Studies towards the Total Asymmetric Synthesis of the Pentacyclic Indole Alkaloid Arboflorine: Asymmetric Synthesis of a Key Intermediate

Yu Du,[a] Hui-Ying Huang,[b] Hui Liu,[a] Yuan-Ping Ruan,[a] Pei-Qiang Huang*[a]

[a] Department of Chemistry and Key Laboratory for Chemical Biology of Fujian Province, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, P. R. of China
Fax +86(592)2186400; E-mail: pqhuang@xmu.edu.cn

[b] School of Life Sciences, Xiamen University, Xiamen, Fujian 361005, P. R. of China

Received 27 November 2010

Abstract: The synthesis of a plausible key intermediate for a biomimetic asymmetric synthesis of indole alkaloid arboflorine is described. The method featured the use of Ellman's sulfinamide chemistry for the establishment of the first chiral center, and the Polonovski–Potier reaction for the formation of the α-aminonitrile moiety.

Key words: indole alkaloids, biogenetic pathway, intermediate, Polonovski–Potier reaction, Ellman's sulfinamide

Indole alkaloids are a class of natural products widely distributed in plants that exhibit structural diversity and significant biological activities.[1] In 2006, Kam and co-workers reported the isolation and structure elucidation of arboflorine (**1**) as a minor alkaloid from the stem bark of the Malayan *Kopsia arborea*.[2] A notable feature of this new alkaloid resides in that it represents a new subclass of monoterpenoid indoles with a novel pentacyclic carbon skeleton. Moreover, the incorporation of a third nitrogen atom embedded within a tryptamine–secologanin-derived monoterpenoid indole is also unusual (Figure 1).

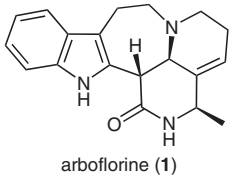
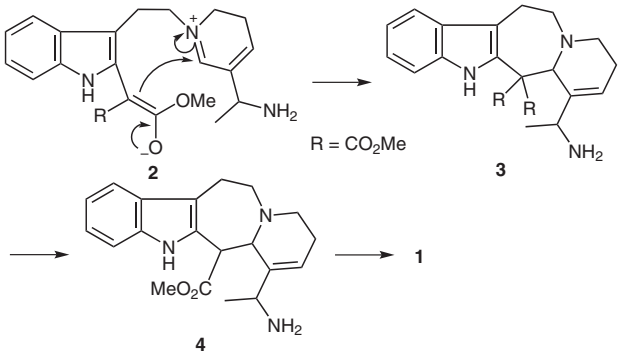


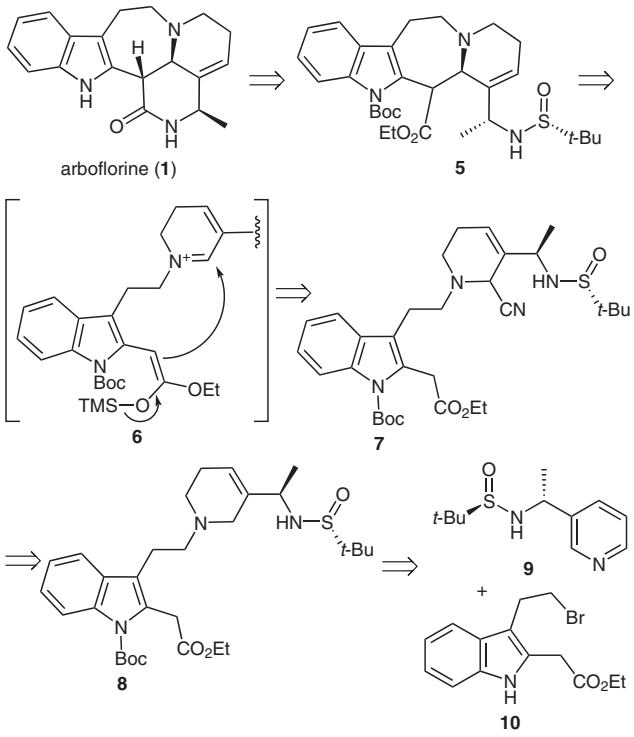
Figure 1 Structure of arboflorine

In continuation of our interest in the asymmetric synthesis of bioactive alkaloids,[3] in particular piperidines[4] and 2-piperidinones,[5] we have embarked on the asymmetric synthesis of arboflorine (**1**), and the preliminary results on the construction of a key intermediate are presented herein.

