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Straightforward Synthesis of α-Substituted Prolines by Cross-Metathesis

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The synthesis of several α-substituted *N*-Boc-protected prolines has been achieved by cross metathesis (CM) of *N*-Boc-allylproline **5** with terminal long chain alkenes and alkenes bearing hydroxy, silyloxy, ester, and *O*-acetylglucosamido groups. The CM occurred with good selectivity and short reaction time under microwave heating conditions, affording yields in the range of 40–92 %. Addition of Ti(O*i*Pr)$_4$ as a Lewis acid allowed a slight increase of the yield in the case of alkenes with Lewis basic substituents. The CM was also successfully applied to allylproline protected with trichloroacetaldehyde **4**, but the intermediate products were less practical for further deprotection and elaboration.

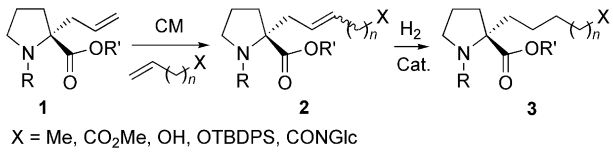
Introduction

It is well known that proline residues play key roles in many biological processes, such as protein folding and protein recognition. Due to its unique structural properties, important conformational attributes are observed when proline is introduced into a peptide sequence. Among the naturally occurring amino acids, proline is unique in that it can form *cis* amide bonds and undergo *cis–trans* isomerization, and is often involved in nucleation of reverse turns, such as β-turns.[1] The induction and stabilization of peptide secondary structures are often adopted in peptidomimetics to induce a 3D arrangement both of the protein backbone and of the side chains, the key features of a pharmacophore.[2] Proline enhances the constraint in a peptide chain, as well as protecting biologically active peptides against enzymatic degradation by limiting their susceptibility to proteolysis.[3] The therapeutic use of many potentially bioactive peptides is limited by their insufficient bioavailability, which is related mainly to their poor membrane solubility. Peptidomimetics and synthetic peptide conjugates have been devised as a way to increase the metabolic stability of peptides, to shape their physical properties with beneficial effects on pharmacokinetics, and to improve their receptor affinity.[4–6] For example, α-amino acids containing long-chain alkyl substituents may favour the interaction of peptides with hydrophobic pockets, and furnish better resistance toward proteolytic enzymes.[7]

α-Substituted proline derivatives[8] show important biological activities.[9] α-Alkylprolines have also found utility as starting materials in the synthesis of natural products[10] and as probes for polymeric structures.[11]

In view of the potential biological role of these types of α,α-disubstituted α-amino acids and their many uses in several branches of science,[12] we have focused our attention on preparing collections of enantiomerically pure 2-substituted prolines employing common advanced building blocks that could be easily functionalised.[13] Protected allylprolines **1** are examples of enantiopure building blocks with the terminal double bond suggesting the well-known and versatile olefin cross-metathesis (CM) reaction as the method of choice for introducing various functionalised chains.[14] Even though olefin CM has emerged as a powerful and convenient synthetic technique in organic chemistry, it has been limited by the lack of predictability in product selectivity and stereoselectivity, although this problem can be overcome by a judicious choice of reagents.[15]

In this paper, the selective olefin CM of protected 2-L-allylprolines **1** and terminal olefins followed by catalytic hydrogenation is described as a general approach towards the synthesis of α-substituted prolines **3** containing various functionalities.[16–18] This versatile process allows the achievement of various novel amino acids containing lipophilic and functionalized side chains from a common enantiomerically pure single precursor (Scheme 1).



Scheme 1. General approach to α-substituted prolines.

Results and Discussion

The enantiomerically pure building blocks **4**[19] and **5**,[20] both possible candidates for the cross-coupling reaction,

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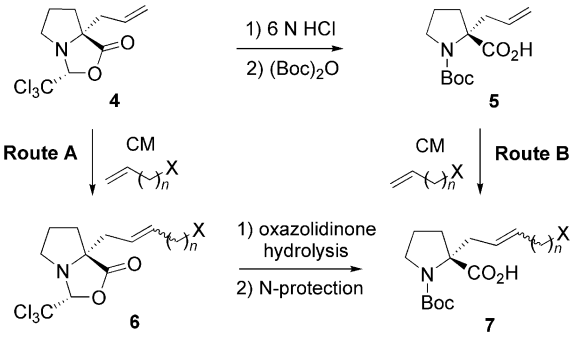
were prepared according to the Seebach methodology of self-reproduction of chirality.[21]

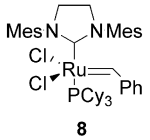
With the aim of synthesizing protected prolines suitable for peptide synthesis, and allowing the best conditions for CM, i.e. absence of nucleophilic unprotected nitrogen atoms, two different strategies could originate from these two building blocks. The CM could be run on oxazolidinone **4** and the resulting product **6** could undergo sequential hydrolysis and N-protection to afford prolines **7** (Route **A**, Scheme 2). On the other hand, allylproline **5**, obtained from **4** by oxazolidinone hydrolysis followed by *N*-Boc protection,[22] could be directly used in CM without protection of the carboxylic group (Route **B**, Scheme 2). As both strategies could furnish advantages to the synthesis, were both tested, starting with examination of Route **A**.



Scheme 2. Two complementary synthetic routes for prolines **7**.

The success of a CM reaction relies on the use of olefin partners with sufficiently diverse steric and/or electronic properties. This brings about a different reactivity in metathesis reactions and usually leads to the selective formation of the heterodimer, avoiding the statistical product distributions of hetero- and homodimers.[15] Allylprolines **4** and **5**, despite having the bulky substitution in the homoallyl position, both appeared to be sufficiently bulky to reduce the homodimerization rate under the reaction conditions. Another important parameter in improving the yield of the cross product is the ratio of the two olefins, however this opportunity is, of course, dependent on the cost of the reagent.

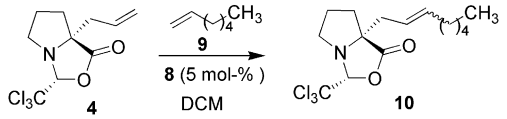
The second-generation Grubbs' catalyst **8** was used in our investigation for its demonstrated efficiency,[14] and for the verified possibility of its use under microwave (MW) induced heating conditions.[23,17a,17d]



8

Allyloxazolidinone **4** was treated with hept-1-ene **9** in a 0.1 M solution of dichloromethane (DCM) in the presence of **8** (5 mol-%) under various reaction conditions in order to determine the best parameters (Table 1).

Table 1. CM between allylproline **4** and hept-1-ene (**9**) under different reaction conditions.[a]

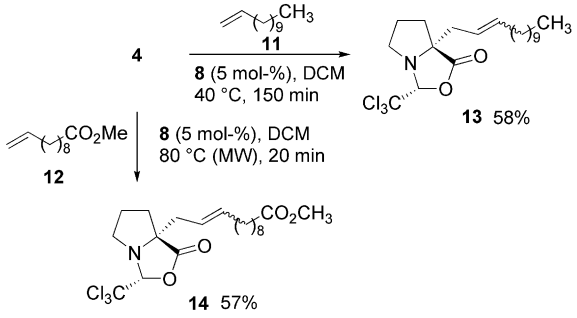


Entry	**9** (equiv.)	Temp.	Time	Yield (%)[b]	*E*/*Z*[c]
1	1.0	25 °C	10 d	–[d]	3.7:1
2	1.0	40 °C	2 h	53	4.8:1
3	2.0	40 °C	2 h	61	6.3:1[e]
4	1.0	80 °C (MW)[f]	20 min	60	5:1
5	2.0	80 °C (MW)[f]	20 min	74	4.4:1

[a] A 0.1 M solution of **4** in DCM, 1–2 equiv. of **9**, and 5 mol-% of **8** were heated conductively (entries 1–3) or by MW irradiation (entries 4 and 5). [b] Isolated yield after flash chromatography. [c] Ratios by ^{13}C NMR analysis of the crude reaction mixture. [d] Low conversion. [e] Ratios by ^{1}H NMR analysis of the purified product. [f] 150 W with simultaneous cooling.

