparation of the starting materials are the main advantages of the synthesis.

Reaction of 1 with aldehydes

Common alkyl halides such as methyl iodide, benzyl bromide or allyl bromide didn't react with the anion of **1** in the usual reaction conditions.

Scheme VIII



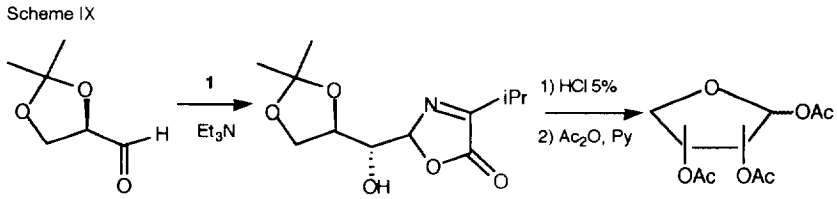
The same behaviour was observed employing epoxides and ketones as electrophilic counterparts of **1**. In all these cases, after prolonged reaction times, 4-isopropyl-3-oxazolin-5-one **4**, the already mentioned tautomer of **1**, was isolated after chromatographic purification. In contrast, nucleophilic addition of **1** to different simple aldehydes proceeded smoothly to afford the 1,2-adducts **17a-f**, the yield being satisfactory especially when aromatic aldehydes were employed. However, in all the examined cases, the hydrolytic step required for revealing the aldehydic function from the adducts, led invariably to the formation of cyclic dimers or oligomers[12], despite the mild conditions involved.(Scheme VIII).

Synthesis of (D)-Erythrose and (L)-4-Deoxy-Ribose

In order to overcome this hurdle, we decided to employ polyoxygenated aldehydes as electrophiles, hoping that the formation of an internal hemiacetal in the hydrolytic step might protect the aldehydes from dimerizaton.

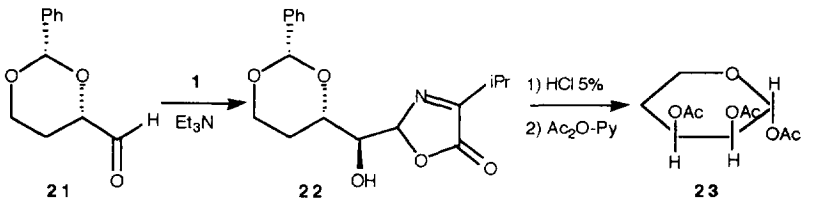
Following known procedures we prepared (R)-glyceraldehyde acetonide **18** by $Pb(OAc)_4$ oxidation of *D*-mannitol 1,2,5,6-diacetonide[13] and 2,4-*O*-benzylidene-2(S),4-dihydroxy-butanal **21** starting from *S*-malic acid[14].

Scheme IX



The two α-oxygenated aldehydes reacted smoothly as the counterpart of **1** forming a mixture of diastereoisomers from which, in both cases the most abundant, **19** and **22** respectively, were easily separated by flash chromatography.(Scheme IX and X).

Scheme X

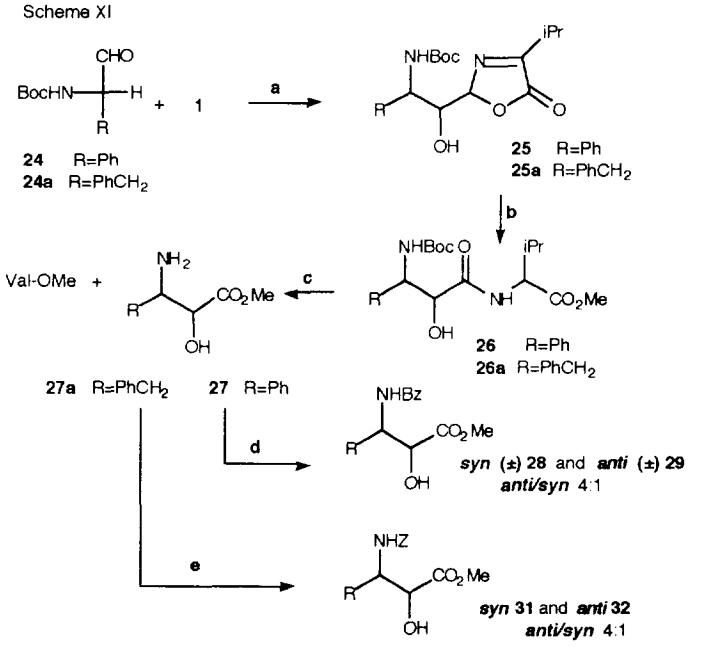


Acid-promoted regeneration of the aldehydic function from the adducts proceeded uneventfully with concomitant hydrolysis of the diol protective groups producing D-eryhthrose and *L*-4-deoxyribose respectively, which were isolated as peracetyl derivatives **20**[15] and **23**[16] by concentration *in vacuo* to dryness and treatment with Ac_2O-Py, the formed α-ketoacid being previously extracted with EtOAc from the aqueous solution.

Synthesis of β-amino α-hydroxy alkanoic acids

Development of new methodologies for the synthesis of non proteinogenic aminoacids is important because of the wide range of biological activities exhibited by these molecules. It is well known the essential role of the phenylisoserine C-13 side chain in the antitumor activity of taxol[17] or the crucial importance of β-amino-α-hydroxy alkanoic acids incorporated in small peptide analogues in determining selective Renin, HIV-protease and LTA4-hydrolase inhibition.[18,19] We initially decided to use the readily available racemic N-(tert-butoxycarbonyl)-phenylglycinal **24** as the electrophilic partner of the anion of **1**.

Scheme XI

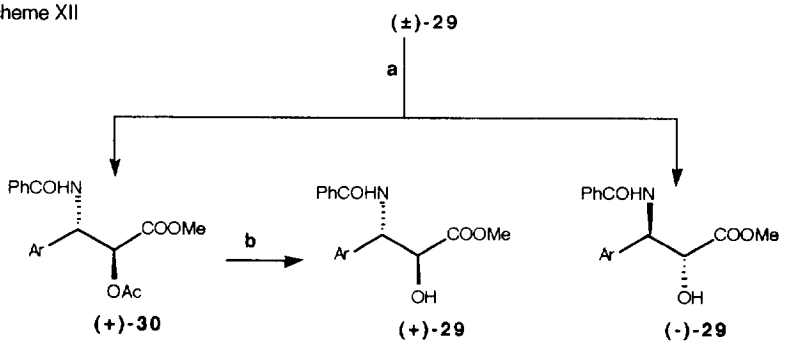


a, cat.Et_3N ; **b**, Et_3N- MeOH; **c**, HCl 6N, 120°C 12h, then $SOCl_2$- MeOH 12h ; **d**, BzCl/Et_3N; **e**, Z_2O.

