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A Short Access to Symmetrically α,α-Disubstituted α-Amino Acids from Acyl Cyanohydrins

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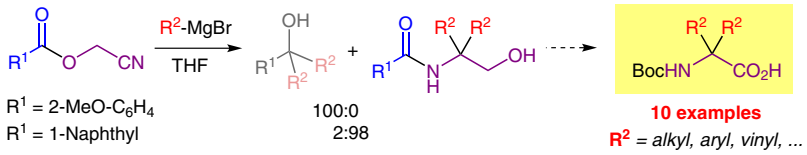

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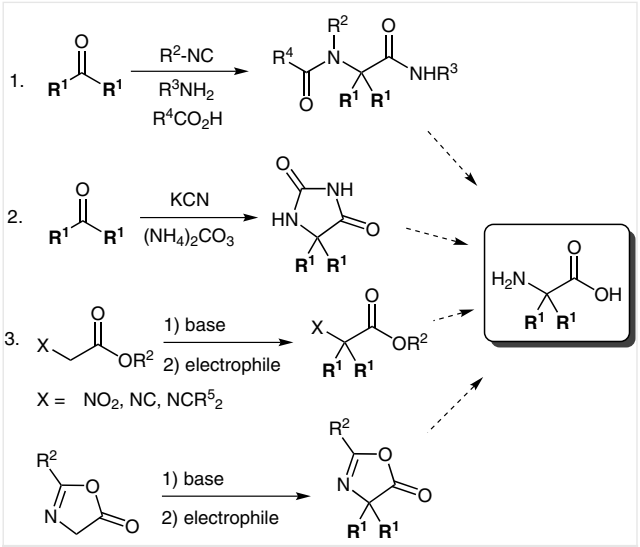
Abstract A straightforward synthesis of symmetrically α,α-disubstituted α-amino acids is presented. The key step of this process relies on the efficient double addition of Grignard reagents to acyl cyanohydrins to provide *N*-acyl amino alcohols selectively in good yields. The chemoselectivity of the reaction was modulated by the nature of the acyl moiety. Eleven amino acids were prepared, including the particularly simple divinylglycine, which is not easily accessible by using conventional methods.

Key words amino acids, cyanohydrins, Grignard reagents, nitriles, solvent effects

The synthesis and use of α,α-disubstituted α-amino acids is the subject of continuing research activity.[1] In addition to their relevance as biologically active molecules,[1e] these building blocks were incorporated into peptides with the aim of limiting their conformational freedom, and thus increasing their selectivity and potency. Indeed, stable secondary structures (β-turns, α-helices, 3_{10}-helices and 2.0_5-helices etc.) were obtained from such short peptides.[2] The simplest member of this family, α-aminoisobutyric acid (Aib) is present in several bioactive peptides, such as chlamydocin[3] and the large peptaibiotic family.[4] Other disubstituted amino acids were also prepared and present a large variety of stable conformations when incorporated in small peptides.[5] In addition, the use of disubstituted amino acids in peptides increases significantly their proteolytic stability.[6]

The most important methods to access α,α-disubstituted α-amino acids may be divided into two main strategies according to the origin of the two R substituents on the targeted amino acids (Scheme 1).[1]



Scheme 1 Classical approaches to α,α-amino acids syntheses

Classical routes involve modification of ketones already displaying the R substituents by Bucherer–Bergs,[7] Strecker,[8] or Ugi[9] reactions, followed by amine deprotection and/or hydrolysis (Scheme 1, routes 1 and 2). Alternatively, the R moiety is introduced from electrophilic sources (organic halides or Michael acceptors), by reaction with nitroacetates, isocyanoacetates, glycine-derived imines or azlactones[10] (route 3). In all cases, subsequent reduction and/or hydrolysis steps are required to afford the free amino acids.

It is clear that some functional groups cannot be easily introduced by using the above methods, such as vinyl or alkynyl moieties,[11] although these unsaturations are widely useful in synthesis and in post-functionalization of peptides (i.e., RCM[12] or click reaction[13]). The development of new methods, that employ mild conditions and allow gen-

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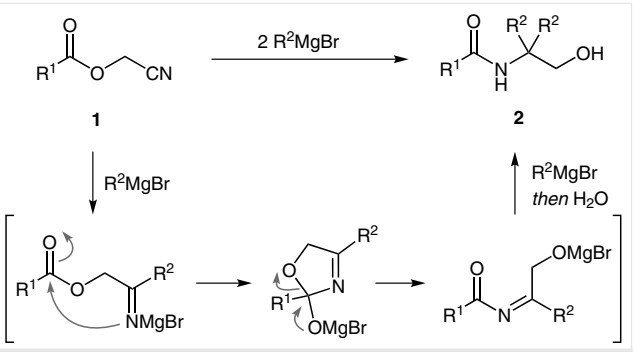
eral access to functionalized α,α-disubstituted amino acids, suitably protected for peptide synthesis, represents an interesting challenge.

During our investigations on the titanium-mediated cyclopropanation of nitriles,[14,15] we developed several synthetic methods to prepare amino acids bearing a cyclopropane moiety.[16] Recently, we demonstrated that the addition of Grignard reagents onto acyl cyanohydrins (**1**)[17] led mainly to α,α,α-trisubstituted carbinamides **2** under particularly mild conditions (Scheme 2).[18]

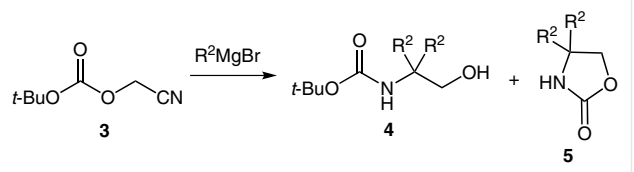


Scheme 2 Addition of Grignard reagents to acyl cyanohydrins leading to α,α-disubstituted α-amino acids

This reaction presents two remarkable facts, the first being a strong solvent effect that was noted for this transformation. Indeed, the expected Grignard addition onto the ester function predominantly occurred when the reaction was performed in Et_2O, whereas the use of THF as solvent led to a preferential addition onto the nitrile moiety. Secondly, the reaction did not stop after the first Grignard addition onto the nitrile functionality, thanks to the formation of an electrophilic acyl imine intermediate that activates the second addition.

In the present study, we propose to apply this concept to the straightforward synthesis of α,α-disubstituted α-amino acids. Indeed, the amino alcohol derivative **2** would be an advanced intermediate for an alternative synthesis of α,α-disubstituted amino acids, in which the two R groups are introduced in a *nucleophilic* manner.

With the aim of developing a more direct access to useful *N*-Boc-protected amino acids, we first investigated cyanohydrins **3** as substrate to provide the protected amino alcohol **4** (Scheme 3).

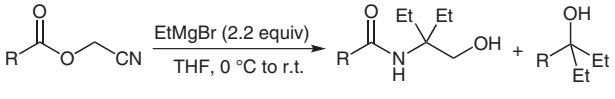


Scheme 3 Attempted preparation of *N*-Boc amino alcohol **4** from **3**

When ethyl and phenyl magnesium bromides were added to cyanohydrin **3** in THF, mixtures of Boc-protected amino alcohols **4** and 4,4-disubstituted oxazolidin-2-ones **5** were observed together with by-products resulting from the addition of Grignard reagents onto the carbonate moiety. Even if the cyclization into oxazolidinone was rather limited when performing the reaction in Et_2O, the separation of **4** from all side-products by chromatography on silica gel was as difficult as for the reaction carried out in THF, and amino alcohol **4** was isolated in only 22% yield in the best case (i.e., addition of EtMgBr in Et_2O).

We then focused on an alternative, higher yielding route to the *N*-Boc-amino alcohol **4** that involves the addition of Grignard reagents onto acyl cyanohydrins **1** followed by amide hydrolysis of **2** and Boc-protection of the free amine. For this purpose, the nature of the acyl group was designed to maximize the yield of hydroxyamide **2** and thus to minimize the formation of tertiary alcohol **6** by double addition onto the ester moiety. Representative results involved in the optimization of this step using EtMgBr are gathered in Table 1.

Table 1 Addition of EtMgBr to Acyl Cyanohydrins **1a–i**



Entry	R	Ratio **2**/**6**[a]	Yield of **2** (%)[b]
1	Ph (**1a**)	83:17	**2aa** (65)
2	Ph (**1a**)[c]	26:74	**2aa** (14)
3	4-$MeOC_6H_4$ (**1b**)	84:16	**2ba** (73)
4	4-BrC_6H_4 (**1c**)	71:29	**2ca** (58)
5	3,4,5-$(MeO)_3C_6H_2$ (**1d**)	84:16	**2da** (68)
6	3,4-$(MeO)_2C_6H_3$ (**1e**)	87:13	**2ea** (65)
7	2-$MeOC_6H_4$ (**1f**)	0:100	**2fa** (–)[d]
8	2-MeC_6H_4 (**1g**)	96:4	**2ga** (72)
9	2-naphthyl (**1h**)	71:29	**2ha** (59)
10	1-naphthyl (**1i**)	96:4	**2ia** (74)
11	1-naphthyl (**1i**)[e]	>98:2	**2ia** (77)

[a] Ratio determined by ^1H NMR spectroscopic analysis of the crude material.
[b] Isolated yield.
[c] Et_2O used instead of THF.
[d] Only 3-(2-methoxyphenyl)pentan-3-ol (**6fa**) was obtained.
[e] Reaction maintained at 0 °C for 30 min.

