One-Pot Conversion of α-Amino Acids into β-Amino Aldehydes or 2-Acetoxyazetidines: Application to the Synthesis of Modified Peptides

Alicia Boto,* Rosendo Hernández,* Carlos J. Saavedra

Instituto de Productos Naturales y Agrobiología CSIC, Avda. Astrofísico Fco. Sánchez, 3, 38206 La Laguna, Tenerife, Spain
Fax +34(922)260135; E-mail: alicia@ipna.csic.es; E-mail: rhernandez@ipna.csic.es

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Dedicated to Prof. Gerry Pattenden on the occasion of his 70th birthday.

Abstract: A direct method for the transformation of α-amino acids into β-amino aldehydes or 2-acetoxyazetidines is described. This work was applied to the modification of peptides.

Key words: amino aldehydes, heterocycles, peptides, radical reactions, domino reactions

The replacement of α-amino acids in peptides by α-amino aldehydes has been used to create peptide analogues with remarkable biological activities.[1] Thus, different peptide aldehydes are potent inhibitors of aspartyl, serine, and cysteine proteases, such as papain, thrombin, trypsin, and viral proteases.[2] For instance, the dipeptide SJA6017 (**1**) inhibits calpain and is a promising anticataract agent.[3a,b] The tetrapeptide Ac-DEVD-H (**2**) is a potent inhibitor of caspase-3, an apoptosis effector.[3c,d]

In contrast, the introduction of β-amino aldehyde units has been scarcely explored.[4] In most cases, α-unsubstituted β-amino aldehyde[5] or α-amino glyoxal units[6] are used. Two representative examples are compounds **3** and **4** (Figure 1); while product **3** is a caspase-1 inhibitor,[4b] the glyoxal **4** inhibits cathepsin L, a protease which degrades bone collagen.[4c]

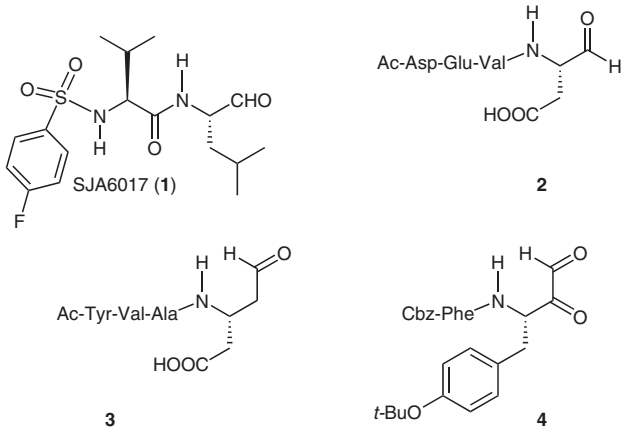
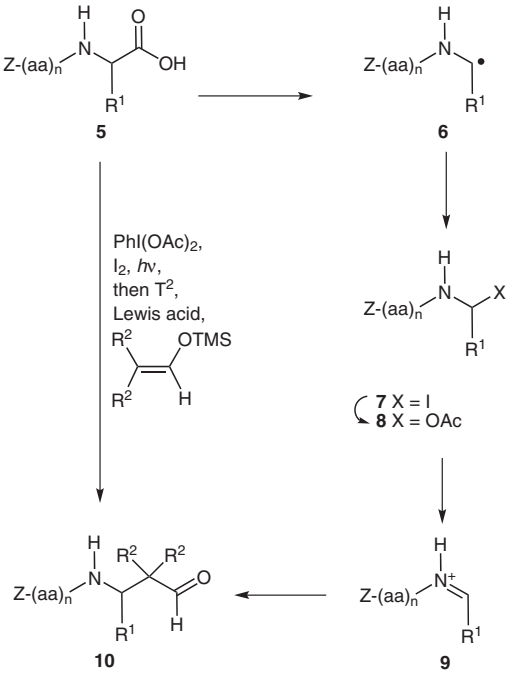


Figure 1 Bioactive peptidyl α- or β-aldehydes

In order to increase the diversity of peptidyl β-aldehyde libraries, α-substituted β-amino aldehydes could be incorporated into the peptide. Such units could bear substituents of different size and polarity, in order to allow the study of their influence on biological activity.