The aldehyde **24** was prepared in excellent yield and satisfactory pure form by applying the two steps of Castro's procedure to the corresponding Boc-amino acid.[20] Under the usual condition the key carbon-carbon bond forming reaction produced the expected diastereomeric mixture **25** in which the heterocyclic ring system is in the 2*H* tautomeric form. With the aim of carrying out the desired isomerization we treated a methanolic solution of the chromatographically isolated mixture of adducts **25** with a catalytic amount of Et_3N, leaving the mixture at room temperature until completion (TLC control). After 36 hours, removal of solvent and chromatography on silica gel of the crude reaction mixture led us to obtain the diastereomeric dipeptides Boc-Phe-isoSer-ValOMe **26**, which resulted through a solvolytic ring cleavage taking place on the tautomer of **25**. Hydrolysis of the peptidic bond was achieved heating **26** in a sealed tube at 110°C for 12 hours. Subsequent treatment of the crude mixture with $SOCl_2$-MeOH, afforded the expected aminoacid methyl esters **27** together with Val-OMe that could be easily removed by chromatography. Selective N-benzoylation of the diastereomeric phenylisoserine methyl esters **27** was obtained by action of the benzoyl chloride/triethylamine system allowing isolation of a 4:1 mixture of racemic *anti* **29** and *syn* **28**. (Scheme XI)

The predominant *anti* racemate **29** could be resolved through enzyme mediated irreversible O-acylation effected by lipase from Pseudomonas *fluorescens* and using vinyl acetate as acyl donor[21] allowing to obtain equimolar quantity of 2(R),3(R)-N-benzoyl-3-phenylisoserine methyl ester (-)-**29**[22] and 2(S)-*O*-acetyl-N-benzoyl-(3S)-phenyl isoserine methyl ester (+)-**30**, which afforded (+)-**29** through p-toluenesulfonic acid-catalyzed methanolysis. The kinetic-enzymatic resolution, which allowed us to obtain in essentially quantitative yield and high optical purity the enantiomers of *anti* 3-phenylisoserine, doesn't work with the minor *syn* racemate (±)-**28**, at least under these experimental conditions.(Scheme XII)

Scheme XII



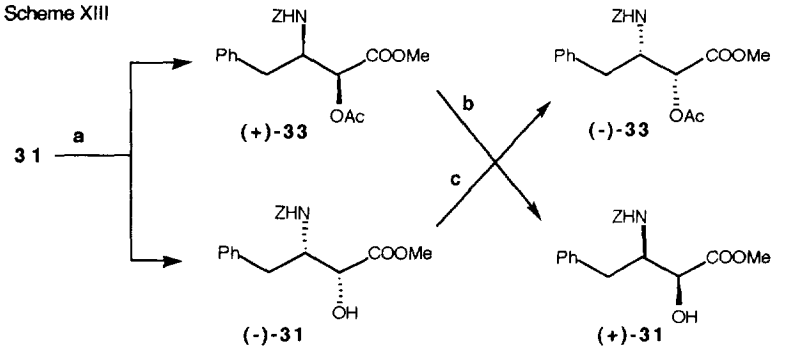
a, Lipase from*Pseudomonas Fluorescens*, tBuOMe, vinyl acetate, r.t., 4 days; **b**, *p*TsOH-MeOH.

In order to extend the methodology we repeated the sequence of chemical transformations reported in Scheme XI, starting from N-Boc-phenylalaninal,[20] in turn available from the inexpensive L-phenylalanine. The use of the natural aminoacid would allow us to prepare β-amino-α-hydroxy-phenylbutanoic acids (AHPBA) as well as to induce asymmetry in the key condensation reaction. However, contrary to our expectation, the N-Boc-phenylalaninal **24a** was rather unstable under the basic reaction medium: as a consequence, the optical purity of the 4:1 mixture of *anti*-**32** and *syn*-**31** AHPBA derivatives, obtained after N-selective benzyloxycarbonyl protection, was rather low (~30%). Fortunately, the kinetic enzymatic resolution, already successfully applied to

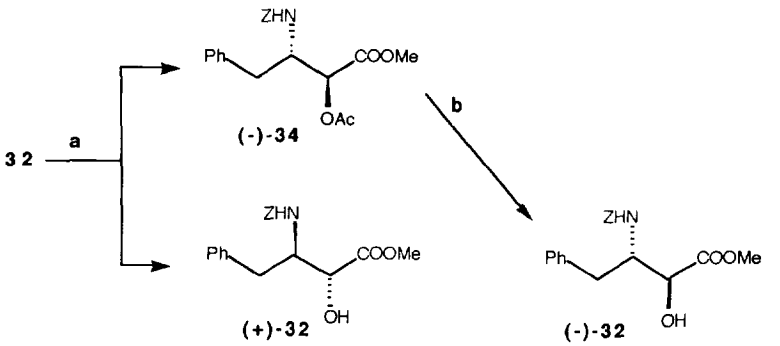
anti-phenylisoserine derivative (±)-**29**, proved to work efficiently for both diastereomers, allowing us to obtain (-)-**34** and (+)-**32** from **32** and (+)-**33** and (-)-**31** from **31**, respectively.

Interestingly, the major *anti*-isomer **32** needed 5 days at 35°C to be resolved, while longer times (20 days) were required for the minor *syn*-**31** and in both cases acetylation occured at the 2(S)-hydroxy functionality (Scheme XIII).

Scheme XIII



a, Lipase from*Pseudomonas Fluorescens* , tBuOMe, vinyl acetate, 37°C, 20days; **b**, *p*TsOH-MeOH; **c**: Ac_2O-Py



a, Lipase from*Pseudomonas Fluorescens*, tBuOMe, vinyl acetate, 37°C, 5days; **b**, *p*TsOH-MeOH.

Comparison between the measured optical rotatory powers with the reported ones[23] for (+)-**32** and (+)-**31** in addition to simple chemical manipulations such as acetylation with Ac_2O-Py of (-)-**31** and acid-catalyzed methanolysis of (+)-**33** and (-)-**34** is supporting evidence that the enzymatic resolution took place with high enantioselectivity.

Therefore, the diastereoselective reaction of a rather uncommon umpoled synthon for carboxyl group with aminoacid derived aldehydes, coupled with enantioselective resolution of the derived α-hydroxy-β-aminoacids, provides an alternative route to the preparation of these important molecules.

In summary, a convenient umpoled synthon for both formyl and hydroxycarbonyl anions has been developed and its chemistry explored. Its chemical behaviour presents several limitations, including its unreactivity towards alkyl halides and epoxides and the low diastereoselectivity in aldol reactions, and many interesting features including: a) facile preparation from common chemicals; b) the mild conditions required for the generation of the

anion and for demasking the functionalities contained in the heterocycle after carbon-carbon bond reaction has occurred; c) the exclusive 1,4-addition in Michael reaction, which make the anion of **1** an attractive tool especially suitable for obtaining 1,4-dicarbonyls and as an homologating agent in sugar chemistry.

Acknowledgment. We gratefully acknowledge Consiglio Nazionale delle Ricerche (Roma) and Ministero Pubblica Istruzione (Fondi 40% and 60%) for generous support.

