



Reactions of Glyoxal-Derived Iminium Ions with Unsaturated Silyl and Silyloxy Reagents

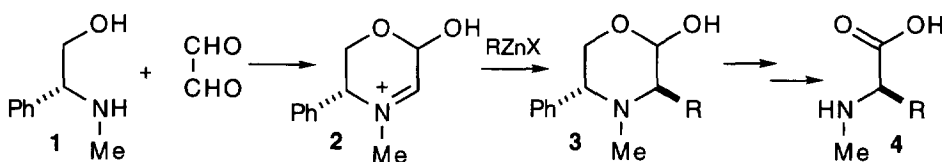
Claude Agami, Dominique Bihan and Catherine Puchot-Kadouri*

Laboratoire de Synthèse Asymétrique (URA CNRS 408), Université Pierre et Marie Curie, 4 place Jussieu, 75005 Paris, France (Fax: 33 1 44 27 25 02. E-mail: agami@ccr.jussieu.fr).

Abstract: Iminium ions derived from a condensation of glyoxal and *N*-methyl (*R*)-phenylglycinol react with allylic silanes (trimethylallyl and trimethylmethallylsilanes) and enoxysilanes (2-trimethylsilyloxypropene and 2-trimethylsilyloxystyrene). These reactions proceed in a totally stereoselective way as evidenced by a chemical correlation and an X-Ray analysis of a compound related to both series of experiments.

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Synthesis of unsaturated amino acids has been intensively explored because of their potential application in peptide chemistry.¹ Owing to its mechanism-based inhibiting properties against pyridoxal-linked enzymes, α -vinylglycine, the simplest member of this series, has focused a great amount of work.² However other more complex unsaturated amino acids seem to hold great promise.³ In previous studies, dealing with a glycine cation equivalent, we have presented a general method which provides access to the synthesis of α -amino acids (Scheme 1).⁴ The key-step of this methodology consists in a highly stereoselective reaction between the intermediate iminium ion **2** and organozinc reagents. Although this procedure allows the formation of enantiopure amino acids when saturated organozinc reagents were used, it cannot be extended to the synthesis of unsaturated derivatives. In fact, it was noticed that allyl zinc bromide reacted with iminium ion **2** with a very poor stereochemical control. This inauspicious report⁴ was ascribed to thermodynamic control since it is well-known that reactions of allyl and crotyl zinc reagents with imines and iminium salts are reversible.⁵ Taking into account the known reactivity of unsaturated silyl derivatives towards iminium salts and other electrophiles,⁶ we directed our attention to these reagents and we now report that the above limitation can be circumvented by using allyl and enoxysilanes.

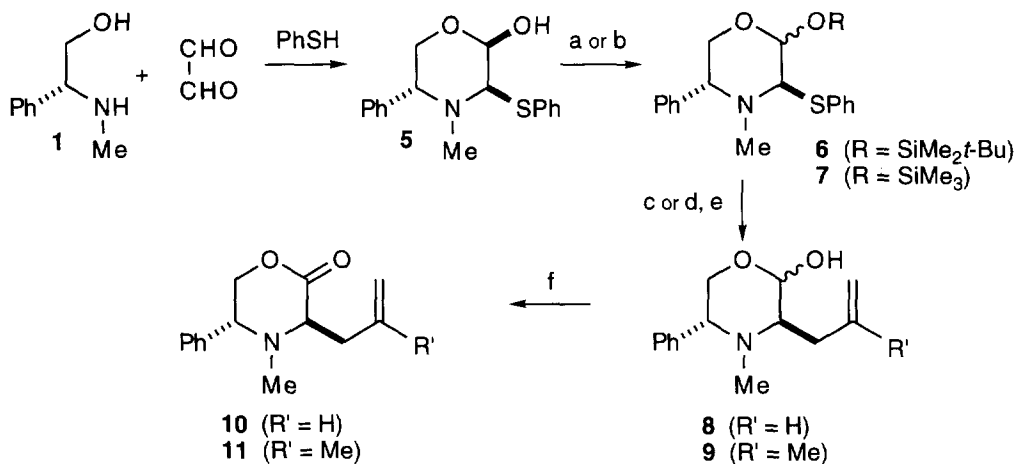


Scheme 1

A. ALLYL AND METHALLYL REAGENTS

As mentioned above (cf. Scheme 1), iminium ion **2** results from the condensation of *N*-methyl (*R*)-phenylglycinol **1** with glyoxal. Under the action of thiophenol, this intermediate **2** was trapped as the aminothioether **5** by following a published procedure.⁷ This reaction is reversible since it has been observed⁴ that heterocycle **5**, when treated with a Lewis acid, affords iminium ion **2**. However direct reaction of amino thioether **5** with an allylsilane, in the presence of zinc bromide, gave an unsatisfactory result and it turned out that the hemiacetal moiety had to be first converted into an *O*-silyl derivative (Scheme 2). Therefore allyl and

methallyl trimethylsilanes were treated with the O-protected amino thioethers **6** and **7** respectively. Lactones **10** and **11** were finally obtained from allyl derivatives **8** and **9** after fluoride ion-mediated desilylation and oxidation of the hemiacetal moiety. The stereochemistry of lactones **10** and **11** will be examined thereafter.

