A Simple Synthesis of α,β-Unsaturated γ-Aminobutyric Acid (GABA) Derivatives from Enamines

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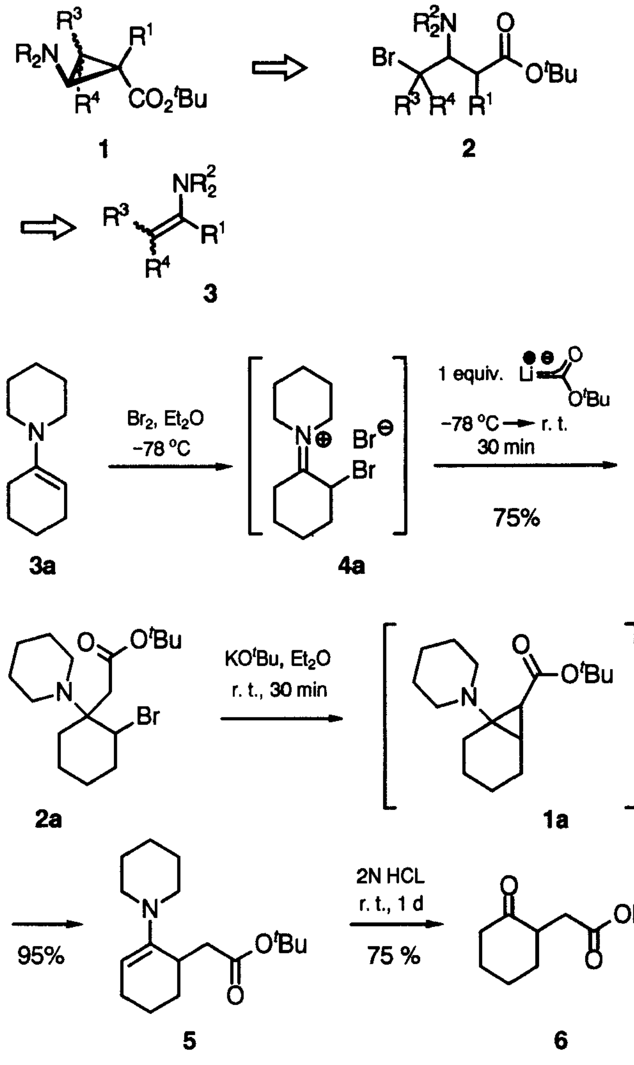
Bromination of enamines **3b–g** at −78 °C and subsequent treatment of the resulting iminium salts **4b–g** with excess *tert*-butyl lithioacetate leads to *tert*-butyl 4-(*N,N*-dialkylamino)carboxylates **9b–g** in good to very good yields. Ester cleavage of the dibenzylamino derivative **9d** with trifluoroacetic acid yields the corresponding acid **10**. Subsequent catalytic hydrogenation of **10** leads to the fully deprotected 4-amino-4-methylpentanoic acid (**12**) in high yield.

Amino acids[1] not only play an essential role as building blocks of proteins, enzymes and glycoproteins, but have various other functions in living systems.[2] Most of the natural ones are α-amino acids, yet the importance of a large number of β- and γ-amino acids has been recognised, e.g. the simple γ-aminobutyric acid (GABA) is regarded as the main inhibitory neurotransmitter in the central nervous system.[3] Conformationally restricted analogues of naturally occurring compounds, e.g. amino acids with an additional double bond,[4] a cyclopropyl or a cyclobutyl group,[5,6] can be used to replace the natural ones in peptides and other biologically active molecules in order to evaluate their biological function.[7,8] Many such non-natural amino acids can act as enzyme inhibitors.[8] We describe here a new access to α,β-unsaturated aminobutyric acid esters.

In an attempt to extend a methodology originally developed for the synthesis of *tert*-butyl cyclopropanecarboxylates[9] to the analogous 2-dialkylamino derivatives, the bromine adducts of enamines **3** were conceived to react with *tert*-butyl lithioacetate to give the *tert*-butyl 3-(dialkylamino)-4-bromobutanoates **2**, which might be cyclised under basic conditions to *tert*-butyl β-aminocyclopropanecarboxylates **1** (Scheme 1).

