Tetrahedron: Asymmetry Vol. 2, No. 10, pp. 1063-1074, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

Single and Double Asymmetric Induction in the Cycloaddition of Chiral Nitrones to Achiral and Chiral Vinylphosphine Oxides

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(*Received* 6 *August* 1991)

Key words: Chiral nitrones; Chiral vinylphosphine oxides; Double asymmetric induction; 1,3-Dipolar cycloaddition; C-Phosphinyl aminotriols

Abstract: The asymmetric 1,3-dipolar cycloadditions of the chiral α,β-dialkoxynitrones (4S)-(Z)-N-(2,2-dimethyl-1,3-dioxolan-4-yl)methylenebenzylamineN-oxide **3** *and (4S,5S)-(Z)-N-(2,2,5-trimethyl-1,3-dioxolan-4-yl) methylene-benzylamine N-oxide* **4a** *to diphenylvinylphosphine oxide* **2** *give, besides complex mixtures of all the possible regio- and diastereoisomers, one major isomer,* **5a** *and* **8a** *respectively, consisting of 65% of the total isomeric amount. This compounds have been assigned the erythro C(3)-C(4') configurations deriving from the most reactive conformation* **A** *or* **B** *through an endo transition state. The cycloaddition of the same nitrones with racemic and enantiomerically pure (–)-S-methylphenylvinylphosphine oxide* (**1**) *allowed the study of the double asymmetric induction. The selectivity towards the erythro compounds increases remarkably to ca. 40:1 for the endo approach, indicating that (2S)-nitrones* **3** *or* **4a** *and (S)-phosphine oxide* **1** *constitute a matched pair of reactants. The synthesized phosphinylisoxazolidines can be conveniently transformed into selectively protected C-phosphinyl- aminotriols. An illustrative example of the synthesis of the novel fully and selectively protected 1-phosphinyl- seco-daunosamine* **22** *is reported.*

The use of 1,3-dipolar cycloaddition reactions as a means to control the stereochemistry in acyclic systems has been extensively exploited.[1] Particularly, chiral isoxazolidine cycloadducts turned out to be highly valuable building blocks for stereoselective synthesis of functionalized molecules.[2]

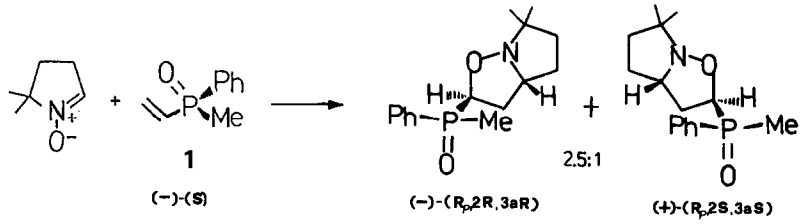
Chiral isoxazolidines can be derived either from chiral nitrones[3] or, less frequently, from chiral dipolarophiles.[4] In a single case both reagents have been employed in an enantiomerically pure form.[5]

Our recent discovery of considerable stereoselectivity in nitrone cycloaddition to chiral and prochiral vinyl phosphine derivatives[6] suggested the use of enantiomerically pure organophosphorus dipolarophiles of this type as chirality inducers in such cycloadditions. The best selectivity (up to 96%) resulted from the use of a prochiral vinylphosphine sulfide having the remaining two substituents highly differentiated in size.[6b] A suitable transition state model, having the largest group antiperiplanar to the

incoming dipole and the polar group inside, has also been derived, which accounts for the formation of the major diastereoisomers.[6b]

Great potential is therefore apparent but immediate utility for efficient production of functionalized chiral isoxazolidine synthons is contingent at the moment, due to the limited availability of nonracemic vinyl phosphorus compounds of the desired substitution pattern.

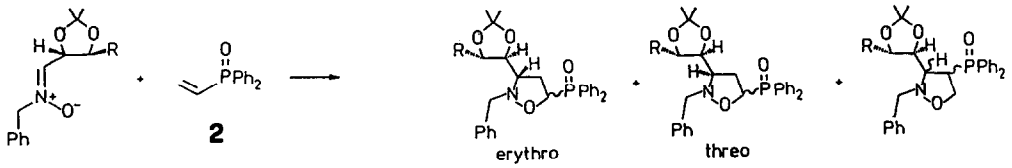
Scheme 1



Knowing already that one of the few readily available enantiomerically pure vinylphosphine derivatives (*i.e.*, oxide 1)[7] imposes only moderate selectivity in its reaction with 2,2-dimethyl-3,4-dihydro-2*H*-pyrrole 1-oxide (Scheme 1),[6] we decided to test the efficiency of chiral nitrones for production of chiral phosphinylisoxazolidines *via* cycloaddition reaction to vinylphosphine oxides.

α,β-Dialkoxynitrones (4*S*)-(*Z*)-*N*-(2,2-dimethyl-1,3-dioxolan-4-yl)methylenebenzylamine *N*-oxide **3**,[3a,b] (4*S*,5*S*)-(*Z*)-*N*-(2,2,5-trimethyl-1,3-dioxolan-4-yl)methylenebenzylamine *N*-oxide **4a**,[3a,b] and its (4*R*,5*R*) enantiomer **4b** were chosen for this study, due to their ready availability from the "chiral pool", their diverse use in analogous cycloadditions,[3a-e] and, mainly, the possibility of synthesizing aminosugar derivatives,[3a-c] namely 1-phosphinylaminosugars.

