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Hemiaminal Generated by Hydration of Ketone-based Nitrone as an *N,O*-Centered Nucleophile in Organic Synthesis

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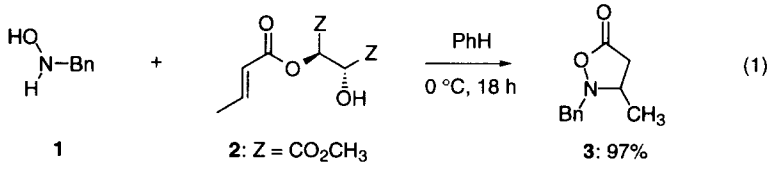
Abstract: Isoxazolidines that are useful precursors for β-amino acids have been prepared relying on intermolecular amino Michael addition-intramolecular S_N2 displacement employing hydroxylamine or hydrate of ketone-based nitrone as an *N*- and *O*-centered binucleophile.

Introduction

In order to explore the potential of hydroxylamines in organic synthesis we have been examining the features of their nucleophilic reactivity with special emphasis placed on their use as an *N,O*-centered tandem nucleophile. The first report[1] from this laboratory in this context involves the reaction of *N*-benzylhydroxylamine (**1** = BHA) with the ester of crotonic acid such as **2** where BHA acts as both *N*-centered Michael donor firstly and *O*-centered nucleophile bringing about acyl substitution reaction secondly to give isooxazolidinone (**3**), a promising precursor for β-amino acid derivatives,[2] in high yield (eq 1). The unusual structure of ester **2** was designed for this reaction to be advanced to the stage of intramolecular transesterification process in one pot under the conditions indicated and to open a route to asymmetric synthesis in this reaction as well.[1]



(1)

1 **2**: Z = CO_2CH_3 **3**: 97%

On the basis of this previous result the similar role of BHA as the *N,O*-centered tandem nucleophile and the eventual formation of isoxazolidine of type **5** can be expected if we employ α,β-unsaturated esters bearing a δ-leaving group such as **4** in place of **2** [eq (2)] which may undergo Michael addition firstly and intramolecular S_N2 displacement secondly.[3]

Another idea featuring the oxygen atom of BHA as the first nucleophile might be to use ketone-based nitrone **6** because it has been known that the intermolecular 1,3-dipolar cycloaddition reaction of **6** with α,β-unsaturated esters is highly sluggish:[4] the negative end of a dipole can act as an oxygen-centered nucleophile[5] to initially attack **4** on its C(5) bearing a leaving group [eq (3)]. If this is the case, the reaction would lead to

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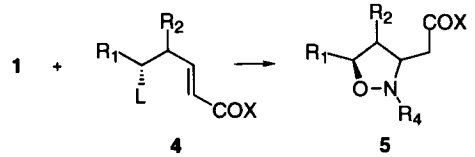
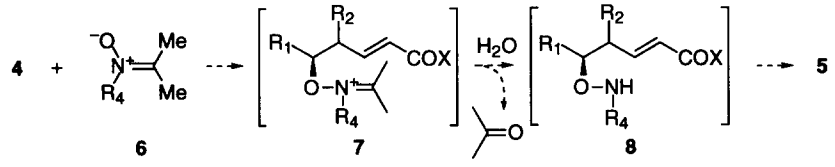
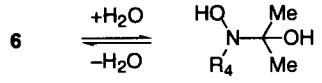
iminium ion intermediate (**7**) which should be highly labile to hydrolysis promoted by the added water to generate an amino group (**8**). If realized, Michael addition would ensue to give **5** probably with much better diastereoselectivity than in the case of eq (2) because **8** to **5** conversion takes place intramolecularly and, therefore, is much controllable in terms of diastereoselection by the C(4)-stereogenic center.[6]



4 **5** (2)



6 **7** **8** (3)



9 (4)

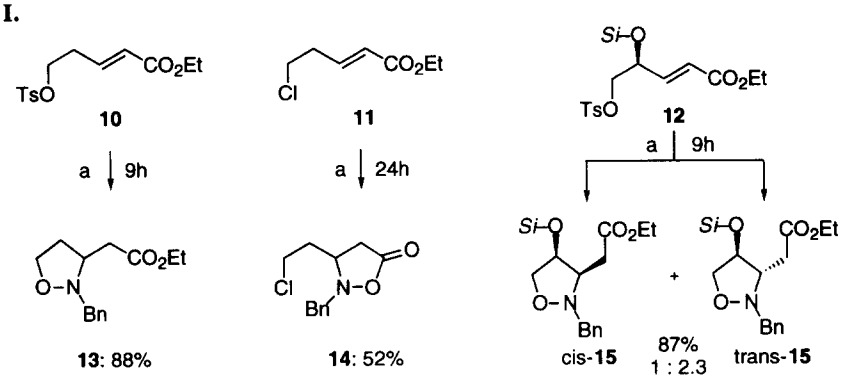
During the work, however, we found the unexpected destiny of the water which was added to be hopefully involved in the hydrolysis of **7** [eq(3)]. It has proven that hemiaminal such as **9**[7] is generated by the hydration of **6** [eq(4)] under the given reaction conditions and acting as the tandem *N,O*-centered nucleophile like BHA. Thus, **9** can be employed in place of BHA in eq (2) to give **5** within much shorter reaction time and at much lower temperature than BHA. In this article the applications of **9** as the *N,O*-centered tandem nucleophile in organic synthesis have been developed and a plausible mechanism is presented by which we can explain why the amino Michael reaction and ensuing intramolecular S_N2 reaction take place highly effectively when **9** is reacted with **4**.

Results and Discussion

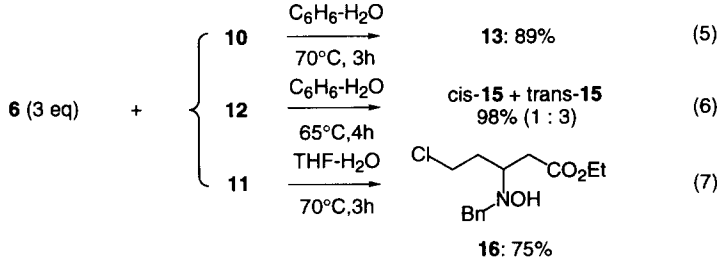
In order to examine the feasibility of the idea outlined in eq (2), α,β-unsaturated esters bearing δ-leaving groups (**10** — **12**) were prepared. Thus, we executed the reaction of **10** with *N*-benzylhydroxylamine (BHA) in benzene at 80 °C for 9 h to result in the formation of isoxazolidine **13** in high yield (87%) as shown in Scheme I. What took place initially was considered to be the Michael addition of BHA to **10** by the amino group and this assumption was given a support by the reaction using less reactive chlorine leaving group **11**: in this case the expected S_N2 reaction did not follow but reasonable transesterification ensued from an initial Michael adduct to give isoxazolidinone (**14**) as an only isolated product.

The reaction of chiral enoate (**12**) with BHA was examined and again gave the high yields (87%) of isoxazolidines (**15**).[8] However, the observed %de for **15** turned out to be unsatisfactory (ca. 40%) that was not surprising in the light of the usual ability of allylic stereogenic center to bias diastereofaces toward intermolecularly approaching reagents.[9]

Scheme I.



In order to examine the feasibility of the second idea outlined in eq (3), the reaction of **10** with **6**, prepared by heating a solution of BHA in acetone under reflux for 1.5 h and contaminated with a nitrone adduct,[10] was carried out employing benzene as a solvent in the presence of several drops of water[11] to confirm that it indeed gave **13** in high yield within much shorter reaction time [3 hr at 70 °C: eq (5)] than that (9 hr at 80 °C) for BHA (Scheme 1). The reaction of **12** with **6** under the same reaction conditions as those mentioned above also afforded a mixture of cis-**15**[8] and trans-**15**[8] in almost quantitative yield with somewhat improved diastereomeric excess (50 %de) [eq (6)] as compared to the case of BHA (Scheme I). These results [eq (5), (6)] looked like what we had expected actually occurred. However, the third experiment [eq (7)] provided us with important information which strongly suggests that what occurred was not what we had expected. Thus, the reaction of **11** with **6** produced only Michael adduct (**16**) which means that **6** never acted as an oxygen nucleophile but could probably be hydrated under the given reaction conditions to generate not BHA but other type of a nitrogen nucleophile such as **9** [eq (4)] or the nitrone adduct[10] because every reaction employed **6** proceeded 3 to 4 times as fast as we expected on the basis of BHA cases. Among these candidates (**9** and the nitrone adduct) the latter was ruled out for some reasons.[12]

