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A new convergent and stereoselective synthesis of 2,5-disubstituted *N*-acylpyrrolidines

Luca Banfi, Andrea Basso, Giuseppe Guanti and Renata Riva*

Dipartimento di Chimica e Chimica Industriale, Via Dodecaneso 31, I-16146 Genova, Italy

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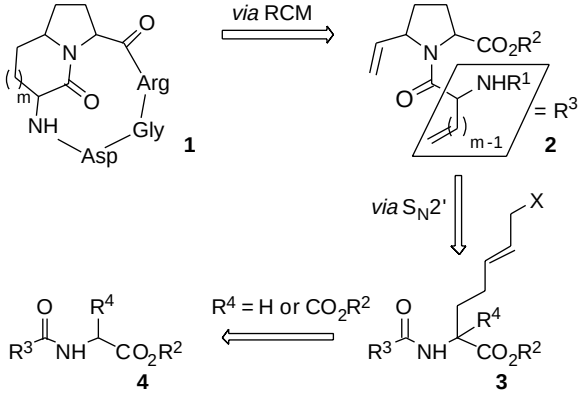
Abstract—A new synthesis of 2,5-disubstituted *N*-acylpyrrolidines through an S_N2' reaction promoted by the nitrogen anion of a secondary amide onto an allylic bromide is reported. A moderate stereoselectivity, in favour of the trans heterocycle, was observed during the cyclization of a chiral precursor, while a good stereoselectivity, this time in favour of the cis one, was obtained when the second stereocentre was introduced after the cyclization step to give the same product.

1. Introduction

Pyrrolidine is a very important heterocycle present in many biologically active compounds, such as proteins or alkaloids and has become one of the priviledged structures in drug discovery.[1] In particular, bicyclic lactams, bearing a pyrrolidine moiety and equipped with suitable appendages, are very popular since they can be used as constrained peptidomimetics.[2] Moreover, they are frequently able to mimic a reverse turn, an important motif responsible for inducing the appropriate conformation in small oligopeptides involved in essential interactions with many biological targets. An example is represented by bicyclic lactams included in a macrocycle together with the RGD sequence: in this case, the bicyclic system acts as an 'external scaffold'[3] and these molecules showed interesting properties as inhibitors of $\alpha_V\beta_3$ or $\alpha_V\beta_5$ integrins.[4] In the last few years, our group has been involved in the synthesis of either mesocyclic lactams[5,6] or bicyclic derivatives[7] as possible inhibitors of integrins.

The previous reported synthesis of [*n*,3,0] (*n*=4, 5, 6, 7) bicyclic systems are based on the construction of the larger ring as the last step, employing usually the highly versatile ring closing metathesis (RCM),[8] but standard lactonization[7] or lactamization reactions[9] or radical cyclizations[10] have been utilized too. Therefore, in the first part of these syntheses, a suitably functionalized pyrrolidine had to be assembled.

In our project, we planned to synthesise a series of [*n*,3,0] bicyclic scaffolds such as **1** (Scheme 1) and, in view of cyclization through RCM as the final step, we would need a convergent synthesis of *N*-acyl-2-carbalkoxy-5-vinylpyrrolidines **2**. An attractive strategy towards this goal involves an S_N2' procedure promoted by a nitrogen nucleophile onto a double bond equipped with a suitable leaving group at the terminal allylic position. The acyclic precursor **3** may be assembled, for example, by alkylation of α-acylaminoesters or malonates **4**. Malonates can be used in place of simple esters; thanks to the possibility of removing the second carbalkoxy group via saponification–decarboxylation. This step can be performed either before or after cyclization. Moreover, for an efficient and convergent approach to **1**, R^3 group should be equipped with both the double bond, to be used in RCM, and NHR^1 group essential, together with



Scheme 1.

Keywords: Pyrrolidine; S_N2'; Peptidomimetics.
* Corresponding author. Tel.: +39 0103536126; fax: +39 0103536118; e-mail: riva@chimica.unige.it

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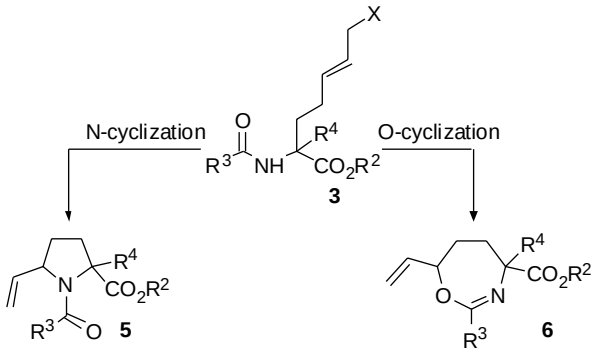
CO_2R^2, for the creation of the macrocyclic peptidic structure including for example RGD motif.

To the best of our knowledge, intramolecular S_N2' reactions, starting from simple secondary amides, were unprecedented. While in a few cases pyrrolidines or piperidines have been prepared through an S_N2' cyclizations under palladium catalysis,[11] those examples involved the use of carbamates. Thus, the success of the envisaged strategy was not obvious, since it is known that in amides there is often a competition between N and O-alkylation, affording, in our case, **5** or **6**, respectively, as outlined in Scheme 2.[12] In carbamates this competition is less important. The development of a protocol leading in one-pot to *N*-acyl derivatives (and not to carbamates) would considerably shorten the approach to key intermediate **2** (that may be in principle obtained also through a Ugi multicomponent reaction). The feasibility of our hypothesis was studied on a model compound, that is the acetamide corresponding to general formula **3** (R^3 =Me).[13]

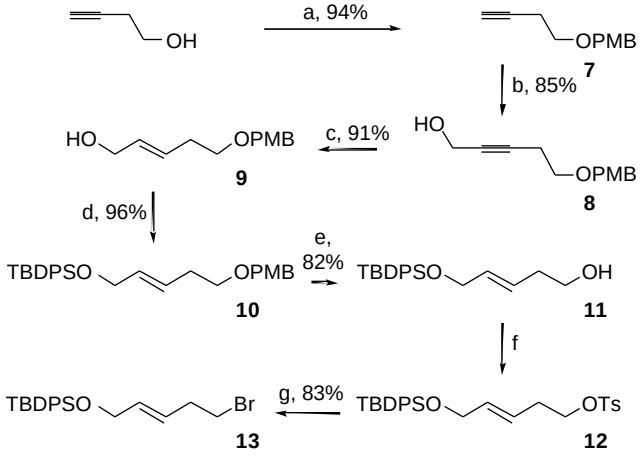


Scheme 2.

2. Results and discussion

N-Acetyl homoallylglycinates are not available commercially either in racemic or in enantiopure form; thus we had to develop a convergent racemic synthesis of them, involving the alkylation of the enolate of unexpensive diethyl acetamido malonate with a suitable homoallylic bromide, equipped with a masked leaving group at the allylic position to be exploited in the cyclization.

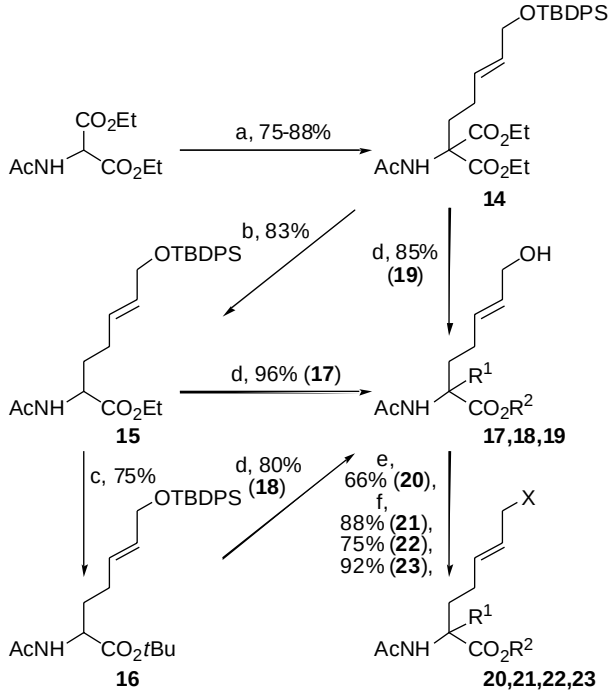
The initial task was therefore the preparation of a 2-pentene substituted at position 5 (a homoallylic carbon) with a good leaving group and at the more reactive position 1 (an allylic carbon), with a poor one. We started from commercially available 3-butyn-1-ol (Scheme 3), that was protected as *p*-methoxybenzyl ether (PMB) and then homologated by treatment of the magnesium acetylide of **7** with paraformaldehyde. Compound **8**, obtained in excellent yield after hydrolysis under basic conditions of the complex mixture of hemiacetalic derivatives of formaldehyde,[14] contained two differentiated primary alcoholic functionalities, that have been elaborated independently during the synthesis.[15] The free propargylic alcohol was reduced to give, with total control of the geometry of the incoming double bond, allylic alcohol **9** in excellent yield.[16] Silylation of **9** allowed to prepare **10**, with two orthogonally protected hydroxy groups. Removal of PMB under oxidative conditions afforded **11**, ready to be converted into bromide



Scheme 3. (a) NaH, *p*-methoxybenzylchloride, DMF, 0 °C; (b) (i) EtMgBr, paraformaldehyde, THF, rt; (ii) K_2CO_3, MeOH, rt; (c) $LiAlH_4$, MeONa, THF, reflux; (d) $Ph_2tBuSiCl$, imidazole, DMF, rt; (e) DDQ, CH_2Cl_2/H_2O 20:1, rt; (f) TsCl, py, rt; (g) KBr, DMF, 100 °C.

13 in excellent overall yield, provided that tosylate **12** is recovered by neutral work-up and submitted immediately to nucleophilic displacement without previous purification. Despite the long preparation, the overall yield of this bromide from 3-butyn-1-ol was a remarkable 48%.

The alkylation of diethyl acetamido malonate was found to be troublesome, most likely because of the propensity of the rather unreactive bromide **13** to undergo competitive reactions, such as elimination, to give the corresponding



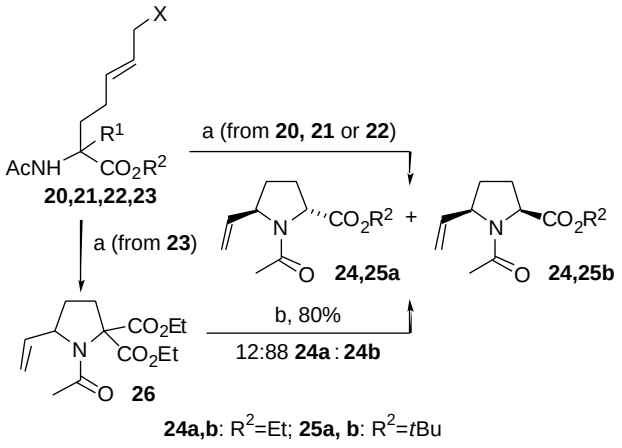
17: R^1 = H, R^2 = Et; **18**: R^1 = H, R^2 = *t*Bu; **19**: R^1 = CO_2Et, R^2 = Et
20: R^1 = H, R^2 = Et, X = Cl; **21**: R^1 = H, R^2 = Et, X = Br;
22: R^1 = H, R^2 = *t*Bu, X = Br; **23**: R^1 = CO_2Et, R^2 = Et, X = Br

Scheme 4. (a) NaH, **13**, DMF, 90 °C; (b) (i) NaOH 6 M in EtOH, EtOH, rt; (ii) H^+; (iii) dioxane, reflux; (c) (i) NaOH 6 N, EtOH, rt; (ii) $CCl_3C(=NH)OtBu$, $BF_3\cdot Et_2O$, CH_2Cl_2, rt; (d) nBu_4NF, THF, rt; (e) CCl_4, PPh_3, reflux; (f) CBr_4, PPh_3, CH_3CN, rt.

conjugated diene. After a careful optimization of the conditions we succeeded in obtaining **14** in good yield (Scheme 4).[17]

Monodecarboxylation, following our protocol developed for structurally similar compounds, afforded finally **15**.[6] As the final step, we studied the transformation of the silyl ether into a halide, via the free alcohol **17**. When we tried to prepare the tosylate,[18] we could not isolate it, but it was readily converted into the corresponding chloride **20**, albeit in unsatisfactory yield. For this reason, we used a direct method, which employed triphenyl phosphine and carbon tetrachloride both as reagent and solvent.[19] Although harsher conditions than the reported ones were required, chloride **20** was finally isolated in acceptable yield. Modified reaction conditions, using carbon tetrabromide and triphenylphosphine in acetonitrile, allowed the preparation of bromide **21** in higher yield and under milder conditions.

