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Synthesis and hydrogenation of 1-methylenecarbapenam

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Summary — A stereoselective synthesis of a bicyclic 1β-methyl intermediate precursor of 1β-methylcarbapenem antibiotics has been developed from 4-acetoxyazetidin-2-one using a π-allyl palladium ring closure strategy and stereoselective hydrogenation.

palladium catalyst / cyclization / stereoselective hydrogenation

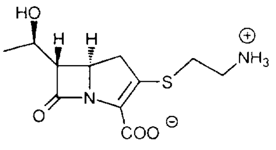
Résumé — Synthèse et hydrogénation de 1-méthylènecarbapéname. *Une synthèse stéréosélective d'un 1β-méthylcarbapéname, intermédiaire bicyclique des antibiotiques de type 1β-méthylcarbapénème, a été mise au point à partir de la 4-acétoxyazétidin-2-one par cyclisation à l'aide des complexes du palladium, suivie d'une hydrogénation stéréosélective.*

catalyseur au palladium / cyclisation / hydrogénation stéréosélective

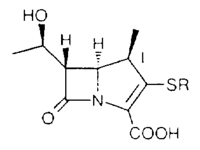
Introduction

The carbapenems are very efficient β-lactam antibiotics [1] closely related to penicillins and cephalosporins. They play an important role in antibacterial therapy owing to their wide range of activity, negligible level of toxicity, and stability to metabolism by β-lactamases. Since the discovery by the Merck group of the first of these antibiotics, (+)thienamycin **1** [2], a natural fungal metabolite, numerous syntheses of analogues have been carried out in attempts to increase their chemical and enzymatic stability [3]. Indeed, thienamycin, is highly active in vitro but is sensitive to renal dehydropeptidase I (DHPI) in vivo and fairly labile in solution.

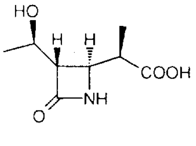
In 1984, the Merck group reported the synthesis of a non-natural 1β-methyl analogue [4] of type **2**, which exhibited higher resistance to deactivation by DHPI and still retained an excellent broad spectrum of antibacterial activity.



1 : (+) thienamycin



2 : 1β-methylcarbapenems



3

Since 1984, the interesting properties of the 1β-methylcarbapenems have attracted the attention of many research groups and numerous syntheses have been described [5], generally using the chiral β-methyl key precursor **3**. Several methods have since been developed to obtain β-methyl intermediates with high optical purity. Hydrogenation of monocyclic unsaturated precursors of **3** is one of the main approaches but it requires the use of chiral catalysts to increase the stereoselectivity [6]. Only one example, to our knowledge, has shown high diastereoselectivity with non-chiral catalysts by hydrogenation of a bicyclic precursor of **3** [7]. In these syntheses, the hydrogenation was always performed before formation of the five-membered ring and did not permit full exploitation of the chiral carbapenem skeleton as an asymmetric inductor. In this paper we wish to report a full description of the synthesis of 1-methylenecarbapenam and its hydrogenation as a straightforward method leading to new 1β-methylcarbapenem precursors.

Results and discussion

In a preliminary account, we developed a short and efficient synthesis [8] of the 1-methylenecarbapenam **5** from 4-acetoxy-3-{(*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl}-azetidin-2-one **4**, the key step being the construction of the bicyclic ring using π-allyl palladium methodology. We stipulated then that the exocyclic double bond

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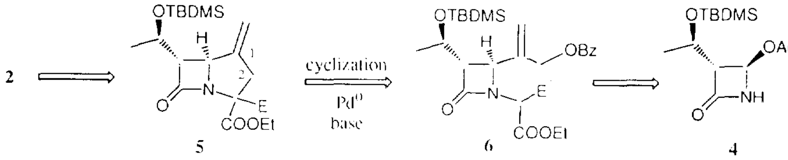


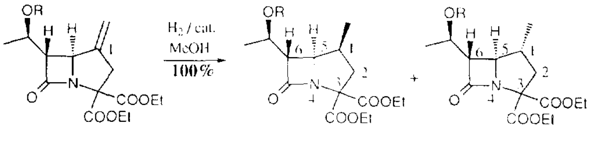
Scheme 1

at the C-1 position is an interesting precursor of the 1β-methyl group by stereoselective hydrogenation, as shown in scheme 1.

The allylic benzoates **6** were obtained from the alcohol **7** (scheme 2), easily prepared as reported, by protection of the alcohol as a benzoyl group, followed by introduction of the acetic ester chain on the nitrogen atom by condensation with ethyl 2-bromoacetate. Substitution at the α-position of the ester group by different electron-withdrawing groups (ethoxycarbonyl, benzyloxycarbonyl or phenylthio), leading to the intermediates **6**, has been shown to increase the acidity of the protons and to be necessary for the cyclization to occur. The cyclization reaction led to the expected bicyclic methylenecarbapenams **5**, appropriate for the hydrogenation studies, in good yields using sodium or potassium hydride as a base and catalytic Pd/dppe (1,2-diphenylphosphinoethane).