Our approach is based on the possible biogenetic pathway proposed by Kam and co-workers,[2] which highlighted the cyclization of the key intermediate **2** (Scheme 1). In our retrosynthetic analysis showed in Scheme 2, compound **7** was designed as a precursor of the key intermediate **6**, which is similar to the proposed biogenetic intermediate **2**. The α-aminonitrile **7** was envisioned to be prepared from piperideine **8** by Li's cross-dehydrogenative-coupling reaction (CDC)[6] or the Polonovski–Potier reaction.[7] Compound **8**, in turn, could be accessible from chiral amine **9** and indole derivative **10**. Chiral amine **9** could be



Scheme 1 Possible biogenetic pathway to **1** (in part) suggested by Kam and co-workers

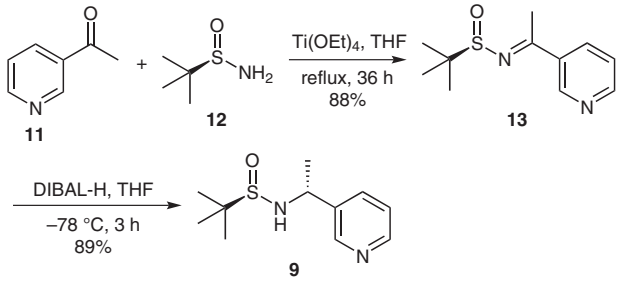


Scheme 2 Retrosynthetic analysis of arboflorine

SYNLETT 2011, No. 4, pp 0565–0568
Advanced online publication: 27.01.2011
DOI: 10.1055/s-0030-1259521; Art ID: W18610ST

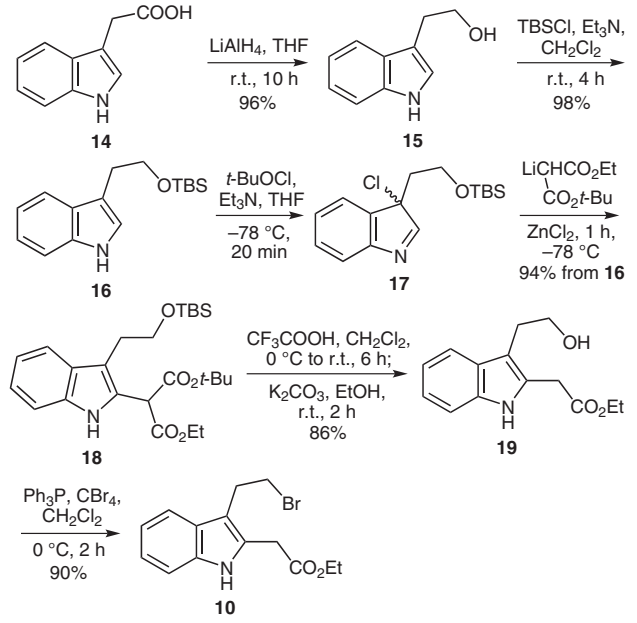
synthesized by chiral directing reduction of Ellman's sulfinamide.[8,9]

The synthesis started with the preparation of the protected (*R*S,*R*)-*N*-*tert*-butanesulfinyl amine **9** by a known procedure (Scheme 3).[9] $Ti(OEt)_4$-mediated[9,10] condensation of 3-acetylpyridine (**11**) with Ellman's (*R*)-sulfinamide **12**[8] afforded sulfinimine **13** in 88% yield. Reduction of sulfinimine **13** with DIBAL-H in THF at –78 °C[9] produced the desired compound **9** in 89% yield.