In this communication we report a one-pot methodology to transform the *C*-terminal amino acid in peptides into a β-amino aldehyde, whose α-position may be either substituted or unsubstituted. This direct transformation would allow the preparation of a library of modified peptide aldehydes from a single peptide precursor **5** (Scheme 1).[7]

The process is initiated by a radical decarboxylation, on treatment of the precursor **5** with (diacetoxyiodo) benzene (DIB) and iodine. The decarboxylation affords a *C*-radical **6** which reacts with iodine to give the unstable α-iodoamine **7**.[7j] The iodide is replaced by acetate derived from the DIB, to give the *N*,*O*-acetal **8**. This acetal is in equilibrium with the acyliminium ion **9**, which can be trapped by silyl enol ethers, to afford the peptide β-aldehydes **10**.



Scheme 1 One-pot conversion of peptides into peptidyl β-aldehydes

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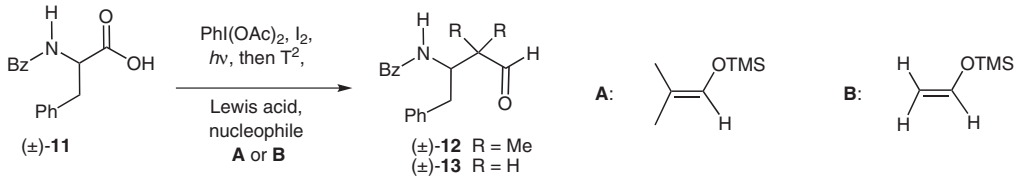
Table 1 Tandem Scission–Alkylation to Yield Compounds **12** and **13**



Ratio of DIB/I_2 (equiv)	Nu (equiv)	Lewis acid (equiv)	Addition temp T^2 (°C)	Product (yield, %)[a]
1.5:0.3	**A** (3)	$TiCl_4$ (2)	–78	**12** (25)
1.5:0.3	**A** (3)	$SnCl_4$ (2)	–78	**12** (51)
1.5:0.3	**A** (3)	TMSOTf (2)	0	**12** (58)
1.5:0.3	**A** (3)	$BF_3{\cdot}OEt_2$ (2)	0	**12** (61)
1.5:0.5	**A** (3)	$BF_3{\cdot}OEt_2$ (2)	0	**12** (53)
2.0:1.0	**A** (5)	$BF_3{\cdot}OEt_2$ (2)	0	**12** (38)
1.5:0.3	**B** (3)	$BF_3{\cdot}OEt_2$ (2)	0	**13** (41)
1.5:0.3	**B** (3)	TMSOTf (2)	0	**13** (40)

[a] Yields for purified products.

Initially, the tandem scission–alkylation was optimized using single amino acid derivatives as substrates. Thus, Bz-DL-Phe-OH (**11**) was treated under the conditions listed in Table 1, varying quantities of reagents and using different Lewis acids and temperatures, to afford the β-amino aldehydes **12** (R = Me) or **13** (R = H).

The best conditions used a catalytic amount of iodine (0.3 equiv) in the scission step, and $BF_3{\cdot}OEt_2$ or TMSOTf at 0 °C in the addition step. These conditions were then used with the other amino acid and peptide substrates **14**–**19** (Scheme 2), to afford the β-amino aldehyde derivatives **20**–**28** in good global yields. Interestingly, in the case of peptides, TMSOTf gave better results than $BF_3{\cdot}OEt_2$.

In the case of substrates **18** and **19**, the reacting residue is attached to an L-amino acid which serves as a chiral auxiliary. Therefore, the scission–addition reaction is stereoselective, affording the L-β-amino aldehyde as the major isomer (L/D ≈ 2:1 in both cases). The diastereomers were readily separated by chromatography, in order to determine structure–biological activity relationships.