Experimental Section

General Remarks. Melting points are uncorrected. Reactions were routinely monitored by thin layer chromatography (TLC) on silica gel coated plates F_{254} (Merck) and visualized with iodine, aqueous potassium permanganate, or methanolic ninhydrin. IR spectra were recorded with a Perkin-Elmer Model 297 instruments. Nuclear magnetic resonance (^{1}H NMR) spectra were taken on a Brüker AC-200 spectrometer for solutions in $CDCl_3$ unless otherwise noted; peak positions are given in parts per million downfield from tetramethylsilane as an internal standard, and δ values are given in Hertz. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Organic solutions were dried over anhydrous magnesium sulfate and evaporated with a rotary evaporator. Petroleum ether refers to the fractions boiling in the range 40-60 °C. Flash chromatography was carried out with Merck silica gel (230-400 mesh). All the reactions were carried out under N_2. Elemental analyses were performed by the microanalytical laboratory of Dipartimento di Chimica, University of Ferrara.

4-(1-Methylethyl)-2-oxazolin-5-one 1. To a stirred solution of N-formyl-valine (4.36 g, 30 mmol) in EtOAc (40 ml), cooled at 0 °C, was added DCC (6.2 g, 30 mmol). The mixture was stirred at room temperature for 2 hours. The precipitated urea was removed by filtration and the organic solvent evaporated under reduced pressure. The crude residue was purified by distillation (b.p. 60-62 °C, 3 mm/Hg) to afford **1** as a pale yellow oil (2.39 g, 62%). IR: (neat), 1820, 1650 cm^{-1}; ^{1}H NMR: δ 0.96 (d, 3H, J=6.8), 1.10 (d, 3H, J=6.8), 2.30 (m, 1H), 4.05 (dd, 1H, J=7, J=2.1), 7.60 (d, 1H, J=2.1). Anal. Calcd. for $C_6H_9NO_2$: C, 56.66; H, 7.14; N, 11.02. Found: C, 56.61; H, 7.13; N, 10.99.

General procedure for Michael addition and aldol condensation. To a stirred solution of **1** (8.5 mmol) in dry benzene or CH_2Cl_2(40 ml), cooled at 0 °C, two drops of triethylamine and the Michael acceptor (8.5 mmol) or aldehyde (8.5 mmol) were added. The mixture was stirred at room temperature for the appropriate time.The solvent was removed under vacuum, and the residue purified by flash chromatography to afford the Michael adducts and the condensation products in good yield.

2,5-Dihydro-4-(1-methylethyl)-5-oxo-2-oxazol-propionic aldehyde 5a. Reaction time: 1h; eluent: ether / petroleum ether 1:1, oil (72%). IR: (neat) 1780, 1725, 1650 cm^{-1}; ^{1}H NMR: δ 1.29 (d, 6H, J=6.8), 2.0-2.4 (m, 2H), 2.7 (t, 2H, J=7), 3.0 (m, 1H), 9.80 (s, 1H). Anal. Calcd. for $C_9H_{13}NO_3$: C, 58.99; H, 7.16; N, 7.65. Found: C, 59.02; H, 7.18; N, 7.65.

2,5-Dihydro-4-(1-methylethyl)-5-oxo-2-(3-oxobutyl)-oxazol-5-one 5b. Reaction time: 1h; eluent: ether / petroleum ether 1:1, oil (70%). IR: (neat) 1780, 1735, 1650 cm^{-1}; ^{1}H NMR: δ 1.28 (d, 6H, J=6.8), 2.12 (s, 3H), 2.0-2.4 (m, 2H), 2.66 (t, 2H, J=7), 3.0 (m, 1H), 9.80 (s, 1H). Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.88; H, 7.67; N, 7.10. Found: C, 60.91; H, 7.73; N, 7.11.

Methyl 2,5-dihydro-4-(1-methylethyl)-5-oxo-2-oxazol-propionate 5c. Reaction time: 1h; eluent: ether / petroleum ether 1: 2, oil (30%). IR: (neat) 1780, 1735, 1650 cm^{-1}; ^{1}H NMR: δ 1.28 (d, 6H, J=7), 2.0-2.4 (m, 2H), 2.5 (pt, 2H, J=7.2), 3.0 (m, 1H), 3.7 (s, 3H), 9.80 (s, 1H). Anal. Calcd. for $C_{10}H_{15}NO_4$: C, 56.31; H, 7.09; N, 6.57. Found: C, 56.29; H, 7.06; N, 6.61.

2,5-Dihydro-4-(1-methylethyl)-2-(2-nitroethyl)-oxazol-5-one 5d. Reaction time: 1h; eluent: ether / petroleum ether 2: 1, oil (70%). IR: (neat) 1780, 1650, 1550, 1360 cm^{-1}; ^{1}H NMR: δ 1.29 (d, 6H, J=7), 2.4-2.85 (m, 2H), 2.9-3.1 (m, 1H), 4.56 (t, 2H, J=6.65), 5.9-6.1 (m, 1H). Anal. Calcd. for $C_8H_{12}N_2O_4$: C, 47.98; H, 6.04; N, 14.0. Found: C, 48.01; H, 6.03; N, 13.99.

Methyl 2,5-dihydro-4-(1-methylethyl)-γ,5-dioxo-2-oxazol-undecanoate 5e. Reaction time: 6h; eluent: ether / petroleum ether 1: 1, oil (50%). IR: (neat) 1780, 1730, 1650 cm^{-1}; ^{1}H NMR: δ 1.1-1.4 (m, 6H), 1.28 (d, 6H, J=7), 1.45-1.70 (m, 4H), 1.9-2.1 (m, 1H), 2.1-2.25 (m, 1H), 2.3 (t, 2H, J=7.5), 2.43 (t, 2H, J=7.5), 2.56 (pt, 2H, J=7.5), 2.85-3.1 (m, 1H), 3.66 (s, 3H), 5.90 (m, 1H). Anal. Calcd. for $C_{18}H_{29}NO_5$: C, 63.68; H, 8.62; N, 4.13. Found: C, 63.65; H, 8.59; N, 4.12.

2,5-Dihydro-4-(1-methylethyl)-2-(3-oxocyclohexyl)-oxazol-5-one 5f. Reaction time: 10h; eluent: ether / petroleum ether 1: 1, oil (20%). IR: (neat) 1780, 1730, 1650 cm^{-1}; ^1H NMR: δ (diastereomeric mixture) 1.29 (d, 6H, J=7), 1.4-2.05 (m, 3H), 2.05-2.7 (m, 6H), 3.0 (m, 1H), 5.76 (m, 1H). Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.54; H, 7.68; N, 6.28. Found: C, 64.61; H, 7.63; N, 6.31.

2,5-Dihydro-4-(1-methylethyl)-2-(3-oxocyclopentyl)-oxazol-5-one 5g. Reaction time: 5h; eluent: ether / petroleum ether 1: 1, oil: (20%). IR: (neat) 1780, 1730, 1650 cm^{-1}; ^1H NMR: δ (diastereomeric mixture) 1.28 (d, 6H, J=7), 1.7-2.6 (m, 6H), 2.6-2.9 (m, 1H), 2.9-3.2 (m, 1H), 5.90 (m, 1H). Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.13; H, 7.23; N, 6.7. Found: C, 63.15; H, 7.23; N, 6.67.