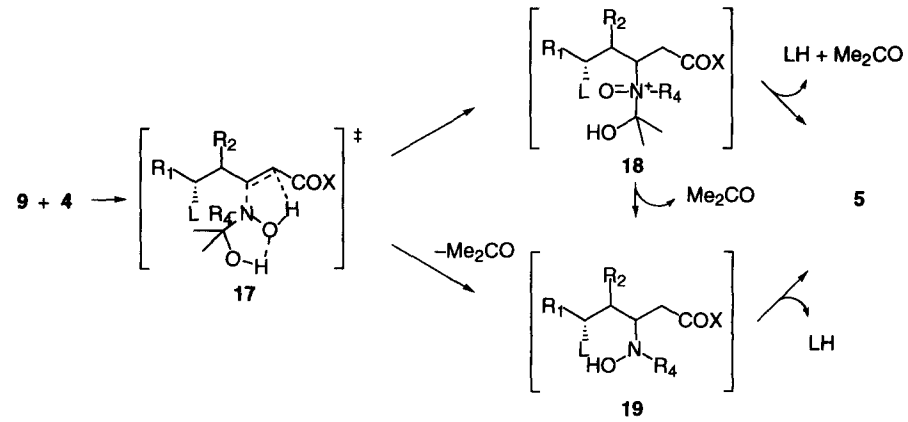


Evidence supporting the formation of **9** [eq (4)] has been obtained from the ^{13}C-NMR spectrum of a mixture of **6** and H_2O (1:1) in $CDCl_3$. At room temperature the spectra indicated the presence of only **6** with typical $C{=}N^+$ resonance at 144 ppm, no hydrated product being detected at all.[13] However, when the mixture was warmed up to 60 °C, a new low-intensity signal appeared at 96 ppm which can reasonably be assigned as a characteristic signal for the *N,O*-acetal carbon, whereas the intensity of the signal at 144 ppm decreased in inverse proportion to the increase in signal intensity at 96 ppm. In addition, no signal to be assigned as BHA was

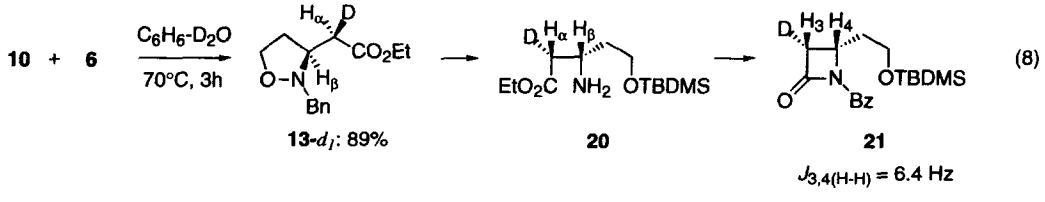
detected at all.[14] It should, therefore, be pointed out that even the partial contribution of BHA to the formation of the isoxazolidines (**13** and **15**) and/or **16** can be ruled out.

In order to make the generation of **9** clearer, labeled **6** prepared from ^{13}C-enriched acetone was subjected to NMR studies as mentioned above and the labeled carbons were found at both 144 and 96 ppm. Thus, it has proven that **6** becomes equilibrated with its hydrate **9** on mixing with water in benzene and is never back to BHA and acetone through hydrolysis under the given reaction conditions.[15] We reasoned that the structural feature of **9** should be responsible for the observed increased rate because the presence of both tertiary and *N*-hydroxy groups in **9** would be highly convenient for the *N*-hydroxy proton to be delivered to the α-carbon of **4** relying on a possible bicyclo[3.3.0]-type transition state (**17**) during the Michael reaction as illustrated in Scheme II.[16]

Scheme II.



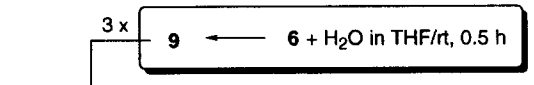
In addition, when the reaction was carried out using benzene-D_2O medium, a deuterium atom was incorporated onto the α-carbon of **13** [**13**-d_1 in eq (8)], as judged from its NMR spectra. The syn stereochemistry of its two consecutive stereogenic centers, if so achieved, with regard to the C_α—D and C_β—N bonds could be strong evidence that the Michael reaction of **9** to α,β-unsaturated ester **10** takes place through a concerted mechanism.[17] This is also consistent with the proposed mechanism involving **17** as a transition state assembly (Scheme II). In order to attest this issue **13**-d_1 was transformed into 2-azetidinone derivative (**21**) in which stereochemical relationship between H_α- and H_β-atoms in **13**-d_1 would eventually be reflected as 3,4-cis relationship. In the event catalytic reduction of **13**-d_1 led to δ-hydroxy-β-amino ester, in which the hydroxyl group was protected as a TBDMS-ether (**20**). Treatment of **20** with EtMgBr in THF followed by *N*-benzoylation gave **21** with $J_{3,4}$-value of 6.4 Hz indicating that such is the case.[18]



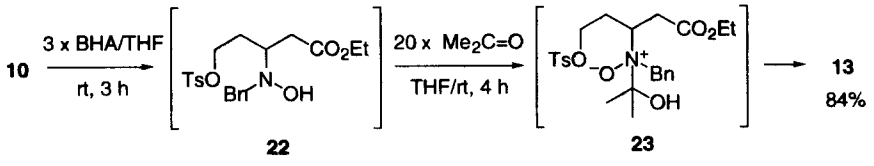
(8)

In any event **9** should be an actual nucleophile capable of attacking the β-carbon of **4** with its nitrogen atom in the first place to give amine oxide derivative (**18**) which may be a strong oxygen-centered nucleophile to undergo an intramolecular S_N2 process leading to **5**. Hydroxylamine derivative (**19**), which might be generated directly or via **18** from **17** accompanied by the liberation of acetone, can not be ruled out as a possible intermediate leading to **5**.

It turned out that a water-miscible solvent such as THF accelerates the formation of **9** from **6**: when **6** placed in an NMR tube was mixed with water in THF-d_8 as solvent, the presence of *N,O*-acetal function was reasonably suggested by the signal appeared at 97.2 ppm (^{13}C-NMR) with strong intensity and a broadened shape even at room temperature while nitrone's C=N$^+$ resonance also appeared with a broadened shape at 142.7 ppm. Since such an NMR study indicated that **9** can be formed quickly at room temperature by using THF as solvent, we have examined whether the reaction of **10** with **9** proceeds even at room temperature in THF or not. Thus, the reaction of **10** with reagent **9** [prepared by stirring **6** in THF (4 mL) containing 4 drops of water for 30 min] proceeded even at room temperature (25 °C) to give **13** in 80% yield after 3 hr [eq (9)].



10 → (THF/rt, 3 h) → **13**, 80% (9)



(10)

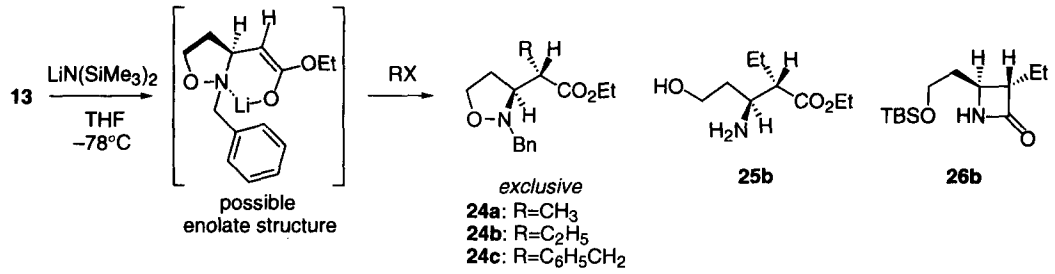
10 → (3 x BHA-Me_2C=O (1:1)/THF, rt, 9 h) → **13**, 95% (11)

The intervention of **18** and the nature of amine *N*-oxide moiety in it as a potent *O*-centered nucleophile have been supported by the following observations. When **10** was reacted with BHA (3 eq) in THF for 3 hr and, after that, acetone (20 eq or more) was added to the reaction, **13** was obtained in 84% yield after additional 4 hr at room temperature [eq (10)]. The tlc monitoring of the reaction indicated that the first step (**10** + BHA in THF) gave only Michael adduct (**22**) and no formation of **13** was witnessed without acetone. This interesting result probably implies that intramolecular S_N2 reaction of **22** is too sluggish to take place at room temperature, but **22**, on reaction with acetone, could be converted to amine *N*-oxide derivative (**23**) which was featuring in the following S_N2 process: the high nucleophilicity of the charged oxygen of **23** should be responsible for the observed remarkable rate enhancement as compared with the hydroxylamine moiety of **22**. The third experiment illustrated in eq(11) where **10** was reacted with BHA (3 eq) in the presence of acetone (equimolar amount to BHA) from the beginning in THF resulted in the formation of **13** in 95% yield at rt for 9 hr. This result is quite consistent with that shown in eq(10). In any event high *N,O*-tandem nucleophilicity of hemiaminal **9** in sequential Michael addition (*N*-centered nucleophile) and intramlecular S_N2 reactions (*O*-centered nucleophile in the form of

adduct between acetone and *tert*-hydroxylamine function) has been approved by these experiments. Thus, the general mechanism indicated in Scheme II would probably involve **18** as an immediate precursor for **5**.

The potential of **13** as a β-amino acid synthon in organic synthesis can be positively evaluated in the light of stereochemistry realized on alkylation at the exocyclic methylene carbon α to the carbonyl group. Indeed, on treatment with lithium bis(trimethylsilyl)amide in THF at –78 °C for 30 min and successively with alkyl halides (MeI, EtI, BnBr), **13** led to alkylated isoxazolidines with very high diastereomeric excess (>99 %de).[19]

Scheme III.