The stereochemistry of these compounds was determined by comparison with similar peptides,[7a] and it was confirmed by oxidation of aldehyde **27** to an acid followed by esterification,[8] to the known dipeptide Bz-L-Leu-L-β-hAla-OMe (58%).[7a]

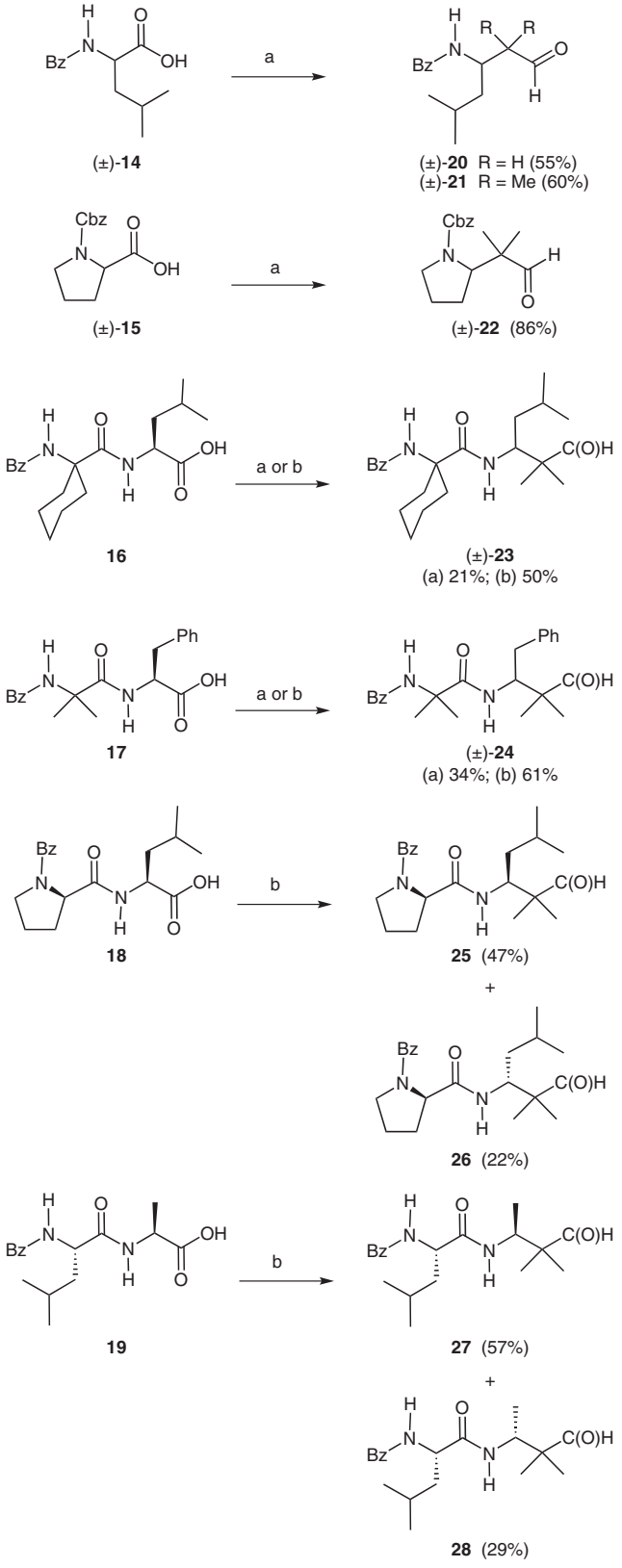
Interestingly, when the silyl enol ether used as the nucleophile was replaced by vinyl acetate[7e] (Scheme 3), the expected β-amino aldehyde derivatives were not formed, and 2-acetoxyazetidines were obtained instead. Thus, substrates **29**, **30**, and **14** were treated under the modified scission–alkylation conditions, affording the 2-acetoxyazetidines **31**–**33** in satisfactory yields.

