JOC*Note*

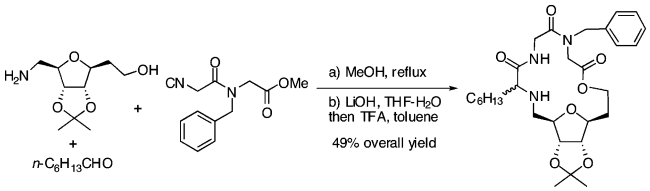
Rapid Synthesis of Cyclodepsipeptides Containing a Sugar Amino Acid or a Sugar Amino Alcohol by a Sequence of a Multicomponent Reaction and Acid-Mediated Macrocyclization

Carine Bughin, Géraldine Masson, and Jieping Zhu*

Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette Cedex, France

zhu@icsn.cnrs-gif.fr

Received October 20, 2006



Cyclodepsipeptides incorporating a sugar amino acid (alcohol) have been synthesized. A three-component reaction of a sugar amino acid (SAA) derivative, an aldehyde, and a dipeptide isonitrile in refluxing methanol afforded the corresponding 5-aminooxazole which, after saponification, underwent a trifluoroacetic acid promoted macrocyclization to furnish the cyclic sugar amino acids.

Amino acids and sugars are two major building blocks from which the biopolymers of life are formed in nature. The sugar amino acids (SAAs), defined as sugars containing at least one amino and at least one carboxyl group, also exist in nature.[1] For example, the sialic acid, responsible for many inter- and intracellular recognition events, is found in all living organisms with the exception of certain bacteria.[2] Glucosaminuronic acid is found in A-40926, a structurally complex glycopeptide of the vancomycine family of antibiotics.[3] Synthetic linear oligomers of SAAs, first introduced by Fuchs and Lehmann in mid 1970s,[4] have been proposed to mimic oligosaccharides and oligonucleotides[5] and have been shown to adopt well-defined three-dimensional structures.[6] On the other hand, cyclic peptides incorporating sugar amino acids belong to a relatively new type of designed hybrid structure. Kessler and co-workers were the first to study and to demonstrate the potential of such molecules as peptidomimetics and artificial receptors for host−guest chemistry.[7] Since then, several types of cyclic oligomers incorporating open-chain,[8] pyranoid,[9] furanoid sugar amino acid[10] and oxetane units[11] have been synthesized and their conformational properties were thoroughly examined.[9−11] It has been demonstrated that incorporation of SAAs into the peptidic backbone can broaden the dynamic spectrum and widen the conformational space of the peptide, increasing consequently the potency as well as the specificity of the given bioactive compounds. Indeed, potent antitumor agents[12] and inhibitors of *P*-selectines[13] have been discovered from these studies indicating the potential of this approach in drug development.

A synthesis allowing one to systematically modify the amino acid and the carbohydrate residues, as well as the size of the macrocycle, is highly needed to fully exploit the potential of such hybride structures in searching for new active compounds. Previously, most of the cyclic SAAs have been synthesized by stepwise amide bond formation followed by macrolactamization.[8−11,14] We report herein an alternative and highly efficient

* To whom correspondence should be addressed. Fax: Int. code + 33 1 69077247.

(1) (a) Gervay-Hague, J.; Weathers, T. M. *J. Carbohydr. Chem.* **2002**, *21*, 867. (b) Gruner, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491. (c) Schweizer, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 230. (d) Chakraborty, T. K.; Jayaprakash, S. *Curr. Med. Chem.* **2002**, *9*, 421.

(2) Simanek, E. E.; McGarvey, G. J.; Jablonowski, J. A.; Wong, C.-H. *Chem. Rev.* **1998**, *98*, 833.

(3) (a) Waltho, J. P.; Williams, D. H.; Selva, E.; Ferrari, P. *J. Chem. Soc., Perkin Trans. I* **1987**, 2103. (b) Zhu, J. *Expert Opin. Ther. Pat.* **1999**, *9*, 1005. (c) Nicolaou, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096.

