Highly efficient macrolactonization of ω-hydroxy acids using benzotriazole esters: synthesis of Sansalvamide A†

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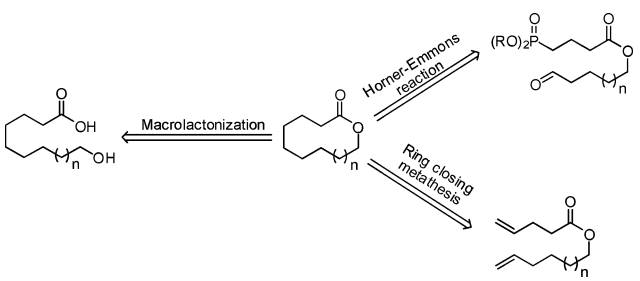
A facile and mild macrolactonization reaction of ω-hydroxy acids was developed based on the transesterification of benzotriazole esters. Treatment of ω-hydroxy acids with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and 1-hydroxy benzotriazole (HOBT) in chloroform provided macrolactones in excellent yields. The reactions were performed under basic, neutral and acidic conditions using *N*,*N*-dimethylaminopyridine (DMAP), tetrabutylammonium tetrafluoroborate ($TBABF_4$) and $BF_3{\cdot}Et_2O$, respectively. A calcined hydrotalcite was also used instead of DMAP. Finally, to test the scope of the protocol in the synthesis of biologically relevant macrolactones, the total synthesis of Sansalvamide A was carried out.

Introduction

Of the various synthetic and naturally occurring heterocyclic structures, the macrolactone nucleus is among the most prevalent. Macrolactones are found in a wide range of natural products and bioactive molecules, including important antitumor agents and immunosuppressants. Synthetic macrolactones,[1] which are an alternative to those found in natural sources,[2] have received much interest. A retrosynthetic analysis reveals that the formation of the macrocycle is a key step in the construction of the macrolactone skeleton. To form the macrocycle, two strategies have mainly been used: i) the lactonization of a seco acid[3] and ii) the intramolecular C–C bond formation of an ester using either a ring-closing metathesis[4] or an intramolecular Horner–Emmons reaction[5] (Scheme 1).



Scheme 1 Retrosynthetic analysis of the formation of the macrolactone skeleton.

Although activation of either an alcohol or carboxylic acid to direct the macrolactonization of a seco acid is necessary, this strategy is still widely used. Many methodologies have been reported in the literature for the preparation of macrolactones. In these methodologies, the formation of large rings is achieved under various conditions. Examples of such methodologies include the Corey,[6] Mitsunobu[7] and Yamaguchi[8] reactions. Recently, Kita[9] pointed out a series of problems that still need to be overcome to achieve an efficient macrolactonization reaction. Such problems included low yields, poor reactivity of the intermediates, side reactions, the necessary use of an excess of reactants and unsatisfactory purification procedures. One of the most important problems is the formation of dimers or oligomers. This problem is usually circumvented by using high-dilution conditions, which can be achieved by employing enormous volumes of solvent or by slow addition of the seco acid to the reaction medium.[10] Based on these observations, we decided to develop a new, efficient synthesis technique for macrolactones. The synthesis involves benzotriazole esters, which are highly reactive and allow mild reaction conditions.

An accurate understanding of the reaction mechanisms involved in the formation of ester bonds using carbodiimides and the formation of peptide bonds using carbodiimides and 1-hydroxy benzotriazole (HOBT)[11] provides the basis for the methods proposed in this paper. It is well known that a carbodiimide dehydrates a carboxylic acid by promoting the nucleophilic addition of an alkoxy group, leading to the corresponding ester[12] or lactone.[13] Boden and Keck demonstrated the importance of the proton transfer step in the synthesis of macrolactones by using DMAP–HCl to prevent the formation of *N*-acylurea. We therefore developed a strategy that involves the formation of benzotriazole esters **I** and **II** (Scheme 2) from ω-hydroxy acids. HOBT was used because, similarly to DMAP–HCl, it participates in the proton transfer step and prevents side reactions such as the formation of *N*-acylureas and the racemisation of the resulting product. Numerous HOBT derivatives [14] have been synthesized to either be used in solution or solid phase. However, in all cases, species **I** and **II** were proposed as reaction intermediates (Scheme 2).[15] We decided to use these intermediates for the macrolactonization reaction because the reaction could be carried out under basic, acid or neutral conditions. Thus, in this study, we describe a

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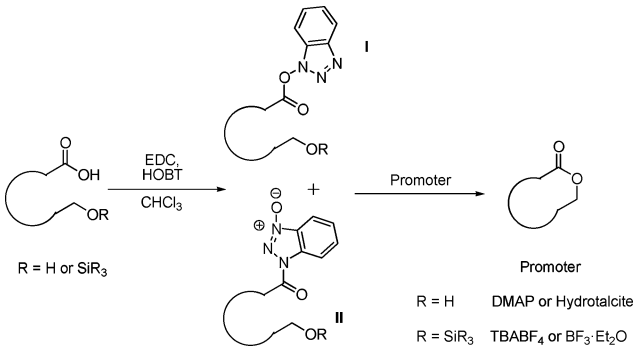


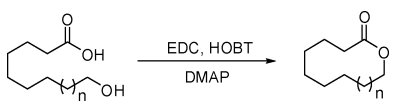
Scheme 2 General idea.

highly efficient macrolactonization reaction using benzotriazole esters and demonstrate the importance of HOBT in the efficiency of the reaction. Finally, we used the reaction in the last step of the total synthesis of Sansalvamide A to demonstrate its synthetic value.

Results and discussion

Taking into consideration that benzotriazole esters **I** and **II** are the precursors of lactones, the reaction conditions were optimized by using different ω-hydroxy acids in the presence of EDC and HOBT. Three different solvents, *i.e.*, THF, $CHCl_3$ and CH_2Cl_2, were also tested. In general, these solvents can be used as a medium for the formation of esters. However, benzotriazole esters were only obtained in chloroform with a yield of 98% at room temperature. The formation of the esters was confirmed by analysis of the NMR spectra of the raw materials. The macrolactonization reaction was then studied in $CHCl_3$ at room temperature and at reflux under high-dilution conditions; the substrate was slowly added to a large volume of solvent (50 mL) using a syringe pump over the course of 18 h.[16] The reaction was essentially performed under basic conditions as 1 equiv. of DMAP was used. High yields of macrolactone were obtained when the reaction was carried out in $CHCl_3$ at reflux (Table 1, entries 1 and 3). When ω-hydroxy acids were used to obtain 13-membered ring lactones, the formation of the dimer was observed but the monomer was still the major product (Table 1, entry 5). For 11-membered ring lactones, the formation of the dimer was favoured. However, the lactone was still predominant, and the total yield of the reaction decreased dramatically (Table 1, entry 7). Even though the benzotriazole esters were formed with a 98% yield at room temperature, the macrolactonization yield obtained at room temperature was notably lower than that obtained at reflux. However, the relationships between the monomer and dimer were similar (Table 1, entries 2, 4, 6 and 8). It is noteworthy that the yield decreased dramatically when the reaction was carried out in the absence of HOBT. Indeed, a yield of only 36% was obtained for a 17-membered ring lactone. A longer reaction time (38 h) did not improve this yield, as evidenced by the signals observed at δ = 3.93 ppm (2H, t, J = 6.8 Hz, CH_2–OR), corresponding to the methylene group of a lactone, and at δ = 3.49 ppm (2H, t, J = 6.8 Hz, CH_2–OH), corresponding to a methylene attached to a hydroxy group, in the ^{1}H NMR spectrum of the crude reaction mixture. A quantitative analysis of these signals allowed the estimation of the reaction yield (36%) (see ESI†). These results indicate that HOBT facilitates the macrolactonization reaction.