Scheme 2



R=H: **3**	90%	**5**	**6**	**7a-d**	
		a **b**	**a** **b**		
		59 11	11 9	5 3 2 1	
R=Me: **4a**	75%	**8**	**9**	**10a-d**	
		a **b**	**a** **b**		
		63 12	2 2	12 7 1 1	

A model reaction utilizing nitrones **3** and **4a** with achiral diphenylvinylphosphine oxide **2** led in each case to the formation of eight isomers consisting of one major product (ca. 65% of the total isomeric amount) besides the other minor products ranging in relative abundance from 12% to 1%. ^{31}P NMR spectroscopy allowed high accuracy in measuring isomeric ratios in crude reaction mixtures. Even isomers present in 1% amount could be detected despite the complexity of the reaction mixtures. The major isomer in both reactions was efficiently separated and characterized, while the isolation and/or characterization of minor isomers was possible only for some of them. For all the other adducts stereochemical assignment is only tentative. All the possible combinations of 5- and 4-phosphinyl

substituted isoxazolidines arising from *endo* and *exo* cycloaddition modes were obtained. This lack of complete regioselectivity is consistent with our previous results on cycloadditions of acyclic nitrones to diphenylvinylphosphine oxide.[10] An accurate spectroscopic analysis, in particular of ^{13}C NMR spectra,[11,10] of the reaction mixtures and of some isolated isomers showed a significant difference between the two cycloadditions. The four major products from nitrone **3** were all 5-substituted regioisomers as no doublet appeared in the 40-50 ppm range of the ^{13}C NMR spectrum of the reaction mixture.[10,11] On the contrary, relatively abundant adducts **10a** and **10b** from the cycloaddition of nitrone **4a** displayed in their ^{13}C NMR spectrum a signal at δ 46.5 and 45.5 ppm, respectively, directly coupled with the phosphorus atom (J_{PC} = 72-73 Hz) proving their structure of 4-phosphinylisoxazolidines.[10,11] Regioisomeric ratios of 90:10 for cycloaddition of nitrone **3** and of 80:20 for nitrone **4a** in favor of the 5-phosphinyl isoxazolidines were then measured.

The major isomer in both cycloadditions has been assigned the *erythro* C(3)-C(4') configuration on the basis of the ^1H NMR data and particularly on the observation of diagnostic coupling constants of H(3)-H(4') protons.[3a-d] H(3) signals were coupled with H(4') with a coupling constant of 7.4 and 7.6 Hz, for **5a** and **8a** respectively, in accord with the values of 7-9 Hz observed for analogous *erythro* compounds.[3a-d]

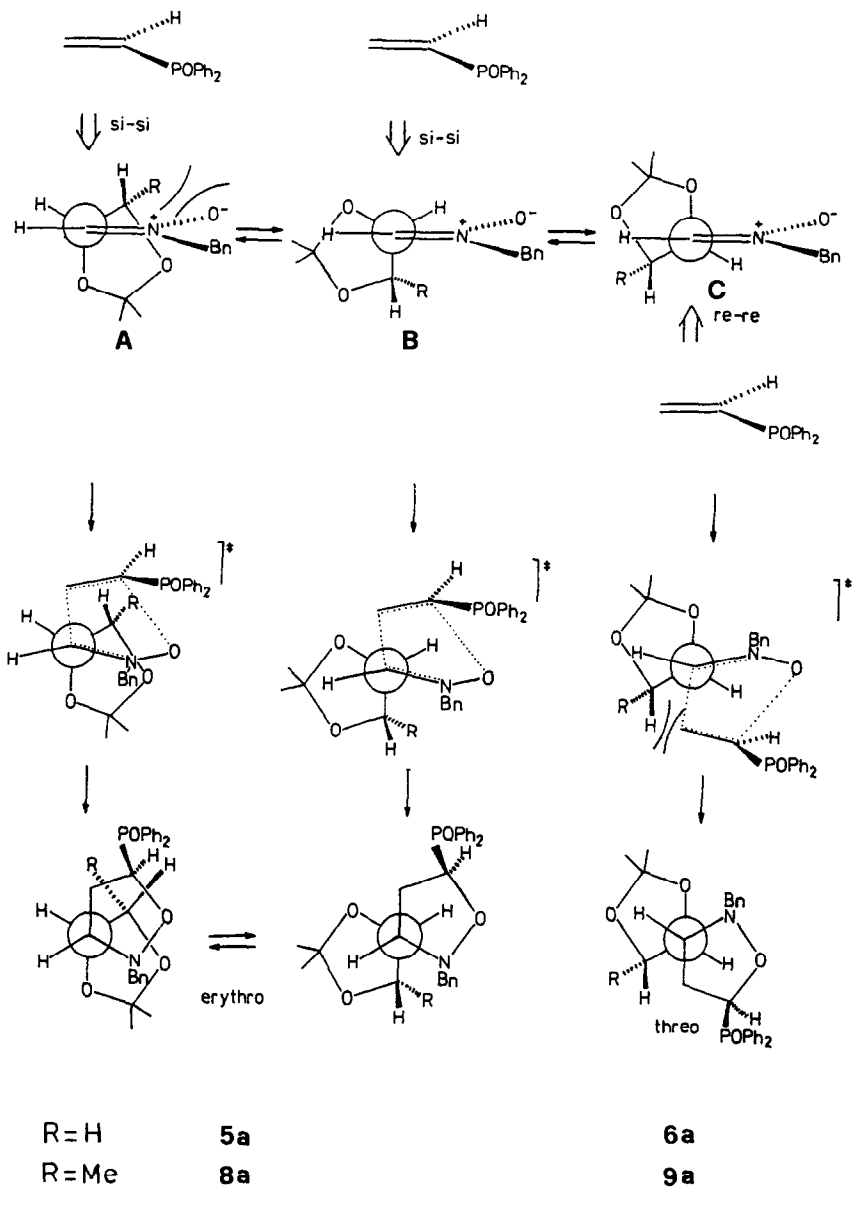
The *trans* C(3)-C(5) stereochemistry in these compounds has been assigned on the basis of the chemical shifts and the coupling constants of the H(3), H(4) and H(5) protons. The more shielded of the two protons on C(4) was *trans* to the phosphinyl group on C(5), since it showed a small coupling constant with phosphorus (5 Hz vs 18 Hz of the geminal proton).[10,12] The same proton has also a *trans* relationship with the H(3) proton, giving no resolvable coupling constant for **5a** or a very small one (1.5 Hz) in **8a**, thus allowing the assignment of a *trans* C(3)-C(5) stereochemistry in **5a** and **8a**, derived from an *endo* transition state in the cycloaddition reaction.

