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A New Approach to the Synthesis of *N*-Alkylated 2-Substituted Azetidin-3-ones

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We report a one-pot methodology for the synthesis of *N*-alkylated 2-substituted azetidin-3-ones based on a tandem nucleophilic substitution followed by intramolecular Michael reaction of primary amines with alkyl 5-bromo-4-oxopent-2-enoates, obtained in turn in three steps from levulinic acid. A mechanistic interpretation of these reactions and an attempted enantioselective approach are also described.

Introduction

Since the azetidin-3-one core has been used as a precursor for the synthesis of the natural sphingosine-type alkaloids penaresidines A and B and penazetidin A,[1] or as an intermediate in the synthesis of polyoxin antibiotics,[2,3] a number of different methodologies to obtain these four-membered heterocycles have previously been described.[4] Cyclisation based on rhodium carbenoid intramolecular NH insertion has been developed by Seebach for the preparation of some azetidine-containing amino alcohol and amino acid derivatives[5] and by Vederas et al. for the synthesis of keto-glutamine analogues,[6] while De Kimpe has recently reported the synthesis of 4-alkyl-1-benzhydryl-2-(methoxymethyl)azetidin-3-ol as the result of stereoselective alkylation at the C-4 position of the corresponding azetidin-3-one obtained through a high-temperature reaction of an *N*-(diphenylmethylidene)-3-bromoamine precursor.[7] Azetidin-3-ones could also be obtained from the corresponding azetidin-3-ol precursors by use of pyridinium dichromate or Swern-type oxidation conditions.[8]

As part of a recently started program aiming at the transformation of non-food/non-feed agricultural products, by-products and waste materials into commodity chemicals we were interested in fine chemistry application of polyfunctionalised building blocks. One such derivative is 4-oxopentanoic acid or levulinic acid (LA; **1**), traditionally obtained through the controlled degradation of hexose sugars by mineral acids.[9] The increasing number of patents directed towards the production of levulinic acid demonstrates its potential as an important basic chemical that could now be cost-efficiently produced from raw materials such as wood, starch, cellulose-containing waste materials, recycled paper, or agricultural residues.[10]

Beside its conversion into methyltetrahydrofuran, a fuel extender, or into δ-aminolevulinic acid, a biodegradable broad spectrum herbicide,[11] levulinic acid (**1**) also offers a great number of other synthetic transformations,[12] such as the synthesis of fused heterocycles prepared from norbornane amino acids and diamines[13] or the synthesis of the antibiotic lissoclinolide.[14]

For a recent synthetic endeavour we needed ethyl 5-bromo-4-oxopent-2-enoate (**3a**) as key intermediate. This levulinic acid derivative appeared to be an even more versatile intermediate for further transformations such as Diels–Alder reactions, coupling reactions, nucleophilic substitutions and conjugate additions, and it was speculated that nucleophilic substitution combined with intramolecular Michael reaction should open a new approach for the synthesis of small-ring aza-heterocycles. Here we describe a simple synthesis for the preparation of *N*-alkyl-2-substituted azetidin-3-ones.

Results and Discussion

Alkyl 5-bromo-4-oxopent-2-enoates **3a**–**b** were obtained from levulinic acid (**1**) by a three-step procedure (Scheme 1). After esterification, unsaturation was introduced by bromination, followed by base-catalysed elimination.[15] 3-Acetylacrylates **2a**–**b** were directly brominated with the recyclable triphenylphosphonium perbromide[16] to afford the unsaturated bromo esters (*E*)-**3a**–**b** in about 50% overall yield after chromatographic purification. Although both methyl and ethyl esters (**3a**) have already been reported,[17] the selective direct bromination of the 3-acetylacrylates **2a**–**b** or related compounds proved unprecedented.

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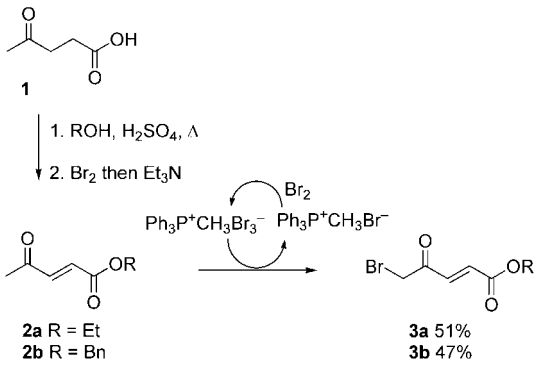
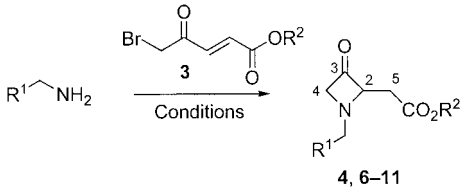


Scheme 1.

The reactivities of these polyfunctional synthons were then studied, since treatment of **3a**–**b** with nucleophiles could potentially give rise to 1,2- or 1,4-additions or to nucleophilic substitution. Treatment of ethyl 5-bromo-4-oxopent-2-enoate (**3a**) with benzylamine in THF at room temperature in the presence of triethylamine gave a moderate yield (37%) of a major product that was unambiguously identified, on the basis of ^{1}H-^{13}C HMBC correlations, as azetidin-3-one **4a** (Scheme 2 and Table 1).



