Nucleophilic additions of chiral non-racemic enolates to N-benzyl-C-(alkoxymethyl) nitrones

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Dedicated to Professor Enrique Meléndez on his 70th birthday

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Abstract

The reaction of N-benzyl-C-(alkoxymethyl) nitrones with lithium and sodium enolates derived from menthyl and bornyl acetates affords mixtures of hydroxylamines and isoxazolidin-5-ones. On the other hand, the reaction with the silyl ketene acetals prepared from the above-mentioned acetates mainly affords the silylated hydroxylamines. In both cases the crude reaction mixtures can be smoothly transformed into enantioenriched mixtures of 3-(alkoxymethyl) isoxazolidin-5-ones which are key intermediates in the synthesis of isoxazolidinyl nucleosides.

Keywords: Isoxazolidines, nitrones, enolates, hydroxylamines

Introduction

Nucleoside analogues in which the furanose ring has been replaced by a different heterocyclic unit (heterocyclic nucleosides) have emerged in recent years as highly promising candidates for the development of new efficient drugs against cancer and viral infections, particularly that of the HIV.[1] Troxacitabine[2] **1** (used in preclinical models both against leukemic and epithelial malignancies) and lamivudine[3] **2** (currently used in combined therapies against AIDS) are the most relevant examples. Among heterocyclic nucleosides, isoxazolidinyl analogues **3** have also attracted considerable attention due to their promising anti AIDS activity in vitro.[4]

In this context, we have amply demonstrated that 3-substituted isoxazolidin-5-ones **4** are key intermediates for the synthesis of isoxazolidinyl nucleosides.[5] Compounds **4** can be readily synthesized by addition of either ester enolates or silyl ketene acetals to the corresponding

nitrones[6] followed by an intramolecular cyclization that in many cases is spontaneous under the reaction conditions employed. This approach is extremely advantageous because it allows the enantiodivergent synthesis of both D- and L-isoxazolidinyl nucleosides on the basis of the stereocontrol that can be exerted during the synthesis of the intermediates **4** when chiral non-racemic α-alkoxy nitrones are used as starting materials.[5d] The major limitation consists of the need of a chiral center to induce diastereoselectivity.

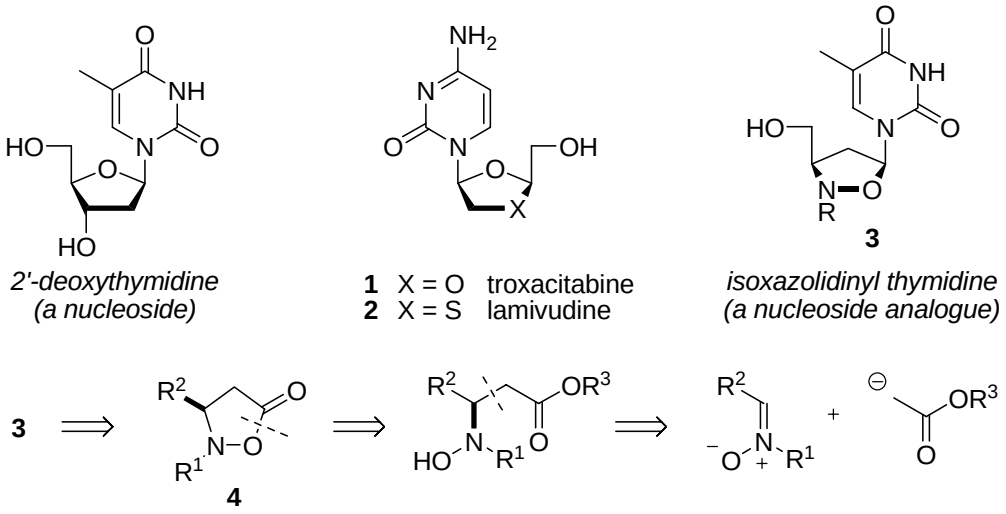
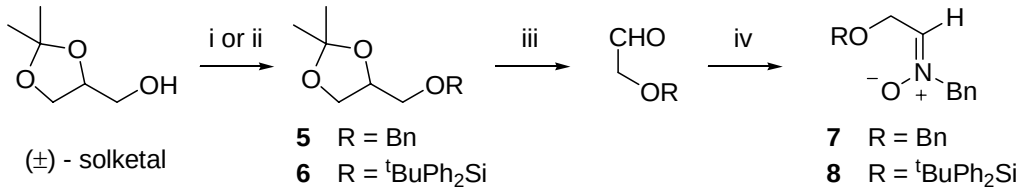


