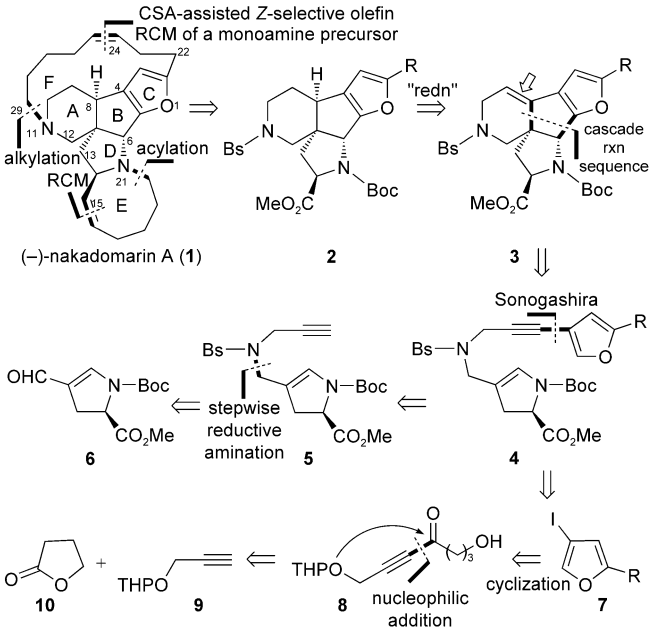
DOI: 10.1002/chem.201102101

Efficient Total Synthesis of Marine Alkaloid (−)-Nakadomarin A

Bin Cheng,[a] Fufang Wu,[a] Xiaobao Yang,[b] Yuedong Zhou,[a] Xiaolong Wan,[b] and Hongbin Zhai*[b, c]

In 1997, Kobayashi and co-workers disclosed the isolation of (−)-nakadomarin A (**1**, Scheme 1) from an Okinawan marine sponge *Amphimedon* sp. Its unique 8/5/5/5/15/6 hexacyclic full-ring structure containing four stereogenic centers and an imbedded furan was shown with extensive NMR spectroscopic analyses including NOE and proton coupling data.[1a] The biological properties of **1** range from prominent cytotoxicity against murine lymphoma L1210 cells to outstanding antimicrobial and CDK4 inhibitory activities.[1b] Since 2003, elegant total and formal syntheses[2] of **1** have been accomplished by the laboratories of Nishida,[2a,b] Kerr,[2c] Dixon,[2d] Mukai,[2e] and Funk,[2f] and relevant synthesis studies have been reported by an array of research teams.[3] Having communicated a rapid construction of the tetracyclic core (ABCD rings) of *ent*-**1** by showcasing the power of a Pt^{II}-promoted cascade reaction sequence,[3i] we report herein a novel total synthesis of (−)-nakadomarin A with higher practicality and efficiency. The synthesis features: 1) the assembly of the tetracyclic core through the $PtCl_2$-catalyzed cascade cyclization strategy[3i] (**4**→**3**, Scheme 1) followed by saturation[3i] of the C8=C9 double bond (**3**→**2**), and 2) CSA-assisted[2d] *Z*-selective olefin ring-closing metathesis (RCM; within **2**→**1**) involving a *monoamine* precursor (**17**, Scheme 2) used to replace Dixon's more polar *diamine* substrate (**19b**)[2d] for the F ring generation. For the rest of our synthesis plan (Scheme 1), the E ring can be forged by typical olefin RCM[2a–c,e] (within **2**→**1**) prior to the F ring formation. Enyne **4** can be obtained through Sonogashira coupling of terminal alkyne **5** with iodofuran **7**. While reductive amination of aldehyde **6** can be implemented to form alkyne **5**, furan **7** can be accessible from cyclization/iodination of conjugated ynone **8** in the presence of hydriodic acid. Finally, ketone **8** can be prepared from **9** and **10**.



Scheme 1. Retrosynthetic analysis of (−)-nakadomarin A (**1**). R: $(CH_2)_3OTBDPS$.