(4) (a) Fuchs, E. F.; Lehmann, J. *Chem. Ber.* **1975**, *108*, 2254. (b) Fuchs, E. F.; Lehmann, J. *Carbohydr. Res.* **1976**, *49*, 267. (c) St Hilaire, P. M.; Meldal, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1162.

(5) (a) Nicolaou, K. C.; Flörke, H.; Egan, M. G.; Barth, T.; Estevez, V. A. *Tetrahedron Lett.* **1995**, *36*, 1775. (b) Goodnow, R. A., Jr.; Richou, A.-R.; Tam, S. *Tetrahedron Lett.* **1997**, *38*, 3195. (c) Goodnow, R. A., Jr.; Tam, S.; Pruess, D. L.; McComas, W. W. *Tetrahedron Lett.* **1997**, *38*, 3199.

(6) Smith, M. D.; Claridge, T. D. W.; Tranter, G. E.; Sansom, M. S. P.; Fleet, G. W. J. *J. Chem. Soc., Chem. Commun.* **1998**, 2041.

(7) Graf von Roedern, E.; Kessler, H. *Angew. Chem., Int. Ed.* **1994**, *33*, 687.

(8) (a) Mayes, B. A.; Stetz, R. J. E.; Ansell, C. W. G.; Fleet, G. W. J. *Tetrahedron Lett.* **2004**, *45*, 153. (b) Mayes, B. A.; Simon, L.; Watkin, D. J.; Ansell, C. W. G.; Fleet, G. W. J. *Tetrahedron Lett.* **2004**, *45*, 157.

(9) (a) Graf von Roedern, E.; Lohof, E.; Hessler, G.; Hoffmann, M.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 10156. (b) Lohof, E.; Planker, E.; Mang, C.; Bukhart, F.; Dechantsreiter, M. A.; Haubner, R.; Wester, H.-J.; Schwaiger, M.; Hölzemann, G.; Goodman, S. L.; Kessler, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2761. (c) Locardi, E.; Stöckle, M.; Gruner, S. A. W.; Kessler, H. *J. Am. Chem. Soc.* **2001**, *123*, 8189. (d) Stöckle, M.; Voll, G.; Gunther, R.; Lohof, E.; Locardi, E.; Gruner, S. A. W.; Kessler, H. *Org. Lett.* **2002**, *4*, 2501. (e) Gruner, S. A. W.; Truffault, V.; Voll, G.; Locardi, E.; Stöckle, M.; Kessler, H. *Chem.−Eur. J.* **2002**, 4365. (f) Van Well, R.; Marinelli, L.; Erkelens, K.; van der Marel, G. A.; Lavecchia, A.; Overkleeft, H.; van Boom, J.; Kessler, H.; Overhand, M. *Eur. J. Org. Chem.* **2003**, 2303. (g) Raunkjaer, M.; El Oualid, F.; van der Marel, G. A.; Overkleeft, H.; Overhand, M. *Org. Lett.* **2004**, *6*, 3167. (h) Ménand, M.; Blais, J.-C.; Hamon, L.; Valéry, J.-M.; Xie, J. *J. Org. Chem.* **2005**, *70*, 4423. (i) Billing, J. F.; Nilsson, U. J. *Tetrahedron* **2005**, *61*, 863.

