Synthesis of 1β-Methylcarbapenem Antibiotic Precursors by Cyclization Using π-Allylpalladium Complexes

Jean-Christophe Galland,[a] Sylvain Roland,[a] Joël Malpart,[a] Monique Savignac,[a] and Jean-Pierre Genet*[a]

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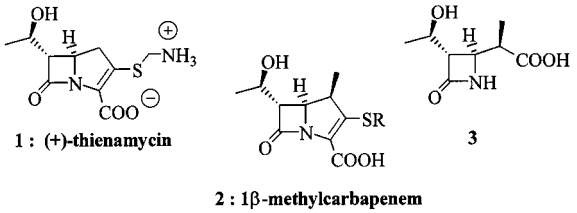
An efficient diastereoselective multi-step synthesis of bicyclic 1β-methylcarbapenem antibiotic precursors has been developed, starting from the commercially available 4-acetoxyazetidin-2-one **4**. Chiral ruthenium catalysts are used in the hydrogenation step to control the β-stereochemistry at the 1-position, and a π-allylpalladium ring-closure strategy is used to form the functionalized carbapenem skeleton.

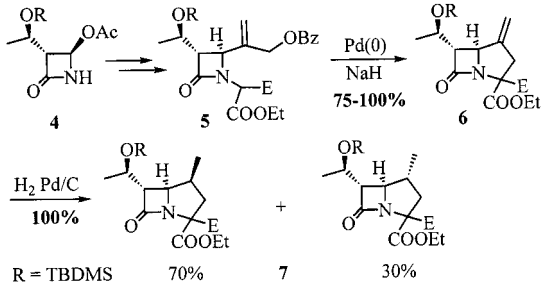
Introduction

Since the discovery by the Merck group in the early 1980s of (+)-thienamycin (**1**),[1] a natural fungal metabolite, the carbapenems and, more recently, the 1β-methylcarbapenems **2**,[2] have attracted considerable attention as some of the more promising β-lactam antibiotics due to their chemical and metabolic stabilities as well as their potent antimicrobial activities. Owing to the lack of practical fermentation methods, various synthetic efforts have been initiated to construct the bicyclic skeleton of thienamycin and numerous modifications have since been made aimed at increasing its stability.[3] This has led to a wide family of carbapenem antibiotics with enhanced activities. The more stable 1β-methylcarbapenems **2**[4] have aroused particular interest since the control of the the four stereogenic centers represents an interesting synthetic challenge. Extensive studies have shown the carboxylic acid **3**, in which all the stereogenic centers are installed, to be an effective intermediate en route to such systems.



Scheme 1

Recently, we succeeded in demonstrating the efficiency of π-allylpalladium methodology in forming the five-membered ring of the carbapenems,[5] and we reported the synthesis of bicyclic intermediates **6**, which were obtained in very good yields by cyclization of the appropriate benzoate precursors **5** using catalytic Pd^0 (Scheme 2). Unfortunately, however, hydrogenation[6] of the exocyclic double bond using non-chiral catalysts led to the expected 1-methyl compound **7** as a 70:30 mixture of the β and α diastereomers.



Scheme 2

With the aim of increasing the diastereoselectivity and of avoiding the final separation step, we developed a second synthetic approach using π-allylpalladium methodology, in which the configuration of the carbon atom at the 1-position was easily controlled. Indeed, we envisaged that the five-membered ring of the carbapenems could also be obtained from a π-allylpalladium intermediate in which the four stereogenic centers were already present prior to cyclization (Scheme 3). This alternative approach appeared to be particularly attractive as the 1-methyl configuration could be introduced at an early stage of the synthesis by hydrogenation of the allylic alcohol **8**[7] under appropriate conditions.[8] The 1β-methyl alcohol **9** could then be used as a precursor of intermediates **15**, suitable for the construction of the carbapenem skeleton.

In this paper, we wish to report our multi-step preparation of intermediates **15**, as well as the results of studies on the palladium-mediated cyclization reactions.

Results and Discussion

The first key step of our procedure was to obtain the 1-methyl alcohol **9** with high diastereoselectivity. This was efficiently achieved by catalytic hydrogenation of **8** using chiral ruthenium complexes.[9] When the reaction was car-

[a] Ecole Nationale Supérieure de Chimie de Paris, Laboratoire de Synthèse Sélective Organique et Produits Naturels UMR CNRS 7573,
11, rue Pierre et Marie Curie, F-75231 Paris, France
Fax: (internat.) + 33-1/44071062
E-mail: genet@ext.jussieu.fr

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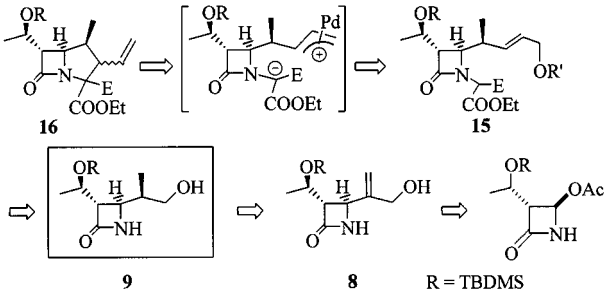
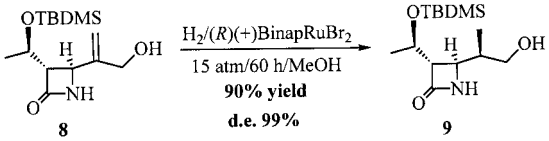
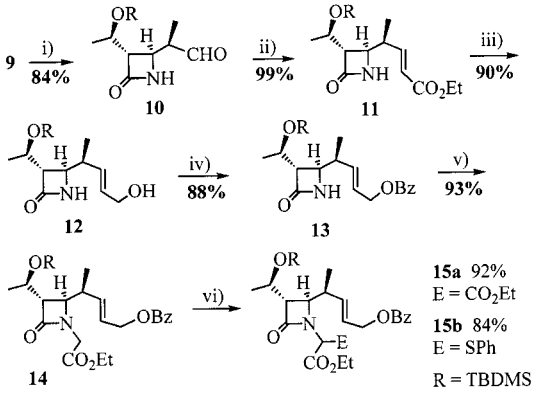