The selectivity found for *erythro* compound **5a** over *threo* **6a** of roughly 5:1 for the *endo* approach, compares well with similar *erythro/threo* ratios recorded for the *endo*-type cycloadditions of the same nitrone **3** to other dipolarophiles.[3a-d] By replacement of nitrone **3** with methyl-substituted nitrone **4a**, despite a less selective regioisomeric ratio and a substantially unaltered *endo/exo* ratio, a considerable increase in the selectivity to favor the *erythro* isomers was observed (ca. eight-fold in both *endo* and *exo* approaches, not precedented in the literature[3a]) giving ratios up to 40:1 in the *endo* mode. The selectivity for the *erythro* product in the *exo* pathway was always negligible and also the diastereoselectivity in the formation of the 4-phosphinylisoxazolidines was consistently lower.[13]

The rationalization of the *erythro-threo* diastereoselectivity (for what concerns the *endo* approach leading to the 5-phosphinylisoxazolidines) rests in the examination of the transition state trajectories in the preferred (or more reactive) nitrone conformations for the attack of the dipolarophile to their *si-si* (which give *erythro* isomers) or *re-re* (which give *threo* products) diastereotopic faces (Scheme 3).[3a-e] The *erythro* product arises from both conformations **A** and **B** of the dipole with the dipolarophile approaching *anti* respectively to the oxygen or CHR groups. Conformation **B** is preferred on a steric basis whereas **A**, ensuring the coplanarity of the C-O allylic bond with the π-system, is more consistent on stereoelectronic grounds.[14] Such electronic interaction is also present in conformation **C**, which is preferred for the attack on the opposite diastereotopic face of the C=N double bond. However, TS **III** derived from conformer **C** experiences a repulsive interaction between the CH_2 of the approaching dipolarophile and the CHR of the dioxolane ring, absent in Transition States **I** and **II**, thus favoring the formation of the *erythro* isomers over *threo* ones.

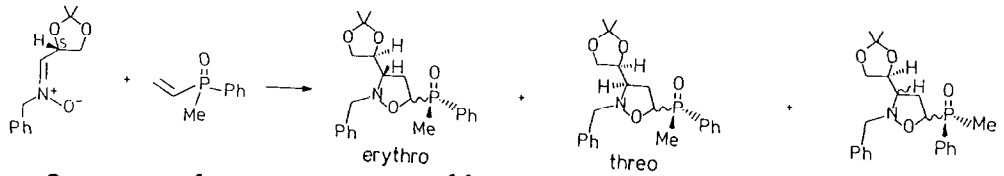
We then considered the cycloaddition of racemic and enantiomerically pure vinylphosphine oxide **1** to the same nitrones, with the aim that the additional stereogenic centre at the phosphorus atom could improve the diastereomeric ratios. Moreover, the replacement of a phenyl phosphorus ligand with a methyl one was expected to greatly diminish the amount of 4-substituted regioisomers as previously observed.[6]

Scheme 3



In fact, reaction of the chiral nitrone **3** with the chiral, optically active phosphine oxide **1** gave only the four possible 5-substituted regioisomeric adducts (over the 1% detection threshold), with a selectivity in favor of *erythro* isomer increased now remarkably to 37:1 and 10:1 in the *endo* (77%) and the *exo* (23%) approach, respectively (Scheme 4).

Scheme 4



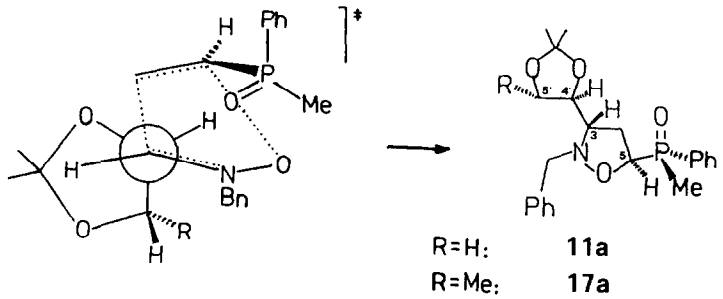
3 1 11 12 13a-d

	a endo (R-C5)	b exo (S-C5)	a endo (S-C5)	b exo (R-C5)
(–)-S 95%	75	21	2	2
rac. 77%	44	10	1	1

16 14 11 3

These relatively high ratios suggest that 3 and (–)-(*S*) 1 constituted a matched pair of reactants. Experiments performed on racemic 1 indeed indicated (Scheme 4) that selection among the four isomeric isoxazolidines derived from the dextrorotatory enantiomer of 1 was decidedly lower than those originating from (–)-(*S*) 1.

Scheme 5

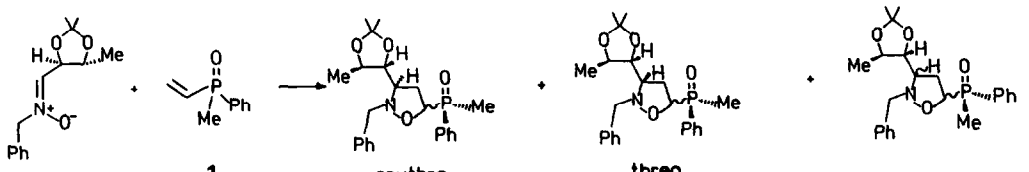


Consideration of nitrone 3 and phosphine oxide 1 reactive conformations led to prediction that (*S*) nitrone and (*S*) phosphine oxide should compose a matched pair of reactants (Scheme 5), since only in the transition state derived from these isomers (or from their enantiomers) can both nitrone and phosphine oxide simultaneously present their most favorable conformations, *i.e.* conformation **B** (or **A**) for the nitrone and the conformation with the phenyl *anti* and the oxygen inside for the vinylphosphine oxide.