During the first cyclization experiment (Scheme 5) we treated chloride **20** with potassium bis(trimethylsilyl)amide (KHMDS) and we were pleased to discover the only products derived from *N*-promoted cyclization. The yield was, however, moderate, whereas a poor diastereoselectivity in favour of the trans stereoisomer **24a** was observed (entry 1, Table 1).[20] Under the same conditions, bromide **21** showed to be, as expected, more reactive, affording **24a**,**b** in higher yield, but with similar diastereoselectivity (entry 2). The following screening was therefore done on the best performing substrate **21**. Other bases, such as NaH gave unsatisfactory results (entry 5), particularly from the stereochemical point of view, while an improved diastereomeric ratio was observed using the lithium anion of bis(trimethylsilyl)amide (LiHMDS).[21] The reaction temperature showed an appreciable influence just on the rate, but not on the stereoselectivity. Also the nature of the solvent was varied, demonstrating that optimal results can be achieved with the aprotic dipolar ones. Interestingly, when apolar toluene was used (entry 7) a reversal of stereoselectivity was observed. However, this reaction was too slow for preparative purposes. Compounds **24a**,**b** showed to be configurationally stable under basic conditions, since no changes in diastereomeric ratio were observed after prolonged storage under the reaction conditions.



Scheme 5. (a) see Table 1; (b) (i) NaOH 6 N, EtOH; (ii) H^+; (iii) dioxane, reflux.

The bulkier *t*-butyl ester **22** was obtained from **15** by a three step procedure (Scheme 4). Its cyclization was slower and required a temperature of at least −50 °C in order to start, while no improvement in the diastereomeric ratio was realized (entry 11).

In order to improve the stereoselectivity and gain access to the minor cis diastereoisomer, we carried out the cyclization also starting from malonate **23** (entry 12). The reaction took place in good yield to give **26**. This reaction is particularly interesting since the monodecarboxylation of **26** affords **24a**,**b** with good stereoselectivity favouring this time the cis diastereoisomer **24b** in a 7.3:1 ratio. Thus, two complementary procedures affording prevailingly either **24a** or **24b** are available and, since the two diastereoisomers can be separated although not easily by chromatography, our protocol constitutes an original new entry for the stereoselective synthesis of vinyl-substituted *N*-heterocycles.

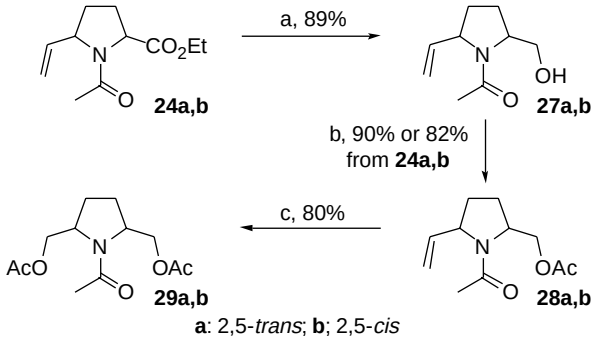
The determination of the relative configuration of **24a** and **24b** was first done tentatively by ^{1}H NMR correlation with

Table 1. Cyclization of halides **20**–**23**, through S_N2' reaction

Entry	Halide	Base[a]	Solvent[b]	Temperature (°C)	Time (h)	Product(s)	Yield (%)[c]	dr[d]
1	**20**	KHMDS[e]	THF/DMF 2:1	−10°→rt	3.5	**24a**,**b**	50	56:44
2	**21**	KHMDS[e]	THF/DMF 2:1	−10°→0°	0.67	**24a**,**b**	80	55:45
3	**21**	LiHMDS[f]	THF/DMF 2:1	−10°	4	**24a**,**b**	81	54:46
4	**21**	LiHMDS[f]	THF/DMF 2:1	−78°→−5°	24	**24a**,**b**	74	67:33
5	**21**	NaH	THF/DMF 2:1	−10°	2	**24a**,**b**	68	51:49
6	**21**	LiHMDS[f]	THF	−10°→rt	46	**24a**,**b**	55	58:42
7	**21**	LiHMDS[f]	Toluene	−10°→rt	50	**24a**,**b**	75	38:62
8	**21**	LiHMDS[f]	THF/DMSO 3:1	−10°→rt	4.25	**24a**,**b**	80	70:30
9	**21**	LiHMDS[f]	DMF	−10°→rt	6	**24a**,**b**	81	63:37
10	**21**	LiHMDS[f]	DMF	−78°	25	**24a**,**b**	90	70:30
11	**22**	LiHMDS[f]	DMF	−78°→−50°	22	**25a**,**b**	75	69:31
12	**23**	LiHMDS[g]	DMF	−15°→8°	2.5	**26**	78	—

[a] 1.5 mol equiv of base.
[b] 0.05–0.07 M with respect to substrate, with the exception of DMF (0.25 M).
[c] In entries 1–11 the yield is referred to the diastereomeric mixture.
[d] By GC–MS.
[e] KHMDS: potassium bis(trimethylsilyl)amide, 0.5 M solution in THF freshly prepared by dissolving solid commercial KHMDS.
[f] LiHMDS: lithium bis(trimethylsilyl)amide, 1.0 M commercial solution in THF.
[g] LiHMDS: 0.5 M solution in THF freshly prepared by dissolving solid commercial LiHMDS.

similar compounds.[22] In particular, while in the trans derivatives the chemical shifts of the terminal vinylic protons are close together, in the cis series a 0.24–0.28 ppm difference was always observed, with the proton trans to the other vinylic one downfield. Moreover, our expectations were confirmed by transforming both stereoisomers into triacetyl derivatives **29a**,**b** (Scheme 6).[23] After chemoselective reduction of the ester with $Ca(BH_4)_2$ and acetylation of the primary alcohol, acetates **28a**,**b** were submitted to ozonolysis and acetylation of the crude product[24] to give, in excellent yield, desired **29a**,**b**. Since **24a** and **24b** are racemic, we reasoned that a different behaviour could, in principle, be observed if **29a** and **29b** are put in a chiral medium, because the first one is racemic and the second one is a *meso* compound. Chiral GLC, using two different functionalized β-cyclodextrin-based columns, always gave one peak for both **29a** and **29b**. On the contrary, HPLC with a Chiralpak AD column, gave an excellent separation, with two peaks eluting with R_t 15.92 and 17.41 min, respectively (see Section 4), for the triacyl compound derived from the major stereoisomer obtained in the S_N2' cyclization. Using the same conditions, the other diastereoisomer eluted as a single peak at R_t 12.65 min. Since, during the transformation of **24a** and **24b** into **29a** and **29b**, the original stereogenic centres were not subjected to manipulations, the behaviour in HPLC allows us to assign the trans stereochemistry to the prevailing stereoisomer obtained in the S_N2' cyclization and the cis stereochemistry to the prevailing stereoisomer obtained in the monodecarboxylation of **26**.



Scheme 6. (a) $Ca(BH_4)_2$, THF/EtOH 2:1, −20 °C; (b) Ac_2O, Et_3N, 4-(dimethylamino)pyridine, CH_2Cl_2, rt; (c) CH_2Cl_2/MeOH 1:1, −78 °C; (ii) $NaBH_4$ −78 °C→rt; (iii) see (b).

3. Conclusions

In this paper, we presented a new high convergent protocol for the synthesis of functionalized *N*-heterocycles that can be further elaborated to more complex structures. Moreover, our methodology could probably be extended for the synthesis of differently sized rings and of different *N*-acylated compounds.

The development of different convergent strategies for the preparation of acyclic precursors **3**, involving, for example, an approach based on multicomponent reactions, may disclose a new way for the synthesis of polycyclic derivatives, through methodologies consistent with diversity oriented synthesis.[25] Studies in this field are still in progress in our laboratory and will be presented in due course.

4. Experimental

4.1. General

NMR spectra were taken in $CDCl_3$ at 200 or 300 MHz (^1H) and 50 or 75 MHz (^{13}C), using TMS as internal standard. Chemical shifts are reported in ppm (δ scale), coupling constants are reported in hertz. Peak assignment in ^1H NMR spectra was also made with the aid of double resonance experiments. Peak assignment in ^{13}C spectra was made with the aid of DEPT experiments. GC–MS were carried out on a HP-5971A instrument, using an HP-1 column (12 m long, 0.2 mm wide), electron impact at 70 eV, and a mass temperature of about 170 °C. Unless otherwise indicated, analyses were performed with a constant He flow of 0.9 ml/min, init. temperature 100 °C, init. time 2 min, rate 20 °C/min, final temperature 260 °C, final time 4 min, inj. temperature 250 °C, det. temperature 280 °C. R_t are in min. HPLC determinations were carried out on a HP-1090 instrument equipped with a DAD detector and using a Chiralpak AD column (25 cm long, 0.4 cm wide). IR spectra were measured with a Perkin–Elmer 881 instrument as $CHCl_3$ solutions. Melting points were determined on a Büchi 535 apparatus and are uncorrected. TLC analyses were carried out on silica gel plates, which were developed by these detection methods: (A) UV; (B) iodine; (C) dipping into a solution of $(NH_4)_4MoO_4\cdot 4H_2O$ (21 g) and $Ce(SO_4)_2\cdot 4H_2O$ (1 g) in H_2SO_4 (31 ml) and H_2O (469 ml) and warming. R_f were measured after an elution of 7–9 cm. Chromatographies were carried out on 220–400 mesh silica gel using the 'flash' methodology. Petroleum ether (40–60 °C) is abbreviated as PE. In extractive work-up, aqueous solutions were always reextracted thrice with the appropriate organic solvent. Organic extracts were washed with brine, dried over Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. All reactions employing dry solvents were carried out under a nitrogen atmosphere, while S_N2' reactions were performed under ultra pure argon.

