Pergamon

Tetrahedron 57 (2001) 10155–10161

TETRAHEDRON

A new simple route for the synthesis of (±)-2-azetidinones starting from β-enaminoketoesters

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Received 26 July 2001; revised 20 September 2001; accepted 11 October 2001

Abstract—β-Enaminoketoesters **1**, obtained through metal-catalysed reaction of methyl acetoacetate with alkyl cyanoformates have been conveniently transformed into β-aminoesters **4**, **5** by reduction of both the carbonyl group and the carbon–carbon double bond of the enaminoester moiety. These intermediates could be easily converted to (±)-2-azetidinones **6**, **7** structurally related to thienamycin in good yield and high diastereoselectivity. © 2001 Elsevier Science Ltd. All rights reserved.

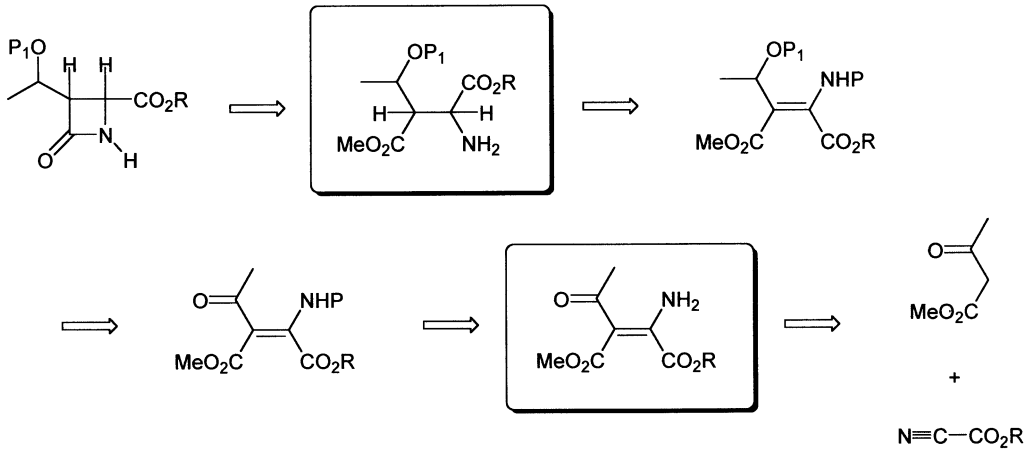
1. Introduction

The 2-azetidinone (β-lactam) ring is the essential feature of a large number of biologically active compounds, namely, penicillins, cephalosporins, carbapenems, norcardins and monobactams.[1] These compounds, which are largely used as chemoterapeutic agents, inhibit the cross-linking of peptidoglycan strands in the final stage of bacterial cell-wall synthesis.[2] The β-lactam nucleus is responsible for this unique mode of action. Indeed, it is well recognized that acid- or β-lactamase-induced ring opening yields products that do not inhibit bacterial growth.

The pharmacological relevance of β-lactam-based antibiotics and the need for compounds having broader activity and enhanced chemical and metabolic stabilities has stimulated synthetic efforts toward the construction of the β-lactam framework in a concise and stereoselective fashion.

The classical routes to 2-azetidinones can be generally classified as (i) [2+2] cycloadditions, (ii) cyclization reactions of β-aminoacids and esters, and (iii) carbene insertion reactions.[3]

As a continuation of our studies on metal-catalysed reactions of β-dicarbonyl compounds with nitriles,[4] we have recently described in preliminary form a new synthetic



Scheme 1.

Keywords: 2-azetidinones; β-enaminoketoesters; diastereoselectivity.
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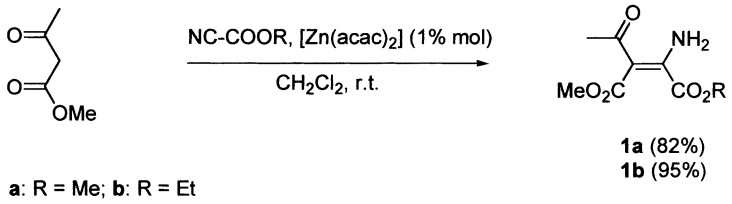
PII: S0040-4020(01)01036-5



Scheme 2.

approach to (±)-2-azetidinones structurally related to thienamycin, entailing on the use of β-enaminoketoesters as the starting materials.[5] We describe the details of our results in this paper.

Our own approach relies on the use of a β-aminoester as the key intermediate for the construction of the 2-azetidinone ring (Scheme 1).

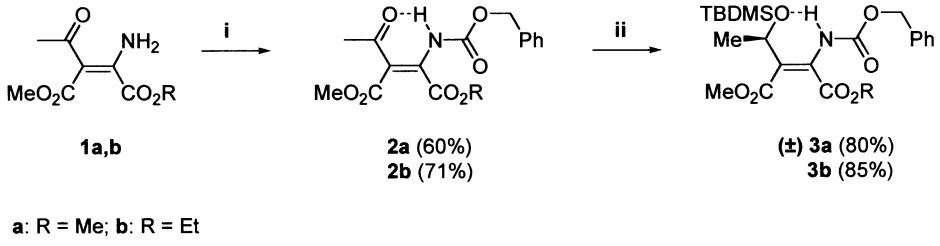
The β-aminoester would be in turn obtained by elaboration of a β-enaminoketoester, conveniently prepared by reaction of methyl acetoacetate with an alkyl cyanoformate.