Our experimental results appear very much in line with this prediction, so that stereochemical assignment for the two newly created centers in the two major products **11a** (3*S*,5*R*) and **11b** (3*S*,5*S*) could be made with sufficient confidence. Further support was provided once again by ^{1}H NMR spectroscopy of the two separated isomers. Coupling constants for C(3) protons (3.30 δ, triplet, J = 7.8 Hz for **11a** and 3.07 δ, quartet, J = 7.8 Hz for **11b**) confirm the *erythro* relationship between the C(3)-C(4') stereocentres.[3a-d] The assignment of the *endo* (C3,C5-*trans*) and *exo* (C3,C5-*cis*) stereochemistry to C(3)-C(4') *erythro* compounds **11a** and **11b** respectively, could also be made directly in this case by analysis of ^{1}H NMR data and for other compounds based on analogy. For example, the two isoxazolidines **11a** and **11b** show two well separated and resolved signals for the C(4) methylene protons. In compound **11a** one of the two protons is at 2.86 δ with a large $^3J_{PH}$ (18.3 Hz), the other at 2.38 δ with a smaller $^3J_{PH}$ (5 Hz). As the $^3J_{PH}$ for *cis* nuclei are typically larger than for *trans*,[11,12] the more deshielded of the two protons must be *cis* to phosphorus, but *trans* to the dioxolane ring on C(3) (*i.e.*

endo) because the proton on C(3) lacks any coupling with the other shielded proton on C(4). In compound **11b** the more shielded C(4) proton shows the larger $^3J_{PH}$ coupling attesting an inversion of configuration at the C(5) carbon derived from an *exo* approach.

Scheme 6

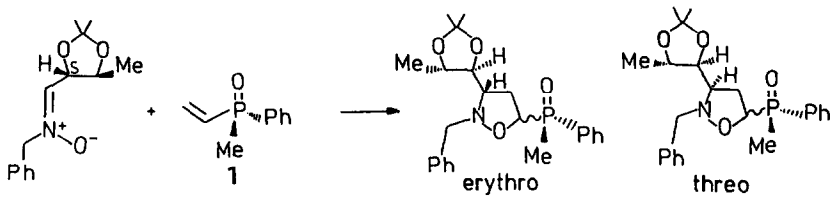


(–)-S	70%					44	30	20	6
rac.	94%	46	2	1	1	19	14	11	3

That the nitrone *S*(C4') configuration is required for the matched interactions with (–)-*S* **1** was further confirmed by analogous results obtained in the cycloaddition of *R*(C4') nitrone **4b** to enantiomerically pure and racemic phosphine oxide **1** (Scheme 6). The cycloaddition to (–)-*S* **1** gave an inseparable mixture of the four possible diastereoisomers **16** with minimal selectivity. On the contrary, starting from racemic **1**, the four diastereoisomers **14** and **15**, derived from the enantiomer (+)-*R* **1**, were formed with very good selectivity in favor of one of them, besides isomers **16a-d**.

The enantiomers **17** and **18** of these four products were cleanly and uniquely obtained by reaction of the enantiomeric nitrone **4a** with (–)-*S* **1** (Scheme 7), with a selectivity >90% for the formation of **17a**.

Scheme 7



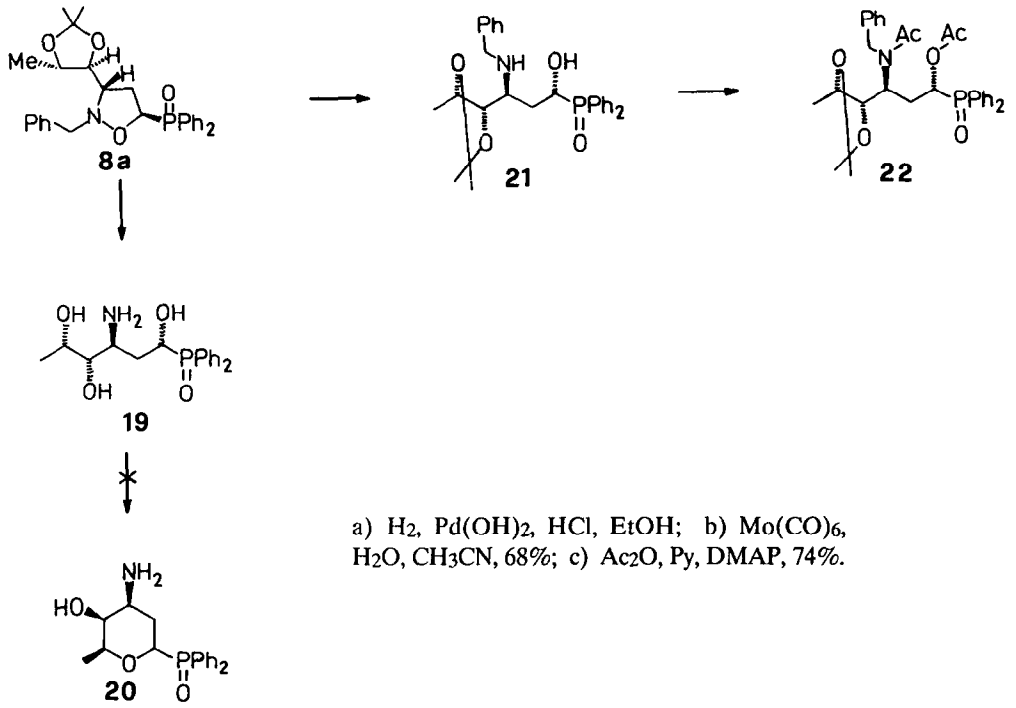
a endo (R-C5)	b exo (S-C5)	a endo (S-C5)	b exo (R-C5)
93	3	2	2

Apparently, an additional C(5') stereogenic centre (*S* in **4a** and *R* in **4b**) does not cooperate with the already matched interactions since the selectivity favoring the *erythro* products was essentially unaffected (46:1 vs 37:1) in the *endo* approach. However, the presence of the methyl substituent in **4a** proved advantageous in terms of *endo* vs *exo* selectivity which was raised to practical values (>30:1 vs 3:1 in the cycloaddition of nitrone **3**). The cycloaddition in scheme 7 is remarkable for highly efficient

creation of the two new stereogenic centres from acyclic precursors in an intermolecular process.