The second key step in this synthesis was the stereoselective reduction of the double bond of **5**. The study first focused on the compound **5a** (E = CO_2Et) leading to only two possible diastereomers **10a** and **10b** (scheme 3). We also studied the hydrogenation of the deprotected intermediate **11** to demonstrate the possible steric role of the bulky *tert*-butyldimethylsilyl (TBDMS) group. The reactions were carried out in methanol using achiral catalysts such as Pd/C or Raney Ni. The results are presented in table I.

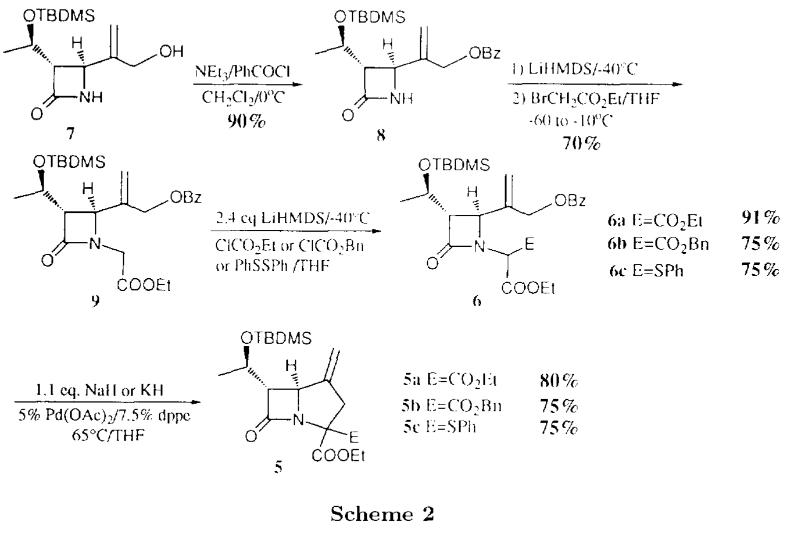
The reduction of **5a** with Pd/C at 25 °C, when R = TBDMS, gives the β-isomer in 30% de (diastereomeric excess) (table I, entry 1). When the reaction is carried out at 0 °C under the same conditions (entry 2) we obtained a better de of 40%. When R = H, using Raney Ni at 0 °C, the formation of the undesired α-stereoisomer was slightly predominant (30% de) (entry 3). However, in only one case were the two diastereomers **10a** and **10b** obtained easily separable by silica gel chromatography and their α- or β-structure was assigned by ^1H NMR nOe (500 MHz). The β isomer **10a** shows an nOe effect between the 1-methyl group and H-6 when the α isomer shows an nOe effect between the 1-methyl group and H-5. The de values were measured by ^1H NMR (250 MHz), since the proton shifts, particularly on the β-lactam ring, were very different in the two diastereomers.



		1β-methyl	1α-methyl
R=TBDMS	5a	10a	10b
R=H	11	12a	12b

Scheme 3

Our results can be explained by the three-dimensional structure of the bicyclic compound **5**. Indeed, when R = TBDMS (fig 1), the stereocontrol of the hydrogenation is not due to the bulky *tert*-butyldimethylsilyl group but rather to the bent structure of the bicylic system itself. The more hindered face is then the β-face and the hydrogenation proceeds predominantly at the α-face to give the expected 1β-methyl compound. On the other hand, when R = H (fig 1), the more hindered face is still the β-face but it is possible that the catalyst can coordinate between the oxygen of the side chain



Scheme 2

Table I. Hydrogenation studies using various catalysts and temperature conditions.

Entry	*R*	*Conditions*	*Ratio β/α*
1	TBDMS	Pd/C, rt	65:35
2	TBDMS	Pd/C, 0 °C	70:30
3	H	Ni Raney, 0 °C	35:65

and the double bond on the β-face. The hydrogenation then proceeds predominantly at the β-face to give the α-methyl compound [9].

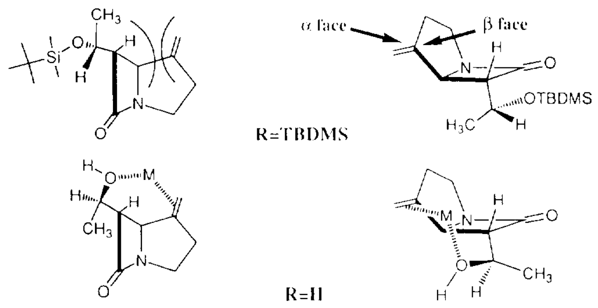


Fig 1

Conclusion

In summary, we have shown that we can easily access 1β-methylcarbapenem derivatives by using our two cyclization/hydrogenation key steps. The π-allyl palladium strategy was very efficient for the five-membered ring formation and the hydrogenation of the *exo* double bond with classical non-chiral catalysts produced quantitatively a mixture of α- and β-isomers which after separation, afforded the pure β-isomer in 70% yield, by using the asymmetric induction of the rigid bicyclic carbapenem skeleton.