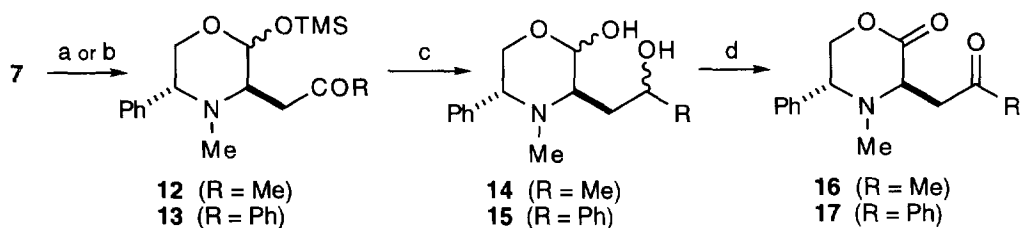


Scheme 2

Reagents and conditions: (a) ClSiMe₃, NEt₃, THF, 0° (84%); (b) ClSiMe₂t-Bu, imidazole, DMF, rt (70%); (c) CH₂=CH-CH₂SiMe₃, ZnBr₂, THF, rt; (d) CH₂=C(CH₃)CH₂SiMe₃, ZnBr₂, THF, rt; (e) *n*-Bu₄NF, THF (64 % overall yield from **6**, 75 % overall yield from **7**); (f) oxalyl chloride, DMSO, -50°, then NEt₃, rt (80%).

B. ENOXYSILANE REAGENTS

As depicted in Scheme 3, trimethylsilyloxy derivative **7** was also used as substrate for the reactions with two enoxysilanes (Me₃SiOC(CH₃)=CH₂ and Me₃SiOC(C₆H₅)=CH₂) and this procedure gave products **12** and **13**. Removal of the O-silyl protecting groups by the fluoride ion-mediated reaction, in a way similar to what has been reported above, was not operative here. In the present case, such reaction led to an addition of the produced oxyanion onto the carbonyl group thus affording a bicyclic material. Therefore compounds **12** and **13** were actually treated with NaBH₄ and the resulting diols **14** and **15** were finally oxidized to give morpholinones **16** and **17**.

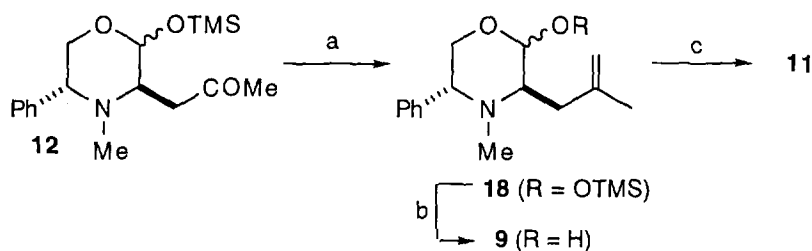


Scheme 3

Reagents and conditions: (a) Me₃SiOC(CH₃)=CH₂, ZnBr₂, THF (75%); (b) Me₃SiOC(C₆H₅)=CH₂, ZnBr₂, THF (80%); (c) NaBH₄, EtOH (70% from **12**, 73% from **13**); (d) oxalyl chloride, DMSO, -50°, then NEt₃, rt (68% from **14**, 70% from **15**).

A chemical correlation was performed between compounds **12** and **11** which result from the two kinds of reactions that are described here, i.e. the iminium-allylsilane and the iminium-enoxysilane condensation respectively. As shown on Scheme 4, silyloxy derivative **12** was submitted to a Wittig reaction and was transformed into the propenyl derivative **18**. Morpholinone **11** was finally obtained after O-silyl deprotection of compound **18** and oxidation of the resulting hemiacetal **9**.

The structure of the unsaturated morpholinone **11** was determined by an X-Ray analysis⁸ (Figure 1) which demonstrates that the phenyl and the methyl substituents are located in a *trans* relative disposition. This result is consistent with previous ones^{4,7} which show that a nucleophilic attack onto iminium ion **2** (or other related iminium ion intermediates)⁹ invariably occurs with an *anti* selectivity in relation to the phenyl substituent which hinders the lower side of the C=N bond. From a conformational point of view, it is worthy to note that the crystalline structure reveals that the morpholinone ring in compound **11** presents a boat geometry.