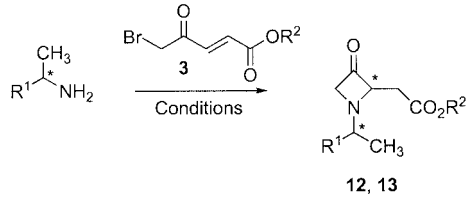
Scheme 2.

Preliminary optimisation, carried out by variation of solvents, temperature and base, showed that the best yield of **4a** was obtained by treatment of benzylamine with two equivalents of brominated compound **3a** in the presence of potassium carbonate in a CH_2Cl_2/water biphasic system (Table 1). To explore the scope and limitations further, we tested other amines under the optimized reaction conditions. As shown in Table 1, formation of azetidin-3-ones proceeded in moderate to good yields with both primary aliphatic and alkylarylamines.

Introduction of an electron-withdrawing or electron-donating group in the *para* position of the aromatic amine modified the yield profoundly, while *p*-bromobenzylamine was used since it offers the possibility of further transformation through cross-coupling reactions.

In their ^{1}H NMR spectra each isolated 2-substituted azetidin-3-one showed a typical ABX pattern for protons H2, H5, and H5′, appearing at δ = 3.8–4.0 ppm ($J \approx$ 5.5 and 7.5 Hz) and at δ = 2.5–2.7 and 2.7–2.9 ppm ($J_{AB} \approx$ 18 Hz) respectively. In the ^{13}C NMR spectra, ketone and ester carbonyl signals were found at δ = 210–212 and 170–172 ppm, respectively.

In the last part of our study we extended this sequential reaction to chiral amines (Scheme 3 and Table 2). (*R*)-1-Phenylethylamine and (*R*)-1-naphthylethylamine were added to ethyl 5-bromo-4-oxopent-2-enoate (**3a**) under our optimized conditions. The yield of the corresponding isolated azetidin-3-one was acceptable, but only poor diastereoselectivity was observed (Entries 1 and 2, Table 2). Similarly, addition onto benzylbromo derivative **3b** proved to be inefficient in terms of both yield and diastereoselectivity (*de* 18%), and addition of different magnesium salts or titanium(IV) isopropoxide to the solution did not increase the selectivity.



Scheme 3.

From a mechanistic point of view, the formation of the azetidin-3-one skeleton involves conjugate addition to the double bond and nucleophilic substitution in a well defined manner. If the first, rate-determining step is the conjugate addition, by analogy with the findings of David or Berkes, the aza-Michael reaction should occur regioselectively at position C-2 to afford pyrrolidin-3-one **5** as the result of subsequent cyclisation.[18,19] In our hands this same C-2 selectivity was confirmed by the regioselective reaction of

Table 1. Synthesis of *N*-substituted azetidin-3-ones.

	R^1	R^2	Solvent	*T* [°C]	Base	Yield [%]
4a	Ph	Et	THF	room temp.	Et_3N	37
4a	Ph	Et	THF	50	Et_3N	46
4a	Ph	Et	DMF	60	K_2CO_3	12
4a	Ph	Et	CH_2Cl_2	room temp.	Et_3N	43
4a	Ph	Et	CH_2Cl_2/H_2O	room temp.	K_2CO_3	76
4b	Ph	Bn	CH_2Cl_2/H_2O	room temp.	K_2CO_3	50
6a	propyl	Et	CH_2Cl_2/H_2O	room temp.	K_2CO_3	74
6b	propyl	Bn	CH_2Cl_2/H_2O	room temp.	K_2CO_3	86
7a	Bn	Et	CH_2Cl_2/H_2O	room temp.	K_2CO_3	53
8a	cyclohexyl	Et	CH_2Cl_2/H_2O	room temp.	K_2CO_3	51
9a	4-MeOPh	Et	CH_2Cl_2/H_2O	room temp.	K_2CO_3	63
10a	4-NO_2Ph	Et	CH_2Cl_2/H_2O	room temp.	K_2CO_3	37
11a	4-BrPh	Et	CH_2Cl_2/H_2O	room temp.	K_2CO_3	57
11b	4-BrPh	Bn	CH_2Cl_2/H_2O	room temp.	K_2CO_3	63

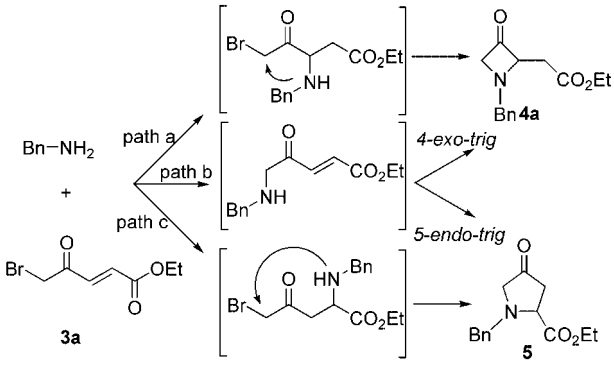
Table 2. Diastereoselective approach.