Experimental section

All solvents were dried and distilled prior to use or were HPLC grade. All reagents were of commercial origin from freshly opened containers or distilled before use. All reactions were carried out under argon with exclusion of moisture. LiHMDS was prepared in situ from BuLi 2.5 M in hexane and HMDS, 30 min at −40 °C in THF. Sodium and potassium hydride, stored as suspensions in oil, were washed before use with pentane. Sat NH_4Cl = saturated aqueous solution of ammonium chloride. ^1H and ^{13}C NMR spectra were recorded on Bruker AC 200 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 983G spectrophotometer. Mass spectra were recorded on Helwett-Packard HP 5989. Elementary analysis were done at the Regional Service of Microanalysis (Université Pierre-et-Marie-Curie, Paris).

(3S,4S)-4-{1-[(Benzoyloxy)methyl]ethenyl}-3-{(R)-1-[(t-butyldimethylsilyl)oxy]ethyl}azetidin-2-one **8**

To a solution of **7** (2.6 g, 9 mmol) in CH_2Cl_2 (90 mL) were added dropwise at 0 °C, 1.1 mL (9.5 mmol) of benzoyl chloride and 2.5 mL (18 mmol) of triethylamine. The solution was stirred 12 h at 0 °C, neutralized with 50 mL of sat NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried on Na_2SO_4, filtrated and concentrated. Purification by silica-gel flash chromatography (ether/cyclohexane, 7:3) gave the expected compound (3.15 g, 90%) as a white crystalline solid: $[\alpha]_D^{25} = -37$ (*c* 1.35, CH_2Cl_2); mp = 76 °C.

IR (neat) 1 765 (ν C=O cycle), 1 725 (ν C=O benzoate), 1 605 (ν C=C).

^1H NMR (200 MHz, $CDCl_3$) δ 0.1 (s, 6H), 0.9 (s, 9H), 1.25 (d, 3H, J = 6.3 Hz), 3.1 (m, 1H), 4.3–4.2 (m, 1H), 4.35 (s, 1H), 4.8 (d, 1H, J = 13.3 Hz), 4.95 (d, 1H, J = 13.3 Hz), 5.4 (s, 2H), 6.2 (s, 1H), 8–7.3 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 168, 166, 142.6, 133, 129.5, 128.4, 114.5, 65.6, 65, 64.3, 51.5, 25.6, 22.5, 17.8, −4.4, −5.

Anal calc for $C_{21}H_{31}NO_4Si$ (M = 389.57): C 64.75, H 8.02, N 3.59; Found: C 64.71, H 8.05, N 3.52.

(3S,4S)-4-{1-[(Benzoyloxy)methyl]ethenyl}-3-{(R)-1-[(t-butyldimethylsilyl)oxy]ethyl}-1-[(ethoxycarbonyl)methyl]azetidin-2-one **9**

To a solution of LiHMDS (2.1 mmol) in THF (16 mL) was added dropwise at −60 °C, a solution of **8** (778 mg, 2 mmol) in THF (2 mL). The solution was stirred 30 min at −60 °C and 244 μL (2.2 mmol) of ethyl 2-bromoacetate were added. The solution was stirred from −60 to −5 °C over 2.5 h, neutralized with sat NH_4Cl and extracted with ether. The organic layer was dried on Na_2SO_4, filtrated and concentrated. Purification by silica-gel medium pressure liquid chromatography (ether/cyclohexane, 1:1) gave the expected compound (665 mg, 70%) as a colorless oil: $[\alpha]_D^{25} = -46$ (*c* 0.65; $CHCl_3$).

IR (neat) 1 767 (ν C=O cycle); 1 740 (ν C=O ester); 1 725 (ν C=O benzoate); 1 601 (ν C=C).

^1H NMR (200 MHz, $CDCl_3$) δ 0.1 (s, 6H), 0.9 (s, 9H), 1.25 (m, 6H), 3.2 (dd, 1H, J = 2.2 and 6.6 Hz), 3.7 (d, 1H, J = 17.8 Hz), 4.3–4.1 (m, 4H), 4.45 (d, 1H, J = 2.2 Hz), 4.8 (d, 1H, J = 13.8 Hz), 4.95 (d, 1H, J = 13.8 Hz), 5.35 (s, 1H), 5.4 (s, 1H), 8–7.4 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 167.9, 167.8, 166, 140.7, 133.1, 129.5, 128.4, 116.7, 66.2, 65, 63.8, 61.3, 57.7, 41.7, 25.6, 22.5, 17.8, 14, −4.5, −4.8.

