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5-Aminooxazole as an Internal Traceless Activator of C-Terminal Carboxylic Acid: Rapid Access to Diversely Functionalized Cyclodepsipeptides

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Abstract: A conceptually novel macrolactonization protocol has been developed. It is a domino process involving a sequence of: 1) protonation of 5-aminooxazole leading to the electrophilic iminium salt; 2) trapping of the iminium species by the neighboring C-terminal carboxylic acid leading to a putative spirolactone; and 3) intramolecular nucleophilic addition of the tethered alcohol to the spirolactone followed by fragmentation. The strategically incorporated 5-aminooxazole serves as an internal traceless activator of the neighboring C-terminal carboxylic acid, since it became an integral part of the peptide backbone after cyclization. No coupling reagent is required and the entire sequence is triggered by just a few equivalents of trifluoroacetic acid under very mild conditions (MeCN as the solvent at room temperature). The spirolactone as an activated form of the carboxylic acid has been evidenced by a sulfur-migration experiment. By combining with a three-component synthesis of 5-aminooxazole, a two-step synthesis of structurally complex cyclodepsipeptides from readily accessible starting materials was developed.

Keywords: cyclization · domino reactions · macrocycles · multicomponent reactions · peptides

Introduction

Cyclodepsipeptides are analogues of cyclopeptides having at least one ester linkage as part of their peptidic backbone. They have been found in many natural environments and show a wide spectrum of biological activities including anticancer, antibacterial, antiviral, antifungal, and anti-inflammatory properties.[1] Cyclodepsipeptides and cyclopeptides are attractive targets for synthesis as they combine several favorable properties: 1) They adopt fewer conformations than their acyclic counterparts, and this results in higher and more specific receptor-binding affinities.[2] Indeed, bioactive linear peptides can exist in a myriad of different conformations, very few of which are able to bind to their receptor. Cyclization is a common approach to force peptides into adopting bioactive conformations and to assess the important structural and dynamic properties of peptides.[3] 2) They are more resistant to in vivo enzymatic degradation. The hydrophobic side chains of cyclodepsipeptides provide a hydrophobic exocyclic surface that can shelter their cleavable amide bonds from degradative peptidases. 3) The absence of ionized N and C termini in cyclodepsipeptide facilitates their crossing lipid membranes and leads to improved bioavailablity.[4] 4) They are useful tools in searching for biological processes involved in cellular regulation.[5] Whereas the synthesis of linear peptides generally proceeds well thanks to the development of new and efficient coupling reagents,[6] access to cyclodepsipeptides is much more difficult since macrocyclization often has low yields.[7] Furthermore, the cyclization outcome is highly dependent on sequence,[8] and this makes the synthesis of cyclodepsipeptide libraries particularly challenging.[9] This last point is particularly unfortunate, since cyclodepsipeptides and cyclopeptides are regarded as privileged structures[10] in medicinal chemistry.[11] Indeed, among the three newly approved antibiotic drugs over the past seven years that are efficacious against vancomycin-resistant enterococci (VRE), two of them are cyclodepsipeptides. Synercid, approved in 1998 is a mixture of two macrocycles, one of which is a 17-membered cyclodepsipeptide (quinupristin), while daptomycin, approved in 2003, is a 31-membered cyclodepsipeptide.[12] The ability to systematically modify the side chains and the size of the macrocycle, as well as the connectivity of amino acid residues, is

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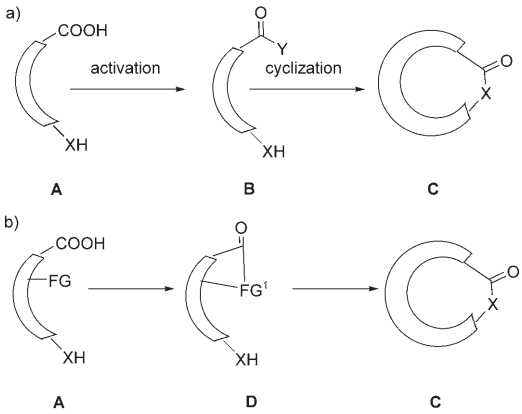
therefore of significant importance and constitutes a bottleneck in the search for peptide-based drugs.[13]

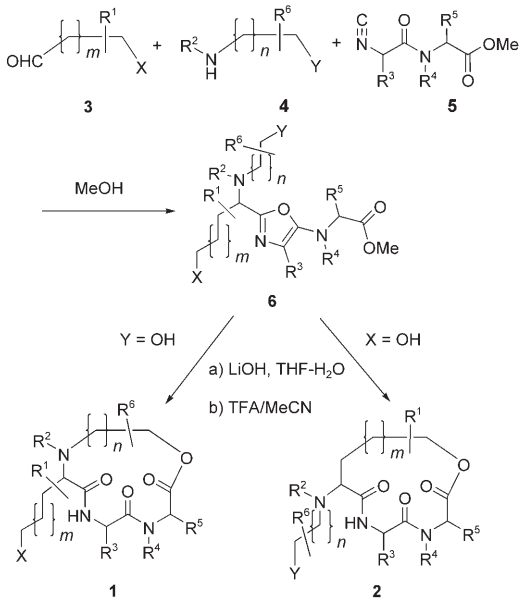
Macrolactamization or macrolactonization of a seco acid is among the most commonly used reactions for the synthesis of cyclodepsipeptides. To perform such transformations, appropriate activation of the carboxylic acid is a prerequisite, usually accomplished by an external coupling reagent (Scheme 1a). Our long-term interest in the development of novel macrocyclization reactions[14] led us to investigate a new strategy for the synthesis of cyclodepsipeptides that avoids the use of external activating agents.[15] The underlying principle that we sought to pursue is shown in Scheme 1b. If a functional group (FG) were incorporated into



Scheme 1. Macrocyclization of a seco acid: general considerations and a new activation mode.