The synthesis of disubstituted furan **7** is described in Scheme 3. Propargyl alcohol THP ether[4] (**9**) was deprotonated and then treated with γ-butyrolactone (**10**) in the presence of $BF_3{\cdot}OEt_2$ to give ynone **8**, treatment[5] of which with hydriodic acid (3 M) effected the desired cyclization/iodination to afford a mixture containing alcohol **11** and its THP ether (generated due to THP migration). Subjecting the above mixture to TsOH in MeOH led to **11** (52%, from **9**) as the sole product, which was silylated to furnish iodofuran **7** in 89% yield.

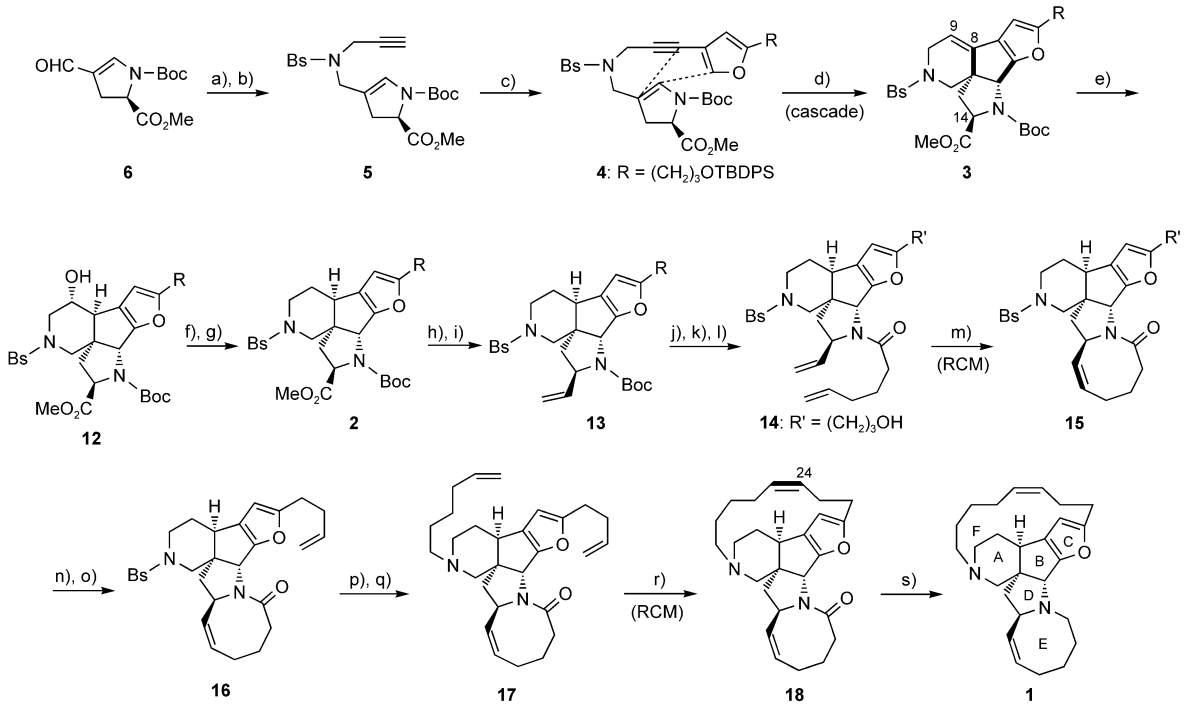
Unsaturated aldehyde **6**[6] was converted into compound **5** (54%, overall yield) by stepwise[3i] reductive amination (propargylamine·HCl, TEA, *t*BuOH, evaporation, $NaBH_4$, MeOH) followed by *N*-sulfonylation (BsCl, TEA, DCM). $[Pd(PPh_3)_2Cl_2]$/CuI-catalyzed Sonogashira coupling of terminal alkyne **5** with furan **7** in degassed TEA/DMF at room temperature gave rise to the key molecule **4** (87%), in which the enecarbamate, alkyne and furan functionalities

[a] Dr. B. Cheng, F. Wu, Y. Zhou
Hefei National Laboratory for Physical Science at Microscale and Department of Chemistry
University of Science and Technology of China
Hefei 230026 (P.R. China)

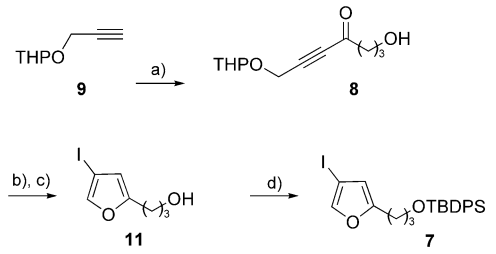
[b] Dr. X. Yang, X. Wan, Prof. Dr. H. Zhai
CAS Key Laboratory of Synthetic Chemistry of Natural Substances and State Key Laboratory of Bioorganic and Natural Products Chemistry
Shanghai Institute of Organic Chemistry
Shanghai 200032 (P.R. China)

[c] Prof. Dr. H. Zhai
State Key Laboratory of Applied Organic Chemistry
Lanzhou University, Lanzhou 730000 (P.R. China)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201102101.