The reaction occurred very slowly at room temperature (Table 1, entry 1). The desired product **10** was obtained in moderate yield with refluxing DCM (Table 1, entries 2 and 3). A slight increase of the yield was obtained by doubling the amount of **9** with respect to **4**. Under MW irradiation, a 74% yield of **10** was reached after 20 min at 80 °C when 2 equiv. of **9** were used (Table 1, entry 5). The oxazolidinone homocoupling product was not detected in any of the reaction mixtures. In all cases, the heterocoupling product **10** was obtained as an inseparable mixture of two isomers in a ratio ranging from 4:1 to 6:1. The two isomers were assigned as the *E*/*Z* diastereomers, although only the major *E* isomer could be assigned by ^{1}H NMR spectroscopy. The observed variation of *E*/*Z* ratios under different reaction conditions did not show any rational trend.

Application of the optimised reaction conditions to longer chain substrates **11** and **12** gave somewhat lower yields of cross products **13** and **14**, respectively (Scheme 3).

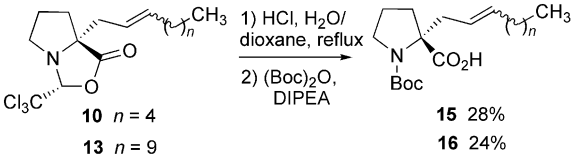


Scheme 3. CM of allylproline **4** with alkenes **11** and **12**.

The successful CM of allylproline **4**, bearing a quaternary homoallylic carbon, needs further comment. Proline **4** must be a type II or III olefin, according to Grubbs' classification,[15] as it undergoes a selective CM with various type I terminal olefins. Nevertheless, the reported result appears quite remarkable as, to the best of our knowledge, only few examples of CM of similar bulky homoallylic substrates

with alkenes have been reported,[24] including a few with electron-deficient alkenes.[25]

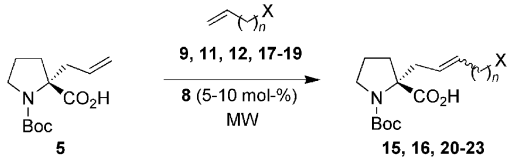
Unfortunately, masked amino acids **10** and **13** led to unacceptably low product yields under common deprotection and *N*-protection reaction conditions, due to their low solubility in water and low stability under the reaction conditions (Scheme 4). Moreover, the double bond could not be reduced in the presence of the (trichloromethyl)oxazolidinone moiety.



Scheme 4. Hydrolysis and *N*-protection of oxazolidinones **10** and **13**.

Therefore, route **B**, i.e. CM between allylproline **5** and a series of terminal olefins catalyzed by **8**, was examined under the reaction conditions optimized in the previous study (Table 2).

Table 2. CM of allylproline **5** with alkenes **9**, **11**, **12**, **17**, **18**, and **19**.[a]

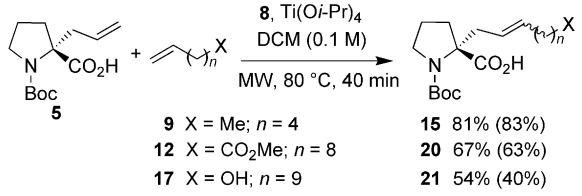


Entry	X	*n*	Alkene (equiv.)	**8** (mol)	Solvent (concd., M)	Prod.	Yield (%)[b]
1	Me	4	**9** (7.0)	5%	DCM (0.1)	**15**	92
2	Me	9	**11** (7.0)	5%	DCM (0.1)	**16**	86
3	CO_2Me	8	**12** (2.0)	5%	DCM (0.1)	**20**	63
4	OH	9	**17** (2.0)	5%	DCM (0.1)	**21**	40
5	OH	9	**17** (5.0)	10%	THF (0.5)[c]	**21**	56
6	OTBDPS	9	**18** (2.0)	10%	DCM (0.5)	**22**	40
7	CONHGlc	8	**19** (2.0)	10%	THF (0.3)	**23**	48[d]

[a] MW irradiation power of 150 W, ramp time of 5 min, with a run time of 40 min at 80 °C and simultaneous cooling was used. [b] Isolated yield after flash chromatography. [c] Reaction temperature: 40 °C. [d] H_2NGlc: 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine.

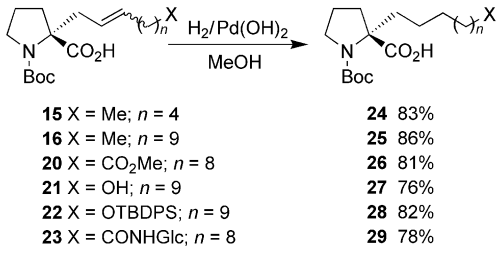
A comparison of the results obtained for CM on the two different scaffolds shows that product yields are comparable. The ^{1}H NMR analysis of the *N*-Boc α-alkylated prolines **15**, **16**, **20**–**23** in $CDCl_3$ showed the presence of a mixture of two conformers, apparently with exclusive *E* configuration (J_{trans} = 15 Hz), as the *Z* isomers could not be detected in the crude reaction mixtures. Analogous to allylproline **4**, the shorter the aliphatic alkene was, the better the reaction occurred (Table 2, entries 1, 2). CM of **5** with ω-functionalized alkenes such as alcohol **17** and amide **19** was more sluggish, but a higher catalyst loading (10 mol-%) provided acceptable yields of the corresponding cross products in these cases (Table 2 entries 4, 5 and 7). Previous protection of the hydroxyl group in **18** as a silyl ether did not improve the CM yield (Table 2 entry 6).

It is known that Lewis acids like Ti(O*i*Pr)$_4$ can be used to improve metathesis yields when Lewis base groups are present in reagents.[26,27] The use of Ti(O*i*Pr)$_4$ (20 mol-%) with **8** (5 mol-%) and 2 equiv. of alkenes **12** and **17** led to a slight yield increase of products **20** and **21**.[28] The control reaction using unsubstituted alkene **9** gave, as expected, the same yield (Scheme 5).



Scheme 5. CM between **5** and olefins **9**, **12**, and **17** (2 equiv.) in the presence of catalyst **8** (5 mol-%) and Ti(O*i*Pr)$_4$ (20 mol-%). In parentheses are yields of products under the same conditions in the absence of Ti(O*i*Pr)$_4$.

The α-substituted prolines **15**, **16**, **20**–**23** could be easily reduced by catalytic hydrogenation on Pd(OH)$_2$, in contrast to the corresponding oxazolidinone derivatives **10**, **13**, and **14**, affording the *N*-Boc-protected prolines **24**–**29** in good yield (Scheme 6).[29]



Scheme 6. Hydrogenations of alkenes **15**, **16**, **20**–**23**.

Conclusions

The synthesis of a collection of new *N*-Boc-protected α-functionalized prolines has been achieved by applying the cross metathesis reaction between *N*-Boc allylproline **5** and the appropriate alkenes followed by hydrogenation. The reaction conditions have been accurately investigated in order to make the method generally available for several different terminal alkene substrates. The new prolines **24** and **25** contain long-chain alkyl groups, suggesting their use as lipidated amino acids.[7] The glucosyl-conjugated proline **29** offers a new interesting example of a glycosylated amino acid, which are objects of intense synthetic efforts for their applications as biological tools in glycopeptidomimetics.[30] Functionalised chains with hydroxy and carboxylic groups in prolines **26**–**28** might serve to link the amino acids to other functionalities, to favor the receptor interactions, or to link them to a solid phase. Peptidomimetic syntheses along these lines will be further studied in our laboratories.