The different results observed in the use of silyl enol ethers and vinyl acetate can be explained using substrate **14** as an example (Scheme 3). The scission–oxidation steps, followed by addition of the nucleophile to the acyliminium intermediate, generated an oxycarbenium ion **34**. When R = TMS, a silyl cation was readily lost to give the aldehyde **20**. However, when R = Ac, the loss of an acyl cation was not favored, so the addition of the amide took place instead, affording the 2-acetoxyazetidine **33**.

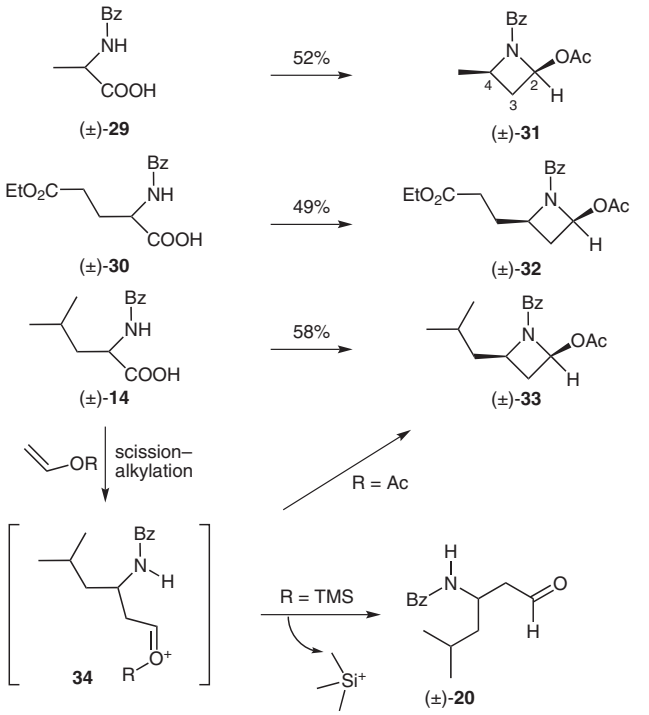
The cyclization was stereoselective, and only the 2,4-*cis*-azetidine was isolated. The 2,4-*trans*-isomer was not detected.[9] A minimum-energy conformation for the oxycarbenium intermediate **34** prior to ring closure is shown in Figure 2.[10] In this conformation, where unfavorable steric interactions are greatly reduced, the nitrogen is correctly positioned for ring closure to occur, affording the 2,4-*cis*-azetidine **33**. The same applied to the other substrates **29** and **30**, affording the 2,4-*cis*-azetidines **31** and **32**, respectively.

The resulting 2-acetoxyazetidines are remarkably useful, not only as aldehyde prodrugs, but also as precursors of azetidines. The introduction of azetidines in peptides by conversion of common amino acids into 2-acetoxyazetidines and addition of other nucleophiles to the *N*,*O*-acetal is particularly interesting.[11] The azetidine ring could be used to generate turns and other secondary structure elements.[12] This possibility is currently under study in our group and will be published in due course.

In conclusion, we have developed an efficient methodology for the direct conversion of α-amino acid derivatives into β-amino aldehydes, using a sequential procedure which couples a radical decarboxylation to an oxidation and to a nucleophilic addition. The procedure allows the



Scheme 2 *Reagents and conditions*: Method A: DIB (1.5 equiv), I_2 (0.3 equiv), CH_2Cl_2, *hν*, r.t., 4 h, then 0 °C, $BF_3{\cdot}OEt_2$ (2 equiv), $R_2C{=}C(OTMS)H$ (3 equiv), 3 h. Method B: similar to A but using TMSOTf as Lewis acid.



Scheme 3 Formation of 2-acetoxyazetidines. *Reagents and conditions*: DIB (1.5 equiv), I_2 (0.3 equiv), CH_2Cl_2, *hν*, r.t., 4 h, then 0 °C, $BF_3{\cdot}OEt_2$ (2 equiv), $CH_2{=}C(OAc)H$ (10 equiv), 3 h.

selective modification of the *C*-terminal residue in small peptides, and therefore, a single α-peptide could be transformed into a library of α,β-peptidyl aldehydes.