Scheme 3

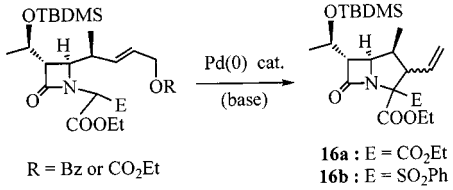
ried out under 15 atm of hydrogen at 25°C in the presence of the chiral ligand (*R*)-(+)-BINAP, the β-methyl diastereomer **9** was obtained in 90% yield with a *de* > 99% (Scheme 4). The catalytically active species (*R*)-(+)-BinapRuBr$_2$ was easily obtained in situ by treatment of the commercially available (cyclooctadiene)(2-methylallyl)$_2$Ru complex with the chiral ligand (*R*)-(+)-BINAP and methanolic hydrobromic acid solution. Similar diastereomeric excesses could be achieved using the chiral ligand (*R*)-MeO-BIPHEP.



Scheme 4



Scheme 5. i) a) $(ClCO)_2$, DMSO, CH_2Cl_2, −60°C, b) Et*i*Pr$_2$N; ii) $Ph_3P{=}CHCO_2Et$, THF, 60°C; iii) DIBALH, THF, −78°C; iv) PhCOCl, Et_3N, CH_2Cl_2, 0°C; v) LiHMDS, THF, $BrCH_2CO_2Et$, −40°C; vi) LiHMDS, THF, −40°C, $ClCO_2Et$ or PhSSPh



Scheme 6

Primary benzoates **15**, suitable for use in the cyclization study, were then obtained by Swern oxidation of the alcohol **9**, which gave the expected aldehyde **10** in 84% yield, followed by Wittig reaction using (ethoxycarbonyl)methylenetriphenylphosphorane, which led quantitatively to the allylic ester **11** (Scheme 5). In this latter step, no epimerization of any of the stereogenic centers was detected. Reduction to the alcohol **12** using diisobutylaluminium hydride followed by benzoylation gave the expected compound **13** in 80% yield. The azetidinone nitrogen atom was then alkylated using lithium hexamethyldisilazanide and ethyl α-bromoacetate to give the ester **14** in 93% yield. The ethoxycarbonylmethyl chain on the nitrogen atom was subsequently treated with 2.4 equivalents of lithium hexamethyldisilazanide and either ethyl chloroformate or diphenyl disulfide. In this way, the benzoates **15a** and **15b** were obtained in yields of 92% and 84%, respectively.

The palladium-catalyzed cyclization (Scheme 6) was first studied under the conditions that gave the best results in our first synthetic approach.

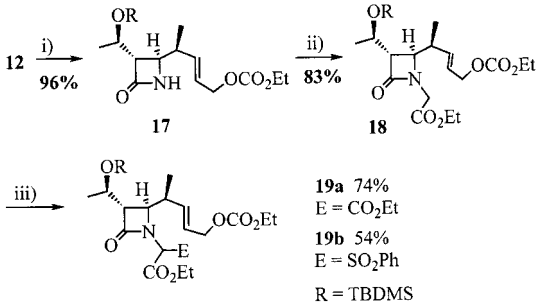
The anions of the two benzoates **15a** and **15b** were generated using sodium or potassium hydride as the base and the reactions were performed in THF in the presence of 0.2 equivalent of Pd/dppe, preformed from Pd(OAc)$_2$ and diphenylphosphanylethane at 25°C. The results of these cyclizations are presented in Table 1.

With E = COOEt (entry 1), the cyclization occurred within 2 h upon heating the solution at 60°C using sodium hydride as the base, giving **16a** in 48% yield as a mixture of two diastereomers. No reaction was observed at lower temperatures. Similar yields (45%) were obtained using potassium hydride instead of sodium hydride (entry 2). These reactions did not go to completion and we noticed that degradation and elimination reactions started to occur at around 40°C. With E = SPh (entry 3), no cyclized compound was observed; only competitive degradation reactions occurred, in particular hydrogenolysis of the thiophenyl group resulting in reversion to the monoester **14**.

To increase the yield of the desired reaction and to avoid competitive elimination reactions, especially in the case of the thiophenyl group, we carried out the cyclization under milder conditions. Specifically, we wanted to avoid the use of hydrides, which seemed to induce the degradation side-reactions. We felt that the carbonate method described by Tsuji,[10] which involves the use of a carbonate rather than an acetate or a benzoate as the leaving group, might be suitable as the reaction occurs under neutral conditions. Indeed, during the formation of the π-allylpalladium intermediate, the base (ethoxide) is gradually generated in situ in the reaction mixture with simultaneous evolution of carbon dioxide.