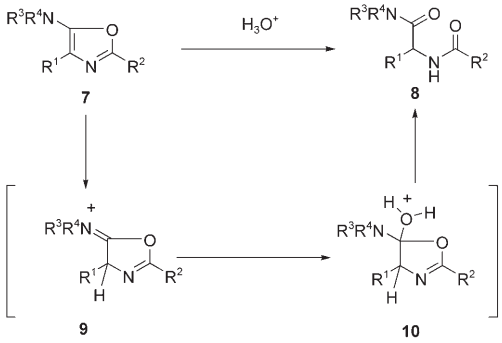
the peptide backbone near the C-terminal carboxylic acid and could react with the nearby C-terminal carboxylic acid to produce a more electrophilic carbonyl group, then cyclization would be expected if a tethered nucleophile were available. To make this approach synthetically useful, an ideal FG must fulfill the following criteria: 1) Its introduction into the peptide backbone should be facile, and the resulting linear peptide should have sufficient shelf stability; 2) Its ability to activate the carboxylic acid should be triggered under very mild conditions without using sophisticated reagents; 3) Activation and cyclization should be performed under the same conditions without requiring isolation of any intermediate; 4) After serving as an activating group, it should become an integral part of the peptide backbone (traceless activating group). We report now that 5-aminooxazole satisfied all these stringent criteria and led to a conceptually new activation/cyclization strategy. In combination with the three-component synthesis of 5-aminooxazole developed by us,[16,17] we report herein a three-step synthesis of complex cyclodepsipeptides (**1** and **2**) from readily accessible starting materials by combination of a multicomponent reaction and a novel cyclization concept (Scheme 2).[18]

Background and design of concept: 5-Aminooxazole is a surrogate of an α-acylamino amide (or a dipeptide) and is readily hydrolyzed back to the diamide under acidic condi-



Scheme 2. A projected synthesis of cyclodepsipeptide by combined use of a three-component reaction and a new cyclization methodology.

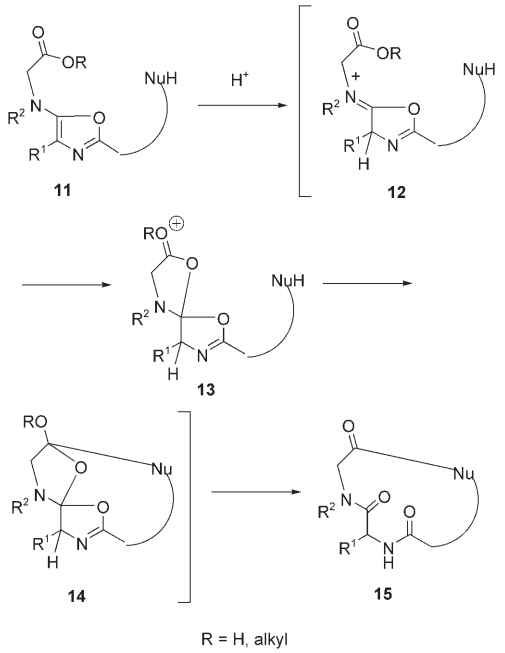
tions. Fleury et al. meticulously examined the hydrolysis mechanism in the 1970s and concluded that hydrolysis is initiated by protonation at C-4 leading to imidate salt **9**, which is trapped by a molecule of water to give **10**, fragmentation of which provides diamide **8** (Scheme 3).[19] The fact that 5-



Scheme 3. Mechanism of hydrolysis of 5-aminooxazole under acidic conditions.

aminooxazole is a masked dipeptide equivalent was elegantly exploited by Lipshutz et al.[20] for the synthesis of a cyclopeptide alkaloid[21] by a sequence of intramolecular *N*-alkylation of 5-aminooxazole followed by hydrolysis.

Based on this mechanistic proposal, a conceptually novel cyclization methodology involving activation of the terminal carboxylic acid by an internal oxazole function was advanced (Scheme 4). Treatment of a suitably functionalized oxazole **11** under acidic conditions should produce iminium cation **12** according to Fleury et al. This electrophilic species could then be trapped either by an external nucleophile leading to simple hydrolysis or, under favorable circum-

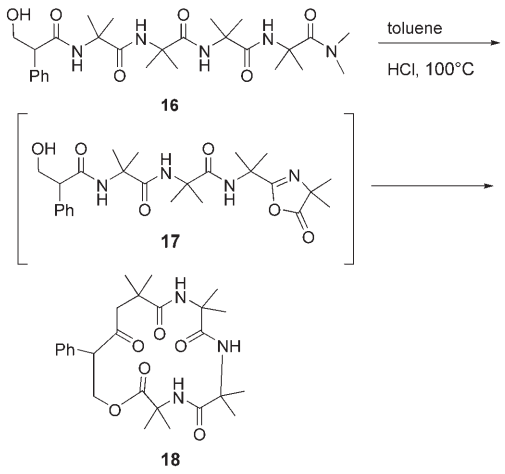


Scheme 4. 5-Aminooxazole as an internal traceless activator of the neighboring carboxylic acid.

stance, by the neighboring carbonyl oxygen atom to give spirolactone **13**. Being highly electrophilic, the carbonyl carbon atom of intermediate **13** could be attacked by the tethered nucleophile to give, after fragmentation, the desired macrocycle. Besides being conceptually novel, the overall transformation is mechanistically intriguing. In fact, it consists of a new domino process[22] involving 1) protonation of oxazole, 2) trapping of the iminium species by the neighboring carbonyl oxygen atom, and 3) trapping of the putative spirolactone by a second internal nucleophile to produce a macrocycle. While an oxazole has been used as a masked form of activated carboxylic acid under photolysis conditions and has been elegantly exploited by Wasserman et al. for macrolactone synthesis,[23] to the best of our knowledge the reaction sequence depicted in Scheme 4 is unknown. The most relevant example, though conceptually different, is the so-called direct amide cyclization, elegantly developed by Heimgartner et al. for the synthesis of cyclodepsipeptides containing α,α-disubstituted amino acid residues.[24] They demonstrated that cyclization of suitably functionalized oligo(α,α-dimethyl glycine) **16** can be realized under acidic conditions (toluene, gaseous HCl, 100 °C, Scheme 5) via 1,3-oxazol-5(4*H*)-one intermediate **17**. The cyclization in this case is favored by the particular conformational preference of this type of linear peptides, which have pronounced tendency to adopt helical conformations (3_{10} helices).[25]

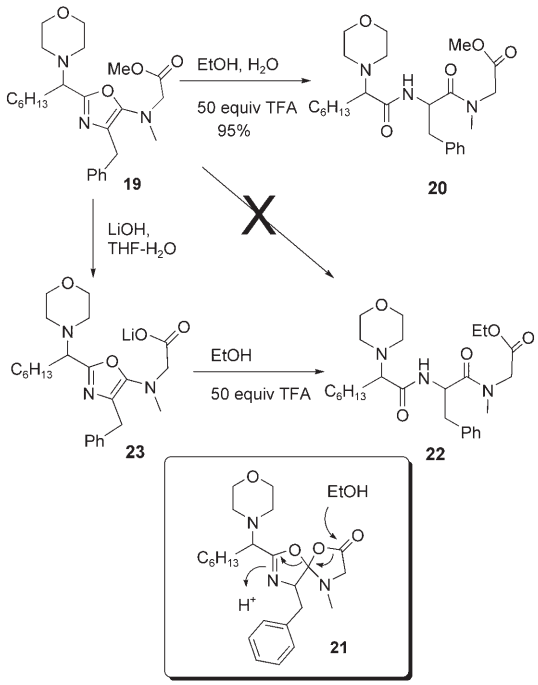
Results and Discussion

Activation of carboxylic acid by an internal oxazole function; proof of concept: At the outset of this work, neither of



Scheme 5. Heimgartner's macrolactonization protocol.

