Total Synthesis of Arylomycin A_2, a Signal Peptidase I (SPase I) Inhibitor

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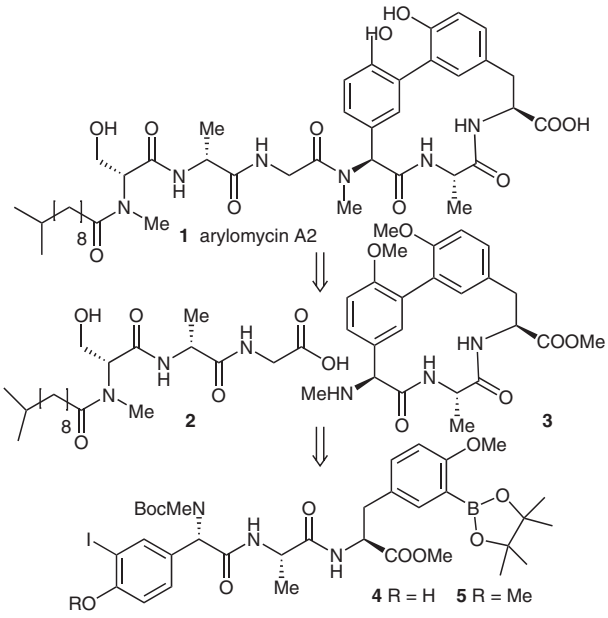
Abstract: A concise total synthesis of arylomycin A_2 has been accomplished featuring a key intramolecular Suzuki–Miyaura reaction for the formation of the 14-membered *meta*,*meta*-cyclophane and direct coupling of a fully elaborated peptide side chain with the macrocyclic core.

Key words: total synthesis, cross-coupling, palladium, macrocycles, antibiotics

Arylomycins are secondary metabolites recently isolated from *Streptomyces Strain Tü 6075* by Friedler, Jung, and co-workers.[1] In 2004, several related lipohexapeptides and glycopeptides have been added to this family of natural products.[2] They display moderate activity against a series of Gram-positive and Gram-negative bacteria. Most importantly, it has been established that these cyclopeptides acted as potent inhibitors of bacterial signal peptidase I (SPase I), an enzyme essential for bacterial viabilitity and growth[3] and blocked bacterial protein secretion in vivo leading to bacterial death. This unique mechanism of action is different from any of the previously known antibiotics. Consequently, they represent ideal candidates for the development of new antibiotics to combat bacterial resistance, a field that gained momentum ever since the emergence of the vancomycin-resistant enterococci.[4] Structurally, arylomycins are hexapeptides (D-MeSer-D-Ala-Gly-L-MeHpg-L-Ala-L-Tyr) having a fatty acid residue attached to the N-terminal amino acid. The aromatic rings of L-MeHpg and L-Tyr are cross-linked by an aryl–aryl bond forming a 14-membered *meta*,*meta*-cyclophane.[5] Due to the ring strain associated with this macrocycle, arylomycins can exist as a mixture of two atropisomers. Interestingly, X-ray crystal structure of an Escherichia coli SPase-arylomycin A_2 complex indicated that only the *P*-configured stereomer of the natural product was bound to the SPase.[6]

We have been interested in this type of macrocyclic natural products and have recently accomplished the total syntheses of biphenomycin and RP-66453.[7] As a continuation of this reseach program, we report herein a total synthesis of arylomycin A_2 (**1**) based on a convergent synthetic scheme involving an intramolecular Suzuki–Miyaura reaction and the coupling of the resulting macrocycle with the fully elaborated peptidic side chain (Scheme 1). During the course of this study, Romesberg et al. reported the first total synthesis of **1** following a similar strategy.[8]



Scheme 1 Retrosynthetic analysis of arylomycin A_2

Our synthesis began with the preparation of *N*-methyl D-4-hydroxy-3-iodophenylglycine (Scheme 2). In order to minimize racemization of this highly base-sensitive amino acid, we decided to leave the phenol group unprotected during the synthesis. We reasoned that the formation of phenoxide could render the α-CH of Hpg less prone to deprotonation avoiding consequently the racemization. The *N*-methyl group was introduced through an oxazolidinone formation–reduction strategy.[9] D-Hydroxyphenylglycine (**6**) was first protected as *tert*-butoxycarbamate and subsequently converted into oxazolidinone **8**. Iodination of **8** by the in situ generated trifluoroacetyl hypoiodite (I_2, CF_3CO_2Ag)[10] furnished the desired amino acid **9** in 47% yield, that is readily separated from the bisiodinated side product. Reduction of the oxazolidinone (Et_3SiH, TFA) followed by reinstallation of the *N*-Boc function afforded the *N*-Boc-*N*-MeHpg **10**[11] in 90% yield.