2. Results and discussion

The preparation of the starting substrates was accomplished through reactions of methyl acetoacetate with methyl or ethyl cyanoformates in the presence of a catalytic amount of [Zn(acac)$_2$] (1 mol%) (Scheme 2).[6]

Initial attempts to reduce the carbon–carbon double bond of **1a**,**b** proved unsuccessful, the enaminone system being very reluctant to undergo reduction under classical conditions. Likely, this behaviour is due to the delocalization of the nitrogen lone pair through the carbon–carbon double bond system of the enaminoester moiety and could be modified through protection of the amino group with an electron-withdrawing group. Thus, β-enaminoketoesters **1a**,**b** were reacted with benzyl chloroformate in the presence of sodium hydride to furnish the *N*-protected enaminoketoesters **2a**,**b** (Scheme 3).

The reduction of the carbonyl group with $NaBH_4$ in methanol followed by transformation of the derived secondary hydroxyl group into the corresponding *tert*-butyl dimethylsilyl ether by reaction with *tert*-butyl dimethylsilyl



Scheme 3. i: $ClCO_2CH_2Ph$, NaH, THF, 0°C; ii: a) $NaBH_4$, MeOH, 0°C; b) TBDMSCl, imidazole, r.t.

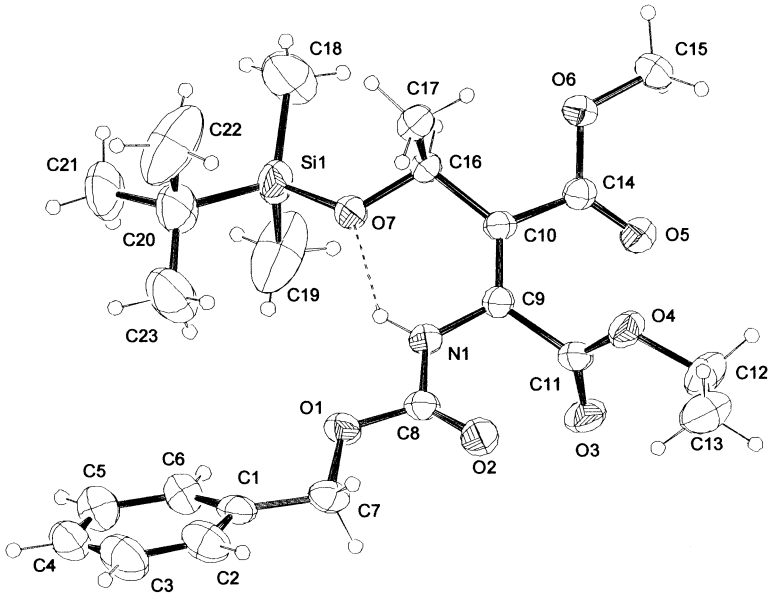
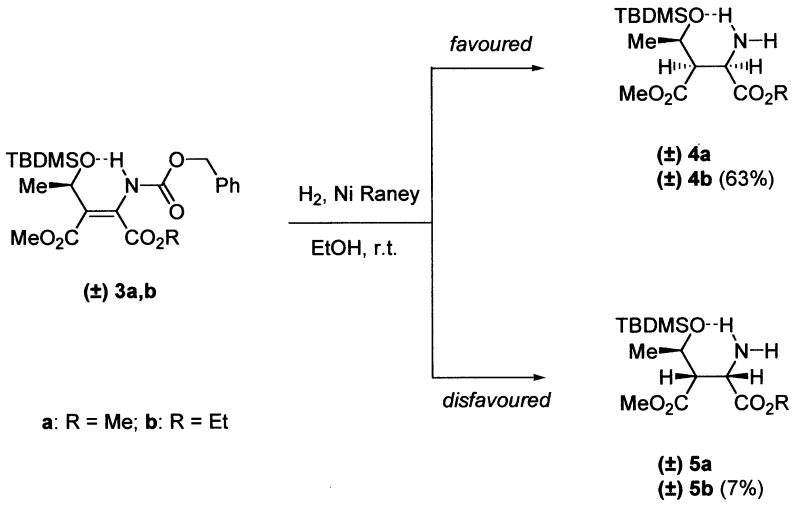


Figure 1. An ORTEP view of one of the enantiomers of compound **3b** displaying the thermal ellipsoids at 30% probability.



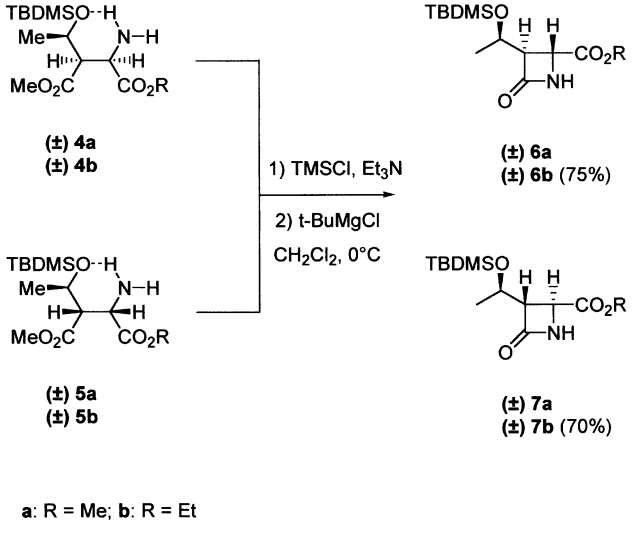
Scheme 4.

chloride (TBDMSCl) in the presence of imidazole, gave compounds **3a**,**b** in very good yield.[7] It is worth mentioning that these intermediates exist in a cyclic structure, which is particularly stable because of strong hydrogen bond between the NH and the oxygen atom linked to silicon, as clearly shown by X-ray analysis of a suitable crystal of **3b**[8] (Fig. 1).