Scheme 2. Synthesis of (−)-nakadomarin (**1**). Reagents and conditions: a) propargylamine·HCl, TEA, *t*BuOH, evaporation, $NaBH_4$, MeOH; b) BsCl, TEA, DCM, 54% (2 steps); c) **7**, $[Pd(PPh_3)_2Cl_2]$, CuI, TEA, DMF, 87%; d) $PtCl_2$, MePh, 80°C, 81%; e) $BH_3{\cdot}SMe_2$, THF, H_2O_2, NaOH, 81%; f) NaH, CS_2, MeI, THF; g) Bu_3SnH, AIBN, MePh, 94% (2 steps); h) DIBAL-H, DCM; i) Wittig, 74% (2 steps); j) $ZnBr_2$, DCM; k) 5-hexenoyl chloride, TEA, DMAP, DCM; l) TBAF, THF, 70% (3 steps); m) Grubbs' second-generation catalyst (20 mol%), DCM, 50°C; n) Swern; o) Wittig, 70% (3 steps); p) Na, naphthalene, THF; q) 6-bromo-1-hexene, K_2CO_3, EtOH, 91% (2 steps); r) Grubbs' first-generation catalyst (25 mol%), (−)-CSA, DCM, 50°C, *Z*/*E* about 2:1, 65% (*E*+*Z*), 31% (pure **18**); s) Red-Al, MePh, 85%. R: $(CH_2)_3OTBDPS$; R′: $(CH_2)_3OH$; Bs: benzenesulfonyl chloride; TEA: triethylamine; AIBN: azodiisobutyronitrile; TBAF: tetrabutylammonium fluoride; CSA: camphorsulfonic acid; Red-Al: sodium bis(2-methoxyethoxy)-aluminum hydride.

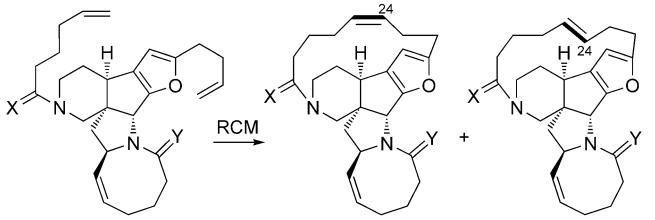


Scheme 3. Synthesis of iodofuran **7**. Reagents and conditions: a) BuLi, $BF_3{\cdot}Et_2O$, THF, **10**; b) HI, MePh; c) TsOH, MeOH, 52% (3 steps); d) TBDPSCl, Im, DMAP, DCM, 89%. TBDPSCl: *tert*-butyldiphenylchlorosilane; Im: imidazole; THP: tetrahydropyranyl.

are properly situated for a Pt^{II}-promoted cascade reaction sequence originally developed by Dake.[7] By adopting our modified procedure,[3i] treatment of **4** (introduced to the reaction system via a syringe pump) with $PtCl_2$ (20 mol%) in toluene at 80°C triggered the anticipated cascade reaction sequence in a seemingly regiospecific (6-*endo* vs. 5-*exo*) and stereospecific fashion. To our delight, tetracycle **3** was produced exclusively, and the yield reached 81%. The mechanism for the process involves three steps and has been discussed elsewhere.[3i,7] No racemization was observed at C14. Since saturation of the C8=C9 double bond within the A ring could not be accomplished by: 1) hydrogenation,[3c,i] 2) reduction with TFA/Et_3SiH,[3i] or 3) hydroboration followed by protonation (with HBr or HOAc),[3i] **3** was subjected to stereoselective hydroboration ($BH_3{\cdot}SMe_2$) followed by oxidation (H_2O_2, NaOH)[3i] to form alcohol **12** (81%), and the C8 configuration was correctly established. Barton–McCombie reaction[8] (Bu_3SnH, AIBN, MePh) with prior xanthate formation[9] (NaH, CS_2, MeI, THF) generated tetracyclic core **2** (ABCD rings) in 94% overall yield.[3i]