The 5-phosphinyl isoxazolidines obtained can be envisaged as suitable precursors for the synthesis of 1-phosphinyl derivatives of aminosugars. C-phosphorus substituted sugars are attracting increasing interest for their biological activity[15] as well as for their utility as reagents for C-C bond formation reactions in sugars.[16] Products **8a** and **17a**, in particular, contain the same stereocenters, with the correct absolute configuration, of daunosamine, the glycosidic moiety of the anthracycline antitumorals daunomycin and adriamycin.[17] By ring cleavage of isoxazolidine **8a** with hydrogen on $Pd(OH)_2$ under acidic conditions, the simultaneous deprotection of amino and hydroxy functional groups and cyclization to the hexose aminosugar **20** should occur. Although these conditions have been used successfully in a similar case by DeShong,[3a,b] we feared that the presence of a phosphinyl group on C(1) in our case might hamper the cyclization step. In fact under these conditions the aminosugar **20** was not formed and only the 1-phosphinyl aminotriol **19** could be detected among several unidentified products. The failure of the cyclization has to be ascribed to the poor aptitude of a phosphinyl group in stabilizing an adjacent positive charge. Aminotriol **19** attracted our interest, however, being the first example of 1-phosphinyl-*seco*-daunosamine. A milder and chemoselective cleavage of the isoxazolidine ring would lead to a more useful, selectively protected form of the 1-phosphinyl-*seco*-daunosamine. This goal was achieved by reduction of **8a** with molybdenum hexacarbonyl and H_2O,[18] to afford the partially protected 1-phosphinyl aminotriol **21** in good yield. Acetylation of residual deprotected functionalities gave the fully and selectively protected 1-diphenylphosphinyl-*seco*-daunosamine **22** suitable for further chemical elaboration as a new 'chiron'[19] (Scheme 8).

Scheme 8



a) H_2, $Pd(OH)_2$, HCl, EtOH; b) $Mo(CO)_6$, H_2O, CH_3CN, 68%; c) Ac_2O, Py, DMAP, 74%.

Further studies on the asymmetric synthesis of phosphinylisoxazolidines and their applications are in progress in our laboratories.[20]

EXPERIMENTAL SECTION

All reactions were carried out under nitrogen. R_f values refer to TLC, carried out on 0.25 mm silica gel plates (Merck F254). Melting points (uncorrected) were measured with a Kofler apparatus. NMR spectra in $CDCl_3$ solutions were recorded on Varian FT-80 A (^{13}C, 20 MHz; ^{31}P, 32.203 MHz) and on Varian Gemini 200 (^1H NMR, 200 MHz) spectrometers: the chemical shifts for ^1H and ^{13}C NMR spectra are given in ppm from TMS; for ^{31}P NMR spectra in ppm from H_3PO_4 85%. Ratios of diastereomeric products were obtained by integration of the corresponding ^{31}P NMR signals of the crude mixtures. ^{13}C NMR signals of aromatic substituents were omitted. Racemic and (–)-*S*-methylphenylvinylphosphine oxide (**1**) was synthesized according to reference 21 and 7 respectively. Diphenylvinylphosphine oxide (**2**) was synthesized according to reference 22. Nitrones **3** , **4a** and **4b** were synthesized according to reference 3b starting from 1,2:5,6-di-O-isopropylidene-D-mannitol, (2*R*,3*S*) and (2*S*,3*R*) methyl 2,3-O-isopropylidene-2,3-dihydroxybutyrate, respectively.

Cycloaddition of 4(S)-(Z)-N-(2,2-dimethyl-1,3-dioxolan-4-yl)methylenebenzylamine N-oxide (**3**) *to diphenylvinylphosphine oxide* (**2**).

A solution of 118 mg (0.5 mmol) of nitrone **3** and 114 mg (0.5 mmol) of **2** in 2 mL of $CHCl_3$ was heated at reflux for 72 h. ^{31}P NMR monitoring of the reaction mixture showed the presence of eight isomers in 59:11:11:9:5:3:2:1 ratio (^{31}P NMR: δ 27.30, 28.59, 28.98, 29.71, 29.41, 30.13, 28.08, 30.47 ppm, respectively). Purification by flash column chromatography (eluant ethyl acetate-petroleum ether 1:1) afforded a fraction at $R_f = 0.38$ (130 mg, 56%) corresponding to **5a** as a colorless oil. Another fraction eluted with ethyl acetate contained all the other isomers (78 mg, 34%).

(3S, 5R, 4'S)-2-benzyl-5-diphenylphosphinyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)isoxazolidine (**5a**): Anal. calcd for $C_{27}H_{30}NO_4P$: C, 69.96; H, 6.52; N, 3.02%; found C, 70.19; H, 6.67; N, 2.80%; ^{31}P NMR: δ 27.30; ^1H NMR: δ 7.78-7.64 (m, 4H), 7.50-7.12 (m, 11 H), 4.75 (ddd, J = 14.9, 10.5, 7.5 Hz, 1H), 4.11 (d, J = 12.8 Hz, 1H), 3.94 (dd, J = 8.1, 6.2 Hz, 1H), 3.86 (ddd, J = 8.8, 6.3, 4.9 Hz, 1H), 3.64 (d, J = 12.8 Hz, 1H), 3.47 (dd, J = 8.3, 4.9 Hz, 1H), 3.13 (t, J = 7.7 Hz, 1H), 2.83 (dddd, J = 18.1, 12.7, 10.7, 7.3 Hz, 1H), 2.46 (ddd, J = 12.7, 8.0, 4.9 Hz, 1H), 1.21 (s, 3H), 1.19 (s, 3H); ^{13}C NMR: δ 109.15 (s), 77.00 (d, $J_{PC} = 78.2$ Hz) (d), 74.75 (d), 67.60 (t), 67.00 (d, $J_{PC} = 5.8$ Hz) (d), 62.58 (t), 30.27 (t), 26.41 (q), 24.78 (q); IR ($CDCl_3$): 3065, 2960, 1593, 1438, 1185 (vs), 1119 cm^{-1}; $[\alpha]_D^{25} = +11.6$ (c 0.39, $CHCl_3$).

Cycloaddition of (4S,5S)-(Z)-N-(2,2,5-trimethyl-1,3-dioxolan-4-yl)methylenebenzylamine N-oxide (**4a**) *to diphenylvinylphosphine oxide* (**2**).