In order to study this new approach, the appropriate allylic carbonates **19** were synthesized from the allylic alcohol **12** (Scheme 7). Derivatization of the latter with ethyl chloroformate gave **17** in 96% yield. Subsequent steps of the synthesis were the same as those in the case of the benzoates. Because of its instability, the crude thiophenyl intermediate was not isolated in this sequence, but was directly

oxidized to sulfone **19b** using Oxone and wet alumina in refluxing chloroform.[11]



Scheme 7. i) $ClCO_2Et$, pyr, CH_2Cl_2, 0°C; ii) LiHMDS, $BrCH_2CO_2Et$, −78°C, $ClCO_2Et$; iii) LiHMDS, $BrCH_2CO_2Et$, −78°C, $ClCO_2Et$ or a) LiHMDS, −78°C, PhSSPh, b) Oxone, Al_2O_3, $CHCl_3$, ΔT

The results of the cyclizations are presented in Table 1 (entries 4−7). Our first attempt was run with diester **19a**, using 10% of the Pd/dppe complex in THF (entry 4). No reaction was observed at temperatures below 60°C. At this temperature, the cyclization appeared to be very slow and stopped after 0.5 h. Increasing the temperature to reflux did not improve the formation of the desired bicyclic compound. Nevertheless, compared to the benzoate method, the reaction was very clean and the cyclized compound **16a** was isolated in 30% yield with no degradation of the recovered starting carbonate. In order to determine whether the difficulties encountered in forming bicyclic compounds were due to intramolecular steric factors or were directly related to the catalyst, the same reaction was run using 1 equivalent of Pd/dppe (entry 5). To our surprise, the cyclized compound **16a** was then obtained quantitatively, showing that the phosphane used (dppe) was unsuitable and probably led to the generation of an unstable palladium catalyst at the temperature used for the reaction. A significant improvement was achieved using the more "open" phosphane diphenylphosphanylbutane (dppb) instead of dppe (entry 6). Indeed, under these conditions, the cyclization occurred at a lower temperature of 30°C, reflecting the increased reactivity of the catalyst. This reaction gave the expected compound **16a** in 67% yield within 0.5 h. Finally, when the same reaction was performed with the sulfonyl substrate **19b**, the bicyclic intermediate **16b** was obtained in 59% yield (entry 7). Reaction conditions (catalyst, ligand/catalyst ratio, solvent, temperature, etc.) were not optimized.

In summary, we have established a route to optically pure 1β-methylcarbapenem precursors using a π-allylpalladium ring-closure strategy. In our procedure, the β-methyl stereochemistry is efficiently controlled by hydrogenation in the presence of chiral ruthenium catalysts. A practical six-step synthesis of the precursors **15** and **19**, suitable for use in cyclization studies, has been developed starting from the β-methyl alcohol **9**, with overall yields ranging from 32% to 56%. The efficiency of the cyclization reaction has been found to be closely related to the nature of the base and the phosphane used. The best results have been obtained using carbonate as the leaving group and Pd/dppb as the catalyst. This strategy has allowed us direct access to bicyclic compounds **16** functionalized at the 2-position.

Table 1. Results of the palladium-mediated cyclizations

Entry	Substrate	Pd complex	Conditions	Yields[a]
1	**15a**	20% Pd/dppe[c]	NaH, 60°C, 2 h	48%
2	**15a**	20% Pd/dppe	KH, 60°C, 2 h	45%
3	**15b**	20% Pd/dppe	NaH, 60°C, 2 h	−[b]
4	**19a**	20% Pd/dppe	60°C, 3 h	30%
5	**19a**	100% Pd/dppe	60°C, 2 h	100%
6	**19a**	10% Pd/dppb[d]	30°C, 0.5 h	67%
7	**19b**	10% Pd/dppb	30°C, 1 h	59%

[a] Yields of isolated compounds. − [b] Degradation of the starting material. − [c] Preformed from 20 mol-% $Pd(OAc)_2$ and 30% dppe. − [d] Preformed from 10 mol-% $Pd(OAc)_2$ and 20% dppb.

Experimental Section

General: All reactions were carried out under argon with exclusion of moisture. Solvents were dried and distilled prior to use or were HPLC grade. All reagents were of commercial origin and were taken from freshly opened containers or distilled before use. Lithium hexamethyldisilazanide (LiHMDS) was prepared in situ from 2.5 M *n*BuLi in hexane and HMDS, which were allowed to react for 30 min at −40°C in THF. Sodium and potassium hydrides, stored as suspensions in oil, were washed with pentane prior to use. Satd. NH_4Cl denotes saturated aqueous ammonium chloride solution. − ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker AC 200 spectrometer. − Infrared spectra were recorded with a Perkin-Elmer 983G spectrophotometer. − Elemental analyses were performed at the Regional Microanalysis Service (Université Pierre-et-Marie-Curie, Paris).

(3*S*,4*R*)-3-{(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-4-[(1*S*)-(2-hydroxy-1-methyl)ethyl]azetidin-2-one (9): To a solution of 5 mg of (+)-(*R*)-Binap (1 mol-%) and 2.6 mg (1 mol-%) of (cod)(2-methylallyl)$_2$Ru in acetone (1 mL), was added 113 μL (0.018 mmol, 2.2 mol-%) of a 0.16 N solution of hydrobromic acid in methanol. The mixture was stirred for 30 min at 25°C and then the solvents were removed under inert atmosphere. The residue was dried in vacuo and a solution of the alcohol **8** (235 mg, 0.824 mmol) in methanol (3 mL) was added. The resulting solution was stirred for 60 h at 25°C under hydrogen at 17 bar. The mixture was then concentrated and the crude product was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 8:2) to give the expected compound (213 mg, 90%) as a white solid; m.p. 86−88°C. − $[\alpha]_D^{25} = -17$ (c = 1.5, $CHCl_3$). − IR: $\tilde{\nu}$ = 3370, 3060, 2915, 2840, 1755 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 6.46 (s, 1 H), 4.13 (dq, 1 H, J = 6.2 and 8.9 Hz), 3.57 (dd, 1 H, J = 4.6 and 11.8 Hz), 3.47 (dd, 1 H, J = 8.4 and 11.8 Hz), 3.28 (dd, 1 H, J = 1.7 and 8.9 Hz), 3.15 (dd, 1 H, J = 2.1 and 8.9 Hz), 1.85 (m, 1 H), 1.35 (d, 3 H, J = 6.2 Hz), 0.91 (s, 9 H), 0.90 (d, 3 H, J = 7.6 Hz), 0.13 (s, 6 H). − ^{13}C NMR ($CDCl_3$): δ = 168.7, 68.2, 66.0, 62.3, 57.0, 40.1, 25.7, 22.8, 17.9, 13.3, −4.5, −4.6.