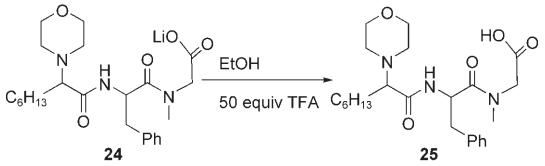
the two steps, namely, activation and cyclization, envisaged in Scheme 4 for the conversion of **11** to **15** was known. To simplify the interpretation of experimental results, we decided to first separate these two steps and to examine whether the concept of activating the terminal carboxylic acid by an oxazole could be realized. For this purpose, oxazole **19** was synthesized and submitted to hydrolysis conditions (Scheme 6). Treatment of an ethanol solution of **19** with trifluoroacetic acid (TFA, 50 equiv) led to tripeptide **20** in over 95 % yield. The formation of **20** can be explained on the basis of the simple hydrolysis of the oxazole without participation (activation) of the terminal methyl ester. If the methyl ester were activated during the hydrolysis of oxazole,



Scheme 6. Activation of a carboxylic acid by a vicinal oxazole: model studies and proof of concept.

tripeptide **22** with an ethyl ester at the C terminus would be produced via, for example, intermediate **21**.

The failure of the oxazole to activate the methyl ester in **19** might be explained by the insufficient nucleophilicity of the ester carbonyl oxygen atom. Indeed, in our mechanistic hypothesis, the putative iminium intermediate needed to be trapped by the carbonyl oxygen atom of the carboxylic ester. In other words, to increase the electrophilicity of the carbonyl carbon atom, the carbonyl oxygen atom should first act as a nucleophile. The simplest way to increase the nucleophilicity of the carbonyl oxygen atom in **19** is its hydrolysis to a carboxylic acid. Based on this assumption, oxazole **19** was converted to the lithium salt of the corresponding carboxylic acid **23** under standard conditions (THF/H_2O, 1 equiv LiOH, evaporation to dryness). Gratifyingly, when a solution of **23** in EtOH was treated with 50 equiv of TFA, a clean transformation occurred to afford the ethyl ester of tripeptide **22** (90%). To demonstrate the key role of oxazole in the esterification of **23**, a lithium salt of tripeptide **24** was synthesized (Scheme 7). Treatment of **24** under the identical

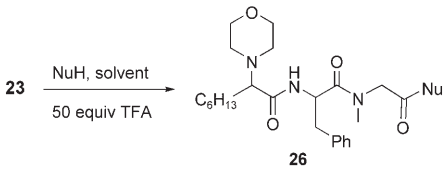


Scheme 7. Hydrolysis of lithium salt of a tripeptide carboxylic acid.

conditions as for **23** (50 equiv TFA in EtOH) did not lead to even trace amounts of ester, and only the corresponding acid **25** was isolated. This control experiment clearly indicated that the oxazole is responsible for esterification of **23**, and hence activation of the carboxylic acid. We speculated that the more pronounced nucleophilicity of the carboxylic acid facilitated formation of spirolactone **21**. Ring opening of this putative intermediate by ethanol led then to the observed product **22**.

Although exact structural information on the activated form of the carboxylic acid is still lacking, we set out to examine the reactivity of this intermediate by reaction of **23** with representative nucleophiles under acidic conditions (Table 1). Acylation took place even with sterically hindered *tert*-butanol to provide the corresponding tripeptide **26b** in reasonable yield (Table 1, entry 2). This result is indicative of the high electrophilicity of the activated form of the carboxylic acid. Aniline failed to react under these conditions, due most probably to protonation of the amine function. However, less basic *p*-nitroaniline was acylated to afford the corresponding tripeptide **26e** in good yield (Table 1, entry 5).

Table 1. Intermolecular esterification; amidation of oxazole **20** under acidic conditions.[a]



Entry	NuH (equiv)	Solvent[a]	Compound	Yield[b] [%]
1	*i*PrOH	*i*PrOH	**26a**	60
2	*tert*-butanol (8)	MeCN	**26b**	41
3	EtSH (8)	MeCN	**26c**	44
4	aniline (10)	MeCN	**26d**	0
5	*p*-nitroaniline (3)	MeCN	**26e**	78

[a] Reaction conditions: room temperature, 4 h. [b] Yield of isolated product after chromatography on silica gel.

Synthesis of oxazole by a three-component reaction: Having validated the concept of activating a C-terminal carboxylic acid by an internal oxazole, we turned our attention to the synthesis of oxazole-containing linear peptides. Synthesis of oxazole has attracted renewed interest due to its presence in a number of bioactive marine natural products[26] and its potential application in the design of conformationally restricted peptidomimetics.[27] Recently, polyfunctionalized oxazoles[28] and oxazole-containing macrocycles[29] have also been designed and used for multidirectional elaboration of combinatorial libraries and for selective molecular recognition of small molecular targets. Thus, new synthetic methodologies are being developed constantly.[30,31] We recently uncovered an expeditious three-component synthesis of 5-aminooxazole from an aldehyde, an amine, and an α-substituted α-isocyano acetamide. Pleasingly, isocyano dipeptide **5**[32] participated well in this multicomponent reaction leading to an efficient synthesis of highly functionalized oxazole **6** (cf. Scheme 2). Thus, simply heating a methanol solution of aldehyde **3**, amine **4**, and dipeptide isocyanide **5** led to the formation of 5-aminooxazole **6** in good to excellent isolated yield. From five aldehydes, nine amines, and six isocyanides (Figure 1), some representative oxazoles were synthesized (Figure 2). This three-component reaction is highly efficient and is applicable to a wide range of substrates.