Entry		R^1	R^2	Conditions	Yield [%] (*de*)[a]
1	**12a**	Ph	Et	$K_2CO_3/CH_2Cl_2–H_2O$/room temp.	56 (20)
2	**13a**	1-naphthyl	Et	$K_2CO_3/CH_2Cl_2–H_2O$/room temp.	45 (10)
3	**12a**	Ph	Et	$Mg(OAc)_2/K_2CO_3/CH_2Cl_2–H_2O$/room temp.	75 (8)
4	**12a**	Ph	Et	$MgCl_2/K_2CO_3/CH_2Cl_2–H_2O$/room temp.	48 (24)
5	**12a**	Ph	Et	$MgCl_2/K_2CO_3/CH_2Cl_2–H_2O$/–10 °C	36 (23)
6	**12a**	Ph	Et	$Ti(OiPr)_4/K_2CO_3/CH_2Cl_2$	29 (17)
7	**12b**	Ph	Bn	$MgCl_2/K_2CO_3/CH_2Cl_2–H_2O$/room temp.	39 (18)

[a] Ratio determined by ^{1}H NMR.

benzylamine with ethyl 3-acetylacrylate (**2a**). From this observation, *path a* (Scheme 4) implying C-3 regioselectivity can therefore be discarded.

In *path b*, the first step is a nucleophilic displacement of bromine followed by an intramolecular 4-*exo*-*trig* ring closure to afford azetidin-3-one **4a** rather than pyrrolidin-3-one **5**, which would be the result of a disfavoured 5-*endo*-*trig* cyclisation (Scheme 4).



Scheme 4.

Similar reaction behaviour has been observed by Carlson et al. on treatment of 1-bromobut-3-en-2-one with a primary amine. By NMR spectroscopy they observed that the nucleophilic displacement of bromine seems to take place in the first step, resulting in pyrrolidinone formation.[20] Primary amino compounds have been found to participate in similar reactions to yield nitrogen-containing heterocycles.[21] In the synthesis of simple five- and six-membered nitrogen and sulfur heterocycles, Bunce established, by GC monitoring, higher reactivity of benzylamine with halide than with crotonate and isolated isothiouronium salts, demonstrating that halide displacement is the initial step of the sequence in the sulfur heterocyclisation.[22] A reaction with *N*-methylbenzylamine could have definitively established the nature of the first step of this sequence, but unfortunately this reaction only generates polymerisation products.

With regard to the reactions with chiral amines (Table 2), similar diasteroselectivities have been observed in some related reactions. Whilst Urbach, for example, described the regioselective addition between (*S*)-alanine benzyl ester and ethyl (*E*)-4-oxo-4-phenylbut-2-enoate with a *de* of 54%, Knollmüller et al. obtained low selectivity (*de* 30%) on treating (*S*)-phenylethylamine with ethyl (*E*)-4-oxo-4-phenylbut-2-enoate.[23,24] These observed poor diastereoselectivities are in accordance with our proposed mechanism.

Conclusion

In summary, we present a quite simple and direct method for the preparation of *N*-substituted azetidin-3-ones by treatment of primary amines with alkyl 5-bromo-4-oxopent-2-enoates **3a**–**b**, derived from levulinic acid. The mechanism of this reaction probably involves an S_N2 displacement of bromine from **3a**–**b**, followed by 4-*exo*-*trig* ring closure to afford azetidin-3-ones. Studies aimed at further exploration of the scope of the reaction, in particular for the synthesis of biologically active compounds, are currently underway.

Experimental Section

General Remarks: All solvents were dried and purified by standard literature methods prior to use. Melting points were determined on a Reichert Thermovar hot-stage apparatus and are uncorrected. IR spectra (film or KBr) were measured with a Bomem FTIR instrument. Mass spectra were recorded with a VG Autospec apparatus. Elemental analyses were carried out by the Microanalysis Service of the University of Reims. Reactions were monitored with Merck TLC aluminium sheets (Kieselgel $60F_{254}$) and preparative chromatography was carried out with silica gel 60 (70–230 mesh ASTM) supplied by Merck. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were acquired on a Bruker AC 300 spectrometer in $CDCl_3$, with TMS as internal standard.

General Procedure for the Preparation of Brominated Levulinates 3a–b: Triphenylmethylphosphonium perbromide (1 equiv.) was added at room temperature to a solution of a 3-acetylacrylate **2a**–**b** (1 equiv.) in THF (2 mL mmol^{-1}). After 1 hour, the mixture was filtered. The filtrate was concentrated, washed with a saturated solution of $NaHCO_3$, extracted with CH_2Cl_2 and dried with $MgSO_4$. After concentration under vacuum, the crude products were purified by column chromatography on silica gel (eluent CH_2Cl_2/petroleum ether, 50:50) to furnish the corresponding brominated derivatives.

Ethyl 5-Bromo-4-oxopent-2-enoate (3a): This compound was prepared by the general procedure from **2a** (1.00 g, 7.4 mmol) and triphenylmethylphosphonium perbromide (3.64 g, 7.4 mmol) to give **3a** as a yellow solid after purification and recrystallisation from hexane (794 mg, 51%). M.p. 34–36 °C. ^{1}H NMR ($CDCl_3$): δ = 1.33 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 4.07 (s, 2 H, $BrCH_2$), 4.29 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 6.80 (d, J = 16.0 Hz, 1 H, CH_{vinyl}), 7.28 (d, J = 16.0 Hz, 1 H, CH_{vinyl}) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH_3), 32.7 ($BrCH_2$), 61.6 (CH_2CH_3), 133.3 135.6 (CH_{vinyl}), 164.8 (CO_2Et), 190.2 (CO) ppm. IR (film): $\tilde{\nu}$ = 2982, 1721, 1701, 1381, 1300, 988 cm^{-1}. $C_7H_9O_3Br$ (220.06): calcd. C 38.20, H 4.12; found C 38.58, H 4.44.