General procedure for the regeneration of the aldehydic compounds. A solution of **5** (10 mmol) in THF (10 mL) was treated with aqueous 5% HCl (5 ml) and stirred at room temperature overnight. The solvent was evaporated under reduced pressure, water (10 ml) was added to the residue and the mixture extracted with EtOAc (3x15 ml). The extracts were washed with aqueous $NaHCO_3$ (20 ml), dried and evaporated to give **6**. The water-soluble compounds were isolated by concentration in vacuo of the aqueous solution to dryness after that the formed α-ketoacid has been extracted with EtOAc.

4-Oxopentanal 6b. Oil, (70%). IR: (neat) 1730, 1725 cm^{-1}; ^1H NMR: δ 2.20 (s, 3H), 2.74 (bs, 4H), 9.78 (s, 1H). Anal. Calcd. for $C_5H_8O_2$: C, 59.97; H, 8.06. Found: C, 59.81; H, 8.13.

Methyl 4-oxobutanoate 6c. Oil, (70%).IR: (neat) 1740 cm^{-1}; ^1H NMR: δ 2.43-3.03 (m, 4H), 3.68 (s, 3H), 9.78 (s, 1H). Anal. Calcd. for $C_5H_8O_3$: C, 51.7; H, 6.95. Found: C, 51.65; H, 7.01.

Methyl 9, 12-dioxododecanoate 6e. Oil, (70%). IR: (neat) 1730, 1725 cm^{-1}; ^1H NMR: δ 1.30 (m, 6H), 1.58 (m, 4H), 2.3 (t, 2H, J=7.3), 2.46 (t, 2H, J=7.3), 2.75 (m, 4H), 3.66 (s, 3H), 9.80 (s, 1H). Anal. Calcd. for $C_{13}H_{22}O_4$: C, 64.42; H, 9.16. Found: C, 64.41; H, 9.13.

3-Formylcyclohexanone 6f. Oil (75%). IR: (neat) 1730, 1725 cm^{-1}; ^1H NMR: δ 1.5-2.7 (m, 8H), 3.24 (m, 1H), 9.77 (s, 1H). Anal. Calcd. for $C_7H_{10}O_2$: C, 66.63; H, 7.99. Found: C, 66.61; H, 7.92.

3-Formylcyclopentanone 6g. Oil (70%). IR: (neat) 1730, 1725 cm^{-1}; ^1H NMR: δ 1.5-2.4 (m, 6H), 2.36 (3.24 (m, 1H), 9.77 (s, 1H). Anal. Calcd. for $C_6H_8O_2$: C, 64.26; H, 7.20. Found: C, 64.31; H, 7.22.

N-(Cyanopropionyl)-valine-3-[4-cyano-2-(1-methylethyl)]-pyridinyl ester 10. Reaction time: 1h; eluent: ether / petroleum ether 1: 1, pink solid, m.p. 139-141°C (ether), (80%). IR: (neat) 3500-3120, 2220, 1770, 1670 cm^{-1}; ^1H NMR: δ 1.13 (t, 6H, J=7.5), 1.23 (d, 3H, J=6.7), 1.25 (d, 3H, J=6.7), 2.4-2.6 (m, 1H), 2.71 (m, 4H), 3.1-3.4 (m, 1H), 4.92 (dd, 1H, J=8.76, J=4.88), 6.3 (d, 1H, J=8.8), 7.41 (d, 1H, J=4.88), 8.65 (d, 1H, J=4.88); ^{13}C NMR: δ 13.08, 17.42, 19.57, 21.18, 21.43, 29.69, 30.42, 31.36, 57.47, 113.65, 115.14, 118.92, 123.43, 143.84, 147.80, 161.90, 169.36, 169.53. Anal. Calcd. for $C_{18}H_{22}N_4O_3$: C, 63.13; H, 6.48; N, 16.37. Found: C, 63.11; H, 6.43; N, 11.34.

2,5-Dihydro-2-(3-hydroxy-4-methoxymethyloxy-2-nitropentyl)-4-(1-methylethyl)-oxazol-5-one 12 and 13. To a cooled (0 °C) mixture of **5d** (0.8 g, 4.3 mmol) and S-(-)-methoxymethyloxypropan-1-al (0.5 g, 4.3 mmol), KF/Al_2O_3 (10% KF in Al_2O_3) (1.2 g) was added. After stirring at room temperature for 24 hours. the catalyst was filtered and washed with CH_2Cl_2. The organic solvents were removed under reduced pressure, and the residue purified by flash chromatography (eluent: ether / petroleum ether 2:1), to afford **12** and **13** as a 1:1 mixture of diastereomers with practically identical spectroscopic characteristics. IR: (neat) 3600-3100, 1780, 1650, 1550 cm^{-1}; ^1H NMR: δ 1.30 (m, 9H), 2.7-3.15 (m, 3H), 3.38 (s, 3H), 3.55-3.85 (m, 2H), 4.5-5.1 (m, 2H), 4.64 (s, 2H), 5.8-6.1 (m, 1H). Anal. Calcd. for $C_{13}H_{22}N_2O_7$: C, 49.03; H, 6.97; N, 8.80. Found: C, 49.01; H, 6.93; N, 8.76.

3-Nitro-2,3,6-trideoxy-hexapyranose 14. To a solution of **12** or **13** (1 g, 3.14 mmol) in dry acetone (20 ml) aqueous 10% HCl (2 ml) was added and the mixture stirred at room temperature for 6h. After this time the solvent was removed under reduced pressure, the residue dissolved in EtOAc (20 ml), the dried organic solution concentrated in vacuo and the crude product purified by flash chromatography (eluent: EtOAc / petroleum ether 1:1) to afford **14** as a yellow oil (0.2 g, 43%), $[\alpha]^D_{25}$ = -61.25 (c 2, EtOH). IR: (neat) 3600-3100, 1550, 1350 cm^{-1}; ^1H NMR: (acetone d_6) δ 1.23 (d, 3H, J=6.1), 2.2 (ddd, 1H, J=12.37, J=3.3, J=1.55), 2.34 (ddd, 1H, J=12.37, J=4.66, J=1.55), 3.65 (dt, 1H, J=9.62, J=3.52, t after exchange with D_2O, J=9.62), 3.93 (dq, 1H, J=9.48, J=6.1), 4.7-4.9 (m, 1H), 4.94 (d, 1H, J=3.52, exchangeable with D_2O), 5.34 (bt, 1H), 5.61 (dd, 1H, J=3.65, J=1.8). Anal. Calcd. for $C_6H_{11}NO_5$: C, 40.66; H, 6.26; N, 7.91. Found: C, 40.70; H, 6.22; N, 7.88.

Methyl Ristosaminide Hydrochloride 15 To a cooled (0 °C) saturated methanolic solution of HCl (20 ml) **14** (0.2 g, 1.12mmol)was added and the mixture stirred at room temperature for 24h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (eluent: EtOAc / petroleum ether 1:2) to afford a pale yellow oil (60 mg, 30%), which was dissolved in methanol (6ml) and treated with acetyl

chloride (0.026 ml, 0.36 mmol). PtO_2 (70 mg, prereduced in 2 ml of methanol) was added and the mixture stirred for 7 days at room temperature under 50 psi of hydrogen. After filtration through a pad of celite, the solvent was evaporated in vacuo to give **15** (40 mg, 55%) as a white solid, m.p; 168-170 °C (methanol : acetone 1:1), $[\alpha]^{D}_{25}$ = -123.8 (c 1, H_2O). Anal. Calcd. for $C_7H_{16}NO_3Cl$: C, 42.62; H, 8.18; N, 7.11. Found: C, 42.67; H, 8.13; N, 7.16.