Anal calc for $C_{25}H_{37}NO_6Si$ (M = 475.66): C 63.13, H 7.84, N 2.94; Found: C 63.11, H 7.89, N 2.89.

(3S,4S)-4-{1-[(Benzoyloxy)methyl]ethenyl}-3-{(R)-1-[(t-butyldimethylsilyl)oxy]ethyl}-1-[bis(ethoxycarbonyl)methyl]azetidin-2-one **6a**

To a solution of LiHMDS (2.67 mmol) in THF (10 mL) were added dropwise at −78 °C, a solution of **9** (528 mg, 1.11 mmol) in THF (3 mL) and 255 μL (2.67 mmol) of ethyl chloroformate. The solution was stirred 2 h at −78 °C, neutralized with 10 mL of sat NH_4Cl and extracted with ethyl acetate. The organic layer was dried on $MgSO_4$, filtrated and concentrated. Purification by silica-gel flash chromatography (ether/cyclohexane, 3:7) gave the expected compound (556 mg, 91%) as a colorless oil: $[\alpha]_D^{25} = -41$ (*c* 0.5; CH_2Cl_2).

IR (neat) 1 770 (ν C=O cycle); 1 740 (ν C=O esters); 1 725 (ν C=O benzoate); 1 650 (ν C=C).

^1H NMR (200 MHz, $CDCl_3$) δ 0.1 (s, 6H), 0.9 (s, 9H), 1.35–1.2 (m, 9H), 3.27 (dd, 1H, J = 2 and 5.2 Hz), 4.35–4.1 (m, 5H), 4.7 (d, 1H, J = 2 Hz), 4.87 (d, 1H, J = 10.8 Hz), 4.97 (d, 1H, J = 10.8 Hz), 5.1 (s, 1H), 5.4 (s, 1H), 5.5 (s, 1H), 7.4–8.1 (m, 5H).

^{13}C NMR (50 MHz, CDCl$_3$) δ 168.3, 166.0, 164.6, 140.6, 133, 130, 129.5, 128.3, 118.3, 66.1, 64.2, 63.5, 62.3, 58.4, 57, 25.6, 22.5, 17.8, 13.8, −4.5, −4.8.

Anal calc for $C_{28}H_{41}NO_8Si$ (M = 547.72): C 61.40, H 7.54, N 2.56; Found: C 61.39, H 7.56, N 2.50.

(3S,4S)-4-{1-[(Benzoyloxy)methyl]ethenyl}-3-{(R)-1-[(t-butyldimethylsilyl)oxy]ethyl}-1-{[(ethoxycarbonyl)benzyloxycarbonyl]methyl}-azetidin-2-one **6b**

To a solution of LiHMDS (0.985 mmol) in THF (5 mL) were added dropwise at −78 °C, a solution of **9** (195 mg, 0.41 mmol) in THF (2 mL) and 150 μL (0.985 mmol) of benzyl chloroformate. The solution was stirred 2 h at −78 °C, neutralized with 5 mL of sat NH_4Cl and extracted with ethylacetate. The organic layer was dried on $MgSO_4$, filtrated and concentrated. Purification by silica-gel flash chromatography (ether/cyclohexane, 3:7) gave the expected compound (184 mg, 75%) as a colorless oil, mixture of two diastereomers.

IR (neat) 1 770 (ν C=O cycle), 1 745 (ν C=O esters), 1 725 (ν C=O benzoate), 1 653 (ν C=C).

^{1}H NMR (200 MHz, CDCl$_3$) δ 0.07 (s, 6H), 0.85 (s, 9H), 1.15–1.3 (m, 6H), 3.3 (m, 1H), 4.1–4.3 (m, 3H), 4.65 (dd, 1H, J = 2.5 and 5.1 Hz), 4.7–5.45 (m, 7H), 7.32–7.35 (m, 5H), 7.4–8.1 (m, 5H).

^{13}C NMR (50 MHz, CDCl$_3$) δ 168.3, 165.8, 164.6, 140.6, 134.6, 133, 129.9, 129.5, 128.5, 128.3, 118.4, 118.2, 67.8, 66.1, 64.3, 64.2, 63.4, 62.3, 58.4, 57.0, 25.6, 22.5, 17.8, 13.8, 13.7, −4.5, −4.8.

Anal calc for $C_{33}H_{43}NO_8Si$ (M = 609.79): C 65.00, H 7.11, N 2.30; Found: C 65.06, H 7.15, N 2.28.