(10) (a) Van Well, R.; Overkleeft, H.; Overhand, M.; Vang Carstenen, E.; van der Marel, G. A.; van Boom, J. *Tetrahedron Lett.* **2000**, *41*, 9331. (b) Van Well, R.; Marinelli, L.; Altona, C.; Erkelens, K.; Siegal, G.; van Raaij, M.; Llamas-Saiz, A. L.; Kessler, H.; Novellino, E.; Lavecchia, A.; van Boom, J.; Overhand, M. *J. Am. Chem. Soc.* **2003**, *125*, 10822. (c) Grotenberg, G. M.; Timmer, M. S. M.; Llamas-Saiz, A. L.; Verdoes, M.; van der Marel, G. A.; van Raaij, M.; Overkleeft, H.; Overhand, M. *J. Am. Chem. Soc.* **2004**, *126*, 3444. (d) Grotenberg, G. M.; Buizert, A. E. M.; Llamas-Saiz, A. L.; Spalburg, E.; van Hooft, P. A. V.; de Neeling, A. J.; Noort, D.; van Raaij, M.; van der Marel, G. A.; Overkleeft, H.; Overhand, M. *J. Am. Chem. Soc.* **2006**, *128*, 7559. (e) Chakraborty, T. K.; Ghosh, S.; Jayaprakash, S. *Curr. Med. Chem.* **2002**, *9*, 421. (f) Chakraborty, T. K.; Srinivasu, P.; Bikshapathy, E.; Nagaraj, R.; Vairamani, M.; Kiran Kumar, S.; Kunwar, A. C. *J. Org. Chem.* **2003**, *68*, 6257.

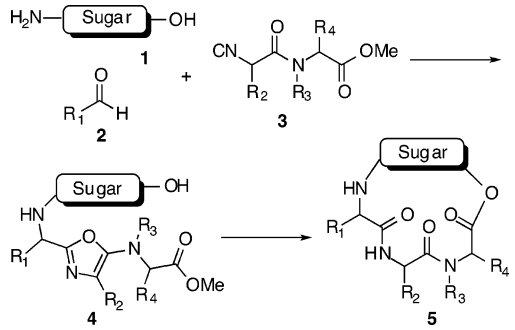
(11) Fleet, G. W. J.; Johnson, S. W.; Jones, J. H. *J. Pept. Sci.* **2006**, *12*, 559.

(12) (a) Gruner, S. A. W.; Kéri, G.; Schwab, R.; Venetianer, A.; Kessler, H. *Org. Lett.* **2001**, *3*, 3723. (b) Haubner, R.; Gratias, R.; Diefenbach, B.; Goodman, S. L.; Jonczyk, A.; Kessler, J. *J. Am. Chem. Soc.* **1996**, *118*, 7461.

(13) Tsai, C.-Y.; Huang, X.; Wong, C.-H. *Tetrahedron Lett.* **2000**, *41*, 9499.

10.1021/jo0621874 CCC: $37.00
Published on Web 01/25/2007

SCHEME 1

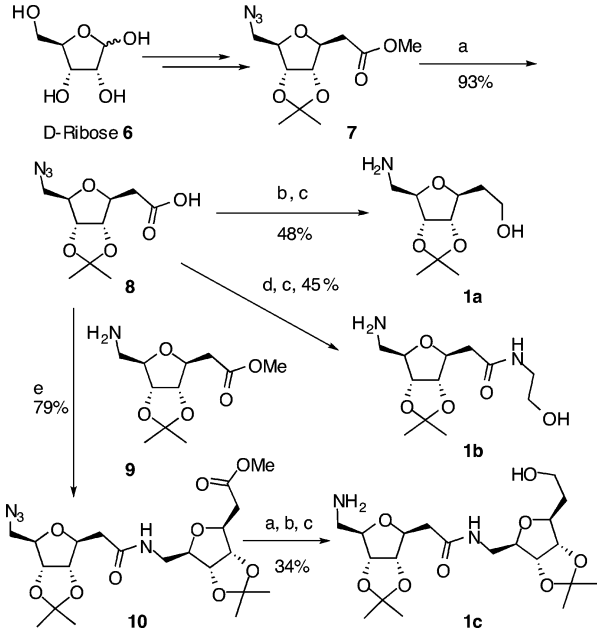


synthesis of cyclic SAAs by a multicomponent reaction/postfunctionalization strategy.[15] The reaction sequence we envisaged is shown in Scheme 1. A three-component reaction of a sugar amino acid derivative **1**, an aldehyde **2**, and an isocyanoacetamide **3** would provide the functionalized oxazole **4**.[16] Saponification of methyl ester followed by acidic treatment should afford the macrocycle according to the chemistry developed previously in this laboratory.[17]