Scheme 4

Reagents and conditions: (a) $\text{Ph}_3\text{MeP}^+\text{Br}^-$, BuLi, THF, 0° (70%); (b) $n\text{-Bu}_4\text{NF}$, THF (95%); (c) oxalyl chloride, DMSO, -50° , then NEt_3 , rt (80%).

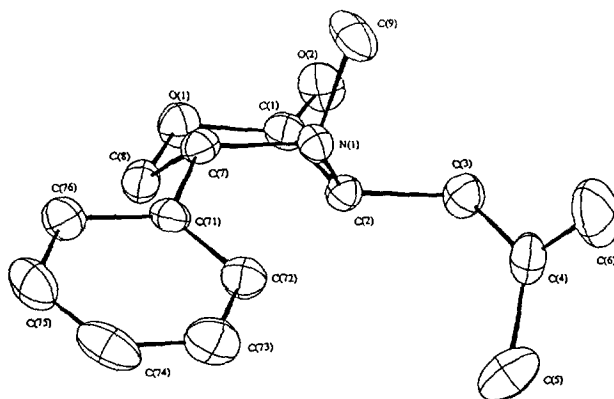
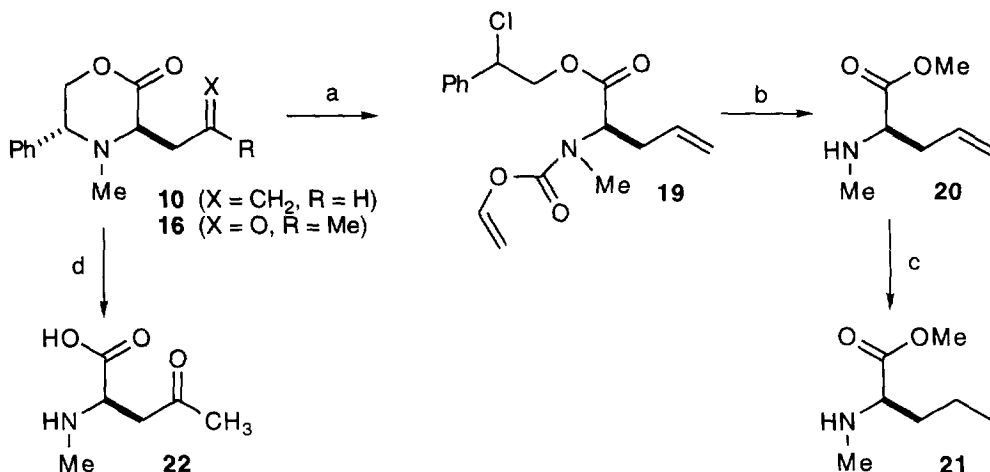


Figure 1. X-Ray structure of morpholinone **11** (crystallographic numbering).

Morpholinones **10** and **16** were respectively transformed into the corresponding *N*-methyl β,γ -unsaturated α -amino ester **20** and into the *N*-methyl β -keto α -amino acid **22** (Scheme 5). Amino ester **20** was hydrogenated in order to afford the known *N*-methyl derivative of *D*-norvaline **21** in an optically pure form.



Scheme 5

Reagents and conditions: (a) $CH_2=CHOCOCI$, CH_2Cl_2 , (87%); (b) 6.5N HCl, MeOH, (88%); (c) H_2 , Pd/C, MeOH (92%); (d) H_2 , $Pd(OH)_2$, EtOH (77%).

In conclusion, unsaturated silyl and silyloxy compounds react with O-silyl protected iminium ions with complete stereoselectivity. This method offers a new access to unsaturated α -amino acid chemistry as illustrated by the synthesis of the α -amino acid derivatives **20** and **22** which show respectively an ethylenic and a carbonyl moiety in the β position.

EXPERIMENTAL SECTION

General comments

1H and ^{13}C spectra ($CDCl_3$ solution unless otherwise stated) were respectively recorded on a Bruker AC 200 spectrometer at 200 and 50 MHz; chemical shifts are reported in ppm from TMS. Optical rotations were determined with a Perkin Elmer 141 instrument. All reactions were carried out under nitrogen except those performed in aqueous solution. Column chromatography was performed on silica gel, 230-400 mesh by using various mixtures of diethyl ether (E) and petroleum ether (EP). THF was distilled from sodium/benzophenone ketyl. Mention of "usual workup" means: (i) decantation of the organic layer, (ii) extraction of the aqueous layer with ether, (iii) drying of the combined organic phases over $MgSO_4$, (iv) solvent evaporation under reduced pressure. Composition of stereoisomeric mixtures was determined by NMR analysis on crude products before any purification.