At this point, how to efficiently construct the E and F rings in **1** became a central problem. Thus, compound **2** was transformed into dienol **14** in 52% overall yield after a five-step reaction sequence: 1) partial reduction (DIBAL-H, DCM) of the ester moiety to afford an aldehyde, 2) Wittig reaction ($MePPh_3Br$, *t*BuOK, THF) to produce the terminal alkene **13**, 3) Boc-deprotection ($ZnBr_2$, DCM, reflux), 4) *N*-acylation (5-hexenoyl chloride, TEA, DMAP, DCM), and 5) desilylation (TBAF, THF). Facile RCM of **14** (2 mM) took place in the presence of Grubbs' second-generation catalyst (20 mol%) to give cleanly pentacycle **15** (ABCDE rings). Swern oxidation[10] and Wittig olefination ($MePPh_3Br$, K_2CO_3, [18]crown-6, DCM)[11] to furnish terminal alkene **16** was achieved in 70% overall yield from **14**. After desulfonation (Na, naphthalene, THF) and *N*-alkylation (6-bromo-1-hexene, K_2CO_3, EtOH), **16** was converted into bis(terminal alkene) **17** in 91% overall yield. Inspired by Dixon's obser-

Table 1. The *Z*/*E* selectivity and separability of the isomeric products from the RCM reactions of **17**, **19a**, and **19b**.



17: X = H_2, Y = O
19a: X = Y = O
19b: X = Y = H_2

18: X = H_2, Y = O
20: X = Y = O
1: X = Y = H_2

(24*E*)-**18**: X = H_2, Y = O
(24*E*)-**20**: X = Y = O
(24*E*)-**1**: X = Y = H_2

RCM products	Data source	RCM type (*Z*/*E* ratio)	*Z*/*E* isomer separability
18/(24*E*)-**18**	current work	*Z* selective (*Z*/*E*, 2:1)	separable (SFC-HPLC)
18/(24*E*)-**18**	Nishida[2i]	regular (*Z*/*E*, 1:2)	*inseparable*
ent-**18**/*ent*-(24*E*)-**18**	Kerr[2c]	regular (*Z*/*E*, 3:5)	*inseparable*
20/(24*E*)-**20**	Nishida[2b]	regular (*Z*/*E*, 1:1.8)	separable (column chromatography)
ent-**20**/*ent*-(24*E*)-**20**	Nishida[2a]	regular (*Z*/*E*, 2:3)	separable (column chromatography)
ent-**20**/*ent*-(24*E*)-**20**	Kerr[2c]	regular (*Z*:*E* unavailable)	separable (column chromatography)
1/(24*E*)-**1**	Dixon[2d]	*Z* selective (*Z*/*E*, 63:37)	separable (NP-HPLC)
1/(24*E*)-**1**	Nishida[2i]	obtained by lactam reduction	*inseparable*
ent-**1**/*ent*-(24*E*)-**1**	Kerr[2c]	obtained by lactam reduction	*inseparable*

vation of amine protonation-assisted *E*/*Z* selectivity reversal in a related investigation,[2d] we attempted treating **17** (0.5 mM) with Grubbs' first-generation catalyst (25 mol%) in the presence of (−)-camphorsulfonic acid (CSA, 200 mol%). The desired RCM proceeded smoothly while the *E*/*Z* selectivity was reversed compared to the amine-free lactam/amide substrates utilized by Nishida[2a,b] and Kerr.[2c]