Macrolactonization under mild acidic conditions; development and generality: The projected domino activation/macrocyclization sequence was examined with **6a** as test substrate. Saponification of the methyl ester (LiOH, THF/H_2O) gave the corresponding lithium salt, which was subjected to varying solvents and acids.[33] Some representative results are summarized in Table 2. The reaction proceeded as planned. Trifluoroacetic acid proved to be the acid of choice among those investigated (Table 2, entry 1 vs entries 5 and

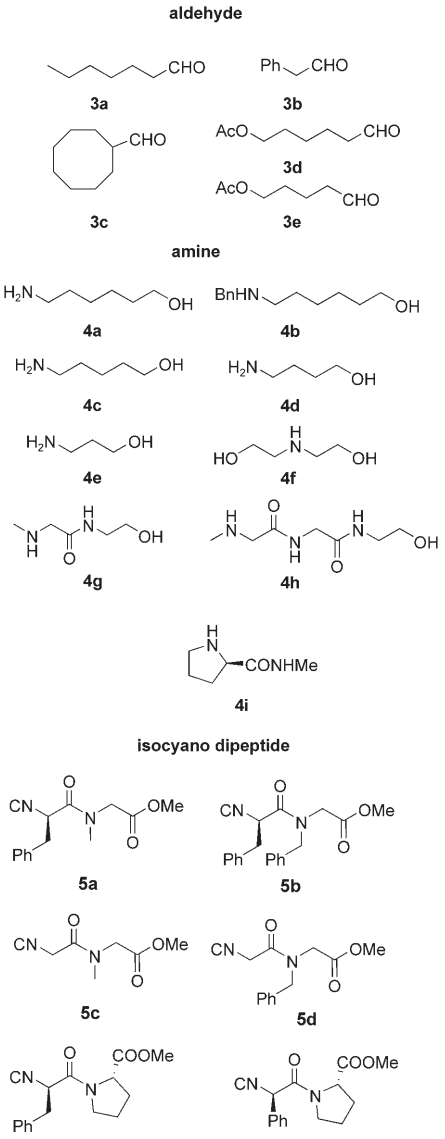


Figure 1. Building blocks for three-component synthesis of oxazole.

6). Curiously, the cyclization worked in both nonpolar and polar aprotic solvents; toluene and acetonitrile were the best reaction media. The tolerance to large spectrum of solvents may have significant future implications when one considers transferring this methodology to solid-phase synthesis. In MeCN, a moderate asymmetric induction in the protonation of the oxazole was observed, which led to two diastereomers in 2:1 ratio. The structure of **1a** was determined by detailed NMR studies. The molecular weight of the cyclodepsipeptides was determined by ESI-MS at high dilution, which enabled us to differentiate between cyclic monomer and cyclic dimer.

Since the new chiral center was generated before the macrocyclization, the observed low 1,4-asymmetric induction across the planar aromatic ring of the flexible linear molecule was not unexpected. Site-selective epimerization of cyclopeptides via a 5-aminooxazole intermediate has been exploited by Oberhauser et al.[34] and Takeya et al.[35] The selectivity of the protonation step was higher in the case of cyclopeptides and especially in the case of oxazolophanes.[20]

By use of the following optimized reaction conditions (LiOH, THF/H_2O, then MeCN/TFA, 0.001 M), oxazoles **6a**–**6w** were converted to their respective macrocyclodepsispetides **1** and **2** (Figures 3 and 4). Keeping in mind its potential application in combinatorial synthesis, the conversion has not been individually optimized. Evidently, the novel macrolactonization protocol is applicable to a wide range of substrates. It is neither sensitive to the amino acid residues nor to ring size. Indeed, good to excellent yields were obtained with 12-, 13-, 14-, 15-, 16-, and 18-membered macrocycles with different peripheral substituents. The configuration of the linear precursor has only a minor effect, if any, on cyclization efficiency, since both diastereomers **6j** and **6k** cyclized to provide their respective cyclodepsipeptides **1j** and **1k** with comparable yields. The acetate functionality of oxazoles **6q** to **6x** was hydrolyzed simultaneously with the saponification of the methyl ester, and thus an additional deprotection step was avoided. Furthermore, the ring type can also be modulated by means of the location of the hydroxyl group. When the hydroxyl group was tethered to the amine, this two-step sequence afforded cyclodepsipetides **1a**–**1p** related to head-to-tail cyclization. However, when the hydroxyl group was tethered to the aldehyde, the same sequence provided a cyclodepsipeptide that is structurally related to a side chain to C-terminal cyclization. Since the linear peptide is synthesized from three readily accessible starting materials, the ring substituents at the periphery of the macrocycle (R^1 to R^7, see general structure of **1** and **2** in Scheme 1) and the ring size of the cyclodepsipeptide can thus be varied easily by changing systematically one of the three starting materials.

Overall, the present synthesis of cyclodepsipeptide is highly efficient in terms of the ability to generate molecular complexity and molecular diversity. Scheme 8 details the synthesis of 18-membered cyclodepsipeptide **1p** from heptanal (**3a**) dipeptidic alcohol **4h**, and an α-isocyano dipeptide **5d**. In this transformation, the only external reagents required are LiOH and TFA, while water and low molecular weight alcohol (MeOH) are the only side products produced. The present approach is thus both atom-economic[36] and ecologically benign.[37]

Evidence for the formation of spirolactone intermediate: While the concept of activating the terminal carboxylic acid by an internal oxazole function seems to be operative, all attempts to detect the presence of the proposed spirolactone intermediate by spectroscopic methods failed. Careful examination of our mechanistic hypothesis led us to propose the following control experiment in order to identify the reactive intermediate. If the reaction did occur as depicted in the Scheme 4, then the formation of two spiro intermediates, that is, **27** and **28**, would be expected with thiocarboxylic acid **26** as a starting material. Since the sulfur atom should in principle be more nucleophilic than the oxygen atom, **27**