(3R,5R)-4-Methyl-5-phenyl-3-phenylsulfanyl-2-tert-butyl dimethylsilyloxy-morpholine **6**

To a solution of compound **5** (0.5 g, 1.6 mmol) in DMF (15 ml) was added imidazole (0.28 g, 4.1 mmol) and *tert*-butyl dimethylsilyl chloride (0.3 g, 2 mmol) at rt. The mixture was stirred for 12 h, then poured into water. After the usual workup, the residue was chromatographed on silica gel (E/EP: 5/95) and compound **6** was obtained as an epimeric mixture (80/20) at C2: (0.5 g, 70%); 1H NMR (major epimer): 0.16 (s, 3H), 0.19 (s, 3H), 0.92 (s, 9H), 2.16 (s, 3H), 3.40-3.85 (m, 3H), 4.42 (d, $J = 1.0$ Hz, 1H), 5.15 (d, $J = 1.0$ Hz, 1H), 7.20-7.65 (m, 10H); ^{13}C NMR (major epimer): -4.9, -4.2, 18.2, 25.9, 40.2, 61.7, 71.4, 84.9, 96.3, 126.4, 128.0, 128.5, 128.7, 133.2, 137.9, 138.7. Anal. Calcd for $C_{23}H_{33}NO_2SSi$: C, 66.48; H, 8.00; N, 3.37. Found: C, 66.49; H, 7.93; N, 3.37.

(3R,5R)-4-Methyl-5-phenyl-3-phenylsulfanyl-2-trimethylsilyloxy-morpholine 7

Trimethylsilylchloride (0.54 g, 4.9 mmol) was added to a mixture of compound **5** (1 g, 3.3 mmol) and triethylamine (0.5 g, 4.9 mmol) in THF (20 ml) at 0°C. After stirring for 45 min, the mixture was poured into water and the usual workup gave product **7** (1 g, 84%) as a mixture (92/8) of two epimers at C2: ¹H NMR (major epimer): 0.23 (s, 9H), 2.20 (s, 3H), 3.35-3.72 (m, 2H), 3.84 (dd, J = 2.4 and 10.0 Hz, 1H), 4.37 (d, J = 1.3 Hz, 1H), 5.18 (d, J = 1.6 Hz, 1H), 7.21-7.34 (m, 8H), 7.59-7.64 (m, 2H); ¹³C NMR (major epimer): 0.3, 40.2, 61.7, 84.9, 95.9, 126.6, 128.0, 128.4, 128.6, 129.0, 133.6, 137.8, 138.1. Anal. Calcd for C₂₀H₂₇NO₂Si: C, 64.29; H, 7.28; N, 3.75. Found: C, 64.28; H, 7.19; N, 3.64.

(3R,5R)-3-Allyl-4-methyl-5-phenyl-3morpholine-2-ol 8

Zinc bromide (3.2 g, 14.2 mmol) and trimethylallylsilane (1.1 g, 9.6 mmol) were successively added to a solution of compound **6** (2 g, 4.8 mmol) in THF (40 ml). The mixture was stirred at rt for 2.5 h. After usual workup, the resulting mixture was dissolved with THF (30 ml) and treated by a 1M solution of tetrabutylammonium fluoride (5 ml) and stirred for 3 h at rt. Usual workup and chromatography (E/EP: 30/70) gave compound **8** (0.72 g, 64%) as a mixture (90/10) of two epimers at C2: ¹H NMR (major epimer): 2.10 (s, 3H), 2.49-2.58 (m, 2H), 2.77-2.84 (m, 1H), 3.47-3.71 (m, 2H), 3.81-3.92 (m, 1H), 5.05-5.23 (m, 3H), 5.67-6.10 (m, 1H), 7.25-7.34 (m, 5H); ¹³C NMR (major epimer): 26.1, 39.6, 61.1, 63.7, 64.6, 90.8, 117.8, 128.1, 128.6, 135.2, 138.6. Anal. Calcd for C₁₄H₁₉NO₂: C, 72.07; H, 8.20; N, 6.00. Found: C, 72.01; H, 8.24; N, 5.85.