A solution of 163 mg (0.16 mmol) of nitrone **4a** and 149 mg (0.16 mmol) of **2** in 2 mL of $CHCl_3$ was heated at reflux for 10 h. ^{31}P NMR monitoring of the reaction mixture showed the presence of eight isomers in 63:12:12:7:2:2:1:1 ratio (^{31}P NMR: δ 27.56, 30.27, 29.38, 29.01, 28.77, 30.95, 30.66, 28.33 ppm, respectively). Purification by flash column chromatography (eluant ethyl acetate-petroleum ether 1:1) afforded a fraction at $R_f = 0.55$ (42 mg, 13%) corresponding to the mixture of the minor isomers. A second fraction ($R_f = 0.35$) contained the isomer **8a** (195 mg, 62%) as a colorless oil. Fractional crystallization of the first fraction afforded pure isomer **10a** (diisopropyl ether, 20 mg, 6%).

(3S, 5R, 4'S, 5'S)-2-benzyl-5-diphenylphosphinyl-3-(2,2,5-trimethyl-1,3-dioxolan-4-yl)isoxazolidine (**8a**): Anal. calcd for $C_{28}H_{32}NO_4P$: C, 70.42; H, 6.75; N, 2.93%; found C, 70.46; H, 6.91; N, 2.99%; ^{31}P NMR: δ 27.56; ^1H NMR: δ 7.85-7.68 (m, 4H), 7.55-7.15 (m, 11H), 4.84 (ddd, J = 14.4, 10.3, 8.0 Hz, 1H), 4.18 (d, J = 12.8 Hz, 1H), 3.72 (d, J = 12.8 Hz, 1H), 3.57 (dq, J = 7.5, 6.0 Hz, 1H), 3.42 (t, J = 7.6 Hz, 1H),

3.19 (dt, J = 1.5, 7.4 Hz, 1H), 2.87 (dddd, J = 17.9, 12.7, 10.3, 7.4 Hz, 1H), 2.57 (dddd, J = 12.8, 7.9, 5.2, 1.6 Hz, 1H), 1.33 (s, 3H), 1.30 (d, J = 5.9 Hz, 3H), 1.22 (s, 3H); ^{13}C NMR: δ 108.17 (s), 80.83 (d), 76.81 (d, J_{PC} = 81.6 Hz) (d), 76.45 (d), 66.66 (d, J_{PC} = 5.5 Hz) (d), 62.67 (t), 30.81 (t), 27.18 (q), 26.74 (q), 18.99 (q); IR ($CDCl_3$): 3064, 2988, 1592, 1452, 1437, 1119 (vs) cm^{-1}; $[\alpha]_D^{25}$ = +13.4 (c 0.65, $CHCl_3$).

(3S, 4S, 4'S, 5'S)-2-benzyl-4-diphenylphosphinyl-3-(2,2,5-trimethyl-1,3-dioxolan-4-yl)isoxazolidine (**10a**): m.p. = 148-149°C; Anal. calcd for $C_{28}H_{32}NO_4P$: C, 70.42; H, 6.75; N, 2.93%; found C, 70.15; H, 6.82; N, 2.66%; R_f = 0.55; ^{31}P NMR: δ 30.27; ^{1}H NMR: δ 7.95-7.80 (m, 4H), 7.55-7.35 (m, 8H), 7.35-7.20 (m, 3H), 4.38-4.04 (m, 2H), 4.34 (d, J = 12.0 Hz, 1H), 4.12 (d, J = 12.0 Hz, 1H), 3.71 (dt, J = 2.9, 9.6 Hz, 1H), 3.49 (ddd, J = 13.9, 9.2, 2.9 Hz, 1H), 3.38 (dd, J = 9.1, 7.2 Hz, 1H), 3.10 (dq, J = 7.2, 6.0 Hz, 1H), 1.23 (d, J = 6.2 Hz, 3H), 1.16 (s, 3H), 0.53 (s, 3H); ^{13}C NMR: δ 107.45 (s), 83.19 (d, J_{PC} = 7.0 Hz) (d), 76.94 (d), 66.58 (d), 66.49 (t), 58.80 (t), 46.51 (d, J_{PC} = 72.4 Hz) (d), 26.92 (q), 25.62 (q), 19.37 (q); IR ($CHCl_3$): 3064, 2990, 2937, 2881, 1591, 1485, 1453, 1438, 1380, 1171, 1115, 1082 cm^{-1}; $[\alpha]_D^{25}$ = –24.1 (c 0.44, $CHCl_3$).

Cycloaddition of (4S)-(Z)-N-(2,2-dimethyl-1,3-dioxolan-4-yl)methylenebenzylamine N-oxide (**3**) *to (–)-(S) and racemic methylphenylvinylphosphine oxide* (**1**).

A solution of 118 mg (0.5 mmol) of nitrone **3** and 83 mg (0.5 mmol) of (–)-*S* phosphine oxide **1** in 1 mL of $CHCl_3$ was left at room temperature for 7days. ^{31}P NMR monitoring of the reaction mixture showed the presence of four isomers in 75:21:2:2 ratio (^{31}P NMR: δ 31.63, 37.34, 36.35, 35.50 ppm, respectively). Purification by flash column chromatography (eluant ethyl acetate) afforded a fraction at R_f = 0.38 (140 mg, 70%) corresponding to **11a** as a colorless oil. A second fraction (R_f = 0.22) contained all the other isomers (50 mg, 25%). Fractional crystallization of the second fraction afforded pure isomer **11b** (diisopropyl ether, 40 mg, 20%).

(3S, 5R, 4'S, R_P)-2-benzyl-5-methylphenylphosphinyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)isoxazolidine (**11a**): Anal. calcd for $C_{22}H_{28}NO_4P$: C, 65.82; H, 7.03; N, 3.49%; found C, 65.88; H, 7.02; N, 3.77%; ^{31}P NMR: δ 31.63 ; ^{1}H NMR: δ 7.75-7.65 (m, 2H), 7.60-7.42 (m, 5H), 7.37- 7.25 (m, 3H), 4.31 (d, J = 12.7 Hz, 1H), 4.29 (ddd, J = 17.3, 10.3, 8.1 Hz, 1H), 4.06 (dd, J = 8.6, 6.3 Hz, 1H), 3.90 (ddd, J = 8.8, 6.1, 5.1 Hz, 1H), 3.88 (d, J = 12.7 Hz, 1H), 3.30 (t, J = 7.8 Hz, 1H), 2.86 (dddd, J = 18.3, 12.8, 10.3, 7.1 Hz, 1H), 2.38 (ddd, J = 12.8, 8.1, 5.1 Hz, 1H), 1.74 (d, J = 13.1 Hz, 3H), 1.29 (s, 3H), 1.26 (s, 3H); ^{13}C NMR: δ 109.40 (s), 78.34 (d, J_{PC} = 80.2 Hz) (d), 75.04 (d), 68.06 (t), 67.91 (d), 62.77 (t), 29.37 (t), 26.64 (q), 24.97 (q), 13.35 (d, J_{PC} = 72.0 Hz) (q); IR ($CDCl_3$): 3066, 2990, 2930, 1602, 1438, 1295, 1181, 1068 cm^{-1}; $[\alpha]_D^{25}$ = –62.1 (c 1.91, $CHCl_3$).