Benzyl 5-Bromo-4-oxopent-2-enoate (3b): This compound was prepared by the general procedure from **2b** (3.47 g, 17 mmol) and triphenylmethylphosphonium perbromide (8.79 g, 17 mmol), to give **3b** as a white oil (2.27 g, 47%). ^{1}H NMR ($CDCl_3$): δ = 4.04 (s, 2 H, BrCH_2), 5.26 (s, 2 H, PhCH_2), 6.86 (d, J = 15.8 Hz, 1 H, CH_{vinyl}), 7.29 (d, J = 15.8 Hz, 1 H, CH_{vinyl}) ppm. ^{13}C NMR ($CDCl_3$): δ = 32.7 (BrCH$_2$), 67.1 (PhCH$_2$), 128.1 128.3 128.5 (Ar CH), 134.9 (Ar C_q), 132.6 136.0 (CH$_{vinyl}$), 164.5 (CO$_2$Bn), 189.9 (CO) ppm. IR (film): $\tilde{\nu}$ = 3025, 2988, 1726, 1718, 1297, 1027 cm^{-1}. $C_{12}H_{11}O_3Br$ (282.13): calcd. C 51.08, H 3.93; found C 50.88, H 4.19.

General Procedure for the Preparation of *N*-Substituted Azetidin-3-ones (4–11): Amine (1 equiv.), an aqueous solution of K_2CO_3 (0.5 mL, 2 equiv.) and tetrabutylammonium hydrogen sulfate (0.1 equiv.) were successively added, at room temperature, to a solution of the brominated compound (**3a**–**b**, 2 equiv.) in CH_2Cl_2 (2.5 mL mmol^{-1}). The mixture was stirred for 4 h at room temperature and was then poured into water. Extraction with CH_2Cl_2, drying over $MgSO_4$ and concentration under vacuum gave the crude products, which were purified by column chromatography on silica gel (eluent CH_2Cl_2/AcOEt, 95:5) to furnish the corresponding azetidin-3-one.

1-Benzyl-2-(ethoxycarbonylmethyl)azetidin-3-one (4a): This compound was synthesized from **3a** (442 mg, 2 mmol) and benzylamine (0.11 mL, 1 mmol), to yield **4a** (188 mg, 76%) as a dark oil. ^{1}H NMR ($CDCl_3$): δ = 1.30 (t, J = 7.1 Hz, 3 H, CH_3), 2.56 (dd, J = 18.1 Hz, J = 5.7 Hz, 1 H, H-5), 2.72 (dd, J = 18.1 Hz, J = 7.7 Hz, 1 H, H-5′), 3.02 (d, J = 17.2 Hz, 1 H, H-4), 3.37 (d, J = 17.2 Hz, 1 H, H-4′), 3.73 (d, J = 13.0 Hz, 1 H, NCH_2Ph), 3.83 (dd, J = 7.7 Hz, J = 5.7 Hz, 1 H, H-2), 3.95 (d, J = 13.0 Hz, 1 H, NCH_2Ph), 4.22 (q, J = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 7.25–7.40 (m, 5 H, C$H_{arom.}$) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2 (CH$_3$), 41.7 (C-5), 57.3 (CH$_2$Ph), 58.8 (C-4), 61.1 ($CO_2CH_2CH_3$), 62.2 (C-2), 127.6 128.4 128.8 (Ar CH), 136.6 (Ar C_q), 171.7 (CO$_2$Et), 210.5 (CO$_{azetidin.}$) ppm. IR (film): $\tilde{\nu}$ = 2928, 2872, 2801, 1763, 1732, 1198, 1177, 1030 cm^{-1}. MS (EI): m/z (%) = 247 [M]$^{+\cdot}$, 174 (100), 149, 137, 130, 115, 106. $C_{14}H_{17}NO_3$ (247.29): calcd. C 68.00, H 6.93, N 5.66; found C 68.23, H 6.99, N 5.41.

1-Benzyl-2-(benzyloxycarbonylmethyl)azetidin-3-one (4b): This compound was synthesized from **3b** (283 mg, 1 mmol) and benzylamine (55 μL, 0.5 mmol), to yield **4b** (77 mg, 50%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ = 2.55 (dd, J = 18.3 Hz, J = 5.5 Hz, 1 H, H-5), 2.69 (dd, J = 18.3 Hz, J = 7.7 Hz, 1 H, H-5′), 3.01 (d, J = 17.2 Hz, 1 H, H-4), 3.31 (d, J = 17.2 Hz, 1 H, H-4′), 3.71 (d, J = 13.1 Hz, 1 H, NCH_2Ph), 3.81 (m, 2 H, H-2, NCH_2Ph), 5.18 (s, 2 H, OCH_2Ph), 7.18–7.49 (m, 10 H, CH$_{arom.}$) ppm. ^{13}C NMR ($CDCl_3$): δ = 41.6 (C-5), 57.2 (NCH$_2$Ph), 58.7 (C-4), 62.0 (C-2), 66.8 (CO_2CH_2Ph), 127.5 128.4 128.5 128.6 128.7 128.8 (Ar CH), 135.2 136.7 (Ar C_q), 171.7 (CO$_2$Bn), 210.8 (CO$_{azetidin.}$) ppm. IR (film): $\tilde{\nu}$ = 2980, 2954, 2901, 1765, 1736, 1254, 1233, 1198 cm^{-1}. MS (EI): m/z (%) = 309 [M]$^{+\cdot}$, 218 (100), 202, 135, 107, 91. $C_{19}H_{19}NO_3$ (309.36): calcd. C 73.77, H 6.19, N 4.53; found C 73.51, H 6.38, N 4.81.