(3*S*,4*R*)-3-{(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-4-[(1*S*)-1-(formyl)ethyl]azetidin-2-one (10): To a solution of 88 μL (1.01 mmol) of oxalyl chloride in CH_2Cl_2 (2 mL), a solution of DMSO (167 μL, 2.354 mmol) in CH_2Cl_2 (2 mL) was added dropwise at −60°C. The mixture was stirred for 30 min at −60°C and then a solution of the alcohol **9** (193 mg, 0.672 mmol) in CH_2Cl_2 (4 mL)

was added. After 1 h at the same temperature, 761 μL (4.371 mmol) of diisopropylethylamine was added. The mixture was allowed to warm to 25°C, diluted with 8 mL of water, and extracted with AcOEt (3 × 10 mL). The combined organic layers were washed with water, dried with Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 8:2) to give the expected compound (161 mg, 84%) as a white solid; m.p. 70−75°C. − $[\alpha]_D^{25} = -17$ (c = 1.36, $CHCl_3$). − IR: $\tilde{\nu}$ = 1760, 1725 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 9.76 (s, 1 H), 5.92 (s, 1 H), 4.2 (m, 1 H), 3.94 (dd, 1 H, J = 2.3 and 5.4 Hz), 3.0 (dd, 1 H, J = 2.3 and 5.2 Hz), 2.67 (m, 1 H), 1.23 (d, 3 H, J = 6.2 Hz), 1.21 (d, 3 H, J = 7.2 Hz), 0.88 (s, 9 H), 0.08 (s, 6 H). − ^{13}C NMR ($CDCl_3$): δ = 202.3, 168.4, 65.6, 61.8, 50.4, 49.3, 25.6, 22.5, 17.8, 9.2, −4.4, −5.0. − $C_{14}H_{27}NO_3Si$ (285.46): calcd. C 58.91, H 9.53, N 4.91; found C 58.92, H 9.45, N 4.79.

(3*S*,4*R*)-3-{(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-4-[(1*S*,2*E*)-(3-ethoxycarbonyl-1-methyl)-1-propenyl]azetidin-2-one (11): A solution of aldehyde **10** (70 mg, 0.246 mmol) and (ethoxycarbonyl)methylenetriphenylphosphorane (99 mg, 0.27 mmol) in THF (1 mL) was stirred at 60°C for 2 h. The solvent was then removed, the residue was redissolved in diethyl ether, and the resulting solution was washed with water. The aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated. The crude residue was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 1:1) to give the expected compound (86 mg, 99%) as a white solid; m.p. 62°C. − $[\alpha]_D^{25} = -25$ (c = 1.2, $CHCl_3$). − IR: $\tilde{\nu}$ = 1753, 1707, 1649 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 6.87 (dd, 1 H, J = 15.7 and 7.8 Hz), 6.2 (s, 1 H), 5.87 (dd, 1 H, J = 15.7 and 1.2 Hz), 4.25−4.1 (m, 3 H), 3.6 (dd, 1 H, J = 7.3 and 2.1 Hz), 2.82 (m, 1 H), 2.5 (m, 1 H), 1.28 (t, 3 H, J = 7 Hz), 1.15 (d, 3 H, J = 6.3 Hz), 1.14 (d, 3 H, J = 10 Hz), 0.87 (s, 9 H), 0.07 (s, 6 H). − ^{13}C NMR ($CDCl_3$): δ = 168.5, 166.0, 148.4, 122.2, 65.0, 62.1, 60.3, 54.0, 40.4, 25.6, 22.8, 17.8, 15.5, 14.1, −4.5, −5.0. − $C_{18}H_{33}NO_4Si$ (355.55): calcd. C 60.81, H 9.35, N 3.94; found C 60.90, H 9.20, N 3.80.

(3*S*,4*R*)-3-{(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-4-[(1*S*,2*E*)-(4-hydroxy-1-methyl)-2-butenyl]azetidin-2-one (12): To a solution of ester **11** (100 mg, 0.282 mmol) in THF (1.5 mL), 1.13 mL of a 1 M solution of diisobutylaluminium hydride in CH_2Cl_2 was added dropwise at −78°C. The mixture was stirred for 2 h at −78°C and then for 0.5 h at 25°C. The solution was subsequently hydrolysed at −78°C by the dropwise addition of 0.5 mL of water. After warming to room temp., 0.5 mL of brine was added and the mixture was filtered through Celite by washing the solid residues with AcOEt. The filtrate was dried with $MgSO_4$, filtered, and concentrated. The residue was taken up in AcOEt, the resulting solution was quickly filtered through silica gel, and concentrated to give 81 mg (90%) of the expected compound as a white solid; m.p. 90°C. − $[\alpha]_D^{25} = -33$ (c = 0.76, $CHCl_3$). − IR: $\tilde{\nu}$ = 3410, 1750, 1685 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 6.0 (s, 1 H), 5.8−5.55 (m, 2 H), 4.25−4.1 (m, 3 H), 3.53 (dd, 1 H, J = 7 and 2 Hz), 2.81 (m, 1 H), 2.37 (m, 1 H), 1.8 (m, 1 H), 1.17 (d, 3 H, J = 6.3 Hz), 1.08 (d, 3 H, J = 6.7 Hz), 0.9 (s, 9 H), 0.07 (s, 6 H). − ^{13}C NMR ($CDCl_3$): δ = 169.4, 132.5, 130.4, 65.2, 63.1, 61.3, 54.8, 39.8, 25.7, 22.9, 17.8, 16, −4.4, −5.0. − $C_{16}H_{31}NO_3Si$ (313.51): calcd. C 61.30, H 9.97, N 4.47; found C 61.39, H 9.85, N 4.34.