(3R,5R)-4-Methyl-3-(2-methyl-allyl)-5-phenyl-3morpholine-2-ol 9

Zinc bromide (7.8 g, 34.6 mmol) was added to a solution of product **7** (4.3 g, 11.5 mmol) in THF (85 ml). Trimethylmethallylsilane (2.9 g, 23 mmol) was then dropped and the mixture was stirred at rt for 2 h. After usual workup, the crude product was dissolved in THF (80 ml) and treated at 0°C by a 1M solution of tetrabutylammonium fluoride (17.3 ml, 17.3 mmol) for 45 min. Usual workup followed by chromatography (E/EP: 15/85) furnished compound **9** (2.1 g, 75%) as an epimeric mixture (95/5) at C2: ¹H NMR (major epimer): 1.80 (s, 3H), 2.13 (s, 3H), 2.39-2.42 (m, 1H), 2.58 (t, J = 13.3 Hz, 1H), 2.92-2.94 (m, 1H), 3.53 (dd, J = 4.0 and 11.6 Hz, 1H), 3.70 (dd, J = 3.9 and 11.2 Hz, 1H), 3.86 (t, J = 11.3 Hz, 1H), 4.87 (d, J = 17.9 Hz, 2H), 5.31 (s, 1H), 7.28-7.35 (m, 5H); ¹³C NMR (major epimer): 22.7, 29.8, 39.5, 61.0, 62.2, 64.6, 91.1, 113.3, 128.1, 128.7, 138.8, 142.5. Anal. Calcd for C₁₅H₂₁NO₂: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.83; H, 8.71; N, 5.75.

General procedure for Swern oxidation

Dimethyl sulfoxide (7.2 mmol) was added dropwise to a solution of oxalyl chloride (3.6 mmol) in CH₂Cl₂ (6 ml) at -50°C. The mixture was stirred for 5 min and a solution of the hemiacetal (2.5 mmol) in CH₂Cl₂ (6 ml) was introduced. After 1h30 at -50°C, triethylamine (12 mmol) was added and the mixture was allowed to warm to rt during 1h. Addition of water followed by usual workup yielded a residue which was purified by flash chromatography. This procedure was followed in order to synthesize the two following compounds.

(3R,5R)-3-Allyl-4-methyl-5-phenyl-morpholine-2-one 10 (E/EP: 30/70) 81%; [α]_D²⁰: +4 (c 1, CHCl₃); ¹H NMR: 2.21 (s, 3H), 2.53-2.60 (m, 2H), 3.58 (t, J = 6.2 Hz, 1H), 3.87 (dd, J = 7.9 and 5 Hz, 1H), 4.28 (dd, J = 7.9 and 10.8 Hz, 1H), 4.53 (dd, J = 5 and 10.8 Hz, 1H), 5.04-5.17 (m, 2H), 5.23-5.92 (m, 1H), 7.25-7.28 (m, 5H); ¹³C NMR: 32.5, 38.5, 60.8, 61.2, 70.9, 117.7, 127.6, 128.1, 128.7, 134.0, 137.1, 170.7. Anal. Calcd for C₁₄H₁₇NO₂: C, 72.69; H, 7.41; N, 6.05. Found: C, 72.52; H, 7.60; N, 6.15.

(3R,5R)-4-Methyl-3-(2-methyl-allyl)-5-phenyl-morpholine-2-one 11 (E/EP: 8/92) 80%; [α]_D²⁰: +18 (c 0.6, CHCl₃); ¹H NMR: 1.82 (s, 3H), 2.28 (s, 3H), 2.49-2.81 (m, 2H), 3.78 (t, J = 6.8 Hz, 1H), 3.98 (dd, J = 5.1 and 8.6 Hz, 1H), 4.41 (dd, J = 8.6 and 11.5 Hz, 1H), 4.56 (dd, J = 5.3 and 11.6 Hz, 1H), 4.89 (d, J = 0.7 Hz, 2H), 7.24-7.39 (m, 5H); ¹³C NMR: 22.3, 35.9, 38.3, 59.6, 60.6, 70.4, 113.4, 127.5, 128.1, 128.7, 137.4, 141.6, 171.1. Anal. Calcd for C₁₅H₁₉NO₂: C, 73.44; H, 7.80; N, 5.71. Found: C, 73.42; H, 7.74; N, 5.68.

Reactions of enoxysilanes with compound 7

Compound **7** (1 mmol) was dissolved in THF (3.5 ml) at rt; zinc bromide (3 mmol) and enoxysilane (1.1 mmol) were successively added. The solution was allowed to stir at rt for 2h. Usual workup and flash chromatography furnished the following compounds.