1-Butyl-2-(ethoxycarbonylmethyl)azetidin-3-one (6a): This compound was synthesized from **3a** (447 mg, 2 mmol) and butylamine (0.10 mL, 1 mmol), to yield **6a** (159 mg, 74%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ = 0.94 [t, J = 7.2 Hz, 3 H, CH_3(CH$_2$)$_3$N], 1.30 (t, J = 7.1 Hz, 3 H, CH_3), 1.36 [m, 2 H, CH$_3$CH_2(CH$_2$)$_2$N], 1.50 (m, 2 H, CH$_3$CH$_2$CH_2CH$_2$N), 2.53–2.70 (m, 4 H, CH$_3$CH$_2$CH$_2$CH_2N, H-5, H-5′), 3.03 (d, J = 17.2 Hz, 1 H, H-4), 3.42 (d, J = 17.2 Hz, 1 H, H-4′), 3.75 (dd, J = 7.5 Hz, J = 5.8 Hz, 1 H, H-2), 4.22 (q, J = 7.1 Hz, 2 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.8 [CH$_3$(CH$_2$)$_3$N], 14.2 (CH$_3$), 20.3 [CH$_3$$CH_2$(CH$_2$)$_2$N], 30.0 (CH$_3CH_2$$CH_2CH_2$N), 41.6 (C-5), 53.4 (CH$_3CH_2CH_2$$CH_2$N), 59.1 (C-4), 61.0 ($CO_2CH_2CH_3$), 62.9 (C-2), 172.0 ($CO_2$Et), 211.5 ($CO_{azetidin.}$) ppm. IR (film): $\tilde{\nu}$ = 2992, 2934, 1763, 1732, 1258, 1182 cm^{-1}. MS (CI): m/z (%) = 214 (13) [M + H], 172 (21), 144 (25), 83, 42. $C_{11}H_{19}NO_3$ (213.27): calcd. C 61.95, H 8.98, N 6.57; found C 61.62, H 8.53, N 6.84.

2-(Benzyloxycarbonylmethyl)-1-butylazetidin-3-one (6b): This compound was synthesized from **3b** (283 mg, 1 mmol) and butylamine (0.50 mL, 0.5 mmol), to yield **6b** (118 mg, 86%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ = 0.88 [t, J = 7.3 Hz, 3 H, CH_3(CH$_2$)$_3$N], 1.31 [m, 2 H, CH$_3$CH_2(CH$_2$)$_2$N], 1.45 (m, 2 H, CH$_3$CH$_2$CH_2CH$_2$N), 2.41–2.72 (m, 4 H, CH$_3$CH$_2$CH$_2$CH_2N, H-5, H-5′), 3.02 (d, J = 17.2 Hz, 1 H, H-4), 3.39 (d, J = 17.2 Hz, 1 H, H-4′), 3.80 (dd, J = 7.6 Hz, J = 5.5 Hz, 1 H, H-2), 5.18 (s, 2 H, OCH_2Ph), 7.34–7.41 (m, 5 H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.8 [CH$_3$(CH$_2$)$_3$N], 20.2 [CH$_3$$CH_2$(CH$_2$)$_2$N], 29.9 (CH$_3CH_2$$CH_2CH_2$N), 41.5 (C-5), 53.3 (CH$_3CH_2CH_2$$CH_2$N), 59.0 (C-4), 62.7 (C-2), 66.7 (CO_2CH$_2$Ph), 128.4 128.5 128.6 (Ar CH), 135.3 (Ar C_q), 171.8 (CO$_2$Bn), 211.3 (CO$_{azetidin.}$) ppm. IR (film): $\tilde{\nu}$ = 3155, 3015, 1919, 1793, 1757, 1560, 1474, 1378 cm^{-1}. MS (CI): m/z (%) = 276 (100) [M + H], 242 (12), 184, 57. $C_{16}H_{21}NO_3$ (275.34): calcd. C 69.79, H 7.69, N 5.09; found C 69.51, H 7.95, N 5.01.

2-(Ethoxycarbonylmethyl)-1-phenethylazetidin-3-one (7a): This compound was obtained from **3a** (221 mg, 1 mmol) and phenethylamine (63 μL, 0.5 mmol): 69 mg (53%) as a dark oil. ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, J = 7.1 Hz, 3 H, CH_3), 2.58 (dd, J = 18.0 Hz, J = 5.2 Hz, 1 H, H-5), 2.69 (dd, J = 18.0 Hz, J = 7.8 Hz, 1 H, H-5′), 2.86 (m, 2 H, NCH$_2$CH_2Ph), 3.01 (m, 2 H, NCH_2CH$_2$Ph), 3.12 (d, J = 17.1 Hz, 1 H, H-4), 3.45 (d, J = 17.1 Hz, 1 H, H-4′), 3.82 (dd, J = 7.8 Hz, J = 5.2 Hz, 1 H, H-2), 4.20 (q, J = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 7.15–7.35 (m, 5 H, C$H_{arom.}$) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2 (CH$_3$), 34.6 (CH$_2$Ph), 41.5 (C-5), 55.0 (NCH$_2$CH$_2$Ph), 59.0 (C-4), 61.1 ($CO_2CH_2CH_3$), 62.6 (C-2), 126.2 128.4 128.5 (Ar CH), 139.3 (Ar C_q), 171.9 (CO$_2$Et), 211.1 (CO$_{azetidin.}$) ppm. IR (film): $\tilde{\nu}$ = 2980, 2949, 2897, 2864, 1771, 1732, 1650, 1432, 1065 cm^{-1}. MS (CI): m/z (%) = 262 [M + H], 170, 157 (100), 105, 91. $C_{15}H_{19}NO_3$ (261.32): calcd. C 68.94, H 7.33, N 5.36; found C 69.35, H 7.68, N 5.18.