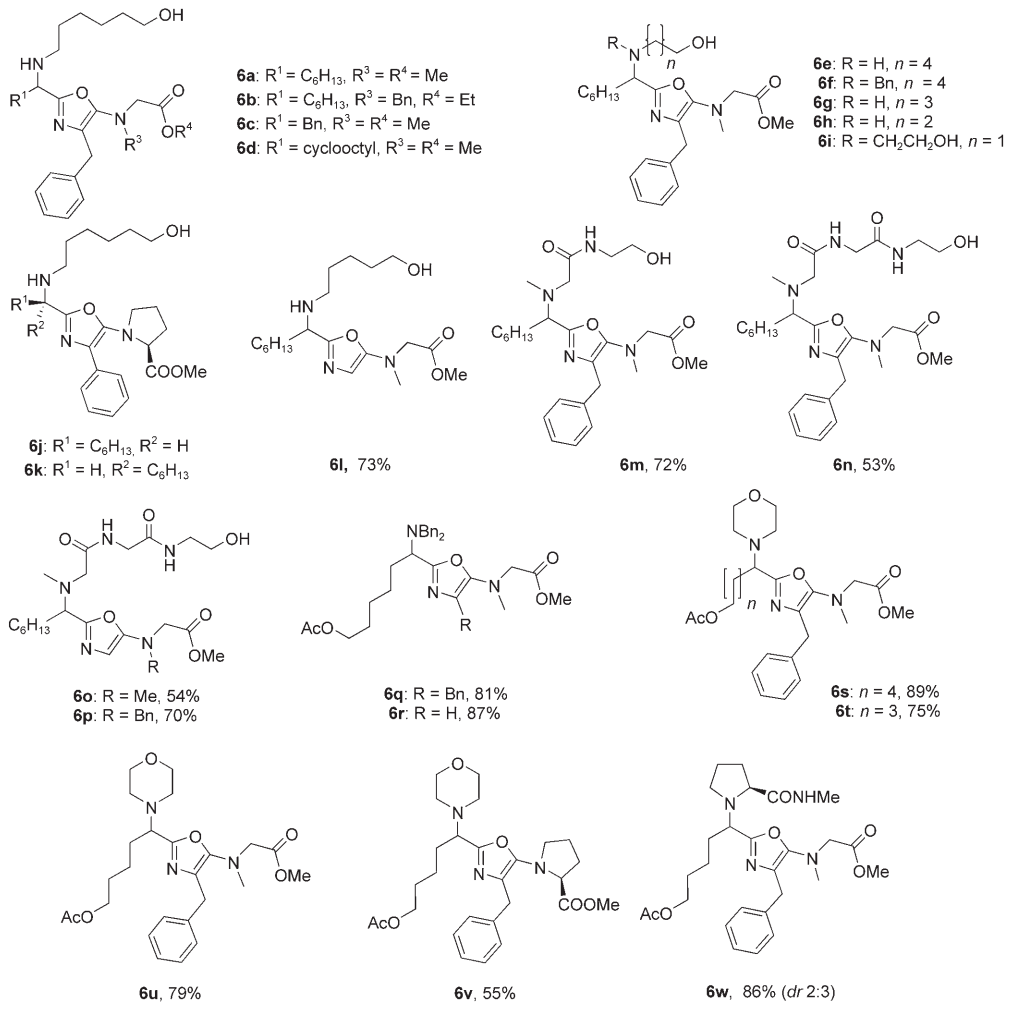
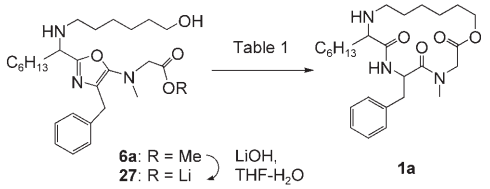


Figure 2. Structure of oxazoles synthesized by three-component reactions.

Table 2. Domino activation/cyclization sequence; survey of cyclization conditions.[a]



Entry	Solvent[a]	Acid	Yield [%][b]	*dr* (A:B)[c]
1	toluene	TFA	85	1:1
2	MeCN	TFA	81	1:2
3	DMF	TFA	63	1:1.9
4	THF	TFA	59	1:2.1
5	toluene	TsOH	9	1:1.7
6	toluene	$HClO_4$	7	1:2.3

[a] Reaction conditions: room temperature, concentration of substrate: 0.001 M. [b] Yield of isolated product after column chromatography. [c] *dr* = diastereomeric ratio; the stereochemistry of diastereomers A and B was not determined. Abbreviations: MeCN = acetonitrile, DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran, TFA = trifluoroacetic acid, TsOH = 4-methylbenzenesulfonic acid.

should be produced predominantly over **28**. Ring opening of **27** by methanol would then afford thioamide **29** in which the sulfur atom has moved from the terminal to the internal position (Scheme 9). Without optimization, compound **26** was prepared from lithium salt **23** via a mixed anhydride intermediate (EtOCOCl, Et_3N, then NaSH, DMF).[38] The yield of **26** was only moderate at best due to concurrent formation of a carboxylic acid and other by-products under these conditions. The crude mixture, after filtration and evaporation, was directly subjected to acidic conditions (MeOH, TFA, room temperature). Thioamide **29** and methyl ester **20** (cf. Scheme 6) were produced in yields of 21 and 31%, respectively. The structure of **29** was determined by detailed spectroscopic analysis. In the ^{13}C NMR spectrum, the appearance of a lower field signal at $\delta = 205$ ppm is characteristic for the thioamide function. The