Table 1 Macrolactonization of ω-hydroxy acids under basic and high-dilution conditions[a,b]



Entry	ω-Hydoxy acid	Lactone ring size	T/°C	Lactone yield (%)[c]	Diolide yield (%)[c]
1	$HO(CH_2)_{15}CO_2H$	17	reflux	97	—
2	$HO(CH_2)_{15}CO_2H$	17	rt	78	—
3	$HO(CH_2)_{14}CO_2H$	16	reflux	95	—
4	$HO(CH_2)_{14}CO_2H$	16	rt	76	—
5	$HO(CH_2)_{11}CO_2H$	13	reflux	86	8
6	$HO(CH_2)_{11}CO_2H$	13	rt	69	9
7	$HO(CH_2)_9CO_2H$	11	reflux	29	13
8	$HO(CH_2)_9CO_2H$	11	rt	18	10

[a] Reagents and conditions for the macrolactonization reaction: ω-hydroxy acid (1 mmol), EDC (1 mmol), HOBT (1 mmol), DMAP (1 mmol), $CHCl_3$ (50 mL), 18 h. [b] The ω-hydroxy acid was dissolved in THF[16] (10 mL) and was slowly added using a syringe pump over the course of 18 h. [c] Yield of isolated product after chromatographic purification.

Table 2 Macrolactonization of ω-hydroxy acids under basic and low-dilution conditions[a,b]

Entry	ω-Hydoxy acid	Lactone ring size	Lactone yield (%)[c]	Diolide yield (%)[c]
1	$HO(CH_2)_{15}CO_2H$	17	55	44
2	$HO(CH_2)_{14}CO_2H$	16	56	40
3	$HO(CH_2)_{11}CO_2H$	13	19	30
4	$HO(CH_2)_9CO_2H$	11	11	26

[a] Reagents and conditions for the macrolactonization reaction: ω-hydroxy acid (1 mmol), EDC (1 mmol), HOBT (1 mmol), DMAP (1 mmol), $CHCl_3$ (50 mL), reflux, 18 h. [b] The reactants were mixed at the beginning of the reaction. [c] Yield of isolated product after chromatographic purification.

The macrolactonization reaction was also carried out under low-dilution conditions (*i.e.*, the substrate was not slowly added) to compare the relationship between the lactone and the diolide (Table 2). The reactions were performed in the presence of EDC, HOBT and DMAP in $CHCl_3$ at reflux. As shown in entries 1–4 of Table 2, the total yields were similar to those obtained under high-dilution conditions; however, the formation of dimers increased notably.

These results are in contrast to those obtained for the macrolactonization of seco acids using calcined hydrotalcite Mg^{2+}/Al^{3+} in a ratio of x = 0.33 instead of DMAP. Surprisingly, in the case of calcined hydrotalcite, the use of high- or low-dilution conditions allowed us to obtain macrolactones with similar yields and selectivities (Table 3, entries 1–4).[17] Hydrotalcites are materials that have basic properties.[18] They can therefore be used to replace traditional bases in solution[19] with the following advantages: ease of separation, reduction of waste streams, possible regeneration of the catalyst and low cost. We decided to use hydrotalcite because the basicity of the calcined product can be modified by changing the Al–Mg ratio.[20]

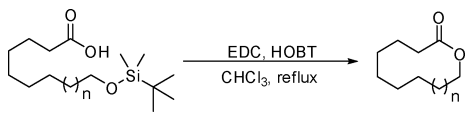
We also considered ω-(*tert*-butyldimethylsilyloxy)-acids as starting materials to explore neutral and acid conditions for the macrolactonization reaction. Several alternative precursors for

Table 3 Macrolactonization of ω-hydroxy acids[a] using calcined Mg–Al hydrotalcite in a ratio of $x = 0.33$ under high-dilution[b] and low-dilution[c] conditions

Entry	Lactone ring size	Lactone yield (%)[d] under high-dilution conditions	Diolide yield (%)[d] under high-dilution conditions	Lactone yield (%)[d] under low-dilution conditions	Diolide yield (%)[d] under low-dilution conditions
1	17	94	—	92	
2	16	96	—	96	
3	13	76	—	38	12
4	11	73	9	29	13

[a] Reagents and conditions for the macrolactonization reaction: ω-hydroxy acid (1 mmol), EDC (1 mmol), HOBT (1 mmol), hydrotalcite (200 mg), $CHCl_3$ (50 mL), reflux, 18 h. [b] The ω-hydroxy acid was dissolved in THF[16] (10 mL) and was slowly added using a syringe pump over the course of 18 h. [c] The reactants were mixed at the beginning of the reaction. [d] Yield of isolated product after chromatographic purification.

Table 4 Macrolactonization of ω-(*tert*-butyldimethylsilyloxy)-acids under high-dilution conditions[a,b]



Entry	ω-Hydoxy acid	Lactone ring size	Promoter	Lactone yield (%)[c]	Diolide yield (%)[c]
1	$TBDMSO(CH_2)_{15}CO_2H$	17	$TBABF_4$	93	—
			$BF_3{\cdot}EtO_2$	90	—
			$SnCl_4$	68	—
			$TiCl_4$	65	—
2	$TBDMSO(CH_2)_{14}CO_2H$	16	$TBABF_4$	91	—
			$BF_3{\cdot}EtO_2$	90	—
			$SnCl_4$	60	—
			$TiCl_4$	54	—
3	$TBDMSO(CH_2)_{11}CO_2H$	13	$TBABF_4$	82	11
			$BF_3{\cdot}EtO_2$	79	10
			$SnCl_4$	20	5
			$TiCl_4$	18	5
4	$TBDMSO(CH_2)_9CO_2H$	11	$TBABF_4$	26	12
			$BF_3{\cdot}EtO_2$	24	11
			$SnCl_4$	10	6
			$TiCl_4$	10	4

[a] Reagents and conditions for the macrolactonization reaction: ω-(*tert*-butyldimethylsilyloxy)-acids (1 mmol), EDC (1 mmol), HOBT (1 mmol), Lewis acid (1 mmol), $CHCl_3$ (50 mL), reflux, 18 h. [b] The ω-(*tert*-butyldimethylsilyloxy)-acid was dissolved in $CHCl_3$ (10 mL) and was slowly added using a syringe pump over the course of 18 h. [c] Yield of isolated product after chromatographic purification.

