Pergamon

Tetrahedron 56 (2000) 8855–8865

TETRAHEDRON

Stereoselective Synthesis of 5-(1-Hydroxyalkyl)-2-pyrrolidinones Utilizing Oxidation of 5-Alkylidene-2-pyrrolidinones to Acyliminium Ion Precursors

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Received 8 August 2000; accepted 18 September 2000

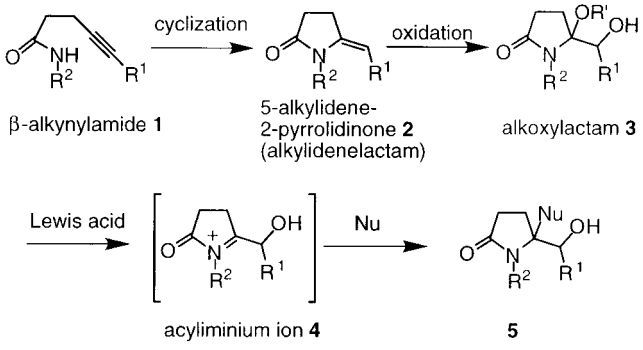
Abstract—A general method was devised for the $LiN(TMS)_2$/AgOTf (=2:1)-catalyzed intramolecular (5-*exo-dig*) cyclization of β-alkynylamides **1** possessing alkyl, aryl or no functional groups at the terminal alkynes, to 5-alkylidene-2-pyrrolidinones **2**. These 5-alkylidene-2-pyrrolidinones were oxidized to the diol-type alkoxylactams **3** by dimethyldioxirane (DMD) or *m*CPBA in MeOH. These alkoxylactams are useful as tertiary *N*-acyliminium ion precursors for the synthesis of *threo*-5-(1-hydroxyalkyl)-2-pyrrolidinone derivatives **5**.

Introduction

N-Acyliminium ions have high potential reactivity to various nucleophilic reagents, a fact which is reflected in the large number of synthetic applications of nitrogen heterocycles. Various methods have been described for the preparation of alkoxycarbamates and alkoxylactams as precursors of the *N*-acyliminium ion.[1] The most frequently used methods to achieve this are partial reduction of the corresponding carbonyl groups of imides, anodic methoxylation of amides, Grignard addition to the cyclic imides, and condensation of ketones or aldehydes with amides or amines.[1,2] On the other hand, one study also described oxidation of endocyclic enamides, a process which provides alkoxycarbamates, alkoxylactams or enamide epoxides as precursors of the *N*-acyliminium ion,[3] whereas only a few studies have investigated exocyclic enamides (such as alkylidenelactams **2**).[4] In such a reaction, oxidation of exocyclic enamides is expected to afford alkoxylactams, which are useful as tertiary *N*-acyliminium ion precursors[5,6] for the synthesis of 5- or 6-membered nitrogen heterocycles. However, as only one example of this type reaction, oxidation of ethylidenetetrahydro-1,3-oxazine-2-one by *m*CPBA (*m*-chloroperbenzoic acid) in MeOH has been reported by Back et al.[4a] and such a method has not been applied to synthesis of pyrrolidine or piperidine derivatives.

In our laboratory, a tertiary *N*-acyliminium ion precursor obtained by oxidation of methylideneisoindolone (exocyclic enamide) has been shown to be a useful intermediate for synthesis of isoindolobenzazepine alkaloids, such as lennoxamine or chilenine.[7] We applied this strategy to the synthesis of 2-pyrrolidinone derivatives, especially 5-(1-hydroxyalkyl)-2-pyrrolidinones **5**, via a tertiary *N*-acyliminium ion **4** derived from diol-type alkoxylactams **3**. These were obtained by oxidation of 5-alkylidene-2-pyrrolidinones **2** (Scheme 1).

We previously reported that alkylidenelactams **2** were readily obtained by base-catalyzed (5-*exo-dig*) cyclization of β-alkynylamides **1** in the presence or absence of AgOTf.[8] Herein, we describe the full experimental details of cyclization of **1** to **2** and a convenient method of the stereoselective synthesis of 5-(1-hydroxyalkyl)-2-pyrrolidinones derivatives **5** utilizing the conversion of alkylidenelactams **2** to the diol-type alkoxylactams **3** as a tertiary *N*-acyliminium ion precursor.



Scheme 1.

Keywords: acyliminium ion; cyclization; oxidation; pyrrolidinone.
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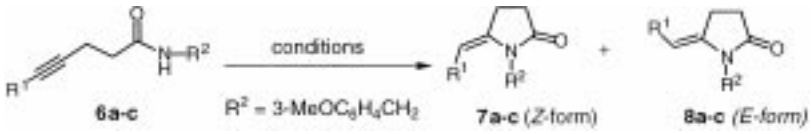
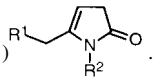
0040–4020/00/$ - see front matter
PII: S0040-4020(00)00841-3

Table 1. Intramolecular cyclization of β-alkynylamides to 5-alkylidene-2-pyrrolidinones



Run	Alkynylamide		Base (equiv.)	Additive (equiv.)	Solvent	Temp (C°)	Time (h)	Product	
	6	R^1						Yield (%)[a]	Isomer ratio[b] **7**(*Z*):**8**(*E*)
1	**6a**	4-$MeOC_6H_4$	LHMDS (1.0)	–	THF	66	18	**a** 42	(85:15)
2	**6a**	4-$MeOC_6H_4$	*n*-BuLi (1.0)	–	THF	0–66	10	**a** 8	(–)
3	**6a**	4-$MeOC_6H_4$	LHMDS (1.0)	–	DMF	60–65	3	**a** 64	(55:45)
4	**6a**	4-$MeOC_6H_4$	KHMDS (0.5)	18-crown-6 (0.4)	THF	rt	4	**a** 71	(64:36)
5	**6b**	H	NaHMDS (0.3)	18-crown-6 (0.3)	toluene	60	3	**b** 89[c]	(–)
6	**6c**	Me	KHMDS (0.3)	18-crown-6 (0.3)	THF	66	18	**c** 0	(–)
7	**6c**	Me	LHMDS (1.0)	–	DMF	60–65	5	**c** 0	(–)

[a] Isolated yield after purification by basic (NH–) silica gel column.
[b] Determined based on ^{1}H NMR spectra of the crude products.
[c] *Endo*-form **7b′** was accompained by the desired product **7b** (*exo*-**7b**/*endo*-**7b′**=14:1)



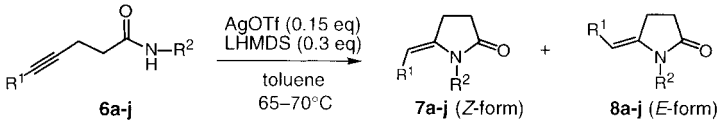
Discussion and Results

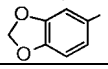
Synthesis of alkilidene-2-pyrrolidinones[8]

Very little research has been directed to the synthesis of lactams by the intramolecular cyclization of alkynylamides, such as Bu_4NF- or $LiAl(NHBn)_4$-catalyzed cyclization of alkynylamides,[9] cyclization of ω-phenylseleno-substituted alkynylamides by *t*-BuOK/18-crown-6,[10] and the synthesis of 1,3-oxazolidine-2-ones by base-catalyzed cyclization of alkynylcarbamates in the presence of Ag-, Cu-salt or Pd.[11] Recently, a similar (5-*exo-dig*) cyclization of 4-pentynamides was reported by Domínguez et al.[12] However, no such cyclization has been reported for β-alkynylamides **1** (R^1=alkyl) possessing alkyl groups at the terminal acetylenes. The cyclization of *o*-ethynylbenzamides derivatives under base conditions ($LiN(TMS)_2$ in THF) has been reported by our laboratory.[13] Hence, the authors sought to establish a general method for the base-catalyzed cyclization of β-alkynylamides **1**. In the initial experiments, we investigated the cyclization of β-alkynylamides **6** possessing aryl, hydrogen or alkyl groups at the terminal alkynes under base conditions. The results are shown in Table 1.