The stereochemistry of exclusive product **24a**—**c** was reasonably determined on the basis of relative stereochemistry observed for a β-lactam derivative synthesized from **24** via β-amino ester intermediates in a similar way as in the case of **13**-d_1. For instance, the reductive cleavage of the isoxazolidine ring of **24b** on its N—O bond readily took place together with the deprotection of the *N*-benzyl group to give diastereomerically pure β-amino ester (**25b**), which was, then, cyclized to known β-lactam derivative (**26b**) whose ^{1}H-NMR spectral data are identical with those reported.[20] The coupling constant determined between the ring protons of **26b** is 2.1 Hz that is representative for a trans-isomer which, in turn, means that the relative stereochemistry of **24b** with regard to the C—N and C—R bonds should be anti as indicated above. This also means that lithium enolate generated from **13** as shown in bracket (Scheme III) should be rigid owing to its chelated structure in which the nitrogen-connecting stereogenic center strongly biases the π-faces of the enolate to result in efficient control over stereochemical consequences in this alkylation processes.

Thus, we have demonstrated that BHA can act as *N,O*-binucleophile with the nitrogen atom as the first nucleophilic center in its reaction with δ-tosyloxy-α,β-unsaturated esters. Furthermore, it has proven that acetone-based nitrone hydrate **9** generated in situ from nitrone **6** can be employed as a more efficient BHA synthon in a practical sense. The synthesis of the isoxazolidines of type **5** has indeed been achieved by such a novel system. In addition, the heterocycles of this class seem to be a promising β-amino acid synthons of diverse structural possibilities.

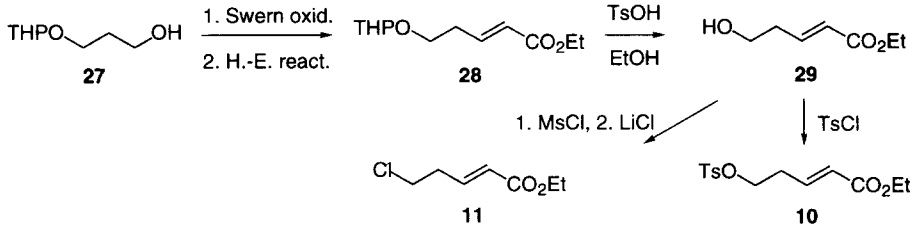
Experimental

General Methods. IR spectra were obtained with a Horiba fourier transform infrared spectrophotometer Model FT-210 instrument, and only the major absorptions are cited. The ^{1}H-NMR (500, 300, and 200 MHz) and ^{13}C-NMR (126, 75, and 50 MHz) spectra were recorded on Varian VXR-500, Mercury-300, and VXR-200 or Gemini-200 instruments with $CDCl_3$ as a solvent unless otherwise indicated. The chemical shifts are given in δ units relative to internal $CHCl_3$ (7.26 ppm for ^{1}H) or $CDCl_3$ (77 ppm for ^{13}C). Splitting patterns are

abbreviated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad: among them s, d, t, and q are also used for ^{13}C spectra to indicate non-protonated, methine, methylene, and methyl carbons, respectively. Optical rotations were measured on a Horiba SEPA-300 digital polarimeter using a 3.5 mm x 0.5 dm Pyrex cell. Mass spectra were obtained on a JEOL JMS-DX303 instrument relying on a JMA-DA5000 mass data system. Elemental analyses were made with a Perkin–Elmer 2400 CHN Elemental Analyzer.

Analytical TLC was executed on pre-coated Merck silica gel 60 F_{254} (0.25 mm thickness). Usual column chromatography over SiO_2 (abbreviated as CC) was carried out with Merck silica gel 60-7743. *N*-Benzylhydroxylamine (BHA) was prepared after the published method.[21] THF was distilled from sodium benzophenone ketyl just before use. Benzene, dichloromethane, pyridine, DMSO, DMF, and triethylamine (Et_3N) were distilled from CaH_2. Acetone was distilled after drying over molecular sieves (4Å). Other reagents were used as received. A series of operation concerned with the isolation of products involving extraction, washing, drying, filtration, and concentration by a rotary evaporator is referred to as, for instance, "a usual workup [(EA)-(SBC)-(SS)]". What is written in bracket means that ethyl acetate (EA), saturated aqueous sodium bicarbonate (SBC), and sodium sulfate (SS) were used as a extraction solvent, washing solution, and drying agent, respectively, in the extractive works. The following abbreviations are also used in such case: diethyl ether = (EE); CH_2Cl_2 = (DCM); 10% aqueous tartaric acid solution = (TA), magnesium sulfate (MS). All reactions were executed in flame-dried glasswares under an atmosphere of dry argon.

Preparation of 10 and 11. A series of routine synthetic transformations as shown below were applied to the synthesis of substrates **10** and **11**. This involves mono-protection of 1,3-propanediol as a tetrahydropyranyl ether (**27**), oxidation of the remaining hydroxy group to aldehyde and subsequent reaction of the aldehyde with Horner-Emmons reagent to give α,β-unsaturated ester (**28**), liberation of the THP-ether to a free alcohol (**29**), and final toluenesulfonylation of the alcohol to **10** or methanesulfonylation-S_N2 displacement with LiCl to **11**.



3-Tetrahydropyranyloxy-1-propanol (**27**). To a solution of 1,3-propanediol (16.1 g, 0.21 mol) in THF (200 ml) were added dihydropyran (12 ml, 0.10 mol) and TsOH (192 mg, 1.01 mmol) at 0 °C. The reaction was stirred at rt for 4 hr and quenched with Et_3N (0.15 ml) and, then, mixed with 5% aqueous $NaHCO_3$ solution and H_2O. A usual workup [(EA)-(MS)] afforded an oil, which was purified by CC to give **27** (10.18 g, 62%) as a colorless oil. **27**: IR (film) 3434, 2943, 2873, 1120 cm^{-1}; ^1H-NMR (200 MHz) δ 1.4—1.9 (m, 8H, CCH_2C), 2.65—2.85 (br, 1H, OH), 3.4—3.6 (m, 2H, OCH_2), 3.65—4.95 (m, 4H, OCH_2), 4,52 (br t, 1H, J = 4.5 Hz, O–CH–O); ^{13}C-NMR (50 MHz) δ 19.6 (t), 25.2 (t), 30.6 (t), 32.0 (t), 61.1 (t), 62.5 (t), 66.0 (t), 99.1 (d).

Ethyl (*E*)-5-Tetrahydropyranyloxy-2-pentenoate (**28**). In a 300 ml round-bottomed flask were placed $(COCl)_2$ (3.4 ml, 39.0 mmol) and CH_2Cl_2 (30 ml) and the flask was cooled to –78 °C. To this solution was introduced a solution of DMSO (5.4 ml, 76.1 mmol) in CH_2Cl_2 (30 ml) at –78 °C with a cannula and the

resulting mixture was stirred for 30 min and a solution of **27** (2.05 g, 12.8 mmol) in CH_2Cl_2 (30 ml) was introduced into the mixture at –78 °C. After 30 min stirring, Et_3N (16.0 ml, 0.115 mol) was added to the mixture at –78 °C. The reaction was continued for 1 hr at –78 °C — rt and quenched with H_2O. A usual workup [(DCM)-(SS)] afforded an oil, which was roughly purified by CC (short column) to give the corresponding aldehyde to be submitted to the next transformation.

In a 300 ml round-bottomed flask were placed NaH (60 % in oil: 563 mg, 14.1 mmol) and THF (40 ml) followed by the addition of $(^iPrO)_2P(O)CH_2CO_2Et$ (3.5 ml) at 0 °C. The reaction was stirred at rt for 30 min, and, then, cooled to –78 °C. To this cold solution was introduced a solution of the aldehyde in THF (40 ml) dropwise with a cannula at –78 °C. The reaction mixture was stirred at –78 — –68 °C for 1.5 hr and quenched with H_2O. A usual workup [(EA)-(MS)] afforded an oil, which was purified by CC to give **28** (2.33 g, 80 %) as a colorless oil. **28**: IR (film) 2943, 2872, 1720, 1034 cm^{-1}; ^{1}H-NMR (500 MHz) δ 1.27 (t, 3H, *J* = 7.0 Hz, O–CCH_3), 1.48—1.61 (m, 4H, CCH_2C), 1.65—1.74 (m, 1H, C*H*H), 1.75—1.84 (m, 1H, CH*H*), 2.49 (dq, 2H, *J* = 6.7, 1.8 Hz, CH_2C=), 3.47—3.53 (m, 2H, OCH_2), 3.8—3.87 (m, 2H, OCH_2), 4.17 (q, 2H, *J* = 7.0 Hz, O–CH_2Me), 4.6 (t, 1H, *J* = 3.1 Hz, O–CH–O), 5.88 (dt, 1H, *J* = 15.9, 1.5 Hz, C=$CHCO_2$), 6.97 (dt, 1H, *J* = 15.9, 7.0 Hz, CH=CCO_2); ^{13}C-NMR (50 MHz) δ 14.1 (q), 19.3 (t), 25.2 (t), 30.4 (t), 32.4 (t), 59.9 (t), 62.0 (t), 65.3 (t), 98.6 (d), 122.7 (d), 145.5 (d), 166.2 (s).