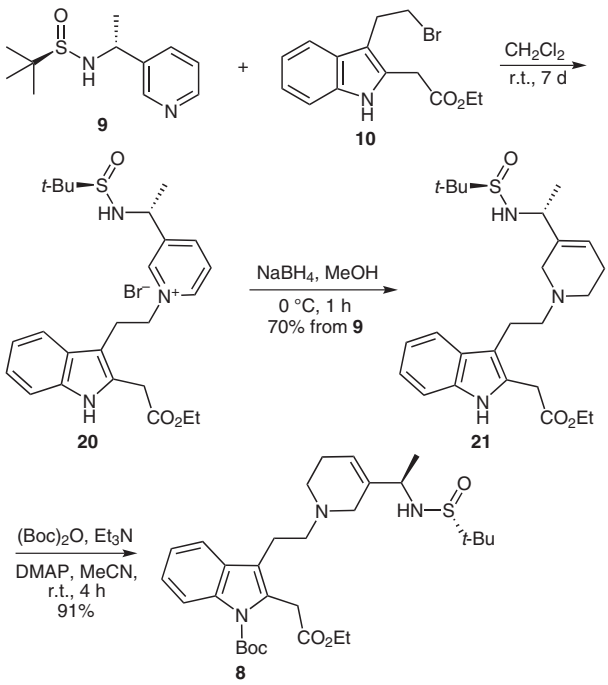
Scheme 3 Synthesis of compound **9**

The synthesis of segment **10** is outlined in Scheme 4, which started with 2-(indol-3-yl)acetic acid (**14**). Reduction of 2-(indol-3-yl)acetic acid (**14**) with lithium aluminum hydride in THF gave the corresponding alcohol **15** in 96% yield, which was protected (TBSCl, Et_3N, CH_2Cl_2) to give compound **16** in 98% yield.



Scheme 4 Synthesis of compound **10**

Oxidative conversion of 3-substituted indole **16** into chloroindolenine **17** and use of this compound for the functionalization at the carbon α to nitrogen by Kuehne's method[11,12] (*t*-BuOCl, Et_3N, THF; $ZnCl_2$, lithium ethyl *tert*-butyl malonate) provided compound **18** in 94% yield. Successive treatment of compound **18** with trifluoroacetic acid and potassium carbonate gave the desilylated and decarboxylated product **19** in an overall yield of 86%. Treatment of indole-alcohol **19** with PPh_3–CBr_4 in CH_2Cl_2 proceeded chemoselectively to give the desired bromide **10** in 90% yield.