1-Cyclohexyl-2-(ethoxycarbonylmethyl)azetidin-3-one (8a): This compound was obtained from **3a** (221 mg, 1 mmol) and cyclohexylamine (57 μL, 0.5 mmol): 60 mg (51%) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ = 1.20 [m, 6 H, NCH(CH$_2$CH_2)$_2$CH_2], 1.30 (t, J = 7.0 Hz, 3 H, CH_3), 1.52–1.98 [m, 4 H, NCH(CH_2CH$_2$)$_2$CH$_2$], 2.47 [m, 2 H, NCH(CH$_2$CH$_2$)$_2$CH$_2$, H-5], 2.71 (dd, J = 17.9 Hz, J = 8.1 Hz, 1 H, H-5′), 3.31 (m, 2 H, H-4, H-4′), 4.02 (dd, J = 8.1 Hz, J = 4.6 Hz, 1 H, H-2), 4.23 (q, J = 7.0 Hz, 2 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2 (CH$_3$), 24.4 24.5 25.8 29.5 31.9 [NCH(CH$_2$CH$_2$)$_2$$CH_2$], 41.7 (C-5), 56.1 (C-4), 58.8 59.1 [NCH(CH$_2$CH$_2$)$_2$CH$_2$, C-2], 60.7 ($CO_2CH_2CH_3$), 172.8 (CO$_2$Et), 212.2 (CO$_{azetidin.}$) ppm. IR (film): $\tilde{\nu}$ = 2897, 2864, 2802, 1765, 1728, 1528, 1280, 1165, 1058 cm^{-1}. MS (CI): m/z (%) = 240 [M + H], 194, 166, 156 (100), 83. HRMS (EI): 239.1506. $C_{13}H_{21}NO_3$ [M]$^+$ requires 239.1521.

2-(Ethoxycarbonylmethyl)-1-(*p*-methoxybenzyl)azetidin-3-one (9a): This compound was synthesized from **3a** (221 mg, 1 mmol) and *p*-methoxybenzylamine (65 μL, 0.5 mmol), to yield **9a** (87 mg, 63%) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ = 1.34 (t, J = 7.2 Hz, 3 H, CH_3), 2.57 (dd, J = 18.1 Hz, J = 5.8 Hz, 1 H, H-5), 2.75 (dd, J = 18.1 Hz, J = 7.6 Hz, 1 H, H-5′), 3.03 (d, J = 17.2 Hz, 1 H, H-4), 3.39 (d, J = 17.2 Hz, 1 H, H-4′), 3.73 (d, J = 12.9 Hz, 1 H, NCH_2Ph), 3.78–3.90 (m, 4 H, H-2 OCH_3), 3.92 (d, J = 12.9 Hz, 1

H, NCH_2Ph), 4.26 (q, J = 7.2 Hz, 2 H, $CO_2CH_2CH_3$), 6.92 (d, J = 10.5 Hz, 2 H, CH_{arom}), 7.24 (d, J = 10.5 Hz, 2 H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2 (CH_3), 41.7 (C-5), 55.2 (OCH_3), 56.6 (CH_2Ph), 58.8 (C-4), 61.1 ($CO_2CH_2CH_3$), 62.0 (C-2), 113.7 130.1 (Ar CH), 128.7 (Ar C_q), 159.0 (MeOC_q), 171.9 (CO_2Et), 211.0 ($CO_{azetidin.}$) ppm. IR (film): $\tilde{\nu}$ = 2921, 2853, 1771, 1717, 1259, 1163 cm^{-1}. MS (CI): m/z (%) = 278 (70) [M + H], 262, 241, 121. HRMS (ESI): 278.1387. $C_{15}H_{20}NO_4$ [M + H]$^+$ requires 278.1392.

2-(Ethoxycarbonylmethyl)-1-(*p*-nitrobenzyl)azetidin-3-one (10a): This compound was prepared by the general procedure from **3a** (221 mg, 1 mmol) and *p*-nitrobenzylamine hydrochloride (95 mg, 0.5 mmol), to give **10a** as a pale yellow oil (54 mg, 37%). ^{1}H NMR ($CDCl_3$): δ = 1.31 (t, J = 7.3 Hz, 3 H, CH_3), 2.58 (dd, J = 18.1 Hz, J = 5.3 Hz, 1 H, H-5), 2.79 (dd, J = 18.1 Hz, J = 7.8 Hz, 1 H, H-5′), 3.03 (d, J = 16.9 Hz, 1 H, H-4), 3.38 (d, J = 16.9 Hz, 1 H, H-4′), 3.85 (d, J = 13.9 Hz, 1 H, NCH_2Ph), 3.92 (dd, J = 7.8 Hz, J = 5.3 Hz, 1 H, H-2), 4.13 (d, J = 13.9 Hz, 1 H, NCH_2Ph), 4.28 (q, J = 7.3 Hz, 2 H, $CO_2CH_2CH_3$), 7.55 (d, J = 8.6 Hz, 2 H, CH_{arom}), 8.21 (d, J = 8.6 Hz, 2 H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2 (CH_3), 41.6 (C-5), 56.6 (CH_2Ph), 58.7 (C-4), 61.3 ($CO_2CH_2CH_3$), 62.2 (C-2), 123.8 129.1 (Ar CH), 144.9 147.4 (Ar C_q), 171.6 (CO_2Et), 210.1 ($CO_{azetidin.}$) ppm. IR (film): $\tilde{\nu}$ = 3147, 2931, 1760, 1724, 1603, 1524, 1344 cm^{-1}. MS (CI): m/z (%) = 293 (28) [M + H], 292 (100), 241, 218, 136. HRMS (ESI): 293.1137. $C_{14}H_{17}N_2O_5$ [M + H]$^+$ requires 293.1137.