When the reaction was performed with cyanomethyl benzoate (**1a**) in THF, the two main products observed were *N*-acyl amino alcohol **2aa** and alcohol **6aa** in a 83:17 ratio (Table 1, entry 1).[19] It is noteworthy that the nature of the solvent is a crucial parameter, since the ratio is nearly inverted when Et_2O was used (entry 2).[18] In that case, the predominant formation of **2** means that the first addition of

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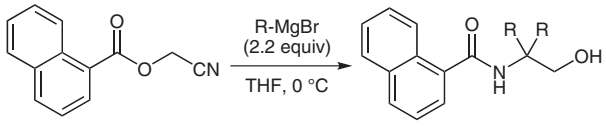
the Grignard reagent must occur faster on the nitrile moiety than on the ester. Lowering the electrophilicity of the ester function may be controlled by modifying the electronic and/or the steric properties of the ester moiety. By comparing the reactivity of substrates **1b** and **1c** in the reaction (entries 3 and 4), it is evident that electron-donating groups on the aromatic moiety support the formation of **2**. Nevertheless, the cyanoesters **1d** and **1e**, bearing two or three methoxy groups, respectively, did not tip the scale in favor of **2** (entries 5 and 6). Interestingly, the 2-methoxy group acts as a strong directing group towards the ester moiety and only unwanted tertiary alcohol **6fa** was obtained (entry 7). In contrast, the use of the 2-methyl substituent inhibits strongly the formation of **6ga**, and an interesting 96:4 ratio was measured (entry 8). A similar steric effect was observed by using the isomeric naphthoic acid derivatives **1h** and **1i** (entries 9 and 10). Whereas cyanomethyl 2-naphthoate **1h** afforded worse selectivity than benzoate derivative **1a**, the 1-naphthoate isomer gave mainly hydroxyamide **2ia**, and this selectivity was even increased by keeping the temperature at 0 °C (entry 11). Under these conditions, the tertiary alcohol side-product was not observed. This short study showed that, in addition to the nature of the solvent, the crowding of the ester group is the main factor governing the chemoselectivity of the addition of Grignard reagents to acylcyanohydrins. The cyanoester **1i** was thus chosen for a general preparation of α,α-disubstituted amino acids and several Grignard reagents were used in the addition step (Table 2).

Good yields were obtained with alkyl and aryl Grignard reagents and, in all cases (Table 2, entries 1–7), the alcohol side product **6** was observed in 0–5% yield, thus simplifying the purification step. Grignard reagents bearing a double bond can also be used without problems (entries 8–10), with the exception of allyl Grignard reagent, which gave disappointing results (entry 11). In THF, the expected product was obtained along with isomers in which the double bond shifted. Indeed, it is known that addition of allylic Grignard reagents to nitriles may result in the formation of mixtures of unsaturated ketones after hydrolysis.[20] The yield obtained here reflects the difficulty of separating the isomers. Interestingly, the yield was better in Et_2O (entry 12), because the double bond isomerization is less significant in this solvent.

The conversion of hydroxyamides **2ia**–**ik** into the corresponding *N*-Boc amino alcohols **4a**–**k** was performed in one pot by cleavage of the amide moiety using NaOH under microwave irradiation and subsequent protection of the released amine function by the addition of Boc_2O (Scheme 4). The use of microwave heating led to a shorter reaction time (10 min) and higher yields than under conventional reflux heating. The isolation of the free amino alcohol intermediate resulted in lower yields than in the two-step, one-pot procedure and was not advantageous here. Despite the highly basic conditions used, the yields were good to excellent, except in the case of vinyl derivative **2ih**, which decomposed completely under these conditions.

Table 2 Addition of Grignard Reagents to Acyl Cyanohydrin **1i**



1i **2ia–2ik**

Entry	Grignard reagent	Yield of amide **2** (%)[a]
1	EtMgBr	**2ia** (77)
2	MeMgBr	**2ib** (73)
3	*n*-$C_5H_{11}MgBr$	**2ic** (68)
4	$PhCH_2MgBr$	**2id** (81)
5	$Ph(CH_2)_3MgBr$	**2ie** (79)
6	PhMgBr	**2if** (70)
7	4-MeO(C_6H_4)MgBr	**2ig** (82)
8	H_2C=CHMgBr	**2ih** (71)
9	H_2C=$CH(CH_2)_2MgBr$	**2ii** (72)
10	H_2C=$CH(CH_2)_3MgBr$	**2ij** (60)
11	H_2C=$CHCH_2MgBr$	**2ik** (26)
12[b]	H_2C=$CHCH_2MgBr$	**2ik** (57)

[a] Isolated yield.
[b] Et_2O used instead of THF.

The last step relies on oxidation of the primary alcohol to the carboxylic acid function. The *N*-Boc protected amino acids **7a**–**g** were easily obtained by oxidation of the primary alcohols **4a**–**g** in one step using the $NaIO_4/RuO_2$ catalytic system. From compounds **4i**–**k**, a two-step oxidation procedure was employed to preserve the alkene moiety. The aldehyde was first prepared by TPAP/NMO mediated oxidation of the primary alcohol, and subsequent oxidation under Dalcanale conditions afforded the acids **7i**–**k**.[21]

Since the deprotection of the divinyl derivative **2ih** failed, an alternative method was carried out for the synthesis of divinylglycine, which is a small amino acid that, to our knowledge, has never been obtained as its free form.[22] The alcohol **2ah**, obtained from **1a** in 71% yield,[18] was then converted into acid **8** in two steps, by Swern oxidation followed by Dalcanale oxidation (Scheme 5). The benzoyl moiety was cleanly removed by heating to reflux in HCl (6 M), to provide divinylglycine (**9**) as its hydrochloride salt in quantitative yield.

In summary, we have developed a general and simple access to symmetrically substituted α,α-amino acids. The robustness of the method is illustrated by the synthesis of several different quaternary amino acids, some of them bearing unsaturated chains, which are useful for further functionalization. The incorporation of such α,α-disubsti-

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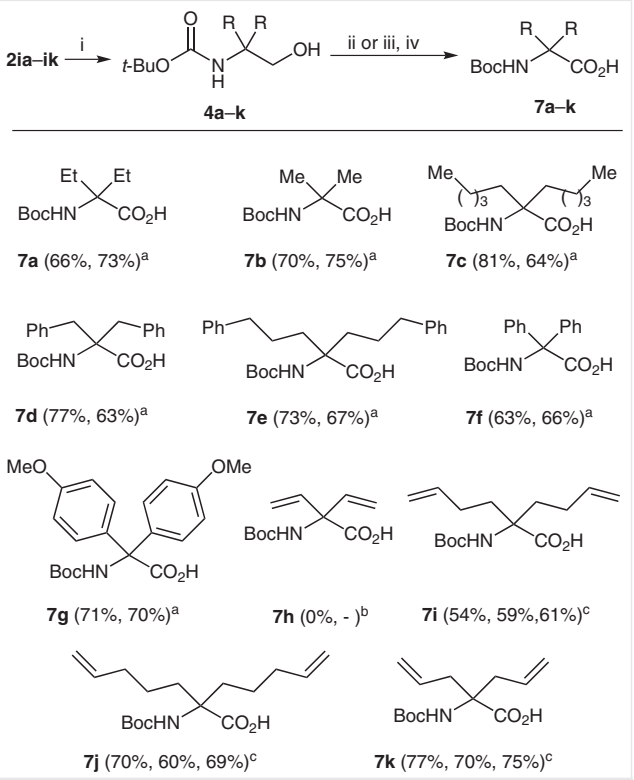
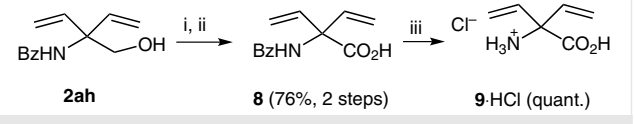


Scheme 4 Preparation of amino acids **7a**–**k**. *Reagents and conditions*: (i) NaOH, EtOH, 135 °C, 10 min in microwave oven, followed by Boc_2O, 40 °C, 2 h; (ii) $NaIO_4$, RuO_2 cat; CCl_4/MeCN/H_2O, r.t., 2 h; (iii) NMO, TPAP (cat.), CH_2Cl_2, r.t., 2 h; (iv) $NaClO_2$, H_2O_2, NaH_2PO_4, MeCN, r.t., 1 h.
[a] Values in parentheses refer to yields in steps i and ii, respectively.
[b] Removal of naphthoyl group was not effective and did not afford **4h**.
[c] Values in parentheses refer to yields in steps i, iii and iv, respectively.



Scheme 5 Preparation of divinylglycine hydrochloride **9**·HCl. *Reagents and conditions*: (i) DMSO, $(COCl)_2$, Et_3N, THF, –35 °C, 15 min; (ii) $NaClO_2$, H_2O_2, NaH_2PO_4, MeCN, r.t., 1 h; (iii) HCl 6 M, reflux.

tuted amino acids into peptides would be interesting for further investigations dealing with their conformational properties.

Experiments involving Grignard reagents were carried out under N_2 atmosphere. Et_2O and THF were purified by passing through neutral alumina columns under nitrogen. The Grignard reagents were prepared in anhydrous Et_2O or THF using conventional methods from the appropriate bromide precursors and Mg turnings with the exception of methylmagnesium bromide, vinylmagnesium bromide, and phenylmagnesium bromide, which were purchased in solution in Et_2O or THF from Sigma–Aldrich. All Grignard reagents were titrated before use according to the B. E. Love method.[23] Reactions carried out under microwave irradiation were performed with a CEM Discover SP apparatus using the Synergy software. Analytical TLC analysis was performed on Alugram SIL G/UV254 silica gel sheets (Macherey–Nagel) by using phosphomolybdic acid or potassium permanganate solution. Column chromatography was carried out using silica gel 60 (0.040–0.063 mm) from Merck. Melting points were determined with a Büchi B-540 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a Bruker DPX-200 or Bruker AC-400 spectrometer. Chemical shifts (δ) are expressed in ppm units, relative to the residual solvent peak. Coupling constants are given in Hz. The multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quadruplet (q), multiplet (m), and broad signal (br). IR spectra were obtained with a Perkin–Elmer Spectrum One spectrometer on a single-reflection diamond ATR unit. High-resolution mass spectra were recorded with a Waters Micromass GCT Premier spectrometer. Cyanoesters **1a**,[17b] **1b**,[17b] **1c**,[17b] **1f**,[24] **1h**,[17b] **1i**,[17b] and cyanocarbonate **3**[16d] were prepared according to previously reported procedures. The following compounds have been reported previously: **2aa**,[18] **2ba**,[18] **2ca**,[18] **2ah**,[18] **4a**,[25] **4b**,[26] **7a**,[25] **7b**,[27] **7d**,[28] **7f**,[29] and **7k**.[30]

Preparation of Acylcyanohydrins 1; General Procedure

To a solution of the appropriate carboxylic acid (40 mmol) in CH_2Cl_2 (40 mL) cooled to 0 °C was added Et_3N (11.1 mL, 80 mmol) and the mixture was stirred at r.t. for 10 min. Chloroacetonitrile (3.81 mL, 60 mmol) was added, then the mixture was stirred at r.t. overnight. H_2O (30 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were successively washed with a sat. aq $NaHCO_3$ (3 × 20 mL) and brine. After drying over $MgSO_4$ and filtration, the organic fraction was concentrated under reduced pressure and the crude acylcyanohydrin was purified either by flash chromatography on silica gel or by recrystallization.