Methyl *N,O*-Diacetylristosaminide 16. To a solution of **15** (0.2 g, 1 mmol) in dry pyridine (2 ml) acetic anhydride (2 ml) was added and the mixture stirred at room temperature for 24 h. The solution was poured in ice-water (50 ml) and extracted with chloroform (3x20ml). The combined organic phases were washed with brine(10 ml), dried and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent: methanol / benzene 15:85) to afford **16** (0.109 g, 40%) as a white solid, m.p. 51-52 °C (ether), $[\alpha]^{D}_{25}$=-134 (c 2, $CHCl_3$); IR: (nujol) 1710, 1670 cm^{-1}; ^1H NMR: δ 1.22 (d, 3H, J=7), 1.89 (ddd, 1H, J=14, J=2.5, J=0.8), 2.0 (s, 3H), 2.02 (s, 3H), 2.09 (ddd, 1H, J=14, J=4, J=3.5), 3.43 (s, 3H), 3.98 (m, 1H), 4.57 (dd, 1H, J=9.5, J=4), 4.66 (m, 1H), 4.79 (dd, 1H, J=4, J=0.8). Anal. Calcd. for $C_{11}H_{19}NO_5$: C, 53.85; H, 7.81; N, 5.71. Found: C, 53.88; H, 7.85; N, 5.66.

2,5-Dihydro-2-(1-hydroxyethyl)-4-(1-methylethyl)-oxazol-5-one 17a. Reaction time: 2h,. eluent: ether / petroleum ether 1: 1, oil (61%). IR: (neat) 3500-3300, 1780, 1630 cm^{-1}; ^1H NMR: δ (diastereomeric mixture) 1.4-1.5 (m, 9H), 2.0 (bs, 1H), 3.0 (m, 1H), 4.11 (m, 1H), 5.8 (m, 1H). Anal. Calcd. for $C_8H_{13}NO_3$: C, 56.11; H, 7.66; N, 8.18. Found: C, 56.11; H, 7.63; N, 8.19.

2,5-Dihydro-2-(1-hydroxypropyl)-4-(1-methylethyl)-oxazol-5-one 17b. Reaction time: 2h, eluent: ether-petroleum ether 1:1, oil (60%). IR: (neat) 3500-3300, 1780, 1630 cm^{-1}; ^1H NMR: δ (diastereomeric mixture) 1.08 (t, 3H, J=7.4), 1.29 (d, 6H, J=6.9), 1.55-1.8 (m, 2H), 3.0 (m, 1H), 3.76 (m, 1H), 5.8 (m, 1H). Anal. Calcd for $C9H15NO_3$.

2,5-Dihydro-4-(1-methylethyl)-5-oxo-2-(α-phenyl)-oxazolemethanol 17c. Reaction time: 8h, eluent: EtOAc / petroleum ether 1: 4, oil (50%). IR: (neat) 3400, 1780 cm^{-1}; ^1H NMR: δ (diastereomeric mixture) 1.08 (d, 3H, J=6.9), 1.19 (d, 3H, J=6.9), 2.8 (s, 1H), 2.9 (m, 1H), 5.5 (m, 1H), 7.3-7.5 (m, 5H). Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.92; H, 6.49; N, 6.01. Found: C, 66.89; H, 6.48; N, 6.03.

2,5-Dihydro-4-(1-methylethyl)-5-oxo-2-[α-(2-nitrophenyl)]-oxazolemethanol 17d. Reaction time: 1h, eluent: EtOAc / petroleum ether 1: 4, pale yellow solid, m.p. 123-124 °C (ether / petroleum ether), (60%). IR: (KBr) 3400, 1760, 1510, 1330 cm^{-1}; ^1H NMR: δ (diastereomeric mixture) 1.25 (d, 3H, J=6.9), 1.27 (d, 3H, J=6.9), 2.9-3.1 (m, 1H), 3.2 (d, 1H, J=6), 5.8 (m, 1H), 6.3 (m, 1H), 7.4-8.1 (m, 5H). Anal. Calcd. for $C_{13}H_{14}N_2O_5$: C, 56.10; H, 5.07; N, 10.07. Found: C, 56.11; H, 5.03; N, 10.09.

2,5-Dihydro-4-(1-methylethyl)-5-oxo-2-[α-(4-nitrophenyl)]-oxazolemethanol 17e. Reaction time: 2h; eluent: ether / petroleum ether 6:4, pale yellow solid, m.p. 121-123 °C (EtOAc / petroleum ether, 3:1), (68%). IR: (KBr) 3400, 1770, 1500, 1340 cm^{-1}; ^1H NMR: δ (diastereomeric mixture) 1.06 (d, 3H, J=6.8), 1.11 (d, 3H, J=6.8), 2.7-3.0 (m, 1H), 5.2 (m, 1H), 6.2-6.4 (m, 2H), 7.65 (d, 2H, J=8.7), 8.2 (d, 2H, J=8.7). Anal. Calcd. for.$C_{13}H_{14}N_2O_5$: C, 56.10; H, 5.07; N, 10.07. Found: C, 56.13; H, 5.09; N, 10.11.

2,5-Dihydro-4-(1-methylethyl)-5-oxo-2-[α-(3-pyridyl)]-oxazolemethanol 17f. Reaction time: 5h; eluent: EtOAc, white solid, m.p. 138-140 °C (ether / petroleum ether, 1:1), (60%). IR: (KBr) 3300-3000, 1770 cm^{-1}; ^1H NMR: δ (diastereomeric mixture) 1.09 (d, 3H, J=6.9), 1.18 (d, 3H, J=6.9), 2.7-3.0 (m, 1H), 5.2 (m, 1H), 6.2 (m, 2H), 7.2-7.4 (m, 1H), 7.7-7.9 (m, 1H), 8.5-8.6 (m, 2H). Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.51; H, 6.03; N, 11.96. Found: C, 61.54; H, 6.00; N, 11.99.

2,5-Dihydro-4-(1-methylethyl)-5-oxo-2-[α-(2,2-dimethyl-1,3-dioxolan-4-yl)]-oxazolemethanol 19. Reaction time: 2h; eluent: EtOAc / petroleum ether 1:4, white solid, m.p. 90-91 °C (ether / petroleum ether 1:1), (60%), $[\alpha]^{D}_{25}$ = -75 (c 0.8, MeOH). IR: (KBr) 3400, 1780 cm^{-1}; ^1H NMR: δ 1.25 (d, 6H, J=6.5), 1.4 (s, 3H), 1.5 (s, 3H), 3.0 (m, 1H), 3.2 (bs, 1H), 4.0-4.2 (m, 3H), 4.3-4.5 (m, 1H), 6.15 (m, 1H); ^{13}C NMR: δ 19.06, 19.19, 25.11, 26.93, 28.36, 66.89, 71.15, 75.26, 98.93, 109.99, 165.41, 169.84. Anal. Calcd. for $C_{12}H_{19}NO_5$: C, 56.00; H, 7.45; N, 5.45. Found: C, 56.04; H, 7.43; N, 5.40.