(3*S*,4*R*)-3-{(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-4-[(1*S*,2*E*)-(4-benzoyloxy-1-methyl)-2-butenyl]azetidin-2-one (13): To a solution of alcohol **12** (88 mg, 0.28 mmol) in CH_2Cl_2 (3.5 mL), 36 μL (0.31 mmol) of benzoyl chloride followed by 82 μL (0.59 mmol) of triethylamine were added at 0°C. The mixture was stirred for 16 h at 0°C, then neutralized with 2 mL of satd. NH_4Cl, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 4:6) to give the expected compound (103 mg, 88%) as a white solid; m.p. 84°C. − $[\alpha]_D^{25} = -24$ (c = 1.32, $CHCl_3$). − IR: $\tilde{\nu}$ = 3410, 1755, 1710 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 8.2−7.85 (m, 5 H), 6.25 (s, 1 H), 5.85−5.68 (m, 2 H), 4.78 (d, 2 H), 4.2 (m, 1 H), 3.53 (dd, 1 H, J = 7.8 and 2.1 Hz), 2.88 (m, 1 H), 2.81 (m, 1 H), 1.08 (d, 3 H, J = 6.3 Hz), 1.05 (d, 3 H, J = 6.7 Hz), 0.88 (s, 9 H), 0.07 (s, 6 H). − ^{13}C NMR ($CDCl_3$): δ = 168.9, 166.2, 136.1, 132.9, 129.5, 128.3, 125.3, 65.05, 64.98, 62.1, 54.7, 40.6, 25.7, 22.9, 17.8, 16.3, −4.4, −5.0. − $C_{23}H_{35}NO_4Si$ (417.62): calcd. C 66.15, H 8.45, N 3.35; found C 66.02, H 8.35, N 3.25.

(3*S*,4*R*)-3-{(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-4-[(1*S*,2*E*)-(4-benzoyloxy-1-methyl)-2-butenyl]-1-[(ethoxycarbonyl)methyl]azetidin-2-one (14): To a solution of LiHMDS (0.1 mmol) in THF (1 mL), a solution of benzoate **13** (40 mg, 0.096 mmol) in THF (2 mL) was added dropwise at −40°C. The mixture was stirred for 15 min at −40°C and then cooled to −78°C, whereupon 19.5 μL (0.115 mmol) of ethyl 2-bromoacetate was added dropwise. The solution was subsequently stirred for 2 h at −40°C and then neutralized by the addition of 2 mL of satd. NH_4Cl. The aqueous layer was extracted with AcOEt. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 2:8) to give the expected compound (45 mg, 93%) as a colourless oil. − $[\alpha]_D^{25} = -34$ (c = 1.4, $CHCl_3$). − IR: $\tilde{\nu}$ = 1765, 1740, 1710 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 8.1−8.0 (m, 2 H), 7.6−7.4 (m, 3 H), 6.0−5.7 (m, 2 H), 4.8 (s, 1 H), 4.77 (s, 1 H), 4.25−4.05 (m, 4 H), 3.9−3.7 (m, 2 H), 2.88 (dd, 1 H, J = 6.1 and 2 Hz), 2.64 (m, 1 H), 1.27 (t, 3 H, J = 7.1 Hz), 1.23 (d, 3 H, J = 6.1 Hz), 1.12 (d, 3 H, J = 6.8 Hz), 0.9 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 168.1, 166.3, 135.9, 132.9, 129.5, 128.2, 125.4, 66.0, 65.1, 61.3, 60.3, 59.9, 42.3, 37.0, 25.7, 22.9, 17.7, 15.8, 14.0, −4.5, −5.0. − $C_{27}H_{41}NO_6Si$ (503.71): calcd. C 64.38, H 8.20, N 2.78; found C 64.33, H 8.08, N 2.81.

(3*S*,4*R*)-3-{(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-4-[(1*S*,2*E*)-(4-benzoyloxy-1-methyl)-2-butenyl]-1-[bis(ethoxycarbonyl)methyl]-azetidin-2-one (15a): To a solution of LiHMDS (0.295 mmol) in THF (1 mL), a solution of benzoate **14** (62 mg, 0.123 mmol) in THF (1 mL) followed by 28 μL (0.295 mmol) of ethyl chloroformate were added dropwise at −78°C. The resulting mixture was stirred for 2 h at −78°C, then neutralized with 1 mL of satd. NH_4Cl, and extracted with AcOEt. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated to give the expected compound (65 mg, 92%) as a colourless oil. − ^1H NMR ($CDCl_3$): δ = 8.1−7.35 (m, 5 H), 6.0 (dd, 1 H, J = 15.6 and 6 Hz), 5.75 (dt, 1 H, J = 15.6 and 6.1 Hz), 5.15 (s, 1 H), 4.8 (d, 2 H, J = 6.1 Hz), 4.35−4.1 (m, 5 H), 4.08 (dd, 1 H, J = 2.5 and 4.9 Hz), 2.88 (dd, 1 H, J = 2.5 and 6.3 Hz), 2.77 (m, 1 H), 1.4−1.15 (m, 9 H), 1.11 (d, 3 H, J = 6.8 Hz), 0.9 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 168.4, 166.2, 165.6, 164.8, 135.3, 132.8, 130.1, 129.5, 128.2, 125.5, 65.9, 65.3, 62.3, 62.2, 61.0, 60.3, 59.9, 56.9, 36.4, 25.7, 22.9, 17.8, 16.1, 13.8, −4.6, −4.7. − $C_{30}H_{45}NO_8Si$ (575.77): calcd. C 62.58, H 7.88, N 2.43; found C 62.61, H 7.89, N 2.40.