(3S,4S)-4-{1-(Benzoyloxymethyl)ethenyl}-3-{(R)-1-[(t-butyldimethylsilyl)oxy]ethyl}-1-{[(phenylthio)ethoxycarbonyl]methyl}azetidin-2-one **6c**

To a solution of LiHMDS (1.03 mmol) in THF (1 mL) were added dropwise at −78 °C, a solution of **9** (203 mg, 0.427 mmol) in THF (2 mL) and a solution of diphenyl sulfide (224 mg, 1.03 mmol) in THF (1 mL). The solution was stirred 2 h at −78 °C, neutralized with 5 mL of sat NH_4Cl and extracted with ethyl acetate. The organic layer was dried on $MgSO_4$, filtrated and concentrated. Purification by silica-gel flash chromatography (ether/cyclohexane, 2:8) gave the expected compound (185 mg, 75%) as a colorless oil, mixture of two diastereomers.

IR (neat): 1 760 (ν C=O cycle), 1 740 (ν C=O ester), 1720 (ν C=O benzoate), 1 650 (ν C=C).

^{1}H NMR (200 MHz, CDCl$_3$) δ 0.01–0.1 (m, 6H), (0.81, 0.84 (s + s, 9H)), (1.13, 1.19 (d + d, 3H, J = 6.1 Hz)), (1.25, 1.26 (t + t, 3H, J = 7.1 Hz)), 3.2–3.3 (m, 1H), 4.1–4.25 (m, 3H), (4.34, 4,69 (d, 1H, J = 2.6 Hz)), 4.8–5.05 (m, 2H), 5.4 (s, 1H), 5.54 (d, 1H, J = 8.5 Hz), (5.7, 5.95 (s + s, 1H)), 7.3–8.1 (m, 10H).

^{13}C NMR (50 MHz, CDCl$_3$) δ 168.4, 167.3, 166.1, 165.9, 140.4, 133, 132.2, 132, 129.9, 129.5, 129.2, 128.3, 128.2, 119.7, 119.2, 67.3, 65.5, 63.6, 63.3, 62.4, 62.1, 59.2, 58.9, 58.5, 58.2 , 25.6, 22.5, 22.2, 17.7, 13.8, −4.5, −4.7, −5.

Anal calc for $C_{31}H_{41}NO_6SSi$ (M = 583.81): C 63.78, H 7.08, N 2.40; Found: C 63.71, H 7.04, N 2.41.

(5S,6S)-6-{(R)-1-[(t-Butyldimethylsilyl)oxy]ethyl}-2,2-bis(ethoxycarbonyl)-4-methylidene-1-azabicyclo[3.2.0]heptan-7-one **5a**

To a suspension of sodium hydride (8.5 mg, 0.354 mmol) in THF (1 mL), was added a solution of **6a** (176 mg, 0.32 mmol) in THF (1 mL). The mixture was stirred 30 min at 25 °C and the catalyst, preformed 1 h at 25 °C from $Pd(OAc)_2$ (3.6 mg, 0.016 mmol) and dppe (9.5 mg, 0.024 mmol) in THF (1 mL), was added. The solution was stirred 3 h at 65 °C, neutralized with sat NH_4Cl and extracted with ether. The organic layer was dried on Na_2SO_4, filtrated and concentrated. Purification by silica-gel flash chromatography (cyclohexane/ether, 8:2) gave the expected compound (108 mg, 80%) as a colorless oil: $[\alpha]_D^{25} = +69$ (c 1.1, CHCl$_3$).

IR (neat) 1 775 (ν C=O cycle); 1 740 (ν C=O ester); 1 660 (ν C=C); 900 (δ C=C).

^{1}H NMR (400 MHz, CDCl$_3$), δ 0.08 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 1.28 (d, 3H, J = 6.5 Hz), 1.33 (t, 6H, J = 7 Hz), 3.05 (dd, 1H, J = 6.5 and 2.5 Hz), 3.15 (d, 1H, J = 17 Hz), 3.48 (d, 1H, J = 17 Hz), 4.4–4.2 (m, 6H), 5.13 (d, 1H, J = 2 Hz), 5.25 (d, 1H, J = 2 Hz).

^{13}C NMR (50 MHz, CDCl$_3$) δ 174.2, 168.2. 165.6, 145.3, 110.0, 72.3, 67.2, 65.7, 62.5, 62.0, 58.6, 44.3, 25.6, 22.4, 17.8, 13.8, 13.6, −4.6, −5.1.

Anal calc for $C_{21}H_{35}NO_6Si$ (M = 425.59): C 59.27, H 8.29, N 3.29. Found: C 59.24, H 8.30, N 3.21.