Table 5 Macrolactonization of ω-(*tert*-butyldimethylsilyloxy)-acids under acidic and low-dilution conditions[a,b]

Entry	ω-Hydroxy acid	Lactone ring size	Lactone yield (%)[c]	Diolide yield (%)[c]
1	$TBDMSO(CH_2)_{15}CO_2H$	17	97	—
2	$TBDMSO(CH_2)_{14}CO_2H$	16	90	—
3	$TBDMSO(CH_2)_{11}CO_2H$	13	77	23
4	$TBDMSO(CH_2)_9CO_2H$	11	75	25

[a] Reagents and conditions for the macrolactonization reaction: ω-(*tert*-butyldimethylsilyloxy)-acids (1 mmol), EDC (1 mmol), HOBT (1 mmol), $BF_3{\cdot}Et_2O$ (1 mmol), $CHCl_3$ (50 mL), reflux, 18 h. [b] The reactants were mixed at the beginning of the reaction. [c] Yield of isolated product after chromatographic purification.

the macrolactonization reaction were screened in the presence of tetrabutylammonium tetrafluoroborate ($TBABF_4$) instead of DMAP. Treatment of ω-(*tert*-butyldimethylsilyloxy)-acids with EDC, HOBT and $TBABF_4$ in $CHCl_3$ under high-dilution conditions at reflux led to macrolactones and diolides in excellent yields (Table 4). The results were similar to those obtained with simple ω-hydroxy acids. It is noteworthy that under these conditions, 17- and 16-membered ring lactones were formed with high yields (Table 4, entries 1 and 2). While dimers were also formed when ω-(*tert*-butyldimethylsilyloxy)-acids were used to obtain 13-membered ring lactones, the corresponding monomers were still the major products (Table 4, entry 3). The total yield of the reaction notably decreased for 11-membered ring lactones (Table 4, entry 4). It was again observed that the absence of HOBT led to poor yields. Even though the use of a *tert*-butyl-dimethylsilane ether instead of an alcohol as the raw material for the formation of macrolactones might seem complicated, it can be a suitable process in cases where the alcohol needs to be protected before the formation of the macrolactone.

We also investigated the *in situ* deprotection of the alkoxy group with various Lewis acids, such as $BF_3{\cdot}Et_2O$, $SnCl_4$, $TiCl_4$ and $AlCl_3$, under appropriate reaction conditions. The effectiveness of $BF_3{\cdot}Et_2O$ was evidenced by the excellent yields obtained for 17- and 16-membered ring lactones under high-dilution conditions (Table 4, entries 1 and 2). The yields decreased dramatically when $SnCl_4$ and $TiCl_4$ were used instead of $BF_3{\cdot}Et_2O$ under the same reaction conditions. No cyclization was observed with $AlCl_3$.

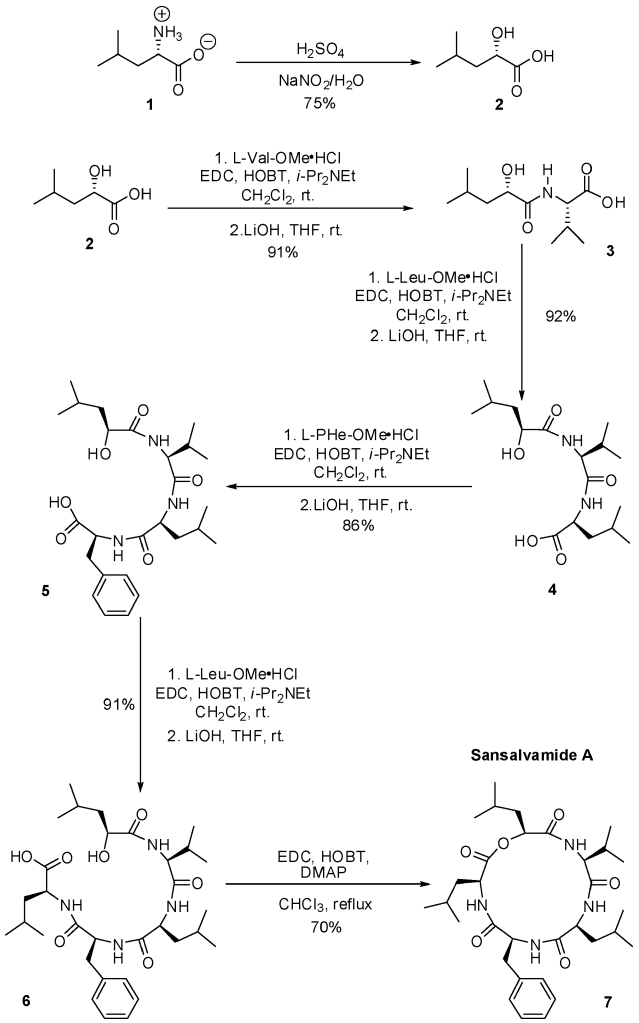
When the reaction was carried out under low-dilution conditions using $BF_3{\cdot}Et_2O$ as the promoter, interesting results were observed (Table 5). Neither the selectivity nor the yield of the reaction were affected, and 13- and 11-membered ring lactones were obtained in good yields (Table 5, entries 3 and 4). The yields for the 11- and 13-membered ring lactones were typically low, and the corresponding diolides were important reaction products. Additionally, it was observed that the use of an anhydrous solvent was not necessary for the reaction to occur. The reasons for these results are currently being investigated by our group.

To determine whether our methodology is useful for the synthesis of complex molecules, we synthesized Sansalvamide A (**7**). This molecule is a cyclic pentadepsipeptide isolated from organic extracts of the mycelium of a fungus of the genus *Fusarium*, which is collected from the surface of the seagrass *Halodule wrightii* that is found on San Salvador Island in the Bahamas. Sansalvamide A has an IC_{50} value of 27.4 mg mL^{-1} against the National Cancer Institute's 60-cell-line panel and an *in vitro* IC_{50} value of 9.8 mg mL^{-1} toward HCT-116 colon carcinoma cells.[21] This natural product is an inhibitor of virus-encoded type-1 topoisomerase, which is likely necessary for the

replication of the molluscum contagiosum virus (MCV).[22] Due to its interesting biological properties and the low availability of Sansalvamide A from natural sources, an elegant solid-phase synthesis of Sansalvamide A was completed by Silverman *et al.*[23,24] and McAlpine *et al.*[25] also prepared Sansalvamide analogues and evaluated their antitumor activity. Jiang *et al.*[26] developed an ionic-liquid-supported total synthesis of a peptide analogue. The total synthesis of the cyclic pentadepsipeptide Sansalvamide A in solution using the above-detailed macrolactonization method is described herein. A retrosynthetic analysis established a linear synthesis involving four amino acids and 2-hydroxy-4-methylpentanoic acid, all having an *S* configuration. The α-hydroxy acid **2** was first prepared by diazotization of leucine (**1**). Thus, sulfuric acid and sodium nitrite were added to (*S*)-leucine (**1**) in an aqueous medium at room temperature. The reaction took place with retention of configuration.[27] Enlargement of the chain was carried out by reaction with the corresponding amino acid methyl ester hydrochlorides in the presence of HOBT, EDC and DIPEA. Thus, the residues of Val, Leu, Phe and Leu form the ω-hydroxy acid **6**. The last step in the synthesis was the macrolactonization reaction, in which the hydroxy acid **6** was treated under high-dilution conditions (see the experimental section) in the presence of EDC, HOBT and DMAP in chloroform under reflux to afford **7** with a 70% yield (Scheme 3).

In the last step of the synthesis, THF was used to dissolve the hydroxy acid **6** because it was poorly soluble in $CHCl_3$. The final product (**7**) had a mp of 143–145 °C (lit.[21] mp 143–152 °C) and an $[\alpha]_D$ of −116 (*c* 0.001 in MeOH) (lit.[21] $[\alpha]_D$ −115 (*c* 0.001 in MeOH)). The spectroscopic data obtained by ^1H and ^{13}C NMR were consistent with those reported for the natural product,[21] and the optical rotation was exactly the same as that reported in the literature.[21] When calcined hydrotalcite was used instead of DMAP, the reaction proceeded with a yield of 66%. No acyl ureas were observed in the ^1H NMR spectra of the crude reaction mixtures. We can therefore conclude that the use of EDC and HOBT prevents the formation of *N*-acylureas and the epimerization of the final product.