(3R,5R)-1-(4-Methyl-5-phenyl-2-trimethylsilyloxy-morpholin-3-yl)-propane-2-one 12 (E/EP: 8/92) 75%; ¹H NMR: 0.12 (s, 9H), 1.98 (s, 3H), 2.27 (s, 3H), 2.35 (dd, J = 3.1 and 15.7 Hz, 1H), 2.98 (dd, J = 7.9 and 15.7 Hz, 1H), 3.28 (dd, J = 3.4 and 10.4 Hz, 1H), 3.45 (t, J = 8 Hz, 1H), 3.53-3.59 (m, 1H), 3.71 (dd, J = 2.6 and 11.2 Hz, 1H), 4.99 (d, J = 2.5 Hz, 1H), 7.18-7.30 (m, 5H); ¹³C NMR: 0.5, 31.4, 32.8, 39.7, 61.3, 61.7, 71.6, 95.8, 128.0, 128.4, 128.7, 138.6, 208.6. Anal. Calcd for C₁₇H₂₇NO₃Si: C, 63.51; H, 8.46; N, 4.35. Found: C, 63.82; H, 8.46; N, 4.14.

(3R,5R)-2-(4-Methyl-5-phenyl-2-trimethylsilyloxy-morpholin-3-yl)-1-phenyl-ethanone 13 (E/EP: 8/92) 80%; ¹H NMR: 0.14 (s, 9H), 2.08 (s, 3H), 2.75 (dd, J = 3.2 and 15.2 Hz, 1H), 3.48-3.84 (m, 5H), 5.10 (d, J = 2.3 Hz, 1H), 7.23-8.08 (m, 10H); ¹³C NMR: 0.5, 27.9, 40.1, 61.4, 62.5, 71.8, 96.1, 128.2, 128.5, 128.6, 128.8, 132.8, 138.0, 138.8, 200.6. Anal. Calcd for C₂₂H₂₉NO₃Si: C, 68.89; H, 7.62; N, 3.65. Found: C, 68.97; H, 7.55; N, 3.62.

(3R,5R)-3-(2-Hydroxypropyl)-4-methyl-5-phenyl-morpholin-2-ol 14

To a solution of sodium borohydride (0.9 g, 2.33 mmol) in absolute ethanol (10 ml) was added a solution of acetal **12** (1.2 g, 3.73 mmol) in absolute ethanol (20 ml). The mixture was stirred for 3h30 at rt; then ethanol was evaporated. Saturated aqueous NaCl solution was added to the residue which was extracted with ether. Combined organic layers were dried over MgSO₄ and evaporated. The residue was chromatographed (E/EP : 60/40) to give product **14** as a mixture of diastereomers (0.65 g, 70%); ¹H NMR (major isomer): 1.24 (d, J = 6.1 Hz, 3H), 1.82-1.92 (m, 1H), 1.97 (s, 3H), 2.97-3.01 (m, 1H), 3.31 (dd, J = 3.4 and 10.4 Hz, 1H), 3.49 (t, J = 5.3 Hz, 1H), 3.72 (dd, J = 3.4 and 11.0 Hz, 1H), 3.75-3.84 (m, 4H), 4.97 (bs, 1H), 7.19-7.25 (m, 5H); ¹³C NMR (major isomer): 24.4, 28.6, 39.2, 60.9, 63.4, 68.4, 71.5, 95.9, 127.9, 128.3, 128.5, 138.4. Anal. Calcd for C₁₄H₂₁NO₃: C, 66.90; H, 8.42; N, 5.57. Found: C, 66.77; H, 8.41; N, 5.56.

(3R,5R)-3-(2-Hydroxy-2-phenyl-ethyl)-4-methyl-5-phenyl-morpholin-2-ol 15

A solution of compound **13** (0.83 g, 2.17 mmol) in absolute ethanol (6 ml) was slowly added to a solution of sodium borohydride (0.05 g, 1.36 mmol) in absolute ethanol (12 ml). The mixture was stirred for 1h30 at rt and ethanol was evaporated. Brine was added to the residue and the mixture was extracted with ether. Combined organic layers dried over MgSO₄ were evaporated and the crude product was chromatographed (E/EP: 60/40) to give a mixture of diastereoisomers (0.49 g, 73%) which was used as such directly in the next step.

Procedure for oxidation of compounds 14 and 15

To a solution of oxalyl chloride (11.4 mmol) in CH₂Cl₂ (9 ml) cooled to -50°C was added dimethyl sulfoxide (22.8 mmol). After stirring for 5 min, a solution of diol (2.8 mmol) in CH₂Cl₂ (9 ml) was added and the mixture was stirred for 2h. Then, triethylamine (28.5 mmol) was added and the mixture was allowed to warm at rt in 1h. After hydrolysis with water and extraction with CH₂Cl₂, organic layers were dried and evaporated to give an oil which was chromatographed to afford following compounds.