4.2. 4-(4-Methoxybenzyl)oxybut-1-yne 7

To a solution of 4-methoxybenzyl chloride (7.89 g, 50.4 mmol) in dry DMF (50 ml) previously cooled in an ice bath, 3-butyn-1-ol (3.47 ml, 45.8 mmol) was added via syringe. NaH (2.02 g, 60% in mineral oil, 50.4 mmol) was added portionwise over a period of 15 min and the resulting slurry was stirred at 0 °C for additional 45 min. After adding NH_4Cl satd soln (20 ml), the mixture was partitioned between water and Et_2O and extracted. Chromatography with PE/Et_2O 9:1→8:2 gave **7** (8.19 g, 94%) as a colourless oil. R_f 0.32 (PE/Et_2O 9:1, A, C). Anal. found C, 75.50; H, 7.40. $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42. IR: ν_{max} 3305, 2965, 2397, 1611, 1243, 1172, 1091, 1031. GC–MS: R_t 5.26; *m*/*z* 190 (M^+, 7.8), 189 (13), 159 (11), 135 (25), 122 (9.6), 121 (100), 91 (7.2), 78 (14), 77 (16), 53 (9.2), 52 (5.6), 51 (8.0), 39 (10). ^1H NMR (200 MHz): 1.99 [1H, t, ≡C*H*, J=2.6 Hz]; 2.49 [2H, dt, $CH_2C\equiv$, J=2.6, 7.0 Hz]; 3.57 [2H, t, CH_2CH_2O, J=7.1 Hz]; 3.81 [3H, s, OCH_3]; 4.49

[2H, s, CH_2Ar]; 6.88 [2H, dt, aromatics *ortho* to OMe, $J=$ 2.4, 8.8 Hz]; 7.28 [2H, d, aromatics *meta* to OMe, $J=$ 8.8 Hz]. ^{13}C NMR (50 MHz): 19.80 [$CH_2C{\equiv}$]; 55.17 [CH_3O]; 67.75 [CH_2CH_2O]; 69.25 [${\equiv}CH$]; 72.55 [CH_2Ar]; 81.28 [$C{\equiv}CH$]; 113.72 [2C, aromatics *ortho* to OMe]; 129.26 [2C, aromatics *meta* to OMe]; 130.00 [quat. aromatic]; 159.17 [C–OMe].

4.3. 5-[(4-Methoxybenzyl)oxy]pent-2-yn-1-ol 8

A solution of **7** (7.22 g, 38.0 mmol) in dry THF (100 ml) was cooled to 0 °C and then EtMgBr (3 M soln in Et_2O, 21.5 ml) was dropped via syringe over a period of 2–3 min. After 10 min, the cooling bath was removed and stirring continued at rt for 30 min. Anhydrous paraformaldehyde (8.11 g, 271 mmol) was then added in one-pot and the resulting suspension was stirred at rt for 1 day. Quenching with NH_4Cl satd soln (70 ml) was followed by stirring at rt for 15 min; then the crude was filtered through a Celite pad, washing Celite with Et_2O and AcOEt. After separation of the two layers two additional extractions with Et_2O were performed. Solvent was removed and the crude was dissolved in MeOH (40 ml) and stirred at rt in the presence of anhydrous K_2CO_3 (1.00 g, 7.24 mmol) for 3 h. After filtration of the solid and solvent evaporation, the residue was partitioned between H_2O and AcOEt and extracted with AcOEt. Chromatography with PE/Et_2O 4:6→1:9 gave **8** (7.11 g, 85%) as a colourless oil. R_f 0.44 (PE/Et_2O 3:7, A, C). Anal. found C, 70.75; H, 7.35. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32. IR: ν_{max} 3401, 3003, 2416, 1612, 1506, 1300, 1172, 1087, 924. GC–MS: R_t 7.52; *m/z* 220 (M^+, 0.70), 201 (6.3), 189 (20), 171 (9.2), 135 (10), 122 (9.7), 121 (100), 91 (6.5), 78 (13), 77 (14), 65 (6.5), 51 (6.4), 39 (10). ^1H NMR (200 MHz): 1.72 [1H, t, O*H*, $J=6.0$ Hz]; 2.52 [2H, tt, $CH_2CH_2C{\equiv}$, $J=2.2$, 7.0 Hz]; 3.55 [2H, t, CH_2CH_2O, $J=6.9$ Hz]; 3.81 [3H, s, OCH_3]; 4.24 [2H, broad dt, CH_2OH, $J=2.1$, 5.8 Hz]; 4.48 [2H, s, CH_2Ar]; 6.88 [2H, dt, aromatics *ortho* to OMe, $J=2.4$, 8.4 Hz]; 7.27 [2H, d, aromatics *meta* to OMe, $J=8.8$ Hz]. ^{13}C NMR (50 MHz): 19.99 [$CH_2CH_2C{\equiv}$]; 50.91 [CH_2OH]; 55.15 [CH_3O]; 67.80 [CH_2CH_2O]; 72.44 [CH_2Ar]; 79.56 and 82.69 [2C, $C{\equiv}C$]; 113.71 [2C, aromatics *ortho* to OMe]; 129.28 [2C, aromatics *meta* to OMe]; 129.85 [quat. aromatic]; 159.15 [C–OMe].

4.4. (*E*)-5-[(4-Methoxybenzyl)oxy]pent-2-en-1-ol 9

A suspension of $LiAlH_4$ (3.16 g, 83.2 mmol) in dry THF (120 ml) was cooled to 0 °C and sodium methoxide (8.07 g, 166 mmol) was added. A solution of **8** (6.11 g, 27.7 mmol) in dry THF (30 ml) was dropped through an addition funnel over a period of 15 min and the cooling bath was removed after 5 min. The funnel was substituted with a refrigerator and the mixture was refluxed for 5 h 15 min. After cooling the flask at 0 °C, a solution of NaOH (370 mg in 12.5 ml of water) was added wery slowly and the mixture was stirred overnight at rt. The white solid was readily filtered and washed with Et_2O. The collected organic layers were dryed over Na_2SO_4 and evaporated to give a yellow oil, pure enough (GC–MS) for the following reaction. For analytical purposes the crude was purified by chromatography with PE/Et_2O 1:1→2:8 to give **9** as a pale yellow oil in 91% yield. R_f 0.31 (PE/Et_2O 3:7, A, C). Anal. found C, 70.40; H, 8.25. $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.16. IR: ν_{max} 3462, 2998, 2929, 2864, 1609, 1533, 1419, 1364, 1190, 1088, 972. GC–MS: R_t 7.28; *m/z* 222 (M^+, 1.0), 150 (10), 137 (6.4), 136 (8.3), 135 (7.2), 122 (10), 121 (100), 78 (8.2), 77 (9.6). ^1H NMR (200 MHz): 1.37 [1H, t, O*H*, $J=5.9$ Hz]; 2.36 [2H, centre of m, $CH_2CH_2C=$]; 3.49 [2H, t, CH_2CH_2O, $J=$ 6.6 Hz]; 3.81 [3H, s, OCH_3]; 4.09 [2H, broad s, CH_2OH]; 4.44 [2H, s, CH_2Ar]; 5.62–5.81 [2H, m, C*H*=C*H*]; 6.88 [2H, dt, aromatics *ortho* to OMe, $J=2.4$, 8.8 Hz]; 7.26 [2H, d, aromatics *meta* to OMe, $J=8.8$ Hz]. ^{13}C NMR (50 MHz): 32.53 [$CH_2CH_2CH=$]; 55.17 [CH_3O]; 63.33 [CH_2OH]; 69.23 [CH_2CH_2O]; 72.44 [CH_2Ar]; 113.70 [2C, aromatics *ortho* to OMe]; 128.96 and 130.98 [2C, C*H*=C*H*]; 129.24 [2C, aromatics *meta* to OMe]; 130.29 [quat. aromatic]; 159.09 [*C*–OMe].

4.5. (*E*)-1-[(*t*-Butyldiphenylsilyl)oxy-5-(4-methoxybenzyl)oxy]pent-2-ene 10

A solution of **9** (5.60 g, 25.2 mmol) in dry DMF (40 ml) was cooled to 0 °C and treated with imidazole (3.09 g, 45.3 mmol) and $Ph_2tBuSiCl$ (8.52 ml, 32.8 mmol). After 5 min, the solution was allowed to stir at rt for 3.5 h. The reaction was diluted with PE/Et_2O 1:1 and water and extracted with PE/Et_2O. Chromatography with PE/Et_2O 92:8→85:15 gave **10** as a pale yellow oil (11.14 g, 96%). R_f 0.33 (PE/Et_2O 9:1, A, C). Anal. found C, 75.70; H, 7.85. $C_{29}H_{36}O_3Si$ requires C, 75.61; H, 7.88. IR: ν_{max} 3465, 3001, 2931, 2856, 1610, 1506, 1190, 1109, 1031, 969. GC–MS (usual method but with final temperature 290 °C): R_t 12.89; *m/z* 403 (M^+-57, 0.30), 199 (2.9), 197 (1.5), 183 (1.1), 181 (1.1), 135 (2.2), 123 (1.0), 122 (9.9), 121 (100), 105 (1.1), 91 (1.4), 78 (1.7), 77 (3.2). ^1H NMR (200 MHz): 1.05 [9H, s, *t*Bu]; 2.34 [2H, centre of m, $CH_2CH_2C=$]; 3.46 [2H, t, CH_2CH_2O, $J=6.8$ Hz]; 3.80 [3H, s, OCH_3]; 4.16 [2H, apparent d, $CH_2OTBDPS$, $J=3.2$ Hz]; 4.44 [2H, s, CH_2Ar]; 5.55–5.77 [2H, m, C*H*=C*H*]; 6.86 [2H, dt, aromatics *ortho* to OMe, $J=2.4$, 8.8 Hz]; 7.23–7.46 [8H, m, aromatics]; 7.65–7.73 [4H, m, aromatics]. ^{13}C NMR (50 MHz): 19.21 [$C(CH_3)_3$]; 26.86 [3C, $C(CH_3)_3$]; 32.71 [$CH_2CH_2CH=$]; 55.22 [CH_3O]; 64.48 [$CH_2OTBDPS$]; 69.57 [CH_2CH_2O]; 72.54 [CH_2Ar]; 113.75 [2C, aromatics *ortho* to OMe]; 127.26 and 130.68 [2C, C*H*=C*H*]; 127.59 [4C, aromatics *meta* to Si]; 129.21 [2C, aromatics *meta* to OMe]; 129.55 [2C, aromatics *para* to Si]; 130.59 [quat. aromatic *para* to OMe]; 133.84 [2C, *C ipso* of Ph]; 135.54 [4C, aromatics *ortho* to Si]; 159.13 [*C*–OMe].