With these results in hand, we tried to extend the example to other promoters of the macrolactonization reaction. The acid **8** could also be a precursor of **7** under the reaction conditions described above. In this case, it was necessary to prepare the silyl ether using TBDMSCl and imidazole. These two reagents were added to the hydroxy acid **6** to obtain both the ether and ester of TBDMS. Selective hydrolysis of the silyl ester was achieved by addition of LiOH; the corresponding carboxylic acid **8** was obtained with a yield of 91% (Scheme 4) The reaction was conducted under neutral conditions using $TBABF_4$ and led to the macrolactone **7** with a 62% yield (Table 6, entry 1). Finally, the reaction was carried out in the presence of a Lewis acid ($BF_3{\cdot}Et_2O$, $SnCl_4$ or $TiCl_4$) under high-dilution conditions. $SnCl_4$ and $TiCl_4$ did not promote the macrolactonization reaction (Table 6, entries 3 and 4), but $BF_3{\cdot}Et_2O$ did. However, the results with $BF_3{\cdot}Et_2O$ were not as good as those observed with $TBABF_4$. Indeed, Sansalvamide A was obtained with a yield of only 30% (Table 6, entry 2).



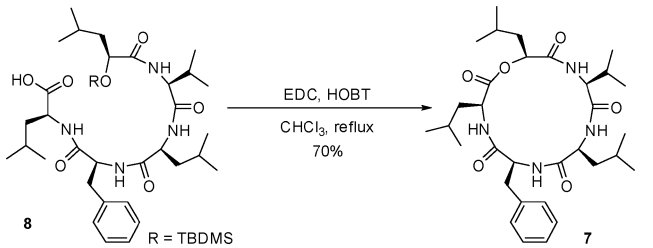
Scheme 3 Synthesis of Sansalvamide A.

Scheme 4 Protection of the alcohol group.

Conclusions

We developed a facile and highly efficient macrolactonization of ω-hydroxy acids based on the high reactivity of benzotriazole esters. To obtain excellent yields, the presence of HOBT was required. The advantage of our approach is that the reaction can be performed under basic, acidic or neutral conditions using DMAP, $BF_3{\cdot}Et_2O$ or $TBABF_4$. A calcinated hydrotalcite was also used as a base instead of DMAP, which led to excellent results. To further demonstrate the synthetic value of our method, we applied the method to the last step of the orthogonal synthesis of the antitumor agent Sansalvamide A. Sansalvamide A was thus obtained with an overall yield of 34%. We believe that our protocol will find use in the efficient macrolactonization of ω-hydroxy acids and facilitate the synthesis of bioactive molecules.

Table 6 Synthesis of Sansalvamide A[a,b]



Entry	Promoter	Yield (%)[c]
1	$TBABF_4$	62
2	$BF_3{\cdot}Et_2O$	30
3	$SnCl_4$	—
4	$TiCl_4$	—

[a] Reagents and conditions for the macrolactonization reaction: acid **8** (1 mmol), EDC (1 mmol), HOBT (1 mmol), promoter (1 mmol), $CHCl_3$ (50 mL), reflux, 18 h. [b] The ω-hydroxy acid was dissolved in $CHCl_3$ (10 mL) and was slowly added using a syringe pump over the course of 18 h. [c] Yield of isolated product after chromatographic purification.

Experimental section

General Experimental

All reactions were conducted under a dried argon stream. All the chemicals were purchased from Aldrich Chemical Co and used without further purification unless stated otherwise. Yields refer to the chromatographically and spectroscopically (^1H and ^{13}C) homogeneous materials, unless otherwise stated. All glassware utilized was flame-dried before use. Reactions were monitored by TLC carried out on 0.25 mm Macherey Nagel silica gel plates. Developed TLC plates were visualized under a short-wave UV lamp and by heating plates that were dipped in $Ce(SO_4)_3$. Flash column chromatography (FCC) was performed using flash silica gel (230–400) and employed a solvent polarity correlated with TLC mobility. Optical rotations were measured at 598 nm on a Jasco DIP-370 digital polarimeter using a 100 mm cell. NMR experiments were conducted on a Varian 300 MHz instrument using $CDCl_3$ (99.9% D) as the solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.26 ppm ^1H, 77.0 ppm ^{13}C) or Me_4Si as an internal reference (0.00 ppm). Chemical shifts are in parts per million (ppm). Mass spectra were recorded on Jeol JS102 high-resolution mass spectrometer.

The hydrotalcite was characterized by powder XRD with Cu-Kα radiation, using a Siemens diffractometer in the range from 4 to 70° (2θ). FT-IR spectra were recorded on a Nicolet Magna 750 spectrometer, data collection was performed using DRIFT and KBr disc techniques. DTA and TGA analyses were carried out in a Dupont thermobalance, using He flow at a heating rate of 10 °C min^{-1}. Specific surface areas were calculated by N_2 adsorption at 75.25 K (BET method) using a Micromeritics ASAP 2000 instrument, the samples were first out-gassed at 523 K.

General procedure for macrolactonization under basic conditions

Synthesis of oxacycloheptadecan-2-one. A solution of HOBT (28 mg, 0.18 mmol), EDC (36 mg, 0.18 mmol) and DMAP (22 mg, 0.18 mmol) in ethanol-free chloroform (50 mL) was brought to reflux. Then, a solution of 16-hydroxyhexadecanoic acid (50 mg, 0.18 mmol) in 10 mL of THF was infused *via* syringe pump over 18 h, the reaction mixture was filtered and evaporated. It was then diluted with ethyl acetate (50 mL), washed with 10% citric acid solution (2 × 30 mL), 10% $NaHCO_3$ solution (2 × 30 mL), brine (2 × 30 mL), dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified through silica gel column chromatography (25 × 2.5 cm). Elution was with hexane and then with 3% THF–hexane. In this way, oxacyclohexadecan-2-one was obtained as white solid (45 mg, 97%). Mp 48 °C; IR (KBr) 2920, 2849, 1733 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.12 (2H, t, J = 5.6 Hz), 2.33 (2H, t, J = 6.4 Hz), 1.62 (4H, m), 1.31 (22H, m); ^{13}C NMR ($CDCl_3$): δ 174, 64.3, 34.7, 29.5, 28.7, 28.2, 27.9, 27.8, 27.7, 27.1, 27, 26.9, 26.8, 25.6, 25; CIMS: m/z 283 [M+29] (20), 255 [M+1] (100), 253 (36), 237 (50), 219 (13), 171 (9), 157 (8), 143 (6).

Synthesis of oxacyclohexadecan-2-one. Following the general procedure, the reaction was carried out starting from HOBT (29 mg, 0.19 mmol), EDC (37 mg, 0.19 mmol), DMAP (23 mg, 0.19 mmol) and 15-hydroxypentadecanoic acid (50 mg, 0.19 mmol) in ethanol-free chloroform (50 mL). When the reaction was finished the reaction crude was purified by flash column chromatography on silica gel using hexane and then with 3% THF–hexane. In this way, oxacyclopentadecan-2-one was obtained as white solid (44 mg, 95%). Mp 34 °C; IR (KBr) 2923, 2850, 1732, 1457, 1164 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.13 (2H dd, J = 5.6, 5.2 Hz), 2.33 (2H, t, J = 6.6 Hz), 1.66 (4H, m), 1.32 (20H, br s); ^{13}C RMN ($CDCl_3$): δ 174, 63.9, 34.4, 28.4, 27.8, 27.1, 26.9, 26.7, 26.4, 26.1, 25.9, 25.1, 24; CIMS: m/z 269 [M+29] (16), 241 [M+1] (100), 223 (54), 205 (18), 185 (5), 171 (6), 157 (7), 143 (7), 139 (7).