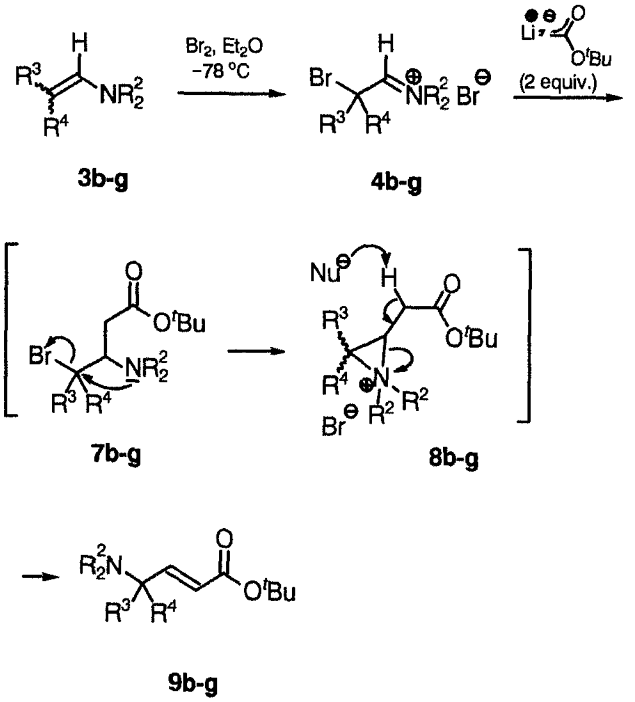
In fact, after bromination of the readily available 1-piperidinylcyclohexene (**3a**) at −78 °C and subsequent treatment of the reaction mixture with 1 equivalent of *tert*-butyl lithioacetate, *tert*-butyl 2-bromo-1-(piperidin-1-yl)cyclohexylacetate (**2a**) was obtained in 75 % yield. Unfortunately, however, all attempts to cyclise compound **2a** in the same manner as the corresponding alkoxy derivatives,[9] including variations of solvent (THF instead of Et_2O), base (LiHMDS instead of LDA), reaction temperature and inverse addition, did not yield cyclopropyl derivatives **1a**, but the formally α-alkylated enamine **5**. This was proved by conversion of the enamine into the known corresponding keto acid **6** by treatment with dilute hydrochloric acid.

To reduce the steric bulk in the intermediate **2** and thereby possibly favor the cyclisation, enamines derived from aldehydes were used in subsequent experiments.[10] But 1-(*N,N*-dimethylamino)-2-methylprop-1-ene (**3b**), when subjected to the same sequence, did not yield *tert*-butyl 2-(*N,N*-dimethylamino)cyclopropanecarboxylate (**1b**), but afforded diastereoselectively *tert*-butyl (*E*)-4-(*N,N*-dimethylamino)-4-methylpent-2-enoate (**9b**) (42 %). By applying 2 equivalents of *tert*-butyl lithioacetate and a slight modification of the reaction and workup conditions the yield of **9b** was improved to 69 % isolated pure product. While the expectedly labile[13] donor–acceptor substituted cyclopropane derivative **1a** most probably was formed as an intermediate in the transformation of **3a** to **5**, the γ-amino α,β-unsaturated carboxylate **9b** must arise from an aziridinium bromide intermediate **8b**, formed by rapid cyclisation of the substitution product **7b** (see Scheme 2). Similar reaction pathways of brominated enamines with migration of the amino moiety by attack of an oxygen-nucleophile are known.[14]



Scheme 1

This transformation of enamines appears to be rather general, as *tert*-butyl 4-alkyl-4-dialkylamino-2-alkenoates 9 were obtained for a variety of examples in good to very good yields (Scheme 2 and Table 1). The possible use of dibenzylaminoalkenes appears to be especially attractive, as dibenzylamino groups can be deprotected by catalytic hydrogenation. Indeed, 1-(*N*,*N*-dibenzylamino)-2-methylprop-1-ene (**3d**) gave 84% of *tert*-butyl 4-dibenzylamino-4-methylpent-2-enoate (**9d**), the highest yield of all cases. Whether the starting enamine was derived from an α-branched aldehyde like isobutyraldehyde or from an *n*-alkanal was unimportant for the formation of **9**. The attempted transformation of 4-morpholino-3-heptene to the corresponding α-substituted γ-amino compound was unsuccessful and gave a complex mixture of unidentified products along with polymers (Scheme 2).