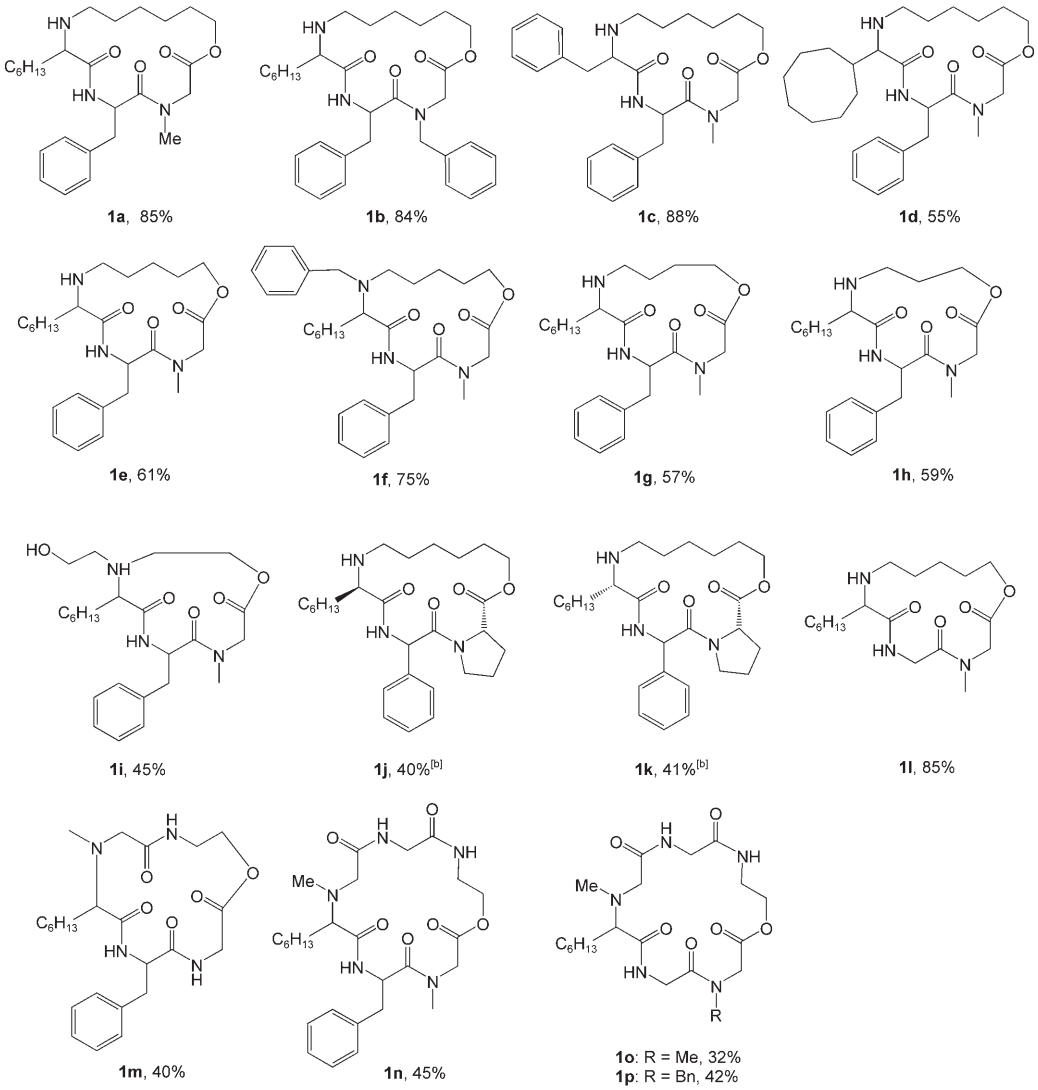


Figure 3. Structure of cyclodepsipeptides from head-to-tail cyclization. All cyclodepsipeptides were produced as a mixture of two separable diastereomers.

formation of thioamide **29** is highly informative, clear-cut evidence for the existence of a spirolactone-type intermediate. From preparative point of view, the present mechanistic study (Scheme 9) constitutes a powerful method for the specific introduction of a thioamide unit into a given peptide, a difficult task that is much sought after in searching for bioactive peptidomimetics.[39]

Efficient activation of the carboxylic acid and favorable conformation of the linear precursor are two key factors that dictate the outcome of a given cyclization. In terms of entropic factor, any structural element that is favorable to the turn conformation would favor the cyclization.[40,41] The forces responsible for favoring one conformation over another are covalent bonds, hydrogen bonding, and steric and electronic interactions of different nature, such as electrostatic interactions, repulsive forces, polarization, and charge transfer. The interplay of these factors of different strengths and to different degrees contributes to the conformation of molecules and hence also to pre-organization of reactive centers. While the carboxylic acid in the form of spirolactone **31** (Figure 5) was certainly activated enough for nucleophilic attack, we think that the cyclization is also driven by the reduced entropic loss. Indeed, comparing the structure of **31** and that of the classic cyclization precursor **32** reveals that the former has at least six fewer free bond rotations, and this decreases the conformational mobility and consequently facilitates end-to-end macrocyclization.

Conclusion

We have developed a conceptually novel macrolactonization protocol that involves a sequence of: 1) protonation of 5-aminooxazole leading to the electrophilic iminium salt; 2) trapping of the iminium species by the neighboring C-terminal carboxylic acid leading to a putative spirolactone in-

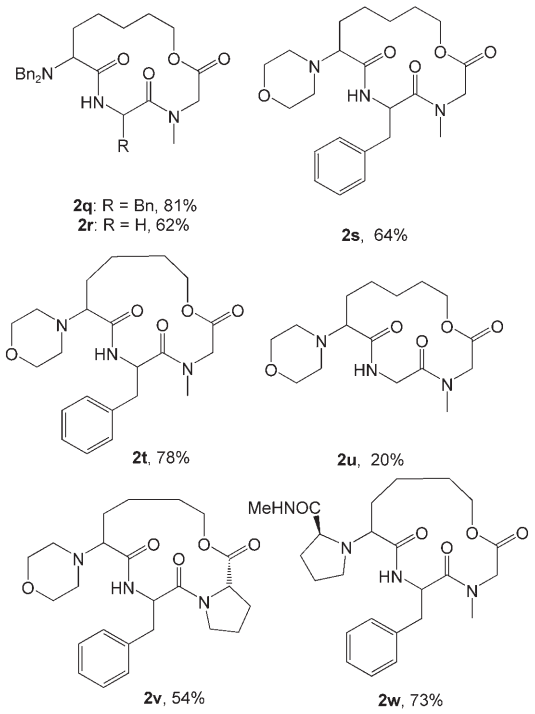
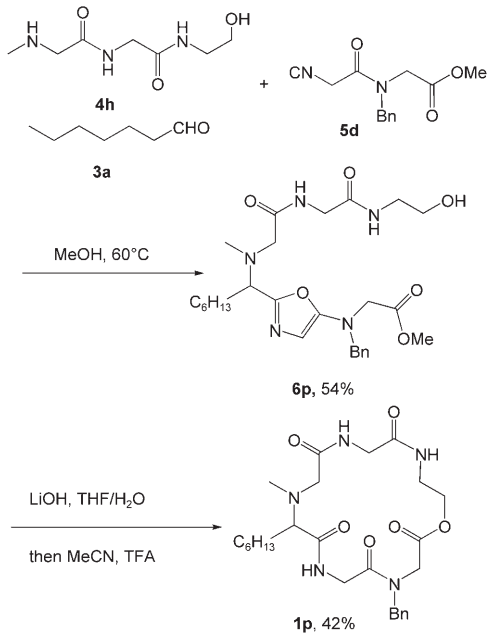
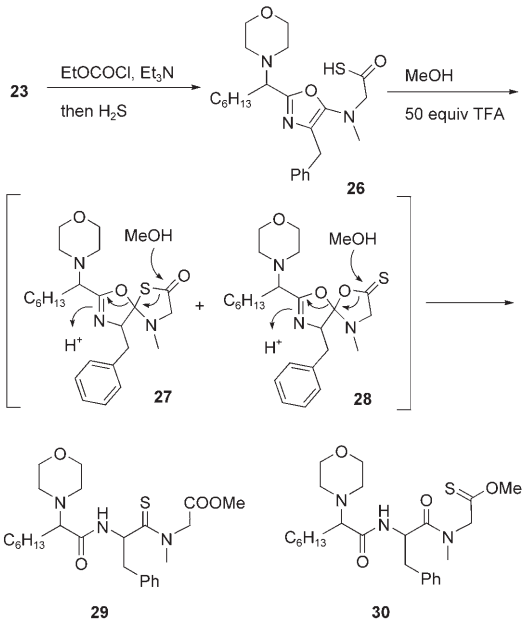


Figure 4. Structure of cyclodepsipeptide from side chain to C-terminal cyclization. All cyclodepsipeptides were produced as a mixture of two separable diastereomers.