Experimental Section

General Remarks: Reactions were carried out in a CEM Discover™ microwave reactor. ^{1}H NMR and ^{13}C NMR spectra were recorded with Varian Gemini (200 MHz) and Varian Mercury plus (400 MHz) instruments using $CDCl_3$ as solvent. The NMR spectroscopic data are reported in δ (ppm) from TMS at 25 °C. In the assignment of NMR spectroscopic data of compounds **10**, **13**, **14**, and **15**, **16**, **20**–**29**, [*ch*] notation indicates atoms (H or C) of the alkyl chain on C-7a and C-2 of the cyclic system. The notation [*Glc*] indicates atoms (H or C) of the glucosyl residue in compounds **23** and **29**. IR spectra were recorded with a Perkin–Elmer 881 spectrophotometer using $CDCl_3$ as solvent. Optical rotations were measured with a Perkin–Elmer 343 polarimeter. Mass spectra were recorded with a QMD 1000 Carlo–Erba instrument by direct inlet; relative percentages are shown in brackets. Elemental analyses were performed with a Perkin–Elmer 2400 analyzer. Flash column chromatography (FCC) was accomplished on SiO_2 32–63 Mesh. R_f = values refer to TLC on 0.25 mm silica gel plates (Merck F_{254}).

Abbreviations: CDMT = 2-chloro-4,6-dimethoxy-1,3,5-triazine, DCM = dichloromethane, NMM = *N*-methylmorpholine.

***tert*-Butyl(diphenyl)(undec-10-enyloxy)silane (18):** Freshly distilled diisopropylethylamine (DIPEA) (420 μL, 2.4 mmol) and *tert*-butyldiphenylchlorosilane (TBDPSCl) (300 μL, 1.2 mmol) were added to a solution of 10-undecen-1-ol (120 mg, 0.8 mmol) in dry DCM under nitrogen atmosphere, at 0 °C. The reaction mixture was stirred at room temp. for 1 d and then concentrated. The residue was dissolved in H_2O (10 mL), and the aqueous solution was extracted with Et_2O (10 mL × 3). The ethereal phase was dried with Na_2SO_4, filtered, and concentrated. Purification of the crude residue by chromatography on silica gel (Et_2O/petroleum ether = 1:5) afforded the pure **18** (196 mg, 60%) as a colorless oil. R_f = 0.83 (Et_2O/petroleum ether = 1:10). ^{1}H NMR (400 MHz): δ = 7.71–7.66 (m, 4 H, H_{Ph}), 7.46–7.35 (m, 6 H, H_{Ph}), 5.83 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1 H, C*H*=CH$_2$), 5.00 (ddt, *J* = 17.1, 2.1, 1.6 Hz, 1 H, CH=C*H*H), 4.94 (ddt, *J* = 10.2, 2.1, 1.2 Hz, 1 H, CH=CH*H*), 3.67 (t, *J* = 6.5 Hz, 2 H, 1-H), 2.09–2.02 (m, 2 H, 9-H), 1.61–1.53 (m, 2 H, 2-H), 1.43–1.24 (m, 12 H, H-3, H-4, H-5, H-6, H-7, H-8), 1.06 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (50 MHz): δ = 139.1 (d; *C*H=CH$_2$), 135.5 (d; 4 C; C_{Ph}), 134.1 (s, 2 C; C_{Ph}), 129.4 (d, 2 C; C_{Ph}), 127.5 (d, 4 C; C_{Ph}), 114.1 (t; CH=*C*H$_2$), 64.0 (t; C-1), 33.9 (t; C-9), 32.6 (t; C-2), 29.6, 29.5, 29.4, 29.2, 29.0, 25.8 (t, C-3, C-4, C-5, C-6, C-7, C-8), 26.9 (q, 3 C; *C*H$_3$), 19.3 (s; CMe$_3$) ppm. IR $\tilde{\nu}$ = 3072, 2929, 1472, 1428, 1111 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 365 (3), 351 (33), 199 (100), 183 (20), 91 (5), 77 (10). $C_{27}H_{40}OSi$ (408.69): calcd. C 79.35, H 9.87; found C 79.24, H 9.65.

2,3,4,6-Tetra-*O*-acetyl-*N*-(10-undecenoyl)-β-D-glucopyranosylamine (19): NMM (148 μL, 1.3 mmol) and CDMT (231 mg, 1.3 mmol) were added under nitrogen to a solution of undecenoic acid (279 mg, 1.5 mmol) in dry THF (1 mL). After 1 h, a solution of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine (408 mg, 1.3 mmol) in dry THF (1.9 mL) was added, and the reaction mixture was stirred overnight at room temp. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc (8 mL) and H_2O (5 mL). The separated organic phase was washed sequentially with H_2O, a saturated solution of $NaHCO_3$, and brine, then dried with Na_2SO_4 and concentrated. The crude product was purified by chromatography on silica gel (EtOAc/petroleum ether = 2:3) to afford the desired product **19** (409 mg, 0.8 mmol, 61%) as a colorless oil. R_f = 0.14 (EtOAc/petroleum ether = 1:2), $[\alpha]_D^{25}$ = +15.6 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz): δ = 6.18 (d, *J* = 9.3 Hz, 1 H, NH), 5.79 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1 H, C*H*=CH$_2$), 5.30 (t, *J* = 9.5 Hz, 1 H, 2-H), 5.25 (t, *J* = 9.5 Hz, 1 H, 1-H), 5.05 (dd, *J* = 10.0, 9.5 Hz, 1 H, 4-H), 4.98 (dm, *J* = 17.1 Hz, 1 H, CH=C*H*H), 4.92 (dm, *J* = 10.2 Hz, 1 H, CH=CH*H*), 4.91 (t, *J* = 9.5 Hz, 1 H, 3-H), 4.31 (dd, *J* = 12.5, 4.3 Hz, 1 H, 6-H), 4.07 (dd, *J* = 12.5, 2.1 Hz, 1 H, 6-H), 3.81 (ddd, *J* = 10.0, 4.3, 2.1 Hz, 1 H, 5-H), 2.24–2.07 (m, 2 H, 2-H$_{[ch]}$), 2.07 (s, 3 H, CH$_3$), 2.03 (s, 3 H, CH$_3$), 2.02 (s, 3 H, CH$_3$), 2.01 (s, 3 H, CH$_3$), 1.63–1.50 (m, 2 H, 9-H$_{[ch]}$), 1.40–1.22 (m, 12 H, 3-H$_{[ch]}$, 4-H$_{[ch]}$, 5-H$_{[ch]}$, 6-H$_{[ch]}$, 7-H$_{[ch]}$, 8-H$_{[ch]}$) ppm. ^{13}C NMR (50 MHz): δ = 173.3 (s; CONH), 170.9 (s; COO), 170.5 (s; COO), 169.8 (s; COO), 169.5 (s; COO), 139.0 (d; *C*H=CH$_2$), 114.1 (t; CH=*C*H$_2$), 78.1 (d; C-1), 73.5 (d; C-5), 72.7 (d; C-2), 70.6 (d; C-3), 68.1 (d; C-4), 61.6 (t; C-6), 36.6 (t; C$_{[ch]}$-2), 33.7, 29.2, 29.1, 29.0, 28.9, 28.8 (t; C$_{[ch]}$-3, C$_{[ch]}$-4, C$_{[ch]}$-5, C$_{[ch]}$-6, C$_{[ch]}$-7, C$_{[ch]}$-8), 25.1 (t; C$_{[ch]}$-9), 20.7 (q; CH$_3$), 20.64 (q; CH$_3$), 20.57 (q, 2 C; CH$_3$) ppm. IR $\tilde{\nu}$ = 3427, 3077, 2923, 2856, 1755, 1697, 1367, 1235, 1043 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 513 (1.51) [M$^+$], 389 (22), 320 (22), 278 (31), 169 (37), 81 (84), 55 (100). $C_{25}H_{39}NO_{10}$ (513.58): calcd. C 58.47, H 7.65, N 2.73; found C 58.08, H 7.80, N 2.46.