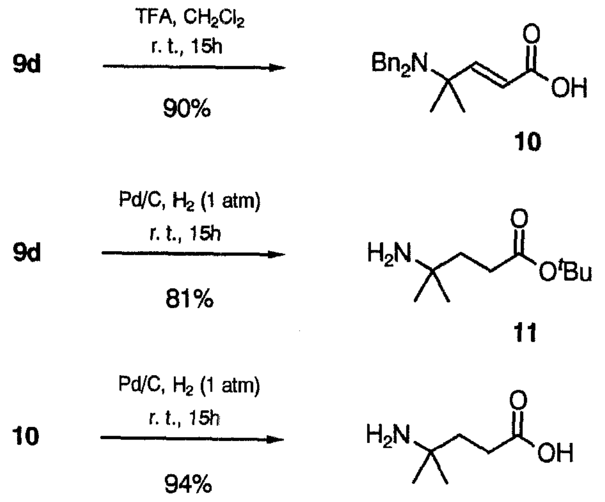
Scheme 2. For details see Table 1.

Table 1. *tert*-Butyl 4-Dialkylaminoalk-2-enoates **9** from Enamines **3** (see Scheme 2)

Starting Material	R^3	R^4	R^2, R^2	Product	Yield[a] (%)
3b	Me	Me	Me, Me	**9b**	69
3c	Me	Me	$-(CH_2)_2O(CH_2)_2-$	**9c**	72
3d	Me	Me	Bn, Bn	**9d**	84
3e	Et	H	$-(CH_2)_2O(CH_2)_2-$	**9e**	72
3f	Bu	H	$-(CH_2)_2O(CH_2)_2-$	**9f**	75
3g	*n*-Hex	H	$-(CH_2)_5-$	**9g**	74

[a] Yield of isolated pure product.

To demonstrate the feasability of this new synthesis, two further transformations were tested with the dibenzylamino derivative **9d**. Mild ester hydrolysis of **9d** was accomplished by treatment with trifluoroacetic acid in dichloromethane at room temperature to give the corresponding acid **10** in very good yield (90%). Catalytic hydrogenation of **9d** in methanol over palladium (5%) on charcoal at room temperature gave the rather sensitive saturated *tert*-butyl 4-amino-4-methylpentanoate (**11**) in 81% yield (Scheme 3). Hydrogenation of **10** under the same conditions resulted in the formation of the deprotected 4-amino-4-methylpentanoic acid (**12**) in an excellent yield of 94%. Thus, the free amino acid **12** was obtained in three simple steps from the dibenzyl enamine **3d** in an overall yield of 71%.[15]



Scheme 3

The reported transformation of enamines **3** may be of pharmacological interest in view of the similarity of the products **9** to GABA. As has been elaborated by Nicholson et al. previously,[18] the "active conformation" of GABA is characterised by an *antiperiplanar* conformation with regard to C(2)–C(3) and a *gauche* conformation around C(3)–C(4). The *trans*-disubstituted double bond in **9** represents a very effective possibility to reduce conformational flexibility in the desired way and the substitution at C(4) could lead to restrictions in free rotation about the C(3)–C(4) bond, too.[19] The yields for this access to 4-alkyl-4-aminoalkenoic acid derivatives[20] are good to very good, and the simplicity makes this procedure interesting for further studies, including the preparation of free unsaturated amino acids derived from compounds **9**,[21] which would be more easily deprotected than the reported ones.

^1H NMR spectra were recorded on a Bruker AM 250 (250 MHz) spectrometer; $\delta = 0$ for tetramethylsilane, 7.26 for $CHCl_3$. ^{13}C NMR spectra were also recorded on a Bruker AM250 (62.9 MHz) spectrometer. IR spectra were run on a Bruker IFS 44 spectrometer. Mass spectra were measured with MAT CH-7 and MAT 311 A (high resolution) instruments. Merck silica gel 60 (200–400 mesh) was used for column chromatography and Macherey-Nagel Silica 60 F_{254} sheets for analytical TLC. Mps were determined with a Büchi instrument and are uncorrected. Elemental analyses were performed by the Mikroanalytisches Laboratorium des Instituts für Organische Chemie der Georg-August-Universität Göttingen. Satisfactory elemental analyses were obtained for **9a–g** and **12**: C ± 0.25, H ± 0.25, N ± 0.20; HRMS obtained for **10**. Petroleum ether (PE) refers to the fraction with bp 35–70 °C. All enamines were synthesised from the corresponding aldehydes or ketones, following literature procedures.[22,23] Compound **3d** was prepared analogous to ref. 23. For physical properties and spectroscopic data of new compounds see Tables 2 and 3.