(3R,5R)-4-Methyl-3-(2-oxo-propyl)-5-phenyl-morpholine-2-one 16

(E/EP: 40/60): 68%; [α]_D²⁰: +33 (c 0.8, CHCl₃); ¹H NMR: 2.28 (s, 6H), 2.93 (dd, J = 4.7 and 17.2 Hz, 1H), 3.11 (dd, J = 6.7 and 17.1 Hz, 1H), 3.92 (dd, J = 5.1 and 8.5 Hz, 1H), 4.17 (dd, J = 4.8 and 6.7 Hz, 1H), 4.44 (dd, J = 8.6 and 11.7 Hz, 1H), 4.66 (dd, J = 5.1 and 11.6 Hz, 1H), 7.28-7.41 (m, 5H); ¹³C NMR: 30.1, 39.3, 41.9, 56.2, 62.2, 70.5, 127.3, 128.0, 128.7, 137.1, 171.2, 204.8.

(3R,5R)-4-Methyl-3-(2-oxo-phenylethyl)-5-phenyl-morpholine-2-one 17

(E/EP:40/60): 70%; [α]_D²⁰: +18 (c 0.8, HCCl₃); ¹H NMR: 2.31 (s, 3H), 3.50 (dd, J = 5.0 and 17.3 Hz, 1H), 3.69 (dd, J = 5.0 and 17.3 Hz, 1H), 3.98 (dd, J = 4.9 and 8.0 Hz, 1H), 4.35 (t, J = 5.4 Hz, 1H), 4.52 (dd, J

= 4.8 and 11.4 Hz, 1H), 4.77 (dd, $J = 4.8$ and 11.4 Hz, 1H), 7.28-7.62 (m, 8H), 8.01-8.04 (m, 2H); ^{13}C NMR: 37.8, 39.6, 56.7, 62.3, 70.8, 127.7, 128.2, 128.7, 128.8, 133.5, 136.5, 137.0, 171.6, 196.5. Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_3$: C, 73.76; H, 6.19; N, 4.52. Found: C, 73.70; H, 6.17; N, 4.41.

(3R,5R)-4-Methyl-3-(2-methyl-allyl)-5-phenyl-morpholine-2-one 11 via a Wittig reaction from compound 12

n-Butyl lithium (5.8 ml, 9.3 mmol) was added dropwise to a suspension of methyl triphenylphosphonium bromide (3.3 g, 9.3 mmol) in THF (50 ml) at 0°C. After stirring for 15 min, a solution of compound **12** (1 g, 3.1 mmol) in THF (15 ml) was dropped and the resulting mixture was stirred for 30 min at 0°C. Addition of saturated aqueous NH_4Cl solution was followed by usual workup. Chromatography of the crude residue (E/EP: 2/98) gave compound **18** (0.7 g, 70%); ^1H NMR: 0.17 (s, 9H), 1.77 (s, 3H), 2.10 (s, 3H), 2.26-2.50 (m, 2H), 2.94-3.08 (m, 1H), 3.44-3.56 (m, 1H), 3.75-3.88 (m, 1H), 4.76-4.77 (m, 2H), 5.04 (d, $J = 2.3$ Hz, 1H), 7.25-7.34 (m, 5H); ^{13}C NMR: 0.1, 23.0, 28.8, 39.7, 60.9, 62.8, 70.7, 96.5, 111.4, 127.7, 128.5, 138.9, 146.0. Anal. Calcd for $\text{C}_{17}\text{H}_{29}\text{NO}_2\text{Si}$: C, 67.66; H, 9.15; N, 4.38. Found: C, 67.62; H, 8.98; N, 4.54. A 1M solution of tetrabutylammonium fluoride (6.2 mmol) was added at 0° to a solution of compound **18** (0.98 g, 3 mmol) in THF (30 ml). Stirring was continued for 1h, then usual workup gave compound **9** as a residue which was purified by chromatography (E/EP: 15/85) (0.72 g, 95%); ^1H NMR and ^{13}C NMR are identical with those reported above. The formation of ketomorpholinone **11** by a Swern oxidation of compound **9** was performed as described above.