Cyanomethyl 3,4,5-Trimethoxybenzoate (1d)[31]

Purification by recrystallization (toluene) afforded **1d**.

Yield: 7.13 g (71%); white solid; mp 113 °C; R_f = 0.34 (cyclohexane–EtOAc, 70:30).

IR (neat): 3006, 2989, 2956, 2937, 2837, 2130, 1731, 1588, 1501, 1445, 1413, 1331, 1215, 1124, 988 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 7.30 (s, 2 H, ArH), 4.97 (s, 2 H, CH_2CN), 3.93 (s, 3 H, OCH_3), 3.92 (s, 6 H, OCH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 164.6 (C=O), 153.1 (2 C_{Ar}), 143.3 (C_{Ar}), 122.6 (C_{Ar}), 114.5 (CN), 107.3 (2 C_{Ar}), 61.0 (OCH_3), 56.3 (2 OCH_3), 48.9 (CH_2).

HRMS (CI-NH_3/CH_4): *m*/*z* [M + NH_4^+] calcd for $C_{12}H_{17}N_2O_5$: 269.1131; found: 269.1137.

Cyanomethyl 3,4-Dimethoxybenzoate (1e)

Purification by recrystallization (toluene) afforded **1e**.

Yield: 6.01 g (68%); white solid; mp 106 °C; R_f = 0.31 (cyclohexane–EtOAc, 70:30).

IR (neat): 3002, 2937, 2845, 2099, 1707, 1591, 1511, 1460, 1447, 1427, 1413, 1264, 1224, 1172, 1099, 1001 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 7.70 (dd, *J* = 8.5, 2.0 Hz, 1 H, ArH), 7.51 (d, *J* = 2.0 Hz, 1 H, ArH), 6.90 (d, *J* = 8.50 Hz, 1 H, ArH), 4.93 (s, 2 H, CH_2CN), 3.94 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 164.8 (C=O), 154.1 (C_{Ar}), 149.0 (C_{Ar}), 124.5 (C_{Ar}), 120.3 (C_{Ar}), 114.8 (CN), 112.2 (C_{Ar}), 110.5 (C_{Ar}), 56.2 (OCH_3), 56.1 (OCH_3), 48.8 (CH_2).

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HRMS (CI-NH_3/CH_4): m/z [M + NH_4^+] calcd for $C_{11}H_{15}N_2O_4$: 239.1032; found: 239.1032.

Cyanomethyl 2-Methylbenzoate (1g)

Purification by flash chromatography afforded **1g**.

Yield: 4.13 g (59%); colorless oil; R_f = 0.60 (cyclohexane–EtOAc, 70:30).

IR (neat): 2968, 2086, 1728, 1601, 1547, 1488, 1425, 1363, 1241, 1073, 781 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 7.97 (dd, J = 8.0, 1.8 Hz, 1 H, ArH), 7.48 (td, J = 7.6, 1.5 Hz, 1 H, ArH), 7.33–7.22 (m, 2 H, ArH), 4.94 (s, 2 H, CH_2CN), 2.63 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 165.4 (C=O), 141.6 (C_{Ar}), 133.4 (C_{Ar}), 132.2 (C_{Ar}), 131.2 (C_{Ar}), 127.0 (C_{Ar}), 126.1 (C_{Ar}), 114.7 (CN), 48.6 (CH_2), 22.0 (CH_3).

HRMS (CI-NH_3/CH_4): m/z [M + NH_4^+] calcd for $C_{10}H_{13}N_2O_2$: 193.0968; found: 193.0977.

Preparation of Hydroxynaphtamide 2; General Procedure

To a solution of acylcyanohydrin **1** (5 mmol) in THF (25 mL) under N_2 atmosphere and cooled to 0 °C was added dropwise the appropriate Grignard reagent (11 mmol). The reaction mixture was stirred for 30 min at 0 °C then 1 M aq HCl (25 mL) and EtOAc (25 mL) were successively added. The layers were separated and the aqueous phase was extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by chromatography on silica gel to afford hydroxyamide **2**.

***N*-[3-(Hydroxymethyl)pentan-3-yl]-3,4,5-trimethoxybenzamide (2da)**

Purification by flash chromatography afforded **2da**.

Yield: 1.06 g (68%); white solid; mp 113 °C; R_f = 0.25 (toluene–EtOAc, 50:50).

IR (neat): 3358, 3284, 3178, 2967, 2939, 1631, 1544, 1499, 1346, 1233, 1123, 1002 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 6.94 (s, 2 H, ArH), 6.07 (br s, 1 H, NH), 4.75 (br s, 1 H, OH), 3.90 (s, 6 H, OCH_3), 3.87 (s, 3 H, OCH_3), 3.75 (s, 2 H, CH_2OH), 1.86–1.68 (m, 4 H, CH_2CH_3), 0.94 (t, J = 7.5 Hz, 6 H, CH_2CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.3 (C=O), 153.2 (2 C_{Ar}), 141.2 (C_{Ar}), 130.5 (C_{Ar}), 104.5 (2 C_{Ar}), 66.9 (CH_2OH), 61.9 (C), 60.9 (OCH_3), 56.4 (2 OCH_3), 26.3 (2 CH_2CH_3), 7.7 (2 CH_2CH_3).

HRMS (ESI+): m/z [M + H^+] calcd for $C_{16}H_{26}NO_5$: 312.1805; found: 312.1799.

***N*-[3-(Hydroxymethyl)pentan-3-yl]-3,4-dimethoxybenzamide (2ea)**

Purification by flash chromatography afforded **2da**.

Yield: 914 mg (65%); yellow oil; R_f = 0.10 (cyclohexane–MeOH, 50:50).

IR (neat): 3353, 3286, 2966, 2938, 2879, 2838, 1630, 1582, 1543, 1500, 1265, 1232, 1123 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.36 (d, J = 2.1 Hz, 1 H, ArH), 7.20 (dd, J = 8.4, 2.1 Hz, 1 H, ArH), 6.82 (d, J = 8.4 Hz, 1 H, ArH), 6.04 (br s, 1 H, NH), 3.90 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 3.74 (s, 2 H, CH_2OH), 1.82–1.67 (m, 4 H, CH_2), 0.91 (t, J = 7.5 Hz, 6 H, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.3 (C=O), 152.0 (C_{Ar}), 149.2 (C_{Ar}), 127.6 (C_{Ar}), 119.2 (C_{Ar}), 110.8 (C_{Ar}), 110.4 (C_{Ar}), 67.3 (CH_2OH), 61.9 (C), 56.1 (2 OCH_3), 26.5 (2 CH_2CH_3), 7.7 (2 CH_2CH_3).

HRMS (ESI+): m/z [M + H^+] calcd for $C_{15}H_{24}NO_4$: 282.1705; found: 282.1700.

***N*-[3-(Hydroxymethyl)pentan-3-yl]-2-methylbenzamide (2ga)**

Purification by flash chromatography afforded **2ga**.

Yield: 846 mg (72%); white solid; mp 91–95 °C; R_f = 0.50 (toluene–EtOAc, 50:50).

IR (neat): 3212, 2980, 2948, 1631, 1553, 1057, 740, 727 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 7.40–7.12 (m, 4 H, ArH), 5.69 (br s, 1 H, NH), 5.02 (t, J = 6.4 Hz, 1 H, OH), 3.78 (d, J = 6.4 Hz, 2 H, CH_2OH), 2.44 (s, 3 H, CH_3), 1.83–1.58 (m, 4 H, CH_2CH_3), 0.94 (t, J = 7.5 Hz, 6 H, CH_2CH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 171.5 (C=O), 136.9 (C_{Ar}), 135.6 (C_{Ar}), 131.0 (C_{Ar}), 129.9 (C_{Ar}), 126.5 (C_{Ar}), 125.8 (C_{Ar}), 67.0 (CH_2OH), 62.1 (C), 26.6 (2 CH_2CH_3), 19.6 (CH_3), 7.6 (2 CH_2CH_3).

HRMS (ESI+): m/z [M + H^+] calcd for $C_{14}H_{22}NO_2$: 236.1645; found: 236.1647.

***N*-[3-(Hydroxymethyl)pentan-3-yl]-2-naphthamide (2ha)**

Purification by flash chromatography afforded **2ha**.

Yield: 800 mg (59%); white solid; mp 102 °C; R_f = 0.15 (cyclohexane–EtOAc, 70:30).

IR (neat): 3231, 3057, 2972, 2879, 1621, 1564, 1454, 1340, 1254, 1150, 1058 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 8.24 (s, 1 H, ArH), 7.99–7.82 (m, 3 H, ArH), 7.77 (dd, J = 8.6, 1.7 Hz, 1 H, ArH), 7.68–7.44 (m, 2 H, ArH), 6.19 (br s, 1 H, NH), 5.06 (t, J = 6.1 Hz, 1 H, OH), 3.82 (d, J = 6.1 Hz, 2 H, CH_2OH), 1.93–1.71 (m, 4 H, CH_2CH_3), 0.97 (t, J = 7.5 Hz, 6 H, CH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 168.7 (C=O), 134.8 (C_{Ar}), 132.6 (C_{Ar}), 132.2 (C_{Ar}), 128.9 (C_{Ar}), 128.7 (C_{Ar}), 127.9 (C_{Ar}), 127.4 (C_{Ar}), 127.0 (C_{Ar}), 123.4 (2 C_{Ar}), 67.4 (CH_2OH), 62.2 (C), 26.6 (2 CH_2CH_3), 7.7 (2 CH_3).