Synthesis of oxacyclotridecan-2-one. Following the general procedure, the reaction was carried out starting from HOBT (35 mg, 0.23 mmol), EDC (44 mg, 0.23 mmol), DMAP (28 mg, 0.23 mmol) and 12-hydroxydodecanoic acid (50 mg, 0.23 mmol) in ethanol-free chloroform (50 mL). When the reaction was finished the reaction crude was purified by flash column chromatography on silica gel using hexane and then with 3% THF–hexane. In this way, oxacyclotridecan-2-one was obtained as white solid (39 mg, 86%). Mp 40 °C; IR (KBr) 2916, 2846, 1727, 1272, 1107 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.12 (2H, t, J = 5.8 Hz), 2.31 (2H, t, J = 6.8 Hz), 1.58 (4H, m), 1.28 (14H, m); ^{13}C NMR ($CDCl_3$): δ 174.3, 64.3, 34.1, 27.4, 26.6, 26.4, 25.4, 25.3, 24.8, 24.5, 24.1; CIMS: m/z 227 [M+29] (65), 199 [M+1] (71), 181 (100), 163 (37), 143 (6) 143 (5), 139 (5), 97 (10).

Synthesis of oxacycloundecan-2-one. Following the general procedure, the reaction was carried out starting from HOBT (149 mg, 0.98 mmol), EDC (187 mg, 0.98 mmol), DMAP (119 mg, 0.98 mmol) and 10-hydroxydecanoic acid (200 mg, 0.98 mmol) in ethanol-free chloroform (100 mL). When the reaction was finished the reaction crude was purified by flash column chromatography on silica gel using hexane and then with 3% THF–hexane. In this way, oxacycloundecan-2-one was obtained as yellow oil (48 mg, 29%). IR (KBr) 2916, 2846, 1726, 1271, 1107 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.13 (2H, t, J = 5.6 Hz), 2.31 (2H, t, J = 6.8 Hz), 1.57 (4H, m), 1.30 (10H, s); ^{13}C NMR ($CDCl_3$): δ 174, 64.3, 34.7, 27.5, 26.7, 26.3, 25.5, 25.3, 24.5, 24.2; CIMS: m/z 199 [M+29] (49), 171 [M+1] (45), 153 (100), 135 (29), 111 (7), 171 (9), 157 (8), 143 (6).

General procedure for the preparation of ω-(*tert*-butyldimethylsilyloxy)-acids

Synthesis of TBDMSO$(CH_2)_{15}CO_2H$. 16-Hydroxyhexadecanoic acid (150 mg, 0.55 mmol), imidazole (187 mg, 2.75 mmol) and TBDMSCl (331 mg, 2.2 mmol) were dissolved in anhydrous CH_2Cl_2 (50 mL) and stirred at room temperature for 48 h. Then, the reaction mixture was concentrated under vacuum and diluted with ethyl acetate (50 mL). The organic layer was washed successively with 10% citric acid solution (2 × 30 mL), 10% $NaHCO_3$ solution (2 × 30 mL) and brine (2 × 30 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. To the crude product in THF (5 mL) was added a 2.5 N aqueous solution of LiOH (3.9 mL, 9.9 mmol) and the mixture was then stirred at room temperature for 4 h. Solid CO_2 was added to the separated THF layer and the mixture was evaporated *in vacuo* to leave a solid which was taken up in water (25 mL), then acidified to pH 4 with citric acid and extracted with ethyl acetate (2 × 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to give a white solid (267 mg, 91%). ^{1}H NMR ($CDCl_3$): δ 3.6 (2H, t, J = 6.4 Hz), 2.35 (2H, t, J = 7.4 Hz), 1.56 (4H, t,t), 1.26 (22H, m), 0.9 (9H, m), 0.1 (1H,s), 0.05 (4H, s); ^{13}C NMR ($CDCl_3$): δ 179.5, 63.4, 34, 32.9, 29.6, 29.4, 29.2, 26, 25.8, 24.7, 18.4, –5.2.

Synthesis of TBDMSO$(CH_2)_{14}CO_2H$. Following the general procedure, the reaction was carried out starting from 15-hydroxypentadecanoic acid (150 mg, 0.58 mmol), imidazole (197 mg, 2.9 mmol) and TBDMSCl (349 mg, 2.3 mmol). In this way, a white solid was obtained (201 mg, 93%). ^{1}H NMR ($CDCl_3$): δ 5.44 (1H, s), 3.6 (2H, t, J = 6.4 Hz), 2.34 (2H, t, J = 7.4 Hz), 1.55 (4H, m), 1.26 (15H, s), 0.90 (14H, m), 0.1 (3H, s), 0.05 (3H, s); ^{13}C NMR ($CDCl_3$): δ 179.2, 63.4, 34, 32.9, 29.6, 29.4, 29.2, 29.1, 26, 25.8, 25.6, 24.7, 18.4, 18, –3.6, –5.2.

Synthesis of TBDMSO$(CH_2)_{11}CO_2H$. Following the general procedure, the reaction was carried out starting from 12-hydroxydodecanoic acid (180 mg, 0.83 mmol), imidazole (283 mg, 4.16 mmol) and TBDMSCl (501 mg, 3.32 mmol). In this way, a white solid was obtained (258 mg, 94%). ^{1}H NMR ($CDCl_3$): δ 6.28 (1H,s), 3.59 (2H, t, J = 6.6 Hz), 2.34 (2H, t, J = 7.4 Hz), 1.55 (4H, t,t), 1.27 (12H, s), 0.9 (12H, s), 0.09 (6H, s,s); ^{13}C NMR ($CDCl_3$): δ 179.4, 63.4, 33.9, 32.9, 29.6, 29.4, 26, 25.8, 24.7, 18.4, –5.2.

Synthesis of TBDMSO$(CH_2)_9CO_2H$. Following the general procedure, the reaction was carried out starting from 10-hydroxydecanoic acid (150 mg, 0.74 mmol), imidazole (252 mg, 3.7 mmol) and TBDMSCl (447 mg, 2.96 mmol). In this way, a white solid was obtained (213 mg, 91%). ^{1}H NMR ($CDCl_3$): δ 5.14 (1H, s), 3.31 (2H, t, J = 6.4 Hz), 2.18 (2H, t, J = 7.4 Hz), 1.60 (4H, m), 1.3 (12H, m), 0.9 (6H, m), 0.1 (3H, m); ^{13}C NMR ($CDCl_3$): δ 179.4, 62.9, 34, 32.5, 29.3, 29.1, 29, 25.6, 24.7, –3.6, –5.2.

General procedure for macrolactonization under neutral conditions

Synthesis of oxacycloheptadecan-2-one. A solution of HOBT (47 mg, 0.31 mmol), EDC (59 mg, 0.31 mmol) and $TBABF_4$ (102 mg, 0.31 mmol) in ethanol-free chloroform (50 mL) was brought to reflux. Then, a solution of 16-(*tert*-butyldimethylsilyoxy)-hexadecanoic acid (120 mg, 0.31 mmol) in 10 mL of chloroform was infused *via* syringe pump over 18 h, the reaction mixture was filtered and evaporated. Then diluted with ethyl acetate (50 mL), washed with 10% citric acid solution (50 mL), 10% $NaHCO_3$ solution (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified through silica gel column chromatography (25 × 2.5 cm). Elution was with hexane and then with 3% THF–hexane. In this way, oxacyclohexadecan-2-one was obtained as white solid (74 mg, 93%).