Figure 1

In order to prepare enantiomerically pure 3-(hydroxymethyl) isoxazolidin-5-ones **4** (R = CH_2OH) in a straightforward way, we envisaged that the use of chiral enolates derived from esters of chiral alcohols could provide a direct entry to **4** and, at the same time, it would allow the recovery of the chiral alcohol used as an auxiliary, after the cyclization step. In this paper we describe our results on the nucleophilic addition of two chiral acetates to two differentially protected N-benzyl-C-(alkoxymethyl) nitrones and the further transformation of the obtained mixtures into isoxazolidinones **4**.

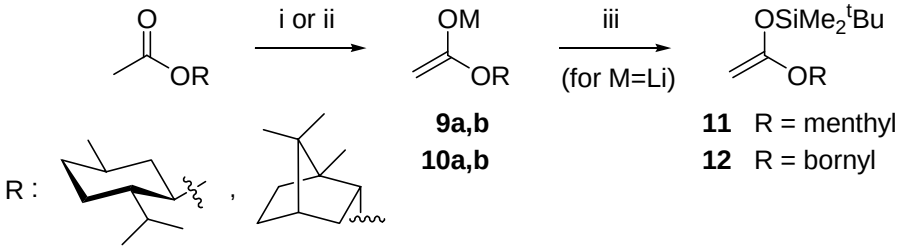
Results and Discussion

We chose for our study the nitrones **7** and **8**. These nitrones were easily prepared from racemic solketal in three steps as indicated in Scheme 1.



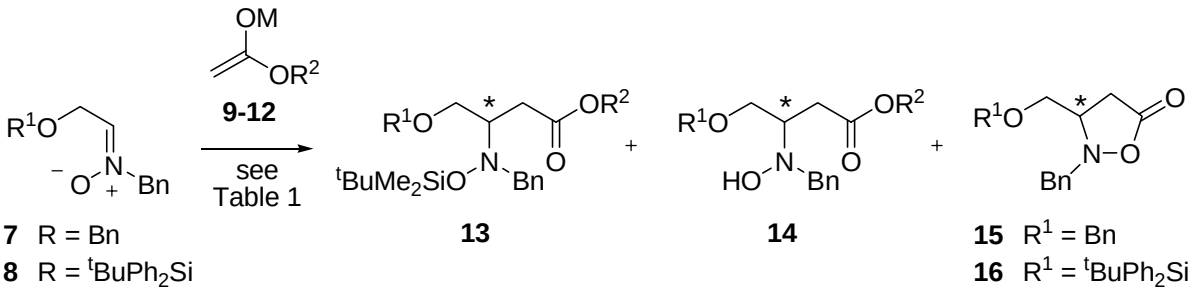
Scheme 1. i, NaH, BnBr, DMF. ii, TBDPSCl, DMF, imidazole. iii, H_5IO_6, Et_2O. iv, BnNHOH, CH_2Cl_2, $MgSO_4$.

As nucleophiles, we used the lithium and sodium enolates **9** and **10** derived from (1*R*)-(-)-menthyl acetate and (1*S*)-(-)-bornyl acetate, respectively. These enolates were generated *in situ* and used immediately (Scheme 2). The corresponding silyl ketene acetals were prepared from the lithium enolates and they were used immediately without purification.



Scheme 2. i, LDA, THF, -80 ºC. ii, NaHMDS, THF, 0 ºC. iii, TBSCl. **9** and **10** refers to menthyl and bornyl derivatives, respectively. **a** and **b** series refers to M = Li and M = Na, respectively.

Whereas the reaction between lithium and sodium enolates and nitrones takes place smoothly at low temperatures (-80 ºC), the addition of ketene silyl acetals needs of activation of the nitrone by a Lewis acid. In all cases a complex mixture of products was obtained (Scheme 3).



Scheme 3

After quenching the reaction both open-chain hydroxylamines **14** and isoxazolidin-5-ones **15** were obtained. From the reaction with silyl ketene acetals the corresponding silylated hydroxylamines **13** were the main products. Of course, pairs of diastereomers were obtained in the case of hydroxylamines and pairs of enantiomers were obtained for isoxazolidin-5-ones **15**. Also, in the cases in which the cyclic compound was obtained, the corresponding chiral alcohol (menthol or borneol) was detected in the reaction mixture. The detailed results of the addition reactions are collected in Table 1.