Synthesis of linear tripeptides **4** and **5** is shown in Scheme 3. L-*N*-Boc-3-iodo-4-methoxyphenyl alanate **11** was prepared from L-tyrosine in three steps according to Joullié.[12] Coupling of **11** with L-Boc-alanine proceeded smoothly to afford **12** in 94% yield (EDC, HOBt, DMF),[13] which underwent the palladium-catalyzed cross-coupling with bis(pinacolato)diboron following Miyaura's proce-

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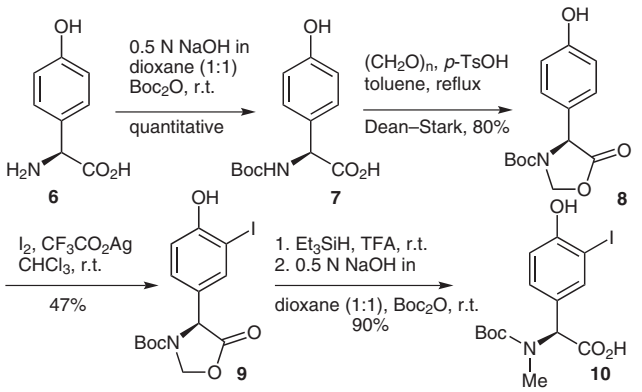
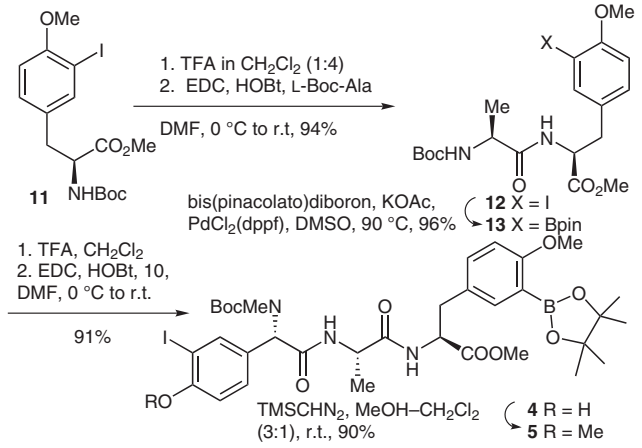


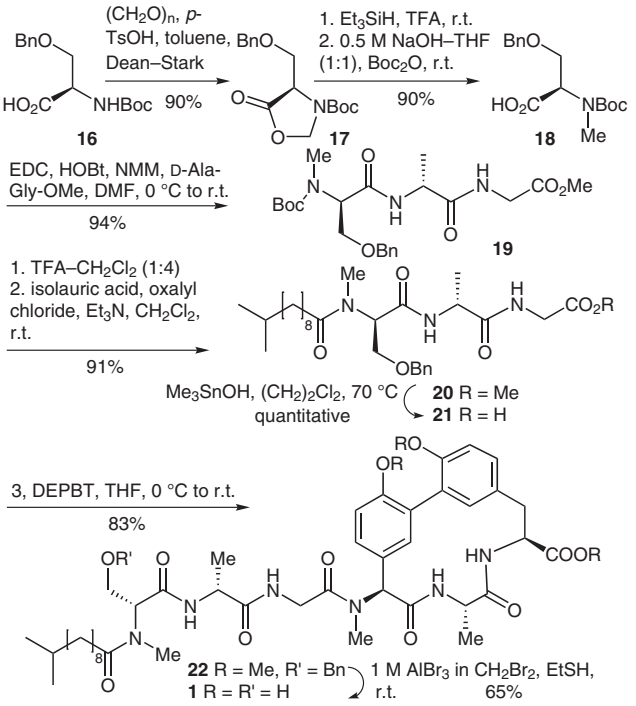
Scheme 2 Synthesis of *N*-methyl-Hpg **10**



Scheme 3 Synthesis of linear tripeptides **4** and **5**

dure to provide the corresponding aryl boronate **13**.[14] N-Deprotection followed by peptide coupling with **10** (EDC, HOBt, DMF) furnished the tripeptide **4** in 96% isolated yield. Finally, methylation of phenol **4** with $TMSCHN_2$ afforded compound **5** in 90% yield.[15]