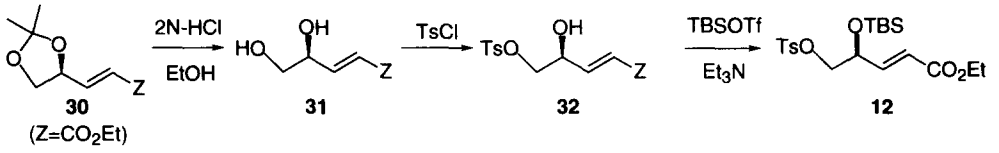
Ethyl (*E*)-5-Hydroxy-2-pentenoate (**29**). To a solution of **28** (2.16 g, 9.47 mmol) in EtOH (14 ml) was added TsOH (90 mg, 0.44 mmol) at 0 °C and the mixture was stirred at rt for 2 hr and was neutralized with $NaHCO_3$. A usual workup [(EA)-(MS)] afforded an oil, which was purified by CC to give **29** (1.26 g, 92 %) as a colorless oil. **29**: IR (film) 3450, 2939, 1718, 1043 cm^{-1}; ^{1}H-NMR (500 MHz) δ 1.28 (t, 3H, *J* = 7.0 Hz, O–CCH_3), 1.7—1.8 (br, 1H, OH), 2.44 (s, 3H, CH_3Ar), 2.46 (qd, 2H, *J* = 6.4, 1.5 Hz, CH_2C=), 3.76 (t, 2H, *J* = 6.4 Hz, HOCH_2), 4.17 (q, 2H, *J* = 7.0 Hz, O-CH_2Me), 5.91 (dt, 1H, *J* = 15.9, 1.5 Hz, –C=$CHCO_2$), 6.95 (dt, 1H, *J* = 15.9, 7.2 Hz, –CH=CCO_2); ^{13}C-NMR (50 MHz) δ 14.1 (q), 35.3 (t), 60.3 (t), 60.8 (t), 123.3 (d), 145.4 (d), 166.5 (s). exact mass, m/z 144.07861 (calcd for $C_7H_{12}O_3$, m/z 144.07864). Anal. Calcd for $C_7H_{12}O_3$, C, 58.32; H, 8.39. Found: C, 58.40; H, 8.33.

Ethyl (*E*)-5-Tosyloxy-2-pentenoate (**10**). To a solution of **29** (989 mg, 6.86 mmol) in pyridine (7.0 ml) was added TsCl (1.57g, 8.23 mmol) at 0 °C and the mixture was stirred at 10 °C for 24 hr and quenched with 1N HCl. A usual workup [(EE)-(MS)] afforded an oil, which was purified by CC to give **10** (1.44 g, 70 %) as a colorless oil. **10**: IR (film) 2981, 1720, 1363, 1176 cm^{-1}; ^{1}H-NMR (500 MHz) δ 1.26 (t, 3H, *J* = 7.0 Hz, O–CCH_3), 2.53 (qd, 2H, *J* = 4.9, 1.5 Hz, –CH_2C=), 4.11 (t, 2H, *J* = 6.4 Hz, OCH_2), 4.15 (dq, 2H, *J* = 7.0 Hz, CO_2CH_2), 5.8 (dq, 1H, *J* = 15, 0.6 Hz, C=$CHCO_2$), 6.75 (dt, 1H, *J* = 15.6, 7.0 Hz, –CH=CCO_2), 7.3 (d, 2H, *J* = 8.5 Hz, ArH), 7.78 (d, 2H, *J* = 8.2 Hz, ArH); ^{13}C-NMR (50 MHz) δ 14.1 (q), 21.6 (q), 31.4 (t), 60.4 (t), 67.9 (t), 124.3 (d), 127.9 (d, 2C), 129.9 (d, 2C), 132.7 (s), 142.0 (d), 144.9 (s), 165.8 (s); exact mass, m/z 266.11539 (calcd for $C_{14}H_{18}O_5$, m/z 144.07864). Anal. Calcd for $C_{14}H_{18}O_5$, C, 63.15; H, 6.81. Found: C, 63.02; H, 6.80.

Ethyl (*E*)-5-Chloro-2-pentenoate (**11**). To a solution of **29** (437 mg, 2.96 mmol) in DMF (30 ml) was added LiCl (691 mg, 16.3 mmol) at rt and the mixture was stirred for 10 min. To this mixture were added pyridine (1.00 ml, 12.4 mmol) and MsCl (0.46 ml, 5.9 mmol) at 0 °C and the resulting mixture was stirred at rt for 22 hr and quenched with saturated aqueous $NaHCO_3$ solution. A usual workup [(EA)-(MS)] afforded an oil, which was purified by CC to give **11** (401 mg, 83 %) as a colorless oil. **11**: IR (film) 2983, 1720, 1274, 1197 cm^{-1}; ^{1}H-NMR (500 MHz) δ 1.27 (t, 3H, *J* = 7.0 Hz, O–CCH_3), 2.66 (qd, 2H, *J* = 6.7, 1.5 Hz, CH_2C=), 3.60 (t, 2H, *J* = 6.7 Hz, $ClCH_2$), 4.19 (q, 2H, *J* = 7.0 Hz, CO_2CH_2), 5.9 (dt, 1H, *J* = 15.6, 1.5 Hz,

C=CHCO$_2$), 6.8 (dt, 1H, J = 15.6, 7.0 Hz, CH=CCO$_2$); ^{13}C-NMR (50 MHz) δ 14.2 (q), 34.9 (t), 42.2 (t), 60.4 (t), 123.9 (d), 143.7 (d), 167 (s); exact mass, m/z 162.04470 (calcd for $C_7H_{11}O_2Cl$, m/z 162.04475).

Preparation of 12. Ethyl (*E*)-(4*R*)-4-*tert*-butyldimethylsiloxy-5-tosyloxy-2-pentenoate (**12**) was prepared as follows. Well-known optically pure acetonide-α,β-unsaturated ester (**30**)[22] derived from D-mannitol was used as a starting material and a series of routine transformations involving deprotection of the acetonide function to 1,2-diol group, selective tosylation of its primary hydroxy group, and final *tert*-butyldimethylsililation of the secondary hydroxy group led to **12** uneventfully.



30 (Z=CO$_2$Et) **31** **32** **12**

Ethyl (*E*)-(4*R*)-4,5-Dihydroxy-2-pentenoate (**31**). To a solution of **30**[22] (1.99 g, 9.94 mmol) in EtOH (20 ml) was added 2N-HCl (10 ml). The mixture was stirred at rt for 2 hr and quenched with NaHCO$_3$. Thus-formed precipitates were filtered off and the filtrate was concentrated by a rotary evaporator to give an oil accompanied by precipitates, which was removed by filtration through a Celite pad. The Celite pad was rinsed with EtOAc and the combined organic solutions were concentrated to give **31** (1.52 g, 95 %) as a colorless oil. **31**: $[\alpha]_D^{25}$ –5.48 (c 1.57, CHCl$_3$); IR (film) 3492, 2983, 1724, 1307, 1182 cm^{-1}; ^{1}H-NMR (200 MHz) δ 1.26 (t, 3H, J = 7.2 Hz, OCCH$_3$), 3.42—3.8 (br, 3H, O–CH$_2$CH–O), 3.89—4.0 (br, 1H, OH), 4.17 (q, 2H, J = 7.2 Hz, CO$_2$CH$_2$–), 4.3—4.45 (br, 1H, OH), 6.1 (dd, 1H, J = 15.7, 1.7 Hz, C=CHCO$_2$), 6.88 (dd, 1H, J = 15.7, 4.4 Hz, CH=CCO$_2$); ^{13}C-NMR (50 MHz) δ 14.1 (q), 60.7 (t), 65.5 (t), 71.6 (d), 121.9(d), 146.2 (d), 166.6 (d).

Ethyl (*E*)-(4*R*)-4-Hydroxy-5-tosyloxy-2-pentenoate (**32**). To a solution of **31** (1.52 g, 9.49 mmol) in CH_2Cl_2 (10 ml) were added 2,4,6-colidine (9.0 ml, 0.068 mol) and TsCl (2.10 g, 11.0 mmol) at 0 °C. The reaction mixture was stirred at rt for 20 hr and quenched with 1N-HCl. A usual workup [(DCM)-(TA)-(MS)] afforded an oil, which was purified by CC to give **32** (2.1 g, 72 %) as a colorless oil. **32**: $[\alpha]_D^{24}$ –15.5 (c 0.830, CHCl$_3$); IR (film) 3492, 2983, 1712, 1176 cm^{-1}; ^{1}H-NMR (200 MHz) δ 1.28 (t, 3H, J = 7.2 Hz, OCCH$_3$), 2.4—2.9 (br, 1H, OH), 2.45 (s, 3H, PhCH$_3$), 3.93 (dd, 1H, J = 10.4, 7.2 Hz, OC*H*H), 4.12 (dd, 1H, J = 10.4, 3.4 Hz, OCH*H*), 4.19 (q, 2H, J = 7.2Hz, CO$_2$CH$_2$–), 4.52—4.64 (m, 1H, C*H*OH), 6.15 (dd, 1H, J = 15.7, 1.9 Hz, C=CHCO$_2$), 6.77 (dd, 1H, J = 15.7, 4.4 Hz, CH=CCO$_2$), 7.36 (d, 2H, J = 8.4 Hz, ArH), 7.79 (d, 2H, J = 8.4 Hz, ArH); ^{13}C-NMR (50 MHz) δ 14.2 (q), 21.7 (q), 60.7 (t), 68.9 (d), 72.0 (t), 123.5 (d), 128.0 (d, 2C), 130.0 (d, 2C), 142.9 (d), 145.4 (s), 165.8 (s); exact mass, m/z 282.11029 (calcd for $C_{14}H_{18}O_6$, m/z 282.11033). Anal. Calcd for $C_{14}H_{18}O_6$, C, 59.57; H, 6.43. Found: C, 59.50; H, 6.42.