Moreover, by changing the reaction conditions, the α-amino acids can be transformed into 2-acetoxyazetidines, which could be useful aldehyde prodrugs. Furthermore, the 2-acetoxyazetidines could be converted into azetidines following reported procedures, in order to generate turns or other secondary structure elements in peptides.

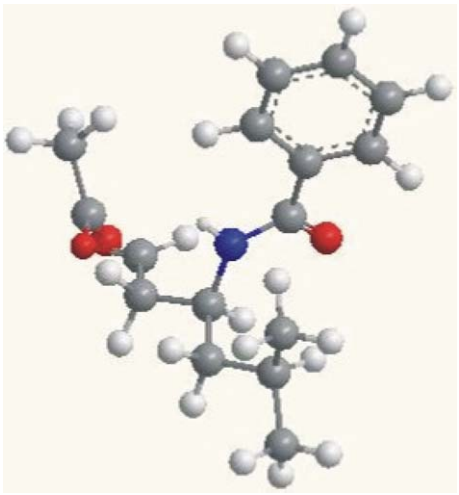


Figure 2 Minimized conformation for oxycarbenium intermediate **34** prior to ring closure

General Procedures for the Scission–Oxidation–Alkylation Sequence

Method A

To a solution of the starting amino acid or peptide (0.2 mmol) in dry CH_2Cl_2 (6 mL) were added I_2 (15 mg, 0.06 mmol, 0.3 equiv) and DIB (97 mg, 0.3 mmol, 1.5 equiv). The reaction mixture was stirred at 25–26 °C for 4 h, under irradiation with visible light. Then the solution was cooled to 0 °C, and vinyloxytrimethylsilane (89 μL, 70 mg, 0.6 mmol, 3 equiv) or 2-methyl-1-(trimethylsilyloxy)-1-propene (110 μL, 86 mg, 0.6 mmol, 3 equiv) or vinylacetate (184 μL, 172 mg, 2 mmol, 10 equiv) was injected, followed by dropwise addition of $BF_3{\cdot}OEt_2$ (51 μL, 57 mg, 0.4 mmol, 2 equiv). The mixture was allowed to reach r.t. and stirred for 3 h; then it was poured into 10% aq $Na_2S_2O_3$–sat. aq $NaHCO_3$ (1:1, 10 mL) and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (hexanes–EtOAc) to give the products.

Method B

As in method A but using TMSOTf (72 μL, 89 mg, 0.4 mmol, 2 equiv) as the Lewis acid.

***N*-Benzoyl-α,α-dimethyl-DL-β-homophenylalaninal (12)**

Phenylalanine derivative (±)-**11** was treated as in method A, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by column chromatography on silica gel (hexanes–EtOAc, 9:1), giving the aldehyde (±)-**12** (61%) as a crystalline solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25 (s, 3 H), 1.31 (s, 3 H), 2.75 (dd, *J* = 11.2, 14.6 Hz, 1 H), 3.10 (dd, *J* = 4.1, 14.2 Hz, 1 H), 4.69 (ddd, *J* = 4.1, 10.2, 10.8 Hz, 1 H), 6.38 (d, *J* = 9.8 Hz, 1 H), 7.18 (dd, *J* = 6.8, 6.8 Hz, 1 H), 7.23–7.28 (m, 4 H), 7.36 (dd, *J* = 7.5, 7.8 Hz, 2 H), 7.45 (dd, *J* = 7.1, 7.8 Hz, 1 H), 7.52 (d, *J* = 7.1 Hz, 2 H), 9.59 (s, 1 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 19.5 (CH_3), 20.1 (CH_3), 36.7 (CH_2), 50.5 (C), 54.7 (CH), 126.7 (3 × CH), 128.5 (4 × CH), 128.9 (2 × CH), 131.3 (CH), 134.6 (C), 137.8 (C), 167.4 (C), 205.3 (CH) ppm. MS: *m/z* (%) = 295 (<1) [M^+], 105 (100) [PhCO]$^+$, 91 (14) [$PhCH_2$]$^+$, 77 (28) [Ph]$^+$. HRMS: *m/z* calcd for $C_{19}H_{21}NO_2$: 295.1572; found: 295.1580; calcd for C_7H_5O: 105.0340; found: 105.0343