Firstly, following a method similar to the one outlined above ($LiN(TMS)_2$ in THF), cyclization of aryl-substituted alkynylamide **6a** was conducted to provide a moderate yield of **7a** and **8a** (Run 1). When DMF was used, the yield increased but product isolation from DMF was sluggish (Run 3). $KN(TMS)_2$/18-crown-6 in THF at room temperature gave the best result (Run 4). In the case of possessing hydrogen, cyclization of **6b** under a catalytic amount of base and mild conditions proceeded more readily than that of **6a** to afford the mixture of *exo*-**7b** and *endo*-**7b′** (14:1) (Run 5). The use of a slightly more basic medium (e.g. $KN(TMS)_2$ in THF)

Table 2. Intramolecular cyclization of β-alkynylamides to 5-alkylidene-2-pyrrolidinones utilizing the catalytic AgOTf/LHMDS-system



Run	Alkynylamide			Time (h)	Product	
	6a–i	R^1	R^2		Isomer ratio **7**(*Z*):**8**(*E*)[a]	Yield (%)[b]
1	**6a**	4-$MeOC_6H_4$	3-$MeOC_6H_4CH_2$	3	96:4	85
2	**6b**	H	3-$MeOC_6H_4CH_2$	3	–	86
3	**6c**	Me	3-$MeOC_6H_4CH_2$	3	100:0	89
4	**6d**	Me	CH_3(Ph)CH (*S*)	3	100:0	89
5	**6e**	Me	$MeOCH_2$(Ph)CH (*R*)	4	100:0	88
6	**6f**	Me		3	100:0	85
7	**6g**	$Cl(CH_2)_3$	3-$MeOC_6H_4CH_2$	4	100:0	84
8	**6h**	*n*-$C_{12}H_{25}$	3-$MeOC_6H_4CH_2$	3	100:0	89
9	**6j**	4-ClC_6H_4	3-$MeOC_6H_4CH_2$	3	97:3	88
10	**6j**		$BnOCH_2CH_2$	3	86:14	89

[a] Determined based on ^{1}H NMR spectra of the crude products.
[b] Isolated yield after purification by basic (NH–) silicagel column.

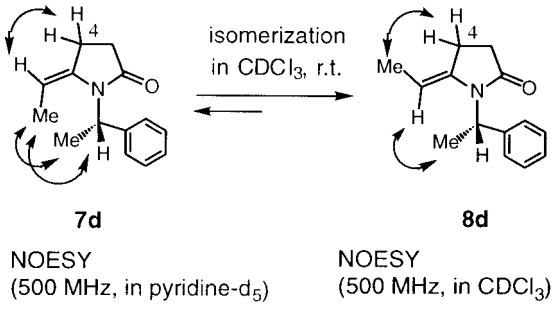
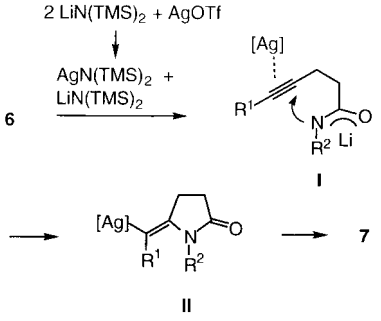


Figure 1. NOE Correlation of **7d** (*Z*-form) and **8d** (*E*-form).



Scheme 2.

led to an increased ratio for the formation of *endo*-**7b′**. In contrast, alkynylamides **6c** having an alkyl group on the terminal alkyne produced no cyclized product in the presence of any bases or phase-transfer-conditions (Runs 6 and 7).

Hence, the authors sought to establish a general method for the base-catalyzed cyclization of β-alkynylamides **6** without influencing substituent (R=H, Ar, alkyl) on the terminal acetylene. The results are summarized in Table 2.

With the catalytic $LiN(TMS)_2$/AgOTf (=2:1) system in toluene, the cyclization of **6c** proceeded more efficiently to yield only a *Z*-form product **7c** (Run 3). The use of THF or dimethoxyethane as a solvent did not promote this cyclization. This catalytic system when used with various alkyl-substituted alkynylamides (R^1=H, chloropropyl, dodecyl, **6b**, **6g**, **6h**, respectively) or alkynylamides having bulky *N*-substituted alkynyl groups (**6d**, **6e**, **6f**) led to satisfactory yields and stereoselectivity (Runs 2, 4–8). Furthermore, when those having aryl-substituted alkynylamides (**6a**, **6i**, **6j**) were applied to this system, the cyclization proceeded smoothly to afford benzylidenelactams (**7a**, **7i**, **7j**, respectively) along with a trace amount of *E*-form **8a**, **8i**, **8j** (respectively) in good yields (85–89%, Runs 1, 9–10). This may have been due to the isomerization of **7** to the thermodynamically stable **8** that occurred during this reaction process.

However, (6-*exo*-*dig*) cyclization of 5-hexynamide to δ-valerolactam under the same conditions failed to occur.

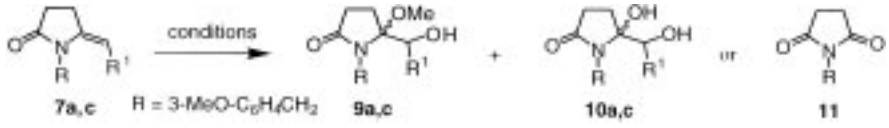
Compound **7** was found to have the *Z*-form structure by NOE (in pyridine-d_5),[14] a fact which was supported by examination of the isomerization of **7d** to the thermodynamically stable product **8d** (*E*-form) in $CDCl_3$ for 5–6 h (30% of *Z*-form converted to *E*-form)[14] or after standing at room temperature for 2 days (46% of *Z*-form converted to *E*-form) (Fig. 1).

The reaction mechanism for the present cyclization remains to be clarified. The $LiN(TMS)_2$/AgOTf (=1:1) system in toluene did not yield any product, thus suggesting the mechanism in Scheme 2. Reaction of **6** with silver- and lithium-amides ($AgN(TMS)_2{\cdot}LiN(TMS)_2$), prepared from a mixture of 1 equiv. of AgOTf and 2 equiv. of $LiN(TMS)_2$, produced the alkyne-Ag species complex and the lithium imidate **I**, which underwent *trans*-aminometallation[11f] to vinylmetal-species **II**, followed by protonolysis[11f] to afford **7**.

Oxidation of alkylidenelactams to alkoxylactams followed by reductive deoxygenation. Synthesis of 5-(1-hydroxyalkyl)-2-pyrrolidinones

The obtained 5-alkylidene-2-pyrrolidinones **7** were then applied to the oxidation reaction in order to produce the 5-alkoxy-2-pyrrolidinones **9**, **10** (diol-type alkoxylactams) as tertiary *N*-acyliminium ion precursors. The results are summarized in Table 3.

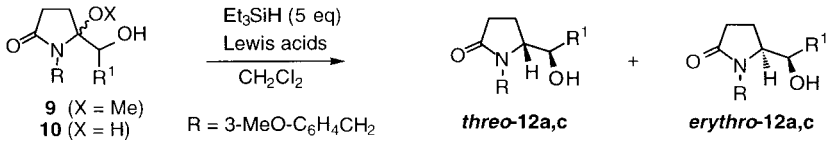
Table 3. Oxidation of 5-alkylidene- or 5-benzylidene-2-pyrrolidinones



Run		Substrate	Condition	Temp.		Product[a] and yield[b] (%)		
						9	**10**	**11**
1	**7a**	R^1=4-MeO–C_6H_4–	*m*-CPBA[c]/CH_2Cl_2	−60°C	**a**	0	0	50
2	**7a**	R^1=4-MeO–C_6H_4–	*m*-CPBA[c]/MeOH-CH_2Cl_2	0 to rt	**a**	83	0	trace
3	**7a**	R^1=4-MeO–C_6H_4–	DMD/acetone	−78 to −30°C	**a**	–	95	0
4	**7c**	R^1=Me	*m*-CPBA[c]/MeOH	0 to rt	**c**	93	0	trace
5	**7c**	R^1=Me	DMD/acetone	−78 to −30°C	**c**	–	96	0
6	**7c**	R^1=Me	DMD/MeOH	−78 to −30°C	**c**	76	17	0

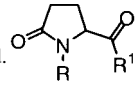
[a] All products (**9**, **10**) were various ratios of diastereomer mixtures.
[b] Isolated yields.
[c] The amount of *m*-CPBA used was 1.3 equiv.

Table 4. Reductive deoxygenation of quarternary methoxy- or hydroxy-lactams by Et_3SiH



Run	Substrate			Lewis acid	Temp.	Product		
		R^1	X			**12**	Yield (%)[a]	*threo:erythro*[b]
1	**9a**	4-MeO–C_6H_4–	Me	$TiCl_4$ (1.1 equiv.)	−60°C	**12a**	0[c]	–
2	**9c**	Me	Me	$TiCl_4$ (1.2 equiv.)	−78 to −20°C	**12c**	86	2:1
3	**9c**	Me	Me	$BF_3{\cdot}OEt_2$ (1.2 equiv.)	−78°C to rt	**12c**	0	–
4	**9c**	Me	Me	$BF_3{\cdot}OEt_2$ (2.2 equiv.)	−78°C to rt	**12c**	97	30:1
5	**10c**	Me	H	$BF_3{\cdot}OEt_2$ (2.2 equiv.)	−78°C to rt	**12c**	89	30:1

[a] Isolated yield after purification by silica gel column.
[b] Determined based on ^1H NMR spectra of the crude product.
[c] Ketone **13a** was given in 80% yield.