Scheme 8. Novel synthesis of cyclodepsipeptide by combined use of a multicomponent reaction and a domino process.

termediate; 3) intramolecular nucleophilic addition of the tethering alcohol to the spirolactone followed by fragmentation. No coupling reagent is required and the entire sequence is triggered by just a few equivalents of trifluoroacetic acid under very mild conditions (MeCN as solvent at room temperature). The key 5-aminooxazole, after serving as an internal activator, becomes an integral part of the peptide backbone. It is thus a traceless internal activator. Combination of this domino process with our previously developed three-component synthesis of 5-aminooxazole allowed us to develop a two-step synthesis of structurally complex cyclodepsipeptides from readily accessible starting materials. The synthesis reported herein is different from any other reported approaches for cyclodepsipeptide synthesis and is particularly appealing in diversity-oriented synthesis programs.[42]



Scheme 9. Spirolactone intermediate as an activated form of C-terminal carboxylic acid: clear-cut evidence.

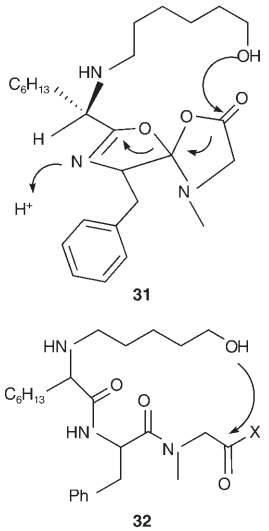


Figure 5. Conformational consideration of macroclactonization.

Experimental Section

Experimental details and ananlytical data for compounds **1b–p**, **2q–s**, **2u–x**, **3d–e**, **5b–f**, **6b–x**, and **29** are given in the Supporting Information.

General procedure for the synthesis of isocyano dipeptide: A solution of *N*-formyl Phe-sarcosine methyl ester (1.5 g, 5.4 mmol) and triethylamine (4.4 mL, 27.0 mmol) in CH_2Cl_2 (75 mL) was cooled to −30 °C. Phosphorus oxychloride (0.8 mL, 8.1 mmol) was added dropwise to the above solution. After being stirred at −20 °C for 2 h, the reaction mixture was quenched by adding a saturated aqueous solution of $NaHCO_3$ and the

aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness under reduced pressure. The crude residue was subjected to flash chromatography (silica gel, heptane/EtOAc 4/1→heptane/EtOAc 1:1) to give compound **5a** (1.3 g, 96%) as a white solid. M.p. 104–106°C; R_f (EtOAc/heptane 1:5) = 0.17; $[\alpha]_D = -8$ ($c = 0.12$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm), two rotamers (4:1): $\delta = 3.08$ (3.02) (s, 3H), 3.15 (dd, 1H, $J = 8.7$, 14.0 Hz), 3.28 (dd, 1H, $J = 5.3$, 14.0 Hz), 3.76 (s, 3H), 4.02 (3.90) (d, 1H, $J = 17.3$ (17.2) Hz), 4.26 (4.09) (d, 1H, $J = 17.3$ (17.2) Hz), 4.62 (4.39) (dd, 1H, $J = 5.3$ (5.5), 8.7 (8.8) Hz), 7.20–7.36 (5H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$, ppm), two rotamers (4:1): $\delta = 36.7$ (35.9), 38.6 (39.0), 50.1 (51.2), 52.4 (52.8), 55.8, 127.7, 128.8 (2C), 129.5 (2C), 135.2, 160.0, 165.8, 168.9; IR ($CHCl_3$): $\tilde{\nu} = 3009$, 2142, 1751, 1677, 1497, 1456, 1439, 1407, 1366, 1238, 1183, 1121, 1080, 1032 cm^{-1}; MS (EI): m/z: 260 $[M]^+$, 233; elemental analysis (%) calcd for $C_{14}H_{16}N_2O_3$: C 64.62, H 6.15, N 10.77; found: C 64.77, H 6.07, N 10.74.

General procedure for three-component synthesis of oxazole 6: A solution of heptanal (**3a**, 23 mg, 0.2 mmol) and aminohexanol (**4a**; 23 mg, 0.2 mmol) in dry methanol (2 mL) was stirred at room temperature for 15 min, and isocyanide **5a** (52 mg, 0.2 mmol) was then added to the solution. The reaction mixture was heated to 70°C for 3 h. The solvent was then removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH 95:5) to give aminooxazole **6a** (56.0 mg, 59%) as a yellow oil. R_f (MeOH/CH_2Cl_2 1:20) = 0.28; ^{1}H NMR (250 MHz, $CDCl_3$, ppm): $\delta = 0.86$ (t, 3H, $J = 6.6$ Hz), 1.13–1.60 (m, 16H), 1.68–1.84 (m, 2H), 2.48 (t, 2H, $J = 7.9$ Hz), 2.87 (s, 3H), 3.59 (t, 2H, $J = 6.5$ Hz), 3.65 (t, 1H, $J = 6.1$ Hz), 3.68 (s, 3H), 3.71 (s, 2H), 3.85 (s, 2H), 7.15–7.27 (m, 5H); ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): $\delta = 14.0$, 22.5, 25.6, 25.9, 27.0, 29.0, 29.9, 31.6, 32.6, 34.5, 40.8, 47.5, 51.8, 55.9, 57.0, 62.5, 62.5, 122.1, 126.0, 128.3 (4C), 139.8, 151.4, 159.9, 170.6; IR ($CHCl_3$): $\tilde{\nu} = 3690$, 3013, 2933, 1749, 1675, 1602, 1456, 1406, 1265, 1223, 1183, 1012 cm^{-1}; MS (EI): m/z: 473 $[M]^+$, 388 $[M-C_6H_{13}]^+$.