With the properly functionalized tripeptide in hand, we set out to examine the desired macrocyclization by the way of an intramolecular Suzuki–Miyaura reaction.[7,16] We were concerned with a potential racemization problem associated with the inherent need of a base in such cross-coupling reaction. Therefore, the study was conducted on both tripeptide **4** and **5** (Table 1). It was assumed that the presence of free phenol could, in certain extent, minimize the epimerization of **4**. In the event, treatment of a DMSO solution of **4** (*c* 0.02 M, 90 °C) in the presence of $PdCl_2$(dppf) (0.05 equiv) and K_2CO_3 (7 equiv) afforded **14** in an encouraging 29% yield (entry 1). Both the solvent and the palladium source influenced the reaction outcome. Acetonitrile turned out to be an ineffective solvent for this reaction, while DMSO or toluene–H_2O (30:1) afforded **14** in comparable yield in the presence of $PdCl_2(SPhos)_2$ as a catalyst (entries 5, 6). Addition of $(n\text{-Bu})_4NBr$ was detrimental to the cyclization (entry 7). Microwave irradiation[17,18] shortened the reaction time, but showed no



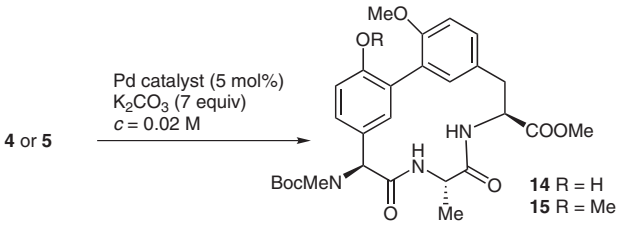
Scheme 4 Synthesis of arylomycin A_2

significant improvement in terms of product yield (entries 8, 9 vs. 5).

Cyclization of compound **5** was next investigated. Contrary to the results obtained in the cyclization of **4**, DMSO (entry 12) was found to be not as good as a mixture of solvent (toluene–H_2O, 30:1). When compound **5** was placed under the best conditions found for phenol **4**, [toluene–H_2O (30:1), $PdCl_2(SPhos)_2$], two cyclized products were isolated. The major compound was identical to a sample prepared through methylation of the phenol-derived macrocycle **14**. We therefore asumed that the major product was the desired macrocycle **15**, while the minor one was an epimer of **15**, most probably resulting from the epimerization of *N*-methyl Hpg unit. Fortunately, when the reaction was conducted in the presence of a weaker base ($NaHCO_3$, entry 14), the extent of epimerization was reduced significantly leading to **15** in 54% yield under this optimized condition [$PdCl_2(S\text{-}Phos)_2$, *c* 0.02 M in toluene–H_2O (30:1), 90 °C, $NaHCO_3$]. Performing the cyclization under high-dilution conditions did not improve the yield of **15** significantly, indicating that **5** may be conformationally preorganized for the intramolecular reaction.[19]

The synthesis of the side chain is depicted in Scheme 4. According to the strategy adopted for methylation of arylglycine **10**, the *N*-Boc Ser(OBn) **16** was converted into oxazolidinone **17**, then into the N-methylated derivative **18** in excellent overall yield. Coupling of **18** with dipeptide D-Ala-Gly-OMe afforded the tripeptide **19** in 94% yield. Removal of *N*-Boc function (TFA, CH_2Cl_2) furnished the amine, which was acylated by isolauric acyl chloride,[20] generated in situ to provide **20** in 91% yield.

Table 1 Palladium-Catalyzed Intramolecular Cyclization of **4** and **5**: Survey of Reaction Conditions