The addition of lithium enolates (entries 1, 3, 5 and 7) took place with lower yields than those of sodium enolates (entries 2, 4, 6 and 8). In all cases the cyclic adduct **15** was the major product of the reaction. However, in contrast to our previous results[5a] considerable amounts of hydroxylamines **14** were obtained. This is probably due to the bulkiness of the ester moiety that in this case did not work so well as a leaving group under the reaction conditions. The

diastereofacial selectivity of the process was moderate, the best result being that corresponding to the additive of enolate **10b** to nitrone **8** (entry 8). The addition of silyl ketene acetals (entries 9-14) was more complex and a moderate selectivity was showed, too. The silylated hydroxylamines was the major compound in all reactions and no dependence was observed on the Lewis acid, although the reactions in the presence of $Zn(OTf)_2$ (entries 11-14) were cleaner than those activated with $BF_3{\cdot}Et_2O$ (entries 9-10).

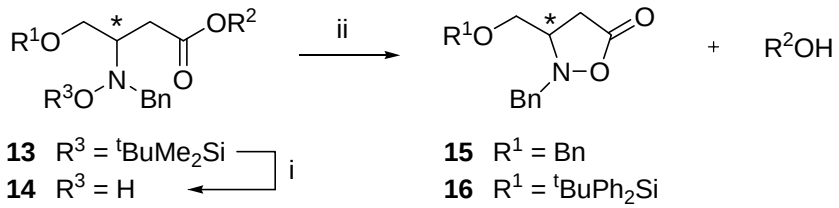
Table 1. Nucleophilic addition of enolates **9-12** to nitrones **7** and **8**[a]

Entry	Nitrone[b]	Enolate[c]	Additive[d]	Yield (%)[e]	**13** : **14** : **15**[f]	*R* / *S*[g]
1	**7**	**9a**	none	59	0 : 40 : 60	66 : 34
2	**7**	**9b**	none	75	0 : 43 : 57	60 : 40
3	**7**	**10a**	none	53	0 : 5 : 95	65 : 35
4	**7**	**10b**	none	88	0 : 5 : 95	74 : 26
5	**8**	**9a**	none	59	0 : 35 : 65	68 : 32
6	**8**	**9b**	none	76	0 : 10 : 90	60 : 40
7	**8**	**10a**	none	52	0 : 38 : 62	65 : 35
8	**8**	**10b**	none	89	0 : 26 : 74	80 : 20
9	**7**	**11**	$BF_3{\cdot}Et_2O$	54	66 : 34 : 0	50 : 50
10	**7**	**12**	$BF_3{\cdot}Et_2O$	62	66 : 34 : 0	70 : 30
11	**7**	**11**	$Zn(OTf)_2$	53	90 : 10 : 0	55 : 45
12	**7**	**12**	$Zn(OTf)_2$	58	88 : 12 : 0	60 : 40
13	**8**	**11**	$Zn(OTf)_2$	72	95 : 5 : 0	68 : 32
14	**8**	**12**	$Zn(OTf)_2$	59	70 : 30 : 0	65 : 35

[a] For detailed reaction conditions see experimental. [b] **7** and **8** refers to R^1 = Bn and R^1 = $^tBuPh_2Si$, respectively. [c] **9** and **11** refers to menthol derivatives; **10** and **12** refers to borneol derivatives; **a** and **b** series refer to Li and Na enolates, respectively. [d] 1.0 equiv was added. [e] calculated as the sum of the isolated yields of the isomeric mixtures of **13**, **14** and **15**. [f] Measured by NMR. [g] referred to **15** and **16**, and measured by comparison with the values of enantiomerically pure isomers after treatment of the crude mixture as indicated in the text (see Scheme 4).