(3*S*,4*R*)-3-{(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-4-[(1*S*,2*E*)-(4-benzoyloxy-1-methyl)-2-butenyl]-1-{[(phenylthio)ethoxycarbonyl]-

methyl}azetidin-2-one (15b): To a solution of LiHMDS (0.48 mmol) in THF (1 mL), a solution of benzoate **14** (100 mg, 0.2 mmol) in THF (1 mL) followed by a solution of diphenyl disulfide (104 mg, 0.48 mmol) in THF (0.5 mL) were added dropwise at −78°C. The solution was stirred for 3.5 h at −78°C, then neutralized with 1 mL of satd. NH_4Cl, and extracted with AcOEt. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 2:8) to give the expected compound (102 mg, 84%) as a pale-yellow oil. The product was obtained as a mixture of two diastereomers, which were not separated. − ^{1}H NMR ($CDCl_3$): δ = 8.15−7.2 (m, 10 H), [6.1, 5.85 (2 s, 1 H)], 6.1−5.65 (m, 2 H), [4.9, 4.68 (2 d, 2 H, *J* = 5.3, 6.0 Hz)], 4.3−4.05 (m, 3 H), 3.7−2.7 (m, 3 H), [1.26, 1.23 (2 t, 3 H, *J* = 7.15 Hz)], [1.19, 1.17 (2 d, 3 H, *J* = 6.2, 6.9 Hz)], [1.11, 1.08 (2 d, 3 H, *J* = 6.0, 6.9 Hz)], 0.85 (s, 9 H), [0.21, 0.07, 0.04, −0.02 (4 s, 6 H)]. − ^{13}C NMR ($CDCl_3$): δ = 168.6, 167.6, 166.7, 166.2, 137−121, 67.5, 65.4, 65.3, 62.5, 62.0, 60.9, 60.8, 59.3, 59.1, 58.5, 58.4, 36.0, 25.5, 22.9, 22.6, 17.8, 16.3, 15.8, 13.9, −4.3, −4.5, −4.8, −5.1. − $C_{33}H_{45}NO_6SiS$ (611.87): calcd. C 64.78, H 7.41, N 2.29; found C 64.64, H 7.28, N 2.24.

(3*S*,4*R*)-3-{(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-4-[(1*S*,2*E*)-(4-ethoxycarbonyloxy-1-methyl)-2-butenyl]azetidin-2-one (17): To a solution of alcohol **12** (573 mg, 1.83 mmol) in CH_2Cl_2 (19.5 mL), 296 μL (3.66 mmol) of pyridine followed by 210 μL (2.2 mmol) of ethyl chloroformate were added at 0°C. The mixture was slowly allowed to warm to 25°C, then stirred at this temperature for 2 h, and neutralized by the addition of 10 mL of satd. NH_4Cl. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried with Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 4:6) to give the expected compound (677 mg, 96%) as a white solid; m.p. 61°C. − $[\alpha]_D^{25}$ = −24 (*c* = 0.75, $CHCl_3$). − IR: $\tilde{\nu}$ = 3235, 1744, 1264 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 5.97 (s, 1 H), 5.85−5.55 (m, 2 H), 4.58 (d, 2 H, *J* = 5.0 Hz), 4.3−4.1 (m, 3 H), 3.51 (dd, 1 H, *J* = 7.6 and 1.9 Hz), 2.79 (m, 1 H), 2.36 (m, 1 H), 1.31 (t, 3 H, *J* = 7.1 Hz), 1.15 (d, 3 H, *J* = 6.3 Hz), 1.08 (d, 3 H, *J* = 6.7 Hz), 0.87 (s, 9 H), 0.06 (s, 6 H). − ^{13}C NMR ($CDCl_3$): δ = 168.6, 154.8, 136.5, 124.7, 67.7, 64.9, 64.0, 61.9, 54.5, 40.4, 25.7, 22.9, 17.9, 16.1, 14.2, −4.4, −5.0. − MS (EI); *m*/*z*: 370, 328. − $C_{19}H_{35}NO_5Si$ (385.57): calcd. C 59.19, H 9.15, N 3.63; found C 59.32, H 9.10, N 3.59.

(3*S*,4*R*)-3-{(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-4-[(1*S*,2*E*)-(4-ethoxycarbonyloxy-1-methyl)-2-butenyl]-1-[(ethoxycarbonyl)-methyl]azetidin-2-one (18): To a solution of carbonate **17** (171 mg, 0.443 mmol) in THF (9 mL), a solution of LiHMDS (0.487 mmol) in THF (4.6 mL) was added dropwise at −40°C. The resulting solution was stirred for 25 min at −40°C, and then 59 μL (0.531 mmol) of ethyl bromoacetate was added dropwise at −78°C. The mixture was stirred for 2 h at −40°C, and then neutralized by the addition of satd. NH_4Cl (8 mL). The aqueous layer was extracted with AcOEt and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 2:8) to give the expected compound (173 mg, 83%) as a yellow oil. − $[\alpha]_D^{25}$ = −41 (*c* = 0.85, $CHCl_3$). − IR: $\tilde{\nu}$ = 1747, 1258 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 6.0−5.5 (m, 2 H), 4.58 (d, 2 H, *J* = 5.9 Hz), 4.3−4.0 (m, 6 H), 3.8 (dd, 1 H, *J* = 5 and 2.2 Hz), 3.76 (d, 1 H, *J* = 17.8 Hz), 2.85 (dd, 1 H, *J* = 6.1 and 2.2 Hz), 2.62 (m, 1 H), 1.35−1.2 (m, 9 H), 1.1 (d, 3 H, *J* = 6.8 Hz), 0.87 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 168.1, 154.8, 136.2, 124.9, 67.8, 65.9, 63.9, 61.3, 60.3, 59.8, 42.2, 37.1, 25.7, 22.9, 17.8, 15.7, 14.2, −4.4, −4.8. − MS (EI); *m*/*z*: 456, 414. − $C_{23}H_{41}NO_7Si$ (471.66): calcd. C 58.57, H 8.76, N 2.97; found C 58.74, H 8.76, N 2.98.