Ethyl (*E*)-(4*R*)-4-*tert*-Butyldimethylsiloxy-5-tosyloxy-2-pentenoate (**12**). To a solution of **32** (2.14 g, 6.82 mmol) in THF (34 ml) were added Et$_3$N (1.2 ml, 8.6 mmol) and TBSOTf (1.90 ml, 8.27 mmol) at 0 °C. The reaction mixture was stirred at 0°C for 15 min and quenched with H_2O. A usual workup [(EA)-(MS)] afforded an oil, which was purified by CC to give **12** (2.19 g, 75 %) as a colorless oil. **12**: $[\alpha]_D^{20}$ +1.09 (c 2.40, CHCl$_3$); IR (film) 2931, 1720, 1367, 1178 cm^{-1}; ^{1}H-NMR (500 MHz) δ 0.03 and 0.05 (s, 3H for each, SiCH$_3$), 1.28 (t, 3H, J = 7.0 Hz, OCCH$_3$), 2.44 (s, 3H, PhCH$_3$), 3.85 (dd, 1H, J = 7.0, 10.1 Hz, OC*H*H), 3.92 (dd, 1H, J = 4.6, 10.1 Hz, OCH*H*), 4.15—4.25 (m, 2H, CO$_2$CH$_2$–), 4.48—4.54 (m, 1H, CHOSi), 6.05 (dd, 1H, J

= 15.6, 1.8 Hz, C=CHCO$_2$), 6.79 (dd, 1H, J = 15.6, 4.3 Hz, CH=CCO$_2$), 7.34 (d, 2H, J = 8.3 Hz, ArH), 7.78 (d, 2H, J = 8.3 Hz, ArH); ^{13}C-NMR (50 MHz) δ –5.0 (q), –5.0 (q), 14.1 (q), 18.0 (s), 21.6 (q), 25.6 (q, 2C), 60.5 (t), 69.6 (d), 71.8 (t), 122.9 (d), 127.9 (d, 2C), 129.8 (d, 2C), 132.5 (s), 144.7 (d), 145 (s), 165.8 (s); exact mass, m/z 396.19677 (calcd for $C_{20}H_{32}O_6Si$, m/z 396.19680). Anal. Calcd for $C_{20}H_{32}O_6Si$, C, 60.58; H, 8.13. Found: C, 60.61; H, 8.12.

2-Benzyl-3-(ethoxycarbonylmethyl)isoxazolidine (13). *Method A* (BHA) (Scheme I): To a solution of **10** (208 mg, 0.700 mmol) in benzene (7.0 ml) was added BHA (264 mg, 2.14 mmol) at rt. The reaction mixture was stirred at 80 °C for 9 hr and quenched with H_2O. A usual workup [(EA)-(MS)] afforded an oil, which was purified by CC to give **13** as a colorless oil (152 mg, 88 %): IR (film) 2979, 1731, 1243, 1174 cm^{-1}; ^{1}H-NMR (500 MHz) δ 1.23 (t, 3H, J = 7.0 Hz, OCCH$_3$), 2.0 (m, 1H, OCC*H*H), 2.4 (dd, 1H, J = 15.6, 7.6 Hz, C*H*HCO$_2$), 2.5 (m, 1H, OCCH*H*), 2.58 (dd, 1H, J = 15.6, 6.4 Hz, CH*H*CO$_2$), 3.5 (m, 1H, NCH), 3.82 & 3.92 (ABq, 2H, J = 13.1 Hz, NC*H*$_2$Ph), 3.9 (td, 1H, J = 8.2, 6.1 Hz, OC*H*H), 4.0 (td, 1H, J = 8.9, 6.1 Hz, OCH*H*), 4.1 (m, 2H, CO$_2$CH$_2$–), 7.2—7.4 (m, 5H, ArH); ^{13}C-NMR (50 MHz) δ 14.1 (q), 33.9 (t), 39.6 (t), 60.4 (t), 60.5 (t), 61.2 (d), 64.9 (t), 127.3 (d), 128.3 (d, 2C), 128.9 (d, 2C), 137.3 (s), 171.4 (s); exact mass, m/z 273.13645 (calcd for $C_{16}H_{19}O_3N$, m/z 273.13648). Anal. Calcd for $C_{16}H_{19}O_3N$, C, 70.31; H, 7.01. Found: C, 70.29; H, 6.99.

Method B (hemiaminal); *Benzene as solvent*: [**6**/C$_6$H$_6$-H$_2$O/70 °C/3 hr; eq(5)]. In a 30 ml round-bottomed flask equipped with a reflux condenser were placed BHA (62.9 mg, 0.510 mmol) and acetone (2 ml). The reaction mixture was heated under reflux for 1.5 hr, allowed to be cooled to rt, and concentrated by a rotary evaporator. The residue was treated under high vacuum for 1.5 hr to give crude nitrone as a solid. This nitrone was dissolved in benzene (1 mL) and to this solution was introduced a solution of **10** (41 mg, 0.14 mmol) in benzene (1.2 ml) followed by the addition of several drops of H_2O. The reaction mixture was stirred at 70 °C for 3 hr and quenched with H_2O. A usual workup [(EA)-(MS)] afforded an oil, which was purified by CC to give **13** as a colorless oil (30 mg, 89%): this is identical with that given through *Method A* in all respects.

Method C (hemiaminal); *THF as solvent*: [**6**/THF-H$_2$O/25 °C/3 hr; eq(9)]. In a 30 ml round-bottomed flask equipped with a reflux condenser were placed BHA (122 mg, 0.99 mmol) and acetone (2 ml). The reaction mixture was heated under reflux for 1 hr, allowed to be cooled to rt, and concentrated by a rotary evaporator. The residue was treated under high vacuum for 1.5 hr to give crude nitrone as a solid. This nitrone was dissolved in THF (1 mL), mixed with 5 drops of water, and allowed to stand at rt for 0.5 hr. To this solution was introduced a solution of **10** (107 mg, 0.360 mmol) in THF (2.6 ml) and thus-obtained mixture was stirred at rt for 3 hr and quenched with H_2O. A usual workup [(EA)-(MS)] afforded an oil, which was purified by CC to give **13** as a colorless oil (71 mg, 79 %): this is identical with that given through *Method A* in all respects.

Method D [BHA/THF/rt, 3 hr and + acetone (20 eq)/rt, 4 hr; eq(10)]. To a solution of **10** (53 mg, 0.18 mmol) in THF (0.9 mL) was added BHA (67.4 mg, 0.550 mmol) and the mixture was stirred at rt for 3. To this mixture was added acetone (0.90 mL, 20 eq). The reaction was stirred at rt for additional 4 hr and quenched with H_2O. A usual workup [(EA)-(MS)] afforded an oil, which was purified by CC to give **13** as a colorless oil (37 mg, 83 %): this is identical with that given through *Method A* in all respects.

Method E [BHA-acetone (1:1)/THF/rt, 9 hr; eq(11)]. To a solution of **10** (80.4 mg, 0.270 mmol) in THF (2.6 mL) were added BHA (100 mg, 0.810 mmol) and acetone (0.060 mL, 0.82 mmol). The reaction was stirred at rt for 9 hr and quenched with H_2O. A usual workup [(EA)-(MS)] afforded an oil, which was purified by CC to give **13** as a colorless oil (64 mg, 95 %): this is identical with that given through *Method A* in all respects.

2-Benzyl-3-(2-chloroethyl)isoxazolidin-5-one (14): IR (film) 3031, 2964, 1782, 1176 cm^{-1}; ^{1}H-

NMR (500 MHz) δ 1.83—1.93 (m, 1H, C*H*HC–N), 2.09—2.18 (m, 1H, CH*H*C–N), 2.45 (dd, 1H, *J* = 17.4, 6.1 Hz, C*H*HCO), 2.9 (dd, 1H, *J* = 17.4, 7.8 Hz, CH*H*CO), 3.54—3.59 (m, 1H, ClC*H*H), 3.64 (ddd, 1H, *J* = 11, 5.2, 8.2 Hz, ClCH*H*), 3.7 (ddd, 1H, *J* = 13.7, 7.6, 6.1 Hz, NCH), 4.16 & 4.18 (ABq, 2H, *J* = 13.4 Hz, NCH_2Ph), 7.3—7.4 (m, 5H, ArH); ^{13}C-NMR (50 MHz) δ 34.6 (t), 36.1 (t), 41.0 (t), 60.5 (d), 62.6 (t), 128.2 (d), 128.7 (d, 2C), 129.4 (d, 2C), 134.5 (s), 174.8 (s); m/z 239.07125 (calcd for $C_{12}H_{14}O_2NCl$, m/z 239.07130). Anal. Calcd for $C_{16}H_{19}O_3N$, C, 60.13; H, 5.89. Found: C, 60.09; H, 5.90.