The preparation of the furanoids **1a**−**c** is outlined in Scheme 2. The D-ribose (**6**) is converted to *β*-*C*-furanoside (**7**) in four conventional steps involving acetalization, Wittig reaction, mesylation, and S_N2 displacement of the mesylate by sodium azide.[9g,18] Saponification of the methyl ester afforded the carboxylic acid **8**, and the synthesis is diverged at this stage. Reduction of acid via the mixed anhydride intermediate followed by hydrogenolysis of the azide furnished the amino alcohol **1a**. On the other hand, EDC-mediated coupling of the acid **8** with 1,2-aminoalcohol followed by the reduction of azide afforded the SAA derivative **1b** in 57% overall yield. In parallel, reduction of azido ester **7** gave the amino ester **9** that was coupled with azido acid **8** to afford compound **10**. Finally, reduction of the ester and the azide functions provided the dimeric SAA derivative **1c** in 34% overall yield.

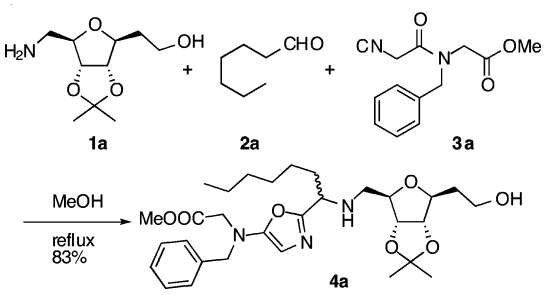
Heating to reflux a methanol solution of amino alcohol **1a**, heptanal (**2a**), and isonitrile **3a**,[19] according to our previously developed conditions,[16] afforded the desired 5-aminooxazole **4a** in 83% yield as a mixture of two diastereoisomers (dr = 1:1) (Scheme 3). Apparently, the chiral environment of the chiral amino alcohol **1a** is not sufficient to induce the diastereoselectivity in the key C−C bond-forming step. Nevertheless, the low diastereoselectivity observed in this 3CR is in accordance with the general trends of isonitrile-based MCRs and reflects the

SCHEME 2[a]



[a] Reagents and conditions : (a) $LiOH·H_2O$, H_2O/THF, rt, 15 h, 93%; (b) $ClCO_2Et$, Et_3N, THF, 0 °C, 1 h; then $NaBH_4$, H_2O, rt, 4 h, 68%; (c) H_2, Pd/C 10%, MeOH, rt, 2 h; (d) 1,2-aminoethanol, EDCI, CH_2Cl_2, rt, 24 h, 57%; (e) **9**, EDCI, CH_2Cl_2, rt, 24 h, 79%.

SCHEME 3



complexity of the reaction mechanism.[20] By varying the structure of the aldehyde, SAA, and isonitrile compounds, we synthesized five other 5-aminooxazoles **4b**−**f**, and their structures were listed in Figure 1.

With compounds **4a**−**f** in hand, we next investigated the key macrolactonization using the 5-aminooxazole as an internal activator of the terminal carboxylic acid. Saponification of the methyl ester **4a** (LiOH, THF−H_2O) gave the corresponding lithium salt, which after evaporation of the solvents was used directly for the next step without further purification. Gratifyingly, simply stirring an acetonitrile solution (0.001 M) of the so-obtained lithium salt in the presence of trifluoroacetic acid (50 equiv) at room temperature provided the macrocycle **5a** in 59% yield (Scheme 4). Two diastereoisomers were separable at this step by preparative TLC. However, the presence of rotamers due to the presence of the tertiary amide in the peptide backbone significantly complicated the ^1H NMR spectrum; therefore, the relative stereochemistry of the two chiral centers was not assigned. In DMSO-d_6, the NMR spectrum of **5a**

(14) For synthesis of a symmetric cyclic dimer by staudinger Aza−Wittig reaction, see: Ménand, M.; Blais, J.-C.; Hamon, L.; Valéry, J.-M.; Xie, J. *J. Org. Chem.* **2006**, *71*, 3295.