1-(*p*-Bromobenzyl)-2-(ethoxycarbonylmethyl)azetidin-3-one (11a): This compound was synthesized from **3a** (221 mg, 1 mmol) and *p*-bromobenzylamine (93 mg, 0.5 mmol), to yield **11a** (91 mg, 57 %) as an orange oil. ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, J = 7.3 Hz, 3 H, CH_3), 2.51 (dd, J = 17.9 Hz, J = 5.8 Hz, 1 H, H-5), 2.68 (dd, J = 17.9 Hz, J = 7.7 Hz, 1 H, H-5′), 2.99 (d, J = 17.2 Hz, 1 H, H-4), 3.41 (d, J = 17.2 Hz, 1 H, H-4′), 3.67 (d, J = 13.0 Hz, 1 H, NCH_2Ph), 3.72 (dd, J = 7.7 Hz, J = 5.8 Hz, 1 H, H-2), 3.89 (d, J = 13.0 Hz, 1 H, NCH_2Ph), 4.22 (q, J = 7.3 Hz, 2 H, $CO_2CH_2CH_3$), 7.21 (d, J = 8.3 Hz, 2 H, CH_{arom}), 7.47 (d, J = 8.3 Hz, 2 H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2 (CH_3), 41.6 (C-5), 56.6 (CH_2Ph), 58.7 (C-4), 61.0 ($CO_2CH_2CH_3$), 62.1 (C-2), 121.3 (C_{Br}), 130.3 131.6 (Ar CH), 136.0 (Ar C_q), 171.7 (CO_2Et), 210.5 ($CO_{azetidin.}$) ppm. IR (film): $\tilde{\nu}$ = 2942, 2810, 1762, 1727, 1484, 1308, 1251 cm^{-1}. MS (CI): m/z (%) = 327 [M + H], 212, 209, 171 (100), 130. $C_{14}H_{16}BrNO_3$ (326.19): calcd. C 51.55, H 4.94, N 4.29; found C 51.38, H 5.02, N 4.43.

2-(Benzyloxycarbonylmethyl)-1-(*p*-bromobenzyl)azetidin-3-one (11b): This compound was synthesized from **3b** (283 mg, 1 mmol) and *p*-bromobenzylamine (93 mg, 0.5 mmol), to yield **11b** (122 mg, 63%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ = 2.55 (dd, J = 18.1 Hz, J = 5.3 Hz, 1 H, H-5), 2.71 (dd, J = 18.1 Hz, J = 7.8 Hz, 1 H, H-5′), 2.98 (d, J = 17.1 Hz, 1 H, H-4), 3.31 (d, J = 17.1 Hz, 1 H, H-4′), 3.62 (d, J = 13.2 Hz, 1 H, NCH_2Ph), 3.84 (d, J = 13.2 Hz, 1 H, NCH_2Ph), 3.91 (dd, J = 7.8 Hz, J = 5.3 Hz, 1 H, H-2), 5.17 (AB, J = 13.4 Hz, 2 H, CO_2CH_2Ph), 7.11 (d, J = 10.5 Hz, 2 H, CH_{arom}), 7.35–7.49 (m, 7 H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$): δ = 41.6 (C-5), 56.4 (CH_2Ph), 58.6 (C-4), 61.9 (C-2), 66.8 (CO_2CH_2Ph), 121.3 (C_{Br}), 128.2 128.4 128.6 130.3 131.5 (Ar CH), 135.1 136.0 (Ar C_q), 171.6 (CO_2Bn), 210.5 ($CO_{azetidin.}$) ppm. IR (film): $\tilde{\nu}$ = 3147, 2937, 1757, 1724, 1488, 1373, 1174 cm^{-1}. MS (CI): m/z (%) = 389 (100) [M + H], 370, 276, 218, 170, 91. HRMS (ESI): 388.0556. $C_{19}H_{19}NO_3Br$ [M + H]$^+$ requires 388.0548.

General Procedure for the Preparation of the Chiral *N*-Substituted Azetidin-3-ones 12, 13: The previously described reaction conditions and treatment were maintained, but complexing salts or titanium(IV) isopropoxide (2 equiv.) were used before the addition of amine.