4.6. (*E*)-5-[(*t*-Butyldiphenylsilyl)oxy]pent-3-en-1-ol 11

A solution of **10** (8.31 g, 18.0 mmol) in CH_2Cl_2 (50 ml) was cooled to 0 °C and treated with water (2.5 ml) and DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) (6.14 g, 27.1 mmol). After 5 min the solution was allowed to stir at rt for 1 h 10 min. The mixture was partitioned between 5% $NaHCO_3$ and CH_2Cl_2 and filtered over a Celite pad. The filtrate was extracted again with CH_2Cl_2. Chromatography with PE/Et_2O 6:4 gave **11** as a colourless oil (5.04 g, 82%). R_f 0.26 (PE/Et_2O 6:4, A, C). Anal. found C, 74.15; H, 8.25. $C_{21}H_{28}O_2Si$ requires C, 74.07; H, 8.29. IR: ν_{max} 3464, 3006, 2927, 2857, 1680, 1598, 1243, 1108, 1029, 927. GC–MS: R_t 9.52; *m/z* 283 (M^+-57, 15), 253 (14), 205 (27), 201 (5.2), 200 (19), 199 (100), 197 (9.8), 187 (5.1), 181 (10), 175 (18),

174 (5.2), 139 (17), 135 (7.7), 127 (5.2), 121 (6.4), 105 (8.3), 78 (5.4), 77 (22), 67 (6.9), 57 (5.2), 45 (14), 41 (12), 39 (5.7). ^{1}H NMR (200 MHz): 1.06 [9H, s, *t*Bu]; 2.29 [2H, broad q, $CH_2CH_2C=$, $J=6.0$ Hz]; 3.63 [2H, t, CH_2CH_2OH, $J=6.0$ Hz]; 4.19 [2H, apparent d, $CH_2OTBDPS$, $J=3.0$ Hz]; 5.54–5.75 [2H, m, C*H*=C*H*]; 7.33–7.47 [6H, m, aromatics]; 7.66–7.71 [4H, m, aromatics]. ^{13}C NMR (50 MHz): 19.22 [$C(CH_3)_3$]; 26.85 [3C, $C(CH_3)_3$]; 35.62 [$CH_2CH_2CH=$]; 61.85 [CH_2OH]; 64.33 [CH_2-OTBDPS]; 126.58 and 132.22 [2C, *C*H=*C*H]; 127.65 [4C, aromatics *meta* to Si]; 129.65 [2C, aromatics *para* to Si]; 133.75 [2C, *C ipso* of Ph]; 135.56 [4C, aromatics *ortho* to Si].

4.7. (*E*)-5-Bromo-1-[(*t*-butyldiphenylsilyl)oxy]pent-2-ene 13

(1) *Tosylate* **12**. A solution of **11** (2.52 g, 7.42 mmol) in dry pyridine (7 ml) was treated at 0 °C with freshly distilled tosyl chloride (1.98 g, 10.4 mmol) and, after 5 min, allowed to stir at rt for 1 h 45 min (in some cases an addition of 0.4 mol equiv of tosyl chloride was required). The solution was poured into water and extracted with AcOEt. Solvent was removed under vacuo employing also heptane to remove azeotropically residue pyridine and crude tosylate was directly submitted to the nucleophilic displacement. For analytical purposes a sample of the crude was chromatographed with PE/Et_2O 9:1→6:4 to give **12** as a pale yellow oil. R_f 0.63 (PE/Et_2O 6:4, A, C). IR: ν_{max} 3004, 2932, 2855, 1599, 1360, 1191, 1110, 969. GC–MS: not feasible. ^{1}H NMR (200 MHz): 1.04 [9H, s, *t*Bu]; 2.27–2.40 [2H, m, $CH_2CH_2C=$]; 2.42 [3H, s, CH_3 (Ts)]; 4.02 [2H, t, CH_2OTs, $J=6.8$ Hz]; 4.11 [2H, apparent d, $CH_2OTBDPS$, $J=3.0$ Hz]; 5.45–5.68 [2H, m, C*H*=C*H*]; 7.29–7.45 [8H, m, aromatics]; 7.62–7.80 [6H, m, aromatics]. ^{13}C NMR (50 MHz): 19.20 [$C(CH_3)_3$]; 21.61 [CH_3 (Ts)]; 26.81 [3C, $C(CH_3)_3$]; 31.71 [$CH_2CH_2CH=$]; 64.03 [$CH_2OTBDPS$]; 69.61 [CH_2OTs]; 124.03 and 132.59 [2C, *C*H=*C*H]; 127.65 [4C, aromatics *meta* to Si]; 127.88, 129.64 and 129.79 [6C, *C*H of Ts and aromatics *para* to Si]; 133.16 [*C*-Me (Ts)]; 133.60 [2C, *C ipso* of Ph]; 135.49 [4C, aromatics *ortho* to Si]; 144.68 [*C*–SO_2]. (2) *Transformation of* **12** *into* **13**. A solution of crude tosylate from the previous reaction in dry DMF (20 ml) was treated with potassium bromide (1.41 g, 11.9 mmol) and heated at 100 °C for 35 min. The crude was poured into water and extracted with Et_2O. The collected organic layers were washed with water and then with brine. After solvent removal chromatography with PE/Et_2O 100:0→97.5:2.5 afforded pure **13** (2.48 g, 83% two steps) as a colourless oil. R_f 0.35 (PE/Et_2O 99:1, A, C). Anal. found C, 62.65; H, 6.70. $C_{21}H_{27}BrOSi$ requires C, 62.52; H, 6.75. IR: ν_{max} 3303, 2930, 2855, 1422, 1110, 1051, 969, 919. GC–MS: R_t 9.96; *m/z* 348 (11), 347 [$M^+(^{81}Br)-57$, 46], 346 (11), 345 [$M^+(^{79}Br)-57$, 43], 265 (12), 264 (18), 263 (100), 262 (18), 261 (99), 211 (5.1), 204 (5.5), 203 (46), 202 (6.1), 201 (49), 200 (9.7), 199 (48), 197 (23), 187 (10), 183 (12), 182 (6.6), 181 (30), 180 (7.0), 155 (5.7), 152 (8.1), 145 (15), 143 (14), 135 (14), 123 (83), 121 (14), 117 (8.7), 115 (5.6), 105 (28), 91 (24), 79 (5.9), 78 (12), 77 (44), 68 (5.1), 67 (56), 65 (8.1), 57 (28), 53 (13), 51 (11), 45 (31), 42 (5.0), 41 (75), 40 (5.4), 39 (23). ^{1}H NMR (200 MHz): 1.06 [9H, s, *t*Bu]; 2.54–2.64 [2H, m, $CH_2CH_2C=$]; 3.37 [2H, t, CH_2CH_2OH, $J=7.1$ Hz]; 4.17–4.19 [2H, m, $CH_2OTBDPS$]; 5.65–5.70 [2H, m, C*H*=C*H*]; 7.33–7.47 [6H, m, aromatics]; 7.66–7.72 [4H, m, aromatics]. ^{13}C NMR (50 MHz): 19.22 [$C(CH_3)_3$]; 26.83 [3C, $C(CH_3)_3$]; 32.31 [$CH_2CH_2CH=$]; 35.57 [CH_2Br]; 64.10 [$CH_2OTBDPS$]; 126.94 and 131.91 [2C, *C*H=*C*H]; 127.64 [4C, aromatics *meta* to Si]; 129.63 [2C, aromatics *para* to Si]; 133.68 [2C, *C ipso* of Ph]; 135.54 [4C, aromatics *ortho* to Si].

4.8. (*E*)-Diethyl 2-acetamido-2-{5-[(*t*-butyldiphenylsilyl)oxy]pent-3-enyl}malonate 14

A suspension of NaH (60% in mineral oil, 388 mg, 9.70 mmol) in dry DMF (10 ml) was cooled to 0 °C. Then a solution of diethyl acetamidomalonate (2.33 g, 10.7 mmol) in DMF (10 ml) was added through an addition funnel over a period of 10 min. After stirring for additional 5 min at rt, the resulting yellow solution was treated with a solution of bromide **13** (2.94 g, 7.29 mmol) in DMF (10 ml) and immediately heated at 90 °C for 3 h. After this time, the reaction was quenched, even if some unreacted bromide was still present. The resulting solution was cautiously added to saturated aqueous NH_4Cl, diluted with water and extracted with Et_2O. Chromatography with PE/Et_2O 8:2→2:8 afforded pure **14** in 75–88% yield as a pale yellow oil. R_f 0.51 (PE/AcOEt 6:4, A, B). Anal. found C, 66.80; H, 7.60. $C_{30}H_{41}NO_6Si$ requires C, 66.76; H, 7.66. IR: ν_{max} 3411, 2998, 2957, 2856, 1736, 1675, 1187, 1105, 1032, 922. GC–MS (usual method but with final temperature 290 °C): R_t 13.32; *m/z* 483 (15), 482 (M^+-57, 44), 260 (8.9), 238 (6.0), 201 (5.6), 200 (18), 199 (100), 197 (20), 183 (12), 181 (14), 178 (11), 174 (6.5), 173 (7.3), 169 (8.3), 168 (72), 167 (7.6), 140 (10), 139 (16), 137 (6.6), 135 (20), 123 (9.6), 122 (7.5), 121 (8.6), 105 (10), 95 (5.2), 94 (21), 79 (7.2), 77 (83), 67 (12), 43 (43). ^{1}H NMR (200 MHz): 1.05 [9H, s, *t*Bu]; 1.26 [6H, t, CH_2CH_3, $J=7.2$ Hz]; 1.83–1.94 [2H, m, $CH_2CH_2C=$]; 2.04 [3H, s, CH_3CO]; 2.42 [2H, centre of m, $CH_2CH_2C=$]; 4.12 [2H, apparent d, $CH_2OTBDPS$, $J=3.0$ Hz]; 4.24 [4H, q, CH_2CH_3, $J=7.1$ Hz]; 5.47–5.69 [2H, m, C*H*=C*H*]; 6.76 [1H, broad s, N*H*]; 7.32–7.43 [6H, m, aromatics]; 7.64–7.69 [4H, m, aromatics]. ^{13}C NMR (50 MHz): 13.90 [2C, CH_2CH_3]; 19.13 [$C(CH_3)_3$]; 22.97 [CH_3CO]; 26.46 [$CH_2CH_2CH=$]; 26.76 [3C, $C(CH_3)_3$]; 31.53 [$CH_2CH_2CH=$]; 62.42 [2C, CH_2CH_3]; 64.20 [CH_2-OTBDPS]; 66.19 [$C(CO_2Et)_2$]; 127.56 [4C, aromatics *meta* to Si]; 128.78 and 129.76 [2C, *C*H=*C*H]; 129.54 [2C, aromatics *para* to Si]; 133.62 [2C, *C ipso* of Ph]; 135.44 [4C, aromatics *ortho* to Si]; 168.01 [2C, CO_2Et]; 168.94 [CH_3CO].