Regular chromatographic purification resulted in a mixture of **18** and its (24*E*)-isomer (65%, combined yield), which upon semipreparative SFC-HPLC gave **18** in a pure form in 31% (unoptimized) yield. Table 1 summarizes the *Z*/*E* selectivity and separability of the isomeric products from the RCM reactions. The substrate polarity is most likely **19b** > **17** > **19a**, and the trend should remain the same for their RCM products. Dixon[2d] and we (in the current work) have separated **1**/(24*E*)-**1** and **18**/(24*E*)-**18**, respectively, despite the related negative results by Nishida[2i] and Kerr.[2c] Note that HPLC separation of **18** and (24*E*)-**18** proved to be much more practical than that of **1** and (24*E*)-**1**;[2a–d] this is consistent with compound polarity considerations. To complete the total synthesis, **18** was reduced with Red-Al in toluene to form (−)-nakadomarin A (**1**) in 85% yield. The $[\alpha]_D^{21}$ of **1** was found to be −66.9 (c = 0.28 in MeOH); $[\alpha]_D^{23}$ = −73.0 (c = 0.08 in MeOH);[2b] $[\alpha]_D^{25}$ = −65.6 (c = 0.66 in MeOH);[2d] $[\alpha]_D$ = −72.7 (c = 0.12 in MeOH);[2f] (*ent*-**1**) $[\alpha]_D^{20}$ = −79.2 (c = 0.12 in MeOH);[2a] (*ent*-**1**) $[\alpha]_D$ = +60.7 (c = 0.27 in MeOH).[2c] The ^{1}H and ^{13}C NMR spectroscopic data were in agreement with those disclosed in the literature.[1a,2a–d,f]

In summary, we have accomplished efficient total synthesis of the complex marine alkaloid (−)-nakadomarin A from aldehyde **6**.[6] Key transformations include: 1) $PtCl_2$-promoted cascade reactions of compound **4** (accessed by Sonogashira coupling) for the assembly of the tetracyclic core (ABCD rings) followed by saturation of the challenging C8=C9 double bond through a three-step protocol, 2) Grubbs' second-generation catalyst-mediated RCM for assembling the eight-membered ring, and 3) Grubbs' first-generation catalyst-promoted, (−)-CSA-assisted *Z*-selective RCM of *monoamine* **17** instead of the more polar diamine substrate (**19b**)[2d] for constructing the fifteen-membered ring.

Acknowledgements

We are grateful for the generous financial support from the National Basic Research Program of China (973 Program: 2010CB833200), "111" Program of MOE, and NSFC (20625204, 20632030, 90713007, 20772141).

Keywords: alkaloids · cascade reactions · monoamines · total synthesis · *Z*-selective RCM

[1] a) J. Kobayashi, D. Watanabe, N. Kawashi, M. Tsuda, *J. Org. Chem.* **1997**, *62*, 9236–9239; b) J. Kobayashi, M. Tsuda, M. Ishibashi, *Pure Appl. Chem.* **1999**, *71*, 1123–1126.

[2] a) T. Nagata, M. Nakagawa, A. Nishida, *J. Am. Chem. Soc.* **2003**, *125*, 7484–7485; b) K. Ono, M. Nakagawa, A. Nishida, *Angew. Chem.* **2004**, *116*, 2054–2057; *Angew. Chem. Int. Ed.* **2004**, *43*, 2020–2023; c) I. S. Young, M. A. Kerr, *J. Am. Chem. Soc.* **2007**, *129*, 1465–1469; d) P. Jakubec, D. M. Cockfield, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 16632–16633; e) F. Inagaki, M. Kinebuchi, N. Miyakoshi, C. Mukai, *Org. Lett.* **2010**, *12*, 1800–1803; f) M. G. Nilson, R. L. Funk, *Org. Lett.* **2010**, *12*, 4912–4915; for reviews, see: g) A. Nishida, T. Nagata, M. Nakagawa, *Top. Heterocycl. Chem.* **2006**, *5*, 255–280; h) D. B. C. Martin, C. D. Vanderwal, *Angew. Chem.* **2010**, *122*, 2893–2895; *Angew. Chem. Int. Ed.* **2010**, *49*, 2830–2832; for a paper written in Japanese, see: i) M. Nakagawa, T. Nagata, K. Ono, A. Nishida, *J. Synth. Org. Chem. Jpn.* **2005**, *63*, 200–210.