(3*S*,4*R*)-3-{(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-4-[(1*S*,2*E*)-(4-ethoxycarbonyloxy-1-methyl)-2-butenyl]-1-[bis(ethoxycarbonyl)-methyl]azetidin-2-one (19a): To a solution of LiHMDS (0.88 mmol) in THF (3 mL), a solution of carbonate **18** (173 mg, 0.367 mmol) in THF (3 mL) followed by 84 μL (0.88 mmol) of ethyl chloroformate were added dropwise at −78°C. The resulting mixture was stirred for 2 h at −78°C, then neutralized with satd. NH_4Cl, and extracted with AcOEt. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 2:8) to give the expected compound (148 mg, 74%) as a colourless oil. − $[\alpha]_D^{25}$ = −57 (*c* = 1.2, $CHCl_3$). − IR: $\tilde{\nu}$ = 1750, 1258 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 5.94 (dd, 1 H, *J* = 15.6 and 6.0 Hz), 5.8−5.5 (m, 1 H), 5.14 (s, 1 H), 4.59 (d, 2 H, *J* = 6.2 Hz), 4.4−4.1 (m, 7 H), 4.1−4.0 (m, 1 H), 2.85 (dd, 1 H, *J* = 6.4 and 2.3 Hz), 2.75 (m, 1 H), 1.31 (t, 9 H, *J* = 7.1 Hz), 1.22 (d, 3 H, *J* = 6.2 Hz), 1.08 (d, 3 H, *J* = 6.9 Hz), 0.87 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 168.3, 165.6, 164.7, 154.8, 135.7, 124.9, 68.0, 65.8, 63.8, 62.3, 62.1, 60.9, 59.8, 56.8, 36.1, 25.6, 22.8, 17.7, 16.0, 14.1, 13.9, −4.6. − MS (EI); *m*/*z*: 561, 544. − $C_{26}H_{45}NO_9Si$ (543.73): calcd. C 57.43, H 8.34, N 2.58; found C 57.46, H 8.39, N 2.56.

(3*S*,4*R*)-3-{(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-4-[(1*S*,2*E*)-(4-ethoxycarbonyloxy-1-methyl)-2-butenyl]-1-{[(phenylsulfonyl)-ethoxycarbonyl]methyl}azetidin-2-one (19b): To a solution of LiHMDS (0.91 mmol) in THF (1.8 mL), a solution of carbonate **18** (179 mg, 0.38 mmol) in THF (2 mL) followed by a solution of diphenyl disulfide (0.46 mmol) in THF (1 mL) were added dropwise at −78°C. The resulting mixture was stirred for 3 h at −78°C, then neutralized with satd. NH_4Cl (2 mL), and extracted with AcOEt. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude product was dissolved in $CHCl_3$ (3 mL) and added to a mixture of Oxone® (2.27 mmol) and wet alumina (758 mg of a homogeneous powder obtained by mixing 1 mL of H_2O with 5 g of alumina). The resulting slurry was refluxed for 4 h, then cooled to 25°C, filtered, and the solid was washed with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 2:8) to give the expected compound (125 mg, 54%) as a pale-yellow oil; mixture of two diastereomers. − IR: $\tilde{\nu}$ = 1748, 1584, 1150 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 8.1−7.5 (m, 5 H), 6.4−5.3 (m, 2 H), [5.77, 5.58 (2 s, 1 H)], [4.65, 4.58 (2 d, 2 H, *J* = 6.2 Hz)], 4.4−4.0 (m, 6 H), 3.3−2.7 (m, 2 H), 1.4−1.0 (m, 12 H), 0.9−0.7 (m, 9 H), 0.2−0.0 (m, 6 H). − ^{13}C NMR ($CDCl_3$): δ = 169.6, 168.8, 162.2, 161.4, 154.9, 138.1, 137.5, 135.8, 135.2, 134.5, 129.3, 129.2, 129.0, 125.5, 125.0, 73.4, 68.2, 67.1, 64.8, 63.9, 62.7, 61.4, 60.6, 59.6, 36.2, 35.2, 25.8, 25.7, 22.8, 17.8, 17.6, 16.3, 15.7, 14.2, 13.7, −4.1, −4.6, −5.0. − MS (EI); *m*/*z*: 629, 612. − $C_{29}H_{45}NO_9SSi$ (611.82): calcd. C 56.93, H 7.41, N 2.29; found C 54.76, H 7.08, N 1.87.