13a: R^1 = 4-MeO-C_6H_4-

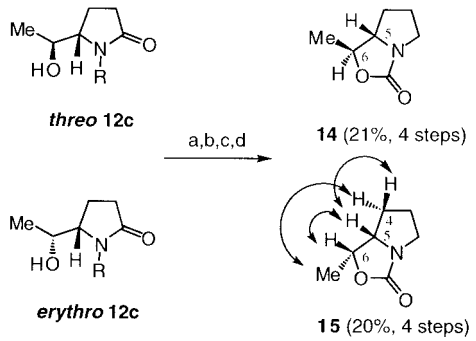
The oxidation of **7a** by *m*CPBA was examined. When done in CH_2Cl_2, an unexpected *N*-(3-methoxybenzyl)succinimide **11a** was obtained (Run 1).[15] According to Back's report,[4a] by carrying out the reaction in the presence of methanol, the desired methoxylactam **9a** could be obtained (Run 2). In contrast, the oxidation[7] of **7a** by DMD (dimethyldioxirane) even in the absence of MeOH proceeded more rapidly than that of *m*CPBA to afford only diol **10a** in 95% yield without inducing formation of **11a** (Run 3). Furthermore, the oxidation of **7c** (R^1=Me) under similar conditions also afforded **9c** and **10c** (by *m*CPBA/MeOH or DMD), both in a high yield (Runs 4–6).

Next, reductive deoxygenation of quarternary methoxy- or hydroxy-group by Et_3SiH[16] in these diol-type alkoxylactams (**9**, **10**) obtained from alkylidenelactams was investigated. The results are shown in Table 4.

Surprisingly, when **9a** possessing the hydroxybenzyl group (R^1=Ar) at the 5-position of the 2-pyrrolidinone ring was treated with $Et_3SiH/TiCl_4$ in CH_2Cl_2, only an unexpected ketone **13a** was found (Run 1). The elimination of benzylic proton via an acyliminium ion intermediate in the presence of Lewis acid would likely proceed rapidly to afford **13a**. In the case of **9c** possessing the hydroxyalkyl group (R^1=Me), the desired deoxygenation reaction via an acyliminium ion intermediate proceeded smoothly to give 5-(1-hydroxymethyl)pyrrolidinone **12c** in good yield (86%), although low *threo*-selectivity was observed (*threo*/*erythro*=2:1, Run 2). However, the use of 2.2 equiv. of $BF_3{\cdot}OEt_2$ instead of $TiCl_4$ provided high threo selectivity (*threo*/*erythro*= 30:1, Run 4).[16] Furthermore, the same *threo*-selectivity was observed during reductive deoxygenation of hydroxylactam **10c** (Run 5).

To determine the structure of the products, the two isomers, *threo*-**12c** and *erythro*-**12c**, were converted to bicyclo-rings **14** and **15**, respectively. Their relative stereochemistries were confirmed by the NOESY spectral data measured in $CDCl_3$ (Scheme 3).

Given that the use of 1.2 equiv. of $BF_3{\cdot}OEt_2$ failed to yield any product (Table 4, Run 3), the stereochemical product of these reductive deoxygenations via an acyliminium ion can be rationalized based on a conformation whereby the hydroxy group coordinated with BF_3 and occupied the 'outside position' to the iminium double bond in order to minimize the electronic repulsion between the positively charged hydroxy group and the iminium ion.[17] This arrangement allows the attack of Et_3SiH from the less hindered



Scheme 3. *Reagent and conditions:* a. $LiAlH_4$, THF rt, 10 h; b. cat. 20%$Pd(OH)_2/H_2$ (1.5 atm), MeOH, 2 days; c. Cbz-Cl, Et_3N, CH_2Cl_2, rt, 10 h; d. K_2CO_3, 18-crown-6, THF, reflux, 10 h.

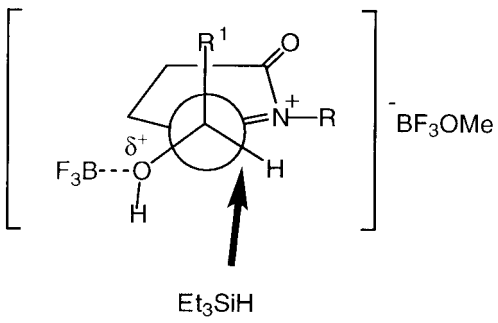
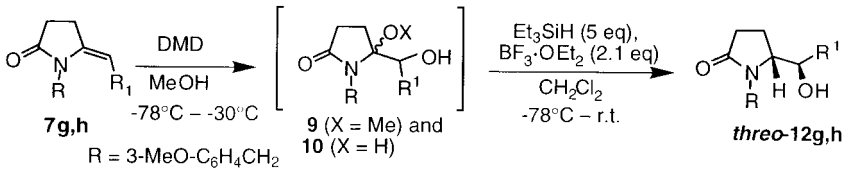


Figure 2. Plausible transition-state structure.

Table 5. Conversion of alkylidenelactams to 5-(1-hydroxy)alkyl-2-pyrrolidinones



Run		Substrate	Ratio of isomer, *threo*:*erythro*	Product and yield (%)	
1	**7g**	R^1=Cl(CH_2)$_3$	99:1	**12g**	71
2	**7h**	R^1=$C_{12}H_{25}$	99≫1	**12h**	77

bottom face and leads to the preferential formation of *threo* product (Fig. 2).

However, the use of $TiCl_4$ resulted in low *threo*-selectivity, the reason for which is not understood at present.

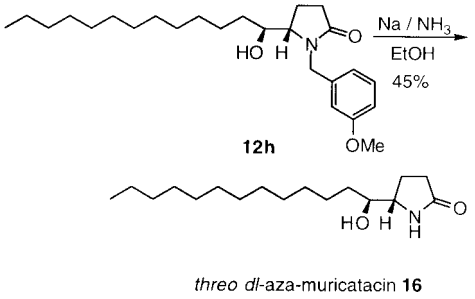
Next, an attempt was made to apply this method to the synthesis of other *threo*-5-(1-hydroxyalkyl)pyrrolidinones **12**, especially aza-muricatacin **16**, which is an aza-analogue of (+)-muricatacin that shows in vitro cytotoxic activity.[18a,b] The conversion of alkylidenelactams **7** to *threo*-5-(1-hydroxyalkyl)pyrrolidinones **12** by the successive procedure (oxidation followed by reductive deoxygenation) is shown in Table 5.

Chloropropylidenelactam **7g** was oxidized by DMD in MeOH to afford the mixture consisting of alkoxylactams **9** and **10**, not followed by purification, which was treated with Et_3SiH in the presence of BF_3·OEt_2 to give **12g** in 71% yield with a high *threo*-selectivity (99:1, Run 1). In the same manner, dodecylidenelactam **7h** afforded *N*-benzyl-*threo*-aza-muricatacin **12h** as the sole product (Run 2).

Finally, debenzylation of **12h** by Birch reduction[19] gave *threo*-DL-aza muricatacin **16** in 45% yield (Scheme 4). The spectral data of synthetic **16** showed complete agreement with those of *threo*-form aza-muricatacin reported in the literature.[18a,c]

Conclusion

In conclusion, the authors have established a new method for the efficient intramolecular cyclization of β-alkynylamides to 5-alkylidene-2-pyrrolidinones. The alkylidenelactames obtained in the present study have been shown to be useful as *N*-acyliminium ion precursors for the synthesis of α-substituted pyrrolidine derivatives.



threo dl-aza-muricatacin **16**

Scheme 4. *threo* -aza-muricatacin **16**.

Experimental

General

AgOTf was purchased from Aldrich Chemical company without further purification. DMD (dimethyldioxirane)–acetone solution (ca. 0.078 M) was prepared according to Adam's method.[20] Tetrahydrofuran (THF) and toluene were distilled from Na/benzophenone ketyl. Dichloromethane was distilled from P_2O_5. Flash chromatography was performed using Fuji Silysia silica gel BW 127 ZH and BW 300, and Chromatorex® as the basic silica gel (NH-silica gel). Melting points were uncorrected. IR spectra of solids were recorded as KBr pellets, and IR spectra of oil were recorded as thin films on NaCl plates. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz or 400 and 100 MHz, respectively in $CDCl_3$ with TMS as an internal standard. The NMR assignments for compounds **7d**, **8d**, **14** and **15** were based on 2D NMR experiments (NOE).

Preparation of 4-pentynamides 6a, b, i, j

5-Arylsubstituted 4-pentynamides **6a**, **i**, **j** and 4-pentynamide **6b** were prepared as reported previously.[21]

***N*-(3-Methoxybenzyl)-5-(4-methoxyphenyl)-4-pentynamide (6a).** Mp 97–98°C (from AcOEt–*i*Pr_2O, colorless crystal); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.51 (t, J=7.0 Hz, 2H), 2.77 (t, J=7.0 Hz, 2H), 3.76 (s, 3H), 3.80 (s, 3H), 4.46 (d, J=5.8 Hz, 2H, $ArCH_2$), 6.03 (br, 1H), 6.77–6.89 (m, 5H), 7.17–7.24 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.9, 35.8, 43.6, 55.1, 55.2, 81.5, 86.7, 112.9, 113.3, 113.8, 115.4, 120.0, 129.7, 132.9, 139.6, 159.2, 159.8, 171.1; IR (KBr) cm^{-1}: 3295, 1620, 1600, 1240; MS *m*/*z*: 323 (M^+); Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.16; H, 6.55; N, 4.47.