2,5-Dihydro-4-(1-methylethyl)-5-oxo-2-[α-(2-phenyl-1,3-dioxan-4-yl)]-oxazolemethanol 22. Reaction time: 1.5h; eluent: ether / petroleum ether 1:1, oil (70%), $[\alpha]^{D}_{25}$ = +13.6 (c 0.8, MeOH). IR: (KBr) 3450, 1770, 1640 cm^{-1}; ^1H NMR: δ 1.27 (d, 6H, J=6.9), 1.7-1.9 (m, 2H), 2.8-3.1 (m, 1H), 3.1 (d, 1H, J=6), 3.9-4.4 (m, 4H), 5.6 (s, 1H), 6.2 (m, 1H), 7.3-7.4 (m, 3H), 7.4-7.5 (m, 2H); ^{13}C NMR: δ 19.04, 19.15, 28.24, 28.36, 66.79, 72.36, 76.25, 98.31, 100.89, 126.03, 128.21, 128.92, 138.11, 165.39, 169.62. Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.92; H, 6.63; N, 4.39. Found: C, 63.97; H, 6.65; N, 4.37.

1,2,3-Tri-*O*-acetyl-D-erythrofuranose 20. A solution of **19** (1.45 g, 5.6 mmol) in THF (25 ml) and aqueous 5% HCl (5 ml) was stirred at room temperature for 4h. The solvent was evaporated under reduced pressure, the residue dissolved in EtOAc (30 mL) and extracted with water (3x15 ml). The aqueous phase was concentrated in vacuo and the residue was exchanged three times with anhydrous pyridine (10 ml) by evaporation at 30°C in vacuo. To a solution of the dried syrup in anhydrous pyridine (10 ml) was added acetic anhydride (2.6 ml) dropwise below 15°C. The reaction mixture was stored overnight at 4°C, then ice-water (30 ml) was added and the solution stirred for 30 min. The mixture was extracted with $CHCl_3$ (3x20 ml), the combined organic extracts were washed with ice-cold saturated aqueous $NaHCO_3$ (3x10 ml), dried and concentrated in vacuo to a syrup which was purified by column chromatography on silica gel (eluent: ether / petroleum ether 6:4) to give **20** as a colorless syrup (0.76g, 55%) containing the mixture of α (12%) and β (88%) anomers as indicated by NMR integration, $[\alpha]^{D}_{25}$ = -67° (c 2.2, $CHCl_3$). IR: (neat) 1750, 1220 cm^{-1}; ^1H NMR: for β anomer: δ 2.08 (s, 6H), 2.11 (s, 3H), 3.98 (dd, 1H, J=4.3 Hz, J=9.9 Hz), 4.31 (dd, 1H, J=5.8 Hz, J=9.9 Hz), 5.32 (m, 1H), 5.47 (m, 1H), 6.15 (d, 1H, J=1.3 Hz), for α anomer 6.34 (d, J=4.6 Hz). ^{13}C NMR δ 20.06, 20.13, 20.60, 70.34, 70.39, 74.60, 98.63, 169.09, 169.13, 169.66.

1,2,3-Tri-O-acetyl-4-deoxy-β-L-erythropyranose 23. A mixture of **22** (0.36 g, 1.12 mmol) in THF (5 ml) and aqueous 5% HCl (1ml) was stirred at room temperature for 4h. The solvent vas evaporated under reduced pressure and the residue dissolved in EtOAc (15 ml) and extracted with water (3x5 ml). The aqueous layer was concentrated in vacuo and the residue dissolved in dry pyridine (1 ml), cooled at 0 °C and treated with acetic anhydride (1 ml). After the mixture has being stirred at room temperature overnight, the solvent was removed under reduced pressure. The residue was dissolved in ether (20 ml) and washed with aqueous 5% sodium bicarbonate. The dried organic phase was evaporated under reduced pressure and the crude residue purified by flash chromatography (eluent: ether / petroleum ether 6:4) to afford **23** (0.2 g, 70%) as a white solid m.p. 86-87 °C (ether / petroleum ether). $[\alpha]^{D}_{25}$ = +51 (c 1.3, $CHCl_3$). IR: (KBr) 1750, 1370, 1220 cm^{-1}; ^1H NMR: δ 1.7-2.2 (m, 2H), 2.0 (s, 3H), 2.13 (s, 6H), 3.9-4.0 (m, 2H), 5.0-5.1 (m, 1H), 5.3-5.5 (m, 1H), 6.0 (d, 1H, J=3.3). ^{13}C NMR δ 20.73, 20.87, 26.49, 60.63, 66.47, 67.53, 91.33, 168.79, 169.77, 169.97. Anal. Calcd. for $C_{11}H_{16}O_7$: C, 50.75; H, 6.20. Found: C, 50.70; H, 6.22.

Reaction between N-(t-butoxycarbonyl)-phenylglycinal 24 or (S)-N-(t-butoxycarbonyl) phenylalaninal 24a and 1. General procedure: to an ice cooled solution of the selected aldehyde (1mmol) in CH_2Cl_2 (10ml) containing two drops of triethylamine, a solution of **1** (1.5mmol) in CH_2Cl_2 (5ml) was added dropwise and the mixture left at room temperature until completion (TLC control). The solvent was evaporated at reduced pressure and the residue was flash chromatographed (eluent: ether: petroleum ether 6:4) to afford the corresponding addition adducts **25** and **25a** respectively.

Methanolysis of the adducts 25 and 25a. General procedure: a solution of the the required compound (1mmol) in methanol (20ml) containing a few drops of triethylamine was stirred at room temperature for 36h. The solvent was removed under reduced pressure and the crude residue used in the next step.

Hydrolysis of methyl esters 26 and 26a. General procedure: the ester (100mg) was dissolved in HCl 6N (100ml) and the resulting solution heated in a sealed tube at 110° C for 12h. The reaction mixture was diluted with ethanol (3ml) and evaporated under reduced pressure. A methanolic solution of $SOCl_2$ (prepared at -10° C by adding $SOCl_2$ (12ml) to methanol (40ml)) was added to the residue and the mixture stirred at room temperature overnight. After the solvent has been evaporated in vacuo, triethylamine (5ml) was added to a solution of the residue in methanol (20ml) and the mixture stirred for 10 min. The solvent was removed under reduced pressure and the residue purified by flash-chromatography (eluent: CH_2Cl_2 / $CHCl_3$ / CH_3OH / NH_4OH, 10:4:1:1) to separate valine methyl ester from the diastereomeric mixtures of aminoacids methyl esters **27** and **27a**, which were N-protected in the subsequent steps.