(15) (a) Marcaccini, S.; Torroba, T. *Post-condensation Modifications of the Passerini and Ugi Reactions* in *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005; p 33. (b) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51. (c) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133. (d) Wessjohann, L. A.; Ruijter, E. *Mol. Diversity* **2005**, *9*, 159. (e) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.

(16) (a) Sun, X.; Janvier, P.; Zhao, G.; Bienaymé, H.; Zhu, J. *Org. Lett.* **2001**, *3*, 877. (b) Janvier, P.; Sun, X.; Bienaymé, H.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 2560. (c) Fayol, A.; Housseman, C.; Sun, X.; Janvier, P.; Bienaymé, H.; Zhu, J. *Synthesis* **2005**, 161.

(17) (a) Zhao, G.; Sun, X.; Bienaymé, H.; Zhu, J. *J. Am. Chem. Soc.* **2001**, *123*, 6700. (b) Bughin, C.; Zhao, G.; Bienaymé, H.; Zhu, J. *Chem.−Eur. J.* **2006**, *12*, 1174.

(18) (a) Ohrui, H.; Jones, G. H.; Moffatt, J. G.; Maddox, M. L.; Christensen, A. T.; Byram, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 4602. (b) McDevitt, J. P.; Lansbury, P. T. *J. Am. Chem. Soc.* **1996**, *118*, 3818.

(19) Zhao, G.; Bughin, C.; Bienaymé, H.; Zhu, J. *Synlett* **2003**, 1153.

(20) Banfi, L.; Basso, A.; Guanti, G.; Riva, R. *Asymmetric Isocyanide-based MCRs* in *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005; pp 1.

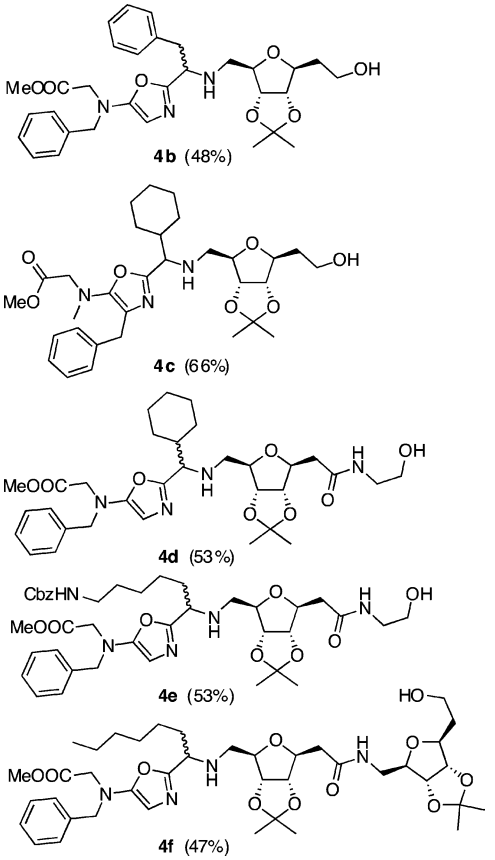
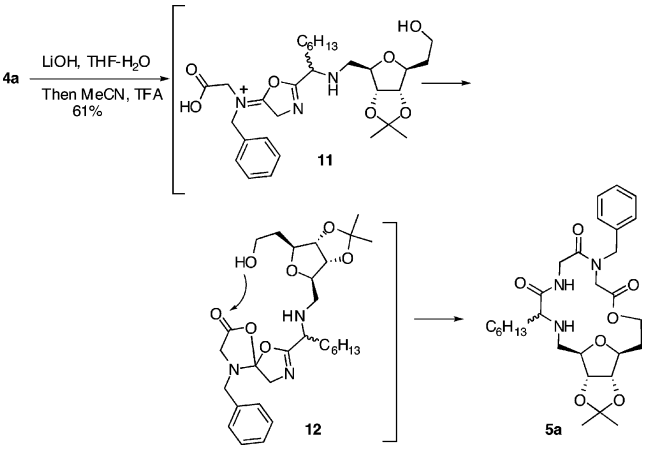


FIGURE 1. 5-Amino oxazoles synthesized by a three-component reaction.