4.9. (±)-(*E*)-Ethyl 2-acetamido-7-[(*t*-butyldiphenylsilyl)oxy]hept-5-enoate 15

(1) *Monohydrolysis*. A solution of **14** (2.07 g, 3.88 mmol) in 96% EtOH (30 ml) was treated with 6 N aqueous NaOH (832 μl) and stirred at rt for 4 h. In some cases, an additional little amount of NaOH (0.2–0.3 mol equiv) was needed and not always the reaction went to completion. It is, however, preferred not to employ an excess of NaOH in order to avoid the double saponification, while the unreacted malonate can be easily recovered and recycled. A solution of concentrated HCl (400 μl in 1.5 ml of 96% EtOH) was added, followed by 5% aqueous $NH_4H_2PO_4$. The mixture was concentrated

under vacuo, partitioned between brine and AcOEt and extracted with AcOEt, after adjusting the pH to 2. R_f 0.36 (PE/AcOEt 7:3+5% AcOH, A, B). (2) *Decarboxylation*. The crude from the previous reaction was dissolved in dioxane (20 ml) and refluxed under nitrogen for 1 h. After solvent removal chromatography with PE/AcOEt 7:3→4:6 gave **15** as a pale yellow oil (1.50 g, 83%) (in some cases up to 16% unreacted malonate can be recovered). R_f 0.31 (PE/AcOEt 6:4, A, B). Anal. found C, 69.50; H, 7.85. $C_{27}H_{37}NO_4Si$ requires C, 69.34; H, 7.97. IR: ν_{max} 2990, 2955, 2928, 2855, 1730, 1669, 1602, 1110, 1037, 973. GC–MS (usual method but with final temperature 290 °C): R_t 12.30; *m/z* 411 (15), 410 (M^+-57, 48), 200 (15), 199 (79), 197 (12), 183 (9.8), 181 (13), 180 (6.3), 166 (5.8), 139 (15), 138 (26), 137 (5.9), 135 (15), 123 (5.9), 121 (9.2), 105 (11), 102 (6.2), 97 (9.5), 96 (100), 91 (5.2), 81 (7.1), 79 (22), 78 (7.1), 77 (27), 74 (5.6), 68 (9.5), 67 (11), 60 (83), 57 (8.8), 45 (13), 44 (5.5), 43 (92), 42 (6.9), 41 (14). ^{1}H NMR (200 MHz): 1.05 [9H, s, *t*Bu]; 1.29 [3H, t, CH_2CH_3, J=7.0 Hz]; 1.60–2.13 [4H, m, CH_2CH_2C=]; 2.02 [3H, s, CH_3CO]; 4.14 [2H, apparent d, $CH_2OTBDPS$, J=3.2 Hz]; 4.21 [2H, q, CH_2CH_3, J=7.2 Hz]; 4.61 [1H, dt, $CHCO_2Et$, J=5.0, 7.6 Hz]; 5.47–5.72 [2H, m, CH=CH]; 5.98 [1H, broad d, NH, J=8.0 Hz]; 7.32–7.43 [6H, m, aromatics]; 7.64–7.69 [4H, m, aromatics]. ^{13}C NMR (50 MHz): 14.09 [CH_2CH_3]; 19.13 [$C(CH_3)_3$]; 23.08 [CH_3CO]; 26.77 [3C, $C(CH_3)_3$]; 27.91 [CH_2CH_2CH=]; 31.99 [CH_2CH_2CH=]; 51.86 [$CHCO_2Et$]; 61.35 [CH_2CH_3]; 64.24 [$CH_2OTBDPS$]; 127.55 [4C, aromatics *meta* to Si]; 128.92 and 129.96 [2C, CH=CH]; 129.52 [2C, aromatics *para* to Si]; 133.67 [2C, *C ipso* of Ph]; 135.44 [4C, aromatics *ortho* to Si]; 169.72 and 172.51 [2C, CO].

4.10. (±)-(*E*)-*t*-Butyl 2-acetamido-7-[(*t*-butyldiphenylsilyl)oxy]hept-5-enoate 16

(1) *Hydrolysis of the ester*. The same procedure described in the above paragraph was followed starting from 363 mg (777 μmol) of **15**, using this time 1.7 mol equiv of 6 N aqueous NaOH. R_f 0.46 (AcOEt/AcOH 95:5, A, B). (2) *Formation of the t-butyl ester*. A solution of crude acid in dry CH_2Cl_2 (20 ml) was treated with *t*-butyl-2,2,2-trichloroacetimidate (278 μl, 1.55 mmol) and stirred at rt for 1 h 10 min, before $BF_3\cdot Et_2O$ (8 μl, 65 μmol) was added. After stirring for additional 2 h 20 min, solid $NaHCO_3$ (17 mg) was added and the crude was filtered and concentrated under vacuo. Chromatography with PE/AcOEt 7:3→1:1 afforded **16** as a pale yellow oil (289 mg, 75% from **15**). R_f 0.30 (PE/AcOEt 6:4, A, B). Anal. found C, 70.15; H, 8.30. $C_{29}H_{41}NO_4Si$ requires C, 70.26; H, 8.34. IR: ν_{max} 3019, 2926, 2857, 1726, 1667, 1603, 1369, 1192, 1153, 1111, 1056, 928, 876. GC–MS: not feasible. ^{1}H NMR (200 MHz): 1.05 [9H, s, Si*t*Bu]; 1.47 [9H, s, O*t*Bu]; 1.60–2.18 [4H, m, CH_2CH_2C=]; 2.01 [3H, s, CH_3CO]; 4.06–4.22 [2H, m, $CH_2OTBDPS$]; 4.51 [1H, dt, $CHCO_2tBu$, J=5.2, 7.6 Hz]; 5.49–5.72 [2H, m, CH=CH]; 6.08 [1H, broad d, NH, J=7.6 Hz]; 7.32–7.43 [6H, m, aromatics]; 7.64–7.69 [4H, m, aromatics]. ^{13}C NMR (50 MHz): 19.21 [$SiC(CH_3)_3$]; 23.27 [CH_3CO]; 26.83 [3C, $SiC(CH_3)_3$]; 27.92 [CH_2CH_2CH=]; 28.00 [3C, $OC(CH_3)_3$]; 32.28 [CH_2CH_2CH=]; 52.42 [$CHCO_2Et$]; 64.36 [$CH_2OTBDPS$]; 82.22 [$OC(CH_3)_3$]; 127.61 [4C, aromatics *meta* to Si]; 129.26 and 129.83 [2C, CH=CH]; 129.59 [2C, aromatics *para* to Si]; 133.74 [2C, *C ipso* of Ph]; 135.53 [4C, aromatics *ortho* to Si]; 169.73 and 171.83 [2C, CO].

4.11. General procedure for TBDPS removal

A solution of silyl ether (1.58 mmol) in dry THF (5 ml) was cooled to 0 °C and treated with 0.7 M solution of nBu$_4$NF in THF (4.51 ml); after 10 min, the solution was allowed to stir a rt for 2 h. After dilution with brine, an extraction with AcOEt was performed.

4.11.1. (±)-(*E*)-Ethyl 2-acetamido-7-hydroxyhept-5-enoate 17. Chromatography with AcOEt/MeOH 100:0→8:2 gave **17** as a colourless oil in 96% yield. R_f 0.47 (AcOEt/MeOH 95:5, B). Anal. found C, 57.60; H, 8.40. $C_{11}H_{19}NO_4$ requires C, 57.62; H, 8.35. IR: ν_{max} 3428, 3005, 2800, 1730, 1671, 1376, 1245, 1136, 1079, 973, 703. GC–MS: R_t 6.87; *m/z* 229 (M^+, 0.11), 186 (5.5), 156 (15), 152 (29), 138 (18), 124 (12), 123 (9.4), 114 (16), 112 (8.4), 103 (9.0), 102 (58), 97 (11), 96 (95), 95 (6.2), 94 (7.7), 86 (5.4), 84 (5.4), 82 (7.8), 81 (5.2), 80 (5.5), 79 (44), 78 (15), 74 (20), 70 (5.7), 69 (5.6), 68 (6.9), 67 (83), 60 (11), 57 (9.1), 56 (7.9), 55 (7.5), 44 (18), 43 (100), 42 (12), 41 (18), 39 (7.1). ^{1}H NMR (200 MHz): 1.22 [3H, t, CH_2CH_3, J=7.1 Hz]; 1.59–2.11 [4H, m, CH_2CH_2C=]; 1.96 [3H, s, CH_3CO]; 4.02 [2H, broad s, CH_2OH]; 4.14 [2H, q, CH_2CH_3, J=7.2 Hz]; 4.56 [1H, dt, $CHCO_2Et$, J=5.4, 7.8 Hz]; 5.50–5.69 [2H, m, CH=CH]; 6.01 [1H, broad d, NH, J=8.0 Hz]. ^{13}C NMR (50 MHz): 13.98 [CH_2CH_3]; 22.83 [CH_3CO]; 27.88 [CH_2CH_2CH=]; 31.52 [CH_2CH_2CH=]; 51.55 [$CHCO_2Et$]; 61.34 [CH_2CH_3]; 62.83 [CH_2OH]; 130.18 and 130.56 [2C, CH=CH]; 170.34 and 172.59 [2C, CO].

4.11.2. (±)-(*E*)-*t*-Butyl 2-acetamido-7-hydroxyhept-5-enoate 18. Chromatography with AcOEt/MeOH 100:0→9:1 gave **18** as a colourless oil in 80% yield. R_f 0.18 (AcOEt, B). Anal. found C, 60.55; H, 9.10. $C_{13}H_{23}NO_4$ requires C, 60.68; H, 9.01. IR: ν_{max} 3429, 2978, 2871, 1723, 1667, 1370, 1193, 1153, 1075, 973. GC–MS: R_t 7.14; *m/z* 239 (M^+-18, 0.099), 184 (8.4), 183 (14), 158 (8.2), 157 (12), 156 (18), 138 (15), 124 (26), 123 (8.0), 114 (21), 99 (7.1), 97 (10), 96 (100), 86 (5.9), 85 (7.1), 79 (21), 74 (9.4), 60 (9.2), 57 (28), 44 (5.6), 43 (29), 41 (12). ^{1}H NMR (200 MHz): 1.48 [9H, s, *t*Bu]; 1.62–2.18 [4H, m, CH_2CH_2C=]; 2.02 [3H, s, CH_3CO]; 4.09 [2H, broad s, CH_2OH]; 4.53 [1H, dt, $CHCO_2tBu$, J=5.0, 7.6 Hz]; 5.58–5.76 [2H, m, CH=CH]; 6.05 [1H, broad d, NH, J=7.8 Hz]. ^{13}C NMR (50 MHz): 23.32 [CH_3CO]; 27.93 [CH_2CH_2CH=]; 28.01 [3C, $C(CH_3)_3$]; 32.19 [CH_2CH_2CH=]; 52.09 [$CHCO_2Et$]; 63.54 [CH_2OH]; 82.31 [$C(CH_3)_3$]; 130.30 and 131.21 [2C, CH=CH]; 169.69 and 171.80 [2C, CO].

4.11.3. (*E*)-Diethyl 2-acetamido-2-5-(hydroxypent-3-enyl)malonate 19. Chromatography with PE/AcOEt 10:90→0:100 gave **19** as a colourless oil in 85% yield. R_f 0.44 (AcOEt, B). Anal. found C, 55.75; H, 7.80. $C_{14}H_{23}NO_6$ requires C, 55.80; H, 7.69. IR: ν_{max} 3411, 2978, 2868, 1736, 1673, 1474, 1370, 1265, 1089, 1010, 974, 856, 736. GC–MS: R_t 7.85; *m/z* 301 (M^+, 0.092), 228 (11), 217 (5.1), 186 (19), 179 (12), 178 (100), 175 (9.5), 174 (15), 171 (48), 169 (12), 168 (65), 164 (8.8), 151 (6.6), 143 (35), 140 (15), 129 (17), 125 (18), 123 (11), 122 (16), 116 (12), 115 (6.1), 112 (13), 101 (6.4), 95 (8.9), 94 (34), 93 (5.7), 88

(5.1), 84 (83), 80 (5.2), 79 (12), 71 (6.2), 70 (6.4), 68 (5.4), 67 (25), 55 (7.3), 54 (6.8), 53 (5.3), 43 (89), 42 (25), 41 (20), 39 (5.7). ^{1}H NMR (300 MHz): 1.25 [6H, t, CH_2CH_3, J=7.1 Hz]; 1.87–1.94 [2H, m, CH_2CH_2C=]; 2.03 [3H, s, CH_3CO]; 2.44 [2H, centre of m, CH_2CH_2C=]; 4.56 [2H, apparent d, CH_2OH, J=3.6 Hz]; 4.24 [4H, q, CH_2CH_3, J=7.2 Hz]; 5.55–5.69 [2H, m, CH=CH]; 6.79 [1H, broad s, NH]. ^{13}C NMR (75 MHz): 13.84 [2C, CH_2CH_3]; 22.85 [CH_3CO]; 26.38 [CH_2CH_2CH=]; 31.35 [CH_2CH_2CH=]; 62.46 [2C, CH_2CH_3]; 63.11 [CH_2OH]; 66.12 [$C(CO_2Et)_2$]; 130.09 and 130.49 [2C, CH=CH]; 167.94 [2C, CO_2Et]; 169.18 [CH_3CO].