HRMS (ESI+): m/z [M + H^+] calcd for $C_{17}H_{22}NO_2$: 272.1643; found: 272.1651.

***N*-[3-(Hydroxymethyl)pentan-3-yl]-1-naphthamide (2ia)**

Purification by flash chromatography afforded **2ia**.

Yield: 1.04 g (77%); white solid; mp 124–126 °C; R_f = 0.20 (cyclohexane–EtOAc, 70:30).

IR (neat): 3297, 2936, 2837, 1610, 1645, 1511, 1249, 1180, 1029, 781 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.26 (dd, J = 8.4, 1.9 Hz, 1 H, ArH), 7.92 (d, J = 8.5 Hz, 1 H, ArH), 7.87 (d, J = 8.5 Hz, 1 H, ArH), 7.59–7.51 (m, 3 H, ArH), 7.45 (dd, J = 8.4, 6.9 Hz, 1 H, ArH), 5.96 (br s, 1 H, NH), 5.00 (br s, 1 H, OH), 3.85 (s, 2 H, CH_2OH), 1.86–1.75 (m, 4 H, CH_2CH_3), 0.96 (t, J = 7.5 Hz, 6 H, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.0 (C=O), 134.9 (C_{Ar}), 133.7 (C_{Ar}), 130.7 (C_{Ar}), 130.0 (C_{Ar}), 128.4 (C_{Ar}), 127.3 (C_{Ar}), 126.6 (C_{Ar}), 125.2 (C_{Ar}), 124.7 (2 C_{Ar}), 67.1 (CH_2OH), 62.5 (C), 26.6 (2 CH_2CH_3), 7.7 (2 CH_3).

HRMS (ESI+): m/z [M + Na^+] calcd for $C_{17}H_{21}NNaO_2$: 294.1464; found: 294.1466.

***N*-(1-Hydroxy-2-methylpropan-2-yl)-1-naphthamide (2ib)**

Purification by flash chromatography afforded **2ib**.

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Yield: 887 mg (73%); white solid; mp 150–151 °C; R_f = 0.23 (cyclohexane–EtOAc, 80:20).

IR (neat): 3237, 3051, 2970, 2855, 1626, 1562, 1460, 1350, 1261, 1175, 1061, 782, 737 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.24 (d, *J* = 8.2 Hz, 1 H, ArH), 7.90 (d, *J* = 8.5 Hz, 1 H, ArH), 7.87 (d, *J* = 7.8 Hz, 1 H, ArH), 7.59–7.49 (m, 3 H, ArH), 7.44 (dd, *J* = 8.2, 7.0 Hz, 1 H, ArH), 6.10 (br s, 1 H, NH), 4.80 (br s, 1 H, OH), 3.75 (s, 2 H, CH_2), 1.44 (s, 6 H, CH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 170.8 (C=O), 134.7 (C_{Ar}), 133.7 (C_{Ar}), 130.7 (C_{Ar}), 130.0 (C_{Ar}), 128.4 (C_{Ar}), 127.3 (C_{Ar}), 126.6 (C_{Ar}), 125.1 (C_{Ar}), 124.8 (C_{Ar}), 124.7 (C_{Ar}), 70.8 (CH_2), 57.1 (C), 24.9 (2 CH_3).

HRMS (ESI+): *m*/*z* [M + Na^+] calcd for $C_{15}H_{17}NNaO_2$: 266.1151; found: 266.1162.

N-[6-(Hydroxymethyl)undecan-6-yl]-1-naphthamide (2ic)

Purification by flash chromatography afforded **2ic**.

Yield: 1.21 g (68%); white solid; mp 73–74 °C; R_f = 0.37 (CH_2Cl_2).

IR (neat): 3222, 3049, 2952, 2922, 2859, 1639, 1510, 1460, 1257, 1030, 780, 728 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.26 (d, *J* = 8.0 Hz, 1 H, ArH), 7.93 (d, *J* = 8.2 Hz, 1 H, ArH), 7.88 (d, *J* = 8.7 Hz, 1 H, ArH), 7.60–7.51 (m, 3 H, ArH), 7.46 (dd, *J* = 8.3, 7.0 Hz, 1 H, ArH), 5.93 (br s, 1 H, NH), 5.05 (br s, 1 H, OH), 3.87 (s, 2 H, CH_2OH), 1.83–1.66 (m, 4 H, CH_2C), 1.45–1.26 (m, 12 H, CH_2), 0.90 (t, *J* = 6.8 Hz, 6 H, CH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 170.9 (C=O), 134.9 (C_{Ar}), 133.7 (C_{Ar}), 130.7 (C_{Ar}), 130.0 (C_{Ar}), 128.4 (C_{Ar}), 127.3 (C_{Ar}), 126.6 (C_{Ar}), 125.2 (C_{Ar}), 124.8 (C_{Ar}), 124.7 (C_{Ar}), 68.0 (CH_2OH), 62.5 (C), 34.7 (2 CH_2), 32.3 (2 CH_2), 23.0 (2 CH_2), 22.6 (2 CH_2), 14.1 (2 CH_3).

HRMS (ESI+): *m*/*z* [M + Na^+] calcd for $C_{23}H_{33}NNaO_2$: 378.2404; found: 378.2394.

N-(2-Benzyl-1-hydroxy-3-phenylpropan-2-yl)-1-naphthamide (2id)

Purification by flash chromatography afforded **2id**.

Yield: 1.60 g (81%); pale-yellow solid; mp 170–171 °C; R_f = 0.19 (petroleum ether–EtOAc, 80:20).

IR (neat): 3411, 3348, 3083, 2940, 1632, 1537, 1316, 1074, 790, 704 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.25–8.23 (m, 1 H, ArH), 7.90–7.84 (m, 2 H, ArH), 7.52–7.50 (m, 2 H, ArH), 7.39–7.38 (m, 2 H, ArH), 7.30–7.26 (m, 10 H, ArH), 6.00 (br s, 1 H, NH), 3.82 (s, 2 H, CH_2OH), 3.64 (br s, 1 H, OH), 3.41 (d, *J* = 13.7 Hz, 2 H, CH_2Ph), 3.17 (d, *J* = 13.7 Hz, 2 H, CH_2Ph).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.6 (C=O), 136.6 (2 C_{Ar}), 134.6 (C_{Ar}), 133.8 (C_{Ar}), 130.9 (C_{Ar}), 130.7 (4 C_{Ar}), 130.0 (C_{Ar}), 128.6 (4 C_{Ar}), 128.4 (C_{Ar}), 127.3 (C_{Ar}), 127.0 (2 C_{Ar}), 126.5 (C_{Ar}), 125.3 (C_{Ar}), 125.0 (C_{Ar}), 124.7 (C_{Ar}), 66.5 (CH_2OH), 61.9 (C), 41.0 (2 CH_2Ph).

HRMS (ESI+): *m*/*z* [M + H^+] calcd for $C_{27}H_{26}NO_2$: 396.1964; found: 396.1966.

N-[4-(Hydroxymethyl)-1,7-diphenylheptan-4-yl]-1-naphthamide (2ie)

Purification by flash chromatography afforded **2ie**.

Yield: 1.78 g (79%); white solid; mp 94 °C; R_f = 0.19 (petroleum ether–EtOAc, 80:20).

IR (neat): 3219, 3055, 2970, 2880, 1634, 1554, 1339, 1252, 1062, 786 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.22–8.20 (m, 1 H, ArH), 7.90 (d, *J* = 8.2 Hz, 1 H, ArH), 7.87–7.85 (m, 1 H, ArH), 7.57–7.40 (m, 4 H, ArH), 7.28–7.24 (m, 4 H, ArH), 7.19–7.13 (m, 6 H, ArH), 5.87 (br s, 1 H, N*H*), 4.89 (br s, 1 H, OH), 3.81 (s, 2 H, CH_2OH), 2.62 (t, *J* = 7.4 Hz, 4 H, CH_2Ph), 1.82–1.55 (m, 8 H, CH_2).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.9 (C=O), 141.9 (2 C_{Ar}), 134.7 (C_{Ar}), 133.8 (C_{Ar}), 130.8 (C_{Ar}), 130.0 (C_{Ar}), 128.5 (5 C_{Ar}), 128.4 (C_{Ar}), 127.4 (C_{Ar}), 126.6 (4 C_{Ar}), 126.1 (C_{Ar}), 125.2 (2 C_{Ar}), 124.7 (2 C_{Ar}), 67.7 (CH_2OH), 62.2 (C), 36.2 (2 CH_2), 34.1 (2 CH_2), 25.3 (2 CH_2).

HRMS (ESI+): *m*/*z* [M + Na^+] calcd for $C_{31}H_{33}NNaO_2$: 474.2404; found: 474.2399.

N-(2-Hydroxy-1,1-diphenylethyl)-1-naphthamide (2if)

Purification by flash chromatography afforded **2if**.

Yield: 1.29 g (70%); pale-yellow foam; mp 186 °C; R_f = 0.17 (petroleum ether–EtOAc, 80:20).

IR (neat): 3222, 3052, 1639, 1510, 1493, 1257, 758, 782, 698 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.34 (d, *J* = 7.9 Hz, 1 H, ArH), 7.95 (d, *J* = 8.2 Hz, 1 H, ArH), 7.89 (dd, *J* = 7.5, 2.0 Hz, 1 H, ArH), 7.74 (d, *J* = 7.0 Hz, 1 H, ArH), 7.59–7.56 (m, 2 H, ArH), 7.48 (dd, *J* = 8.4, 7.0 Hz, 1 H, ArH), 7.42–7.32 (m, 10 H, ArH), 6.90 (br s, 1 H, NH), 5.29 (br s, 1 H, OH), 4.60 (s, 2 H, CH_2).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.8 (C=O), 142.0 (2 C_{Ar}), 134.1 (C_{Ar}), 133.8 (C_{Ar}), 131.3 (C_{Ar}), 130.2 (C_{Ar}), 128.8 (4 C_{Ar}), 128.5 (C_{Ar}), 128.0 (2 C_{Ar}), 127.5 (C_{Ar}), 127.4 (4 C_{Ar}), 126.7 (C_{Ar}), 125.3 (C_{Ar}), 124.8 (C_{Ar}), 124.7 (C_{Ar}), 70.1 (CH_2OH), 69.8 (C).