(*E*)- and (*Z*)-(3*R*,7a*R*)-3-(Trichloromethyl)-7a-(tridec-2-enyl)tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-1-one (13): To a solution of allylproline **4** (185 mg, 0.65 mmol) in DCM (6.5 mL) and alkene **11** (220 mg, 1.3 mmol) was added the catalyst **8** (27.6 mg, 0.03 mmol). The solution was heated at 40 °C for 150 min under vigorous stirring, then concentrated under vacuum. The crude product was purified by chromatography on silica gel (petroleum ether/Et_2O = 10:1) to afford the desired product **13** (163 mg, 0.38 mmol, 58%) as a colorless oil. Oxazolidinone **13** was obtained as a mixture of isomers tentatively assigned as *E* and *Z* isomers in ca 4:1 ratio. Only the major isomer is reported. R_f = 0.61 (petroleum ether/Et_2O = 6:1), ^{1}H NMR (400 MHz): δ = 5.65–5.53 (m, J_{trans} = 15 Hz, 1 H, 3-H$_{[ch]}$), 5.52–5.41 (m, J_{trans} = 15 Hz, 1 H, 2-H$_{[ch]}$), 4.96 (s, 1 H, 3-H), 3.24–3.10 (m, 2 H, 5-H), 2.56 (ddd, *J* = 13.8, 6.3, 1.1 Hz, 1 H, 1-H$_{[ch]}$a), 2.47 (dd, *J* = 13.8, 7.7 Hz, 1 H, 1-H$_{[ch]}$b), 2.17–2.07 (m, 1 H, 7-Ha), 2.06–1.96 (m, 3 H, 7-Hb, 4-H$_{[ch]}$), 1.94–1.83 (m, 1 H, 6-Ha), 1.70–1.56 (m, 1 H, 6-Hb), 1.42–1.16 and 0.92–0.80 (m, 19 H, 5-H$_{[ch]}$, 6-H$_{[ch]}$, 7-H$_{[ch]}$, 8-H$_{[ch]}$, 9-H$_{[ch]}$, 10-H$_{[ch]}$, 11-H$_{[ch]}$, 12-H$_{[ch]}$, 13-H$_{[ch]}$) ppm. ^{13}C NMR (50 MHz): δ = 177.0 (s; CO), 136.3 (d; C$_{[ch]}$-2), 122.8 (d; C$_{[ch]}$-3), 102.3 (d; C-3), 100.2 (s; CCl_3), 71.6 (s; C-7a), 58.4 (t; C-5), 40.4 (t; C$_{[ch]}$-1), 35.2 (t; C-7), 32.8, 32.0, 29.6, 29.4, 29.2 (t, C$_{[ch]}$-4, C$_{[ch]}$-5, C$_{[ch]}$-6, C$_{[ch]}$-7, C$_{[ch]}$-8, C$_{[ch]}$-9, C$_{[ch]}$-10, C$_{[ch]}$-11), 25.4 (t, C-6), 22.8 (t; C$_{[ch]}$-12), 14.2 (q; C$_{[ch]}$-13) ppm. IR $\tilde{\nu}$ = 2927, 2855, 1799, 1457, 1354, 1323, 1275, 1261, 1193, 1105 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 424 (3.10) [M$^+$], 369 (4), 268 (13), 209 (28), 85 (36), 83 (43), 71 (65), 57 (100), 55 (99). $C_{20}H_{32}Cl_3NO_2$ (424.83): calcd. C 56.54, H 7.59, N 3.30; found C 56.38, H 7.68, N 3.20.

General Procedure for Cross-Metathesis under Microwave Irradiation: To a solution of allylprolines **4** or **5**, in DCM or in THF (10^{-5}–10^{-1} M), was added the alkene (2–7 equiv.) followed by the Grubbs' catalyst **8** (5–10 mol-%). The vial was sealed and irradiated in the microwave reactor using an irradiation power of 150 W (with simultaneous cooling) at the appropriate temperature (from 40 °C to 80 °C), under vigorous stirring for the appropriate time. The solution was then concentrated under vacuum, and the crude reaction mixture was purified by chromatography on silica gel. In the case of oxazolidinone products, a second purification was necessary to remove all the traces of Ru catalyst to get analytically pure samples, whereas prolines **15**, **16**, **20**–**23**, remained as brownish oils after purification, not allowing exact elemental analyses. The structural identity of prolines **15**, **16**, **20**–**23** was indirectly confirmed by the following analysis of the corresponding reduction products (see below). Oxazolidinones **10** and **14** were obtained as mixtures of isomers tentatively assigned as *E* and *Z* isomers in ca 4:1 ratio. Pro-

lines **15**, **16**, **20**–**23** were obtained as mixtures of conformers in ca 2:1 ratio. NMR spectra of the major isomer/conformer are reported.

(*E*)- and (*Z*)-(3*R*,7a*R*)-7a-(Oct-2-enyl)-3-(trichloromethyl)tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-1-one (10): According to the general procedure using **4** (89 mg, 0.31 mmol), the product **10** (81 mg, 0.23 mmol, 74%) was obtained as a colorless oil. R_f = 0.38 (petroleum ether/Et_2O = 6:1). ^1H NMR (400 MHz): δ = 5.66–5.53 (m, J_{trans} = 15 Hz, 1 H, 3-$H_{[ch]}$), 5.52–5.42 (m, J_{trans} = 15 Hz, 1 H, 2-$H_{[ch]}$), 4.96 (s, 1 H, 3-H), 3.24–3.10 (m, 2 H, 5-H), 2.56 (broad dd, J = 14; 6.3 Hz, 1 H, 1-$H_{[ch]}$), 2.47 (dd, J = 13.9, 7.8 Hz, 1 H, 1-$H_{[ch]}$), 2.17–1.94 (m, 4 H, 7-H, 4-$H_{[ch]}$), 1.93–1.82 (m, 1 H, 6-H), 1.72–1.58 (m, 1 H, 6-H), 1.40–1.21 (m, 6 H, 5-$H_{[ch]}$, 6-$H_{[ch]}$, 7-$H_{[ch]}$), 0.88 (t, J = 6.9 Hz, 3 H, 8-$H_{[ch]}$) ppm. ^{13}C NMR (50 MHz): δ = 176.4 (s; CO), 136.4 (d, $C_{[ch]}$-2), 122.9 (d; $C_{[ch]}$-3), 102.4 (d; C-3), 100.5 (s; CCl_3), 71.6 (s; C-7a), 58.3 (t; C-5), 40.4 (t; $C_{[ch]}$-1), 35.1 (t; C-7), 32.6 (t; $C_{[ch]}$-4), 31.3, 29.0 (t; $C_{[ch]}$-5, $C_{[ch]}$-6), 25.3 (t; C-6), 22.4 (t; $C_{[ch]}$-7), 14.0 (q; $C_{[ch]}$-8) ppm. IR $\tilde{\nu}$ = 2958, 2928, 1799, 1458, 1354, 1323, 1275, 1192, 1105 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 354 (0.45) [M^+], 246 (30), 244 (91), 242 (93) [M – C_8H_{15}], 96 (100), 68 (33), 55 (20). $C_{15}H_{22}Cl_3NO_2$ (354.70): calcd. C 50.79, H 6.25, N 3.95; found C 50.50, H 6.48, N 4.02.