(5S,6S)-2-Benzyloxycarbonyl-6-{(R)-1-[(t-butyldimethylsilyl)oxy]ethyl}-2-ethoxycarbonyl-4-methylidene-1-azabicyclo[3.2.0]heptan-7-one **5b**

To a suspension of sodium hydride (8 mg, 0.33 mmol) in THF (1 mL), was added a solution of **6b** (184 mg, 0.302 mmol) in THF (2 mL). The mixture was stirred 30 min at 25 °C and the catalyst, preformed 1 h at 25 °C from $Pd(OAc)_2$ (3.4 mg, 0.015 mmol) and dppe (8.9 mg, 0.023 mmol) in THF (1.5 mL), was added. The solution was stirred 3 h at 65 °C, neutralized with sat NH_4Cl and extracted with ether. The organic layer was dried on Na_2SO_4, filtrated and concentrated. Purification by silica-gel flash chromatography (diethyl ether/cyclohexane, 2:8) gave the expected compound (106 mg, 72%) as a colorless oil, mixture of two diastereomers.

IR (neat): 1 775 (ν C=O cycle); 1 745 (ν C=O esters); 1 661 (ν C=C).

^{1}H NMR (200 MHz, CDCl$_3$) δ 0.02 (s, 6H), 0.8 (s, 9H), 1–1.2 (m, 6H), 2.95 (m, 1H), 3–3.45 (m, 2H), 4–4.3 (m, 4H), 5–5.3 (m, 4H), 7.3 (s, 5H).

^{13}C NMR (50 MHz, CDCl$_3$) δ 174.4, 168.1, 165.6, 145.1, 134.8, 128, 110.2, 72.7, 68, 67.5, 67.3, 65.8, 65.5, 62.6, 62.1, 58.8, 58.6, 44.2, 25.6, 22.5, 17.8, 13.7, 13.6, −4.3, −5.

Anal calc for $C_{26}H_{37}NO_6Si$ (M = 487.66): C 64.04, H 7.65, N 2.87. Found: C 64.14, H 7.69, N 2.74.

(5S,6S)-6-{(R)-1-[(t-Butyldimethylsilyl)oxy]ethyl}-2-ethoxycarbonyl-4-methylidene-2-phenylthio-1-azabicyclo[3.2.0]heptan-7-one **5c**

To a suspension of potassium hydride (14 mg, 0.35 mmol) in THF (2 mL), was added a solution of **6c** (185 mg, 0.317 mmol) in THF (2 mL). The mixture was stirred 15 min at 25 °C and the catalyst, preformed 1 h at 25 °C from $Pd(OAc)_2$ (3.6 mg, 0.016 mmol) and dppe (9.5 mg, 0.024 mmol) in THF (1.5 mL), was added. The solution was stirred 3 h at 25 °C, neutralized with sat NH_4Cl and extracted with ether. The organic layer was dried on

Na_2SO_4, filtrated and concentrated. Purification by silica-gel flash chromatography (ether/cyclohexane, 2:8) gave the expected compound (33 mg, 33%) as a colorless oil, mixture of two diastereomers.

IR (neat): 1 770 (ν C=O cycle), 1 740 (ν C=O ester), 1 655 (ν C=C).

^1H NMR (200 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.9 (s, 9H), 1.1–1.3 (m, 6H), 2.97 (dd, 1H, J = 3 and 7 Hz), 2.78–3.42 (m, 2H), 4.1–4.3 (m, 3H), 4.35 (m, 1H), 5.1–5.25 (m, 2H), 7.25–7.8 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 174.5, 167.5, 145.9, 135.9, 134.9, 130.8, 129.2, 128.6, 110.1, 77, 67.9, 66.5, 65.5, 65, 62, 58.7, 57.6, 46.2, 25.7, 22.4, 17.9, 13.6, −4.5, −4.9.

Anal calc for $C_{24}H_{35}NO_4SSi$ (M = 461.69): C 62.44, H 7.64, N 3.03. Found: C 62.49, H 7.66, N 3.00.

(5S,6S)-2,2-Bis(ethoxycarbonyl)-6-[(R)-1-hydroxyethyl]-4-methylidene-1-azabicyclo[3.2.0]heptan-7-one **11**

To a solution of **5a** (348 mg, 0.82 mmol) in THF (4 mL), were added dropwise at 0 °C 820 μL (0.9 mmol) of Bu_4NF 1.1 M in THF. The solution was stirred for 3 h at 25 °C, neutralized by sat NH_4Cl and extracted with ether. The organic layer was washed with brine, dried on Na_2SO_4, filtrated and concentrated. Purification by silica-gel flash chromatography (cyclohexane/ethyl acetate, 6:4) gave the expected compound (198 mg, 78%) as a colorless oil: $[\alpha]_D^{25}$ = +83 (*c* 1.5, $CHCl_3$).

IR (neat): 3 500 (ν OH), 1 770 (ν C=O cycle), 1 740 (ν C=O esters), 1 660 (ν C=C).