HRMS (ESI+): *m*/*z* [M + Na^+] calcd for $C_{25}H_{21}NNaO_2$: 390.1464; found: 390.1462.

N-[2-Hydroxy-1,1-bis(4-methoxyphenyl)ethyl]-1-naphthamide (2ig)

Purification by flash chromatography afforded **2ig**.

Yield: 1.75 g (82%); yellow foam; mp 187 °C; R_f = 0.35 (petroleum ether–EtOAc, 70:30).

IR (neat): 3273, 2837, 1640, 1610, 1511, 1249, 1180, 1029, 781 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.34 (d, *J* = 7.8 Hz, 1 H, ArH), 7.94 (d, *J* = 8.4 Hz, 1 H, ArH), 7.88 (dd, *J* = 7.9, 2.3 Hz, 1 H, ArH), 7.71 (dd, *J* = 7.1, 1.0 Hz, 1 H, ArH), 7.61–7.52 (m, 2 H, ArH), 7.47 (dd, *J* = 8.3, 7.1 Hz, 1 H, ArH), 7.29 (dd, *J* = 6.7, 2.2 Hz, 4 H, ArH), 6.91 (dd, *J* = 6.7, 2.2 Hz, 4 H, ArH), 6.87 (br s, 1 H, NH), 5.37 (br s, 1 H, OH), 4.52 (s, 2 H, CH_2), 3.81 (s, 6 H, 2 CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.3 (C=O), 159.1 (2 C_{Ar}), 134.3 (C_{Ar}), 134.2 (4 C_{Ar}), 133.8 (C_{Ar}), 131.2 (C_{Ar}), 130.1 (4 C_{Ar}), 128.5 (2 C_{Ar}), 127.5 (C_{Ar}), 126.7 (C_{Ar}), 125.3 (C_{Ar}), 124.8 (C_{Ar}), 124.6 (C_{Ar}), 114.0 (2 C_{Ar}), 70.3 (CH_2), 69.0 (C), 55.3 (2 CH_3).

HRMS (ESI+): *m*/*z* [M + H^+] calcd for $C_{27}H_{26}NO_4$: 428.1845; found: 428.1856.

N-[3-(Hydroxymethyl)penta-1,4-dien-3-yl]-1-naphthamide (2ih)

Purification by flash chromatography afforded **2ih**.

Yield: 949 mg (71%); pale-yellow solid; mp 74 °C; R_f = 0.13 (petroleum ether–EtOAc, 80:20).

IR (neat): 3338, 3171, 3052, 1632, 1510, 1259, 780 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.34 (d, *J* = 7.9 Hz, 1 H, ArH), 7.95 (d, *J* = 8.5 Hz, 1 H, ArH), 7.89 (dd, *J* = 7.8, 1.9 Hz, 1 H, ArH), 7.68 (dd, *J* = 6.9, 1.4 Hz, 1 H, ArH), 7.60–7.52 (m, 2 H, ArH), 7.48 (dd, *J* = 8.4, 7.0 Hz, 1 H,

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ArH), 6.32 (br s, 1 H, NH), 6.09 (dd, *J* = 17.3, 10.6 Hz, 2 H, C*H*=CH$_2$), 5.38 (d, *J* = 10.6 Hz, 2 H, C*H*$_2$=CH), 5.37 (d, *J* = 17.3 Hz, 2 H, C*H*$_2$=CH), 4.41 (t, *J* = 6.5 Hz, 1 H, OH), 3.89 (d, *J* = 6.5 Hz, 2 H, C*H*$_2$OH).

^{13}C NMR (CDCl$_3$, 100 MHz): δ = 170.2 (C=O), 137.6 (2 *C*H=CH$_2$), 134.3 (C$_{Ar}$), 133.8 (C$_{Ar}$), 131.1 (C$_{Ar}$), 130.1 (C$_{Ar}$), 128.4 (C$_{Ar}$), 127.4 (C$_{Ar}$), 126.7 (C$_{Ar}$), 125.2 (C$_{Ar}$), 124.8 (C$_{Ar}$), 124.7 (C$_{Ar}$), 116.1 (2 *C*H$_2$=CH), 68.0 (CH$_2$OH), 65.6 (C).

HRMS (ESI+): *m*/*z* [M + Na$^+$] calcd for C$_{17}$H$_{17}$NNaO$_2$: 290.1151; found: 290.1164.

N-[5-(Hydroxymethyl)nona-1,8-dien-5-yl]-1-naphthamide (2ii)

Purification by flash chromatography afforded **2ii**.

Yield: 1.16 g (72%); yellow solid; mp 96 °C; R_f = 0.33 (petroleum ether–EtOAc, 85:15).

IR (neat): 3255, 3065, 2928, 1639, 1510, 1451, 1261, 1244, 1059, 996, 910, 782 cm^{-1}.

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 8.26 (dd, *J* = 8.1, 1.6 Hz, 1 H, ArH), 7.93 (d, *J* = 8.3 Hz, 1 H, ArH), 7.88 (dd, *J* = 8.0, 2.0 Hz, 1 H, ArH), 7.60–7.52 (m, 3 H, ArH), 7.46 (dd, *J* = 8.2, 7.1 Hz, 1 H, ArH), 6.03 (br s, 1 H, NH), 5.85 (ddt, *J* = 17.1, 10.1, 6.6 Hz, 2 H, C*H*=CH$_2$), 5.08 (dd, *J* = 17.1, 1.7 Hz, 2 H, C*H*$_2$=CH), 4.99 (dd, *J* = 10.1, 1.7 Hz, 2 H, C*H*$_2$=CH), 4.86 (br s, 1 H, O*H*), 3.91 (s, 2 H, C*H*$_2$OH), 2.27–2.09 (m, 4 H, C*H*$_2$CH$_2$), 1.93–1.88 (m, 4 H, C*H*$_2$CH$_2$).

^{13}C NMR (CDCl$_3$, 100 MHz): δ = 170.8 (C=O), 137.9 (2 *C*H=CH$_2$), 134.7 (C$_{Ar}$), 133.8 (C$_{Ar}$), 130.9 (C$_{Ar}$), 130.0 (C$_{Ar}$), 128.5 (C$_{Ar}$), 127.4 (C$_{Ar}$), 126.7 (C$_{Ar}$), 125.2 (C$_{Ar}$), 124.7 (2 C$_{Ar}$), 115.4 (2 *C*H$_2$=CH), 67.6 (CH$_2$OH), 62.1 (C), 34.0 (2 *C*H$_2$CH=CH$_2$), 27.8 (2 *C*H$_2$CH$_2$).

HRMS (ESI+): *m*/*z* [M + H$^+$] calcd for C$_{21}$H$_{26}$NO$_2$: 324.1948; found: 324.1958.

N-[6-(Hydroxymethyl)undeca-1,10-dien-6-yl]-1-naphthamide (2ij)

Purification by flash chromatography afforded **2ij**.

Yield: 1.05 mg (60%); brown solid; mp 52–55 °C; R_f = 0.20 (petroleum ether–EtOAc, 80:20).

IR (neat): 3285, 3064, 2928, 2862, 1639, 1510, 1261, 996, 909, 782 cm^{-1}.

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 8.25 (d, *J* = 8.1 Hz, 1 H, ArH), 7.92 (d, *J* = 8.3 Hz, 1 H, ArH), 7.87 (dd, *J* = 7.3, 1.8 Hz, 1 H, ArH), 7.59–7.51 (m, 3 H, ArH), 7.45 (dd, *J* = 8.2, 7.1 Hz, 1 H, ArH), 5.96 (br s, 1 H, NH), 5.80 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 2 H, C*H*=CH$_2$), 5.06–4.97 (m, 4 H, C*H*$_2$=CH), 4.95 (br s, 1 H, OH), 3.85 (d, *J* = 6.0 Hz, 2 H, C*H*$_2$OH), 2.14–2.07 (m, 4 H, C*H*$_2$CH=CH$_2$), 1.84–1.70 (m, 4 H, CH$_2$), 1.56–1.37 (m, 4 H, CH$_2$).

^{13}C NMR (CDCl$_3$, 100 MHz): δ = 170.8 (C=O), 138.2 (2 *C*H=CH$_2$), 134.8 (C$_{Ar}$), 133.8 (C$_{Ar}$), 130.8 (C$_{Ar}$), 130.0 (C$_{Ar}$), 128.4 (C$_{Ar}$), 127.3 (C$_{Ar}$), 126.6 (C$_{Ar}$), 125.1 (C$_{Ar}$), 124.8 (C$_{Ar}$), 124.7 (C$_{Ar}$), 115.3 (2 *C*H$_2$=CH), 67.8 (CH$_2$OH), 62.3 (C), 34.2 (2 CH$_2$), 34.0 (2 CH$_2$), 22.7 (2 CH$_2$).

HRMS (ESI+): *m*/*z* [M + H$^+$] calcd for C$_{23}$H$_{30}$NO$_2$: 352.2277; found: 352.2269.

N-[4-(Hydroxymethyl)hepta-1,6-dien-4-yl]-1-naphthamide (2ik)

Purification by flash chromatography afforded **2ik**.

Yield: 842 mg (57%); orange solid; mp 74 °C; R_f = 0.28 (petroleum ether–EtOAc, 80:20).

IR (neat): 3211, 3056, 2915, 2361, 1635, 1562, 1438, 920, 786 cm^{-1}.

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 8.29 (d, *J* = 8.3 Hz, 1 H, ArH), 7.91 (d, *J* = 8.3 Hz, 1 H, ArH), 7.86 (dd, *J* = 7.6, 2.6 Hz, 1 H, ArH), 7.58–7.49 (m, 3 H, ArH), 7.43 (dd, *J* = 8.3, 7.1 Hz, 1 H, ArH), 6.23 (br s, 1 H, NH), 5.91 (dddd, *J* = 17.8, 9.5, 8.3, 6.9 Hz, 2 H, C*H*=CH$_2$), 5.23–5.17 (m, 4 H, C*H*$_2$=CH), 4.96 (t, *J* = 5.8 Hz, 1 H, OH), 3.82 (d, *J* = 5.8 Hz, 2 H, C*H*$_2$OH), 2.65 (dd, *J* = 14.0, 6.9 Hz, 2 H, CH$_2$), 2.47 (dd, *J* = 14.0, 8.3 Hz, 2 H, CH$_2$).