Reduction of the carbon–carbon double bond of **3a**,**b** was easily achieved by catalytic hydrogenation in the presence of Raney Nickel W-2 (Scheme 4).

This operation proceeded smoothly at room temperature with concomitant deprotection of the amine function to give the aminoesters **4** and **5** in 9:1 ratio (^{1}H NMR analysis) and 65–70% overall yield, the ethyl esters **4b** and **5b** being easily separated by flash chromatography. On the contrary, all the attempts to isolate **4a** and **5a** proved unsuccesful.

The high diastereoselectivity observed in these reactions could be ascribed to the afore-mentioned cyclic structure of the intermediate **3**. Its catalytic reduction can preferentially occur from the less hindered side of the molecule (*favoured* pathway) giving rise to the amino esters **4**, in which the hydrogens linked to C-2, C-3 and C-4 carbon atoms are on the same side of the molecule, while the minor isomers **5** could derive from hydrogenation of **3** from the more hindered side of the molecule (*disfavoured* pathway).



Scheme 5.

Now the stage was set to perform the cyclization step for the construction of the 2-azetidinone ring. To this end, we first used the inseparable mixture of β-aminoesters **4a** and **5a** as the model compound to find the optimal experimental conditions.

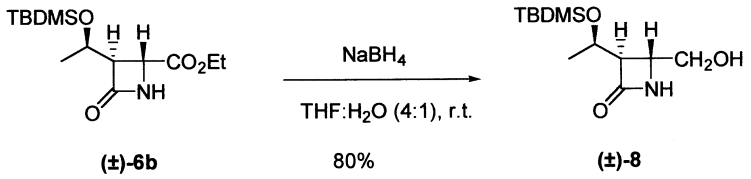
The reported route to β-lactam rings (Salzmann's procedure)[9] involves the in situ formation of the *N*-trimethylsilyl derivative of the starting β-aminoester by reaction with trimethylsilyl chloride and triethylamine in ether, followed by filtration of the triethylamine hydrochloride. Treatment of the intermediate thus formed with *t*-butyl magnesium chloride eventually gives the expected heterocyclic compound.

Following this literature protocol, we prepared the *N*-trimethylsilyl derivatives of β-aminoesters **4a** and **5a**, but disappointingly they were very difficult to manipulate for their high sensitivity to moisture, furnishing the corresponding β-lactams **6a** and **7a** in low yields.

Better results were instead observed following the modified procedure reported by Lynch et al.,[10] using CH_2Cl_2 as the solvent, which allowed us to avoid the filtration of the ammonium salts.

In this way, 2-azetidinones **6a** and **7a** were obtained in very good overall yield (65%), the main diastereomer **6a** being easily separated by flash chromatography (Scheme 5).

Likewise, treatment of the separated aminoesters **4b** and **5b** with trimethylsilyl chloride in the presence of triethylamine, followed by addition of *tert*-butyl magnesium chloride furnished the azetidinones **6b** and **7b** in 75 and 70% yields, respectively.



Scheme 6.

For each of the compounds so obtained, the *trans* configuration of the vicinal protons at C-3 and C-4 was established on the basis of their ^{1}H NMR coupling constants ($J_{3,4}$=2.6–2.7 Hz). This result may be attributed to the fact that both the intramolecular cyclization of **4** and **5** requires a rotation of the C2-C3 single bond furnishing *trans*-azetidinones **6** and **7**, respectively. To assign definitively the relative stereochemistry of the three stereocenters of these compounds, we transformed **6b**, obtained in larger quantities, into the corresponding primary alcohol **8**. This was achieved by reduction with $NaBH_4$ according to the protocol described in the literature[11] (Scheme 6).

The alcohol **8** could be recrystallized from ether at −18°C to afford crystals,[5] whose X-ray analysis (Fig. 2) allowed us to univocally assign the relative configuration of the three asymmetric centres created in the reductive steps.

Both the structure of **8** and the afore-mentioned spectroscopic informations let us to assign definitively either the relative configuration of C-3 and C-4 carbon atoms of the 2-azetidinone rings or the structures of β-aminoesters **4** and **5**.

3. Conclusions

In summary, the β-enaminoketoesters **1** has been conveniently used to obtain (±)-2-azetidinones in good yield and high diastereoselectivity. The ready accessibility of the starting materials and the simplicity of all the synthetic steps makes our approach very practical for the synthesis of 2-azetidinones bearing a 1-hydroxyethyl substituent, a structural feature common to thienamycin and related natural compounds.

4. Experimental

4.1. General remarks

Melting points were determined on a Büchi-Tottoli apparatus and are uncorrected. Infrared (IR) spectra were recorded on a FT-IR Paragon 500 spectrometer. Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were taken on a Bruker AC spectrometer at 200 and 50 MHz, respectively, for solutions in $CDCl_3$ unless otherwise noted. Chemical shifts are given in parts per million downfield from tetramethylsilane as the internal standard and coupling constants are given in Hz. Organic solutions were dried over anhydrous magnesium sulphate and evaporated with a rotary evaporator. Light petroleum refers to the fractions boiling in the range 40–60°C and ether to diethyl ether. Flash-chromatography was carried out with Merck silica gel (230–400 mesh). All reactions were performed under N_2 or Ar atmosphere. Elemental analyses were effected by the microanalytical laboratory of Dipartimento di Chimica, University of Ferrara.