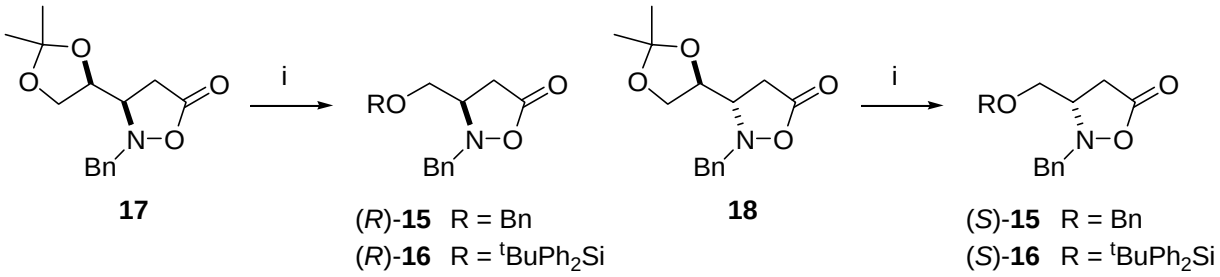
Since a complete analysis (considering both diastereoselectivity and enantioselectivity) of the reaction mixtures would have been not only rather tedious but also quite risky considering the possibility of kinetic resolutions, we decided to work-up the crude mixtures in order to transform all the intermediates into the targeted N-benzyl-3-(hydroxymethyl) isoxazolidin-5-ones **15** and **16**. Thus, the reaction mixtures coming from the addition of lithium and sodium enolates (table 1, entries 1-8) were treated with a catalytic amount of sodium methoxide in methanol to induce complete intramolecular cyclization (Scheme 4). In the case of the addition of silyl ketene acetals (Table 1, entries 9-14) a previous treatment with acetic acid in THF (to desilylate the

hydroxyamino functionality) was needed. This methodology consisting of the treatment of the crude mixture had been successfully used in our laboratory and it was demonstrated that no racemization occured.[5d] From the cyclization step the alcohol used as a chiral auxiliary could be recovered in good yield.



Scheme 4. i, AcOH, THF. ii, NaOMe, MeOH.

The assignment of the absolute configuration of compounds **15** and **16** was made by comparison with enantiomerically pure (*R*)-**15** and (*S*)-**16** prepared from **17** and **18**, respectively (Scheme 5). Compounds **17** and **18** had been previously prepared in a stereodivergent way in our laboratory and completely characterized.[5a,d]



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Scheme 5. i, H_5IO_6, Et_2O, then $NaBH_4$, MeOH, then BnBr, NaH or $^tBuPh_2SiCl$, DMF, imidazole.

Conclusions

In conclusion, we have studied the addition of chiral enolates to C-(alkoxymethyl) nitrones in order to produce enantioenriched mixtures of 3-(hydroxymethyl) isoxazolidin-5-ones which could be used for preparing isoxazolidinyl nucleosides, a new class of nucleoside analogues. Further studies to improve both selectivity and chemical yields of this methodology are currently ongoing in our laboratory.

Experimental Section

General Procedures. The reaction flasks and other glass equipment were heated in an oven at 130°C overnight and assembled in a stream of Ar. All reactions were monitored by TLC on silica gel 60 F254; the position of the spots was detected with 254 nm UV light or by spraying with 5% ethanolic fosfomolibdic acid and iodine. Preparative flash column chromatography was performed on columns of silica gel (40-60 microns). Melting points were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity or on a Bruker 300 instrument in $CDCl_3$. Chemical shifts are reported in ppm (δ) relative to the solvent used. Optical rotations were taken at 25 °C on a Perkin-Elmer 241 polarimeter. Elemental analysis was performed on a Perkin Elmer 240B microanalyzer.

***O*-Benzyl solketal (5).** To a well-stirred cooled (0 °C) solution of solketal (5 g, 37.8 mmol) in DMF (10 mL) was added NaH (1.60 g of a 60% suspension in mineral oil, 40 mmol) and the resulting suspension was stirred at 0 °C for 5 min at which time benzyl bromide (7.70 g, 45 mmol) was added dropwise. The reaction mixture was stirred for 8 h at ambient temperature and then treated with solid NaOMe (0.54 g, 10 mmol) to destroy the excess of benzyl bromide. After 1h of additional stirring the reaction mixture was diluted carefully with EtOAc (100 mL) and water (100 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and rotatory evaporated to give the crude product which was purified by flash chromatography (hexane / EtOAc, 80:20) to give pure **7** (8.23 g, 98%) as an oil. ^{1}H NMR ($CDCl_3$) δ1.34 (s, 3H), 1.40 (s, 3H), 3.45 (dd, 1H, J = 5.5, 9.9 Hz), 3.53 (dd, 1H, J = 5.5, 9.9 Hz), 3.72 (dd, 1H, J = 6.6, 8.0 Hz), 4.03 (dd, 1H, J = 6.6, 8.0 Hz), 4.23-4.33 (m, 1H), 4.50-4.60 (m, 2H), 7.21-7.42 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 25.4, 26.8, 66.9, 71.1, 73.5, 74.8, 109.4, 127.7, 128.4 (2C), 138.0. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.35; H, 8.09.