Entry	Reagent	Solvent	Catalyst	Temp, time	Yield (%)[a]
1	**4**	DMSO	$PdCl_2$(dppf)	90 °C, 2 h	29
2		MeCN	$PdCl_2$(dppf)	80 °C, 2 h	9
3		toluene–H_2O (30:1)	$PdCl_2$(dppf)	90 °C, 2 h	23
4		toluene–H_2O (30:1)	$Pd(dba)_2$ + (*R*)-MOP	90 °C, 2 h	13
5		toluene–H_2O (30:1)	$PdCl_2(SPhos)_2$	90 °C, 2 h	35
6		DMSO	$PdCl_2(SPhos)_2$	90 °C, 2 h	37
7[b]		toluene–H_2O (30:1)	$PdCl_2(SPhos)_2$	90 °C, 2 h	0
8		toluene–H_2O (30:1)	$PdCl_2(SPhos)_2$	MW 90 °C, 1 h	39
9		toluene–H_2O (30:1)	$PdCl_2(SPhos)_2$	MW 110 °C, 0.5 h	38
10	**5**	toluene–H_2O (30:1)	$PdCl_2(SPhos)_2$	MW 90 °C, 1 h	40 + 20
11		toluene–H_2O (30:1)	$PdCl_2(SPhos)_2$	90 °C, 2 h	39 + 17
12		DMSO	$PdCl_2$(dppf)	90 °C, 2 h	12
13		EtCN	$PdCl_2(SPhos)_2$	90 °C, 18 h	28+9
14[c]		toluene–H_2O (30:1)	$PdCl_2(SPhos)_2$	90 °C, 2 h	54+9

[a] Isolated yield.
[b] In the presence of 1 equiv of $(n\text{-Bu})_4NBr$.
[c] Sodium bicarbonate (7 equiv) was used instead of K_2CO_3.

Hydrolysis of methyl ester **20** was performed in the presence of Me_3SnOH[21] furnishing quantitatively acid **21**.

Coupling of a sterically encumbered secondary amine to a peptide could be problematic. One solution is the stepwise elongation of the secondary amine[22] and this was indeed a strategy employed in Romesberg's synthesis. However, we found that using DEPBT[23] as a coupling reagent, the reaction of secondary amine **3**, obtained quantitatively by N-deprotection of **15** (TFA in CH_2Cl_2) with **21** afforded **22** in 83% yield. Finally, global deprotection of **22** under push–pull conditions (1 M $AlBr_3$ in CH_2Br_2, excess of Et-SH) afforded arylomycin A_2 (**1**) in 65% yield. The spectroscopic data (^1H NMR, ^{13}C NMR, HRMS) of synthetic material were identical to those reported for the natural product. As found for natural product, synthetic arylomycin A_2 (**1**) existed as a mixture of atropoisomers/rotamers in its ^1H NMR spectrum.

In summary, we have accomplished a concise total synthesis of arylomycin A_2 (**1**) in a longest linear sequence of twelve steps from commercially available L-3 iodotyrosine in 20% overall yield. Key features of our approach are: a) formation of 14-membered *meta*,*meta*-cyclophane by an intramolecular Suzuki–Miyaura reaction; b) incorporation of *N*-MeHpg in the cyclization precursor thus avoiding the difficult and low-yielding N-methylation of macrocycle; and c) direct coupling of a fully elaborated peptide side chain to the macrocycle making the synthesis more convergent. Work is currently in progress towards the synthesis of members of this family of natural products as well as their analogues.

Acknowledgment

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References and Notes

(1) (a) Höltzel, A.; Schmid, D. G.; Nicholson, G. J.; Stevanovic, S.; Schimana, J.; Gebhardt, K.; Friedler, H. P.; Jung, G. J. *J. Antibiot.* **2002**, *55*, 571. (b) Schimana, J.; Gebhardt, K.; Höltzel, A.; Schmid, D. G.; Süssmuth, R.; Müller, J.; Pukall, R.; Friedler, H. P. *J. Antibiot.* **2002**, *55*, 565.