SCHEME 4



recorded at 297 K was well resolved and two sets of peaks were identified. Particularly, two broad triplets that appeared at $\delta =$ 8.39 and 8.13 ppm were attributed to the amide NH proton of the two rotamers by a COSY spectrum. These two peaks coalesced at $\delta = 8.05$ ppm when the ^{1}H NMR spectrum was recorded at 353 K (cf. Supporting Information).

A possible reaction sequence leading to the macrocycle **5a** is depicted in Scheme 4.[17b] Thus, protonation of the C-4 carbon of the oxazole would provide the iminium intermediate **11** that would be trapped by the vicinal carbonyl oxygen to afford the spirolactone **12**. The intramolecular nucleophilic addition of the tethered hydroxy group to the lactone followed by fragmentation then provided the observed macrocycle **5a**. In this conceptually

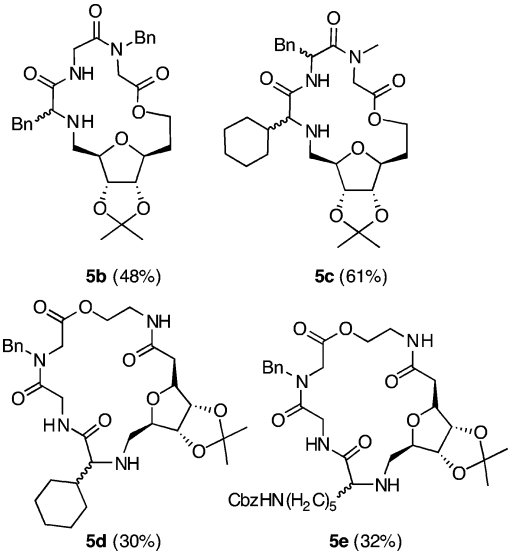


FIGURE 2. Cyclic sugar amino acids synthesized.

novel macrolactonization process, the oxazole served as an internal activator of the terminal carboxylic acid and became an integral part of the peptide backbone after cyclization. The cyclization worked equally well in toluene. However, the structure of acids can significantly influence the reaction efficiency and only a trace amount of macrolactone was isolated when the cyclization was performed in the presence of *para*-toluenesulfonic acid.

Figure 2 lists macrocyclic SAAs synthesized from the corresponding linear oxazolo-SAAs. Although yields remained moderate to good, the cyclization seems to be quite general because the representative 16-membered and 19-membered rings are readily accessed. In the case of **5c** wherein a new chiral center was generated, four diastereomers were produced with an overall yield of 61%. However, only one of them was separated from the diastereomeric mixture. We emphasize that the present synthesis is highly step-efficient because only two operations are required for the synthesis of these structurally complex macrocycles from readily accessible starting materials (**1**−**3**).[21] Furthermore, an amino acid is created in the course of the three-component reaction thus facilitating the incorporation of a non-proteinogenic amino acid unit into the cyclic SAAs.

In conclusion, we have developed a new synthesis of highly functionalized cyclic sugar amino acids that allows us to access macrocycles in two steps from simple starting materials. In this two-step process, only two molecules of water are lost, whereas lithium hydroxide and trifluoroacetic acid are the only reagents used to mediate the formation of these macrocycles.