***O*-(tert-Butyldiphenylsilyl) solketal (6).** To a warmed (70°C), stirred solution of solketal (5 g, 37.8 mmol) and imidazole (15.46 g, 226.8 mmol) in anhydrous DMF (50 mL) was added *tert*-butyldiphenylsilyl chloride (18.8 g, 113.4 mmol). The mixture was stirred at 70°C for 4 h and then cooled to ambient temperature, treated with MeOH (1 mL), stirred for additional 15 min, diluted with H_2O, and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the crude product by column chromatography on silica gel (Hexane / EtOAc, 90:10) gave **8** (13.03 g, 93%) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9H), 1.35 (s, 3H), 1.38 (s, 3H), 3.65 (dd, 1H, J = 6.2, 10.3 Hz), 3.72 (dd, 1H, J = 4.5, 10.3 Hz), 3.91 (dd, 1H, J = 6.4, 8.1 Hz), 4.05 (dd, 1H, J = 6.2, 8.1 Hz), 4.20 (ddt, 1H, J = 4.5, 6.2, 6.4 Hz), 7.30-7.40 (m, 6H), 7.76-7.81 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 19.3, 25.6, 26.7, 26.8, 64.6, 66.8, 76.1, 109.2, 127.8, 127.9, 128.6 (2C), 129.8 (2C), 133.4, 135.6. Anal. Calcd for $C_{22}H_{30}O_3Si$: C, 71.31; H, 8.16. Found: C, 71.49; H, 8.25.

***N*-Benzyl-*C*-(benzyloxymethyl) nitrone (7).** To a well-stirred suspension of periodic acid (9.12 g, 40 mmol) in dry Et_2O, compound **5** (3.78 g, 17 mmol) was added at ambient temperature

under argon atmosphere in one portion. Stirring was maintained for an additional 4 h at which time the reaction mixture was filtered. The filtrate was evaporated under reduced pressure to give the crude aldehyde which was dissolved in CH_2Cl_2 (50 mL). To the resulting solution N-benzylhydroxylamine (2.09 g, 17 mmol) and $MgSO_4$ (6 g, 50 mmol) were added. After stirring for 4 h at ambiente temperature, the reaction mixture was filtered and the filtrate evaporated. The crude product was purified by flash chromatography (hexane / EtOAc, 1:1) to give the pure nitrone **7** (3.82 g, 88%) as a white solid; m.p. 95-97 ºC; Lit.[7] m.p. 95-96 ºC. ^{1}H NMR ($CDCl_3$) δ 4.43-4.47 (m, 2H), 4.52 (s, 2H), 4.85 (s, 2H), 6.79 (t, 1H, J = 4.2 Hz), 7.30-7.46 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 66.2, 69.0, 73.8, 128.0, 128.1, 128.6, 129.1, 129.2, 129.7, 132.1, 137.2, 137.5. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6,71; N, 5.49. Found: C, 75.38; H, 6.64; N, 5.23.

***N*-Benzyl-C-(*tert*-butyldiphenylsiloxymethyl) nitrone (8).** To a well-stirred suspension of periodic acid (9.12 g, 40 mmol) in dry Et_2O, compound **6** (6.30 g, 17 mmol) was added at ambient temperature under argon atmosphere in one portion. Stirring was maintained for an additional 4 h at which time the reaction mixture was filtered. The filtrate was evaporated under reduced pressure to give the crude aldehyde which was dissolved in CH_2Cl_2 (50 mL). To the resulting solution N-benzylhydroxylamine (2.09 g, 17 mmol) and $MgSO_4$ (6 g, 50 mmol) were added. After stirring for 4 h at ambiente temperature, the reaction mixture was filtered and the filtrate evaporated. The crude product was purified by flash chromatography (hexane / EtOAc, 3:2) to give the pure nitrone **8** (5.9 g, 86%) as a white solid; m.p. 73-75 ºC. ^{1}H NMR ($CDCl_3$) δ 1.03 (s, 9H), 4.64-4.66 (m, 2H), 4.77 (s, 2H), 6.76 (t, 1H, J = 3.9 Hz), 7.22-7.44 (m, 10H), 7.55-7.61 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 19.1, 26.8, 66.8, 68.7, 127.8, 127.9, 128.9, 129.0, 129.1, 129.4, 129.9, 132.7, 132.8, 135.4, 135.5, 139.9. Anal. Calcd for $C_{25}H_{29}NO_2Si$: C, 74.40; H, 7.24; N, 3.47. Found: C, 74.32; H, 7.49; N, 3.65.