***N*-(3-Methoxybenzyl)-4-pentynamide (6b).** Mp 64–65°C (from AcOEt–*i*Pr_2O, colorless crystal); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.00 (t, J=2.6 Hz, 1H, C≡CH), 2.44 (m, 2H), 2.51 (m, 2H), 3.80 (s, 3H), 4.44 (d, J=5.8 Hz, 2H, $ArCH_2$), 5.93 (br, 1H), 6.80–6.89 (m, 3H), 7.25 (dt, J=1.0, 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.3, 35.8, 44.0, 55.6, 69.8, 83.4, 113.3, 113.8, 120.4, 130.1, 140.1, 160.3, 171.2; IR (KBr) cm^{-1}: 3380, 1630, 1260, 1050; MS *m*/*z*: 217 (M^+);

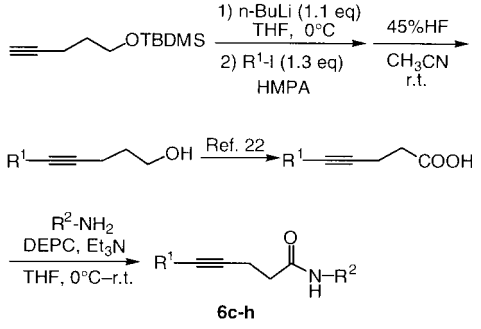
Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.89; H, 6.96; N, 6.45. Found: C, 71.78; H, 7.01; N, 6.45.

***N*-(3-Methoxybenzyl)-5-(4-chlorophenyl)-4-pentynamide (6i).** Mp 108.5–109.0°C (from iPr$_2$O–hexane, colorless crystal); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.51 (t, J=7.1 Hz, 2H), 2.79 (t, J=7.1 Hz, 2H), 3.76 (s, 3H), 4.46 (d, J=5.7 Hz, 2H, $ArCH_2$), 5.94 (b, 1H), 6.80–6.89 (m, 3H), 7.18–7.27 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.9, 35.5, 43.6, 55.1, 80.5, 89.4, 112.8, 113.4, 119.9, 121.8, 128.4, 129.7, 132.7, 133.7, 139.6, 159.8, 170.9; IR (KBr) cm^{-1}: 3300, 1640, 1500, 1265; MS m/z: 327 (M^+, Cl^{35}), 329 (M^+, Cl^{37}); Anal. Calcd for $C_{19}H_{18}NO_2Cl$: C, 69.62; H, 5.53; N, 4.27. Found: C, 69.62; H, 5.56; N, 4.17.

***N*-[2-(Benzyloxy)ethyl]-5-(3,4-methylenedioxyphenyl)-4-pentynamide (6j).** Mp 99–100°C (from AcOEt–hexane, colorless crystal); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.46 (uneven t, $J\cong$7.2 Hz, 2H), 2.72 (uneven t, $J\cong$7.2 Hz, 2H), 3.49–3.60 (m, 4H), 4.49 (s, 2H), 5.95 (s, 2H), 6.06 (b, 1H), 6.70 (d, J=8.0 Hz, 1H), 6.84 (d, J=1.5 Hz, 1H), 6.90 (dd, J=1.5, 8.0 Hz, 1H), 7.27–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.8, 35.7, 39.4, 68.9, 73.1, 81.3, 86.6, 101.1, 108.3, 111.6, 116.7, 126.0, 127.7, 127.8, 128.5, 137.8, 147.3, 147.4, 171.2; IR (KBr) cm^{-1}: 3310, 1640, 1220, 1100; MS m/z: 351 (M^+); Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.81; H, 6.17; N, 4.07.

Preparation of 4-pentynamides 6c–h

5-Alkylsubstituted 4-pentynamides **6c–h** were prepared according to the procedures outline below.



***N*-(3-Methoxybenzyl)-4-hexynamide (6c).** To a solution of *O*-silylated 4-pentyn-1-ol (6.19 g, 31.23 mmol) in THF (30 ml) under Ar was added dropwise *n*-BuLi in hexane (1.52 M, 22.6 ml, 34.35 mmol) at −5°C. After the solution was stirred for 1.5 h, MeI (5.76 g, 40.60 mmol) in HMPA (15 ml) was added dropwise at the same temperature. The reaction mixture was stirred at rt for 10 h, quenched with ice-water and the mixture was extracted with Et_2O according to a conventional work-up. The residue was chromatographed (silica gel, hexane–iPr$_2$O=15:1) to give *O*-silylated 4-hexyn-1-ol (5.92 g, 90%) as a colorless oil, which was used in the next step. To a solution of *O*-silylated 4-hexyn-1-ol (5.92 g, 27.9 mmol) in MeCN (100 g) was added 45% HF (8 g) at 0°C. The reaction mixture was stirred at rt for 0.5 h, quenched by adding sat. $NaHCO_3$ and the mixture was extracted with Et_2O, washed with sat. NaCl, dried over $MgSO_4$, filtered and then evaporated at 40°C under reduced pressure (200–100 mmHg) to give a crude product, which was used in the next step without further purification. To a solution of this crude product and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) (305 mg, 1.95 mmol) in MeCN (176 ml) and phosphate buffer (132 ml, pH=6.86) was added 5% NaClO (0.79 ml) in H_2O (14.9 ml) and $NaClO_2$ (5.05 g, 55.8 mmol) in H_2O (36 ml) simultaneously over 2 h at 37°C.[22] After the mixture was stirred at 37°C for 3 h, cooled at 0°C, diluted with water (100 ml), quenched by adding 10% $Na_2S_2O_3$ and then acidified to pH 2–3 by adding 5% HCl. After further addition of 10% $Na_2S_2O_3$, the mixture was extracted with *t*-BuOMe according to a conventional work-up to give a white solid. The crude solid was recrystallized from hexane to give 4-hexynoic acid (2.4 g, 76%) as a colorless crystal. Mp 95–96°C.[23] Condensation of 4-hexynoic acid (1.18 g, 10.5 mmol) with 3-methoxybenzylamine (1.44 g, 10.5 mmol) was carried out according to Shioiri's method[24] to give **6c** (2.33 g, 96%). Mp 100–101°C (from iPr$_2$O–hexane, colorless crystal); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.71 (t, J=2.5 Hz, 3H, ≡CCH_3), 2.38 (m, 2H), 2.49 (m, 2H), 3.79 (s, 3H), 4.43 (d, J=5.6 Hz, 2H, $ArCH_2$), 6.00 (br, 1H), 6.78–6.89 (m, 3H), 7.24 (t, J=7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 3.35, 15.3, 35.9, 43.6, 55.2, 77.6, 112.8, 113.4, 119.9, 129.7, 139.8, 159.9, 171.3; IR (KBr) cm^{-1}: 3270, 1630, 1590, 1260, 1050; MS m/z: 231 (M^+); Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.53; H, 7.39; N, 6.01.

***N*-[(1S)-1-phenylethyl]-4-hexynamide (6d).** Mp 96–98°C (from iPr$_2$O–hexane, colorless crystal); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.50 (d, J=6.8 Hz, 3H), 1.72 (t, J=2.5 Hz, 3H, ≡CCH_3), 2.34 (m, 2H), 2.47 (m, 2H), 5.15 (m, 1H, PhCH), 6.05 (br, 1H), 7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 3.35, 15.3, 21.8, 35.9, 48.7, 77.1, 77.7, 126.1, 127.2, 128.6, 143.1, 171.0; IR (KBr) cm^{-1}: 3260, 1640, 1540; MS m/z: 215 (M^+); $[\alpha]_D^{23}$=−87.16 (c 1.01, toluene); Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.19; H, 7.92; N, 6.50.

***N*-[(1R)-2-Methoxy-1-phenylethyl]-4-hexynamide (6e).** Mp 81–82°C (from iPr$_2$O–hexane, colorless crystal); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.76 (t, J=2.5 Hz, 3H), 2.40–2.50 (m, 4H), 3.36 (s, 3H), 3.68 (d, J=4.7 Hz, 2H), 5.19 (m, 1H, PhCH), 6.49 (br, 1H), 7.25–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 3.36, 15.2, 35.9, 52.5, 59.0, 75.0, 77.7, 126.7, 127.3, 128.4, 139.9, 171.0; IR (KBr) cm^{-1}: 3280, 1640, 1540, 1120; MS m/z: 245 (M^+); $[\alpha]_D^{26}$=−25.4 (c 1.02, toluene); Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.37; H, 7.74; N, 5.74.

***N*-[(1R)-2-(1,1-dimethylpropyl)oxy-1-phenylethyl]-4-hexynamide (6f).** Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.79 (t, J=7.5 Hz, 3H), 1.07 (s, 3H), 1.08 (s, 3H), 1.46 (q, J=7.4 Hz, 2H), 1.77 (t, J=2.5 Hz, 3H, ≡CCH_3), 2.40–2.52 (m, 4H), 3.56 (dd, J=4.1, 9.1 Hz, 1H), 3.62 (dd, J=4.1, 9.1 Hz, 1H), 5.10 (m, 1H, PhCH), 6.53 (br, 1H), 7.20–7.40 (m, 5H); IR (neat) cm^{-1}: 3270, 2950, 2900, 1640, 1540; MS m/z: 302 (M^+-1); $[\alpha]_D^{21}$=−9.83 (c 0.99, toluene).