***Syn* and *anti*-(±)-2-Hydroxy-3-(benzoylamino)-3-phenylpropanoic acid methyl esters 28 and 29.** A cooled (0°C) solution of **27** (0.5g, 2.6mmol) in CH_2Cl_2 (10ml) was treated with benzoyl chloride (0.3ml, 2.6mmol), triethylamine (0.37ml, 2.6mmol) and catalytic 4-dimethylaminopyridine and the mixture stirred at room temperature for 30 min. The reaction mixture was washed with brine (10ml), dried and evaporated. The residue was chromatographed through a flash silica gel column (eluent: EtOAc : petroleum ether 4:6) to give **28** and **29** (0.61g, 80% yield). IR: (KBr): 3510, 3440, 1750, 1640 cm^{-1}; (±)-syn isomer **28**, m.p.164 °C; ^1H NMR: δ 3.5 (bs, 1H), 3.82 (s, 3H), 4.62 (d, 1H, J=2), 5.74 (dd, 1H, J=2, 9), 7.05 (d, 1H, J=9), 7.25-7.5 (m, 8H), 7.73-7.78 (m, 2H); (±) anti-isomer **29**, m.p.135 °C; ^1H NMR: δ 3.3 (d, 1H, J=6.6), 3.70 (s, 3H), 4.69 (dd, 1H, J=3.6, 6.5), 5.61 (dd, 1H, J=3.6, 8.6), 7.2-7.6 (m, 9H), 7.8-7.83 (m, 2H). Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.20; H, 5.73; N, 4.68. Found: C, 68.15; H, 5.80; N, 4.66.

(2R,3R)-2-Hydroxy-3-(benzoylamino)-3-phenylpropanoic acid methyl ester (-)-29 and (2S,3S)-2-Acetyloxy-3-(benzoylamino)-3-phenylpropanoic acid methyl ester (+)-30. To a solution of the anti racemate (±)-**29** (120mg, 0.4mmol) in anhydrous t-butyl methyl ether (20ml) vinyl acetate (0.11ml, 1.2mmol) and Lipase from *Pseudomonas Fluorescens* (8mg) were added. The suspension was vigorously stirred at room temperature for 4 days. After filtration of the enzyme, the solvent was evaporated under reduced pressure and the residue purified by flash column chromatography (eluent: EtOAc : petroleum ether 3:7 then EtOAc : petroleum ether 1:1) to give the (2R,3R) anti isomer (-)-**29** (54mg, 90%) as a white solid, m.p.158 °C; $[\alpha]^{D}_{25}$ = -9 (c 1, MeOH). IR: (KBr) 3510, 3440, 1750, 1640 cm^{-1}; ^1H NMR: δ 3.3 (d, 1H, J=6.6), 3.70 (s, 3H), 4.69 (dd, 1H, J=3.6, 6.5), 5.61 (dd, 1H, J=3.6, 8.6), 7.2-7.6 (m, 9H), 7.8-7.83 (m, 2H). Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.20; H, 5.73; N, 4.68. Found: C 68.15; H, 5.70; N, 4.76. (2S,3S) anti isomer (+)-**30** (61mg, 90%), as an oil: $[\alpha]^{D}_{25}$ = +28.7 (c 2, MeOH). IR: (neat): 3440, 1750, 1640 cm^{-1}; ^1H NMR: δ 2.14 (s, 3H), 3.62 (s, 3H), 5.47 (d, 1H, J=5.1), 5.78 (dd, 1H, J=5.1, 8), 7.2 (d, 1H, J=8), 7.3-7.6 (m,8H), 7.78-7.82 (m, 2H). Anal. Calcd. for $C_{19}H_{19}NO_5$: C, 66.84; H, 5.61; N, 4.10. Found: C, 66.80; H, 5.70; N, 4.05.

(2S,3S)-2-Hydroxy-3-(benzoylamino)-3-phenylpropanoic acid methyl ester (+)-29. To a solution of (+)-**30** (100mg, 29mmol) in methanol (10ml), a few crystals of p-TsOH were added and the mixture stirred at room temperature overnight. The solvent was evaporated and the residue purified by flash column chromatography (eluent: EtOAc : petroleum ether 3:7) to give (+)-**29** (70mg, 80%) as a white solid, m.p.164-165 °C; $[\alpha]^{D}_{25}$ = +8 (c 1, MeOH). IR: (KBr) 3510, 3440, 1750, 1640 cm^{-1}; ^1H NMR: δ 3.3 (d, 1H, J=6.6), 3.70 (s, 3H), 4.69 (dd, 1H, J=3.6, 6.5), 5.61 (dd, 1H, J=3.6, 8.6), 7.2-7.6 (m, 9H), 7.8-7.83 (m, 2H). Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.20; H, 5.73; N, 4.68. Found: C 68.15; H, 5.70; N, 4.76.

***Syn* and *anti* 2-Hydroxy-3-(benzyloxycarbonylamino)-4-phenylbutanoic acid methyl esters 31 and 32.** To a cooled (0° C) solution of **27a** (350mg, 1.67mmol) in CH_2Cl_2 (20ml) dibenzyl-dicarbonate (480mg, 1.67mmol) was added and the mixture stirred at room temperature for 1h. The solvent was evaporated and the residue chromatographed through a flash silica gel column (eluent: EtOAc / petroleum ether 3:7) to give **31** and **32** (0.48g, 85%). IR: (KBr): 3510, 3440, 1750, 1640 cm^{-1}; *syn*-isomer **31**: $[\alpha]^{578}_{25}$ = -27.5 (c=1, MeOH), (optical purity:.~30%); m.p.88-90 °C; ^1H NMR: δ 2.95 (m, 2H), 3.15 (d, 1H, J=4.2), 3.7 (s, 3H), 4.08 (m, 1H), 4.3 (m, 1H), 5.03 (s, 2H), 5.1 (d, 1H, J=9), 7.3 (m, 10H); *anti*-isomer **32**: m.p.112-114 °C; $[\alpha]^{578}_{25}$ = -2 (c 1, MeOH), (optical purity:.~30%); ^1H NMR: δ 2.8 (m, 2H), 3.10 (d, 1H, J=4), 3.56 (s, 3H), 4.40 (m, 2H), 5.05 (s, 2H), 5.1 (d, 1H, J=9), 7.3 (m, 10H). Anal. Calcd. for $C_{19}H_{21}NO_5$: C, 66.44; H, 6.17; N, 4.08. Found: C, 66.50; H, 6.15; N, 4.04.