Synthesis of oxacyclohexadecan-2-one. Following the general procedure, the reaction was carried out starting from HOBT (44 mg, 0.29 mmol), EDC (55 mg, 0.29 mmol), $TBABF_4$ (95 mg, 0.29 mmol) and 15-(*tert*-butyldimethylsilyoxy)-pentadecanoic acid (110 mg, 0.29 mmol) in ethanol-free chloroform (50 mL). When the reaction was finished the reaction crude was purified by flash column chromatography on silica gel using hexane and then with 3% THF–hexane. In this way, oxacyclopentadecan-2-one was obtained as white solid (63 mg, 91%).

Synthesis of oxacyclotridecan-2-one. Following the general procedure, the reaction was carried out starting from HOBT (153 mg, 1 mmol), EDC (206 mg, 1 mmol), $TBABF_4$ (329 mg, 1 mmol) and 12-(*tert*-butyldimethylsilyoxy)-dodecanoic acid (341 mg, 1 mmol) in ethanol-free chloroform (50 mL). When the reaction was finished the reaction crude was purified by flash column chromatography on silica gel using hexane and then with 3% THF–hexane. In this way, oxacyclotridecan-2-one was obtained as white solid (162 mg, 86%).

Synthesis of oxacycloundecan-2-one. Following the general procedure, the reaction was carried out starting from HOBT (153 mg, 1 mmol), EDC (206 mg, 1 mmol), $TBABF_4$ (329 mg, 1 mmol) and 10-(*tert*-butyldimethylsilyoxy)-decanoic acid (303 mg, 1 mmol) in ethanol-free chloroform (50 mL). When the reaction was finished the reaction crude was purified by flash column chromatography on silica gel using hexane and then with 3% THF–hexane. In this way, oxacycloundecan-2-one was obtained as yellow oil (48 mg, 29%).

General procedure for macrolactonization under acid conditions

Synthesis of oxacycloheptadecan-2-one. A solution of HOBT (38 mg, 0.25 mmol), EDC (48 mg, 0.25 mmol) and $BF_3{\cdot}Et_2O$ (35 mg, 0.25 mmol) in ethanol-free chloroform (50 mL) was brought to reflux. Then, a solution of 16-(*tert*-butyldimethylsilyoxy)-hexadecanoic acid (100 mg, 0.25 mmol) in 10 mL of chloroform was infused *via* syringe pump over 18 h, the reaction mixture was filtered and evaporated. Then diluted with ethyl acetate (50 mL), washed with 10% citric acid solution (50 mL), 10% $NaHCO_3$ solution (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified through silica gel column chromatography (25 × 2.5 cm). Elution was with hexane and then with 3% THF–hexane. In this way, oxacyclohexadecan-2-one was obtained as white solid (58 mg, 90%).

Synthesis of oxacyclohexadecan-2-one. Following the general procedure, the reaction was carried out starting from HOBT (49 mg, 0.32 mmol), EDC (61 mg, 0.32 mmol), $BF_3{\cdot}Et_2O$ (45 mg, 0.32 mmol) and 15-(*tert*-butyldimethylsilyoxy)-pentadecanoic

acid (120 mg, 0.32 mmol) in ethanol-free chloroform (50 mL). When the reaction was finished the reaction crude was purified by flash column chromatography on silica gel using hexane and then with 3% THF–hexane. In this way, oxacyclopentadecan-2-one was obtained as white solid (69 mg, 90%).

Synthesis of oxacyclotridecan-2-one. Following the general procedure, the reaction was carried out starting from HOBT (64 mg, 0.42 mmol), EDC (206 mg, 0.42 mmol), $BF_3{\cdot}Et_2O$ (59 mg, 0.42 mmol) and 12-(*tert*-butyldimethylsilyoxy)-dodecanoic acid (140 mg, 0.42 mmol) in ethanol-free chloroform (50 mL). When the reaction was finished the reaction crude was purified by flash column chromatography on silica gel using hexane and then with 3% THF–hexane. In this way, oxacyclotridecan-2-one was obtained as white solid (65 mg, 79%).

Synthesis of oxacycloundecan-2-one. Following the general procedure, the reaction was carried out starting from HOBT (50 mg, 0.33 mmol), EDC (63 mg, 0.33 mmol), $BF_3{\cdot}Et_2O$ (46 mg, 0.33 mmol) and 10-(*tert*-butyldimethylsilyoxy)-decanoic acid (100 mg, 0.33 mmol) in ethanol-free chloroform (50 mL). When the reaction was finished the reaction crude was purified by flash column chromatography on silica gel using hexane and then with 3% THF–hexane. In this way, oxacycloundecan-2-one was obtained as yellow oil (13 mg, 24%).

Synthesis of Sansalvamide A.

2-Hydroxy-4-methyl-pentanoic acid ***2***. To stirred solution of L-leucine (1 g, 7.62 mmol) in 0.5 mol H_2SO_4 (30 mL) was added dropwise a solution of $NaNO_2$ (3 g) in water (10 mL) over a period of 3 h at 0 °C, after which it was left for 24 h at room temperature. Then the solution was extracted with ethyl ether (2 × 50 ml). The combined extracts were washed with brine (2 × 50 ml), dried over Na_2SO_4, filtered and concentrated in vacuum. The sticky solid residue was recrystallized from hexane to give white solid (754 mg, 75%, m.p. 78–80 °C).^{1}H NMR ($CDCl_3$): δ 7.6 (2H, br, s), 4.23 (1H, dd, J = 7.8, 5.4 Hz), 1.89 (1H, m), 1.62 (1H, ddd J = 13.8, 6.6, 5.4 Hz), 1.57 (1H, ddd, J = 13.8, 7.8, 6.6 Hz), 0.95 (6H, d, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 178.5, 68.7, 43, 24.3, 23, 21.3; IR (Pellet/KBr): 3426, 2958, 2702, 2627, 2486, 1710, 1269, 1227, 1138, 1082, 900, 688, 525 cm^{-1}.

O-*LeuValOH* ***3***. *General procedure.* A solution of L-valine methyl ester hydrochloride (1.04 g, 6.24 mmol) and DIPEA (1 g, 7.8 mmol) in anhydrous CH_2Cl_2 (30 mL) was stirred at 0 °C under an argon atmosphere. Then a solution of α-hydroxy carboxylic acid **2** (680 mg, 5.2 mmol), HOBT (0.79 g, 5.2 mmol) and EDC (1.07 g, 5.2 mmol) CH_2Cl_2 (30 mL) was added and stirred for 1 h at 0 °C under argon atmosphere. After stirring for 18 h at room temperature, the reaction mixture was filtered and evaporated. The residue was dissolved in ethyl acetate (50 ml) and washed successively with 10% citric acid solution (2 × 25 mL), 10% $NaHCO_3$ solution (2 × 25 mL), 10% K_2CO_3 solution (2 × 25 mL) and brine (2 × 25 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuum to give crude hydroxy ester which was used in the next reaction without further purification. To the crude product in THF (25 mL) was added a 2.5 N aqueous solution of LiOH (21.6 mL, 54 mmol) and the mixture was then stirred at room temperature for 4 h. Solid CO_2 was added to the separated THF layer and the mixture was evaporated *in vacuo* to leave a solid which was taken up in water (30 mL), then acidified to pH 3 with citric acid and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to give white solid (1.09 g, 91%). ^{1}H NMR ($CDCl_3$): δ 7.27 (1H, d, J = 9 Hz), 6.13 (2H, s), 4.46 (1H, dd, J = 9, 4.8), 4.22 (1H, dd J = 9.3, 3.9 Hz), 2.26 (1H, m), 1.86 (1H, m), 1.59 (1H, ddd J = 13.8, 9.3, 6.6 Hz), 1.54 (1H, ddd J = 13.8, 6.6, 3.9 Hz), 0.98 (6H, d, J = 6.9 Hz) y 0.95 (6H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 176.4, 174.7, 71, 56.8, 43.56, 30.5, 24.6, 23.4, 21.4, 19, 17.5; IR (Pellet/KBr): 3381, 3211, 2961, 2874, 1747, 1636, 1536, 1391, 1144, 597, 497. HRMS (FAB) calcd for $C_{11}H_{22}O_4N_1$ 232.1549, found 232.1548.