Table 2. Physical Properties of New Compounds

Product	mp (°C)	IR (neat) ν (cm^{-1})	MS (70 eV) m/z (%)
2a	–	2936, 1724, 1455, 1392, 1368, 1144, 1060, 962, 672	361 (18), 359 (15), 302 (5), 224 (91), 182 (100), 57 (75)
9b	–	2977, 1715, 1650, 1315, 1150	213 (7), 198 (28), 142 (100), 140 (20), 86 (32)
9c	44	2977, 1709, 1658, 1321, 1153, 1117	255 (13), 240 (48), 184 (100), 128 (45), 86 (44)
9d	78	2985, 2876, 2611, 1727, 1661, 1294, 1201, 1024	365 (6), 350 (38), 294 (49), 264 (34), 218 (42), 91 (100)
9e	–	2968, 2251, 1707, 1652, 1155, 910, 733	255 (1), 226 (22), 198 (14), 182 (15), 170 (100)
9f	–	2958, 1715, 1652, 1367, 1153, 1119	199 (7), 184 (100), 128 (13)
9g	–	2931, 2856, 1716, 1649, 1367, 1152	323 (1), 266 (11), 224 (37), 168 (100)
10	148	3072, 2994, 2796, 1720, 1658, 1414, 1194, 1140	309 (7), 294 (69), 91 (100)
11	–	2974, 1729, 1603, 1367, 1153	116 (26), 114 (29), 98 (17), 58 (100), 41 (17)
12	140	3420, 3088, 2928, 1722, 1684, 1514, 1424, 1194, 1128	131 (2), 114 (4), 98 (28), 95 (8), 69 (100), 58 (24), 51 (42), 45 (98)