General procedure for addition of lithium enolates to nitrones

To a cooled (0 ºC) solution of diisopropylamine (0.223 g, 2.2 mmol) in dry THF (8 mL) was added BuLi (1.31 mL of a 1,6 M solution in hexanes, 2.1 mmol). The resulting solution was stirred for 15 min, cooled to -80 ºC and treated with methyl acetate (0.148 g, 2 mmol). After 30 min of stirring at -80 ºC a solution of the corresponding nitrone (1 mmol) in THF (10 mL) was added dropwise and stirring was maintained for additional 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and warmed to room temperature. The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and rotatory evaporated to give the crude reaction mixture, which was analyzed by NMR (see Table 1).

General procedure for addition of sodium enolates to nitrones

To a cooled (-80 ºC) solution of methyl acetate (0.148 g, 2 mmol) in dry THF (8 mL) was added NaHMDS (2.1 mL of a 1 M solution in hexanes, 2.1 mmol). The resulting solution was stirred for 15 min, at -80 ºC and treated with a solution of the corresponding nitrone (1 mmol) in THF (10 mL). After stirring for additional 30 min the reaction mixture was quenched with saturated

aqueous NH_4Cl (10 mL) and warmed to room temperature. The organic layer was separated and the aquous layer extracted with EtOAc (2 x mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and rotatory evaporated to give the crude reaction mixture, which was analyzed by NMR (see Table 1).

General procedure for synthesis of silyl ketene acetals

To a cooled (0 ºC) solution of diisopropylamine (0.223 g, 2.2 mmol) in dry THF (8 mL) was added BuLi (1.31 mL of a 1,6 M solution in hexanes, 2.1 mmol). The resulting solution was stirred for 15 min, cooled to -80 ºC and treated with the corresponding acetate (2 mmol). After 30 min of stirring at -80 ºC a solution of *tert*-butyldimethylsilyl chloride (0.301 g, 2 mmol) was added and stirring was maintained for additional 8 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and warmed to room temperature. The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and rotatory evaporated to give the crude product which was immediately used without further purification.

General procedure for addition of silyl ketene acetals to nitrones

A cooled (-80 °C) and stirred solution of the corresponding nitrone (1 mmol) in anhydrous THF (10 mL) was treated sequentially with a solution of the corresponding silyl ketene acetal (1.5 mmol) in THF (10 mL) and the additive (1.5 mmol) indicated in Table 1. During the addition, the temperature of the reaction mixture was not allowed to raise above -70 °C. The mixture was stirred for 2 h, quenched with saturated NH_4Cl (10 mL), stirred again at ambient temperature for 10 min, and diluted with diethyl ether (20 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give the crude reaction mixture which was analyzed by NMR (see Table 1).

Synthesis of isoxazolidin-5-ones (15) and (16)

From the addition of lithium and sodium enolates. The crude mixture obtained from the addition of lithium and sodium enolates to nitrones **7** and **8** was dissolved in methanol (10 mL) and treated with sodium methoxide (11 mg, 0.2 mmol). The resulting mixture was stirred for 8 h at which time the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography to give the enantioenriched mixtures of **15** and **16** (see Table 1).

From the addition of silyl ketene acetals. The crude mixture obtained from the addition of silyl ketene acetals to nitrones **7** and **8** was dissolved in a 3:1:1 mixture of THF-AcOH-H_2O (10 mL), and the resulting solution was stirred at ambient temperature for 8 h. The mixture was neutralized with saturated aqueous $NaHCO_3$ and diluted with ethyl acetate (15 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was taken up in methanol (10 mL) and treated with sodium methoxide (11 mg,

0.2 mmol). The resulting mixture was stirred for 8 h at which time the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography to give the enantioenriched mixtures of **15** and **16** (see Table 1).