***N*-Benzoyl-DL-β-homophenylalaninal (13)**

Amino acid (±)-**11** was treated as indicated in method A, using vinyloxytrimethylsilane as nucleophile. The reaction mixture was purified by column chromatography on silica gel (hexanes–EtOAc, 7:3), yielding product (±)-**13** (41%) as an amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.73 (ddd, *J* = 1.6, 6.0, 17.3 Hz, 1 H), 2.77 (ddd, *J* = 1.3, 5.4, 17.7 Hz, 1 H), 2.97 (dd, *J* = 7.6, 13.6 Hz, 1 H), 3.09 (dd, *J* = 6.9, 13.6 Hz, 1 H), 4.76 (m, 1 H), 6.58 (d, *J* = 8.2 Hz, 1 H), 7.21–7.25 (m, 3 H), 7.32 (dd, *J* = 7.3, 7.6 Hz, 2 H), 7.40 (dd, *J* = 7.6, 7.6 Hz, 2 H), 7.48 (dd, *J* = 7.3, 7.6 Hz, 1 H), 7.68 (d, *J* = 7.6 Hz, 2 H), 9.77 (dd, *J* = 0.6, 0.9 Hz, 1 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 40.1 (CH_2), 46.7 (CH_2), 46.9 (CH), 126.9 (3 × CH), 128.6 (2 × CH), 128.8 (2 × CH), 129.2 (2 × CH), 131.6 (CH), 134.3 (C), 137.3 (C), 167.0 (C), 201.2 (CH) ppm. MS: *m/z* (%) = 268 (12) [M^+ + H], 176 (69) [M^+ – $PhCH_2$], 105 (100) [PhCO]$^+$, 91 (37) [$PhCH_2$]$^+$, 77 (81) [Ph]$^+$. HRMS: *m/z* calcd for $C_{17}H_{18}NO_2$: 268.1338; found: 268.1327; calcd for C_7H_5O: 105.0340; found: 105.0341.

(Benzoyl-L-leucyl)-α,α-dimethyl-L-β- (27) and (Benzoyl-L-leucyl)-α,α-dimethyl-D-β-homoalaninal (28)

The products were generated from dipeptide **19** according to method B, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by rotatory chromatography on silica gel (hexanes–EtOAc, 4:1), affording compounds **27** (57%) and **28** (29%).

Compound **27**: ^{1}H NMR (500 MHz): δ = 0.95 (d, *J* = 6.3 Hz, 6 H), 1.05 (d, *J* = 8.2 Hz, 3 H), 1.06 (s, 3 H), 1.07 (s, 3 H), 1.67–1.72 (m, 3 H), 4.23 (dddd, *J* = 6.8, 6.8, 6.8, 9.4 Hz, 1 H), 4.67 (ddd, *J* = 7.5, 7.5, 7.5 Hz, 1 H), 6.87 (br d, *J* = 9.0 Hz, 1 H), 6.94 (d, *J* = 7.9 Hz, 1 H), 7.40 (dd, *J* = 7.7, 7.7 Hz, 2 H), 7.49 (dd, *J* = 7.3, 7.6 Hz, 1 H), 7.78 (d, *J* = 7.5 Hz, 2 H), 9.45 (s, 1 H) ppm. ^{13}C NMR (100.7 MHz): δ = 15.8 (CH_3), 17.9 (CH_3), 19.2 (CH_3), 22.2 (CH_3), 22.8 (CH_3), 25.0 (CH), 41.4 (CH_2), 48.6 (CH), 50.0 (C), 52.5 (CH), 127.1 (2 × CH), 128.6 (2 × CH), 131.8 (CH), 133.8 (C), 167.6 (C), 171.9 (C), 204.7 (CH) ppm. MS: *m/z* (%) = 333 (1) [M^+ + H], 190 (100) [M^+ – CONHCH(Me)CMe_2CHO], 105 (91) [PhCO]$^+$. HRMS: *m/z* calcd $C_{19}H_{29}N_2O_3$: 333.2178; found: 333.2181; calcd for $C_{12}H_{16}NO$: 190.1232; found: 190.1239.