Experimental Section

General Procedure for the Three-Component Synthesis of 5-Aminooxazole. A solution of amino sugar **1** (1.1 equiv) and aldehyde **2** (1.1 equiv) in dry methanol (0.1 mol/L) was stirred at room temperature for 15 min, and isocyanide **3** (1.0 equiv) was

(21) For recent examples of one-step multicomponent synthesis of macrocycles, see: (a) Wessjohann, L. A.; Voigt, B.; Rivera, D. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4785. (b) Rivera, D. G.; Wessjohann, L. A. *J. Am. Chem. Soc.* **2006**, *128*, 7122. (c) Kreye, O.; Westermann, B.; Rivera, D. G.; Johnson, D. V.; Orru, R. V. A.; Wessjohann, L. A. *QSAR Comb. Sci.* **2006**, *5*−*6*, 461. (e) Pirali, T.; Tron, G. C.; Zhu, J. *Org. Lett.* **2006**, *8*, 4145.

then added to the solution. The reaction was heated at 70 °C, and the progress of the reaction was followed by TLC. When isocyanide was fully consumed, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH 95:5) to give the aminooxazole **4**. **Compound 4a:** yield 83%; R_f (heptane/AcOEt 4:1) 0.19; IR ($CHCl_3$) ν 1076, 1158, 1263, 1383, 1455, 1496, 1581, 1616, 1746, 2852, 2932, 3532 cm^{-1}; NMR ^1H ($CDCl_3$, 300 MHz, 293 K, ppm) two diastereoisomers, 1:1 ratios δ 0.83 (t, $J = 7.9$ Hz, 3H), 1.09−1.28 (m, 9H), 1.49 (s, 3H), 1.61−1.88 (m, 4H), 2.07 (brs, 1H), 2.51−2.75 (m, 2H), 3.64 (t, $J = 7.8$ Hz, 1H), 3.67 (s, 3H), 3.69−3.75 (m, 2H), 3.80 (s, 2H), 3.94−4.03 (m, 2H), 4.35−4.53 (m, 1H), 4.38 (s, 2H), 4.45−4.53 (m, 1H), 5.88 (s, 1H), 7.20−7.31 (m, 5H); NMR ^{13}C ($CDCl_3$, 75 MHz, 293 K, ppm) two diastereoisomers 1:1 ratios δ 14.0, 22.6 (25.5), 25.9 (27.3), 29.0, 31.7, 34.3, 35.7, 49.1, 50.0, 52.0, 54.6, 56.8, 60.5, 83.9−83.6, 84.9, 101.5, 114.5, 127.9−128.3 (2C), 129.0 (2C), 136.2, 114.5, 156.8, 156.9, 170.3; MS (IE) (*m*/*z*) 559 $[M]^+$, 474 $[M - C_6H_{13}]^+$; HRMS (ESI) calcd for $[M + Na]^+ = 582.3155$; *m*/*z* found 582.3169.