Table 3. Spectroscopic Data of New Compounds

Product	^{1}H NMR (CDCl$_3$) δ, J (Hz)	^{13}C NMR (CDCl$_3$) δ
2a	1.30–2.11 (m, 14H, CH$_2$), 1.43 [s, 9H, C(CH$_3$)$_3$], 2.38 (d, ^2J = − 14.1 Hz, 1H, 2-H), 2 % 62 (d, ^2J = − 14.1 Hz, 1H, 2-H), 2.74 (m, 4H, NCH$_2$), 4.70 (dd, ^3J = 4.8, ^3J = 2.4 Hz, CHBr)	21.74, 25.22, 26.94 (CH$_2$), 28.12 [C(*C*H$_3$)$_3$], 32.23 (CH$_2$), 38.08 (CH$_2$), 45.90 (NCH$_2$), 79.81 [*C*(CH$_3$)$_3$], 170.68 (C-1)
9b	1.15 (s, 6H, 4-H), 1.47 [s, 9H, C(CH$_3$)$_3$], 2.22 [s, 6H, N(CH$_3$)$_2$], 5.74 (d, $^3J_{2,3}$ = 16.0 Hz, 1H, 2-H), 6.89 (d, $^3J_{2,3}$ = 16.0 Hz, 1H, 3-H)	22.42 (C-5), 28.08 [C(*C*H$_3$)$_3$], 38.98 [N(*C*H$_3$)$_2$], 57.37 (C-4), 80.17 [*C*(CH$_3$)$_3$], 121.16 (C-3), 153.81 (C-2), 165.99 (C-1)
9c	1.15 (s, 6H, 4-H), 1.45 [s, 9H, C(CH$_3$)$_3$], 2.51 (m, 4H, NCH$_2$), 3.68 (m, 4H, OCH$_2$), 5.69 (d, $^3J_{2,3}$ = 16.0 Hz, 1H, 2-H), 6.78 (d, $^3J_{2,3}$ = 16.0 Hz, 1H, 3-H)	22.82 (C-5), 28.15 [C(*C*H$_3$)$_3$], 47.52 (NCH$_2$), 58.15 (C-4), 68.01 (OCH$_2$), 80.95 [*C*(CH$_3$)$_3$], 121.92 (C-3), 154.51 (C-2), 166.01 (C-1)
9d	1.20 (s, 6H, 4-H), 1.48 [s, 9H, C(CH$_3$)$_3$], 3.68 (s, 4H, NCH$_2$), 5.80 (d, $^3J_{2,3}$ = 16.0 Hz, 1H, 2-H), 7.03–7.27 (m, 11H, 3-H, Ph)	24.22 (C-5), 28.01 [C(*C*(*C*H$_3$)$_3$], 54.49 (CH$_2$), 59.60 (C-4), 80.04 [*C*(CH$_3$)$_3$], 120.47 (C-3), 126.24 (Ph), 127.74 (Ph), 128.19 (Ph), 141.59 (Ph), 155.17 (C-4), 165.96 (C-1)
9e	0.83 (t, ^3J = 7.5 Hz, 3H, 6-H), 1.45 [s, 9H, C(CH$_3$)$_3$], 1.64 (m, 2H, 5-H), 2.47 (m, 4H, NCH$_2$), 2.72 (m, 1H, 4-H), 3.65 (t, J = 4.7 Hz, 4H, OCH$_2$), 5.76 (d, ^3J = 5.7 Hz 1H, 2-H), 6.68 (dd, $^3J_{2,3}$ = 15.7, $^3J_{3,4}$ = 9.0 Hz, 1H, 3-H)	10.44 (C-6), 23.68 (C-5), 28.05 [C(*C*H$_3$)$_3$], 50.23 (NCH$_2$), 67.14 (OCH$_2$), 68.06 (C-4), 80.33 [*C*(CH$_3$)$_3$], 125.43 (C-3), 146.30 (C-2), 165.25 (C-1)
9f	0.84 (t, ^3J = 7.5 Hz, 3H, 8-H), 1.20 (m, 4H, 6-H, 7-H), 1.44 [s, 9H, C(CH$_3$)$_3$], 1.59 (m, 2H, 5-H), 2.46 (m, 4H, NCH$_2$), 2.78 (m, 1H, 4-H), 3.64 (m, 4H, OCH$_2$), 5.73 (d, $^3J_{2,3}$ = 15.6 Hz, 1H, 2-H), 6.66 (dd, $^3J_{2,3}$ = 15.6, $^3J_{3,4}$ = 8.2 Hz, 1H, 3-H)	13.81 (C-8), 22.53 (C-7), 27.95 (C-6), 28.02 [C(*C*H$_3$)$_3$], 30.47 (C-5), 50.01 (NCH$_2$), 66.39 (C-4), 67.02 (OCH$_2$), 80.21 [*C*(CH$_3$)$_3$], 125.16 (C-3), 146.33 (C-2), 165.15 (C-1)
9g	0.83 (t, ^3J = 6.5 Hz, 3H, 11-H), 1.21 (bs, 10H, CH$_2$), 1.45 [s, 9H, C(CH$_3$)$_3$], 1.48–1.59 (m, 8H, CH$_2$), 2.42 (m, 4H, NCH$_2$), 2.81 (m, 1H, 4-H), 5.71 (d, $^3J_{2,3}$ = 15.6 Hz, 1H, 2-H), 6.74 (dd, $^3J_{2,3}$ = 15.6, $^3J_{3,4}$ = 9.1 Hz, 1H, 3-H)	14.01 (C-11), 22.55, 24.59, 26.31, 26.37 (CH$_2$), 28.06 [C(*C*H$_3$)$_3$], 29.10, 31.35, 31.75 (CH$_2$), 50.56 (NCH$_3$), 66.84 (C-4), 124.59 (C-3), 147.25 (C-2), 165.52 (C-1)
10	1.84 (s, 6H, CH$_3$), 4.46 (s, 4H, NCH$_2$), 6.28 (d, ^3J = 15 Hz, 1H, 2-H), 7.13–7.39 (m, 11H, Ph, 3-H)[a]	13.07 (C-5), 46.57 (NCH$_2$), 60.57 (C-4), 116.69 (C-3), 120.44, 121.0, 122.48, 122.63 (Ph), 137.23 (C-2), 158.74 (C-1)[b]
11	1.09 (s, 6H, 5-H), 1.43 [s, 9H, C(CH$_3$)$_3$], 1.66 (m, 2H, 3-H), 2.27 (m, 2H, 2-H)	28.05 [C(*C*H$_3$)$_3$], 30.12 (C-5), 31.13 (C-3), 39.38 (C-2), 49.15 (C-4), 80.11 [*C*(CH$_3$)$_3$], 173.42 (C-1)
12	1.20 [s, 9H, C(CH$_3$)$_3$], 1.79 (m, 2H, 3-H), 2.30 (m, 2H, 2-H), 8.03 (bs, 2H, NH$_2$), 12 (bs, 1H, COOH)[b]	24.67 (C-5), 28.36 (C-3), 34.60 (C-2), 52.99 (C-4), 173.86 (C-1)[b]