^{13}C NMR (CDCl$_3$, 100 MHz): δ = 170.8 (C=O), 134.5 (C$_{Ar}$), 133.8 (C$_{Ar}$), 132.7 (2 *C*H=CH$_2$), 130.9 (C$_{Ar}$), 130.0 (C$_{Ar}$), 128.4 (C$_{Ar}$), 127.3 (C$_{Ar}$), 126.6 (C$_{Ar}$), 125.2 (C$_{Ar}$), 124.9 (C$_{Ar}$), 124.7 (C$_{Ar}$), 120.0 (2 *C*H$_2$=CH), 68.0 (CH$_2$OH), 61.0 (C), 39.1 (2 *C*H$_2$CH=CH$_2$).

HRMS (ESI+): *m*/*z* [M + Na$^+$] calcd for C$_{19}$H$_{21}$NNaO$_2$: 318.1464; found: 318.1471.

Preparation of *N*-Boc-Protected Amino Alcohols 4; General Procedure

A microwave tube was charged with **2i** (1 mmol), NaOH (120 mg, 3 mmol), and EtOH (10 mL). The tube was sealed, placed in a microwave oven and heated (*T* = 135 °C; *t* = 10 min). After release, Boc$_2$O (655 mg, 3 mmol) was added at r.t. and the reaction mixture was stirred for 2 h at 40 °C. H$_2$O (10 mL) and Et$_2$O (20 mL) were added and the layers were separated. The aqueous phase was extracted with Et$_2$O (2 × 20 mL) and the combined organic layers were dried over MgSO$_4$, filtered, and the solvent was removed in vacuo. The crude residue was purified on silica gel chromatography (cyclohexane–EtOAc, 95:5 to 40:60) to afford the desired *N*-Boc-protected amino alcohol **4**.

tert-Butyl 6-(Hydroxymethyl)undecan-6-ylcarbamate (4c)

Purification by flash chromatography afforded **4c**.

Yield: 244 mg (81%); white solid; mp 60–62 °C; R_f = 0.21 (cyclohexane–EtOAc, 80:20).

IR (neat): 3270, 3069, 2924, 2857, 1680, 1553, 1467, 1367, 1290, 1179, 1084, 869, 784, 691 cm^{-1}.

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 4.51 (br s, 1 H, NH), 4.25 (br s, 1 H, OH), 3.65 (d, *J* = 6.3 Hz, 2 H, C*H*$_2$OH), 1.57–1.46 (m, 4 H, CH$_2$C), 1.43 (s, 9 H, CH$_3$C), 1.36–1.16 (m, 12 H, CH$_2$), 0.89 (t, *J* = 7.0 Hz, 6 H, CH$_3$).

^{13}C NMR (CDCl$_3$, 50 MHz): δ = 156.4 (C=O), 79.8 (*C*CH$_3$), 68.2 (CH$_2$OH), 59.5 (C), 34.3 (2 CH$_2$), 32.3 (2 CH$_2$), 28.4 (3 *C*H$_3$C), 22.8 (2 CH$_2$), 22.6 (2 CH$_2$), 14.1 (2 CH$_3$).

HRMS (ESI+): *m*/*z* [M + Na$^+$] calcd for C$_{17}$H$_{35}$NNaO$_3$: 324.2509; found: 324.2503.

tert-Butyl 2-Benzyl-1-hydroxy-3-phenylpropan-2-ylcarbamate (4d)

Purification by flash chromatography afforded **4d**.

Yield: 264 mg (77%); pale-brown solid; mp 132–133 °C; R_f = 0.19 (cyclohexane–EtOAc, 80:20).

IR (neat): 3490, 3388, 2942, 1680, 1520, 1363, 1287, 1160, 1065, 1007, 864, 760, 730, 707 cm^{-1}.

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.32–7.21 (m, 10 H, ArH), 4.53 (br s, 1 H, NH), 3.54 (d, *J* = 5.6 Hz, 2 H, C*H*$_2$OH), 3.19 (d, *J* = 13.7 Hz, 2 H, CH$_2$Ph), 2.94 (d, *J* = 13.7 Hz, 2 H, CH$_2$Ph), 2.80 (br s, 1 H, OH), 1.48 (s, 9 H, CH$_3$).

^{13}C NMR (CDCl$_3$, 50 MHz): δ = 155.8 (C=O), 137.0 (2 C$_{Ar}$), 130.6 (4 C$_{Ar}$), 128.4 (4 C$_{Ar}$), 126.7 (2 C$_{Ar}$), 79.7 (*C*CH$_3$), 65.9 (CH$_2$OH), 59.4 (C), 40.9 (2 CH$_2$), 28.5 (3 CH$_3$).

HRMS (CI+, NH$_3$/CH$_4$): *m*/*z* [M + H$^+$] calcd for C$_{21}$H$_{28}$NO$_3$: 342.2068; found: 342.2069.

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***tert*-Butyl 4-(Hydroxymethyl)-1,7-diphenylheptan-4-ylcarbamate (4e)**

Purification by flash chromatography afforded **4e**.

Yield: 290 mg (73%); white solid; mp 111 °C; R_f = 0.23 (cyclohexane–EtOAc, 80:20).

IR (neat): 3283, 2971, 2954, 2859, 1676, 1553, 1460, 1372, 1294, 1171, 1054, 873, 750, 698 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.30–7.24 (m, 4 H, ArH), 7.22–7.12 (m, 6 H, ArH), 4.45 (br s, 1 H, N*H*), 4.07 (br s, 1 H, OH), 3.63 (d, *J* = 6.0 Hz, 2 H, C*H*$_2$OH), 2.63–2.53 (m, 4 H, CH_2Ph), 1.59–1.45 (m, 8 H, CH_2), 1.41 (s, 9 H, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.2 (C=O), 142.1 (2 C_{Ar}), 128.4 (8 C_{Ar}), 125.9 (2 C_{Ar}), 80.0 (*C*CH_3), 67.8 (*C*H_2OH), 59.3 (C), 36.2 (2 CH_2), 33.7 (2 CH_2), 28.4 (3 CH_3), 25.1 (2 CH_2).

HRMS (CI+, NH_3/CH_4): *m*/*z* [M + H^+] calcd for $C_{25}H_{36}NO_3$: 398.2679; found: 398.2695.

***tert*-Butyl 2-Hydroxy-1,1-diphenylethylcarbamate (4f)**

Purification by flash chromatography afforded **4f**.

Yield: 197 mg (63%); beige solid; mp 164 °C; R_f = 0.20 (cyclohexane–EtOAc, 80:20).

IR (neat): 3281, 1680, 1525, 1447, 1287, 1261, 1168, 959, 859, 761, 730, 704 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.38–7.27 (m, 10 H, ArH), 5.55 (br s, 1 H, NH), 4.83 (br s, 1 H, OH), 4.38 (d, *J* = 6.4 Hz, 2 H, CH_2), 1.42 (s, 9 H, CH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 156.6 (C=O), 142.6 (2 C_{Ar}), 128.5 (4 C_{Ar}), 127.6 (2 C_{Ar}), 127.4 (4 C_{Ar}), 80.8 (*C*CH_3), 70.3 (CH_2), 67.3 (C), 28.3 (3 CH_3).

HRMS (CI+, NH_3/CH_4): *m*/*z* [M + H^+] calcd for $C_{19}H_{24}NO_3$: 314.1739; found: 314.1756.

***tert*-Butyl 2-Hydroxy-1,1-bis(4-methoxyphenyl)ethylcarbamate (4g)**

Purification by flash chromatography afforded **4g**.

Yield: 265 mg (71%); white solid; mp 168 °C; R_f = 0.26 (cyclohexane–EtOAc, 80:20).

IR (neat): 3242, 3045, 2838, 1683, 1510, 1460, 1298, 1257, 1171, 1091, 1033, 959, 821, 778 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.18 (d, *J* = 8.9 Hz, 4 H, ArH), 6.87 (d, *J* = 8.9 Hz, 4 H, ArH), 5.47 (br s, 1 H, NH), 4.88 (br s, 1 H, OH), 4.30 (d, *J* = 6.2 Hz, 2 H, CH_2), 3.80 (s, 6 H, CH_3O), 1.42 (s, 9 H, CH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 158.9 (2 C_{Ar}), 156.6 (*C*=O), 134.9 (2 C_{Ar}), 128.5 (4 C_{Ar}), 113.8 (4 C_{Ar}), 80.6 (*C*CH_3), 70.6 (CH_2OH), 66.5 (C), 55.3 (2 CH_3O), 28.3 (3 CH_3).

HRMS (ESI+): *m*/*z* [M + Na^+] calcd for $C_{21}H_{27}NNaO_5$: 396.1781; found: 396.1778.

***tert*-Butyl 5-(Hydroxymethyl)nona-1,8-dien-5-ylcarbamate (4i)**

Purification by flash chromatography afforded **4i**.

Yield: 145 mg (54%); white solid; mp 72 °C; R_f = 0.19 (cyclohexane–EtOAc, 80:20).

IR (neat): 3263, 3080, 2980, 2931, 2861, 1678, 1553, 1451, 1365, 1289, 1246, 1166, 1046, 998, 910, 868, 784, 700 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 5.79 (ddt, *J* = 17.1, 10.3, 6.6 Hz, 2 H, C*H*=CH_2), 5.02 (dd, *J* = 17.1, 1.7 Hz, 2 H, CH_2=CH), 4.95 (dd, *J* = 10.3, 1.7 Hz, 2 H, CH_2=CH), 4.62 (br s, 1 H, NH), 4.20 (br s, 1 H, OH), 3.65 (s, 2 H, CH_2OH), 2.15–1.95 (m, 4 H, CH_2CH=CH_2), 1.76–1.62 (m, 4 H, CH_2), 1.42 (s, 9 H, CH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 156.2 (C=O), 138.2 (2 *C*H=CH_2), 114.9 (2 *C*H_2=CH), 79.9 (*C*CH_3), 67.5 (CH_2OH), 59.1 (C), 33.7 (2 *C*H_2CH=CH_2), 28.4 (3 CH_3), 27.6 (2 CH_2).