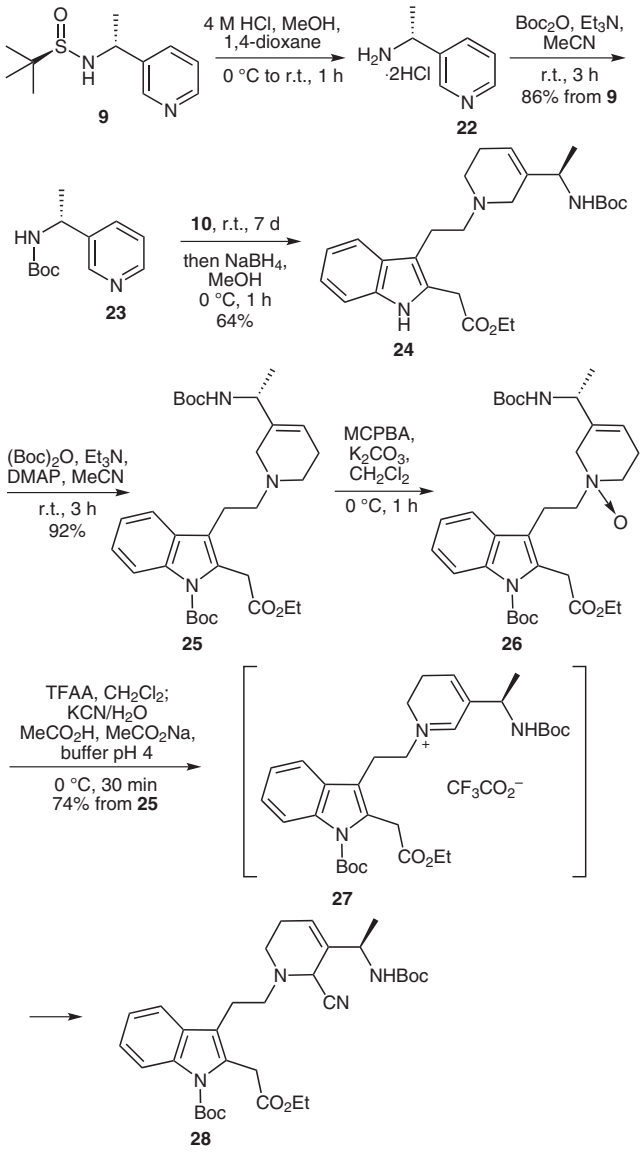
Scheme 5 Synthesis of compound **8**

For the synthesis of compound **8**, a CH_2Cl_2 solution of **9** and **10** was stirred at room temperature for seven days to give the presumed pyridinium[13] **20** that was reduced with $NaBH_4$ in one pot to give piperideine[14] **21** in 70% yield. *N*-Protection [$(Boc)_2O$, Et_3N, DMAP, MeCN] of the indole nitrogen in compound **21** produced *N*-Boc derivative **8** in 91% yield (Scheme 5).

The next task was the regioselective introduction of a cyano group at C-2 of the piperideine ring of compound **8** to give compound **7**. Attempted cyanation at C-2 of piperideine **8** by Li's CDC reaction[6,15] using either CuCl, CuBr or $RuCl_3$ in the presence of O_2, or H_2O_2, or *t*-BuOOH was unsuccessful. It was found that the oxidative dehydrogenation occurred more readily at the carbon α to the *tert*-butanesulfinamide group than at the piperidine α-carbon. We then resorted to the Polonovski–Potier reaction.[7,16,17] However, successive treatment of compound **8** with MCPBA and NaCN gave only the corresponding sulfone in 45% yield.

At this stage, modification of our synthetic plan by substitution of the sulfoxide group of *tert*-butanesulfinamide by a Boc group was indicated. For this purpose, compound **9** was treated with a 4 M HCl in methanol solution[9] to give amine dihydrochloride salt **22** that was protected [$(Boc)_2O$, Et_3N, MeCN] to give compound (*R*)-**23** in 86% yield over two steps (Scheme 6). Successive treatment of pyridine derivative **23** with bromide **10** and $NaBH_4$ in methanol afforded compound **24** in 64% yield. Treatment

of compound **24** with $(Boc)_2O$ in the presence of Et_3N and DMAP in MeCN gave fully protected compound **25** in 92% yield (Scheme 6).



Scheme 6 Synthesis of the key intermediate **28**

Compound **25** was subjected to Polonovski–Potier reaction to generate 2-cyano-Δ^3-piperideine **28**. In the event, piperideine **25** was treated with MCPBA, K_2CO_3 in CH_2Cl_2 to give the *N*-oxide **26**, which was treated with TFAA in CH_2Cl_2, and the presumed iminium intermediate **27** was trapped by KCN in an aqueous AcOH–NaOAc buffer solution (pH 4) to afford, in one pot, the desired nitrile **28** as an inseparable diastereomeric mixture in 74% yield (Scheme 6). The diastereomeric ratio was determined to be 58:42 by ^{1}H NMR analysis.[18]

In summary, an efficient synthesis of 2-cyano-Δ^3-piperideine **28**, a plausible synthetic equivalent of the key intermediate for a biomimetic synthesis of pentacyclic indole alkaloid arboflorine (**1**) has been disclosed. Work is in progress on the key decyanative cyclization[16,19] and the completion of the total synthesis of arboflorine (**1**).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

The authors are grateful to the NSF of China (No. 20832005), the NFFTBS (No. J1030415), and the National Basic Research Program (973 Program) of China (Grant No. 2010CB833200) for financial support.