O-*LeuValLeuOH* ***4***. Following the general procedure, the reaction was carried out starting from L-leucine methyl ester hydrochloride (654 mg, 3.6 mmol), hydroxy carboxylic acid **3** (708 mg, 3 mmol), DIPEA (581 mg, 4.51 mmol), HOBT (459 mg, 3 mmol) and EDC (465 mg, 3 mmol), to give 957 mg of a white solid (92%). ^{1}H NMR ($CDCl_3$): δ 7.38 (1H, d, J = 9 Hz), 7.27 (1H, d, J = 7.8 Hz), 4.47 (1H, ddd, J = 9,3, 7.8, 5.1 Hz), 4.35 (1H, dd, J = 9, 6 Hz), 4.09 (1H, dd, J = 9.9, 3.3 Hz), 2.2 (1H, m), 1.87 (1H, m), 1.73-1.42 (5H, m), 0.95 (3H, d, J = 6.9 Hz), 0.94 (3H, d, J = 6.6 Hz), 0.94 (6H, d, J = 6.3 Hz), 0.93 (3H, d, J = 6.6 Hz), 0.9 (3H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 176.9, 173.9, 170.7, 71.1, 56.9, 50.3, 43.4, 30.5, 24.6, 23.4, 21.4, 19, 17.5; IR (Pellet/KBr): 3281, 2961, 2879, 1724, 1645, 1467, 1240, 1144, 1078, 682, 580. HRMS (FAB) calcd for $C_{17}H_{33}O_5N_2$ 345.2389, found 345.2385.

O-*LeuValLeuPheOH* ***5***. Following the general procedure, the reaction was carried out starting from L-phenylalanine methyl ester hydrochloride (719 mg, 3.33 mmol), hydroxy carboxylic acid **4** (957 mg, 2.78 mmol), DIPEA (538 mg, 4.17 mmol), HOBT (425 mg, 2.78 mmol) and EDC (430 mg, 2.78 mmol), to give 1.17 g of a white solid (86%). ^{1}H NMR ($CDCl_3$): δ 7.42 (1H, d, J = 8.4 Hz), 7.31 (1H, d, J = 9.9 Hz), 7.29-7.16 (5H, m), 7.02 (1H, d, J = 7.5 Hz), 5.67 (2H, brs), 4.71 (1H, ddd, J = 7.5, 6.6, 5.4 Hz), 4.41 (1H, td, J = 8.4, 5.4 Hz), 4.32 (1H, dd, J = 9.3, 6 Hz), 4.09 (1H, dd, J = 9.6, 3.3 Hz), 3.19 (1H, dd, J = 14.1, 5.7 Hz), 3 (1H, dd, J = 14.1, 6.6 Hz), 2.2 (1H, m), 1.6-1.5 (5H, m), 1.8 (1H, m), 0.92 (3H, d, J = 6.6 Hz), 0.91 (6H, d, J = 6.6 Hz), 0.9 (6H, d, J = 6.3 Hz), 0.86 (3H, d, J = 6.6 Hz);^{13}C NMR ($CDCl_3$): δ 175.2, 172.6, 171.4, 171.1, 136.3, 129.1, 128, 126.4, 70.4, 57.3, 53, 51.6, 43.3, 40.2, 37.1, 30.3, 24.3, 24.2, 23.2, 22.6, 21.4, 21.1, 19, 17.2; IR (Pellet/KBr): 3366, 3281, 3095, 2961, 2879, 1724, 1645, 1535, 1467, 1389, 1276, 1240, 1144, 1078, 927, 682, 580, 466. HRMS (FAB) calcd for $C_{26}H_{42}O_6N_3$ 492.3074, found 492.3078.

O-*LeuValLeuPheLeuOH* ***6***. Following the general procedure, the reaction was carried out starting from L-leucine methyl ester hydrochloride (521 g, 2.86 mmol), hydroxy carboxylic acid **5** (1.17 g, 2.39 mmol), DIPEA (463 mg, 3.58 mmol), HOBT (365 mg, 2.39 mmol) and EDC (370 mg, 2.39 mmol), to give 1.317 mg of a white solid (91%). ^{1}H NMR (CD_3OD): δ 8.12 (1H d, J = 8.4 Hz), 8.00 (1H, d, J = 7.8. Hz), 7.9 (1H, d, J = 8.1 Hz), 7.5 (1H, d, J = 9 Hz), 7.23-7.14 (5H, m), 4.54 (1H, td, J = 8.4, 4.8 Hz), 4.26 (ddd, 1H, J = 7.8, 6.9, 6.6 Hz), 4.26 (1H, ddd, J = 7.8, 6.9, 6.6 Hz) 4.17 (1H, dd, J = 9, 2.7 Hz), 3.85 (1H, td, J = 9, 4.2 Hz), 3.02 (1H, dd, J = 14.1, 4.8 Hz), 2.79 (1H, dd, J = 14.1, 8.7 Hz), 1.89 (1H, m), 1.73 (1H, m), 1.59 (3H, m), 1.52-1.32 (5H, m), 0.84 (6H, d, J = 6.6 Hz), 0.83 (6H, d, J = 6.6 Hz), 0.82 (3H, d, J = 6.6 Hz), 0.78 (3H, d, J = 6.6 Hz), 0.75 (3H, d, J = 6.6 Hz), 0.70 (3H, d, J = 6.6 Hz); ^{13}C NMR (CD_3OD): δ 174.4, 174.2, 171.5, 170.5, 137.6, 129.2, 128, 126.2, 69.7, 56.4, 53.2, 51.15, 50.7, 43.7, 40.9,

40.6, 37.2, 31.3, 24.2, 24.1, 24, 23.4, 22.9, 21.7, 21.5, 19.2, 17.7; IR (Pellet/KBr): 3286, 3084, 2959, 2931, 2872, 1720, 1642, 1549, 697. HRMS (FAB) calcd for $C_{32}H_{53}O_7N_4$ 605.3914, found 605.3906.