Compound **1b** was prepared according to the literature.[6]

4.1.1. Methyl 2-amino-3-methoxycarbonyl-4-oxo-2-pentenoate (1a). To a stirred solution of methyl cyanoformate (0.87 ml, 11 mmol) and methyl acetoacetate (1.10 ml, 10 mmol) in dry CH_2Cl_2 (2 ml), zinc acetylacetonate (26 mg, 0.10 mmol) was added. After being stirred for

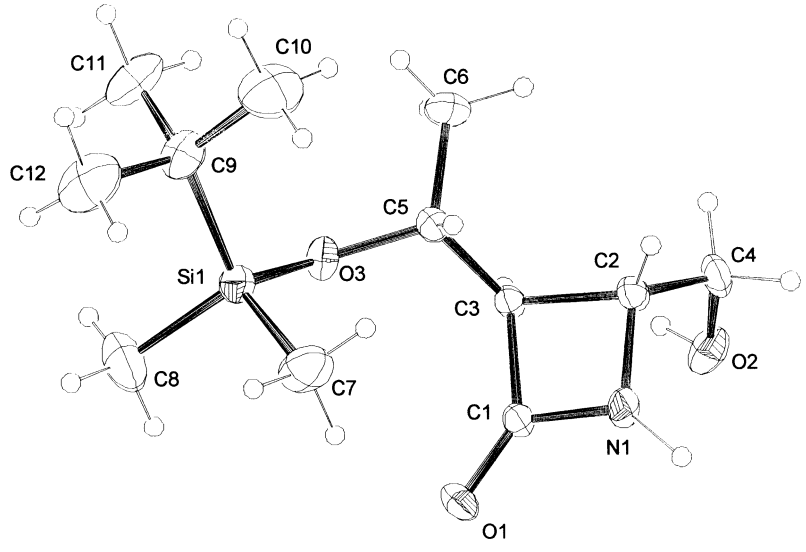


Figure 2. An ORTEP view of one of the enantiomers of compound **8** displaying the thermal ellipsoids at 30% probability.

1.5 h at room temperature, the mixture was filtered through celite and the solvent was evaporated. The solid residue was recrystallized (EtOAc–light petroleum) to furnish **1a** (1.65 g, 82%) as colourless crystals, mp 78–80°C. IR (KBr): 3268, 3100, 1745, 1689, 1587 cm^{-1}. ^1H NMR: two isomers are present in 80:20 ratio. The major isomer shows resonances at: δ 2.38 (s, 3H, CH_3CO), 3.76 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.10 (br, 1H, NH), 10.60 (br, 1H, NH) while the minor isomer shows distinctive resonances at: δ 2.43 (s, 3H, CH_3CO), 3.82 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 8.90 (br, 1H, NH). ^{13}C NMR resonances for the major isomer: δ 30.18 (q, J=127.6 Hz, CH_3CO), 51.82 (q, J=146.0 Hz, OCH_3), 53.28 (q, J=147.7 Hz, OCH_3), 101.58 (s, C-3), 156.33 (s, C-2), 164.54 (s, COO), 168.17 (s, COO), 198.74 (s, CO) and for the minor isomer: δ 30.87 (q, J=127.6 Hz, CH_3), 51.28 (q, J=146.3 Hz, OCH_3), 53.15 (q, J=147.3 Hz, OCH_3), 100.50 (s, C-3), 158.45 (s, C-2), 165.56 (s, COO), 168.67 (s, COO), 197.01 (s, CO). Found: C, 47.83; H, 5.55; N, 7.10. $C_8H_{11}NO_5$ requires C, 47.76; H, 5.51; N, 6.96.

4.2. General procedure for the synthesis of compounds (2a,b)

A solution of **1a** or **b** (10 mmol) in dry THF (10 ml) was added dropwise to a cooled (0°C) suspension of 75% NaH (12 mmol) in dry THF (12 ml) and the mixture was kept at the same temperature for 30 min. A solution of benzyl chloroformate (15 mmol) in dry THF (15 ml) was successively dropped and stirring was continued at room temperature for 12 h. The solution was cooled at 0°C, diluted with EtOAc and acidified by adding 20% HCl. The two phases were separated, the aqueous phase was extracted with EtOAc (3×10 ml) and the combined organic extracts were dried and evaporated. The residue was purified by flash-chromatography (eluent EtOAc–light petroleum 1:3) to give **2a** or **b**.

4.2.1. Methyl 2-[(*N*-benzyloxycarbonyl)-amino]-3-methoxycarbonyl-4-oxo-2-pentenoate (2a). This compound was obtained from **1a** by using the afore-mentioned general procedure as a colourless solid, yield 60%, mp 91–93°C. IR (KBr): 3300, 1742, 1724, 1647, 1570, 1452 cm^{-1}. ^1H NMR: δ 2.41 (s, 3H, CH_3CO), 3.76 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.17 (s, 2H, OCH_2), 7.35 (s, 5H, Ph), 10.5 (br, 1H, NH). ^{13}C NMR: δ 31.12 (q, J=128.3 Hz, CH_3CO), 52.43 (q, J=146.8 Hz, OCH_3), 53.16 (q, J=147.4 Hz, OCH_3), 68.80 (t, J=148.7 Hz, OCH_2), 108.70 (s, C-3), 128.54 (d, J=159.7 Hz, Ph), 128.66 (d, J=159.7 Hz, Ph), 128.79 (d, J=159.7 Hz, Ph), 134.38 (s, Ph), 149.62 (s, C-2), 151.63 (s, NHCOO), 162.61 (s, COO), 165.84 (s, COO), 200.36 (s, CO). Found: C, 57.37; H, 5.19; N, 4.27. $C_{16}H_{17}NO_7$ requires C, 57.31; H, 5.11; N, 4.18.