4.12. (±)-(*E*)-Ethyl 2-acetamido-7-chlorohept-5-enoate 20.

A solution of **17** (200 mg, 872 μmol) in dry CCl_4 (1 ml) was treated with PPh_3 (366 mg, 1.40 mmol) and refluxed for 6 h. The reaction was poured into NH_4Cl saturated solution and extracted with AcOEt. Chromatography with Et_2O/AcOEt/8:2 gave **20** as a pale yellow oil in 66% yield. R_f 0.42 (Et_2O/AcOEt 8:2, A, C). Anal. found C, 53.30; H, 7.45. $C_{11}H_{18}ClNO_3$ requires C, 53.33; H, 7.32. IR: ν_{max} 3430, 2978, 1731, 1671, 1494, 1375, 1187, 1125, 1092, 966. GC–MS: R_t 7.31; m/z 249 [M^+(^{37}Cl), 0.039], 247 [M^+(^{35}Cl), 0.12], 212 (40), 176 (5.9), 174 (18), 170 (12), 166 (9.5), 152 (14), 145 (6.5), 138 (18), 134 (25), 133 (5.4), 132 (77), 103 (5.1), 102 (23), 99 (15), 96 (46), 85 (5.5), 81 (5.0), 79 (22), 78 (5.1), 74 (12), 67 (7.3), 60 (17), 53 (14), 44 (8.5), 43 (100), 42 (11), 41 (12), 39 (8.0). ^{1}H NMR (200 MHz): 1.29 [3H, t, CH_2CH_3, J=7.2 Hz]; 1.67–2.18 [4H, m, CH_2CH_2C=]; 2.03 [3H, s, CH_3CO]; 4.02 [2H, apparent d, CH_2Cl, J=6.2 Hz]; 4.21 [2H, q, CH_2CH_3, J=7.2 Hz]; 4.62 [1H, dt, $CHCO_2Et$, J=5.0, 7.8 Hz]; 5.57–5.83 [2H, m, CH=CH]; 6.08 [1H, broad d, NH, J=7.4 Hz]. ^{13}C NMR (50 MHz): 14.16 [CH_2CH_3]; 23.24 [CH_3CO]; 27.82 [CH_2CH_2CH=]; 31.77 [CH_2CH_2CH=]; 45.01 [CH_2Cl]; 51.74 [$CHCO_2Et$]; 61.61 [CH_2CH_3]; 127.15 and 133.94 [2C, CH=CH]; 169.77 and 172.37 [2C, CO].

4.13. General procedure for the direct transformation of alcohols into bromides

To a solution of alcohol (2.85 mmol) in dry CH_3CN (15 ml), previously cooled to 0 °C, PPh_3 (4.27 mmol) and CBr_4 (4.27 mmol) were added and, after 5 min, the resulting solution was allowed to stir at rt for about 35 min. After dilution with saturated aqueous $NaHCO_3$, an extraction with AcOEt was performed.

4.13.1. (±)-(*E*)-Ethyl 2-acetamido-7-bromohept-5-enoate 21. Chromatography with Et_2O/AcOEt 100:0→9:1 gave **21** as a white-gray solid in 88% yield. Crystallization from CH_2Cl_2/iPr_2O afforded white crystals. Mp: 70.1–70.6 °C (CH_2Cl_2/iPr_2O). R_f 0.51 (Et_2O/AcOEt 8:2, A, B, C). Anal. found C, 45.30; H, 6.15. $C_{11}H_{18}BrNO_3$ requires C, 45.22; H, 6.21. IR: ν_{max} 3428, 3004, 1730, 1670, 1376, 1193, 1019, 967. GC–MS: R_t 7.31; m/z 248 [M^+(^{81}Br)−45, 1.1], 246 [M^+(^{79}Br)−45, 0.92], 220 (7.2), 219 (7.1), 213 (5.6), 212 (44), 178 (28), 176 (28), 170 (18), 166 (17), 138 (28), 102 (19), 97 (7.4), 93 (84), 85 (8.2), 81 (6.3), 79 (20), 74 (9.9), 67 (8.1), 60 (27), 53 (11), 44 (6.3), 43 (100), 42 (11), 41 (12), 39 (7.9). ^{1}H NMR (200 MHz): 1.30 [3H, t, CH_2CH_3, J=7.2 Hz]; 1.69–2.22 [4H, m, CH_2CH_2C=]; 2.04 [3H, s, CH_3CO]; 3.87–4.01 [2H, m, CH_2Br]; 4.22 [2H, q, CH_2CH_3, J=7.1 Hz]; 4.62 [1H, dt, $CHCO_2Et$, J=5.0, 7.7 Hz]; 5.69–5.80 [2H, m, CH=CH]; 6.06 [1H, broad d, NH, J=7.6 Hz]. ^{13}C NMR (50 MHz): 14.17 [CH_2CH_3]; 23.25 [CH_3CO]; 27.85 [CH_2CH_2CH=]; 31.74 [CH_2CH_2CH=]; 32.94 [CH_2Br]; 51.62 [$CHCO_2Et$]; 61.62 [CH_2CH_3]; 127.54 and 134.39 [2C, CH=CH]; 169.77 and 172.36 [2C, CO].

4.13.2. (±)-(*E*)-*t*-Butyl 2-acetamido-7-bromohept-5-enoate 22. Chromatography with ETP/AcOEt 2:8 gave **22** as a white foam in 75% yield. R_f 0.50 (ETP/AcOEt 2:8, A, B, C). Anal. found C, 48.75; H, 6.85. $C_{13}H_{22}BrNO_3$ requires C, 48.76; H, 6.92. IR: ν_{max} 3009, 2958, 1723, 1666, 1189, 1149, 1097, 1010, 922. GC–MS: R_t 7.60; m/z 248 [M^+(^{81}Br)−73, 3.1], 246 [M^+(^{79}Br)−73, 3.1], 220 (13), 218 (13), 185 (8.4), 184 (84), 178 (44), 176 (46), 142 (29), 140 (8.0), 138 (20), 97 (5.4), 96 (46), 86 (11), 85 (7.9), 81 (5.5), 79 (14), 74 (11), 60 (19), 57 (67), 56 (6.7), 53 (11), 44 (10), 43 (100), 42 (9.8), 41 (40), 39 (10). ^{1}H NMR (200 MHz): 1.48 [9H, s, *t*Bu]; 1.63–2.18 [4H, m, CH_2CH_2C=]; 2.02 [3H, s, CH_3CO]; 3.86–4.02 [2H, m, CH_2Br]; 4.52 [1H, dt, $CHCO_2tBu$, J=5.4, 7.2 Hz]; 5.63–5.84 [2H, m, CH=CH]; 6.04 [1H, broad d, NH, J=7.6 Hz]. ^{13}C NMR (50 MHz): 23.32 [CH_3CO]; 27.85 [CH_2CH_2-CH=]; 28.02 [3C, $C(CH_3)_3$]; 31.95 [CH_2CH_2CH=]; 33.01 [CH_2Br]; 52.22 [$CHCO_2Et$]; 82.39 [$C(CH_3)_3$]; 127.36 and 134.68 [2C, CH=CH]; 169.65 and 171.54 [2C, CO].

4.13.3. Diethyl 2-acetamido-2-5-(bromopent-3-enyl)-malonate 23. Chromatography with PE/AcOEt/ 2:8→0:100 gave **23** as a pale yellow oil in 92% yield. R_f 0.61 (Et_2O, A, B, C). Anal. found C, 46.25; H, 6.05. $C_{14}H_{22}BrNO_5$ requires C, 46.17; H, 6.09. IR: ν_{max} 3410, 3005, 1734, 1676, 1481, 1369, 1268, 1230, 1094, 1006, 969. GC–MS: R_t 8.28; m/z 320 [M^+(^{81}Br)−45, 0.84], 318 [M^+(^{79}Br)−45, 0.84], 284 (30), 250 (17), 248 (19), 243 (6.1), 242 (42), 238 (5.2), 174 (7.3), 171 (5.0), 169 (11), 168 (98), 151 (5.1), 140 (9.9), 135 (5.3), 133 (6.9), 123 (9.4), 122 (8.6), 116 (5.6), 115 (14), 112 (5.2), 111 (8.3), 96 (6.1), 95 (9.4), 94 (34), 80 (5.0), 79 (15), 77 (6.0), 71 (83), 67 (28), 60 (6.9), 55 (5.3), 54 (8.1), 53 (16), 43 (100), 42 (19), 41 (22), 39 (7.5). ^{1}H NMR (300 MHz): 1.22 [6H, t, CH_2CH_3, J=7.2 Hz]; 1.87–1.94 [2H, m, CH_2CH_2C=]; 2.01 [3H, s, CH_3CO]; 2.40 [2H, centre of m, CH_2CH_2C=]; 3.82–3.95 [2H, m, CH_2Br]; 4.21 [4H, q, CH_2CH_3, J=7.0 Hz]; 5.59–5.73 [2H, m, CH=CH]; 6.77 [1H, broad s, NH]. ^{13}C NMR (75 MHz): 13.85 [2C, CH_2CH_3]; 22.91 [CH_3CO]; 26.34 [CH_2CH_2CH=]; 31.08 [CH_2CH_2CH=]; 32.79 [CH_2Br]; 62.47 [2C, CH_2CH_3]; 66.02 [$C(CO_2Et)_2$]; 127.10 and 134.26 [2C, CH=CH]; 167.77 [2C, CO_2Et]; 169.00 [CH_3CO].

4.14. General procedure for the S_N2' cyclization

Several experiments have been performed, adding the desired base to a solution of halide (compounds **20**–**23**) (for solvent and base, see Table 1) under argon. Reaction times, temperatures, yields and dr are reported in Table 1. Quenching with 5% aqueous $NH_4H_2PO_4$ was followed by extraction with AcOEt.