References and Notes

(1) For some recent reviews, see: (a) Kam, T.-S.; Lim, K.-H. *Alkaloids of Kopsia,* In *The Alkaloids: Chemistry and Biology*, Vol. 66; Cordell, G. A., Ed.; Academic Press: Amsterdam, **2008**, 1–111. (b) Ishikura, M.; Yamada, K.; Abe, T. *Nat. Prod. Rep.* **2010**, *27*, 1630. (c) Li, S.-M. *Nat. Prod. Rep.* **2010**, *27*, 57.
(2) Lim, K.-H.; Kam, T.-S. *Org. Lett.* **2006**, *8*, 1733.
(3) Huang, P.-Q. *Synlett* **2006**, 1133.
(4) (a) Xiao, K.-J.; Liu, L.-X.; Huang, P.-Q. *Tetrahedron: Asymmetry* **2009**, *20*, 1181. (b) Lin, G.-J.; Huang, P.-Q. *Org. Biomol. Chem.* **2009**, *7*, 4491. (c) Zheng, X.; Chen, G.; Ruan, Y.-P.; Huang, P.-Q. *Sci. China, Ser. B: Chem.* **2009**, *52*, 1631. (d) Yang, R.-F.; Huang, P.-Q. *Chem. Eur. J.* **2010**, *16*, 10319. (e) Xiao, K.-J.; Wang, Y.; Ye, K.-Y.; Huang, P.-Q. *Chem. Eur. J.* **2010**, *16*, 12792.
(5) (a) Liu, L.-X.; Xiao, K.-J.; Huang, P.-Q. *Tetrahedron* **2009**, *52*, 3834. (b) Fu, R.; Du, Y.; Li, Z.-Y.; Xu, W.-X.; Huang, P.-Q. *Tetrahedron* **2009**, *65*, 9765. (c) Fu, R.; Chen, J.; Guo, L.-C.; Ruan, Y.-P.; Huang, P.-Q. *Org. Lett.* **2009**, *11*, 5242. (d) Fu, R.; Ye, J.-L.; Dai, X.-J.; Ruan, Y.-P.; Huang, P.-Q. *J. Org. Chem.* **2010**, *75*, 4230. (e) Zheng, X.; Zhu, W.-F.; Huang, P.-Q. *Sci. China, Ser. B: Chem.* **2010**, *53*, 1914.
(6) (a) Li, Z.-P.; Li, C.-J. *Eur. J. Org. Chem.* **2005**, 3173. (b) Baslé, O.; Li, C.-J. *Green Chem.* **2007**, *9*, 1047. (c) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.
(7) (a) Grierson, D. *Org. React. (N.Y.)* **1990**, *39*, 85. (b) Polonovski, M. *Bull. Soc. Chim. Belg.* **1930**, *39*, 1. (c) Potier, P. *Annu. Proc. Phytochem. Soc. Eur.* **1980**, *17*, 159.
(8) (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (b) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39. (c) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Han, Z.; Gallon, E. *Aldrichimica Acta* **2005**, *38*, 93. (d) Daniel, M.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869.
(9) Chelucci, G.; Baldino, S.; Chessa, S.; Pinna, G. A.; Soccolini, F. *Tetrahedron: Asymmetry* **2006**, *17*, 3163.
(10) (a) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278. (b) Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268. (c) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403.
(11) (a) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1997**, *62*, 7950. (b) Schkeryantz, J. M.; Woo, J. C. G.; Siliphaivanh, P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11964.
(12) For an alternative method, see: Johansen, M. B.; Kerr, M. A. *Org. Lett.* **2010**, *12*, 4956.
(13) Fry, E. M.; Beisler, J. A. *J. Org. Chem.* **1970**, *35*, 2809.