(3S, 5S, 4'S, R_P) -2-benzyl-5-methylphenylphosphinyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)isoxazolidine (**11b**): m.p. = 153-154°C; Anal. calcd for $C_{22}H_{28}NO_4P$: C, 65.82; H, 7.03; N, 3.49%; found C, 65.46; H, 7.20; N, 3.68%; ^{31}P NMR: δ 37.34; ^{1}H NMR: δ 7.85-7.70 (m, 2H), 7.60-7.40 (m, 3H), 7.40-7.22 (m, 5H), 4.36 (d, J = 13.2 Hz, 1H), 4.29 (dt, J = 3.5, 8.4 Hz, 1H), 4.21 (dt, J = 7.9, 6.4 Hz, 1H), 4.10 (dd, J = 8.3, 6.4 Hz, 1H), 3.77 (d, J = 13.2 Hz, 1H), 3.73 (dd, J = 8.3, 6.4 Hz, 1H), 3.07 (q, J = 7.8 Hz, 1H), 2.65 (dq, J = 13.2, 8.4 Hz, 1H), 2.36 (ddt, J = 16.5, 13.2, 7.7 Hz, 1H), 1.66 (d, J = 13.4 Hz, 3H), 1.39 (s, 3H), 1.37 (s, 3H); ^{13}C NMR: δ 110.22 (s), 77.70 (d), 76.83 (t), 74.10 (d, J_{PC} = 84.2 Hz) (d), 67.67 (d, J_{PC} = 2.8 Hz) (d), 66.97 (t), 32.72 (t), 26.65 (q), 25.43 (q), 12.4 (d, J_{PC} = 67.8 Hz) (q); IR ($CHCl_3$): 3065, 2991, 2959, 2859, 1591, 1494, 1437, 1382, 1372, 1295, 1158, 1112, 1068 cm^{-1}. $[\alpha]_D^{25}$ = +152.1 (c 1.44, $CHCl_3$).

A solution of 118 mg (0.5 mmol) of nitrone **3** and 83 mg (0.5 mmol) of racemic phosphine oxide **1** in 1 mL of $CHCl_3$ was left at room temperature for 7 days. ^{31}P NMR monitoring of the reaction mixture showed the presence of eight isomers **11a,b**, **12a,b** and **13a-d** in 44:16:14:11:10:3:1:1 ratio (^{31}P NMR: δ 31.75, 35.99, 33.61, 34.00, 37.45, 37.00, 36.36, 35.58 ppm, respectively). Purification by chromatography on a short pad of silica gel (eluant ethyl acetate) afforded 155 mg (77%) of a colorless oil.

Cycloaddition of (4R,5R)- (Z)-N-(2,2,5-trimethyl-1,3-dioxolan-4- yl)methylenebenzylamine N-oxide (**4b**) *to racemic and (–)-S-methylphenylvinylphosphine oxide* (**1**).

A solution of 480 mg (2 mmol) of nitrone **4b** and 233 mg (1.4 mmol) of racemic phosphine oxide **1** in 3 mL of $CHCl_3$ was heated at reflux for 3 h. ^{31}P NMR monitoring of the reaction mixture showed the presence of eight isomers in 46:19:14:11:3:2:1:1 ratio (^{31}P NMR: δ 31.89, 36.43, 34.33, 33.51, 34.46, 37.95, 36.70, 35.03 ppm, respectively). Purification by flash column chromatography (eluant ethyl acetate-petroleum ether 1:1) afforded a fraction at $R_f = 0.35$ (245 mg, 40%) corresponding to **14a** as a colorless oil. A second fraction eluted with ethyl acetate contained all the other isomers (325 mg, 54%).

(3R, 5S, 4'R, 5'R, S_P) -2-benzyl-5-methylphenylphosphinyl-3-(2,2,5-trimethyl-1,3-dioxolan-4-yl) isoxazolidine (**14a**). Anal. calcd for $C_{23}H_{30}NO_4P$: C, 66.49; H, 7.28; N, 3.37%; found C, 66.22; H, 7.63; N, 2.88%; R_f = 0.35; ^{31}P NMR: δ 31.89; ^1H NMR: δ 7.85-7.18 (m, 10H), 4.28 (d, J = 12.8 Hz, 1H), 4.25 (ddd, J = 15.6, 10.1, 8.1 Hz, 1H), 3.86 (d, J = 12.8 Hz, 1H), 3.65 (quintet, J = 6.0 Hz, 1H), 3.36 (t, J = 8.2 Hz, 1H), 3.29 (t, J = 8.1 Hz, 1H), 2.84 (dddd, J = 17.0, 12.6, 10.2, 6.7 Hz, 1H), 2.36 (dddd, J = 12.8, 8.1, 5.0, 1.0 Hz, 1H), 1.71 (d, J = 13.2 Hz, 3H), 1.33 (d, J = 6.0 Hz, 3H), 1.28 (s, 3H), 1.19 (s, 3H); ^{13}C NMR: δ 108.29 (s), 81.00 (d), 78.34 (d, J_{PC} = 80.4 Hz) (d), 76.75 (d), 67.63 (d, J_{PC} = 5.0 Hz) (d), 62.66 (t), 29.70 (t), 27.06 (q), 26.64 (q), 19.05 (q), 13.35 (d, J_{PC} = 72.1 Hz) (q); IR ($CDCl_3$): 3066, 2990, 1592, 1438, 1181, 1068 cm^{-1}; $[\alpha]_D^{25}$ = +50.4 (c 4.75, $CHCl_3$).