Methyl (*E*)- and (*Z*)-12-[(3*R*,7a*R*)-1-Oxo-3-(trichloromethyl)dihydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-7a(5*H*)-yl]dodec-10-enoate (14): According to the general procedure using **4** (105 mg, 0.37 mmol), the product **14** (95 mg, 0.21 mmol, 57%) was obtained as a colorless oil. R_f = 0.39 (petroleum ether/Et_2O = 6:1). ^1H NMR (400 MHz): δ = 5.65–5.53 (m, J_{trans} = 15 Hz, 1 H, 3-$H_{[ch]}$), 5.52–5.42 (m, J_{trans} = 15 Hz, 1 H, 2-$H_{[ch]}$), 4.96 (s, 1 H, 3-H), 3.66 (s, 3 H, OCH_3), 3.24–3.11 (m, 2 H, 5-H), 2.55 (broad dd, J = 14, 6.3 Hz, 1 H, 1-$H_{[ch]}$a), 2.47 (dd, J = 13.9, 7.6 Hz, 1 H, 1-$H_{[ch]}$b), 2.30 (t, J = 7.5 Hz, 2 H, 11-$H_{[ch]}$), 2.15–2.07 (m, 1 H, 7-Ha), 2.06–1.93 (m, 3 H, 7-Hb, 4-$H_{[ch]}$), 1.92–1.83 (m, 1 H, 6-Ha), 1.71–1.57 (m, 3 H, 6-Hb, 10-$H_{[ch]}$), 1.40–1.23 (m, 10 H, 5-$H_{[ch]}$, 6-$H_{[ch]}$, 7-$H_{[ch]}$, 8-$H_{[ch]}$, 9-$H_{[ch]}$) ppm. ^{13}C NMR (100 MHz): δ = 176.3 (s; CO), 174.2 (s; $C_{[ch]}O$), 136.2 (d; $C_{[ch]}$-2), 123.0 (d; $C_{[ch]}$-3), 102.3 (d; C-3), 100.5 (s; CCl_3), 71.6 (s; C-7a), 58.3 (t; C-5), 51.4 (q; OMe), 40.3 (t; $C_{[ch]}$-1), 35.1 (t; C-7), 34.0 (t; $C_{[ch]}$-11), 32.6 (t; $C_{[ch]}$-4), 29.3, 29.2 (2 C), 29.1, 29.0, (t, $C_{[ch]}$-5, $C_{[ch]}$-6, $C_{[ch]}$-7, $C_{[ch]}$-8, $C_{[ch]}$-9), 25.2 (t; C-6), 24.9 (t; $C_{[ch]}$-10) ppm. IR $\tilde{\nu}$ = 2929, 2856, 1799, 1730, 1437, 1354, 1323, 1275, 1193, 1105 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 455 (0.1) [M^+], 424 (0.76), 280 (6), 246 (30), 244 (97), 242 (100), 96 (95), 68 (37), 55 (35). $C_{20}H_{30}Cl_3NO_4$ (454.82): calcd. C 52.82, H 6.65, N 3.08; found C 52.47, H 6.76, N 2.82.

1-(*tert*-Butoxycarbonyl)-2-[(2*E*)-oct-2-enyl]-L-proline (15): According to the general procedure using **5** (35 mg, 0.14 mmol), the product **15** (41 mg, 0.13 mmol, 92%) was obtained. R_f = 0.33 (*n*-hexane/EtOAc = 2:1). ^1H NMR (400 MHz): δ = 5.61–5.47 (m, J_{trans} = 15 Hz, 1 H, 3-$H_{[ch]}$), 5.36–5.15 (m, J_{trans} = 15 Hz, 1 H, 2-$H_{[ch]}$), 3.55–3.45 (m, 1 H, 5-H), 3.30–3.20 (m, 1 H, 5-H), 2.85 (dd, J = 13.5, 7.5 Hz 1 H, 1-$H_{[ch]}$), 2.60 (dd, J = 13.5, 7.5 Hz 1 H, 1-$H_{[ch]}$), 2.04–1.70 (m, 6 H, 3-H, 4-H, 4-$H_{[ch]}$), 1.48 (s, 9 H, Boc), 1.38–1.21 (m, 6 H, 5-$H_{[ch]}$, 6-$H_{[ch]}$, 7-$H_{[ch]}$); 0.88 (t, J = 6.9 Hz, 3 H, 8-$H_{[ch]}$) ppm. IR $\tilde{\nu}$ = 2929, 2856, 1739, 1711, 1689, 1609, 1403, 1162 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 327 (0.03) [M^+], 224 (33), 180 (26), 114 (86), 96 (17), 57 (100).

1-(*tert*-Butoxycarbonyl)-2-[(2*E*)-tridec-2-enyl]-L-proline (16): According to the general procedure using **5** (56 mg, 0.22 mmol), the product **16** (75 mg, 0.19 mmol, 86%) was obtained. R_f = 0.14 (petroleum ether/Et_2O = 1:1). ^1H NMR (400 MHz): δ = 5.60–5.46 (m, J_{trans} = 15 Hz, 1 H, 3-$H_{[ch]}$), 5.37–5.26 (m, J_{trans} = 15 Hz, 1 H, 2-$H_{[ch]}$), 3.68 (ddd J = 10.6, 7.6, 5.8 Hz, 1 H, 5-Ha), 3.37 (dt, J = 10.6, 7.0 Hz, 1 H, 5-Hb), 2.87 (broad dd, J = 14.1, 6.5 Hz, 1 H, 1-$H_{[ch]}$a), 2.51 (dd, J = 14.1, 8.0 Hz, 1 H, 1-$H_{[ch]}$b), 2.26–1.76 (m, 6 H, 3-H, 4-H, 4-$H_{[ch]}$), 1.53 (s, 9 H, Boc), 1.55–1.23 (m, 16 H, 5-$H_{[ch]}$, 6-$H_{[ch]}$, 7-$H_{[ch]}$, 8-$H_{[ch]}$, 9-$H_{[ch]}$, 10-$H_{[ch]}$, 11-$H_{[ch]}$, 12-$H_{[ch]}$); 0.88 (t J = 6.8 Hz, 3 H, 13-$H_{[ch]}$) ppm. IR $\tilde{\nu}$ = 2928, 2855, 1740, 1686, 1608, 1436, 1406, 1369, 1162 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 395 (0.32) [M^+], 308 (18), 294 (45), 250 (32), 186 (19), 114 (100), 96 (21), 57 (90).

1-(*tert*-Butoxycarbonyl)-2-[(2*E*)-12-methoxy-12-oxododec-2-enyl]-L-proline (20): According to the general procedure using **5** (49 mg, 0.19 mmol), the product **20** (51 mg, 0.12 mmol, 63%) was obtained. R_f = 0.31 (EtOAc/petroleum ether = 1:2). ^1H NMR (400 MHz): δ = 5.60–5.50 (m, J_{trans} = 15 Hz, 1 H, 3-$H_{[ch]}$), 5.28–5.17 (m, J_{trans} = 15 Hz, 1 H, 2-$H_{[ch]}$), 3.66 (m, 3 H, OMe), 3.52–3.45 (m, 1 H, 5-Ha), 3.30–3.21 (m, 1 H, 5-Hb), 2.85–2.77 (m, 1 H, 1-$H_{[ch]}$a), 2.67–2.57 (m, 1 H, 1-$H_{[ch]}$b), 2.29 (t, J = 7.5 Hz, 2 H, 11-$H_{[ch]}$), 2.03–1.71 (m, 6 H, 3-H, 4-H, 4-$H_{[ch]}$), 1.65–1.56 (m, 2 H, 10-$H_{[ch]}$), 1.48 (s, 9 H, Boc), 1.46–1.43 and 1.36–1.23 (m, 10 H, 5-$H_{[ch]}$, 6-$H_{[ch]}$, 7-$H_{[ch]}$, 8-$H_{[ch]}$, 9-$H_{[ch]}$) ppm. IR $\tilde{\nu}$ = 2930, 2856, 1732, 1689, 1609, 1436, 1401, 1368, 1167 cm^{-1}, MS (70 eV, EI): *m*/*z* (%) = 425 (8.3) [M^+], 280 (22), 220 (8), 114 (50), 165 (20), 83 (43), 57 (100).