[a] In CD$_3$OD.
[b] In DMSO-d_6.

(1-Dibenzylamino)-2-methylprop-1-ene (3d):
Enamine **3d** was prepared in close analogy to the reported procedure,[23] using dibenzylamine (19.7 g, 100 mmol) and isobutyraldehyde (100 mL).

IR (film): ν = 3028, 2924, 2361, 1453, 1153, 697 cm^{-1}.

^{1}H NMR: δ = 1.52 (s, 3H, CH$_3$), 1.67 (s, 3H, CH$_3$), 3.20 (s, 4H, NCH$_2$), 5.34 (s, 1H, CH), 7.21–7.32 (m, 10H, Ph).

^{13}C NMR: δ = 17.51 (Me), 22.21 (Me), 59.14 (NCH$_2$), 123.51, 126.60, 126.85, 128.23, 134.94 (Ph), 140.32 (NCH).

***tert*-Butyl 2-[2-Bromo-(1-piperidin-1-yl)cyclohexenyl]acetate (2a):**
Br$_2$ (1.6 g, 10 mmol) was added dropwise to a well stirred solution of 1-piperidylcyclohexene (**3a**) (1.65 g, 10 mmol) in anhydr. Et$_2$O (100 mL) at − 78 °C. The mixture was then stirred for 0.5 h and *tert*-butyl lithioacetate was added in one portion {prepared in situ by dropwise addition of *tert*-butyl acetate (2.32 g, 20 mmol) to LDA at − 78 °C [prepared by dropwise addition of butyllithium (8.3 mL, 20 mmol, 2.4 M in *n*-hexane) to diisopropylamine (2.02 g, 20 mmol) in anhydrous Et$_2$O (30 mL) at − 78 °C]}. The reaction mixture was allowed to warm to r. t., stirred for another 30 min and then treated

with sat. aq NH_4Cl (50 mL). After extraction with Et_2O (2 × 50 mL), washing with water (2 × 30 mL), sat. aq NaCl (5 mL), drying ($MgSO_4$) and removal of the solvents under reduced pressure, the resulting residue was chromatographed over 50 g silica gel (PE/Et_2O, 5:1) to give 2.69 g (75%) of **2a**.

tert-Butyl 2-[2-(Piperidin-1-yl)cyclohex-2-enyl]acetate (5):
To a well stirred solution of **2a** (360 mg, 1 mmol) in anhydr. Et_2O (2 mL) at r.t. was added potassium *tert*-butoxide (228 mg, 2 mmol) in one portion. After 5 min, the reaction mixture was poured into 10 mL water. Extraction of the aq phase with Et_2O (3 × 5 mL), washing of the organic phases with water and drying ($MgSO_4$) led, after removal of the solvents, to 267 mg (95%) of **5**.

^{1}H NMR: δ = 1.42 [s, 9 H, $C(CH_3)_3$], 1.49 (m, 10 H), 2.04 (AB-part of an ABX-system, 2 H, $^2J = -10.4$ Hz, $^3J = 15$ Hz, 2-H), 2.46 (m, 2 H, 4′-H), 2.66 (dd, 1 H, ^3J = 2.8, 3.2 Hz, 6′-H), 2.82 [m, 4 H, 2″(6″)-H], 4.72 (ddd, 1 H, ^3J = 4, 4, ^4J = 0.8 Hz, 3′-H).

^{13}C NMR: δ = 19.55, 24.75, 25.00, 26.25 (C-5′,6′,3″,4″,5″), 28.06 [$C(CH_3)_3$], 28.60 (C-4′), 31.68 (C-1′), 40.03 (C-2), 50.18 (C-2″,6″), 79.81 [$C(CH_3)_3$], 103.64 (C-3′), 149.51 (C-2′), 173.36 (C-1).