4.2.2. Ethyl 2-[(*N*-benzyloxycarbonyl)-amino]-3-methoxycarbonyl-4-oxo-2-pentenoate (2b). This compound was obtained from **1b** by using the afore-mentioned general procedure as a yellowish oil, yield 71%. IR (film): 3300, 1746, 1649, 1569, 1431 cm^{-1}. In the ^1H NMR spectrum, two isomeric species are detectable in 85:15 ratio. The prevalent isomer shows resonances at: δ 1.35 (t, J=7.0 Hz, 3H, OCH_2CH_3), 2.42 (s, 3H, CH_3CO), 3.77 (s, 3H, OCH_3), 4.35 (q, J=7.0 Hz, 2H, OCH_2CH_3), 5.18 (s, 2H, OCH_2Ph), 7.36 (s, 5H, Ph), 12.11 (br, 1H, NH). The minor isomer shows characteristic resonances at: δ 3.83 (s, OCH_3), 10.53 (s, br, 1H, NH). ^{13}C NMR resonances for the major isomer: δ 13.81 (q, J=126.6 Hz, OCH_2CH_3), 31.09 (q, J=128.3 Hz, CH_3CO), 52.40 (q, J=146.7 Hz, OCH_3), 62.74 (t, J=147.8 Hz, OCH_2CH_3), 68.80 (t, J=148.3 Hz, OCH_2Ph), 108.84 (s, C-3), 128.58 (d, J=160.8 Hz, Ph), 128.71 (d, J=160.1 Hz, Ph), 128.82 (d, J=160.0 Hz, Ph), 134.53 (s, Ph), 149.81 (s, C-2), 151.68 (s, NHCOO), 162.13 (s, COO), 166.03 (s, COO), 200.36 (s, CO) and for the minor isomer: δ 13.62 (q, J=126.5 Hz, OCH_2CH_3), 31.26 (q, J=127.6 Hz, CH_3CO), 68.70 (t, J=148.1 Hz, OCH_2Ph). Found: C, 58.52; H, 5.55; N, 4.06. $C_{17}H_{19}NO_7$ requires C, 58.45; H, 5.48; N, 4.01.

4.3. General procedure for the synthesis of compounds (3a,b)

To a cooled (0°C) solution of **2a** or **b** (3 mmol) in methanol (6 ml) was added sodium borohydride (3.3 mmol) in one portion. After the reaction was complete (10 min), the solvent was removed under reduced pressure and the residue was partitioned between water and EtOAc. The two phases were separated and the aqueous phase was extracted with EtOAc (3×10 ml). The combined organic extracts were dried and evaporated. The residue was immediately dissolved in dry DMF (5 ml) and the resulting solution was cooled at 0°C. Imidazole (10 mmol) and *tert*-butyl dimethylsilyl chloride (6.6 mmol) were successively added and the mixture was stirred at room temperature until completion (1.5 h). The solvent was evaporated and the residue was purified by flash-chromatography (eluent EtOAc–light petroleum 1:4) to give **3a** or **b**.

4.3.1. (±)-Methyl 2-[(*N*-benzyloxycarbonyl)-amino]-3-methoxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-pentenoate (3a). This compound was obtained from **2a** by using the afore-mentioned general procedure as a white solid, yield 80%, mp 76–77°C. IR (KBr): 3307, 1758, 1745, 1712, 1624, 1496 cm^{-1}. ^1H NMR: δ 0.06 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.86 (s, 9H, *t*-Bu), 1.38 (d, J=6.5 Hz, 3H, CH_3CHO), 3.70 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.96 (q, J=6.5 Hz, 1H, CHOSi), 5.13 and 5.15 (AB system, J=13.3 Hz, 2H, OCH_2Ph), 7.35 (s, 5H, Ph), 9.49 (br, 1H, NH). ^{13}C NMR: δ −5.32 (q, J=118.0 Hz, $SiCH_3$), −5.20 (q, J=118.0 Hz, $SiCH_3$), 17.87 (s, $C(CH_3)_3$), 22.70 (q, J=127.1 Hz, CH_3CHO), 25.64 (q, J=124.4 Hz, *t*-Bu), 52.09 (q, J=146.4 Hz, OCH_3), 52.74 (q, J=146.6 Hz, OCH_3), 67.87 (t, J=147.2 Hz, OCH_2Ph), 68.23 (d, J=146.7 Hz, CHOSi), 113.40 (s, C-3), 128.19 (d, J=159.2 Hz, Ph), 128.41 (d, J=159.2 Hz, Ph), 128.51 (d, J=159.2 Hz, Ph), 135.15 (s, Ph), 140.35 (s, C-2), 151.53 (s, NHCOO), 164.12 (s, COO), 165.65 (s, COO). Found: C, 58.59; H, 7.43; N, 3.15. $C_{22}H_{33}NO_7Si$ requires C, 58.51; H, 7.37; N, 3.10.