(3*R*,4*S*)-2-Benzyl-3-(ethoxycarbonyl)methyl-4-(*tert*-butyldimethylsiloxy)isoxazolidine (cis-**15**): $[\alpha]_D^{22}$ –76.2 (c 1.30, $CHCl_3$); IR (film) 2929, 1735, 1257, 1182 cm^{-1}; ^{1}H-NMR (500 MHz) δ 0.01 and 0.02 (s, 3H for each, CH_3Si), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.25 (t, 3H, *J* = 7.0 Hz, $OCCH_3$), 2.35—2.4 (br, 1H, C*H*HCO_2), 2.83 (dd, 1H, *J* = 17.1, 8.9 Hz, CH*H*CO_2), 3.28—3.35 (br, 1H, CHN), 3.55—3.6 (br, 1H, OC*H*H), 3.84 and 3.99 (ABq, 2H, *J* = 14.2 Hz, NCH_2Ph), 4.06—4.19 (m, 3H, OCH*H* and CO_2CH_2), 4.7 (q, 1H, *J* = 6.4, 11 Hz, SiOCH), 7.2—7.4 (m, 5H, ArH); ^{13}C-NMR (50 MHz) δ –5.4 (q), –4.7 (q), 14.1 (q), 17.9 (s), 25.7 (q, 3C), 32 (t), 60.5 (t), 65.9 (d), 73.5 (t), 75.2 (d), 127.3 (d), 128.3 (d, 2C), 128.9 (d, 2C), 137.1 (s), 171.8 (s).m/z 379.21787 (calcd for $C_{20}H_{33}O_4NSi$, m/z 379.21787). Anal. Calcd for $C_{20}H_{33}O_4NSi$, C, 63.29; H, 8.76. Found: C, 63.22; H, 8.77.

(3*S*,4*S*)-2-Benzyl-3-(ethoxycarbonyl)methyl-4-(*tert*-butyldimethylsiloxy)isoxazolidine (trans-**15**): $[\alpha]_D^{22}$ +37.5 (c 1.06, $CHCl_3$) ; IR (film) 2929, 1736, 1254, 1117 cm^{-1}; ^{1}H-NMR (500 MHz) δ 0.08 and 0.11 (s, 3H for each, CH_3Si), 0.93 (s, 9H, $SiC(CH_3)_3$), 1.23 (t, 3H, *J* = 7.0 Hz, O–CCH_3), 2.39 (dd, 1H, *J* = 15.6, 7.3 Hz, C*H*HCO_2), 2.51 (dd, 1H, *J* = 15.6, 7.0 Hz, CH*H*CO_2), 3.49 (ddd, 1H, *J* = 7.0, 7.2, 1.5 Hz, NCH), 3.94 (dd, 1H, *J* = 9.0, 3.2 Hz, OC*H*H), 4.08—4.15 (m, 3H, O–CH_2CH_3, OCH*H*, and a part of ABq of $PhCH_2N$), 4.25 (a part of ABq, 1H, *J* = 13.2 Hz, PhCH*H*N), 4.51—4.54 (m, 1H, TBSOC*H*), 7.20—7.40 (m, 5H, ArH); ^{13}C-NMR (50 MHz) δ –5.0 (q), –4.8 (q), 14.1 (q), 17.8 (s), 25.6 (q, 3C), 37.6 (t), 60.5 (t), 60.6 (t), 69.6 (d), 74.1 (t), 80.5 (d), 127.2 (d), 128.3 (d, 2C), 129.1 (d, 2C), 137.6 (s), 171.0 (s).

Ethyl 3-*N*-Benzylhydroxylamino-5-chloropentanoate (**16**): IR (film) 3454, 2981, 1732, 1713, 1286 cm^{-1}; ^{1}H-NMR (500 MHz) δ 1.26 (t, 3H, *J* = 7.3 Hz, $OCCH_3$), 1.94—2.02 (m, 1H, ClCC*H*H), 2.2—2.28 (m, 1H, ClCCH*H*), 2.46 (dd, 1H, *J* = 15.3, 7.3 Hz, C*H*HCO_2), 2.85 (dd, 1H, *J* = 15.3, 5.8 Hz, CH*H*CO_2), 3.53 (m, 1H, CHN), 3.62 (dt, 1H, *J* = 6.4, 10.9 Hz, ClC*H*H), 3.72 (dt, 1H, *J* = 7.0, 10.7 Hz, ClCH*H*), 3.93 (s, 2H, NCH_2Ph), 4.1—4.2 (m, 2H, CO_2CH_2–), 5.6—6.2 (br, 1H, N-OH), 7.2—7.4 (m, 5H, ArH); ^{13}C-NMR (50 MHz) δ 14.1 (q), 33.8 (t), 34.2 (t), 42.0 (t), 60.3 (d), 60.7 (t, 2C), 127.6 (d), 128.4 (d, 2C), 129.3 (d, 2C), 136.8 (s), 172.2 (s).

2-Benzyl-3-[(ethoxycarbonyl)deuteriomethyl]isoxazolidine (**13-*d*$_1$**). This compound was obtained by means of *method B* (*vide supra*) in which D_2O was employed in place of H_2O: ^{1}H-NMR (500 MHz) δ 1.23 (t, 3H, *J* = 7.0 Hz, $OCCH_3$), 1.98—2.0 (m, 1H, OCC*H*H), 2.4 (dd, 1H, *J* = 7.6 Hz, C*H*DCO_2), 2.5—2.6 (m, 1H, OCCH*H*), 3.49—3.53 (m, 1H, NCH), 3.85 and 3.92 (ABq, 2H, *J* = 13.1 Hz, NCH_2Ph), 3.9 (td, 1H, *J* = 8.2, 6.1 Hz, N–OC*H*H), 4.0 (td, 1H, *J* = 8.6, 6.1 Hz, N–OCH*H*), 4.07—4.14 (m, 2H, CO_2CH_2–), 7.2—7.4 (m, 5H, ArH); ^{13}C-NMR (50 MHz) δ 14.1 (q), 33.9 (t), 39.3 (*J* = 19.3 Hz), 60.4 (t), 60.5 (t), 61.2 (d), 64.9 (t), 127.3 (d), 128.3 (d, 2C), 128.9 (d, 2C), 137.3 (s), 171.4 (s).

Ethyl (±)-(2*RS*,3*SR*)-3-Amino-5-*tert*-butyldimethylsiloxy-2-deuteriopentanoate (**20**). To a black suspension of Pd-C (30 mg) in AcOEt (1 ml) were added a solution of **13-*d*$_1$** (33.1 mg, 0.130 mmol) in AcOEt (2 ml) and 5 drops of AcOH. The mixture was stirred at rt for 18 hr under H_2 atmosphere and, then, filtered through a Celite pad. The filtrate was concentrated by a rotary evaporator to give a colorless oil, which

was dissolved in THF (1.5 ml), and the this THF solution were added imidazole (27 mg, 0.30 mmol) and TBDMSCl (55 mg, 0.36 mmol) at rt. The mixture was stirred at rt for 24 hr and quenched with saturated aqueous $NaHCO_3$ solution. A usual workup [(EA)-(MS)] afforded an oil, which was purified by CC to give **20** (16.7 mg, 45%) as a colorless oil. IR (film) 2929, 2858, 1732, 1097 cm^{-1}; ^{1}H-NMR (500 MHz) δ 0.05 (s, 6H, $SiCH_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.26 (t, 3H, J = 7.0 Hz, $OCCH_3$), 1.52—1.68 (m, 2H, $OCCH_2$), 1.80—1.85 (br, 2H, NH_2), 2.43—2.47 (br, 1H, $CDHCO_2$), 3.34—3.4 (m, 1H, HC–N), 3.68—3.78 (m, 2H, $SiOCH_2$), 4.14 (q, 2H, J = 7.0 Hz, CO_2–CH_2–).

(±)-(3*RS*,4*SR*)-1-Benzoyl-4-(2-*tert*-butyldimethylsiloxy)ethyl-3-deuterio-2-azetidinone (21). To a solution of **20** (17 mg, 0.060 mmol) in THF (1.0 ml) was added EtMgBr (1.0M in THF, 0.18 ml) at 0 °C. The mixture was stirred at rt for 33 hr and quenched with saturated aqueous NH_4Cl solution. A usual workup [(EA)-(MS)] afforded an oil, which was purified by CC to give a β-lactam derivative (8.3 mg, 73%) as a colorless oil. To a solution of this oil in THF (1 mL) was added n-BuLi (1.63 M in hexane, 0.02 mL, 0.033 mmol) at –78 °C and the mixture was stirred at that temperature for 10 min. Then, benzoyl chloride (0.004 mL, 0.035 mmol) was added to this cold solution and the reaction was stirred at –78 — –60 °C for 2 hr and quenched with saturated NH_4Cl aqueous solution. A usual workup [(EA)-(MS)] afforded an oil, which was purified by CC to give **21** (7 mg, 58%): IR (film) 1799, 1680, 1323, 1255, 1099 cm^{-1}; ^{1}H-NMR (300 MHz) δ 0.07 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 1.81—1.93 (m, 1H, C–C*H*H–C–O), 2.40—2.50 (m, 1H, C–CH*H*–C–O), 3.17 (bd, 1H, J = 6.4 Hz, CDH–CO), 3.79—3.83 (m, 2H, C–H_2C–O), 4.34 (ddd, J = 9.1, 6.4, 3.6 Hz, CHN), 7.43—7.49 (m, 2H, ArH), 7.53—7.60 (m, 1H, ArH), 7.92—7.98 (m, 1H, ArH); ^{13}C-NMR (50 MHz) δ –5.5 (q, 2C), 18.2 (s), 25.9 (q, 3C), 35.2 (t), 41.6 (C–D triplet, J = 14.4 Hz), 49.0 (d), 60.2 (t), 128.1 (d, 2C), 129.8 (d, 2C), 132.3 (s), 133.1 (d), 164.5 (s), 166.5 (s).