(14) Passarella, D.; Martinelli, M.; Llor, N.; Amat, M.; Bosch, J. *Tetrahedron* **1999**, *55*, 14995.
(15) (a) Murahashi, S. I.; Komiya, N.; Terai, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 6931. (b) Murahashi, S. I.; Nakae, T.; Terai, H.; Komiya, N. *J. Am. Chem. Soc.* **2008**, *130*, 11005.
(16) (a) Grierson, D. S.; Harris, M.; Husson, H.-P. *J. Am. Chem. Soc.* **1980**, *102*, 1064. (b) Grierson, D. S.; Vuilhorgne, M.; Husson, H.-P. *J. Org. Chem.* **1982**, *47*, 4439. (c) Sundberg, R. J.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.* **1984**, *49*, 2400.
(17) Bonjoch, J.; Solé, D.; García-Rubio, S.; Bosch, J. *J. Am. Chem. Soc.* **1997**, *119*, 7230.
(18) All new compounds gave satisfactory analytical and spectral data.
Experimental Procedure for the Synthesis of the Key Intermediate 28: A solution of MCPBA (72%, 84 mg, 0.35 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a solution of compound **25** (138 mg, 0.25 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C. After stirring at 0 °C for 1 h, K_2CO_3 (70 mg, 0.5 mmol) was added. After stirring for an additional 1 h at 0 °C, the mixture was filtered through celite. The residue was purified by flash column chromatography on silica gel (R_f 0.18, eluent: CH_2Cl_2–MeOH, 15:1) to give *N*-oxide **26** (140 mg, 98%), which was dissolved in anhyd CH_2Cl_2 (2.0 mL) and cooled to 0 °C. TFAA (0.07 mL, 0.5 mmol) was added. After being stirred for 30 min at 0 °C, an aqueous solution (0.5 mL) of KCN (65 mg, 1.0 mmol) was added, and the solution was buffered to pH 4 by addition of AcOH and NaOAc. After stirring for 1 h at 0 °C, the mixture was basified with K_2CO_3 and extracted with CH_2Cl_2 (3 × 3 mL). The combined extracts were successively washed with H_2O (2 mL) and brine (1 mL), dried over anhyd Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on neutral Al_2O_3 (R_f = 0.4, eluent: EtOAc–*n*-hexane, 1:4) to give compound **28** (108 mg, 74% from **25**) as a white amorphous solid. IR (film): 3370, 2978, 2934, 2216 (w, CN), 1730 (s), 1511, 1458, 1392, 1367, 1328, 1248, 1169, 1133 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$; diastereomeric mixture and rotamers): δ = 1.25 (m, 3 H, CH_2CH_3), 1.33 (m, 3 H, $CHCH_3$), 1.44 [m, 9 H, $C(CH_3)_3$], 1.65 [s, 9 H, $C(CH_3)_3$], 2.08–2.18 (m, 1 H, C=$CHCH_2$), 2.26–2.44 (m, 1 H, C=$CHCH_2$), 2.53–2.63 (m, 1 H, C=$CHCH_2CH_2$), 2.70–2.95 (m, 5 H, C=$CHCH_2CH_2$, $ArCH_2CH_2N$), 4.03 (s, 2 H, CH_2CO_2), 4.16 (m, 2 H, CH_2CH_3), 4.27 (s, 1 H, CHCN), 4.22–4.38 (m, 1 H, $CHCH_3$), 4.57 (br s, 1 H, NH), 5.86, 5.89 (br s, 1 H, C=CH), 7.24 (t, *J* = 7.3 Hz, 1 H, ArH), 7.29 (t, *J* = 7.3 Hz, 1 H, ArH), 7.53 (d, *J* = 7.8 Hz, 1 H, ArH), 8.09 (d, *J* = 7.8 Hz, 1 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$; diastereomeric mixture and rotamers): d = 14.2, 22.4, 22.5, 25.1, 25.2, 28.1, 28.25, 28.29, 28.33, 28.7, 29.6, 33.17, 33.2, 45.6, 45.65, 47.5, 52.4, 55.2, 55.3, 60.8, 79.8, 80.1, 84.0, 115.7, 115.9, 116.1, 118.0, 118.1, 118.2, 122.5, 124.2, 124.449, 124.458, 129.2, 129.7, 129.8, 134.08, 134.14, 135.8, 150.4, 155.3, 170.12, 170.18. HRMS: *m*/*z* [M + Na^+] calcd for $C_{32}H_{44}N_4NaO_6$: 603.3159; found: 603.3153.
(19) Agami, C.; Couty, F.; Evano, G. *Org. Lett.* **2000**, *2*, 2085.