4.14.1. (2*R,5*R**)- and (2*R**,5*S**)-Ethyl 1-acetyl-5-vinylpyrrolidine-2-carboxylate 24a and 24b.** Chromatography with Et_2O/AcOEt 8:2→6:4 gave diastereomeric products as a pale yellow oil. The same chromatography also allowed to obtain analytically pure diastereoisomers. *trans Derivative (2R*,5R*)*: R_f 0.40 (Et_2O/AcOEt 8:2, B). Anal. found C, 62.60; H, 8.05. $C_{11}H_{17}NO_3$ requires C, 62.54; H, 8.11. IR: ν_{max} 2956, 2919, 2853, 1735, 1631, 1407, 1177, 1094, 1011, 921. GC–MS: R_t 5.42; *m/z* 211 (M^+, 2.3), 138 (30), 97 (7.2), 96 (100), 79 (7.1), 68 (9.1), 43 (25), 41 (9.0), 39 (5.1). ^{1}H NMR (200 MHz): 1.25 [3H, t, CH_2CH_3, J=7.2 Hz]; 1.70–2.42 [4H, m, H_3 and H_4]; 2.04 [3H, s, CH_3CO]; 4.12–4.23 [2H, m, CH_2CH_3]; 4.37–4.60 [2H, m, H_2 and H_5]; 5.07 [1H, dt, CH*H*=CH, J=1.2, 17.2 Hz]; 5.17 [1H, dt, C*H*H=CH, J=1.1, 10.4 Hz]; 5.80 [1H, ddd; CH_2=C*H*, J=5.2, 10.2, 16.8 Hz]. ^{13}C NMR (50 MHz): 14.11 [CH_2CH_3]; 22.06 [CH_3CO]; 26.45 [C_3]; 30.71 [C_4]; 59.15 and 60.71 [2C, C_2 and C_5]; 61.02 [CH_2CH_3]; 115.18 [CH_2=CH]; 137.64 [CH_2=*C*H]; 170.27 and 172.14 [2C, *C*O]. *cis Derivative (2R*,5S*)*: R_f 0.30 (Et_2O/AcOEt 8:2, B). Anal. found C, 62.55; H, 8.15. $C_{11}H_{17}NO_3$ requires C, 62.54; H, 8.11. IR: ν_{max} 3002, 1737, 1637, 1406, 1375, 1356, 1194, 1029, 919. GC–MS: R_t 5.55; *m/z* 211 (M^+, 8.8), 139 (5.2), 138 (59), 97 (6.7), 96 (100), 79 (5.4), 68 (5.2), 43 (8.7). ^{1}H NMR (200 MHz): 1.28 [3H, t, CH_2CH_3, J=7.1 Hz]; 1.81–2.27 [4H, m, H_3 and H_4]; 2.05 [3H, s, CH_3CO]; 4.12–4.52 [4H, m, CH_2CH_3, H_2 and H_5]; 5.22 [1H, dt, CH*H*=CH, J=1.1, 10.4 Hz]; 5.46 [1H, dt, C*H*H=CH, J=1.3, 17.2 Hz]; 5.93 [1H, ddd; CH_2=C*H*, J=6.6, 10.2, 17.2 Hz]. ^{13}C NMR (50 MHz): 14.15 [CH_2CH_3]; 22.13 [CH_3CO]; 27.47 [C_3]; 32.42 [C_4]; 59.98 and 61.07 [2C, C_2 and C_5]; 61.63 [CH_2CH_3]; 116.52 [CH_2=CH]; 137.97 [CH_2=*C*H]; 170.14 and 172.26 [2C, *C*O].

4.14.2. (2*R,5*R**)- and (2*R**,5*S**)-*t*-Butyl 1-acetyl-5-vinylpyrrolidine-2-carboxylate 25a and 25b.** Chromatography with PE/AcOEt 4:6 gave separated diastereomeric products as pale yellow oils. The relative configuration was established to be trans for the major and cis for the minor product on the basis of spectroscopic analogies with the ethyl ester series. *trans Derivative (2R*,5R*)*: R_f 0.37 (PE/AcOEt 4:6, B). Anal. found C, 65.40; H, 8.80. $C_{13}H_{21}NO_3$ requires C, 65.25; H, 8.84. IR: ν_{max} 3001, 1731, 1632, 1407, 1368, 1150. GC–MS: R_t 5.79; *m/z* 239 (M^+, 2.4), 166 (7.0), 139 (8.0), 138 (67), 97 (11), 96 (100), 94 (6.1), 79 (9.3), 68 (9.2), 67 (5.8), 57 (15), 43 (29), 41 (17), 39 (7.0). ^{1}H NMR (200 MHz): 1.45 [9H, s, $C(CH_3)_3$]; 1.62–2.42 [4H, m, H_3 and H_4]; 2.04 [3H, s, CH_3CO]; 4.26–4.52 [2H, m, H_2 and H_5]; 5.07 [1H, dt, CH*H*=CH, J=1.2, 16.8 Hz]; 5.16 [1H, broad d, C*H*H=CH, J=10.6 Hz]; 5.80 [1H, ddd; CH_2=C*H*, J=5.4, 10.6, 17.2 Hz]. ^{13}C NMR (50 MHz): 22.13 [CH_3CO]; 26.52 [C_3]; 27.98 [3C, $C(CH_3)_3$]; 30.72 [C_4]; 59.95 and 60.78 [2C, C_2 and C_5]; 81.17 [$C(CH_3)_3$]; 115.08 [CH_2=CH]; 137.91 [CH_2=*C*H]; 170.10 and 171.40 [2C, *C*O]. *cis Derivative (2R*,5S*)*: R_f 0.23 (PE/AcOEt 4:6, B). Anal. found C, 65.30; H, 8.90. $C_{13}H_{21}NO_3$ requires C, 65.25; H, 8.84. IR: ν_{max} 3005, 1732, 1633, 1407, 1240, 1097, 1009, 924. GC–MS: R_t 5.88; *m/z* 239 (M^+, 1.3), 139 (5.4), 138 (46), 97 (7.3), 96 (100), 79 (5.6), 68 (5.4), 57 (8.7), 43 (16), 41 (9.4). ^{1}H NMR (200 MHz): 1.47 [9H, s, $C(CH_3)_3$]; 1.67–2.35 [4H, m, H_3 and H_4]; 2.04 [3H, s, CH_3CO]; 4.22–4.70 [2H, m, H_2 and H_5]; 5.21 [1H, dt, CH*H*=CH, J=1.0, 10.2 Hz]; 5.43 [1H, dt, C*H*H=CH, J=1.0, 17.2 Hz]; 5.94 [1H, ddd; CH_2=C*H*, J=6.6, 10.6, 17.2 Hz]. ^{13}C NMR (50 MHz): 22.20 [CH_3CO]; 27.50 [C_3]; 28.01 [3C, $C(CH_3)_3$]; 32.42 [C_4]; 60.83 and 61.72 [2C, C_2 and C_5]; 81.16 [$C(CH_3)_3$]; 116.36 [CH_2=CH]; 138.25 [CH_2=*C*H]; 169.82 and 169.89 [2C, *C*O].

4.14.3. (±)-Diethyl 1-acetyl-5-vinylpyrrolidine-2,2-dicarboxylate 26. Chromatography with PE/Et_2O 1:9→0:100 gave diastereomeric products as a colourless oil. R_f 0.43 (Et_2O, B). Anal. found C, 59.50; H, 7.40. $C_{14}H_{21}NO_5$ requires C, 59.35; H, 7.47. IR: ν_{max} 2978, 2869, 1735, 1654, 1394, 1191, 1128, 1092, 1016, 925. GC–MS: R_t 6.79; *m/z* 283 (M^+, 3.6), 240 (2.5), 210 (6.6), 169 (10), 168 (100), 140 (5.3), 94 (4.7), 67 (3.5), 43 (5.0). ^{1}H NMR (300 MHz): 1.28 and 1.27 [6H, 2t, CH_2CH_3, J=7.2 Hz]; 1.73–2.47 [4H, m, H_3 and H_4]; 2.06 [3H, s, CH_3CO]; 4.23 [4H, centre of m, CH_2CH_3]; 4.47 [1H, centre of m, H_5]; 5.22 [1H, broad d, CH*H*=CH, J=10.5 Hz]; 5.40 [1H, dt, C*H*H=CH, J=1.1, 17.1 Hz]; 5.86 [1H, ddd; CH_2=C*H*, J=5.7, 10.2, 16.8 Hz]. ^{13}C NMR (75 MHz): 13.90 and 13.96 [2C, CH_2CH_3]; 22.36 [CH_3CO]; 31.27 and 33.64 [2C, C_3 and C_4]; 61.65 [C_5]; 61.87 and 61.95 [2C, CH_2CH_3]; 73.01 [$C(CO_2Et)_2$]; 116.48 [CH_2=CH]; 137.54 [CH_2=*C*H]; 168.58, 168.75 and 170.16 [3C, *C*O].

4.15. (2*R,5*R**)- and (2*R**,5*S**)-Ethyl 1-acetyl-5-vinylpyrrolidine-2-carboxylate 24a,b from 26**

The same two step procedure described to obtain compound **15** was followed to give **24a**,**b** in 80% overall yield, as a 12:88 trans:cis mixture.

4.16. (2*R,5*R**)- and (2*R**,5*S**)-1-Acetyl-2-hydroxymethyl-5-vinylpyrrolidine 27a and 27b**

Dry $CaCl_2$ (274 mg, 2.47 mmol) was suspended in a solution of dry THF–EtOH (2/1, 4.5 ml) and cooled to −20 °C. Solid $NaBH_4$ (156 mg, 4.12 mmol) was rapidly added and the resulting slurry was stirred for 30 min at −20 °C. A solution of ester **24** (174 mg, 823 μmol) in dry THF (4 ml) was added and the reaction was allowed to stir at the same temperature overnight. Quenching with a 2:1 solution of NH_4Cl (satd soln)/KH_2PO_4 (1 M) was followed by addition of AcOEt and filtration over a Celite pad. After saturation with solid NaCl, the extraction was performed with AcOEt/MeOH 9:1. The crude can then be used as such for the following reaction, or purified by chromatography with AcOEt/MeOH 100:0→95:5 to give pure alcohol as a colourless oil (124 mg, 89%). *trans Derivative (2R*,5R*)*: R_f 0.36 (AcOEt/MeOH 95:5, B). Anal. found C, 63.70; H, 8.90. $C_9H_{15}NO_2$ requires C, 63.88; H, 8.93. IR: ν_{max} 3389, 2985, 2876, 1608, 1411, 1064, 993, 968, 924. GC–MS (parameters changed in the usual method: init. temperature 80 °C, init. time 2 min, rate 10 °C/min, final temperature 260 °C, final time 4 °C, inj. temperature 200 °C): R_t 8.26; *m/z* 169 (M^+, 2.4), 151 (1.4), 139 (5.2), 138 (41), 97 (7.1), 96 (100), 79 (12), 68 (6.3), 43 (23), 41 (7.2), 39 (5.5). ^{1}H NMR (300 MHz): 1.60–2.24 [4H, m, H_3 and H_4]; 2.06 [3H, s, CH_3CO]; 3.61–3.75 [2H, m (became the AB part of an ABX system after exchange with D_2O, ν: 3.59 and 3.70, J_{AB}=11.1 Hz, J_{AX}, J_{BX}=3.6, 7.8 Hz), CH_2OH]; 4.30–4.41 [2H, m, H_2 and H_5]; 4.72 [1H, broad s, O*H*]; 5.05 [1H, d,