^1H NMR (200 MHz, $CDCl_3$) δ 1.1–1.3 (m, 9H), 2.9–3.05 (m, 2H), 3.4 (m, 1H), 4–4.3 (m, 6H), 5.05 (d, 1H, J = 2 Hz), 5.15 (d, 1H, J = 2 Hz).

^{13}C NMR (50 MHz, $CDCl_3$) δ 174.5, 168.1, 165.4, 144.7, 110.6, 73, 66.9, 65.1, 62.7, 62.2, 58.6, 44.1, 21.6, 13.8, 13.7.

Anal calc for $C_{15}H_{21}NO_6$ (M = 311.33): C 57.87, H 6.80, N 4.50. Found: C 57.88, H 6.83, N 4.48.

Hydrogenation of the bicyclic compound 5a

A solution of **5a** (553 mg, 1.3 mmol) and 5% Pd/C in methanol (30 mL), was stirred 12 h under hydrogen (1 atm), filtrated through celite and concentrated to give 553 mg (100%) of the expected compound as a mixture of two diastereomers easily separable by silica-gel chromatography (cyclohexane/ether, 8:2):

IR (neat): 1 775 (ν C=O cycle); 1 740 (ν C=O esters).

Anal calc for $C_{21}H_{37}NO_6Si$ (M = 427.61): C 58.99, H 8.72, N 3.28; Found: C 58.91, H 8.73, N 3.25.

(4S,5R,6S)-6-{(R)-1-[(t-Butyldimethylsilyl)oxy]ethyl}-2,2-bis(ethoxycarbonyl)-4-methyl-1-aza-bicyclo[3.2.0]heptan-7-one **10a**

The β-methyl isomer was obtained as a white crystallized solid (389 mg, 70%); mp = 52 °C; $[\alpha]_D^{25}$ = +126 (*c* 1.2, $CHCl_3$).

^1H NMR (500 MHz, $CDCl_3$) δ −0.02 (s, 6H), 0.8 (s, 9H), 1.04 (d, 3H, J = 6.7 Hz), 1.13 (d, 3H, J = 6.1 Hz), 1.2 (t, 6H, J = 8.4 Hz), 2.21 (dd, 1H, J = 9.1 and 12.7 Hz), 2.38–2.5 (m, 2H), 3 (dd, 1H, J = 2.5 and 6.5 Hz), 3.88 (dd, 1H, J = 2.5 and 7.4 Hz), 4.05–4.25 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 174.5, 168.4, 165.6, 73.6, 66.2, 62.3, 61.9, 59.8, 59.7, 44.7, 32.1, 25.6, 22.5, 17.9, 15.3, 13.9, 13.7, −4.3, −5.

(4R,5R,6S)-6-{[(R)-1-[(t-Butyldimethylsilyl)oxy]ethyl}-2,2-bis(ethoxycarbonyl)-4-methyl-1-aza-bicyclo[3.2.0]heptan-7-one **10b**

The α-methyl isomer was obtained as a colorless oil (166 mg, 30%).

^1H NMR (500 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.8 (s, 9H), 1.04 (d, 3H, J = 6.2 Hz), 1.14 (d, 3H, J = 6.1 Hz), 1.2 (t, 6H, J = 8.4 Hz), 2.22 (dm, 1H, J = 12.8 Hz), 2.28 (m, 1H), 2.64 (dd, 1H, J = 12.8 and 5.6 Hz), 2.85 (d, 1H, J = 5.7 Hz), 3.3 (d, 1H, J = 8.5 Hz), 4.1 (m, 1H), 4.16 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 171.6, 168.8, 167.4, 71.9, 65.5, 63.4, 62.3, 61.8, 48.4, 38.4, 25.6, 22.5, 17.9, 14.9, 13.9, 13.8, −4.3, −5.

Hydrogenation of the bicyclic compound 11

A solution of **11** (60 mg, 0.193 mmol) and 5% Raney Ni in methanol (3 mL), was stirred 12 h under hydrogen (1 atm), filtered through celite and concentrated to give 60 mg (100%) of the expected compound as an inseparable mixture of two diastereomers characterized by NMR.

IR (neat): 3 500 (ν OH); 1 770 (ν C=O cycle); 1 740 (ν C=O esters).

Anal calc for $C_{15}H_{23}NO_6$ (M = 313.35): C 57.50, H 7.40, N 4.47. Found: C 57.52, H 7.43, N 4.41.