[3] a) A. Fürstner, O. Guth, A. Rumbo, G. Seidel, *J. Am. Chem. Soc.* **1999**, *121*, 11108–11113; b) A. Fürstner, O. Guth, A. Düffels, G. Seidel, M. Liebl, B. Gabor, R. Mynott, *Chem. Eur. J.* **2001**, *7*, 4811–

4820; c) T. Nagata, A. Nishida, M. Nakagawa, *Tetrahedron Lett.* **2001**, *42*, 8345–8349; d) P. Magnus, M. R. Fielding, C. Wells, V. Lynch, *Tetrahedron Lett.* **2002**, *43*, 947–950; e) E. Leclerc, M. A. Tius, *Org. Lett.* **2003**, *5*, 1171–1174; f) K. A. Ahrendt, R. M. Williams, *Org. Lett.* **2004**, *6*, 4539–4541; g) I. S. Young, J. L. Williams, M. A. Kerr, *Org. Lett.* **2005**, *7*, 953–955; h) M. G. Nilson, R. L. Funk, *Org. Lett.* **2006**, *8*, 3833–3836; i) H. Deng, X. Yang, Z. Tong, Z. Li, H. Zhai, *Org. Lett.* **2008**, *10*, 1791–1793; j) T. Haimowitz, M. E. Fitzgerald, J. D. Winkler, *Tetrahedron Lett.* **2011**, *52*, 2162–2164.

[4] a) J. T. Lowe, W. Youngsaye, J. S. Panek, *J. Org. Chem.* **2006**, *71*, 3639–3642; b) J. A. H. Inkster, I. Ling, N. S. Honson, L. Jacquet, R. Gries, E. Plettner, *Tetrahedron: Asymmetry* **2005**, *16*, 3773–3784.

[5] a) D. Obrecht, *Helv. Chim. Acta* **1989**, *72*, 447–456; b) A. Abson, N. J. P. Broom, P. A. Coates, J. S. Elder, A. K. Forrest, P. C. T. Hannan, A. J. Hicks, P. J. O'Hanlon, N. D. Masson, N. D. Pearson, J. E. Pons, J. M. Wilson, *J. Antibiot.* **1996**, *49*, 390–394.

[6] For the preparation of *ent*-(5*S*)-(−)-**6** (ref. [3i]), see: a) E. Coudert, F. Acher, R. Azerad, *Synthesis* **1997**, 863–865; b) J. Yu, V. Truc, P. Riebel, E. Hierl, B. Mudryk, *Tetrahedron Lett.* **2005**, *46*, 4011–4013; c) T. Shono, Y. Matsumura, K. Tsubata, Y. Sugihara, S. Yamane, T. Kanazawa, T. Aoki, *J. Am. Chem. Soc.* **1982**, *104*, 6697–6703. Compound **6** {(5*R*)-(+)-, $[\alpha]_D^{18} = +42.8$ ($c = 0.99$ in $CHCl_3$)} was synthesized by Vilsmeier formylation (ref. [6c]; DMF, $POCl_3$, CH_2Cl_2, 0 °C) of the corresponding enecarbamate (CAS No. 1260617-47-7, according to a recent SciFinder search). The most enatiopure commercial D-pyroglutamic acid, which was the starting material, was found to be 95.1 % *ee*, as determined by HPLC analysis of its benzyl ester (Chiralpak AD-H column (250 × 4.6 mm), UV detector 214 nm, eluent 2-propanol/hexane (1:9), flow-rate 0.7 mL min^{-1}).

[7] T. J. Harrison, B. O. Patrick, G. R. Dake, *Org. Lett.* **2007**, *9*, 367–370.

[8] a) D. H. R. Barton, S. W. McCombie, *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574–1585; b) F.-T. Hong, L. A. Paquette, *Chemtracts* **1998**, *11*, 67–72.

[9] J. R. Williams, D. Chai, J. D. Bloxton II, H. Gong, W. R. Solvibile, *Tetrahedron* **2003**, *59*, 3183–3188.

[10] a) K. Omura, A. K. Sharma, D. Swern, *J. Org. Chem.* **1976**, *41*, 957–962; b) S. L. Huang, D. Swern, *J. Org. Chem.* **1978**, *43*, 4537–4538; c) K. Omura, D. Swern, *Tetrahedron* **1978**, *34*, 1651–1660.

[11] a) S. C. Nigam, A. Mann, M. Taddei, C. G. Wermuth, *Synth. Commun.* **1989**, *19*, 3139–3142; b) H. Mizutani, J. Takayama, T. Honda, *Synlett* **2005**, 328–330.

Received: July 8, 2011
Published online: September 29, 2011