(4*S*,5*R*,6*S*)-6-{(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-2,2-bis(ethoxycarbonyl)-3-(1-ethenyl)-4-methyl-1-azabicyclo[3.2.0]-heptan-7-one (16a). − Method A (Benzoates): To a suspension of sodium hydride (3.5 mg, 0.14 mmol) in THF (0.5 mL), a solution of benzoate **15a** (61 mg, 0.106 mmol) in THF (0.5 mL) was added at 0°C. The mixture was stirred for 15 min at 25°C and then the catalyst, preformed for 1 h at 25°C from 4.8 mg (20 mol-%) of

$Pd(OAc)_2$ and 12.7 mg (30 mol-%) of dppe in THF (0.5 mL), was added. The resulting mixture was heated at 60°C for 2 h, then neutralized by the addition of 2 mL of satd. NH_4Cl, and extracted with diethyl ether. The organic layer was dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 2:8) to give the expected compound (24 mg, 48%) as a colourless oil; mixture of two diastereomers. − **Method B (Carbonates):** To the catalyst, preformed for 0.5 h at 30°C from 2.1 mg (10 mol-%) of $Pd(OAc)_2$ and 7.8 mg (20 mol-%) of dppb (diphenylphosphanylbutane) in THF (0.5 mL), a solution of carbonate **19a** (50 mg, 0.09 mmol) in THF (1 mL) was added dropwise. The resulting mixture was stirred for 1 h at 30°C, then diluted with AcOEt, neutralized by the addition of satd. NH_4Cl (2 mL), and extracted with AcOEt. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 1:9, + 0.75% Et_3N) to give the expected compound (27 mg, 67%) as a colourless oil; mixture of two diastereomers. − IR: $\tilde{\nu}$ = 3235, 1770, 1740 cm^{-1}. − **Diastereomer 1:** ^1H NMR ($CDCl_3$): δ = 5.68 (ddd, 1 H, *J* = 16.8 and 9.8 Hz), 5.33 (dd, 1 H, *J* = 16.8 and 2.0 Hz), 5.20 (dd, 1 H, *J* = 9.8 and 2.0 Hz), 4.4−4.0 (m, 6 H), 4.0−3.8 (m, 1 H), 3.13 (dd, 1 H, *J* = 2.3 and 4.9 Hz), 2.45 (m, 1 H), 1.4−1.15 (m, 9 H), 1.1 (d, 3 H, *J* = 7.6 Hz), 0.9 (s, 9 H), 0.07 (s, 6 H). − ^{13}C NMR ($CDCl_3$): δ = 168.9, 168.3, 165.2, 131.9, 120.4, 73.4, 65.1, 62.2, 62.0, 59.0, 58.7, 58.5, 38.8, 25.6, 22.4, 17.8, 13.8, 10.8, −4.4, −5.2. − **Diastereomer 2:** ^1H NMR ($CDCl_3$): δ = 5.57 (ddd, 1 H, *J* = 17.3, 9.9 and 7.7 Hz), 5.29 (dd, 1 H, *J* = 17.3 and 1.7 Hz), 5.20 (dd, 1 H, *J* = 10.6 and 1.7 Hz), 4.4−4.0 (m, 6 H), 3.1 (dd, 1 H, *J* = 7.1 and 3.3 Hz), 3.0 (dd, 1 H, *J* = 11.6 and 7.7 Hz), 2.45 (m, 1 H), 1.4−1.15 (m, 9 H), 1.1 (d, 3 H, *J* = 7.6 Hz), 0.9 (s, 9 H), 0.1 (s, 6 H). − IR: $\tilde{\nu}$ = 3235, 1770, 1740 cm^{-1}. − MS (EI); *m/z*: 438, 398. − $C_{23}H_{39}NO_6Si$ (453.65): calcd. C 60.90, H 8.66, N 3.09; found C 60.91, H 8.56, N 2.99.

(4*S*,5*R*,6*S*)-6-{(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-2-ethoxycarbonyl-2-phenylsulfonyl-3-(1-ethenyl)-4-methyl-1-azabicyclo-[3.2.0]heptan-7-one (16b): To the catalyst, preformed for 0.5 h at 30°C from 4.1 mg (10 mol-%) of $Pd(OAc)_2$ and 15.6 mg (20 mol-%) of dppb in THF (1 mL), a solution of sulfone **19b** (112 mg, 0.18 mmol) in THF (2 mL) was added dropwise. The resulting mixture was stirred for 1 h at 30°C, then diluted with AcOEt, neutralized by the addition of satd. NH_4Cl (3 mL), and extracted with AcOEt. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 15:85) to give the expected compound (56 mg, 59%) as a white solid; mixture of four diastereomers. − IR: $\tilde{\nu}$ = 1770, 1740, 1150 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 8.04 (s, 1 H), 7.7−7.4 (m, 3 H), 5.8−5.55 (m, 1 H), 5.47 (dd, 1 H, *J* = 16.8 and 1.9 Hz), 5.32 (dd, 1 H, *J* = 9.6 and 1.8 Hz), 4.4−4.0 (m, 5 H), 3.20 (dd, 1 H, *J* = 2.5 and 5.5 Hz), 2.68 (m, 1 H), 1.25 (d, 3 H, *J* = 6.1 Hz), 1.15 (t, 3 H, *J* = 7.1 Hz), 1.09 (d, 3 H, *J* = 7.6 Hz), 0.92 (s, 9 H), 0.12 (s, 6 H). − ^{13}C NMR ($CDCl_3$): δ = 167.5, 162.7, 137.1, 134.0, 130.7, 130.6, 128.5, 122.2, 88.0, 65.6, 62.9, 60.7, 59.7, 58.1, 39.4, 25.7, 22.5, 17.9, 13.7, 11.4, −4.3, −4.7. − MS (EI); *m/z*: 438, 398. − $C_{26}H_{39}NO_6SSi$ (521.75): calcd. C 59.85, H 7.53, N 2.68; found C 59.86, H 7.55, N 2.65.

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