CH*H*=CH, J=17.1 Hz]; 5.19 [1H, d, C*H*H=CH, J=10.5 Hz]; 5.78 [1H, ddd; CH_2=C*H*, J=5.4, 10.2, 17.1 Hz]. ^{13}C NMR (75 MHz): 22.96 [CH_3CO]; 25.40 [C_3]; 30.56 [C_4]; 60.65 and 61.74 [2C, C_2 and C_5]; 66.11 [CH_2OH]; 115.04 [CH_2=CH]; 137.42 [CH_2=*C*H]; 172.46 [*C*O]. *cis Derivative (2R*,5S*)*: R_f 0.43 (AcOEt/MeOH 95:5, B). Anal. found C, 63.75; H, 8.85. $C_9H_{15}NO_2$ requires C, 63.88; H, 8.93. IR: ν_{max} 3403, 3344, 2956, 2872, 1612, 1410, 1358, 1252, 1198, 1085, 1009, 926. GC–MS (parameters changed in the usual method: init. temperature 80 °C, init. time 2 min, rate 10 °C/min, final temperature 260 °C, final time 4 °C, inj. temperature 200 °C): R_t 8.30; *m/z* 169 (M^+, 1.7), 151 (1.4), 139 (5.3), 138 (44), 97 (6.8), 96 (100), 79 (12), 68 (5.3), 43 (24), 41 (7.2), 39 (5.4). ^{1}H NMR (200 MHz): 1.47–2.18 [4H, m, H_3 and H_4]; 2.10 [3H, s, CH_3CO]; 3.56–3.65 [2H, m (became the AB part of an ABX system after exchange with D_2O, ν: 3.61 and 3.69, J_{AB}=11.5 Hz, J_{AX}, J_{BX}=2.0, 8.0 Hz), CH_2OH]; 4.40 and 4.18 [2H, centrers of 2 m, H_2 and H_5]; 5.19 [1H, dt, CH*H*=CH, J=1.3, 18.2 Hz]; 5.22 [1H, dt, C*H*H=CH, J=1.3, 9.4 Hz]; 5.52 [1H, broad d, O*H*, J=7.4 Hz]; 5.80 [1H, ddd; CH_2=C*H*, J=5.6, 10.6, 16.8 Hz]. ^{13}C NMR (50 MHz): 22.63 [CH_3CO]; 26.44 [C_3]; 30.71 [C_4]; 62.60 and 62.63 [2C, C_2 and C_5]; 67.48 [CH_2OH]; 115.89 [CH_2=CH]; 137.82 [CH_2=*C*H]; 172.94 [*C*O].

4.17. (2*R**,5*R**)- and (2*R**,5*S**)-2-Acetoxymethyl-1-acetyl-5-vinylpyrrolidine 28a and 28b

A solution of **27** (110 mg, 650 μmol) in dry CH_2Cl_2 (3 ml) was cooled to 0 °C and treated with Et_3N (270 μl, 1.94 mmol), Ac_2O (184 μl, 1.94 mmol) and 4-(dimethylamino)pyridine (7.9 mg, 64.8 μmol). After 5 min the reaction mixture was stirred at rt for 1–2 h and then diluted with water and extracted with CH_2Cl_2. Chromatography with AcOEt/MeOH 100:0→98:2 gave **28** as a colourless oil (123 mg, 90%). When the reaction was performed on crude alcohol the overall yield from **24** was 82%. *trans Derivative (2R*,5R*)*: R_f 0.60 (AcOEt/MeOH 95:5, B). Anal. found C, 62.65; H, 8.00. $C_{11}H_{17}NO_3$ requires C, 62.54; H, 8.11. IR: ν_{max} 2957, 1729, 1640, 1401, 1247, 1186, 1029, 991, 919. GC–MS (parameters changed in the usual method: init. temperature 80 °C, init. time 2 min, rate 7 °C/min, final temperature 200 °C, then: rate 20 °C/min, final temperature 260 °C, final time 4 °C): R_t 11.82; *m/z* 211 (M^+, 1.5), 151 (12), 138 (33), 126 (2.7), 109 (3.5), 97 (6.7), 96 (100), 79 (5.1), 68 (3.5), 43 (24), 41 (4.2). ^{1}H NMR (300 MHz): 1.68–2.32 [4H, m, H_3 and H_4]; 2.01 and 2.03 [6H, 2s, CH_3CO]; 4.12 and 4.25 [2H, AB part of an ABX system, CH_2OAc, J_{AB}=10.7 Hz, J_{AX}, J_{BX}=3.1, 7.3 Hz]; 4.00–4.39 [2H, m, H_2 and H_5]; 5.03 [1H, dt, CH*H*=CH, J=1.0, 17.1 Hz]; 5.16 [1H, dt, C*H*H=CH, J=1.0, 10.5 Hz]; 5.79 [1H, ddd; CH_2=C*H*, J=5.4, 10.5, 17.1 Hz]. ^{13}C NMR (75 MHz): 20.76 and 22.91 [2C, CH_3CO]; 24.59 [C_3]; 30.33 [C_4]; 55.91 and 60.82 [2C, C_2 and C_5]; 63.05 [CH_2OAc]; 114.82 [CH_2=CH]; 137.86 [CH_2=*C*H]; 170.46 and 170.64 [2C, *C*O]. *cis Derivative (2R*,5S*)*: R_f 0.41 (AcOEt/MeOH 95:5, B). Anal. found C, 62.70; H, 8.20. $C_{11}H_{17}NO_3$ requires C, 62.54; H, 8.11. IR: ν_{max} 2925, 2852, 1732, 1630, 1402, 1185, 1081, 989. GC–MS (parameters changed in the usual method: init. temperature 80 °C, init. time 2 min, rate 7 °C/min, final temperature 200 °C, then: rate 20 °C/min, final temperature 260 °C, final time 4 °C): R_t 11.94; *m/z* 211 (M^+, 0.36), 151 (13), 138 (27), 109 (5.2), 97 (7.0), 96 (100), 94 (2.7), 81 (2.5), 79 (6.9), 68 (2.8), 67 (3.1), 54 (2.5), 43 (27), 41 (4.1), 39 (2.7). ^{1}H NMR (300 MHz): 1.60–2.20 [4H, m, H_3 and H_4]; 2.04 and 2.06 [6H, 2s, CH_3CO]; 4.19 and 4.28 [2H, AB part of an ABX system, CH_2OAc, J_{AB}=10.9 Hz, J_{AX}, J_{BX}=3.8, 6.8 Hz]; 4.10–4.41 [2H, m, H_2 and H_5]; 5.18 [1H, d, CH*H*=CH, J=9.9 Hz]; 5.19 [1H, d, C*H*H=CH, J=17.1 Hz]; 5.79 [1H, ddd; CH_2=C*H*, J=6.6, 10.2, 17.1 Hz]. ^{13}C NMR (75 MHz): 20.87 and 22.68 [2C, CH_3CO]; 26.33 [C_3]; 31.63 [C_4]; 56.61 and 61.71 [2C, C_2 and C_5]; 64.37 [CH_2OAc]; 115.54 [CH_2=CH]; 138.85 [CH_2=*C*H]; 170.73 and 170.80 [2C, *C*O].

4.18. (2*R**,5*R**)- and (2*R**,5*S**)-2,5-Bis(acetoxymethyl)-1-acetylpyrrolidine 29a and 29b

(1) *Ozonolysis*. A solution of **28** (100 mg, 475 μmol) in dry CH_2Cl_2/MeOH (1:1, 10 ml) was cooled to −78 °C and ozonolyzed for about 5 min (at maximum power and at a flow of 90 l/h). Ozone production was interrupted and the apparatus was put under a static nitrogen atmosphere. Then the solution was treated with 105 μl of Me_2S, followed by addition of $NaBH_4$ (54 mg, 1.42 mmol). The temperature was allowed to rise to 0 °C in 2 h and the reaction was stirred for additional 5 min at rt. Slowly, addition of NH_4Cl satd soln was followed by dilution with few ml of brine and extraction with $CHCl_3$/MeOH 9:1. After solvent removal the crude yellow oil was submitted directly to acetylation. (2) *Acetylation*. The same procedure described for the preparation of **28** from **27** was followed. However, since the starting alcohols cannot be detected in TLC, an equivalent amount of the reagents was added again after 1 h and the resulting solution was stirred at rt for 2 h. Chromatography with AcOEt/MeOH 100:0→95:5 gave **29** as a colourless oil in 80% overall yield. Since compounds **29** were difficult to be detected in TLC (iodine) the chromatographic purification was followed by GC–MS. *trans Derivative (2R*,5R*)*: R_f 0.44 (AcOEt, B). HPLC (hexane/*i*PrOH 87:13, 0.8 ml/min, λ 220 nm): R_t 15.92 and 17.41 min. Anal. found C, 55.95; H, 7.35. $C_{12}H_{19}NO_5$ requires C, 56.02; H, 7.44. IR: ν_{max} 2999, 1738, 1631, 1385, 1187, 1031. GC–MS (parameters changed in the usual method: init. temperature 80 °C, init. time 2 min, rate 7 °C/min, final temperature 200 °C, then: rate 20 °C/min, final temperature 260 °C, final time 4 °C): R_t 15.80; *m/z* 257 (M^+, 0.0099), 197 (7.1), 184 (14), 155 (5.4), 143 (11), 142 (100), 100 (46), 82 (38), 69 (7.1), 68 (12), 55 (18), 43 (76), 42 (7.9), 41 (7.8). ^{1}H NMR (300 MHz): 1.80–2.18 [4H, m, H_3 and H_4]; 2.03, 2.06 and 2.16 [9H, 3s, CH_3CO]; 3.83 and 4.14 [2H, 2 dd, CH_2OAc, J=8.1, 10.5; 7.8, 10.8 Hz]; 4.04 and 4.29 [2H, 2 broad dt, H_2 and H_5, J=3.9, 7.7; 3.3, 7.1 Hz]; 4.15 and 4.20 [2H, AB part of an ABX system, CH_2OAc, J_{AB}=10.8 Hz, J_{AX}, J_{BX}=2.0, 3.1 Hz]. ^{13}C NMR (75 MHz): 20.76, 20.88 and 22.75 [3C, CH_3CO]; 25.31 and 27.27 [2C, C_3 and C_4]; 56.05 and 57.08 [2C, C_2 and C_5]; 63.10 and 64.40 [2C, CH_2OAc]; 169.82, 170.54 and 170.70 [3C, *C*O]. *cis Derivative (2R*,5S*)*: R_f 0.31 (AcOEt, B). HPLC (hexane/*i*PrOH 87:13, 0.8 ml/min, λ 220 nm): 12.65 min. Anal. found C, 56.15; H, 7.40. $C_{12}H_{19}NO_5$ requires C, 56.02; H, 7.44. IR: ν_{max} 2997, 1736, 1632, 1385, 1365, 1199, 1036. GC–MS (parameters changed in the usual method: init. temperature 80 °C, init. time 2 min, rate 7 °C/min, final temperature 200 °C, then: rate 20 °C/min, final temperature 260 °C, final

time 4 °C): R_t 15.65; *m/z* 214 (M^+-43, 0.11), 197 (5.2), 184 (7.3), 143 (8.7), 142 (100), 100 (41), 82 (37), 69 (5.2), 68 (9.7), 55 (18), 43 (80), 42 (8.0), 41 (7.5). ^{1}H NMR (300 MHz): 1.69–2.16 [4H, m, H_3 and H_4]; 2.06, 2.09 and 2.16 [9H, 3s, CH_3CO]; 3.94–4.33 [5H, m, CH_2OAc, H_2 or H_5]; 4.33 [1H, dd, H_2 or H_5, J=4.8, 12.6 Hz]. ^{13}C NMR (75 MHz): 20.82, 20.93 and 22.58 [3C, *C*H_3CO]; 25.54 and 27.46 [2C, C_3 and C_4]; 56.46 and 57.47 [2C, C_2 and C_5]; 64.06 and 64.94 [2C, *C*H_2OAc]; 170.43, 170.68 and 170.73 [3C, *C*O].

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