(2-Oxocyclohexyl)acetic acid (6):[24]
A solution of **5** (250 mg, 0.84 mmol) in 2 N aq HCl (5 mL) was stirred for 1 d at r.t. Extraction with Et_2O (3 × 10 mL), washing of the combined extracts with water, drying ($MgSO_4$) and evaporation of the solvents led to 98 mg (75%) of **6**.

^{1}H NMR: δ = 1.40 (m, 1 H), 1.65 (m, 2 H), 1.77 (m, 1 H), 2.13 (m, 3 H), 2.38 (m, 2 H), 2.80 (m, 2 H), 7.5–8.5 (bs, 1 H).

^{13}C NMR: δ = 25.10, 27.69, 33.75, 34.21, 41.70 (C-2,3′,4′,5′,6′), 46.86 (C-1′), 178.15 (C-1), 211.11 (C-2′).

tert-Butyl 4-Dibenzylamino-4-methylpent-2-enoate (9d); Typical Procedure:
Br_2 (1.6 g, 10 mmol) was added dropwise to an efficiently stirred solution of 1-(*N,N*-dibenzylamino)-2-methylprop-1-ene (**3d**) (2.51 g, 10 mmol) in anhydr. Et_2O (100 mL) at −78 °C, whereupon a thick, light yellow solid precipitated. To this mixture, warmed and then kept at 0 °C, was added dropwise a solution of *tert*-butyl lithioacetate at −78 °C {prepared in situ by dropwise addition of *tert*-butyl acetate (2.32 g, 20 mmol) to a solution of LDA at −78 °C [prepared by dropwise addition of butylllithium (8.47 mL, 20 mmol, 2.36 M in *n*-hexane) to diisopropylamine (2.02 g, 20 mmol) in anhydrous Et_2O (30 mL) at −78 °C]}. During this addition, the precipitate dissolved, and a pale yellow solution was obtained. The reaction mixture was allowed to warm to r.t. and stirred for an additional 1 h. After removal of the solvents under reduced pressure, the mixture was washed with water (20 mL) and the aq phase extracted with Et_2O (2 × 30 mL). The combined organic phases were dried ($MgSO_4$) and the solvents evaporated under reduced pressure. The residue was chromatographed over 50 g silica gel (PE/Et_2O 30:1 containing 5% Et_3N) to yield 3.06 g (84%) of **9d**.

4-Dibenzylamino-4-methylpent-2-enoic Acid (10):
To a stirred solution of **9d** (1.00 g, 2.74 mmol) in CH_2Cl_2 (20 mL) at r.t. was added dropwise trifluoroacetic acid (TFA) (2 mL). After 12 h of stirring, the solvents and TFA were evaporated and the resulting pale yellow oil crystallized by addition of Et_2O. Recrystallisation from THF/Et_2O yielded 760 mg (90%) of **10** as a colourless crystalline compound, mp 148 °C.

tert-Butyl 4-Amino-4-methylpentanoate (11):
To a solution of **8d** (300 mg, 0.82 mmol) in dry MeOH (40 mL) was added palladium-on-charcoal (10 mol%, 172 mg of 5% Pd/C). The reaction flask was flushed with N_2 for a few minutes. The mixture was stirred vigorously under a hydrogen atmosphere (slightly pressurized by a rubber balloon). After 15 h the reaction mixture was centrifuged. Decantation and careful concentration on a rotary evaporator yielded 124 mg (81%) of **11** as a colourless oil. Even at −25 °C this compound was rather unstable and totally decomposed after a few days.

4-Amino-4-methylpentanoic Acid (12):
To a solution of 4-dibenzylamino-4-methylpent-2-enoic acid (**10**) (500 mg, 1.62 mmol) in dry MeOH (40 mL) was added palladium-on-charcoal (10 mol%, 175 mg of 5% Pd/C). The reaction flask was flushed with nitrogen for a few minutes. The mixture was stirred vigorously under a hydrogen atmosphere (slightly pressurized by a rubber balloon). After 15 h the reaction mixture was centrifuged. Decantation and careful concentration on a rotary evaporator yielded a colourless oil which was crystallized by addition of Et_2O/MeOH. Recrystallization from the same solvent system yielded 196 mg (94%) of **12** as a white solid, mp 140 °C.

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