(2) Kulanthaivel, P.; Kreuzman, A. J.; Strege, M. A.; Belvo, M. D.; Smitka, T. A.; Clemens, M.; Swartling, J. R.; Minton, K. L.; Zheng, F.; Angleton, E. L.; Mullen, D.; Jungheim, L. N.; Klimkowski, V. J.; Nicas, T. I.; Thompson, R. C.; Peng, S.-B. *J. Biol. Chem.* **2004**, *279*, 36250.
(3) Paetzel, M.; Karla, A.; Strynadka, N. C.; Dalbey, R. E. *Chem. Rev.* **2002**, *102*, 4549.
(4) (a) Brown, E. D.; Wright, G. D. *Chem. Rev.* **2005**, *105*, 759. (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. (d) Williams, D.; Bardsley, B. *Angew. Chem. Int. Ed.* **1999**, *38*, 1172. (e) Kahne, D.; Leimkuhler, C.; Lu, W.; Walsh, C. T. *Chem. Rev.* **2005**, *105*, 425.
(5) For reviews on aryl-bridged natural products, see: (a) Feliu, L.; Planas, M. *Int. J. Pept. Res. Ther.* **2005**, *11*, 53. (b) Zhu, J.; Islas-Gonzalez, G.; Bois-Choussy, M. *Org. Prep. Proced. Int.* **2000**, *32*, 505.
(6) Paetzel, M.; Goodall, J. J.; Kania, M.; Dalbey, R. E.; Paghe, M. G. *J. Biol. Chem.* **2004**, *279*, 30781.
(7) For biaryl-containing macrocycles, see: (a) Carbonnelle, A.-C.; Zhu, J. *Org. Lett.* **2000**, *2*, 3477. (b) Boisnard, S.; Carbonnelle, A.-C.; Zhu, J. *Org. Lett.* **2001**, *3*, 2061. (c) Jia, X.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2007**, *9*, 2401. (d) Lépine, R.; Zhu, J. *Org. Lett.* **2005**, *7*, 2981. (e) Bois-Choussy, M.; Cristau, P.; Zhu, J. *Angew. Chem. Int. Ed.* **2003**, *42*, 4238. (f) Jia, X.; Bois-Choussy, M.; Zhu, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 4167.
(8) Roberts, T. C.; Smith, P. A.; Cirz, R. T.; Romesberg, F. E. *J. Am. Chem. Soc.* **2007**, *129*, 15830.
(9) (a) Freidinger, R. M.; Hinkle, J. S.; Perlow, D. S.; Arison, B. H. *J. Org. Chem.* **1983**, *48*, 77. (b) Aurelio, L.; Browlee, R. T. C.; Hughes, A. B.; Sleebs, B. E. *Aust. J. Chem.* **2000**, *53*, 425. (c) Aurelio, L.; Browlee, R. T. C.; Hughes, A. B. *Chem. Rev.* **2005**, *104*, 5823.
(10) Barnett, R.; Andrews, L. J.; Keefer, R. M. *J. Am. Chem. Soc.* **1972**, *94*, 6129.
(11) **Selected Physical and Spectroscopic Data**
Compound **10**: $[\alpha]_D^{25}$ +86 (*c* 0.9, MeOH). ^{1}H NMR (300 MHz, MeOD): δ = 7.61 (d, *J* = 2.0 Hz, 1 H), 7.12 (dd, *J* = 8.3, 2.0 Hz, 1 H), 6.84 (d, *J* = 8.3 Hz, 1 H), 5.47 (s, 1 H), 2.66 (s, 3 H), 1.48 (s, 9 H) ppm. HRMS (ES$^+$): *m/z* calcd for $C_{14}H_{18}NO_5NaI$ [M + Na]$^+$: 430.0127; found: 430.0128.
Compound **5**: $[\alpha]_D^{25}$ +16 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of rotamers): δ = 7.72 and 7.71 (d, *J* = 2.2 Hz, 1 H), 7.42 and 7.30 (d, *J* = 2.3 Hz, 1 H), 7.29–7.24 (m, 0.5 H, overlapped with solvent), 7.22 (dd, *J* = 8.5, 2.2 Hz, 0.5 H), 7.22 (dd, *J* = 8.5, 2.2 Hz, 0.5 H), 7.10 (dd, *J* = 8.5, 2.2 Hz, 0.5 H), 6.78 (d, *J* = 8.5 Hz, 1 H), 6.71 (d, *J* = 8.5 Hz, 1 H), 6.58–6.32 (m, 1 H), 6.54 and 6.37 (d, *J* = 7.3 Hz, 1 H), 5.67–6.57 (m, 1 H), 4.81–4.70 (m, 1 H), 4.59–4.46 (m, 1 H), 3.88 and 3.87 (s, 3 H), 3.79 and 3.77 (s, 3 H,), 3.72 and 3.71 (s, 3 H), 3.11–2.96 (m, 2 H), 2.71 and 2.69 (s, 3 H), 1.48 and 1.47 (s, 9 H), 1.41–1.24 (m, 15 H) ppm. MS (ES$^+$): *m/z* = 832 [M + Na]$^+$. Anal. Calcd for $C_{35}H_{49}N_3O_{10}IB$: C, 51.93; H, 6.10; N, 5.19. Found: C, 51.83; H, 6.30; N, 5.10.