A solution of 200 mg (0.8 mmol) of nitrone **4b** and 116 mg (0.7 mmol) of (–)-*S* phosphine oxide **1** in 1 mL of $CHCl_3$ was left at room temperature for 7 days. ^{31}P NMR monitoring of the reaction mixture showed the presence of four isomers in 44:30:20:6 ratio (^{31}P NMR: δ 36.59, 34.54, 33.70, 34.67 ppm, respectively). Purification by chromatography on a short pad of silica gel (eluant ethyl acetate) afforded 200 mg (70%) of a mixture of the four isomers as a colorless oil. Anal. (mixture of isomers) calcd for $C_{23}H_{30}NO_4P$: C, 66.49; H, 7.28; N, 3.37%; found C, 66.50; H, 7.57; N, 3.25%.

Cycloaddition of (4S, 5S)- (Z)-N-(2,2,5-trimethyl-1,3 dioxolan-4-yl)methylenebenzylamine N-oxide (**4a**) *to (–)- (S)-methylphenylvinylphosphine oxide* (**1**).

A solution of 125 mg (0.5 mmol) of nitrone **4a** and 83 mg (0.5 mmole) of (–)-*S* phosphine oxide **1** in 1 mL of $CHCl_3$ was left at room temperature for 7 days. ^{31}P NMR monitoring of the reaction mixture showed the presence of four isomers in 93:3:2:2 ratio (^{31}P NMR: δ 31.86, 37.87, 36.60, 35.01 ppm, respectively). Purification by flash column chromatography (eluant ethyl acetate-petroleum ether 1:1) afforded a fraction at $R_f = 0.35$ (150 mg, 72%) corresponding to **17a** as a colorless oil. A second fraction eluted with ethyl acetate contained all the other isomers (12 mg, 6%).

(3S, 5R, 4'S, 5'S, R_P)-2-benzyl-5-methylphenylphosphinyl-3-(2,2,5-trimethyl-1,3-dioxolan-4- yl) isoxazolidine (**17a**). Anal. calcd for $C_{23}H_{30}NO_4P$: C, 66.49; H, 7.28; N, 3.37%; found C, 66.88; H, 7.36; N, 2.95%; $[\alpha]_D^{25}$ = – 52.6 (c 1.42, $CHCl_3$). Spectroscopic data were identical with those of enantiomeric compound **14a**.

Synthesis of (1R, 3S, 4S, 5S)-1-acetoxy-3-(N-benzyl)acetamido-4,5-(O-isopropylidene)-dihydroxy-1-diphenylphosphinylhexane (**22**) *(protected seco-1- phosphinyldaunosamine).*

A solution of 160 mg (0.33 mmol) of isoxazolidine **8a** and 88 mg (0.33 mmol) of $Mo(CO)_6$ in 7 mL of acetonitrile and 0.5 mL of water was refluxed for 2 h under nitrogen atmosphere. The compound **21**, obtained by purification of the crude mixture on a short pad of silica gel (eluant ethyl acetate, 110 mg, colorless oil, 68% yield), was directly used for the next step.

21: ^1H NMR: δ 8.04-7.61 (m, 5H), 7.60-7.35 (m, 5H), 7.34-7.08 (m, 5H), 4.87 (t, J = 4.8 Hz, 1H), 3.83-3.62 (m, 2H), 3.63 (d, J = 10.1 Hz, 1H), 3.28 (d, J = 10.1 Hz, 1H), 3.09 (dt, J = 9.2, 3.9 Hz, 1H), 2.28-1.87 (m, 2H), 1.34 (s, 3H), 1.28 (s, 3H), 1.24 (d, J = 6.2 Hz, 3H). ^{13}C NMR: δ 108.28 (s), 81.68 (d),

73.92 (d), 70.01 (d, J_{PC} = 86.2 Hz) (d), 55.96 (d, J_{PC} = 6.9 Hz) (d), 50.46 (t), 27.70 (t), 27.24 (q), 26.77 (q), 18.19 (q).

A solution of 80 mg (0.17 mmol) of **21** and 20 mg of DMAP in 1 mL of acetic anhydride and 1 mL of pyridine was stirred at room temperature for 24 h. The crude reaction mixture was purified by flash column chromatography (eluant ethyl acetate) to afford 70 mg (74% yield) of **22** as a colorless oil.

22: R_f = 0.35. Anal. calcd for $C_{32}H_{38}NO_6P$: C, 68.19; H, 6.80; N, 2.48%; found C, 68.48; H, 6.67; N, 2.07%; ^{31}P NMR: δ 31.24; ^1H NMR: δ 7.91-7.75 (m, 2H), 7.68-7.15 (m, 13H), 5.70 (m, 1H, HCOP), 4.97 (m, 1H, HCN), 4.56 (d, J = 17.6 Hz, 1H) and 4.44 (d, J = 17.6 Hz, 1H) (AB system), 3.65 (dq, J = 8.3, 5.8 Hz, 1H, H_5CO), 3.52 (broad d, J = 7.5, 1H, H_4CO), 1.97 (s, 3H), 1.82 (s, 3H), 1.18 (d, J = 5.8 Hz, 3H), 1.11 (s, 3H), 0.97 (s, 3H); ^{13}C NMR: δ 172.70 (s), 169.50 (s), 108.52 (s), 84.14 (d, C_4), 74.08 (d, C_5), 66.69 (d, J_{PC} = 84.8 Hz) (d, C_1), 48.03 (d, C_3), 48.01 (t), 26.67 (q, 2C), 24.92 (t, C_2), 22.12 (q), 20.57 (q), 17.69 (q, C_6); IR ($CDCl_3$): 3066, 2988, 2936, 1737, 1642, 1439, 1369, 1245, 1222 cm^{-1}; $[\alpha]_D^{25}$ = − 42.1 (c 0.51, $CHCl_3$).

Acknowledgments: Financial support of this study by Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) and Consiglio Nazionale delle Ricerche (CNR)-Italy, and Polish Academy of Sciences (CPBP-01.13)-Poland is gratefully acknowledged.

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