*TBDMSO-LeuValLeuPheLeuOH **8**.* Hydroxy acid **8** (250 mg, 0.41 mmol), imidazole (139 mg, 2 mmol) and TBDMSCl (247 mg, 1.6 mmol) were dissolved in anhydrous CH_2Cl_2 and stirred at room temperature for 48 h. Then the reaction mixture was concentrated under vacuum, diluted with ethyl acetate (50 mL). The organic layer was washed successively with 10% citric acid solution (2 × 30 mL), 10% $NaHCO_3$ solution (2 × 30 mL) and brine (2 × 30 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. To the crude product in THF (5 mL) was added a 2.5 N aqueous solution of LiOH (2.9 mL, 7.38 mmol) and the mixture was then stirred at room temperature for 4 h. Solid CO_2 was added to the separated THF layer and the mixture was evaporated *in vacuo* to leave a solid which was taken up in water (25 mL), then acidified to pH 4 with citric acid and extracted with ethyl acetate (2 × 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to give a white solid (267 mg, 91%). ^{1}H NMR (CD_3OD): δ 8.12 (1H d, J = 8.4 Hz), 8.00 (1H, d, J = 7.8. Hz), 7.9 (1H, d, J = 8.1 Hz), 7.5 (1H, d, J = 9 Hz), 7.23-7.14 (5H, m), 4.54 (1H, td, J = 8.4, 4.8 Hz), 4.26 (ddd, 1H, J = 7.8, 6.9, 6.6 Hz), 4.26 (1H, ddd, J = 7.8, 6.9, 6.6 Hz) 4.17 (1H, dd, J = 9, 2.7 Hz), 3.85 (1H, td, J = 9, 4.2 Hz), 3.02 (1H, dd, J = 14.1, 4.8 Hz), 2.79 (1H, dd, J = 14.1, 8.7 Hz), 1.89 (1H, m), 1.73 (1H, m), 1.59 (3H, m), 1.52-1.32 (5H, m), 0.86 (9H, s), 0.84 (6H, d, J = 6.6 Hz), 0.83 (6H, d, J = 6.6 Hz), 0.82 (3H, d, J = 6.6 Hz), 0.78 (3H, d, J = 6.6 Hz), 0.75 (3H, d, J = 6.6 Hz), 0.70 (3H, d, J = 6.6 Hz), 0.04 (6H, s); ^{13}C NMR (CD_3OD): δ 174.4, 174.2, 171.5, 170.5, 137.6, 129.2, 128, 126.2, 69.7, 56.4, 53.2, 51.15, 50.7, 43.7, 40.9, 40.6, 37.2, 31.3, 29.4, 25.8, 24.2, 24.1, 24, 23.4, 22.9, 21.7, 21.5, 19.2, 17.7, –5.2; IR (Pellet/KBr): 3285, 3082, 2960, 2930, 2871, 1722, 1643, 1548, 699. HRMS (FAB) calcd for $C_{38}H_{67}O_7N_4Si$ 719.0387, found 719.0386.

*Macrolactonization of hydroxyacid **6** under basic conditions.* A solution of HOBT (29 mg, 0.19 mmol), EDC (39 mg, 0.19 mmol) and DMAP (36 mg, 0.19 mmol) in ethanol-free chloroform (50 mL), was brought to reflux. Then a solution of hydroxy acid **6** (100 mg, 0.16 mmol) in 10 mL of THF was infused *via* syringe pump over 18 h, the reaction mixture was filtered and evaporated. It was then diluted with ethyl acetate (50 mL), washed with 10% citric acid solution (2 × 30 mL), 10% $NaHCO_3$ solution (2 × 30 mL), brine (2 × 30 mL), dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified through silica gel column chromatography (25 × 2.5 cm). Elution was with hexane and then with 70% ethyl acetate–hexane. In this way, Sansalvamide A **7** was obtained as white solid (64 mg, 69%, m.p. 143–145 °C). ^{1}H NMR (CD_3OD): δ 7.28-7.23 (5H, m), 5.6 (1H, dd, J = 9, 4.8 Hz), 4.71 (1H, dd, J = 9.6, 5.7 Hz), 4.55 (1H, dd, J = 10.8, 4.8 Hz), 4.09 (1H, d, J = 8.4 Hz), 3.72 (1H, dd, J = 9, 5.1 Hz), 3.24 (1H, dd, J = 13.8, 4.8 Hz), 3.08 (1H, dd, J = 13.8, 10.8 Hz), 2.07 (1H, oct, J = 6.6 Hz), 1.86-1.64 (2H, m), 1.76–1.88 (2H, m), 1.72 (1H, m), 1.6–1.64 (1H, m), 1.62 (1H, m), 1.41 (1H, m), 1.38 (1H,m), δ 0.99 (6H, d, J = 6.6 Hz), 0.96 (6H, d, J = 6.6 Hz), 0.92 (3H, d, J = 6.6 Hz), 0.86 (3H, d, J = 6.6 Hz), 0.85 (3H, d, J = 6.6 Hz), 0.81 (3H, d, J = 6.6 Hz; ^{13}C NMR ($CDCl_3$): δ 174.09, 174.01, 173.6, 172.8, 171.4, 138.7, 130.2, 129.7, 128, 76.3, 60.6, 58.1, 56.4, 52.5, 41.7, 41.3, 39.6, 38, 32.1, 26.2, 26.1, 25.9, 23.5, 23.3, 23.1, 22.4, 22.1, 19.9, 18.7; IR (Pellet/KBr): 3397, 3277, 2963, 2934, 2873, 1746, 16665, 1533, 1467, 1372, 1276, 1053. HRMS (FAB) calcd for $C_{32}H_{51}O_6N_4$ 587.3809, found 587.3812. ESI MS (M+H) 587.4

*Macrolactonization of hydroxy acid **6** under neutral conditions.* A solution of HOBT (49 mg, 0.32 mmol), EDC (66 mg, 0.32 mmol) and $TBABF_4$ (105 mg, 0.32 mmol) in ethanol-free chloroform (50 mL) was brought to reflux. Then a solution of hydroxy acid **8** (200 mg, 0.27 mmol) in 10 mL of chloroform was infused *via* syringe pump over 18 h, the reaction mixture was filtered and evaporated. Then diluted with ethyl acetate (75 mL), washed with 10% citric acid solution (50 mL), 10% $NaHCO_3$ solution (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified through silica gel column chromatography (25 × 2.5 cm). Elution was with hexane and then with 70% ethyl acetate–hexane. In this way, Sansalvamide A **7** was obtained as white solid (98 mg, 62%, m.p. 143–144 °C)

*Macrolactonization of hydroxy acid **6** under acidic conditions.* A solution of HOBT (49 mg, 0.32 mmol), EDC (66 mg, 0.32 mmol) and $BF_3{\cdot}Et_2O$ (45 mg, 0.32 mmol) in ethanol-free chloroform (50 mL), was brought to reflux. Then a solution of hydroxy acid **8** (200 mg, 0.27 mmol) in 10 mL of chloroform was infused *via* syringe pump over 18 h, the reaction mixture was filtered and evaporated, then diluted with ethyl acetate (75 mL), washed with 10% citric acid solution (50 mL), 10% $NaHCO_3$ solution (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified through silica gel column chromatography (25 × 2.5 cm). Elution was with hexane and then with 70% ethyl acetate–hexane. In this way, Sansalvamide A **7** was obtained as white solid (98 mg, 62%, m.p. 143–144 °C)

Preparation of calcined Mg–Al hydrotalcite. Hydrotalcites Mg–Al with x = Al/(Al + Mg) ratio 0.33 was prepared by coprecipitation following the procedure described by RLeichle.[28] $Mg_{10}Al_2(OH)_{24}CO_3{\cdot}6H_2O$:$Al(NO_3)_3{\cdot}9H_2O$ (0.01 mol) and $Mg(NO_3)_2{\cdot}6H_2O$ (0.05 mol) were dissolved in deionized water (70 mL). A second deionized water solution (100 mL) of Na_2CO_3 (0.1 mol) and NaOH (0.35 mol) was prepared. The first solution was slowly added to the second one. The resulting mixture was heated at 338 K with vigorous stirring for 18 h. After the heating period, the slurry was cooled to room temperature, washed with deionized water until pH ≈ 9 and dried at 383 K for 18 h. Hydrotalcites were activated by calcination at a rate of 2 °C min^{-1} up to 773 K and maintained for 2 h in a flow of air. Samples were then cooled in dry nitrogen and stored.

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