(2R,3R)-2-Hydroxy-3-(benzyloxycarbonylamino)-4-phenylbutanoic acid methyl ester (+)-32 and (2S,3S)-2-Acetyloxy-3-(benzyloxycarbonylamino)-4-phenylbutanoic acid methyl ester (-)-34. To a solution of **32** (100mg, 0.3mmol) in anhydrous t-butyl methyl ether (20ml) vinyl acetate (0.08ml, 0.9mmol) and Lipase from *Pseudomonas Fluorescens* (7mg) were added. The suspension was vigorously stirred at 35°C for 5d. After filtration of the enzyme, the solvent was evaporated under reduced pressure and the residue purified by flash column chromatography (eluent: EtOAc : petroleum ether 3:7 then EtOAc : petroleum ether 1:1) to afford (+)-**32** (140mg) and (-)-**34** (35mg) as white solids (90% yield). (2R,3R) *anti*-isomer (+)-**32**, m.p.121 °C; $[\alpha]^{578}_{25}$ = +6 (c 1, MeOH). IR: (KBr): 3510, 3440, 1750, 1640 cm^{-1}; ^1H NMR: δ 2.8 (d, 2H, J=7), 3.25 (m, 1H), 3.57 (s, 3H), 4.34 (m, 2H), 5.05 (s, 2H), 5.1 (d, 1H, J=9), 7.3 (m, 10H). Anal. Calcd. for $C_{19}H_{21}NO_5$: C, 66.44; H, 6.17; N, 4.08. Found: C, 66.40; H, 6.15; N, 4.14. (2S,3S) *anti*-isomer (-)-**34**: m.p. 84 °C; $[\alpha]^{578}_{25}$ = -24.5 (c 1, MeOH). IR: (KBr): 3440, 1750, 1640 cm^{-1}; ^1H NMR: δ 2.2 (s, 3H), 2.87 (d, 2H, J=7), 3.66 (s, 3H), 4.5 (m, 1H), 4.95 (d, 1H, J=8.8), 5.03 (s, 2H), 5.16 (bs, 1H), 7.3 (m, 10H). Anal. Calcd. for $C_{21}H_{23}NO_6$: C, 65.43; H, 6.02; N, 3.64. Found: C, 65.47; H, 6.00; N, 3.62.

(2S,3S)-2-Hydroxy-3-(benzyloxycarbonylamino)-4-phenylbutanoic acid methyl ester (-)-32. To a solution of (-)-**34** (100mg, 0.26mmol) in methanol (10ml), a crystal of pTsOH was added and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by flash column chromatography (eluent: EtOAc : petroleum ether 3:7) to give (-)-**32** (75mg, 85%) as a white solid: m.p. 121 °C; $[\alpha]^{578}_{25}$=-7 (c 0.7, MeOH). IR: (KBr): 3510, 3440, 1750, 1640 cm^{-1}; ^1H NMR: δ 2.81 (m, 2H), 3.22 (d, 1H, J=7), 3.57 (s, 3H), 4.33 (m, 2H), 5.05 (s, 2H), 5.1 (d, 1H, J=9), 7.3 (m, 10H). Anal. Calcd. for $C_{19}H_{21}NO_5$ requires C, 66.44; H, 6.17; N, 4.08. Found: C, 66.40; H, 6.15; N, 4.14.

(2R,3S)-2-Hydroxy-3-(benzyloxycarbonylamino)-4-phenylbutanoic acid methyl ester (-)-31 and (2S,3R)-2-Acetyloxy-3-(benzyloxycarbonylamino)-4-phenylbutanoic acid methyl ester (+)-33. To a solution of **31** (100mg, 0.3mmol) in anhydrous t-butyl methyl ether (20ml) vinyl acetate (0.08ml, 0.9mmol) and Lipase from *Pseudomonas Fluorescens* (7mg) were added. The suspension was vigorously stirred at 35°C for 20d. After filtration of the enzyme, the solvent was evaporated under reduced pressure and the

residue purified by flash column chromatography (eluent: EtOAc : petroleum ether 3:7 then EtOAc : petroleum ether 1:1) to give (-)-**31** (102mg) as a white solid, m.p. 96° C; $[\alpha]^{578}_{25}$ = -86 (c 1.05, MeOH). IR: (KBr): 3510, 3440, 1750, 1640 cm^{-1}; ^1H NMR: δ 2.93 (m, 2H), 3.15 (bs, 1H), 3.70 (s, 3H), 4.08 (d, 1H, J=1.64), 4.3 (m, 1H), 5.04 (s, 2H), 5.1 (d, 1H, J=9), 7.3 (m, 10H). Anal. Calcd. for $C_{19}H_{21}NO_5$: C, 66.44; H, 6.17; N, 4.08. Found: C, 66.40; H, 6.15; N, 4.14, and (+)-**33** (24mg) as an oil (80% yield), $[\alpha]^{578}_{25}$ = +62 (c 1.25, MeOH). IR: (neat): 3440, 1750, 1640 cm^{-1}; ^1H NMR: δ 2.19 (s, 3H), 2.8 (dd, 1H, J=8.7, 13.6), 2.95 (dd, 1H, J=6.7, 13.6), 3.66 (s, 3H) 4.5 (m, 1H), 4.93 (d, 1H, J=1.99), 5.05 (d, 2H, J=1.68), 5.15 (d, 1H, J=10), 7.3 (m, 10H). Anal. Calcd. for $C_{21}H_{23}NO_6$: C, 65.43; H, 6.02; N, 3.64. Found: C, 65.47; H, 6.00; N, 3.62.

(2S,3R)-2-Hydroxy-3-(benzyloxycarbonylamino)-4-phenylbutanoic acid methyl ester (+)-31. To a solution of (+)-**33** (100mg, 0.26mmol) in methanol (10ml), a few crystals of p-TsOH were added and the mixture stirred at room temperature overnight. The solvent was evaporated and the residue flash chromatographed (eluent: EtOAc : petroleum ether 3:7) to afford (+)-**31** (75mg, 85%) as a white solid: m.p. 93-95 °C; $[\alpha]^{578}_{25}$=+80 (c 0.95, MeOH). IR: (KBr): 3510, 3440, 1750, 1640 cm^{-1}; ^1H NMR: δ 2.93 (m, 2H), 3.15 (bs, 1H), 3.70 (s, 3H), 4.08 (d, 1H, J=1.64), 4.3 (m, 1H), 5.04 (s, 2H), 5.1 (d, 1H, J=9.5), 7.3 (m, 10H). Anal. Calcd. for $C_{19}H_{21}NO_5$: C, 66.44; H, 6.17; N, 4.08. Found: C, 66.40; H, 6.15; N, 4.14.

(2R,3S)-2-Acetyloxy-3-(benzoyloxycarbonylamino)-4-phenylbutanoic acid methyl ester (-)-33. To a cooled (0°C) solution of (-)-**31** (100mg, 0.29mmol) in pyridine (10ml) Ac_2O (0.027ml, 0.29mmol) was added and the mixture stirred at room temperature for 4h. The reaction mixture was washed with brine (10ml), dried and evaporated. The residue was chromatographed on a silica gel column (eluent: EtOAc : petroleum ether 3:7) yielding (-)-**33** (97mg, 87%) as an oil: $[\alpha]^{578}_{25}$ = -59 (c 1.05, MeOH); IR (neat): 3150,1750,1640 cm^{-1}; ^1H NMR: δ 2.16 (s, 3H), 2.93 (m, 2H), 3.15 (bs, 1H), 3.70 (s, 3H), 4.08 (d, 1H, J=1.64), 4.3 (m, 1H), 5.04 (s, 2H), 5.19 (d, 1H, J=9), 7.3 (m, 10H). Anal. Calcd. for $C_{21}H_{23}NO_6$: C 65.43; H, 6.02; N, 3.64. Found: C, 65.47; H, 6.00; N, 3.62.

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