General Procedure for the Acid-Promoted Macrolactonization. A solution of 5-aminooxazole and $LiOH\cdot H_2O$ (1.05 equiv) in THF/H_2O (3:1) was stirred at room temperature for 3 h and evaporated to dryness in vacuo. The residue obtained was dissolved in MeCN (10^{-3} M), and TFA (50 equiv) was added under a stream of argon. The reaction mixture was stirred at room temperature and followed by TLC. When the reaction was completed, the volatile was evaporated under reduced pressure. The crude product was diluted with ethyl acetate and washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness. Purification by preparative TLC afforded the desired macrocycle. **Compound 5a:** **y**ield 59%; reaction was performed at 0.1 mmol scale. Diastereoisomer A: white solid; yield 26%; R_f (CH_2Cl_2/ MeOH 95:5) 0.62; IR ($CHCl_3$) ν 1062, 1716, 1672, 1643, 1737, 3324 cm^{-1}; NMR ^1H ($CDCl_3$, 300 MHz, 293 K, ppm) two rotamers 1:3 ratio δ 0.85−0.88 (m, 3H), 1.03−1.50 (m, 10H), 1.37 (1.39) (s, 3H), 1.54 (1.58) (s, 3H), 1.58−1.85 (m, 1H), 1.95−2.03 (m, 1H), 2.75 (dd, $J = 14.1$ Hz, 4.7 Hz, 1H), 2.90 (2.88) (dd, $J = 14.1$ Hz, 8.4 Hz, 1H), 3.04−3.07 (3.12) (m, 1H), 3.53 (d, $J = 18.0$ Hz, 1H), 3.75−3.82 (m, 1H), 3.83−4.00 (m, 2H), 4.05−4.20 (m, 1H), 4.29 (d, $J = 18.0$ Hz, 1H), 4.27−4.35 (m, 4H), 4.36−4.52 (m, 1H), 4.75 (4.88) (d, $J = 15.9$ (14.1) Hz, 1H), 7.23−7.38 (m, 1H), 8.01 (7.88) (brs, 1H); NMR ^{13}C ($CDCl_3$, 75 MHz, 293 K) two rotamers 1:3 ratio δ 14.0, 22.5, 25.5 (25.6), 26.0 (27.3), 29.1 (29.4), 29.2 (29.7), 31.7 (32.5), 34.1, 40.9 (40.1), 49.9 (49.7), 51.8 (50.8), 51.8 (52.6) (2C), 61.6 (62.7), 64.5 (63.3), 82.2 (81.5), 82.4, 82.7 (83.5), 83.3 (84.3), 115.0 (115.7), 127.1 to 129.1−135.2 (136.0), 168.7 (168.1), 170.1 (169.6), 175.4; MS (ESI) (*m*/*z*) 546.4 [M + 1], 568.2 $[M + Na]^+$; MS (HRMS) *m*/*z* calcd for $[M + 1]^+ = 546.3179$; *m*/*z* found 546.3166; calcd for $[M + Na]^+ = 568.2999$; *m*/*z* found 568.2974. Diastereoisomer B: white solid; yield 33%; R_f (CH_2Cl_2/ MeOH 95:5) 0.54; NMR ^1H ($CDCl_3$, 500 MHz, 293 K) two rotamers 2:1 ratio δ 0.80 (t, $J = 7.8$ Hz, 3H), 1.08−1.75 (m, 10H), 1.32 (1.33) (s, 3H), 1.49 (1.50) (s, 3H), 1.80−2.09 (m, 1H), 2.49−2.53 (m, 2H), 2.88−2.91 (m, 1H), 2.91−3.02 (m, 1H), 3.23 (d, $J = 13.6$ Hz, 1H), 3.38 (3.41) (d, $J = 15.9$ (15.1) Hz, 1H), 3.55−3.61 (m, 1H), 3.65−4.02 (m, 2H), 4.08 (4.49) (d, $J = 14.7$ (16.6) Hz, 1H), 4.12−4.30 (m, 3H), 4.56 (dd, $J = 15.9$ Hz, 8.7 Hz, 1H), 5.06 (4.75) (d, $J = 14.7$ (16.6) Hz, 1H), 7.10−7.29 (m, 5H), 8.02 (7.73) (brs, 1H); NMR ^{13}C ($CDCl_3$, 75 MHz, 293 K) two rotamers 2:1 ratio δ 14.0, 22.5, 26.1 (25.6), 27.6 (27.3), 29.4 (29.3), 31.6 (31.1), 34.5 (33.5), 39.3 (40.9), 49.7 (49.3), 50.5 (51.3), 52.6 (52.9), 53.8 (55.0), 61.8 (62.5), 65.2 (63.1), 80.5, 82.8 (82.7), 83.1 (84.7), 85.9, 116.3 (115.4) 127.1−129.1, 136.2 (135.6), 167.9 (168.6), 171.2 (170.3), 175.6 (175.1); MS (ESI) (*m*/*z*) 546.3 [M + 1], 568.3 $[M + Na]^+$; MS (HRMS) *m*/*z* calcd for $[M + 1]^+ = 546.3179$, *m*/*z* found 546.3162; calcd for $[M + Na]^+ = 568.2999$, *m*/*z* found 568.2982.

Acknowledgment. We thank CNRS and our institute for financial support. C.B. thanks Ministère de l'Enseignement Supérieur et de la Recherche for a doctoral fellowship.

Supporting Information Available: Syntheses, physical data of **1a**−**c**, **4a**−**f**, and **5a**−**f**, and copies of ^1H NMR of **1a**−**c**, **4a**−**f**, and **5a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0621874