4.3.2. (±)-Ethyl 2-[(*N*-benzyloxycarbonyl)-amino]-3-methoxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-pentenoate (3b). This compound was obtained from **2b** by using the afore-mentioned general procedure as a colourless solid, yield 85%, mp 52–55°C. IR (KBr): 3291, 1756, 1625, 1499 cm^{-1}. ^1H NMR: δ 0.07 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.86 (s, 9H, *t*-Bu), 1.35 (t, J=6.9 Hz, 3H, OCH_2CH_3), 1.39 (d, J=6.4 Hz, 3H, CH_3CHO), 3.70 (s,

3H, OCH_3), 4.33 (q, J=6.9 Hz, 2H, OCH_2CH_3), 4.95 (q, J=6.4 Hz, 1H, CH_3CHO), 5.12 and 5.14 (AB system, J=12.2 Hz, 2H, OCH_2Ph), 7.35 (m, 5H, Ph), 9.47 (br, 1H, NH). ^{13}C NMR: δ −5.30 (q, J=116.4 Hz, $SiCH_3$), −5.19 (q, J=116.4 Hz, $SiCH_3$), 13.81 (q, J=126.3 Hz, OCH_2CH_3), 17.86 (s, $C(CH_3)_3$), 22.70 (q, J=129.6 Hz, CH_3CHO), 25.64 (q, J=124.4 Hz, *t*-Bu), 51.92 (q, J=146.3 Hz, OCH_3), 61.97 (t, J=147.0 Hz, OCH_2CH_3), 67.77 (t, J=146.7 Hz, OCH_2Ph), 68.32 (d, J=146.8 Hz, CH_3CHO), 113.52 (s, C-3), 128.14 (d, J=159.3 Hz, Ph), 128.36 (d, J=159.3 Hz, Ph), 128.48 (d, J=159.3 Hz, Ph), 135.25 (s, Ph), 140.47 (s, C-2), 151.51 (s, NHCOO), 163.60 (s, COO), 165.75 (s, COO). Found: C, 59.37; H, 7.65; N, 3.03. $C_{23}H_{35}NO_7Si$ requires C, 59.33; H, 7.58; N, 3.01.

4.3.3. (±)-Methyl 2-amino-3-methoxycarbonyl-4-*tert*-butyldimethylsilyloxy-pentanoate (4a) and (5a). A solution of **3a** (300 mg, 0.66 mmol) in ethanol (10 ml) was hydrogenated in a Parr apparatus in the presence of Ni–Raney W-2 as the catalyst for 8 h. The suspension was filtered through celite and the solvent evaporated under reduced pressure to give the mixture of **4a** and **5a** (136 mg, 65%) as a yellow oil. IR (film): 3395, 1743, 1606 cm^{-1}. ^{1}H NMR: the isomers **4a** and **5a** are present in 9:1 ratio; **4a** shows resonances at: δ 0.02 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.85 (s, 9H, *t*-Bu), 1.26 (d, J=6.1 Hz, 3H, CH_3CHO), 1.72 (br, 2H, NH_2), 2.91 (dd, J=7.9, 4.9 Hz, 1H, $CHCO_2CH_3$), 3.66 (s, 3H, OCH_3), 3.71 (m, 1H, $CHNH_2$), 3.72 (s, 3H, OCH_3); **5a** shows resonances at: δ 0.02 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.85 (s, 9H, *t*-Bu), 1.26 (d, J=6.1 Hz, 3H, CH_3CHO), 1.72 (br, 2H, NH_2), 2.72 (dd, J=7.9, 3.8 Hz, 1H, $CHCO_2CH_3$), 3.66 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.92 (d, J=3.8 Hz, 1H, $CHNH_2$), 4.3 (q, J=6.1 Hz, 1H, CH_3CHO). ^{13}C NMR resonances for **4a**: δ −5.37 (q, J=117.6 Hz, $SiCH_3$), −4.31 (q, J=117.6 Hz, $SiCH_3$), 17.75 (s, $C(CH_3)_3$), 21.13 (q, J=125.3 Hz, CH_3CHO), 25.55 (q, J=126.0 Hz, *t*-Bu), 51.53 (q, J=146.1 Hz, OCH_3), 52.15 (q, J=146.4 Hz, OCH_3), 53.65 (d, J=139.7 Hz, CH), 56.05 (d, J=132.6 Hz, CH), 67.55 (d, J=203.4 Hz, CH), 172.34 (s, COO), 174.94 (s, COO) and for **5a**: δ −5.37 (q, J=117.6 Hz, $SiCH_3$), −4.31 (q, J=117.6 Hz, $SiCH_3$), 14.07 (s, $C(CH_3)_3$), 22.29 (q, J=125.3 Hz, CH_3CHO), 25.67 (q, J=126.0 Hz, *t*-Bu), 51.53 (q, J=146.1 Hz, OCH_3), 52.15 (q, J=146.4 Hz, OCH_3), 53.65 (d, J=139.7 Hz, CH), 56.05 (d, J=132.6 Hz, CH), 66.36 (d, J=203.4 Hz, CH), 172.30 (s, COO), 174.90 (s, COO).

4.3.4. (±)-Ethyl 2-amino-3-methoxycarbonyl-4-*tert*-butyldimethylsilyloxy-pentanoate (4b) and (5b). A solution of **3b** (1 g, 2.15 mmol) in ethanol (30 ml) was hydrogenated in a Parr apparatus in the presence of Ni–Raney W-2 as the catalyst for 8 h. The suspension was filtered through celite and the solvent evaporated under reduced pressure. The residue was purified by flash-chromatography (eluent EtOAc–light petroleum 1:3) to give **4b** (450 mg, 63%) and **5b** (50 mg, 7%) as yellow oils.