Compound **28**: ^{1}H NMR (500 MHz): δ = 0.96 (d, *J* = 6.5 Hz, 3 H), 0.97 (d, *J* = 6.3 Hz, 3 H), 1.00 (s, 3 H), 1.03 (s, 3 H), 1.13 (d, *J* = 6.9 Hz, 3 H), 1.63–1.82 (m, 3 H), 4.24 (1 H, dddd, *J* = 6.9, 6.9, 6.9, 9.5 Hz), 4.61 (ddd, *J* = 6.0, 6.3, 8.2 Hz, 1 H), 6.67 (d, *J* = 8.2 Hz, 1 H), 6.75 (d, *J* = 9.8 Hz, 1 H), 7.43 (dd, *J* = 7.4, 7.4 Hz, 2 H), 7.50 (dd, *J* = 7.3, 7.6 Hz, 1 H), 7.78 (d, *J* = 6.9 Hz, 2 H), 9.43 (s, 1 H) ppm. ^{13}C NMR (100.7 MHz): δ = 16.0 (CH_3), 17.9 (CH_3), 19.0 (CH_3), 22.3 (CH_3), 22.9 (CH_3), 25.0 (CH), 40.4 (CH_2), 48.4 (CH), 50.1 (C), 52.2 (CH), 127.1 (2 × CH), 128.6 (2 × CH), 131.8 (CH), 133.9 (C), 167.9 (C), 171.3 (C), 204.8 (CH) ppm. MS: *m/z* (%) = 333 (2) [M^+ + H], 190 (86) [M^+ – CONHCH(Me)CMe_2CHO], 105 (100) [PhCO]$^+$. HRMS: *m/z* calcd $C_{19}H_{29}N_2O_3$: 333.2178; found: 333.2177; calcd for C_7H_5O: 105.0340; found: 105.0340.

1-Benzoyl-4-isobutylazetidin-2-yl Acetate (33)

Formed from leucine derivative (±)-**14** according to method A, using vinyl acetate as the nucleophile. After purification by column chromatography on silica gel (hexanes–EtOAc, 97:3) the product was isolated as a syrup (58%).

^{1}H NMR (500 MHz): δ = 0.98 (d, *J* = 6.9 Hz, 3 H), 0.98 (d, *J* = 6.9 Hz, 3 H), 1.40 (m, 1 H), 1.58–1.69 (m, 2 H), 2.00 (ddd, *J* = 6.6, 6.9, 13.6 Hz, 1 H), 2.17 (s, 3 H), 2.20 (ddd, *J* = 3.8, 4.4, 13.2 Hz, 1 H), 3.67 (m, 1 H), 6.47 (dd, *J* = 3.8, 8.8 Hz, 1 H), 7.35 (dd, *J* = 7.3, 7.6 Hz, 2 H), 7.41 (dd, *J* = 6.9, 7.6 Hz, 1 H), 7.92 (d, *J* = 7.5 Hz, 2 H) ppm. ^{13}C NMR (125.7 MHz): δ = 21.1 (CH_3), 22.7 (CH_3), 22.8 (CH_3), 24.6 (CH), 32.0 (CH_2), 46.2 (CH_2), 49.7 (CH), 91.0 (CH), 127.4 (2 × CH), 128.0 (2 × CH), 130.6 (CH), 132.8 (C), 152.8 (C), 169.4 (C) ppm. MS: *m/z* (%) = 275 (7) [M^+], 105 (100) [PhCO]$^+$. HRMS: *m/z* calcd for $C_{16}H_{21}NO_3$: 275.1521; found: 275.1532; calcd for C_7H_5O: 105.0340; found: 105.0340.

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