2-(Ethoxycarbonylmethyl)-1-[(*R*)-1-phenylethyl]azetidin-3-one (12a): This compound was synthesized from **3a** and (*R*)-1-phenylethylamine to yield the diastereoisomeric mixture **12a** as a colourless oil. ^{1}H NMR ($CDCl_3$) (minor isomer): δ = 1.26 (t, J = 7.1 Hz, 3 H, CH_3) (1.20), 1.40 (d, J = 6.6 Hz, 3 H, CHCH_3), 2.44 (dd, J = 18.5 Hz, J = 2.4 Hz, 1 H, H-5) (2.38), 2.78 (dd, J = 18.5 Hz, J = 8.4 Hz, 1 H, H-5′) (2.62), 2.97 (d, J = 17.5 Hz, 1 H, H-4) (3.39), 3.20 (d, J = 17.5 Hz, 1 H, H-4′) (3.48), 3.79 (q, J = 6.6 Hz, 1 H, CHCH$_3$) (3.87), 4.10–4.28 (m, 3 H, H-2 $CO_2CH_2CH_3$), 7.20–7.31 (m, 5 H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$) (minor isomer): δ = 14.0 (CH_3), 20.6 (CHCH_3) (22.3), 41.8 (C-5), 57.3 (C-4) (56.2), 59.5 61.2 (C-2 CHCH$_3$) (59.7 60.5), 60.8 ($CO_2CH_2CH_3$) (60.7), 126.8 127.3 128.3 (Ar CH), 143.4 (Ar C_q) (141.7), 172.4 (CO_2Et), 211.7 ($CO_{azetidin.}$) ppm. IR (film): $\tilde{\nu}$ = 2949, 2897, 1768, 1732, 1206 cm^{-1}. MS (EI): m/z (%) = 261 [M]$^{+\cdot}$, 246, 219, 188, 105 (100). HRMS (EI): 261.1372. $C_{15}H_{19}NO_3$ [M]$^+$ requires 261.1365.

2-(Benzyloxycarbonylmethyl)-1-[(*R*)-1-phenylethyl]azetidin-3-one (12b): This compound was synthesized from **3b** (283 mg, 1 mmol) and (*R*)-1-phenylethylamine (65 µL, 0.5 mmol), to yield the diastereoisomeric mixture **12b** (61 mg, 39%) as a colourless oil. ^{1}H NMR ($CDCl_3$) (minor isomer): δ = 1.48 (d, J = 6.6 Hz, 3 H, CH_3) (1.46), 2.48 (dd, J = 18.0 Hz, J = 2.4 Hz, 1 H, H-5) (2.39), 2.75 (dd, J = 18.0 Hz, J = 8.4 Hz, 1 H, H-5′) (2.68), 2.92 (d, J = 17.5 Hz, 1 H, H-4) (3.37), 3.19 (d, J = 17.5 Hz, 1 H, H-4′) (3.55), 3.71 (q, J = 6.6 Hz, 1 H, CHCH$_3$) (3.85), 4.27 (dd, J = 8.4 Hz, J = 2.4 Hz, 1 H, H-2), 5.15 (m, 2 H, CH_2Ph), 7.15–7.38 (m, 10 H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$) (minor isomer): δ = 20.8 (CH_3) (22.5), 41.8 (C-5), 57.4 (C-4) (56.3), 59.6 60.8 (C-2 CHCH$_3$) (59.7 60.2), 66.5 (CO_2CH_2Ph), 126.9 127.4 127.5 128.4 128.5 128.8 (Ar CH), 135.3 143.6 (Ar C_q) (141.9), 172.3 (CO_2Bn), 211.6 ($CO_{azetidin.}$) ppm. IR (film): $\tilde{\nu}$ = 3079, 3034, 2949, 2864, 1765, 1728, 1405, 1067 cm^{-1}. MS (CI): m/z (%) = 324 (100) [M + H], 261, 220, 105. HRMS (ESI): 324.1594. $C_{20}H_{22}NO_3$ [M + H]$^+$ requires 324.1600.

2-(Ethoxycarbonylmethyl)-1-[(*R*)-1-(naphth-1-yl)ethyl]azetidin-3-one (13a): This compound was prepared by the general procedure from **3a** (111 mg, 0.5 mmol) and (*R*)-1-(1-naphthyl)ethylamine (41 µL, 0.25 mmol), to give **13a** as a dark oil (35 mg, 45%). ^{1}H NMR ($CDCl_3$) (minor isomer): δ = 1.33 (t, J = 7.5 Hz, 3 H, CH_3) (1.25), 1.55 (d, J = 6.6 Hz, 3 H, CHCH_3) (1.48), 2.55 (dd, J = 18.0 Hz, J = 2.6 Hz, 1 H, H-5) (2.48), 2.83 (dd, J = 18.0 Hz, J = 8.4 Hz, 1 H, H-5′) (2.72), 3.05 (d, J = 17.0 Hz, 1 H, H-4) (3.39), 3.18 (d, J = 17.0 Hz, 1 H, H-4′) (3.48), 3.92 (q, J = 6.6 Hz, 1 H, CHCH$_3$), 4.15–4.35 (m, 3 H, H-2 $CO_2CH_2CH_3$), 7.32–7.78 (m, 7 H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$) (minor isomer): δ = 14.2 (CH_3), 20.3 (CHCH_3) (21.9), 41.5 (C-5), 56.9 (C-4) (56.0), 60.1 61.8 (C-2 CHCH$_3$), 61.2 ($CO_2CH_2CH_3$), 126.8 127.2 127.3 128.3 128.4 (Ar CH), 143.3 (Ar C_q) (141.9), 172.5 (CO_2Et), 211.7 ($CO_{azetidin.}$) ppm. IR (film): $\tilde{\nu}$ = 3085, 3024, 2949, 2868, 1760, 1735, 1342, 1208 cm^{-1}. MS (CI): m/z (%) = 312 [M + H], 210, 155 (100), 129. $C_{19}H_{21}NO_3$ (311.37): calcd. C 73.29, H 6.80, N 4.50; found C 73.58, H 6.99, N 4.78.

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