1-(*tert*-Butoxycarbonyl)-2-[(2*E*)-12-hydroxydodec-2-enyl]-L-proline (21): According to the general procedure using **5** (46 mg, 0.18 mmol), the product **21** (41 mg, 0.10 mmol, 56%) was obtained. R_f = 0.31 (*n*-hexane/EtOAc = 1:5). ^1H NMR (400 MHz): δ = 5.59–5.50 (m, J_{trans} = 15 Hz, 1 H, 3-$H_{[ch]}$), 5.29–5.18 (m, J_{trans} = 15 Hz, 1 H, 2-$H_{[ch]}$), 3.63 (t, J = 6.6 Hz, 2 H, 12-$H_{[ch]}$), 3.53–3.45 (m, 1 H, 5-Ha), 3.31–3.21 (m, 1 H, 5-Hb), 2.83–2.76 (m, 1 H, 1-$H_{[ch]}$), 2.66–2.60 (m, 1 H, 1-$H_{[ch]}$), 2.06–1.51 (m, 8 H, 3-H, 4-H, 4-$H_{[ch]}$, 11-$H_{[ch]}$), 1.48 (s, 9 H, Boc), 1.40–1.24 (m, 12 H, 5-$H_{[ch]}$, 6-$H_{[ch]}$, 7-$H_{[ch]}$, 8-$H_{[ch]}$, 9-$H_{[ch]}$, 10-$H_{[ch]}$) ppm. IR $\tilde{\nu}$ = 3507, 2931, 2856, 1742, 1607, 1407, 1265, 1161 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 352 (0.3), 338 (0.3), 324 (0.5), 310 (0.3), 297 (1.2), 252 (34), 114 (100), 96 (15), 57 (97).

1-(*tert*-Butoxycarbonyl)-2-[(2*E*)-12-{[*tert*-butyl(diphenyl)silyl]oxy}-dodec-2-enyl]-L-proline (22): According to the general procedure using **5** (50 mg, 0.20 mmol), the product **22** (52 mg, 0.08 mmol, 40%) was obtained. R_f = 0.30 (EtOAc/petroleum ether = 1:3). ^1H NMR (400 MHz): δ = 7.69–7.65 (m, 4 H, H_{Ph}), 7.44–7.34 (m, 6 H, H_{Ph}), 5.63–5.51 (m, J_{trans} = 15 Hz, 1 H, 3-$H_{[ch]}$), 5.28–5.17 (m, J_{trans} = 15 Hz, 1 H, 2-$H_{[ch]}$), 3.65 (t, J = 6.5 Hz, 2 H, 12-$H_{[ch]}$), 3.53–3.44 (m, 1 H, 5-Ha), 3.33–3.20 (m, 1 H, 5-Hb), 2.85–2.76 (m, 1 H, 1-$H_{[ch]}$a), 2.72–2.60 (m, 1 H, 1-$H_{[ch]}$b), 2.07–1.67 (m, 6 H, 3-H, 4-H, 4-$H_{[ch]}$), 1.59–1.51 (m, 2 H, 11-$H_{[ch]}$), 1.49 (s, 9 H, Boc), 1.38–1.22 (m, 12 H, 5-$H_{[ch]}$, 6-$H_{[ch]}$, 7-$H_{[ch]}$, 8-$H_{[ch]}$, 9-$H_{[ch]}$, 10-$H_{[ch]}$), 1.01 (s, 9 H, CH_3 TBDPS) ppm. IR: $\tilde{\nu}$ = 2931, 2857, 1686, 1611, 1467, 1428, 1368, 1171, 1112 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 536 (1.41) [M^+], 522 (1), 477 (1), 234 (2), 199 (15), 114 (21), 83 (13), 57 (100).

1-(*tert*-Butoxycarbonyl)-2-[(2*E*)-12-oxo-12-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)dodec-2-enyl]-L-proline (23): According to the general procedure using **5** (80 mg, 0.31 mmol), the product **23** (110 mg, 0.15 mmol, 48%) was obtained. R_f = 0.32 (DCM/MeOH = 25:1). ^1H NMR (400 MHz): δ = 6.22 (d, J = 9.8 Hz, 1 H, NH), 5.71–5.57 (m, 1 H, 3-$H_{[ch]}$), 5.30 (t, J = 9.5 Hz, 1 H, 2-$H_{[Glc]}$), 5.26 (broad t, J = 9.1 Hz, 1 H, 1-$H_{[Glc]}$), 5.23–5.09 (m, 1 H, 2-$H_{[ch]}$), 5.06 (dd, J = 10.1, 9.4 Hz, 1 H, 4-$H_{[Glc]}$), 4.91 (dt, J = 2.6, 9.6 Hz, 1 H, 3-$H_{[Glc]}$), 4.31 (dd, J = 12.5, 4.3 Hz, 1 H, 6-$H_{[Glc]}$ a), 4.07 (dd, J = 12.5, 2.1 Hz, 1 H, 6-$H_{[Glc]}$ b), 3.81 (ddd, J = 10.1, 4.3, 2.1 Hz, 1 H, 5-$H_{[Glc]}$), 3.55–3.45 (m, 1 H, 5-Ha), 3.34–3.21 (m, 1 H, 5-Hb), 2.90 (dd, J = 13.7, 7.1 Hz, 1 H, 1-$H_{[ch]}$ a), 2.85–2.49 (m, 4 H, 3-Ha, 1-$H_{[ch]}$ b, 4-$H_{[ch]}$), 2.24–2.09 (m, 2 H, 11-$H_{[ch]}$), 2.07 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 2.03 (s, 3 H, OAc), 2.01 (s, 3 H, OAc),

2.03–1.52 (m, 5 H, 3-Hb, 4-H, 10-$H_{[ch]}$), 1.48 (s, 9 H, Boc), 1.47–1.38 and 1.36–1.22 (m, 10 H, 5-$H_{[ch]}$, 6-$H_{[ch]}$, 7-$H_{[ch]}$, 8-$H_{[ch]}$, 9-$H_{[ch]}$) ppm. IR: $\tilde{\nu}$ = 3427, 2931, 2856, 1747, 1711, 1689, 1404, 1369, 1228, 1040 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 741 (0.52) [M^+], 595 (33), 266 (11), 248 (21), 169 (31), 114 (98), 96 (40), 70 (53), 57 (100), 55 (57).

General Procedure for Catalytic Hydrogenation: A solution of CM products in MeOH (10^{-1} M), along with 20% $Pd(OH)_2$/C (10 mol-%) was stirred under H_2 at atmospheric pressure overnight. The reaction mixture was filtered, concentrated and purified by column chromatography to afford the hydrogenated products. A mixture of two conformers was obtained in unresolved ratio. Only signals of the major conformers are reported.

1-(*tert*-Butoxycarbonyl)-2-octyl-L-proline (24): Colorless oil, 83% yield, R_f = 0.31 (*n*-hexane/EtOAc = 1:1), $[\alpha]_D^{24}$ = –29.1 (*c* = 0.6, $CHCl_3$). ^1H NMR (400 MHz): δ = 3.53–3.45 (m, 1 H, 5-Ha), 3.34–3.25 (m, 1 H, 5-Hb), 2.77–2.66 (m, 1 H, 3-Ha), 2.22–2.07 (m, 1 H, 1-$H_{[ch]}$a), 1.89–1.69 (m, 4 H, 3-Hb, 4-H, 1-$H_{[ch]}$b), 1.49 (s, 9 H, Boc), 1.35–1.12 (m, 12 H, 2-$H_{[ch]}$, 3-$H_{[ch]}$, 4-$H_{[ch]}$, 5-$H_{[ch]}$, 6-$H_{[ch]}$, 7-$H_{[ch]}$), 0.87 (t, *J* = 6.8 Hz, 3 H, 8-$H_{[ch]}$) ppm. ^{13}C NMR (100 MHz): δ = 174.3 (s; COOH), 157.5 (s; CO Boc), 82.2 (s; *C*Me_3), 70.9 (s; C-2), 49.4 (t; C-5), 34.9 (t; C-3), 34.4 (t; $C_{[ch]}$-1), 31.8 (t; $C_{[ch]}$-2), 29.5, 29.4, 29.1, 24.0, 22.7, 22.6 (t; 6 C; C-4, $C_{[ch]}$-3, $C_{[ch]}$-4, $C_{[ch]}$-5, $C_{[ch]}$-6, $C_{[ch]}$-7), 28.4 (q, 3 C; CH_3 Boc), 14.1 (q; $C_{[ch]}$-8) ppm. MS (70 eV, EI): *m*/*z* (%) = 226 (52), 212 (9), 182 (28), 96 (12), 83 (26), 57 (100), 55 (39). $C_{18}H_{33}NO_4$ (327.46): calcd. C 66.02, H 10.16, N 4.28; found C 65.69, H 10.38, N 3.96.