***N*-(3-Methoxybenzyl)-8-chloro-4-octynamide (6g).** Mp 43–44°C (from iPr$_2$O–hexane, colorless crystal); ^{1}H NMR

(300 MHz, $CDCl_3$) δ: 1.85 (m, 2H), 2.28 (m, 2H), 2.38 (m, 2H), 2.50 (m, 2H), 3.58 (t, J=6.3 Hz, 2H, $ClCH_2$), 3.79 (s, 3H), 4.42 (d, J=6.3 Hz, 2H, $ArCH_2$), 6.10 (br, 1H), 6.82 (m, 3H, Ar-H), 7.24 (t, J=7.7 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.2, 16.0, 31.4, 35.8, 43.5, 43.7, 55.2, 79.5, 79.6, 112.7, 113.5, 119.9, 129.7, 139.7, 159.8, 171.2; IR (KBr) cm^{-1}: 3360, 2900, 1640, 1610, 1590, 1540, 1480, 1430, 1290, 1250, 1210, 1150; MS *m/z*: 293 (M^+).

***N*-(3-Methoxybenzyl)-4-heptadecynamide (6h).** Mp 83–84°C (from AcOEt–hexane, colorless crystal); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, J=6.7 Hz, 3H), 1.20–1.45 (m, 20H), 2.08 (m, 2H), 2.41 (m, 2H), 2.52 (m, 2H), 3.81 (s, 3H), 4.44 (d, J=5.8 Hz, 2H, $ArCH_2$), 6.04 (br, 1H), 6.80–6.90 (m, 3H), 7.25 (t, J=7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 15.4, 18.6, 22.7, 28.9, 29.1, 29.3, 29.5, 29.6, 31.9, 36.1, 43.6, 55.2, 78.4, 82.0, 112.8, 113.4, 119.9, 129.7, 139.8, 159.9, 171.4; IR (KBr) cm^{-1}: 3270, 2900, 1630, 1540, 1460; MS *m/z*: 385 (M^+); Anal. Calcd for $C_{25}H_{39}NO_2$: C, 77.87; H, 10.19; N, 3.63. Found: C, 77.59; H, 10.25; N, 3.68.

(*Z*)-*N*-(3-Methoxybenzyl)-5-(4-methoxybenzylidene)-2-pyrrolidinone (7a) and (*E*)-*N*-(3-methoxybenzyl)-5-(4-methoxybenzylidene)-2-pyrrolidinone (8a). A mixture of **6a** (100 mg, 0.31 mmol), 18-crown-6 (20 mg, 0.12 mmol), KHMDS (31 mg, 0.15 mmol) and THF (1.5 ml) was stirred under Ar at rt for 3 h. The reaction was quenched by adding 10% citric acid solution, and the mixture was extracted with AcOEt. The organic phase was washed with sat. NaCl, dried over $MgSO_4$, filtered and then evaporated. The residue was chromatographed (basic silica gel, hexane–AcOEt=8:1) to give **7a** and **8a** (71 mg, 71%; **7a/8a**=64:36).

7a(*Z*): Mp 79–80°C (from AcOEt–hexane, colorless crystal); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.62 (m, 2H), 2.79 (m, 2H), 3.67 (s, 3H), 3.79 (s, 3H), 4.57 (s, 2H, $ArCH_2$), 5.61 (s, 1H, =CH), 6.10 (s, 1H, H_{arom}), 6.27 (d, J=7.5 Hz, 1H, H_{arom}), 6.65–6.73 (m, 3H), 6.84 (d, J=7.8 Hz, 2H, H_{arom}), 7.00 (t, J=7.9 Hz, 1H, H_{arom}); IR (KBr) cm^{-1}: 1700, 1660, 1350, 1240; MS *m/z*: 323 (M^+); Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.18; H, 6.56; N, 4.35.

8a(*E*): Mp 80–81°C (from AcOEt–hexane, colorless crystal); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.65 (m, 2H), 2.97 (m, 2H), 3.77 (s, 6H), 4.77 (s, 2H, $ArCH_2$), 5.70 (s, 1H, =CH), 6.77–6.87 (m, 5H), 7.09 (d, J=8.8 Hz, 2H), 7.23 (t, J=7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.6, 28.9, 43.7, 55.0, 55.1, 103.4, 112.3, 112.8, 113.7, 119.2, 128.6, 129.0, 129.5, 137.5, 139.7, 157.3, 159.7, 175.3; IR (KBr) cm^{-1}: 2950, 1710, 1650, 1520, 1250; MS *m/z*: 323 (M^+); Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.17; H, 6.48; N, 4.37.

General procedure for the preparation of 5-alkylidene-2-pyrrolidinone (7a, c–j) utilizing LHMDS/AgOTf system

(*Z*)-*N*-(3-Methoxybenzyl)-5-ethylidene-2-pyrrolidinone (7c). To a solution of alkynylamide **6c** (2.01 g, 8.72 mmol) and AgOTf (336 mg, 1.31 mmol) in toluene (45 ml) stirred under Ar a solution of $LiN(TMS)_2$ in hexane (1.0 M, 2.62 ml, 2.62 mmol) was added slowly at rt. After 0.5 h, the mixture, which consisted of a clear solution and a black-brown paste, was stirred at 65–70°C for 3 h, whereupon the system became a black suspension. The reaction mixture was quenched with ice-water, diluted with AcOEt and filtered through celite by suction. The filtrate was extracted with AcOEt. The organic phase was washed with sat. NaCl, dried over $MgSO_4$, filtered and then evaporated. The residue was chromatographed (basic silica gel, hexane–AcOEt=15:1) to give **7c** (1.75 g, 89%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.57 (dt, J=7.5, 1.6 Hz, 3H, CH_3), 2.56 (m, 2H), 2.64 (m, 2H), 3.79 (s, 3H), 4.48 (tq, J=1.6, 7.5 Hz, 1H, CH=), 4.92 (s, 2H, $ArCH_2$), 6.69 (s, 1H, H_{arom}), 6.73–6.80 (m, 2H), 7.24 (t, J=7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.2, 26.2, 29.3, 45.0, 55.1, 96.4, 111.8, 111.9, 118.1, 129.6, 137.6, 139.2, 159.8, 177.2; IR (neat) cm^{-1}: 2950, 1720, 1670, 1600; MS *m/z*: 231 (M^+); Anal. Calcd for $C_{14}H_{17}NO$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.48; H, 7.32; N, 5.96.

(*Z*)-*N*-[(1*S*)-(1-phenylethyl)]-5-ethylidene-2-pyrrolidinone (7d). Cyclization of **6d** (72 mg, 0.33 mmol) under the same conditions described in the general procedure and subsequent chromatography (basic silica gel, hexane–AcOEt=15:1) gave **7d** (64 mg, 89%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.36 (dt, J=7.5, 1.6 Hz, 3H, CH_3C=), 1.79 (d, J=7.1 Hz, 3H), 2.40–2.70 (m, 4H), 4.51 (tq, J=1.6, 7.5 Hz, 1H, CH=), 5.62 (q, J=7.1 Hz, 1H, PhCH), 7.20–7.36 (m, 5H); ^{1}H NMR (300 MHz, pyridine-d_5) δ: 1.23 (d, J=7.4 Hz, 3H, CH_3C=), 1.66 (d, J=7.1 Hz, 3H), 2.20–2.40 (m, 4H), 4.25 (q, J=7.4 Hz, 1H, CH=), 5.60 (q, J=7.1 Hz, 1H, PhCH), 7.10–7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.3, 18.2, 28.4, 30.5, 51.7, 97.4, 126.3, 126.8, 128.8, 138.3, 141.8, 177.9; IR (neat) cm^{-1}: 1730, 1670, 1310; MS *m/z*: 215 (M^+); $[\alpha]_D^{23}$=−5.97 (c 1.01, toluene); Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.00; H, 7.90; N, 6.49.

(*Z*)-*N*-[(1R)-(2-Methoxy-1-phenylethyl)]-5-ethylidene-2-pyrrolidinone (7e). Cyclization of **6e** (400 mg, 1.63 mmol) under the same conditions described in the general procedure and subsequent chromatography (basic silica gel, hexane–AcOEt=20:1) gave **7e** (353 mg, 88%). Mp 73–74°C (from iPr_2O–hexane, colorless crystal). ^{1}H NMR (300 MHz, $CDCl_3$) δ; 1.53 (d, J=7.4 Hz, 3H), 2.48 (m, 2H), 2.55–2.80 (m, 2H), 3.42 (s, 3H), 4.00 (dd, J=5.9, 9.7 Hz, 1H), 4.35 (dd, J=8.2, 9.7 Hz, 1H), 4.52 (q, J=7.4 Hz, 1H, CH=), 5.38 (dd, J=5.9, 8.2 Hz, PhCH), 7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) 12.3, 27.9, 30.3, 58.5, 58.7, 72.8, 96.8, 126.6, 127.2, 128.4, 138.4, 139.6, 178.0; IR (KBr) cm^{-1}: 2900, 1670, 1320; MS *m/z* 245 (M^+); $[\alpha]_D^{24}$=+70.1° (c 1.02, toluene); Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.42; H, 7.81; N, 5.68.