4b: IR (film): 3393, 1740, 1606 cm^{-1}. ^{1}H NMR: δ 0.02 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.85 (s, 9H, *t*-Bu), 1.20–1.40 (m, 6H, CH_3CHO and OCH_2CH_3), 1.85 (br, 2H, NH_2), 2.90 (dd, J=7.9, 4.9 Hz, 1H, $CHCO_2CH_3$), 3.63–3.68 (m, 1H, $CHNH_2$), 3.72 (s, 3H, OCH_3), 4.10–4.40 (m, 3H, CH_3CHO and OCH_2CH_3). ^{13}C NMR: δ −5.54 (q, J=117.7 Hz, $SiCH_3$), −4.51 (q, J=117.7 Hz, $SiCH_3$), 13.89 (q, J=118.8 Hz, OCH_2CH_3), 17.56 (s, $C(CH_3)_3$), 20.97 (q, J=124.4 Hz, CH_3CHO), 25.39 (q, J=129.6 Hz, *t*-Bu), 51.13 (q, J=145.9 Hz, OCH_3), 53.54 (d, J=139.2 Hz, CH), 55.76 (d, J=133.4 Hz, CH), 60.85 (t, J=146.8 Hz, OCH_2CH_3), 67.49 (d, J=144.4 Hz, CH_3CHO), 172.15 (s, COO), 174.23 (s, COO). Found: C, 54.10; H, 9.43; N, 4.30. $C_{15}H_{31}NO_5Si$ requires C, 54.02; H, 9.37; N, 4.20.

5b: IR (film): 3393, 1740, 1609 cm^{-1}. ^{1}H NMR: δ 0.09 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.86 (s, 9H, *t*-Bu), 1.20–1.32 (m, 6H, CH_3CHO and OCH_2CH_3), 1.79 (br, 2H, NH_2), 2.90 (dd, 1H, J=7.9, 3.8 Hz, $CHCO_2CH_3$), 3.66 (s, 3H, OCH_3), 3.92 (d, J=3.8 Hz, 1H, $CHNH_2$), 4.10–4.40 (m, 3H, CH_3CHO and OCH_2CH_3). ^{13}C NMR: δ −4.90 (q, J=122.4 Hz, $SiCH_3$), −4.17 (q, J=117.6 Hz, $SiCH_3$), 14.24 (q, J=126.1 Hz, OCH_2CH_3), 17.99 (s, $C(CH_3)_3$), 22.37 (q, J=124.7 Hz, CH_3CHO), 25.84 (q, J=124.2 Hz, *t*-Bu), 51.64 (q, J=146.2 Hz, OCH_3), 53.10 (d, J=139.4 Hz, CH), 56.19 (d, J=131.3 Hz, CH), 61.23 (t, J=146.8 Hz, OCH_2CH_3), 66.59 (d, J=143.1 Hz, CH_3CHO), 172.09 (s, COO), 174.66 (s, COO). Found: C, 54.09; H, 9.44; N, 4.28. $C_{15}H_{31}NO_5Si$ requires C, 54.02; H, 9.37; N, 4.20.

4.4. General procedure for the synthesis of the 2-azetidinones (6) and (7)

A cooled (0°C) solution of the appropriate β-aminoester **4** or **5** (1 mmol) in dry CH_2Cl_2 (5 ml) was treated with triethylamine (1.1 mmol) and trimethylchlorosilane (1.1 mmol). The resulting solution was stirred at the same temperature for 30 min, then *tert*-butylmagnesium chloride (2 M in diethyl ether, 6.6 mmol) was added and stirring was continued at room temperature until completion (12 h). Water (10 ml) was added and the precipitated magnesium salts were filtered through celite. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3×10 ml) and the combined organic extracts were dried and evaporated. The crude residue thus obtained was purified by flash-chromatography (eluent EtOAc–light petroleum 1:3).

4.4.1. (±)-3-[(1-*tert*-Butyldimethylsilyloxy)-ethyl]-4-methoxycarbonyl-azetidin-2-one (6a). This compound was obtained from the mixture of **4a** and **5a** by using the afore-mentioned general procedure as a yellowish oil. IR (film): 3285, 1778, 1743 cm^{-1}. ^{1}H NMR: δ 0.09 (s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, *t*-Bu), 1.34 (d, J=6.4 Hz, 3H, CH_3CHO), 3.34 (br, 1H, $CHCONH$), 3.77 (s, 3H, OCH_3), 4.09 (d, J=2.7 Hz, 1H, $CHNH$), 4.15–4.30 (m, 1H, CHOSi), 6.40 (br, 1H, NH). ^{13}C NMR: δ −5.01 (q, J=117.6 Hz, $SiCH_3$), −4.13 (q, J=117.9 Hz, $SiCH_3$), 18.04 (s, $C(CH_3)_3$), 20.76 (q, J=125.5 Hz, CH_3CHO), 25.73 (q, J=124.8 Hz, *t*-Bu), 50.03 (d, J=152.3 Hz, CH), 52.52 (q, J=146.9 Hz, OCH_3), 64.06 (d, J=136.9 Hz, CH), 64.99 (d, J=140.9 Hz, CH), 167.21 (s, NHCOO), 171.98 (s, COO). Found: C, 54.40; H, 8.82; N, 4.88. $C_{13}H_{25}NO_4Si$ requires C, 54.32; H, 8.77; N, 4.87.