1-(*tert*-Butoxycarbonyl)-2-tridecyl-L-proline (25): Colorless oil, 86% yield, R_f = 0.28 (*n*-hexane/EtOAc = 5:1), $[\alpha]_D^{24}$ = –7.3 (*c* = 0.7, $CHCl_3$). ^1H NMR (400 MHz): δ = 3.54–3.45 (m, 1 H, 5-Ha), 3.36–3.26 (m, 1 H, 5-Hb), 2.79–2.68 (m, 1 H, 3-Ha), 2.24–2.09 (m, 1 H, 1-$H_{[ch]}$a), 1.91–1.70 (m, 4 H, 3-Hb, 4-H, 1-$H_{[ch]}$b), 1.49 (s, 9 H, Boc), 1.34–1.23 (m, 22 H, 2-$H_{[ch]}$, 3-$H_{[ch]}$, 4-$H_{[ch]}$, 5-$H_{[ch]}$, 6-$H_{[ch]}$, 7-$H_{[ch]}$, 8-$H_{[ch]}$, 9-$H_{[ch]}$, 10-$H_{[ch]}$, 11-$H_{[ch]}$, 12-$H_{[ch]}$); 0.88 (t, *J* = 6.8 Hz, 3 H, 13-$H_{[ch]}$) ppm. ^{13}C NMR (100 MHz): δ = 174.1 (s; COOH), 157.6 (s; CO Boc), 82.3 (s; CMe_3), 71.0 (s; C-2), 49.4 (t; C-5), 34.9 (t; C-3), 34.5 (t; $C_{[ch]}$-1), 31.9 (t; $C_{[ch]}$-2), 29.6, 29.5 (4 C), 29.4 (2 C), 29.2, 23.9, 22.7, 22.6 (t; 11 C; C-4, $C_{[ch]}$-3, $C_{[ch]}$-4, $C_{[ch]}$-5, $C_{[ch]}$-6, $C_{[ch]}$-7, $C_{[ch]}$-8, $C_{[ch]}$-9, $C_{[ch]}$-10, $C_{[ch]}$-11, $C_{[ch]}$-12), 28.3 (q, 3 C; CH_3 Boc), 14.0 (q; $C_{[ch]}$-13) ppm. IR: $\tilde{\nu}$ = 2928, 2855, 1741, 1689, 1405, 1369, 1162 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 398 (0.05) [M^+], 296 (100), 282 (29), 252 (55), 114 (29), 96 (24), 57 (93). $C_{23}H_{43}NO_4$ (397.59): calcd. C 69.48, H 10.90, N 3.52; found C 69.29, H 11.14, N 3.45.

1-(*tert*-Butoxycarbonyl)-2-(12-methoxy-12-oxododecyl)-L-proline (26): Yellowish oil, 81% yield, R_f = 0.24 (*n*-hexane/EtOAc = 3:2), $[\alpha]_D^{26}$ = –27.3 (*c* = 0.4, $CHCl_3$). ^1H NMR (400 MHz): δ = 3.66 (m, 3 H, OMe), 3.52–3.46 (m, 1 H, 5-Ha), 3.34–3.25 (m, 1 H, 5-Hb), 2.80–2.72 (m, 1 H, 3-Ha), 2.30 (t, *J* = 7.5 Hz, 2 H, 11-$H_{[ch]}$), 2.26–2.15 (m, 1 H, 1-$H_{[ch]}$a), 1.86–1.68 (m, 4 H, 3-Hb, 4-H, 1-$H_{[ch]}$b), 1.61 (tt, *J* = 7.5, 7.1 Hz, 2 H, 10-$H_{[ch]}$), 1.49 (s, 9 H, Boc), 1.32–1.22 (m, 16 H, 2-$H_{[ch]}$, 3-$H_{[ch]}$, 4-$H_{[ch]}$, 5-$H_{[ch]}$, 6-$H_{[ch]}$, 7-$H_{[ch]}$, 8-$H_{[ch]}$, 9-$H_{[ch]}$) ppm. ^{13}C NMR (100 MHz): δ = 174.3 (s, 2 C; CO-OMe, CO Boc), 82.4 (s; CMe_3), 69.9 (s; C-2), 51.4 (q; OMe), 49.6 (t; C-5), 34.4 (t; $C_{[ch]}$-10), 34.1 (t; $C_{[ch]}$-11), 34.8 (t; C-3), 31.6, 29.5 (2 C), 29.4, 29.2, 29.1, 24.9, 24.0, 22.7, 22.6 (t, 10 C; C-4, $C_{[ch]}$-1, $C_{[ch]}$-2, $C_{[ch]}$-3, $C_{[ch]}$-4, $C_{[ch]}$-5, $C_{[ch]}$-6, $C_{[ch]}$-7, $C_{[ch]}$-8, $C_{[ch]}$-9), 28.4 (q, 3 C; CH_3 Boc) ppm. IR: $\tilde{\nu}$ = 2929, 2855, 1732, 1438, 1408, 1369, 1164 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 412 (4.7), 282 (83), 268 (37), 114 (10), 96 (30), 57 (100). $C_{23}H_{41}NO_6$ (427.57): calcd. C 64.61, H 9.67, N 3.28; found C 64.21, H 9.57, N 3.33.

1-(*tert*-Butoxycarbonyl)-2-(12-hydroxydodecyl)-L-proline (27): Yellowish oil, 76% yield, R_f = 0.34 (*n*-hexane/EtOAc = 2:1), $[\alpha]_D^{25}$ = –22.1 (*c* = 0.8, $CHCl_3$). ^1H NMR (400 MHz): δ = 3.64 (t, *J* = 6.6 Hz, 2 H, 12-$H_{[ch]}$), 3.52–3.44 (m, 1 H, 5-Ha), 3.34–3.25 (m, 1 H, 5-Hb), 2.80–2.71 (m, 1 H, 3-Ha), 2.26–2.15 (m, 1 H, 1-$H_{[ch]}$a), 1.85–1.70 (m, 4 H, 1-$H_{[ch]}$b, 3-Hb, 4-H), 1.56 (tt, *J* = 7.1, 6.9 Hz, 2 H, 11-$H_{[ch]}$), 1.49 (s, 9 H, Boc), 1.37–1.22 (m, 18 H, 2-$H_{[ch]}$, 3-$H_{[ch]}$, 4-$H_{[ch]}$, 5-$H_{[ch]}$, 6-$H_{[ch]}$, 7-$H_{[ch]}$, 8-$H_{[ch]}$, 9-$H_{[ch]}$, 10-$H_{[ch]}$) ppm. ^{13}C NMR (50 MHz): δ = 173.8 (s; CO_2H), 157.3 (s; CO Boc), 82.3 (s; CMe_3), 70.9 (s; C-2), 63.2 (t; $C_{[ch]}$-12), 49.6 (t; C-5), 35.1 (t; C-3), 34.3 (t; $C_{[ch]}$-1), 33.0 (t; $C_{[ch]}$-11), 29.8 (6 C), 29.6 (2 C), 25.9 (t, 9 C; $C_{[ch]}$-2, $C_{[ch]}$-3, $C_{[ch]}$-4, $C_{[ch]}$-5, $C_{[ch]}$-6, $C_{[ch]}$-7, $C_{[ch]}$-8, $C_{[ch]}$-9, $C_{[ch]}$-10), 28.5 (q, 3 C; CH_3 Boc), 22.9 (t; C-4) ppm. IR: $\tilde{\nu}$ = 2930, 2855, 1736, 1610, 1406, 1265, 1162 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 341 (3), 254 (7), 120 (68), 108 (26), 91 (100), 77 (45), 57 (53). $C_{22}H_{41}NO_5$ (399.56): calcd. C 66.13, H 10.34, N 3.51; found C 65.82, H 10.35, N 3.15.