(*Z*)-*N*-[(1*R*)-2-[(1,1-Dimethylpropyl)oxy]-1-phenylethyl]-5-ethylidene-2-pyrrolidinone (7f). Cyclization of **6f** (300 mg, 0.99 mmol) under the same conditions described in the general procedure and subsequent chromatography (basic silica gel, hexane–AcOEt=20:1) gave **7f** (225 mg, 85%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.86 (t, J=7.4 Hz, CH_2CH_3), 1.12 (s, 3H), 1.13 (s, 3H), 1.49 (q, J=7.4 Hz, 2H, CH_2CH_3), 1.55 (dt, J=7.5, 1.5 Hz,

1H, CH_3C═), 2.46 (m, 2H), 2.63 (m, 2H), 3.93 (dd, *J*=5.5, 9.1 Hz, 1H), 4.25 (dd, *J*=8.2, 9.1 Hz, 1H), 4.51 (tq, J =1.5, 7.5 Hz, 1H, CH═), 5.26 (dd, *J*=5.5, 8.2 Hz, 1H, PhCH), 7.20–7.40 (m, 5H); IR (neat) cm^{-1}: 2960, 1720, 1670, 1310; MS *m/z*: 301 (M^+); $[\alpha]_D^{22}$=+30.47 (c 1.17, toluene); Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.68; H, 9.08; N, 4.72.

(*Z*)-*N*-(3-Methoxybenzyl)-5-(4-chlorobutylidene)-2-pyrrolidinone (7g). Cyclization of **6g** (199 mg, 0.68 mmol) under the same conditions described in the general procedure and subsequent chromatography (basic silica gel, hexane–AcOEt=15:1) gave **7g** (167 mg, 84%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.58 (m, 2H), 2.11 (m, 2H), 2.57 (m, 2H), 2.70 (m, 2H), 3.31 (t, *J*=6.6 Hz, 2H, $ClCH_2$), 3.79 (s, 3H), 4.32 (m, 1H, CH═), 4.91 (s, 2H), 6.73 (m, 3H), 7.24 (t, *J*=7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.1, 26.1, 29.1, 33.5, 44.2, 45.1, 55.2, 101.1, 111.8, 112.0, 118.0, 129.7, 137.5, 138.6, 159.9, 177.2; IR (neat) cm^{-1}: 2950, 1720, 1670, 1600, 1440, 1400, 1360, 1280; MS *m/z*: 293 (M^+).

(*Z*)-*N*-(3-Methoxybenzyl)-5-tridecylidene-2-pyrrolidinone (7h). Cyclization of **6h** (280 mg, 0.73 mmol) under the same conditions described in the general procedure and subsequent chromatography (basic silica gel, hexane–AcOEt=30:1) gave **7h** (250 mg, 89%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, *J*=7.0 Hz, 3H), 1.05–1.30 (m, 20H), 1.95 (m, 2H), 2.55 (m, 2H), 2.67 (m, 2H), 3.77 (s, 3H), 4.36 (t, *J*=7.0 Hz, 1H, CH═), 4.87 (s, 2H, $ArCH_2$), 6.65 (s, 1H, H_{arom}), 6.70–6.77 (m, 2H), 7.22 (t, *J*=7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.7, 25.7, 26.2, 29.0, 29.2, 29.3, 29.55, 25.59, 29.61, 29.64, 30.9, 31.9, 45.2, 55.1, 103.6, 111.8, 111.9, 118.1, 129.6, 136.2, 138.9, 159.9, 177.2. IR (neat) cm^{-1}: 2900, 1720, 1670, 1360; MS *m/z*: 385 (M^+); Anal. Calcd for $C_{25}H_{39}NO_2$: C, 77.87; H, 10.20; N, 3.63. Found: C, 77.78; H, 10.17; N, 3.64.

(*Z*)-*N*-(3-Methoxybenzyl)-5-(4-chlorobenzylidene)-2-pyrrolidinone (7i). Cyclization of **6i** (100 mg, 0.31 mmol) under the same conditions described in the general procedure and subsequent chromatography (basic silica gel, hexane–AcOEt=10:1) gave **7i** and **8i** (88 mg, 88%). Major product, **7i**(*Z*): mp 96–97°C (from tBuOMe–hexane, colorless crystal). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.64 (m, 2H), 2.81 (m, 2H), 3.68 (s, 3H), 4.55 (s, 2H, $ArCH_2$), 5.57 (s, 1H, ═CH), 6.06 (s, 1H, H_{arom}), 6.21 (d, *J*=8.0 Hz, 1H), 6.67 (dd, *J*=2.3, 8.0 Hz, 1H), 6.81 (d, *J*=8.1 Hz, 2H), 7.03 (t, *J*=8.0 Hz, 1H), 7.11 (d, *J*=8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.8, 29.1, 44.8, 55.0, 102.2, 111.6, 112.6, 118.4, 127.6, 129.0, 130.9, 132.1, 134.2, 137.5, 139.1, 159.4, 177.5; IR (KBr) cm^{-1}: 1720, 1660, 1600, 1260; MS *m/z*: 327 (M^+, Cl^{35}), 329 (M^+, Cl^{37}); Anal. Calcd for $C_{19}H_{18}NO_2Cl$: C, 69.61; H, 5.54; N, 4.27. Found: C, 69.57; H, 5.73; N, 4.34.

(*Z*)-*N*-[2-(Benzyloxy)ethyl]-5-(3,4-methylendioxybenzylidene)-2-pyrrolidinone (7j). Cyclization of **6j** (92 mg, 0.26 mmol) under the same conditions described in the general procedure and subsequent chromatography (basic silica gel, hexane–AcOEt=15:1) gave **7j** and **8j** (82 mg, 81%).

***N*-(3-Methoxybenzyl)-5-methylidene-2-pyrrolidinone (7b).** To a solution of **6b** (100 mg, 0.46 mmol) in toluene (1 ml) was added toluene solution (0.6 ml) of LHMDS/AgOTf complex generated from LHMDS (0.14 ml, 0.14 mmol, 1 M hexane-solution) and AgOTf (17.6 mg, 0.07 mmol) at rt, followed by the same manner described in the general procedure subsequent chromatography (basic silica gel, hexane–AcOEt=15:1) gave **7b** (86 mg, 86%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.60 (m, 2H), 2.72 (m, 2H), 3.79 (s, 3H), 4.13 (d, *J*=1.8 Hz, 1H, CH_2═), 4.20 (d, *J*=2.0 Hz, 1H, CH_2═), 4.65 (s, 2H, $ArCH_2$), 6.78–6.84 (m, 3H), 7.23 (t, *J*=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.7, 28.9, 43.5, 55.1, 85.4, 112.5, 113.0, 119.5, 129.5, 137.6, 146.2, 159.8, 175.9; IR (neat) cm^{-1}: 1620, 1660, 1600, 1400; MS *m/z*: 217 (M^+); Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.60; H, 6.96; N, 6.38.

***N*-(3-Methoxybenzyl)-5-[hydroxy(4-methoxyphenyl)-methyl]-5-methoxy-2-pyrrolidinone (9a).** To a solution of **7a** (527 mg, 1.63 mmol) in abs. MeOH (30 ml) and CH_2Cl_2 (15 ml) was added dropwise a solution of *m*CPBA (475 mg, 2.20 mmol) in CH_2Cl_2 (15 ml) at −50°C under Ar. The reaction mixture was allowed to stand at rt and then stirred for 1 h. The reaction was quenched by adding 10% $Na_2S_2O_3$ and sat. $NaHCO_3$ and the mixture was extracted with CH_2Cl_2. The organic phase was washed with sat. NaCl, dried over $MgSO_4$, filtered and then evaporated. The residue was chromatographed (silica gel, hexane–acetone=5:1) to give **9a** (498 mg, 83%) as a mixture of diastereomers (less polar/more polar=4.3:1). **9a** (less polar): colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ:1.51 (m, 1H), 2.30–2.50 (m, 4H+OH), 3.01 (s, 3H), 3.780 (s, 3H), 3.789 (s, 3H), 4.02 (d, *J*=15.0 Hz, 1H), 4.63 (d, *J*=3.5 Hz, 1H, *CH*(OH)), 4.97 (d, *J*=15.0 Hz, 1H), 6.79–7.32 (m, 8H). **9a** (more polar): mp 133–134°C (from toluene–hexane, colorless crystal). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.48 (m, 1H), 1.82 (m, 1H), 2.05–2.23 (m, 2H), 2.90 (d, *J*=3.1 Hz, 1H, OH, D_2O exchangeable), 2.91 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 4.46 (d, *J*=14.5 Hz, 1H), 4.69 (d, *J*=14.5 Hz, 1H), 4.84 (d, *J*=3.1 Hz, 1H, *CH*(OH), after D_2O exchange, d converted to s), 6.78–6.85 (m, 3H), 7.08–7.27 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.5, 29.3, 43.8, 49.7, 55.15, 55.21, 75.2, 97.9, 113.2, 113.5, 114.7, 121.6, 128.1, 129.4, 139.5, 159.3, 159.6, 175.4; IR (KBr) cm^{-1} 3340, 1680, 1250. MS *m/z*: 371 (M^+), 339 (M−MeOH); Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.95; H, 6.67; N, 3.54.