(4S,5R,6S)-2,2-Bis(ethoxycarbonyl)-6-[(R)-1-hydroxy-ethyl]-4-methyl-1-azabicyclo[3.2.0]heptan-7-one **12a**

^1H NMR (200 MHz, $CDCl_3$) δ 1.1 (d, 3H, J = 6.5 Hz), 1.2–1.35 (m, 9H), 2.1 (s, 1H), 2.25–2.6 (m, 3H), 3.1 (dd, 1H, J = 3.1 and 6.7 Hz), 4 (dd, 1H, J = 3.1 and 7.4 Hz), 4.1–4.4 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 174.6, 168.4, 165.5, 73.8, 65.5, 62.5, 62.1, 59.5, 59.3, 44.7, 32.1, 21.6, 15.2, 13.9, 13.7.

(4R,5R,6S)-2,2-Bis(ethoxycarbonyl)-6-[(R)-1-hydroxy-ethyl]-4-methyl-1-azabicyclo[3.2.0]heptan-7-one **12b**

^1H NMR (200 MHz, $CDCl_3$) δ 1.15 (d, 3H, J = 6.1 Hz), 1.2–1.4 (m, 9H), 2.1 (s, 1H), 2.15–2.5 (m, 2H), 2.75 (m, 1H), 3 (dd, 1H, J = 2 and 6.3 Hz), 3.45 (dd, 1H, J = 2 and 8.3 Hz), 4.1–4.3 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 171.7, 168.6, 167.2, 72.2, 65.1, 62.8, 62.5, 62, 48.3, 38.4, 21.6, 14.8, 13.9, 13.8.

References

1 Morin RB, Gorman M, *Chemistry and Biology of β-Lactams Antibiotics*, Academic, New York, 1982, vols 1–3

2 a) Kahan JS, Kahan F, Goegelman R, Currie SA, Jackson M, Stapley EO, Miller TW, Miller AK, Hendlin D, Mochales S, Hernandez S, Woodruf HB, Birnbaum J, *J Antibiot* (1979) 32, 1
b) Albers-Schönberg G, Arison BH, Hensens OD, Hirshfield J, Hoogsteen K, Kaczka EA, Rhodes RE, Kahan JS, Kahan FM, Ratcliffe RW, Walton E, Ruswinkle LJ, Morin RB, Christensen BG, *J Am Chem Soc* (1978) 100, 6491

3 Kropp H, Sundelof JG, Hadju R, Kahan FM, *Antimicrob Agents Chemotherapy* (1982) 22, 62

4 a) Shih DH, Baker F, Cama L, Christensen BG, *Heterocycles* (1984) 21, 29
b) Shih DH, Cama L, Christensen BG, Abstract 33,

23rd Interscience Conference on Antimicrobiol Agents & Chemiotherapy, Las Vegas, NV, 1983

5 a) Shih DH, Baker F, Cama L, Christensen BG, *Heterocycles* (1984) 21, 29
b) Imori T, Shibasaki M, *Tetrahedron Lett* (1986) 27, 2149
c) Endo M, Droghini R, *Can J Chem* (1988) 66, 1400
d) Kim CU, Luh B, Partyka RA, *Tetrahedron Lett* (1987) 28, 507
e) Ito Y, Terashima S, *Tetrahedron Lett* (1987) 28, 6625
f) Shirai F, Nakai T, *J Org Chem* (1987) 52, 5491
g) Martel A, Davis JP, Bachand C, Corbeil J, Menard M, *Can J Chem* (1988) 66, 1537
h) Deziel R, Favreau D, *Tetrahedron Lett* (1986) 27, 5687
i) Fliri H, Mak Ching-Pong, *J Org Chem* (1985) 50, 3438
j) Nagao Y, Kumagai T, Tamai S, Abe T, Kuramoto Y, Taga T, Aoyagi S, Nagase Y, Ochiai M, Inoue Y, Fujita E, *J Am Chem Soc* (1986) 108, 4673
k) Nagao Y, Kumagai T, Nagase Y, Tamai S, Inoue Y, Shiro M, *J Org Chem* (1992) 57, 4232
l) Fuentes LM, Shinkai I, Salzmann TN, *J Am Chem Soc* (1986) 108, 4675
m) Shibata T, Lino K, Takana T, Hashimoto T, Kameyama Y, Sugimura Y, *Tetrahedron Lett* (1985) 26, 4739
n) Meyers AI, Sowin TJ, *J Org Chem* (1988) 53, 4156

6 Kitamura M, Nagai K, Hsiao Y, Noyori R, *Tetrahedron Lett* (1990) 31, 549

7 Fuentes LM, Shinkai I, King A, Purick R, Reamer RA, Schmitt SM, Cama L, Christensen BG, *J Org Chem* (1987) 52, 2563

8 Roland S, Durand JO, Savignac M, Genêt JP, Jung F, *Tetrahedron Lett* (1995) 36, 3007

9 For hydroxyl participating group see review: Hoveyda, AH, Evans DA, Fu GC, *Chem Rev* (1993) 93, 1307