1-(*tert*-Butoxycarbonyl)-2-(12-{[*tert*-butyl(diphenyl)silyl]oxy}-dodecyl)-L-proline (28): Colorless oil, 82% yield, R_f = 0.30 (EtOAc/petroleum ether = 1:3), $[\alpha]_D^{25}$ = –15.7 (*c* = 0.6, $CHCl_3$). ^1H NMR (400 MHz): δ = 7.69–7.64 (m, 4 H, H_{Ph}), 7.44–7.34 (m, 6 H, H_{Ph}), 3.65 (t, *J* = 6.6 Hz, 2 H, 12-$H_{[ch]}$), 3.53–3.46 (m, 1 H, 5-Ha), 3.35–3.25 (m, 1 H, 5-Hb), 2.79–2.70 (m, 1 H, 3-Ha), 2.25–2.16 (m, 1 H, 1-$H_{[ch]}$a), 1.88–1.70 (m, 4 H, 1-$H_{[ch]}$b, 3-Hb, 4-H), 1.55 (tt, *J* = 6.8, 6.5 Hz, 2 H, 11-$H_{[ch]}$), 1.49 (s, 9 H, Boc), 1.37–1.21 (m, 18 H, 2-$H_{[ch]}$, 3-$H_{[ch]}$, 4-$H_{[ch]}$, 5-$H_{[ch]}$, 6-$H_{[ch]}$, 7-$H_{[ch]}$, 8-$H_{[ch]}$, 9-$H_{[ch]}$, 10-$H_{[ch]}$), 1.05 (s, 9 H, CH_3 *t*Bu) ppm. ^{13}C NMR (100 MHz): δ = 174.0 (s; COOH), 157.5 (s; CO Boc), 135.5 (d, 4 C; C_{Ph}), 134.1 (d, 2 C; C_{Ph}), 129.4 (d, 2 C; C_{Ph}), 127.5 (d, 4 C; C_{Ph}), 82.3 (s; $OCMe_3$), 71.0 (s; C-2), 64.0 (t; $C_{[ch]}$-12), 49.4 (t; C-5), 34.9 (t; C-3), 34.4 (t; $C_{[ch]}$-1), 32.6 (t; $C_{[ch]}$-11), 29.8 (2 C), 29.6 (2 C), 29.3 (2 C), 25.8, 24.0, 22.7, 19.2, (t; 10 C; C-4, $C_{[ch]}$-2, $C_{[ch]}$-3, $C_{[ch]}$-4, $C_{[ch]}$-5, $C_{[ch]}$-6, $C_{[ch]}$-7, $C_{[ch]}$-8, $C_{[ch]}$-9, $C_{[ch]}$-10), 28.4 (q, 3 C; CH_3 Boc), 26.9 (q, 3 C; CH_3 TBDPS), 19.3 (s; $SiCMe_3$) ppm. IR: $\tilde{\nu}$ = 2930, 2856, 1738, 1609, 1428, 1407, 1369, 1159, 1111 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 493 (8), 481 (9), 466 (10), 199 (24), 96 (20), 83 (32), 57 (100), 55 (59). $C_{38}H_{59}NO_5Si$ (637.96): calcd. C 71.54, H 9.32, N 2.20; found C 71.14, H 9.44, N 2.16.

1-(*tert*-Butoxycarbonyl)-2-[12-oxo-12-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)dodecanoyl]-L-proline (29): Colorless oil, 78% yield, R_f = 0.17 (*n*-hexane/EtOAc = 5:1), $[\alpha]_D^{25}$ = 8.7 (*c* = 0.3, $CHCl_3$). ^1H NMR (400 MHz): δ = 6.19 (d, *J* = 9.4 Hz, 1 H, NH), 5.30 (t, *J* = 9.5 Hz, 1 H, 2-$H_{[Glc]}$), 5.26 (t, *J* = 9.4 Hz, 1 H, 1-$H_{[Glc]}$), 5.06 (t, *J* = 9.6 Hz, 1 H, 4-$H_{[Glc]}$), 4.91 (t, *J* = 9.6 Hz, 1 H, 3-$H_{[Glc]}$), 4.31 (dd, *J* = 12.5, 4.3 Hz, 1 H, 6-$H_{[Glc]}$), 4.07 (dd, *J* = 12.5, 2.1 Hz, 1 H, 6-$H_{[Glc]}$), 3.81 (ddd, *J* = 10.1, 4.3, 2.1 Hz, 1 H, 5-$H_{[Glc]}$), 3.53–3.45 (m, 1 H, 5-Ha), 3.34–3.25 (m, 1 H, 5-Hb), 2.81–2.71 (m, 1 H, 3-Ha), 2.36–2.09 (m, 3 H, 1-$H_{[ch]}$a, 11-$H_{[ch]}$), 2.08 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 2.03 (s, 3 H, OAc), 2.02 (s, 3 H, OAc), 1.88–1.10 (m, 22 H, 3-Hb, 4-H, 1-$H_{[ch]}$b, 2-$H_{[ch]}$, 3-$H_{[ch]}$, 4-$H_{[ch]}$, 5-$H_{[ch]}$, 6-$H_{[ch]}$, 7-$H_{[ch]}$, 8-$H_{[ch]}$, 9-$H_{[ch]}$, 10-$H_{[ch]}$), 1.49 (s, 9 H, CH_3 Boc) ppm. ^{13}C NMR (50 MHz): δ = 173.8 (s; COOH), 173.3 (s; CONH), 170.9 (s; MeCO), 170.5 (s; MeCO), 169.7 (s; Me*C*O), 169.5 (s; Me*C*O), 157.6 (s; CO Boc), 82.4 (s; CMe_3), 78.1 (d; $C_{[Glc]}$-1), 73.5 (d; $C_{[Glc]}$-5), 72.7 (d; $C_{[Glc]}$-4), 70.6 (d; $C_{[Glc]}$-2), 68.1 (d; $C_{[Glc]}$-3), 61.6 (t; $C_{[Glc]}$-6), 49.5 (t; C-5), 36.7 (t; $C_{[ch]}$-11), 34.9 (t; C-3), 34.4, 34.2, 29.6 (2 C), 29.5 (2 C), 29.3 (2 C), 29.1, 26.2, 25.2 (t, 11 C; C-2, $C_{[ch]}$-1, $C_{[ch]}$-2, $C_{[ch]}$-3, $C_{[ch]}$-4, $C_{[ch]}$-5, $C_{[ch]}$-6, $C_{[ch]}$-7, $C_{[ch]}$-8, $C_{[ch]}$-9, $C_{[ch]}$-10), 28.3 (q, 3 C; CH_3 Boc), 22.7 (t; C-4), 20.8 (q; *C*H_3CO), 20.7 (q; *C*H_3CO), 20.6 (q, 2 C; *C*H_3CO) ppm. IR: $\tilde{\nu}$ = 3427, 2930, 2855, 1746, 1694, 1369, 1227, 1039 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 724 (7), 366 (9), 244 (11), 169 (87), 109 (77), 97 (55), 81 (94), 70

(34), 57 (100), 55 (80). $C_{36}H_{58}N_2O_{14}$ (742.85): calcd. C 58.21, H 7.87, N 3.77; found C 57.84, H 7.92, N 3.42.

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