4.4.2. (±)-3-[(1-*tert*-Butyldimethylsilyloxy)-ethyl]-4-ethoxycarbonyl-azetidin-2-one (6b). This compound was obtained from **4b** by using the afore-mentioned general procedure as a yellowish oil, yield 75%. IR (film): 3306,

1776, 1747 cm^{-1}. ^1H NMR: δ 0.09 (s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, *t*-Bu), 1.20–1.40 (m, 6H, OCH_2CH_3 and CH_3CHO), 3.33 (br, 1H, *CH*CONH), 4.06 (d, J=2.6 Hz, 1H, *CH*NH), 4.15–4.35 (m, 3H, CH_3CHO and OCH_2CH_3), 6.64 (br, 1H, NH). ^{13}C NMR: δ −5.08 (q, J=118.1 Hz, $SiCH_3$), −4.28 (q, J=118.0 Hz, $SiCH_3$), 14.10 (q, J=126.3 Hz, OCH_2CH_3), 17.95 (s, $C(CH_3)_3$), 20.62 (q, J=126.5 Hz, CH_3CHO), 25.67 (q, J=124.4 Hz, *t*-Bu), 50.03 (d, J=154.2 Hz, *CH*NH), 61.52 (t, J=147.0 Hz, OCH_2CH_3), 63.85 (d, J=139.3 Hz, *CH*CONH), 64.93 (d, J=141.1 Hz, CH_3CHO), 167.46 (s, NHCOO), 171.53 (s, COO). Found: C, 55.82; H, 9.09; N, 4.70. $C_{14}H_{27}NO_4Si$ requires C, 55.78; H, 9.03; N, 4.65.

4.4.3. (±)-3-[(1-*tert*-Butyldimethylsilyloxy)-ethyl]-4-ethoxycarbonyl-azetidin-2-one (7b). This compound was obtained from **5b** by using the afore-mentioned general procedure as a yellowish oil, yield 70%. IR (film): 3306, 1776, 1747 cm^{-1}. ^1H NMR: δ 0.06 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.88 (s, 9H, *t*-Bu), 1.20–1.40 (m, 6H, OCH_2CH_3 and CH_3CHO), 3.26 (br, 1H, *CH*CONH), 4.20–4.40 (m, 4H, CH_3CHO, OCH_2CH_3 and *CH*NH), 6.00 (br, 1H, NH). Found: C, 55.80; H, 9.07; N, 4.70. $C_{14}H_{27}NO_4Si$ requires C, 55.78; H, 9.03; N, 4.65.

4.4.4. (±)-3-[(1-*tert*-Butyldimethylsilyloxy)-ethyl]-4-hydroxymethyl-azetidin-2-one (8). Sodium borohydride (60 mg, 1.60 mmol) was added in one portion to a cooled (0°C) solution of **6b** (440 mg, 1.46 mmol) in THF–H_2O (4:1, 10 ml) and the mixture was stirred at room temperature for 2 h. EtOAc (10 ml) was added, the phases were separated, the aqueous phase was extracted with EtOAc (3×10 ml) and the combined organic extracts were dried and evaporated. The purification of the residue by flash-chromatography (eluent ether–light petroleum 6:1) followed by recrystallization (ether, −18°C) of the solid thus obtained, yielded **8** (300 mg, 80%) as colourless crystals, mp 62–66°C. IR (KBr): 3200, 1731, 1466 cm^{-1}. ^1H NMR: δ 0.07 (s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, *t*-Bu), 1.29 (d, J=6.4 Hz, 3H, CH_3CHO), 2.36 (br, 1H, OH), 3.07 (dd, J=3.1, 2.4 Hz, 1H, *CH*CONH), 3.60–3.90 (m, 3H, CH_2OH and *CH*NH), 4.17 (dq, J=6.4, 4.2 Hz, 1H, CH_3CHO), 6.33 (br, 1H, NH). ^{13}C NMR: δ −4.93 (q, J=117.5 Hz, $SiCH_3$), −4.30 (q, J=117.5 Hz, $SiCH_3$), 18.02 (s, $C(CH_3)_3$), 20.74 (q, J=127.3 Hz, CH_3CHO), 25.79 (q, J=124.4 Hz, *t*-Bu), 51.68 (d, J=149.6 Hz, CH), 59.29 (d, J=142.5 Hz, CH), 63.60 (t, J=142.3 Hz, CH_2OH), 65.07 (d, J=141.4 Hz, CH), 169.67 (s, NHCOO). Found: C, 55.60; H, 9.78; N, 5.50. $C_{12}H_{25}NO_3Si$ requires C, 55.56; H, 9.71; N, 5.40.

4.5. X-Ray crystal structure analysis of 3b

Suitable crystals were obtained from ether solution at −18°C. Crystal data: $C_{23}H_{35}NO_7Si$; monoclinic, space group $P2_1/c$; a=7.621(2), b=28.639(11), c=11.915(2) Å, β=93.60(2)°, V=2595(1) $Å^3$, Z=4, D_c=1.192 g cm^{-3}. Intensity data collected with $\theta \leq 26°$ using Mo Kα radiation (0.71073 Å) on an Enraf–Nonius CAD4 diffractometer; T=295 K, 5093 independent reflections measured; 2466 reflections observed [$I \geq 2\sigma(I)$]; solution by direct methods[12] [SIR92]; full matrix least-squares refinement using SHELXL-97;[13] non-hydrogens anisotropic, hydrogens atoms included at calculated positions except H1, bonded to N1, which was refined isotropically. Final R index=0.0897. An ORTEP view[14] of the molecule is shown in Fig. 1. The molecules in the crystal form an intramolecular hydrogen bond: N1–H1···O7 [N1–H1=0.79(5), N1···O7=2.712(6) Å, N1–H1···O7=129(4)°].

Acknowledgements

This work was financially supported by MURST COFIN-2000 (Italy).

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