General procedure for macrocyclization: A solution of 5-aminooxazole **6a** (43 mg, 0.09 mmol) and $LiOH\cdot H_2O$ (42 mg, 0.10 mmol) in THF/H_2O (4 mL, 3:1) was stirred at room temperature for 3 h and evaporated to dryness in vacuo. The residue obtained was dissolved in MeCN (200 mL, $c = 10^{-3}$ M), and TFA (405 mg, 9.20 mmol) was added under a stream of argon. The reaction mixture was stirred at room temperature for 2 h. When the reaction was completed, the volatile substances were evaporated under reduced pressure. The residue obtained was dissolved in ethyl acetate and washed with a saturated aqueous solution of potassium bicarbonate. The organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The light yellow residue was subjected to purification by preparative TLC (heptane/EtOAc 1:1) to give **1a** (isomer A, 18 mg) and compound **1a′** (isomer B, 17 mg) (85%, total 35%). Isomer A: white solid; yield 43%; R_f (EtOAc/heptane 1.5:1) = 0.39; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): $\delta = 0.89$ (t, 3H, $J = 6.6$ Hz), 1.15–1.70 (m, 19H), 2.46–2.56 (m, 2H), 2.75 (s, 3H), 2.97–3.10 (m, 3H), 3.17 (d, 1H, $J = 16.5$ Hz), 3.88 (m, 1H), 4.47 (m, 1H), 4.51 (d, 1H, $J = 16.5$ Hz), 5.15 (dt, 1H, $J = 4.7$, 8.0 Hz), 7.23–7.27 (m, 5H), 7.86 (d, 1H, $J = 8.0$ Hz, NH); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): $\delta = 14.2$, 22.7, 25.1, 25.2, 26.1, 28.9, 29.2, 29.3, 31.7, 34.5, 36.9, 40.0, 47.8, 50.0, 51.7, 64.8, 65.2, 127.0, 128.4 (2C), 129.6 (2C), 136.6, 169.0, 171.7, 174.7; IR ($CHCl_3$): $\tilde{\nu} = 3355$, 3005, 2932, 2858, 1734, 1645, 1496, 1456, 1418, 1267, 1189, 1131 cm^{-1}; MS (EI): m/z: 459 $[M]^+$; MS (APCI, diluted): m/z: 460 $[M+H]^+$; HRMS: m/z: calcd for $C_{26}H_{41}N_3O_4+H$: 460.3176; found: 460.3189.

Isomer B: White solid; yield 41%; R_f (EtOAc/heptane 1.5:1) = 0.12; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): $\delta = 0.88$ (t, 3H, $J = 6.8$ Hz), 1.16–1.54 (m, 19H), 2.36–2.54 (m, 2H), 2.90 (s, 3H), 2.91–3.10 (m, 3H), 3.20 (d, 1H, $J = 16.7$ Hz), 4.00 (dt, 1H, $J = 4.0$ Hz, 10.9 Hz), 4.32 (dt, 1H, $J = 5.6$ Hz, 10.9 Hz), 4.77 (d, 1H, $J = 16.7$ Hz), 5.27 (m, 1H), 6.78 (d, 1H, $J = 8.6$ Hz, NH), 7.19–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): $\delta = 14.2$, 22.7, 24.5, 25.3, 26.1, 28.0, 28.2, 29.3, 31.7, 32.9, 36.6, 39.4, 45.8, 49.9, 50.8, 62.8, 65.4, 127.2, 128.6, 128.7, 129.4 (2C), 136.2, 168.9, 171.2, 175.0; IR ($CHCl_3$): $\tilde{\nu} = 3419$, 3008, 2932, 2859, 1734, 1648, 1497, 1456, 1417, 1379, 1276, 1191, 1126, 1092 cm^{-1}; MS (EI): m/z: 459 $[M]^+$; MS (APCI, diluted): m/z: 460 $[M+H]^+$; HRMS: m/z: calcd for $C_{26}H_{41}N_3O_4+H$: 460.3176; found: 460.3192.

Compound 2t: Cyclization of **6t** was performed under identical conditions as described for **1a**. The light yellow residue was subjected to purification by preparative TLC (CH_2Cl_2/MeOH 1:1) to give **2t** (isomer A, 69 mg) and **2t′** (isomer B, 68 mg) (78% total). Isomer A: White solid; yield 39%; ^{1}H NMR (300 MHz, $CDCl_3$, ppm), two rotamers: $\delta = 1.20$–1.80 (m, 6H), 2.14–2.48 (m, 4H), 2.76 (dd, 1H, $J = 4.0$ Hz, 11.1 Hz), 3.00 (2.86) (s, 3H), 2.87–3.10 (m, 2H), 3.23 (d, 1H, $J = 16,9$ Hz), 3.55–3.67 (m, 4H), 3.71–3.80 (m, 1H), 4.16–4.20 (4.05–4.10) (m, 1H), 4.64 (4.42) (d, 1H, $J = 16.9$ (18.7 Hz)), 5.16 (5.41) (m, 1H), 6.71 (6.80) (d, 1H, $J = 9.8$ (6.8 Hz)), 7.16–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): $\delta = 26.5$, 27.8, 28.1, 37.9, 38.5, 49.0, 51.0, 51.2, 63.8, 67.3, 69.9, 127.2, 128.9 (2C), 129.6 (2C), 136.6, 168.5, 171.3, 173.4; IR ($CHCl_3$): $\tilde{\nu} = 1505$, 1648, 1673, 1739, 3016, 3372 cm^{-1}; MS (IE): m/z: 417 $[M]^+$.

Isomer B: White solid; yield 39%; ^{1}H NMR (300 MHz, $CDCl_3$, ppm), two rotamers: $\delta = 1.12$–1.80 (m, 6H), 2.06–2.14 (m, 2H), 2.24–2.38 (m, 2H), 2.57–2.62 (m, 1H), 2.9–3.01 (m, 2H), 3.11 (s, 3H), 3.24 (d, 1H, $J = 15,6$ Hz), 3.47–3.60 (m, 4H), 4.01–4.06 (m, 2H), 4.58 (d, 1H, $J = 15.6$ Hz), 5.38 (5.06) (m,1H), 7.09–7.19 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): $\delta = 27.8$, 28.4, 29.6, 38.1, 38.3, 48.1, 51.9, 52.4, 54.1, 67.2, 67.6, 69.8, 127.2, 128.9, 129.6, 136.7, 168.7, 173.0, 173.0%; IR ($CHCl_3$): $\tilde{\nu} = 3372$, 3016, 1739, 1673, 1648, 1505 cm^{-1}; MS (IE): m/z: 417 $[M]^+$; MS (ESI, positive mode): m/z: 440.2 $[M+H]^+$; HRMS: m/z: calcd for $C_{22}H_{31}N_3O_5+Na$: 440.21.61; found: 440.2161.

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