(3*R*)-2-Benzyl-3-(benzyloxymethyl) isoxazolidin-5-one ((*R*)-15). To a well-stirred suspension of periodic acid (0.912 g, 4 mmol) in dry Et_2O, compound **17** (0.5 g, 1.8 mmol) was added at ambient temperature under argon atmosphere in one portion. Stirring was maintained for an additional 4 h at which time the reaction mixture was filtered. The filtrate was evaporated under reduced pressure to give the crude aldehyde which was dissolved in MeOH (10 mL). The resulting solution was cooled to 0 ºC, treated with $NaBH_4$ (0.38 g, 10 mmol) and stirred for 1 h. The reaction mixture was diluted with EtOAc (20 mL) and water (20 mL), the organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced presure. The residue was taken up in DMF (5 mL), cooled to 0 °C and treated with NaH (80 mg of a 60% suspension in mineral oil, 2 mmol) and the resulting suspension was stirred at 0 °C for 5 min at which time benzyl bromide (0.193 g, 1.13 mmol) was added dropwise. The reaction mixture was stirred for 8 h at ambient temperature and then treated with solid NaOMe (13.5 mg, 0.25 mmol) to destroy the excess of benzyl bromide. After 1h of additional stirring the reaction mixture was diluted carefully with EtOAc (10 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and rotatory evaporated to give the crude product which was purified by flash chromatography (hexane / EtOAc, 80:20) to give pure **(*R*)-15** (0.332 g, 62%) as an oil. $[\alpha]_D^{25}$ +37 (c 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.68 (dd, 1H, J = 8.3, 17.6 Hz), 2.71 (dd, 1H, J = 7.3, 17.6 Hz), 3.52 (dd, 1H, J = 5.4, 9.8 Hz), 3.60 (dd, 1H, J = 4.9, 9.8 Hz), 3.65 (dddd, 1H, J = 4.9, 5.4, 7.3, 8.3 Hz), 4.15 (d, 1H, J = 14.2 Hz), 4.32 (d, 1H, J = 14.2 Hz), 4.50 (d, 1H, J = 12.2 Hz), 4.86 (d, 1H, J = 12.2 Hz), 7.29-7.38 (m, 10 H). ^{13}C NMR ($CDCl_3$) δ 36.4, 41.4, 67.0, 73.8, 76.9, 131.0, 131.3 (2C), 131.9 (2C), 132.7, 138.4, 140.7, 177.2. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.79; H, 6.35; N, 4.92.

(3*S*)-2-Benzyl-3-(benzyloxymethyl) isoxazolidin-5-one ((*S*)-15). The same procedure described above for the conversion of **17** to **(*R*)-15** was applied to compound **18** (0.5 g, 1.8 mmol) . After column chromatography on silica gel ((Hexane / Et_2O, 80:20) of the crude product, pure **(*S*)-15** (0.321 g, 60%) was obtained. The physical and spectroscopic data were identical to those of **(*R*)-15** except by the sign of the optical rotation. $[\alpha]_D^{25}$ -35 (c 0.60, $CHCl_3$).

(3*R*)-2-Benzyl-3-((*tert*-butyldimethylsiloxy)methyl) isoxazolidin-5-one ((*R*)-16). To a well-stirred suspension of periodic acid (0.912 g, 4 mmol) in dry Et_2O, compound **17** (0.5 g, 1.8 mmol) was added at ambient temperature under argon atmosphere in one portion. Stirring was maintained for an additional 4 h at which time the reaction mixture was filtered. The filtrate was evaporated under reduced pressure to give the crude aldehyde which was dissolved in MeOH (10 mL). The resulting solution was cooled to 0 ºC, treated with $NaBH_4$ (0.38 g, 10 mmol) and stirred for 1 h. The reaction mixture was diluted with EtOAc (20 mL) and water (20 mL), the organic layer was separated and the aqueous layer was extracted with EtOAc (2 x

10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced presure. The residue was taken up in DMF (5 mL), warmed to 70°C and treated sequentially with
imidazole (0.736 g, 10.8 mmol) and *tert*-butyldiphenylsilyl chloride (0.895 g, 5.4 mmol). The mixture was stirred at 70°C for 4 h and then cooled to ambient temperature, treated with MeOH (1 mL), stirred for additional 15 min, diluted with H_2O, and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the crude product by column chromatography on silica gel (Hexane / EtOAc, 90:10) gave **(*R*)-16** (0.513 g, 64%) as an oil. $[\alpha]_D^{25}$ +108 (c 0.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.02 (s, 9H), 2.66-2.70 (m, 2H), 3.58 (ddt, 1H, J = 4.8, 5.9, 8.0 Hz), 3.70 (dd, 1H, J = 4.8, 11.0 Hz), 3.77 (dd, 1H, J = 5.9, 11.0 Hz), 4.12 (d, 1H, J = 14.0 Hz), 4.32 (d, 1H, J = 14.0 Hz), 7.29-7.45 (m, 11H), 7.60-7.66 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 19.1, 26.7, 32.7, 63.4, 64.7, 65.4, 127.8 (2C), 127.9, 128.6, 129.2, 130.0 (2C), 132.5, 132.8, 135.2, 135.5, 135.6, 174.2. Anal. Calcd for $C_{27}H_{31}NO_3Si$: C, 72.77; H, 7.01; N, 3.14. Found: C, 72.84; H, 7.14; N, 3.00.