(±)-(3*SR*)-2-Benzyl-3-[(1*SR*)-1-(ethoxycarbonyl)ethyl]isoxazolidine (24a). To a solution of **13** (27 mg, 0.11 mmol) in THF (1.1 ml) was added LHMDS (1.0 M in THF, 0.22 ml) at –78 °C. The mixture was stirred at this temperature for 1 hr followed by the addition of MeI (0.02 ml, 0.31 mmol). The reaction mixture was stirred at –75 °C for 1.5 hr and quenched with saturated aqueous NH_4Cl solution. A usual workup [(EA)-(MS)] afford an oil, which was purified by CC to give **24a** as a colorless oil (29.3 mg, 100%). **24a**: IR (film) 2977, 1733, 1463, 1178 cm^{-1}; ^{1}H-NMR (500 MHz) δ 1.15 (d, 3H, J = 7.0 Hz, $CCCH_3$), 1.24 (t, 3H, J = 7.3 Hz, $OCCH_3$), 2.0—2.1 (12 line m, 1H, OCC*H*H), 2.36—2.44 (9 line m, 1H, OCCH*H*), 2.52—2.6 (virtually q, 1H, C*H*Me), 3.35—3.4 (td, 1H, J = 8.6, 4.9 Hz, NCH), 3.85 and 3.94 (ABq, 2H, J = 13.7 Hz, CH_2Ph), 3.88 (td, 1H, J = 5.2, 8.2 Hz, N–OC*H*H), 4.02 (virtually q, 1H, N–OCH*H*), 4.07—4.18 (symm m, 2H, CO_2CH_2), 7.2—7.4 (m, 5H, ArH); ^{13}C-NMR (50 MHz) δ 13.4 (q), 14.2 (q), 31.5 (t), 44.1 (d), 60.3 (t), 60.8 (t), 65.1 (t), 67.0 (d), 127.2 (d), 128.2 (d, 2C), 128.9 (d, 2C), 137.7 (s), 175 (s); exact mass, m/z 263.15210 (calcd for $C_{15}H_{21}O_3N$, m/z 263.15213). Anal. Calcd for $C_{15}H_{21}O_3N$, C, 68.42; H, 8.04. Found: C, 68.40; H, 8.10.

(±)-(3*SR*)-2-Benzyl-3-[(1*SR*)-(ethoxycarbonyl)propyl]isoxazolidine (24b): IR (film) 2966, 2937, 2877, 1729, 1176 cm^{-1}; ^{1}H-NMR (500 MHz) δ 0.83 (t, 3H, J = 7.6 Hz, $CCCH_3$), 1.18 (t, 3H, J = 7.0 Hz, $OCCH_3$), 1.47—1.55 (m, 2H, C*H*HMe), 1.96—2.02 (m, 1H, OCC*H*H), 2.28—2.38 (m, 2H, OCCH*H* and $CHCO_2$), 3.29 (td, 1H, J = 8.6, 4.5 Hz, NCH), 3.7 and 3.9 (ABq, 2H, J = 13.4 Hz, CH_2Ph), 3.8 (td, 1H, J = 5.1, 8.2 Hz, N–OC*H*H), 3.96 (q, 1H, J = 7.9, 15.6 Hz, N–OC*H*H), 4.0—4.1 (m, 2H, CO_2CH_2), 7.1—7.3 (m, 5H, ArH); ^{13}C-NMR (50 MHz) δ 11.7 (q), 14.3 (q), 22.5 (t), 31.9 (t), 52.2 (d), 60.2 (t), 60.7 (t), 64.9 (t), 66.5 (d), 127.1 (d), 128.1 (d, 2C), 128.8 (d, 2C), 137.8 (s), 174.4 (s); exact mass, m/z 277.16760 (calcd for $C_{16}H_{23}O_3N$, m/z 277.16778). Anal. Calcd for $C_{16}H_{23}O_3N$, C, 69.29; H, 8.36. Found: C, 69.15; H, 8.29.

(±)-(3*SR*)-2-Benzyl-3-[(1*SR*)-ethoxycarbonyl-2-phenyl)ethyl]isoxazolidine (24c): IR (film) 3029, 2979, 2875, 1724, 1162 cm^{-1}; ^{1}H-NMR (500 MHz) δ 1.06 (t, 3H, *J* = 7.0 Hz, $OCCH_3$), 2.17—2.24 (m, 1H, OCC*H*H), 2.47 (dtd, 1H,*J* = 12.5, 8.2, 5.2 Hz, OCCH*H*), 2.73 (4 line m, 1H, *J* = 15.6, 7.6 Hz, $BnCHCO_2$), 2.87 (d, 2H, *J* = 7.3 Hz, $PhCH_2$), 3.4—3.44 (td, 1H, *J* = 8.2, 4.3 Hz, NCH), 3.80 and 3.96 (ABq, 2H, *J* = 13.7 Hz, CH_2Ph), 3.9—4.1 (m, 4H, N–OCH_2 and CO_2CH_2), 7.05—7.40 (m, 10H, ArH); ^{13}C-NMR (50 MHz) δ 14.0 (q), 32.2 (t), 35.3 (t), 52.4 (d), 60.2 (t), 60.8 (t), 65.1 (t), 66.4 (d), 126.3 (d), 127.3 (d), 128.2 (d, 2C), 128.3 (d, 2C), 128.8 (d, 2C), 128.9 (d, 2C), 137.5 (s), 138.8 (s), 173.6 (s); exact mass, m/z 339.18429 (calcd for $C_{21}H_{25}O_3N$, m/z 339.18434). Anal. Calcd for $C_{21}H_{25}O_3N$, C, 74.31; H, 7.42. Found: C, 74.22; H, 7.40.

Ethyl (±)-(3*SR*,4*SR*)-3-Amino-5-*tert*-Butyldiphenylsiloxy-2-ethylpentanoate (25b). In a Parr hydrogenation apparatus were placed $Pd(OH)_2$/C (108 mg), **24b** (182 mg, 0.660 mmol), MeOH (2.5 ml), H_2O (1 ml), and AcOH (0.2 ml). The apparatus was shaken at rt for 12 hr under H_2 atmosphere (4 kg/cm^2) and the content of the apparatus was filtered through a Celite pad. The filtrate was concentrated by a rotary evaporator to give a colorless oil, which was dissolved in CH_2Cl_2 (3.0 ml). To this solution were added Et_3N (0.28 ml, 2.0 mmol) and TBDPSCl (0.34 ml, 1.3 mmol) at rt and the mixture was stirred at rt for 24 hr and quenched with saturated aqueous $NaHCO_3$ solution. A usual workup [(EA)-(MS)] afforded an oil, which was purified by CC to give **25b** (183 mg, 65% for 2 steps) as a colorless oil and single diastereomer. **25b**: IR (film) 3390, 2962, 2931, 1728, 1110 cm^{-1}; ^{1}H-NMR (500 MHz) δ 0.91 (t, 3H, *J* = 7.3 Hz, $CCCH_3$), 1.05 (s, 9H, $SiC(CH_3)_3$), 1.25 (t, 3H, *J* = 7.0 Hz, $OCCH_3$), 1.4—1.8 (m, 6H, CH_2COSi, CCH_2C, and NH_2), 2.27 (dt, 1H, *J* = 9.8, 4.9 Hz, $HCCO_2$), 3.11—3.15 (m, 1H, NCH), 3.76—3.85 (m, 2H, $SiOCH_2$), 4.07—4.22 (m, 2H, OCH_2Me), 7.38—7.42 (m, 6H, ArH), 7.60—7.70 (m, 4H, ArH); ^{13}C-NMR (50 MHz) δ 11.9 (q), 14.3 (q), 19.0 (s), 22.5 (t), 26.8 (q, 3C), 38.0 (t), 50.3 (d), 53.8 (d), 59.9 (t), 61.5 (t), 127.6 (d, 4C), 129.6 (d, 2C), 133.6 (s), 133.7 (s), 135.5 (d, 4C), 174.9 (s).

(±)-(3*SR*,4*SR*)-4-(2-*tert*-Butyldiphenylsiloxyethyl)-3-ethyl-2-azetidinone (26b). To a solution of **25b** (108 mg, 0.250 mmol) in THF (2.5 ml) was added EtMgBr (1.0 M in THF, 0.75 ml) at 0 °C. The reaction mixture was stirred at rt for 1.5 hr and quenched with saturated aqueous NH_4Cl solution. A usual workup [(EA)-(MS)] afforded an oil, which was purified by CC to give **26b** (64 mg, 66%) as a colorless oil. **26b**: IR (film) 3233, 2931, 1751, 1110, 702 cm^{-1}; ^{1}H-NMR (500 MHz) δ 1.01 (t, 3H, *J* = 7.3 Hz, CCH_2Me), 1.06 (s, 9H, $SiC(CH_3)_3$), 1.60—1.90 (m, 4H, CH_2Me and H_2CC–O), 2.75 (dddd: virtually tq, 1H, *J* = 8.2, 6.1, 2.1, 1.2 Hz, $HCCO_2$), 3.46 (ddd, 1H, *J* = 7.6, 5.5, 2.1 Hz, N–CH), 3.70—3.78 (12-line m, 2H, CH_2OSi), 5.85 (br, 1H, NH), 7.38—7.45 (m, 6H, ArH), 7.60—7.63 (m, 4H, ArH); ^{13}C-NMR (50 MHz) δ 11.3 (q), 19.1 (s), 21.4 (t), 26.9 (q, 3C), 37.5 (t), 52.6 (d), 58.4 (d), 61.8 (t), 127.8 (d, 4C), 129.8 (d, 2C), 133.2 (s, 2C), 135.5 (d, 2C), 170.8 (s); exact mass, m/z 381.21233 (calcd for $C_{23}H_{31}O_2NSi$, m/z 381.21239). Anal. Calcd for $C_{23}H_{31}O_2NSi$, C, 72.40; H, 8.19. Found: C, 72.38; H, 8.15.