Compound **15**: $[\alpha]_D^{26}$ +44 (*c* 1.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 1:1.9 mixture of rotamers): δ = 7.20–7.25 (m, 1 H), 6.98 (d, *J* = 8.4 Hz, 1 H), 6.94 and 6.93 (d, *J* = 8.5 Hz, 1 H), 6.85 (d, *J* = 8.4 Hz, 1 H), 6.78 and 6.73 (s, 1 H), 6.75 and 6.68 (s, 1 H), 6.34–6.27 (m, 1 H), 6.26 and 6.21 (d, *J* = 8.5 Hz, 1 H), 5.93 and 5.61 (s, 1 H), 4.95–4.87 (m, 1 H), 4.77–4.67 (m, 1 H), 3.83 (s, 3 H), 3.82 and 3.81 (s, 6 H), 3.58–3.47 (m, 1 H), 3.05 and 3.04 (dd, *J* = 15.9, 6.9 Hz, 1 H), 2.71 and 2.70 (s, 3 H), 1.51 and 1.49 (br s, 9 H), 1.42–1.37 (m, 3 H) ppm. ^{1}H NMR (500 MHz, DMSO-d_6, 1:1 mixture of rotamers): δ = 9.06–9.01 (m, 1 H), 8.37 and 8.31 (d, *J* = 8.3 Hz, 1 H), 7.24–7.11 (m, 2 H), 7.10–7.05 (m, 1 H), 7.00 (d, *J* = 8.5 Hz, 1 H), 6.70–6.60 (m, 2 H), 5.92 and 5.74 (s, 1 H), 4.91–4.79 (m, 1 H,), 4.78–4.65 (m, 1 H), 3.78 (s, 3 H), 3.74 (s, 3 H), 3.70 (s, 3 H), 3.33–3.27 (m, 1 H, overlapped with solvent), 3.07–2.96 (m, 1 H), 2.53 (s, 3 H, overlapped with solvent), 1.44 and 1.41 (s, 9 H), 1.18 (d, *J* = 6.8 Hz, 3 H) ppm. HRMS (ES$^+$): *m/z* calcd for $C_{29}H_{37}N_3O_8Na$ [M + Na]$^+$: 578.2478; found: 578.2490.
Arylomycin $A_{2\,(}$**1**): $[\alpha]_D^{24}$ +29 (*c* 0.3, MeOH). ^{1}H NMR (500 MHz, MeOD, 1:6.4 mixture of isomers): δ = 8.91 (d, *J* = 8.0 Hz, 1 H), 8.61 (d, *J* = 8.1 Hz, 1 H), 8.17–8.05 (m, 2 H), 7.23 and 7.13 (d, *J* = 8.3 Hz, 1 H), 7.11 (d, *J* = 8.3 Hz, 1 H), 7.03 (br s, 1 H), 7.00 (br s, 1 H), 6.96 (d, *J* = 8.4 Hz, 1 H), 6.87 (d, *J* = 8.4 Hz, 1 H), 6.35 and 5.87 (s, 1 H), 4.99–4.94 (m, 1 H), 4.57–4.51 (m, 2 H, overlapped with solvent), 4.56–4.46 (m, 1 H), 4.25 (d, *J* = 17.1 Hz, 1 H), 4.08–4.00 (m, 2 H), 3.95–3.85 (m, 1 H), 3.46–3.36 (m, 1 H), 3.16–3.07 (m, 1 H), 3.11 and 2.89 (s, 3 H), 2.80 and 2.76 (s, 3 H), 2.57–2.42 (m, 2 H), 1.67–1.58 (m, 2 H), 1.52 (sept, *J* = 6.6 Hz, 1 H), 1.41 (d, *J* = 7.0 Hz, 3 H), 1.35 (d, *J* = 6.6 Hz, 3 H), 1.42–1.26 (m, 10 H), 1.21–1.15 (m, 2 H), 0.88 (d, *J* = 6.6 Hz, 6 H) ppm. ^{1}H NMR (500 MHz, DMSO-d_6, 1:3.1 mixture of isomers): δ = 12.81 (br s, 1 H), 9.69 (br s, 2 H), 9.07–8.95 and 8.35–8.27 (m, 1 H), 8.62–8.54 (m, 1 H), 8.03–7.87 (m, 2 H), 7.14 and 7.10 (d, *J* = 7.8 Hz, 1 H), 6.98 (d, *J* = 8.5 Hz, 1 H), 6.95 and 6.93 (br s, 1 H), 6.91–6.80 (m, 3 H), 6.29 and 5.85 (s, 1 H), 5.03–4.98 and 4.91–4.84 (m, 1 H), 4.97 and 3.44 (dd, *J* = 8.2, 5.8 Hz, 1 H), 4.83–4.73 (m, 1 H), 4.69–4.61 (m, 1 H), 4.41–4.30 (m, 1 H), 4.20 and 4.02 (d, *J* = 17.3 Hz, 1 H), 3.96 (dd, *J* = 17.3, 4.4 Hz, 1 H), 4.85–4.74 (m, 1 H), 3.71–3.62 (m, 1 H), 3.28–3.20 (m, 1 H), 3.16–3.07 (dd, *J* = 16.7, 12.1 Hz, 1 H), 2.93 and 2.76 (s, 3 H), 2.69 and 2.63 (s, 3 H), 2.39–2.27 (m, 2 H), 1.56–1.45 (m, 3 H), 1.25 (d, *J* = 7.3 Hz, 3 H), 1.32–1.20 (m, 10 H), 1.18 (d, *J* = 6.7 Hz, 3 H), 1.18–1.11 (m, 2 H), 0.85 (d, *J* = 6.6 Hz, 6 H). HRMS (ES$^-$): *m/z* calcd for $C_{42}H_{59}N_6O_{11}$ [M – H]$^-$ 823.4242; found: 823.4269.
(12) Chiarello, J.; Joullié, M. M. *Synth. Commun.* **1988**, *18*, 2211.
(13) Abbreviations: DEPBT = 3-(diethyloxyphosphoryloxy)-1,2,3-benzotriazin-4 (3*H*)-one; EDC = 1-[3-(eimethylamino)propyl]-3-ethylcarbodiimide; HOBt = *N*-hydroxybenzotriazole, SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl; MOP = (diphenylphosphino)-2′-methoxy-1,1′-binaphtyl; NMP = *N*-methylpyrolidinone.
(14) Ishiyama, T.; Murata, M.; Miyaura, M. *J. Org. Chem.* **1995**, *60*, 7508.
(15) For a related methylation of boron-containing peptide, see: Deng, H.; Jung, J.-K.; Liu, T.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 9032.
(16) (a) Elder, A. M.; Rich, D. H. *Org. Lett.* **1999**, *1*, 1443. (b) Li, W.; Burgess, K. *Tetrahedron Lett.* **1999**, *40*, 6527. (c) Lobrégat, V.; Alcaraz, G.; Bienaymé, H.; Vaultier, M. *Chem. Commun.* **2001**, 817. (d) Kaiser, M.; Siciliano, C.; Assfalg-Machleidt, I.; Groll, M.; Milbradt, A. G.; Moroder, L. *Org. Lett.* **2003**, *5*, 3435. (e) Shinohara, T.; Deng, H.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 7334.
(17) Microwave experiments were conducted using a Discover microwave reactor from CEM. All experiments were performed in sealed tubes (capacity 10 mL) under argon atmosphere. Microwave irradiation of 300 W was used, the temperature being ramped from r.t. to 90 °C or 110 °C in 1 min. Once this temperature was reached, the reaction mixture was held at 90 °C or 110 °C for the indicated time.
(18) For recent reviews, see: (a) Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250. (b) de la Hoz, A.; Diaz-Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164.

(19) For a review on conformation-directed macrocyclization, see: Blankenstein, J.; Zhu, J. *Eur. J. Org. Chem.* **2005**, 1949.
(20) We synthesized isolauric acid following a Cu-catalyzed coupling of a Grignard reagent with an alkylbromide according to: Cahiez, G.; Chaboche, C.; Jézéquel, M. *Tetrahedron* **2000**, *56*, 2733.
(21) (a) Furlan, R. L. E.; Mata, E. G.; Mascaretti, A. O. *J. Chem. Soc., Perkin Trans. 1* **1998**, 355. (b) Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem. Int. Ed.* **2005**, *44*, 1378.
(22) Bigot, A.; Tran Huu Dau, M. E.; Zhu, J. *J. Org. Chem.* **1999**, *64*, 6283.
(23) Li, H.; Jiang, X.; Fan, C.; Romoff, T.; Goodman, M. *Org. Lett.* **1999**, *1*, 91.