HRMS (ESI+): *m*/*z* [M + Na^+] calcd for $C_{15}H_{27}NNaO_3$: 292.1883; found: 292.1881.

***tert*-Butyl 6-(Hydroxymethyl)undeca-1,10-dien-6-ylcarbamate (4j)**

Purification by flash chromatography afforded **4j**.

Yield: 208 mg (70%); yellow oil; R_f = 0.32 (cyclohexane–EtOAc, 80:20).

IR (neat): 3280, 3077, 2982, 2928, 2868, 1678, 1562, 1460, 1367, 1296, 1251, 1177, 1045, 971, 909, 784, 702 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 5.79 (ddt, *J* = 17.1, 10.4, 6.8 Hz, 2 H, C*H*=CH_2), 5.02 (d, *J* = 17.1 Hz, 2 H, CH_2=CH), 4.97 (d, *J* = 10.4 Hz, 2 H, CH_2=CH), 4.51 (br s, 1 H, NH), 4.18 (br s, 1 H, OH), 3.66 (d, *J* = 5.7 Hz, 2 H, CH_2OH), 2.06 (m, 4 H, CH_2CH=CH_2), 1.61–1.25 (m, 8 H, CH_2), 1.43 (s, 9 H, CH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 156.3 (C=O), 138.4 (2 *C*H=CH_2), 115.0 (2 *C*H_2=CH), 79.9 (*C*CH_3), 67.9 (CH_2OH), 59.3 (C), 34.0 (2 CH_2), 33.9 (2 CH_2), 28.4 (3 CH_3), 22.5 (2 CH_2).

HRMS (ESI+): *m*/*z* [M + Na^+] calcd for $C_{17}H_{31}NNaO_3$: 320.2196; found: 320.2198.

***tert*-Butyl 4-(Hydroxymethyl)hepta-1,6-dien-4-ylcarbamate (4k)**

Purification by flash chromatography afforded **4k**.

Yield: 186 mg (77%); white solid; mp 41 °C; R_f = 0.25 (cyclohexane–EtOAc, 80:20).

IR (neat): 3406, 3077, 2978, 2931, 1687, 1642, 1499, 1369, 1290, 1244, 1166, 1054, 993, 860 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 5.82 (dddd, *J* = 17.1, 10.3, 8.2, 6.9 Hz, 2 H, C*H*=CH_2), 5.16 (d, *J* = 10.3 Hz, 2 H, CH_2=CH), 5.15 (d, *J* = 17.1 Hz, 2 H, CH_2=CH), 4.71 (br s, 1 H, NH), 4.20 (br s, 1 H, OH), 3.65 (d, *J* = 5.1 Hz, 2 H, CH_2OH), 2.42 (dd, *J* = 14.0, 6.9 Hz, 2 H, CH_2CH=CH_2), 2.29 (dd, *J* = 14.0, 8.2 Hz, 2 H, CH_2), 1.42 (s, 9 H, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.3 (C=O), 132.9 (2 *C*H=CH_2), 119.4 (2 *C*H_2=CH), 80.0 (*C*CH_3), 68.1 (CH_2OH), 58.4 (C), 38.9 (2 CH_2), 28.3 (3 CH_3).

HRMS (ESI+): *m*/*z* [M + Na^+] calcd for $C_{13}H_{23}NNaO_3$: 264.1570; found: 264.1569.

Preparation of *N*-Boc-Protected Amino Acids 7a–g from 4a–g; General Procedure

To a solution of N-protected amino alcohol **4a**–**g** (0.5 mmol) in a 2:2:3 mixture of CCl_4/MeCN/H_2O (7 mL) were successively added $NaIO_4$ (321 mg, 1.5 mmol) and RuO_2·xH_2O (3.5 mg, 0.025 mmol) at r.t. The resulting dark mixture was vigorously stirred for 2 h at r.t. then CH_2Cl_2 (10 mL) and H_2O (10 mL) were added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed in vacuo. The black residue was purified by chromatography on silica gel (CH_2Cl_2–MeOH, 99:1 to 95:5) to afford the *N*-Boc-protected amino acid **7a**–**g**.

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2-(*tert*-Butoxycarbonylamino)-2-pentylheptanoic Acid (7c)

Purification by flash chromatography afforded **7c**.

Yield: 101 mg (64%); brown oil; R_f = 0.19 (cyclohexane–EtOAc, 50:50).

IR (neat): 3423, 2957, 2928, 2862, 1704, 1499, 1395, 1369, 1249, 1169, 1071, 1009, 778, 730 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 5.40 (br s, 1 H, NH), 2.32–2.10 (m, 2 H, CH_2C), 1.88–1.68 (m, 2 H, CH_2C), 1.44 (s, 9 H, CH_3C), 1.39–1.19 (m, 10 H, CH_2), 1.18–1.02 (m, 2 H, CH_2), 0.86 (t, *J* = 6.6 Hz, 6 H, CH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 179.0 (CO_2H), 154.4 (C=O), 79.4 (CCH_3), 63.7 (C), 35.4 (2 CH_2), 31.6 (2 CH_2), 28.4 (3 CH_3C), 23.5 (2 CH_2), 22.4 (2 CH_2), 14.0 (2 CH_3).

HRMS (CI+, NH_3CH_4): *m*/*z* [M + H^+] calcd for $C_{17}H_{34}NO_4$: 316.2488; found: 316.2501.

2-(*tert*-Butoxycarbonylamino)-5-phenyl-2-(3-phenylpropyl)pentanoic Acid (7e)

Purification by flash chromatography afforded **7e**.

Yield: 145 mg (67%); colorless oil; R_f = 0.22 (cyclohexane–EtOAc, 50:50).

IR (neat): 3253, 2917, 1680, 1603, 1508, 1291, 1249, 1164, 1030, 818, 655 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.28–7.09 (m, 10 H, ArH), 5.36 (br s, 1 H, NH), 2.63–2.52 (m, 4 H, CH_2), 2.35–2.12 (m, 2 H, CH_2), 1.87–1.74 (m, 2 H, CH_2), 1.67–1.53 (m, 2 H, CH_2), 1.48–1.23 (m, 11 H, CH_2 + CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 177.0 (CO_2H), 153.1 (C=O), 140.8 (2 C_{Ar}), 127.3 (2 C_{Ar}), 127.2 (4 C_{Ar}), 124.8 (4 C_{Ar}), 78.6 (CCH_3), 62.3 (CCO_2H), 34.6 (2 CH_2), 33.9 (2 CH_2), 27.3 (3 CH_3), 24.7 (2 CH_2).

HRMS (ESI+): *m*/*z* [M + Na^+] calcd for $C_{25}H_{33}NO_4Na$: 434.2302; found: 434.2281.

2-(*tert*-Butoxycarbonylamino)-2,2-bis(4-methoxyphenyl)acetic Acid (7g)

Purification by flash chromatography afforded **7g**.

Yield: 144 mg (70%); yellow solid; mp 147–150 °C; R_f = 0.20 (cyclohexane–EtOAc, 50:50).

IR (neat): 3273, 2837, 1640, 1610, 1511, 1249, 1180, 1029, 781 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.41–7.09 (m, 4 H, ArH), 6.86 (d, *J* = 8.8 Hz, 4 H, ArH), 5.83 (br s, 1 H, NH), 3.81 (s, 6 H, CH_3O), 1.48–1.01 (m, 9 H, CH_3C).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.9 (CO_2H), 159.3 (C=O), 132.3 (2 C_{Ar}), 132.0 (2 C_{Ar}), 129.3 (4 C_{Ar}), 113.5 (4 C_{Ar}), 82.2 (CCH_3), 66.0 (CCO_2H), 55.3 (2 CH_3O), 28.2 (3 CH_3).

HRMS (ESI+): *m*/*z* [M + Na^+] calcd for $C_{21}H_{25}NNaO_6$: 410.1574; found: 410.1587.

Preparation of *N*-Boc-Protected Aminoaldehyde Intermediates from 4i–k; General Procedure

Under an argon atmosphere, a Schlenk flask was charged with 4 Å molecular sieves and flame dried. A solution of N-protected amino alcohol **4j–l** (0.5 mmol) in CH_2Cl_2 (2 mL) was added and the solution was stirred for 5 min. Then, NMO (176 mg, 1.5 mmol) was added followed by TPAP (9 mg, 0.025 mmol) at r.t. The reaction mixture was stirred for 2 h at r.t. and the progress of the reaction was monitored by TLC. Upon completion of the reaction, the reaction mixture was filtered over a silica gel pad and washed with either CH_2Cl_2 (100 mL) or 99:1 mixture of CH_2Cl_2–MeOH (100 mL). The solvent was removed in vacuo to yield the N-protected amino aldehyde intermediate, which was pure enough to be used in the next step without further purification.

***tert*-Butyl 5-Formylnona-1,8-dien-5-ylcarbamate**

Obtained from **4i** as a colorless oil (79 mg, 59% yield).

IR (neat): 3078, 2980, 2929, 2862, 1709, 1642, 1493, 1460, 1369, 1253, 1166, 1074, 994, 782 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 9.25 (s, 1 H, CHO), 5.73 (ddt, *J* = 17.2, 10.2, 6.4 Hz, 2 H, CH=CH_2), 5.33 (br s, 1 H, NH), 5.01–4.93 (m, 4 H, CH_2=CH), 2.30 (m, 2 H, CH_2CH=CH_2), 1.99 (m, 2 H, CH_2CH=CH_2), 1.78 (m, 4 H, CH_2), 1.44 (s, 9 H, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 200.3 (CHO), 154.2 (C=O), 137.3 (2 CH=CH_2), 115.5 (2 CH_2=CH), 79.6 (CCH_3), 65.7 (C), 32.2 (2 CH_2CH=CH_2), 28.4 (3 CH_3), 27.8 (2 CH_2).

HRMS (CI+, NH_3CH_4): *m*/*z* [M + H^+] calcd for $C_{15}H_{26}NO_3$: 268.1913; found: 268.1924.