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(3) Socha, D.; Jurczak, M.; Chmielewski, M. *Tetrahedron Lett.* **1995**, *36*, 135–138 and *Tetrahedron* **1997**, *53*, 739–746; isoxazolidinone bearing C(4)-side chain in which there exists 2'-tosyloxy group turned out to lead to an isoxazolidine skeleton similar to **5** on treatment with MeOH containing anhydrous K_2CO_3 through methanolysis and intramolecular S_N2 pathway.

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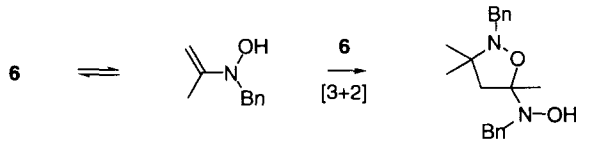
(8) The relative stereochemistry between –OTBDMS and $-CH_2CO_2Et$ substituents of **15** has been determined to be cis for that which led to a lactone (95%) and trans for that which did not lead to it but resulted only in deprotection (85%) on treatment with TBAF (1.5 eq in THF) for 2 hr at rt. ^{1}H-NMR spectrum for the lactone (200 MHz, $CDCl_3$) δ 2.51 (dd, 1H, *J* = 19.0, 2.9 Hz, C*H*HC=O), 2.68 (dd, 1H, *J* = 19.0, 7.9 Hz, CH*H*C=O), 3.65—3.80 (m, 1H, NCH), 3.89 & 4.05 (ABq, 2H, *J* = 13.1 Hz, $PhCH_2N$), 3.98 (dd, 1H, *J* = 10.5, 2.4 Hz, OCHH), 4.27 (dd, *J* = 10.5, 5.5 Hz, OCHH), 5.31 (ddd, 1H, *J* = 6.6, 5.5, 2.5 Hz, CHO), 7.26—7.42 (m, 5H, ArH); ^{1}H-NMR spectrum for the hydroxy ester (300 MHz, $CDCl_3$) δ 1.27 (t, 3H, *J* = 7.1 Hz, O-C-Me), 2.51 (dd, 1H, *J* = 17.0, 9.1 Hz, C*H*HC=O), 2.61 (dd, 1H, *J* = 17.0, 5.8 Hz, C*H*HC=O), 3.00—3.09 (br, 1H, OH), 3.15 (ddd, *J* = 9.1, 5.5, 3.3 Hz, NCH), 3.93 (dd, *J* = 9.3, 3.0 Hz, OC*H*H), 4.03 (dd, 1H, *J* = 9.6, 6.1 Hz, OCH*H*), 4.06 (s, 2H, NCH_2Ph), 4.16 (q, 2H, *J* = 7.1 Hz, OCH_2), 4.42—4.52 (br, 1H, C*H*OH), 7.2—7.4 (m, 5H, ArH).

(9) To the best of our knowledge the diastereoselectivity for reactions of this class ranges from 1:1 to 4:1 in general: see Arrowsmith, R. J.; Carter, K.; Dann, J. G.; Davies, D. E.; Harris, C. J.; Morton, J. A.; Lister, P.; Robinson, J. A.; Williams, D. J. *J. Chem. Soc. Chem. Commun.* **1986**, 755–757; see also (b) Cha, J. K.; Christ, W. J.; Kishi Y. *Tetrahedron Lett.* **1983**, *24*, 3943–3946. (c) Saito, S.; Hirohara, Y.; Narahara, O.; Moriwake, T. *J. Am. Chem. Soc.* **1989**, *111*, 4533–4535. (d) Saito, S.; Morikawa, Y.; Moriwake, T. *J. Org. Chem.* **1990**, *55*, 5424–5426.

(10) ^{13}C-NMR data for **6** (50 MHz, $CDCl_3$); δ 19.7, 20.3, 63.6, 127.4, 127.8, 128.5, 133.4, 143.8. Other signals detected in this NMR experiment as very minor components are assigned as those of nitrone adduct

(**33**). The adduct can be formed by the reaction of the nitrone with its tautomer *N*-hydroxyenamine as indicated below and turned out to be so stable that it can be isolated by silica gel clolumn chromatography to be characterized by NMR spectroscopy and never converted back to nitrone. NMR data of **33**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.31 (s, 3H), 1.51 (s, 3H), 2.08 and 3.12 (ABq, J = 12.9 Hz, 2H), 3.48 and 3.91 (ABq, J = 13.7 Hz, 2H), 3.67 and 3.80 (ABq, J = 14.0 Hz, 2H), 7.18—7.45 (m, 10H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 21.3, 23.5, 23.9, 53.5, 53.8, 56.4, 63.8, 95.7, 126.7, 127.3, 128.1, 128.3, 128.7, 128.9, 138.1, 138.8 ppm. For nitrone tautomerization and adducts, see Foster, R.; Iball, J.; Nash, R. *J. Chem. Soc. Perkin Trans.* 2, **1974**, 1210-1214.



33: nitrone adduct

(11) The [3+2] cycloaddition reaction of **6** (3 eq) with **10** did not take place at all when a solution of these compounds in benzene was heated under reflux for 3 hr. Also the trace of any other reactions has been detected but **10** was recovered unchanged quantitatively.

(12) Since we were intrigued with the structural similarity between the nitrone adduct **33** (see ref. 9) and **9**, we examined the reaction of **33** with **10** under the identical reaction conditions as those for the case of **6** + H_2O (benzene, 80 °C), which indeed gave **13** and, however, required much longer reaction time (14 h) and resulted in much lower yield (45%). This finding led us to conclude that **33** was not responsible for 3 to 4 times faster rate and high chemical yield realized under such conditions [**6** + H_2O (benzene, 80 °C)]. In any event the fact that **33** actually reacted with **10** is highly suggestive that the proposed mechanism involving **9** (Scheme II) is reasonable and tertiary hydroxylamines such as **9** or **33** have enhanced nucleophilicity.

(13) ^{13}C-NMR data for the mixture of **6** and H_2O (1:1) at rt (50 MHz, $CDCl_3$): δ 19.8, 20.4, 63.5, 127.4, 127.8, 128.5, 133.3, 144.7. These data indicated that no hydration of **6** took place at rt. The same mixture, however, gave the following signals after heating at 60 °C for 20 min; δ 19.7, 20.3, 22.6, 58.0, 63.6, 95.7, 127.4, 127.5, 127.7, 127.8, 128.4, 128.5, 133.5, 144.5 (underlined for **9**) together with those for the nitrone adduct **33** (see ref. 9), the amount of which increased after such a thermal treatment as judged from the signal intensity.

(14) ^{13}C-NMR data for BHA (50 MHz, $CDCl_3$): δ 58.0, 127.6, 128.4, 129.2, 136.8. The signal of benzyl methylene group of BHA appeared at 58.0 ppm coincidentally with that of **9** whereas the signal of substituted aromatic ring carbon of BHA appeared at 136.8 ppm which was not observed for the mixture of **6** and H_2O [see ref (9)]. This is pointing out the absence of BHA under the conditions examined.

(15) On the basis of the relative intensity of NMR signals appeared at 144 and 96 ppm, it can be estimated that the equilibrium at rt shifts on the nitrone side with a 4:1 ratio, which becomes a 1:1 ratio at 60 °C.

(16) Although definite conclusion on this issue must await future study, the hydrogen bonding between the acetone-based hydroxy group and the oxygen atom attached to the nitrogen atom would probably enhance the polarization of the O—H bond attached to the nitrogen atom.

(17) The mechanism of Michael addition reaction of amines to α,β-unsaturated ester has been the question under debate: see Bernasconi, C. F. *Tetrahedron* **1989**, 45, 4017–4090 and Pardo, L.; Osman, R.; Weinstein,

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(18) The hydrogen at C(3) of **21** appeared at 3.17 ppm as a broad doublet (J = 6.4 Hz for the doublet). This signal became broad singlet with shoulders on irradiating the hydrogen at C(4) probably because of geminal spin-spin couplings of this hydrogen with the deuterium, which, in this case, must be very small (< 1 Hz). Since the geminal coupling constant of hydrogens at C(3) has been known to be, in general, around 14 Hz (see Wang and Roskamp, *J. Am. Chem. Soc.*, **1993**, *115*, 9417–9420), the geminal spin coupling constant between the hydrogen and deuterium at C(3) in this case is expected to be around 2 Hz on the theoretical basis.

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