***N*-(3-Methoxybenzyl)-5-[hydroxy(4-methoxyphenyl)-methyl]-5-hydroxy-2-pyrrolidinone (10a).** To a DMD–acetone solution was added dropwise a solution of **7a** (169 mg, 0.523 mmol) in acetone (2 ml) at −78°C. The reaction mixture was allowed to warm to −30°C over 20 min, and an additional 15 min at the same temperature. The reaction mixture was cooled to ca. −60°C, and then quenched with 10% $Na_2S_2O_3$. After removal of organic solvents by a rotary evaporator, the residue was extracted with AcOEt, washed with sat. NaCl, dried over $MgSO_4$, filtered and then evaporated. The residue was chromatographed (silica gel, hexane–acetone=3:1–2:1) to give **10a** (178 mg, 95%) as a mixture of diastereomers (less polar/more polar=6:1). **10a** (less polar): colorless oil; ^1H NMR

(300 MHz, $CDCl_3$) δ: 1.53 (m, 2H), 2.16 (m, 2H), 2.9 (b, 1H, OH, D_2O exchangeable), 3.77 (s, 6H), 4.02 (b, 1H, OH, D_2O exchangeable), 4.50 (d, J=15.1 Hz, 1H), 4.66 (d, J=15.1 Hz, 1H), 4.67 (bs, 1H, *CH*(OH), after D_2O exchange, bs converted to s), 6.76–7.25 (m, 8H, Ar-H); **10a** (more polar): mp 121–122°C (from dist. $CHCl_3$–hexane, colorless crystal); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.58 (m, 1H), 2.10–2.21 (m, 1H+OH), 2.30–2.50 (m, 2H), 3.21 (b, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 4.45 (d, J=15.3 Hz, 1H), 4.69 (d, J=3.2 Hz, 1H, *CH*(OH)), 4.81 (d, J=15.3 Hz, 1H), 6.79–7.33 (m, 8H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.6, 29.1, 42.9, 55.2, 75.2, 94.1, 112.9, 113.5, 113.7, 120.0, 128.5, 129.9, 130.1, 140.2, 159.4, 159.9, 176.1; MS *m/z*: 358 (M^++1), 339 (M−H_2O); HRMS (EI) calcd for $C_{20}H_{21}NO_4$ (M^+-H_2O) 339.1471, found 339.1468.

***N*-(3-Methoxybenzyl)-5-(1-hydroxyethyl)-5-methoxy-2-pyrrolidinone (9c).** Oxidation of **7c** (681 mg, 2.94 mmol) in the same manner as described for **9a** and subsequent chromatography (silica gel, hexane–AcOEt=3:1) gave **9c** (766 mg, 93%) as a mixture of diastereomers (less polar/more polar=1:2.7). **9c** (less polar): colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.08 (d, J=6.4 Hz, 3H), 1.22 (b, OH, D_2O exchangeable), 1.88 (m, 1H), 2.45 (m, 1H), 2.50 (m, 2H), 3.07 (s, 3H), 3.71 (dq, J=2.6, 6.4 Hz, 1H, C*H*(OH), after D_2O exchange, dq converted to q, J=6.4 Hz), 3.78 (s, 3H), 3.83 (d, J=14.9 Hz, 1H), 4.92 (d, J=14.9 Hz, 1H), 6.82 (d, J=8.1 Hz, 1H, Ar–H), 6.99 (m, 2H, Ar–H), 7.27 (t, J=8.1 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.3, 21.0, 29.9, 42.3, 49.5, 55.6, 68.4, 99.5, 113.8, 114.0, 120.4, 129.9, 140.3, 160.4, 177.3; IR ($CHCl_3$) cm^{-1}: 3400, 2900, 1720, 1640, 1450; MS *m/z*: 279 (M^+). **9c** (more polar): mp 91–92°C (from AcOEt–hexane, colorless crystal); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.78 (d, J=6.4 Hz, 3H), 1.94 (m, 1H), 2.23 (m, 1H), 2.30 (s, 1H, OH, D_2O exchangeable), 2.47 (m, 2H), 3.00 (s, 3H), 3.78 (s, 3H), 3.94 (dq, J=2.6, 6.4 Hz, 1H, C*H*(OH), after D_2O exchange, dq converted to q, J=6.4 Hz), 4.07 (d, J=14.6 Hz, 1H), 4.61 (d, J=14.6 Hz, 1H), 6.79 (d, J=7.6 Hz, 1H), 6.96 (m, 2H), 7.20 (t, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.2, 20.9, 29.7, 43.4, 49.5, 55.6, 71.2, 98.9, 113.5, 114.9, 121.6, 129.8, 139.8, 160.0, 176.4; IR (KBr) cm^{-1}: 3330, 2900, 1660, 1600, 1400, 1260; MS *m/z*: 279 (M^+); Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.23; H, 7.51; N, 4.97.

***N*-(3-Methoxybenzyl)-5-hydroxy-5-(1-hydroxyethyl)-2-pyrrolidinone (10c).** Oxidation of **7c** (178 mg, 2.94 mmol) in the same manner as described for **10a** and subsequent chromatography (silica gel, hexane–acetone=2:1) gave **10c** (195 mg, 96%) as a mixture of diastereomers (2:1). Recrystallization from AcOEt–hexane gave a colorless crystal as a mixture of diastereomer (1.5:1*). The stereochemistry of each isomer was not assigned. Diastereomer mixture of **10c**: mp 117–120°C, ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.98 (d, J=6.4 Hz, 1H*), 1.15 (d, J=6.3 Hz, 1H), 1.53 (d, J=4.1 Hz, 1H, OH, D_2O exchangeable), 1.81–1.94 (m, 1H+1H*), 2.19 (d, J=3.6 Hz, 1H*, OH, D_2O exchangeable), 2.26–2.65 (m, 3H+3H*), 3.24 (s, 1H, OH, D_2O exchangeable), 3.49 (s, 1H*, OH, D_2O exchangeable), 3.79 (s, 3H+3H*), 3.78–3.90 (m, 1H+1H*, C*H*(OH), after D_2O exchange, m converted to q, J=6.5 Hz), 4.27 (d, J=15.4 Hz, 1H), 4.37 (d, J=15.4 Hz, 1H*), 4.62 (d, J=15.4 Hz, 1H*), 4.73 (d, J=15.4 Hz, 1H), 6.78–7.29 (m, 4H+4H*, Ar–H); IR (KBr) cm^{-1}: 3250, 3210, 1650, 1440, 1250; MS *m/z*: 265 (M^+), 247 (M−H_2O); Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.45; H, 7.20; N, 5.10.

***N*-(3-Methoxybenzyl)-5-(4-methoxybenzoyl)-2-pyrrolidinone (13a).** A CH_2Cl_2 (1 ml) solution of **9a** (98 mg, 0.26 mmol) and Et_3SiH (104 mg, 0.39 mmol) under Ar was cooled at −78°C, and $TiCl_4$ in CH_2Cl_2 (2.3 M, 0.13 ml, 0.29 mmol) was then added dropwise to the solution. The reaction mixture was allowed to warm to −20°C over 30 min, and then stirred at −20°C for 1 h. The reaction mixture was quenched with sat. $NaHCO_3$, extracted with CH_2Cl_2, washed with sat. NaCl, dried over $MgSO_4$, filtered and then evaporated. The residue was chromatographed (silica gel, hexane–AcOEt=4:1) to give **13a** (86 mg, 80%) as a dark yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.96 (m, 1H), 2.46 (m, 3H), 3.72 (s, 3H), 3.75 (d, J=14.8 Hz, 1H), 3.87 (s, 3H), 4.87 (dd, J=3.3, 9.1 Hz, 1H, CHN), 5.23 (d, J=14.8 Hz, 1H), 6.70 (d, J=1.9 Hz, 1H, H_{arom}), 6.73 (d, J=7.5 Hz, 1H), (dd, J=2.5, 8.1 Hz, 1H), 6.92 (m, 2H), 7.18 (t, J=7.5 Hz, 1H), 7.81 (m, 2H); IR (neat) cm^{-1}: 3050, 1730, 1650, 1480, 1300; MS *m/z*: 339 (M^+).