***tert*-Butyl 6-Formylundeca-1,10-dien-6-ylcarbamate**

Obtained from **4j** as a colorless oil (89 mg, 60% yield).

IR (neat): 3092, 2981, 2870, 1708, 1652, 1453, 1270, 1095, 760 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 9.23 (s, 1 H, CHO), 5.73 (ddt, *J* = 17.2, 10.2, 6.7 Hz, 2 H, CH=CH_2), 5.27 (br s, 1 H, NH), 5.00–4.92 (m, 4 H, CH_2=CH), 2.14 (m, 2 H, CH_2C), 2.02 (m, 4 H, CH_2CH=CH_2), 1.65 (m, 2 H, CH_2C), 1.43 (s, 9 H, CH_3), 1.33 (m, 2 H, CH_2), 1.11 (m, 2 H, CH_2).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 200.7 (CHO), 154.3 (C=O), 138.0 (2 CH=CH_2), 115.2 (2 CH_2=CH), 79.5 (CCH_3), 65.8 (C), 33.5 (2 CH_2C), 32.2 (2 CH_2CH=CH_2), 28.4 (3 CH_3), 22.7 (2 CH_2).

HRMS (ESI+): *m*/*z* [M + Na^+] calcd for $C_{17}H_{29}NNaO_3$: 318.2040; found: 318.2034.

***tert*-Butyl 4-Formylhepta-1,6-dien-4-ylcarbamate**

Obtained from **4k** as a pale-yellow oil (84 mg, 70% yield).

IR (neat): 3077, 2934, 2865, 1699, 1645, 1501, 1370, 1262, 1178, 773 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 9.39 (s, 1 H, CHO), 5.64 (m, 2 H, CH=CH_2), 5.16–5.08 (m, 5 H, CH_2=CH, NH), 2.77 (m, 2 H, CH_2), 2.51 (dd, *J* = 13.8, 7.5 Hz, 2 H, CH_2), 1.43 (s, 9 H, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 200.3 (CHO), 154.5 (C=O), 131.4 (2 CH=CH_2), 119.8 (2 CH_2=CH), 79.9 (CCH_3), 64.7 (C), 37.2 (2 CH_2), 28.3 (3 CH_3).

HRMS (ESI+): *m*/*z* [M + Na^+] calcd for $C_{13}H_{21}NNaO_3$: 262.1414; found: 262.1412.

Preparation of *N*-Boc-Protected Amino Acids 7i–k from *N*-Boc-Protected Aminoaldehyde Intermediates; General Procedure

To a solution of N-protected amino aldehyde (0.2 mmol) in MeCN (4 mL) cooled to 0 °C were successively added $NaH_2PO_4·2H_2O$ (62 mg, 0.4 mmol), H_2O_2 (30% w/w in H_2O, 31 µL, 0.4 mmol) and $NaClO_2$ (34 mg, 0.3 mmol). The reaction mixture was stirred at r.t. and the progress of the reaction was monitored by TLC. Na_2SO_3 (25 mg, 0.2 mmol) was then added and the reaction mixture was stirred for 1 h. The solvent was removed in vacuo, then EtOAc (10 mL) and saturated $NaHCO_3$ (10 mL) were added to the residue. The layers were separated and the organic phase was washed with sat. aq $NaHCO_3$ (2 × 5 mL). The combined aqueous layers were acidified by adding concentrated HCl and

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with EtOAc (2 × 10 mL). After drying over $MgSO_4$, the combined organic layers were concentrated in vacuo to provide the pure *N*-Boc-protected amino acid **7i–k**.

2-(But-3-enyl)-2-(*tert*-butoxycarbonylamino)hex-5-enoic Acid (7i)

Concentration in vacuo afforded *N*-Boc amino acid **7i**.

Yield: 37 mg (61%); pale-yellow oil.

IR (neat): 3393, 3075, 2969, 2922, 2859, 1704 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 5.78 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 2 H, C*H*=CH_2), 5.48 (br s, 1 H, NH), 5.01 (dd, *J* = 17.1, 1.9 Hz, 2 H, C*H*$_2$=CH), 4.94 (dd, *J* = 10.2, 1.9 Hz, 2 H, C*H*$_2$=CH), 2.51–2.33 (m, 2 H, CH_2), 2.13–1.86 (m, 6 H, CH_2), 1.45 (s, 9 H, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 178.4 (CO_2H), 153.8 (C=O), 137.6 (2 *C*H=CH_2), 128.5 (C), 115.3 (2 *C*H$_2$=CH), 79.7 (*C*CH_3), 63.1 (2 CH_2), 34.6 (2 *C*H_2CH=CH_2), 28.4 (3 CH_3).

HRMS (ESI+): *m*/*z* [M + Na^+] calcd for $C_{15}H_{25}NO_4Na$: 306.1681; found: 306.1677.

2-(*tert*-Butoxycarbonylamino)-2-(pent-4-enyl)hept-6-enoic Acid (7j)

Concentration in vacuo afforded *N*-Boc amino acid **7j**.

Yield: 41 mg (69%); white solid; decomposition above 180 °C.

IR (neat): 3393, 3075, 2969, 2922, 2859, 1704, 1618, 1458, 1367, 1257, 1171, 1063, 910, 776 cm^{-1}.

^1H NMR (DMSO-d_6, 400 MHz): δ = 6.53 (br s, 1 H, NH), 5.73 (ddt, *J* = 17.2, 10.3, 6.6 Hz, 2 H, C*H*=CH_2), 4.94 (d, *J* = 17.2 Hz, 2 H, C*H*$_2$=CH), 4.88 (d, *J* = 10.3 Hz, 2 H, C*H*$_2$=CH), 1.95–1.87 (m, 6 H, C*H*$_2$CH=CH_2, CCH_2), 1.59–1.49 (m, 2 H, CCH_2), 1.35 (s, 9 H, CH_3), 1.23–1.04 (m, 4 H, CH_2).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 174.8 (CO_2H), 153.0 (C=O), 139.2 (2 *C*H=CH_2), 114.1 (2 *C*H$_2$=CH), 76.4 (*C*CH_3), 62.6 (C), 35.6 (2 *C*CH_2), 33.6 (2 *C*H_2CH=CH_2), 28.3 (3 CH_3), 23.7 (2 CH_2).

HRMS (ESI+): *m*/*z* [M + Na^+] calcd for $C_{17}H_{29}NO_4Na$: 334.1989; found: 334.1984.

2-Benzamido-2-vinylbut-3-enoic Acid (8)

To a solution of oxalyl chloride (0.26 mL, 3 mmol) in THF (10 mL) cooled to –78 °C under argon was added DMSO (0.23 mL, 3.2 mmol). The mixture was warmed to –35 °C then cooled to –78 °C. A solution of alcohol **2ah** (434 mg, 2 mmol) in THF (2 mL) was added. The mixture was warmed to –35 °C, and stirred at this temperature for 15 min, then Et_3N (1.7 mL) was added. After 15 min, H_2O (10 mL) was added. The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with saturated NH_4Cl solution (10 mL). After drying over $MgSO_4$, the organic fraction was concentrated in vacuo to give the corresponding aldehyde, which was directly dissolved in MeCN (7 mL). The solution was cooled to 0 °C and a solution of NaH_2PO_4 (154 mg, 1.28 mmol) in H_2O (3 mL), a 31% aqueous solution of H_2O_2 (0.30 mL), and a solution of $NaClO_2$ (271 mg, 3.0 mmol) in H_2O (4 mL) were successively added. The mixture was allowed to warm to r.t. and vigorously stirred at this temperature until TLC showed complete consumption of the starting material (1 h). Na_2SO_3 (300 mg) was added to destroy the excess of oxidant and the solution was stirred for an additional 1 h. After acidification by adding 1 M aqueous HCl solution, the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by filtration through a pad of silica gel (cyclohexane–EtOAc, 50:50) to afford pure acid **8**.

Yield: 351 mg (76%); white solid; mp 156–158 °C.

IR (neat): 3350, 2929, 1713, 1639, 1615, 1573, 1531, 1490, 1410, 1395, 1320, 1294, 1232, 1202, 922 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 7.4 Hz, 2 H, ArH), 7.55 (t, *J* = 7.4 Hz, 1 H, ArH), 7.46 (t, *J* = 7.4 Hz, 2 H, ArH), 6.88 (br s, 1 H, NH), 6.28 (dd, *J* = 17.3, 10.5 Hz, 2 H, CH), 5.43 (d, *J* = 10.5 Hz, 2 H, CH_2), 5.40 (d, *J* = 17.3 Hz, 2 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6 (CO_2H), 167.4 (C=O), 135.3 (2 CH), 133.4 (1 C_{Ar}), 132.5 (1 C_{Ar}), 128.9 (2 C_{Ar}), 127.3 (2 C_{Ar}), 117.8 (2 CH_2), 65.8 (C).

HRMS (ESI+): *m*/*z* [M + H^+] calcd for $C_{13}H_{14}NO_3$: 232.0974; found: 232.0928.

2-Amino-2,2-divinylacetic Acid Hydrochloride (9·HCl)

A 6 M solution of HCl (1 mL) was added to acid **8** (63 mg, 0.27 mmol) in a sealed tube and the mixture was heated at 100 °C for 3 days until TLC showed no remaining starting material. The aqueous phase was extracted with EtOAc (3 × 2 mL) and the combined organic layers were discarded. The aqueous layer was evaporated to dryness under reduced pressure to provide the pure amino acid **9** as its hydrochloride salt.

Yield: 45 mg (quant.); white solid; mp > 300 °C.

IR (neat): 3371, 3163, 2805, 1720, 1510, 1394, 1224 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 9.57 (s, 1 H, COOH), 6.07 (dd, *J* = 17.5, 10.9 Hz, 2 H), 5.48 (d, *J* = 10.9 Hz, 2 H), 5.45 (d, *J* = 17.5 Hz, 2 H), 4.57 (br s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.2 (CO_2H), 133.2 (2 *C*H=CH_2), 1118.5 (2 *C*H_2=CH), 64.0 (C).

HRMS (CI+, NH_3): *m*/*z* [M – HCl + H^+] calcd for $C_6H_{10}NO_2$: 128.0712; found: 128.0713.

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Supporting Information

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