(3*S*)-2-Benzyl-3-((*tert*-butyldimethylsiloxy)methyl) isoxazolidin-5-one ((*S*)-16). The same procedure described above for the conversion of **17** to **(*R*)-16** was applied to compound **18** (0.5 g, 1.8 mmol) . After column chromatography on silica gel ((Hexane / Et_2O, 80:20) of the crude product, pure **(*S*)-16** (0.521 g, 65%) was obtained. The physical and spectroscopic data were identical to those of **(*R*)-15** except by the sign of the optical rotation. $[\alpha]_D^{25}$ -109 (c 0.54, $CHCl_3$).

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References

1. Merino, P. *Curr. Med. Chem. AIA* **2002**, *1*, 389 and references cited therein.
2. (a) Giles, F.J. *Expert Rev. Anticancer Ther.* **2002**, *2*, 261. (b) Grove, K.L.; Guo, X.; Liu, S.H.; Gao, Z.; Chu, C.K.; Cheng, Y.C. *Cancer Res.* **1995**, *55*, 3008.
3. (a) Jarvis, B.; Faulds, D. *Drugs* **1999,** *58*, 101. (b) Perry, C.M.; Faulds, D. *Drugs* **1997**, *53*, 657.
4. Chiacchio, U.; Corsaro, A.; Pistara, V.; Rescifina, A.; Iannazzo, D.; Piperno, A.; Romeo, G.; Romeo, R.; Grassi, G. *Eur. J. Org. Chem.* **2002**, 1206 and references cited therein.
5. (a) Merino, P.; Franco, S.; Garces, N.; Merchan, F.L.; Tejero, T. *Chem. Commun.* **1998**, 493. (b) Merino, P.; Franco, S.; Merchan, F.L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*, 3945. (c) Merino, P.; Franco, S.; Merchan, F.L.; Tejero, T. *Tetrahedron Lett.* **1998**, *39*,

6411. (d) Merino, P.; Alamo, E.M.; Bona, M.; Franco, S.; Merchan, F.L.; Tejero, T.; Vieceli, O. *Tetrahedron Lett.* **2000**, *41*, 9239. (e) Merino, P.; Franco, S.; Merchan, F.L.; Tejero, T. *J. Org. Chem.* **2000**, *65*, 5575.

6. The addition of enolates to nitrones have been extensively studied by Trombini and coworkers: (a) Camiletti, C.; Dhavale, D.D.; Gentilucci, L.; Trombini, C. *J. Chem. Soc. Perkin Trans 1* **1993**, 3157. (b) Castellari, C.; Lombardo, M.; Pietropaolo, G.; Trombini, C. *Tetrahedron: Asymmetry* **1996**, *7*, 1059. (c) Camiletti, C.; Dhavale, D.D.; Donati, F.; Trombini, C. *Tetrahedron Lett.* **1995**, *36*, 7293. For other additions of ester enolates to nitrones see: (d) Kobayashi, K.; Matoba, T.; Irisawa, S.; Takanohashi, A.; Tanmatsu, M.; Morikawa, O.; Konishi, H. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2805. (e) Kita, Y.; Itoh, F.; Tamura, O.; Ke, Y.Y.; Tamura, Y. *Tetrahedron Lett.* **1987**, *28*, 1431. (f) Jost, S.; Gimbert, Y.; Greene, A.E.; Fotiadu, F. *J. Org. Chem.* **1997**, *62*, 6672. (g) Qian, C:; Wang, L. *Tetrahedron* **2000**, *56*, 7193. (h) Kawakami, T.; Ohtake, H.; Arakawa, H.; Okachi, T.; Imada, Y.; Murahashi, S.-I. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2423. (i) Murahashi, S.-I.; Imada, Y.; Kawakami, T.; Harada, K.; Yonemushi, Y.; Tomita, N. *J. Am. Chem. Soc.* **2002**, *124*, 2888.

7. DeGiorgis, F.; Lombardo, M.; Trombini, C. *Synthesis* **1997**, 1243.