***threo* and *erythro*-*N*-(3-Methoxybenzyl)-5-(1-hydroxyethyl)-2-pyrrolidinone (12c).** *Reductive deoxygenation of **9c** by $Et_3SiH/TiCl_4$ (Run 2 in Table 4).* A CH_2Cl_2 (0.5 ml) solution of **9c** (50 mg, 0.18 mmol) and Et_3SiH (104 mg, 0.90 mmol) under Ar was cooled at −78°C, and $TiCl_4$ in CH_2Cl_2 (1.03 M, 0.21 ml, 0.21 mmol) was then added dropwise to the solution. The reaction mixture was allowed to warm to −20°C. over 30 min, and then stirred at −20°C for 2 h. The reaction mixture was quenched with sat. $NaHCO_3$, extracted with CH_2Cl_2, washed with sat. NaCl, dried over $MgSO_4$, filtered and then evaporated. The residue was chromatographed (silica gel, hexane–acetone=2:1) to give **12c** (38 mg, 86%) as an inseparable mixture of diastereomers (*threo*/*erythro*=2:1).

***erythro*-12c:** ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.08 (d, J=6.6 Hz, 3H, CH_3), 1.89 (m, 1H, CH_2), 2.06 (m, 1H, CH_2), 2.39 (m, 1H), 2.51 (m, 1H, CHN), 3.35 (m, 1H), 3.77 (s, 3H), 3.80 (b, 1H, OH, D_2O exchangeable), 4.06 (d, J=15.1 Hz, 1H), 4.14 (m, 1H, C*H*(OH)), 4.94 (d, J=15.1 Hz, 1H), 6.79 (m, 3H, H_{arom}), 7.23 (t, J=7.7 Hz, 1H);

***threo*-12c:** colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.10 (d, J=6.3 Hz, 3H, CH_3), 1.84 (m, 1H, CH_2), 1.99 (m, 1H, CH_2), 2.31 (b, 1H, OH, D_2O exchangeable), 2.31–2.54 (m, 2H), 3.49 (m, 1H, CHN), 3.78 (s, 3H), 3.92 (m, 1H, C*H*(OH), after D_2O exchange, m converted to quint, J=6.3 Hz), 4.22 (d, J=14.9 Hz, 1H), 4.91 (d, J=14.9 Hz, 1H), 6.80 (m, 3H, Ar–H), 7.22 (t, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.9, 20.5, 30.7, 46.2, 55.6, 62.5, 69.5, 113.1, 114.0, 120.6, 130.1, 138.9, 160.2, 176.4; MS *m/z*: 249 (M^+); HRMS (EI) calcd for $C_{14}H_{19}NO_3$ (M^+) 249.1365, found 249.1368.

*Reductive deoxygenation of **9c** by $Et_3SiH/BF_3{\cdot}OEt_2$ (Run 4 in Table 4).* A CH_2Cl_2 (4 ml) solution of **9c** (490 mg, 1.75 mmol) and Et_3SiH (1.1 g, 8.75 mmol) under Ar was

cooled at −78°C, and $BF_3{\cdot}OEt_2$ (0.49 ml, 3.85 mmol) was then added dropwise to the solution. The reaction mixture was allowed to warm to rt over 30 min, and then stirred overnight. The reaction mixture was cooled to 0°C, quenched with sat. $NaHCO_3$, extracted with CH_2Cl_2, washed with sat. NaCl, dried over $MgSO_4$, filtered and then evaporated. The residue was chromatographed (silica gel, hexane–acetone=2:1) to give **12c** (427 mg, 97%) as a mixture of diastereomers (*threo*/*erythro*=30:1).

***threo*-*N*-(3-Methoxybenzyl)-5-(4-chloro-1-hydroxybutyl)-2-pyrrolidinone (12g).** To a DMD–acetone solution was added dropwise the solution of **7g** (182 mg, 0.62 mmol) in abs. MeOH (2 ml) at −78°C. The reaction mixture was allowed to warm to −30°C over 20 min, and an additional 15 min at the same temperature. The reaction mixture was cooled to ca. −60°C, and then quenched by adding 10% $Na_2S_2O_3$. After removal of organic solvents by a rotary evaporator, the residue was extracted with AcOEt, washed with sat. NaCl, dried over $MgSO_4$, filtered and then evaporated to give a mixture of **9g** and **10g**. This crude mixture and Et_3SiH were dissolved in CH_2Cl_2 (2 ml) under Ar, and the solution was cooled at −78°C. $BF_3{\cdot}OEt_2$ (0.16 ml, 1.36 mmol) was added dropwise, and the reaction mixture was allowed to warm to rt over 30 min, and stirred overnight. The reaction mixture was cooled to 0°C, quenched with sat. $NaHCO_3$, extracted with CH_2Cl_2, washed with sat. NaCl, dried over $MgSO_4$, filtered and then evaporated. The residue was chromatographed (silica gel, hexane–acetone=2:1) to give **12g** (137 mg, 71%, *threo*/*erythro*=99:1). *threo*-**12g**: colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.56 (m, 3H, CH_2CH_2), 1.96 (m, 3H, CH_2CH_2), 2.42 (m, 3H, CH_2CH_2), 3.51 (t, J=6.4 Hz, 2H, $ClCH_2$), 3.54 (m, 1H, CHN), 3.68 (1H, m, C*H*(OH)), 3.79 (3H, s, $ArOCH_3$), 4.30 (d, J=15.0 Hz, 1H, $ArCH_2$), 4.82 (d, J=15.0 Hz, 1H, $ArCH_2$), 6.80 (m, 3H, Ar–H), 7.23 (t, J=7.4 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.4, 28.7, 29.1, 30.1, 44.8, 46.0, 55.1, 61.9, 72.3, 112.6, 113.6, 120.1, 129.7, 138.4, 159.8, 176.1; IR ($CHCl_3$) cm^{-1}: 3330, 2930, 1660, 1600, 1430, 1260, 1150; MS *m*/*z*: 311 (M^+).

***threo*-*N*-(3-Methoxybenzyl)-5-(1-hydroxytridecyl)-2-pyrrolidinone (12h).** Oxidation of **7h** (254 mg, 0.659 mmol) was followed by reductive deoxygenation in the same manner as described for **12g** and subsequent chromatography (silica gel, hexane–acetone=3:1) gave *threo*-**12h** (205 mg, 77%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, J=6.7 Hz, 1H), 1.20–1.45 (m, 1H), 1.53 (d, J=5.4 Hz, 1H, OH), 1.87 (m, 1H), 2.02 (m, 1H), 2.34–2.57 (m, 2H), 3.53 (m, 1H), 3.63 (m, 1H, CHOH), 3.79 (s, 3H), 4.29 (d, J=14.9 Hz, 1H), 4.86 (d, J=14.9 Hz, 1H), 6.79–6.84 (m, 2H), 7.24 (t, J=7.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 20.5, 22.6, 25.8, 29.3, 29.55, 29.60, 30.2, 31.9, 32.0, 46.0, 55.2, 61.7, 73.3, 112.7, 113.5, 120.1, 129.6, 138.7, 159.8, 176.0; IR (neat) cm^{-1}: 3350, 2900, 1660, 1600, 1460, 1260; MS *m*/*z*: 403 (M^+); Anal. Calcd for $C_{14}H_{19}NO_4$: C, 74.40; H, 10.24; N, 3.47. Found: C, 74.28; H, 10.11; N, 3.39.

***threo*-5-(1-Hydroxytridecyl)-2-pyrrolidinone (*threo* DL-Aza-muricatacin) (16).**[18a,c] Ammonia was condensed into a stirred solution of **12h** (100 mg, 0.25 mmol) in THF (2 ml) and abs. EtOH (0.15 ml) at −78°C. To the resulting cold (−30°C), was added enough lithium to produce a dark blue color, and the solution was let stand for an additional 40 min at the same temperature. The reaction was then quenched by the addition of a small amount of NH_4Cl (solid). The resulting white solution was allowed to warm to rt over 1 h. After removal of organic solvents by a rotary evaporator, the residue was diluted with water, extracted with $CHCl_3$, washed with sat. NaCl, dried over $MgSO_4$, filtered and then evaporated. The residue was chromatographed (silica gel, hexane–acetone=2:1) to give **16** (31 mg, 45%). Mp 78.3–78.5°C (from AcOEt–hexane, colorless crystal); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, J=6.6 Hz, 3H), 1.20–1.50 (m, 22H), 1.77 (m, 1H), 2.16 (m, 1H), 2.36 (m, 2H), 3.14 (d, J=6.1 Hz, 1H, OH, D_2O exchangeable), 3.36 (m, 1H, CH–N), 3.53 (t, J=7.0 Hz, 1H, C*H*(OH)), 6.86 (bs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.7, 23.8, 25.4, 29.3, 29.59, 29.64 (several C), 30.5, 31.9, 33.4, 59.6, 75.3, 178.7; IR (KBr) cm^{-1}: 3400, 3200, 2900, 2850, 1690, 1460; MS *m*/*z*: 283 (M^+); Anal. Calcd for $C_{17}H_{33}NO_2$: C, 72.04; H, 11.73; N, 4.94. Found: C, 71.89; H, 11.69; N, 5.09.

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