X-Ray structure determination of ketomorpholinone 11. Data were collected at room temperature on an Enraf-Nonius CAD4 diffractometer. Accurate cell dimensions (obtained by least-squares refinements of 25 accurately centered reflections) are $a = 6.694(3)$, $b = 9.079(1)$, $c = 23.343(4)$ Å, $V = 1418.7(7)$ Å³. The unit cell is orthorhombic, no centrosymmetric $P 2_1 2_1 2_1$ space group, $Z = 4$, $D_c = 1.15$ g.cm⁻³, $\mu(\text{Mo-K}\alpha) = 0.79$ cm⁻¹. No significant variations were observed in the intensities of two checked reflections during data collection. The data were corrected for Lorentz and polarization effects. The program used was CRYSTALS. The structure was solved by use of SHELXS86 program, G.M. Sheldrick, Program for Crystal Structure Solution, University of Göttingen, 1986, and refined by full-matrix least-squares analysis with anisotropic thermal parameters for all non hydrogen atoms. H atoms were introduced in calculated positions in the last refinement. The final refinement of 165 parameters using 828 reflections (with $(F_o)^2 > 2\sigma(F_o)^2$) were used to solve and refine the structure to $R = 0.0466$ and $R_w = 0.0406$.

Urethane derivative 19

A solution of **10** (0.12 g, 0.5 mmol) and vinyl chloroformate (0.27 g, 25 mmol) in CH_2Cl_2 (5 ml) was refluxed for 3 days. Evaporation and flash chromatography of the residue (E/EP: 5/95) yielded carbamate **19** (0.15 g, 87%); ^1H NMR: 2.25-2.49 (m, 1H), 2.55-2.70 (m, 1H), 2.75 (s, 3H), 4.37-4.45 (m, 3H), 4.63-4.81 (m, 2H), 4.98-5.09 (m, 3H), 5.45-5.65 (m, 1H), 7.05-7.16 (m, 1H), 7.25-7.32 (m, 5H); ^{13}C NMR: 30.7, 32.2, 58.3, 59.0, 68.2, 95.7, 118.1, 127.3, 128.7, 128.9, 133.0, 137.1, 142.4, 170.0. Anal. Calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_4\text{Cl}$: C, 60.26; H, 6.24; N, 4.13. Found: C, 60.63; H, 6.13; N, 4.15.

(2R)-2-Methylamino-pent-4-enoic acid methyl ester hydrochloride 20

Compound **19** (0.13 g, 0.38 mmol) was refluxed for 4 days in a 6.5 N solution of HCl in MeOH (2.5 ml). Solvent was then evaporated to remove excess of HCl. The residue was dissolved in water (5 ml) and the aqueous solution was extracted with ether (2 x 8 ml). Removal of water and further drying under reduced pressure yielded compound **20** (0.06 g, 88%); $[\alpha]_D^{20}$: -4 (c 1.8, MeOH); ^1H NMR: 2.69-2.80 (m, 5H), 3.85 (s, 3H), 4.21 (t, $J = 5.5$ Hz, 1H), 5.28-5.35 (m, 2H), 5.66-5.76 (m, 1H); ^{13}C NMR: 31.7, 33.2, 53.9, 60.3, 122.1, 129.6, 169.7.

(2R)-2-Methylamino-pentanoic acid methyl ester hydrochloride 21

Unsaturated amino ester **20** (0.07 g, 0.39 mmol) in MeOH (5 ml) was submitted to the action of hydrogen (1 atm) in the presence of palladium on carbon (0.015 g) for 3h. After filtration and evaporation, pure saturated amino-ester was isolated (0.065 g, 92%); $[\alpha]_{\text{D}}^{20}$: -25 (*c* 3, MeOH), [lit.⁴ $[\alpha]_{\text{D}}^{20}$: +24.4 (*c* 0.9, MeOH) for *ent*-**21**]; ¹H NMR (D₂O): 0.74 (t, *J* = 7.1 Hz), 1.12-1.25 (m, 2H), 1.65-1.80 (m, 2H), 2.53 (s, 3H), 3.66 (s, 3H), 3.90 (t, *J* = 2.5 Hz, 1H).

(2R)-2-Methylamino-4-oxo-pentanoic acid 22

A solution of morpholinone **16** (0.11 g, 0.44 mmol) in absolute ethanol (3 mL) was injected into a hydrogenation flask containing a suspension of 20% Pd(OH)₂ (0.30 g) in absolute ethanol (3 mL). This mixture was placed under hydrogen (1 atm) for 2 h. The catalyst was removed by filtration and the filtrate was evaporated to dryness to afford compound **22** (0.05 g, 77%); $[\alpha]_{\text{D}}^{20}$: -17 (*c* 0.4, 3N HCl), ¹H NMR (D₂O): 2.12 (s, 3H), 2.60 (s, 3H), 3.12 (d, *J* = 5.3, 2H), 3.66 (t, *J* = 5.3 Hz, 1H); ¹³C NMR (D₂O): 29.5, 32.5, 41.8, 58.9, 173.0, 210.8.

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