SHORT COMMUNICATION

EurJOC European Journal of Organic Chemistry

DOI: 10.1002/ejoc.201200881

Electrophilic Cyclization and Ring-Closing Metathesis as Key Steps in the Synthesis of a 12-Membered Cyclic Enediyne

Natalia Danilkina,[a] Martin Nieger,[b] Stanislav Selivanov,[a] Stefan Bräse,*[c] and Irina Balova*[a]

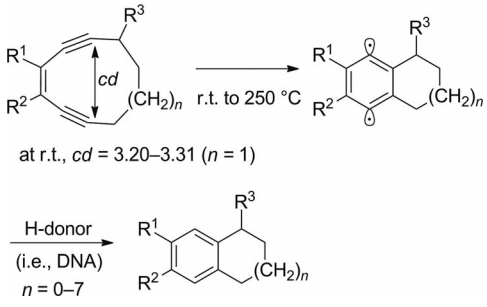
Keywords: Alkynes / Diynes / Alkenes / Cyclization / Metathesis / Macrocycles

For the first time, electrophilic cyclization and ring-closing metathesis were used as key steps in the synthesis of a macrocyclic enediyne system, which allowed a 12-membered dienediyne containing a thiophene-fused ring to be obtained. The macrocycle synthesized represents a class of compounds that possess planar chirality and exists in the solid state as two enantiomers, whereas in solution the rate of interconversion is rapid as a result of unhindered switching of the double bond through the macrocycle.

Introduction

Enediyne antibiotics are potent, naturally occurring, antineoplastic agents that were first isolated from the bacteria *Streptomyces macromomyceticus* (neocarzinostatin),[1a] *Actinomadura verrucosospora* (esperamicins),[1b–1d] and *Micromonospora echinospora* (calicheamicins).[1e,1f] It was determined that the biological activity of enediynes is due to the ability of these compounds to undergo Bergman cyclization,[2a,3a,3b] or Myers–Saito cyclization[2b,2c,3c] in the case of neocarzinostatin, with the formation of biradical species. Consequent abstraction of hydrogen atoms from DNA leads to double-stranded DNA cleavage, followed by cell death.

Many naturally occurring enediynes, as well as their synthetic analogs, have been isolated and synthesized.[1g–1j] It has been shown that the main factors responsible for the cycloaromatization of enediynes include the *cd* distance,[1g,4] the electronic properties of the substituents or annulated fragments,[5] and the difference in strain energies between the ground state and the transition state (Scheme 1).[6] Thus, acyclic (*Z*)-3-ene-1,5-diynes and high-membered macrocycles possessing the enediyne moiety undergo thermal Bergman cycloaromatization only at elevated temperatures (above 200 °C).[1g,1j,4,7] However, incorporation of the enediyne system in a 10-membered ring lowers the activation energy so that cycloaromatization may occur even at room temperature. Not surprisingly, in the case of most natural enediynes the crucial ring size is found to be ten.[1g–1j]



Scheme 1. Bergman cyclization.

Natural enediynes are too labile for practical use; in addition, they have low antitumor selectivity.[8] Therefore, there is a significant interest in developing efficient syntheses of more readily accessed enediyne compounds. Recently, we proposed a new approach towards heterocycle-fused enediyne systems that is based on the cyclization of *ortho*-functionalized buta-1,3-diynylarenes.[9] Two types of cyclization were investigated: first, Richter-type cyclization of diazonium salts that affords 4-bromo(chloro)-3-ethynylcinnolines,[9b,5b] and secondly, the electrophilic cyclization of functionalized diynes.[9c] Herein we describe the development of the proposed methodology by the synthesis of a cyclic benzothiophene-fused enediyne using electrophilic cyclization followed by ring-closing metathesis (RCM).

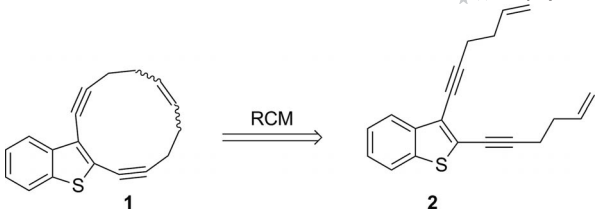
[a] Saint-Petersburg State University, Department of Organic Chemistry,
Universitetskiy pr. 26, 198504, Saint-Petersburg, Russian Federation
Fax: +7-812-4286939
E-mail: balova.irina@chem.spbu.ru
Homepage: www.chem.spbu.ru/org/537-organics
[b] Laboratory of Inorganic Chemistry, Department of Chemistry, University of Helsinki,
P. O. Box 55, 00014 University of Helsinki, Finland
[c] Karlsruhe Institute of Technology, Campus South, Institute of Organic Chemistry,
Fritz-Haber-Weg 6, 76131 Karlsruhe, Germany
Fax: +49-721-6088581
E-mail: braese@kit.edu
Homepage: www.ioc.kit.edu/braese

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201200881.

Results and Discussion

It should be noted that despite the fact that RCM is a useful method for the construction of cyclic molecules including macrocycles,[10a] this reaction has not been applied in the construction of macrocyclic enediynes.[10b] This is not surprising, as selectivity issues between the multiple unsaturated moieties can be readily imagined. Common methods used for the critical cyclization step in the synthesis of analogs of naturally occurring enediynes are the Nozaki–Hiyama–Kishi reaction,[11,5b] McMurry and pinacol couplings,[12] and the synthesis of sulfur-containing macrocycles followed by Ramberg–Bäcklund reaction.[1g,13] In this work, we decided to depart from these more established methods and focus on the RCM reaction as a decisive step in the synthesis of macrocyclic enediynes. The advantage of RCM is the one-pot macrocyclization/double bond formation, leading directly to the ***di***enediyne systems. Up until now, only highly strained 10-membered ***di***enediynes have been prone to undergo spontaneous cyclization during preparation,[14] and stable 12-membered ***tetra***enediynes[12a] are known. Therefore, to ensure the stability of our target ***di***enediyne during preparation by RCM, we chose to avoid the obvious 10-membered scaffold and instead focused on the synthesis of 12-membered benzothiophene-fused ***di***enediyne **1** (Scheme 2).

Recently, we have developed a short and convenient synthetic route to acyclic enediynes fused to five-membered heterocycles. This route is based on electrophilic cyclization of *o*-(buta-1,3-diyn-1-yl)anisole, -thioanisole, and -*N*,*N*-dimethylaniline derivatives.[9c] In the present work, this

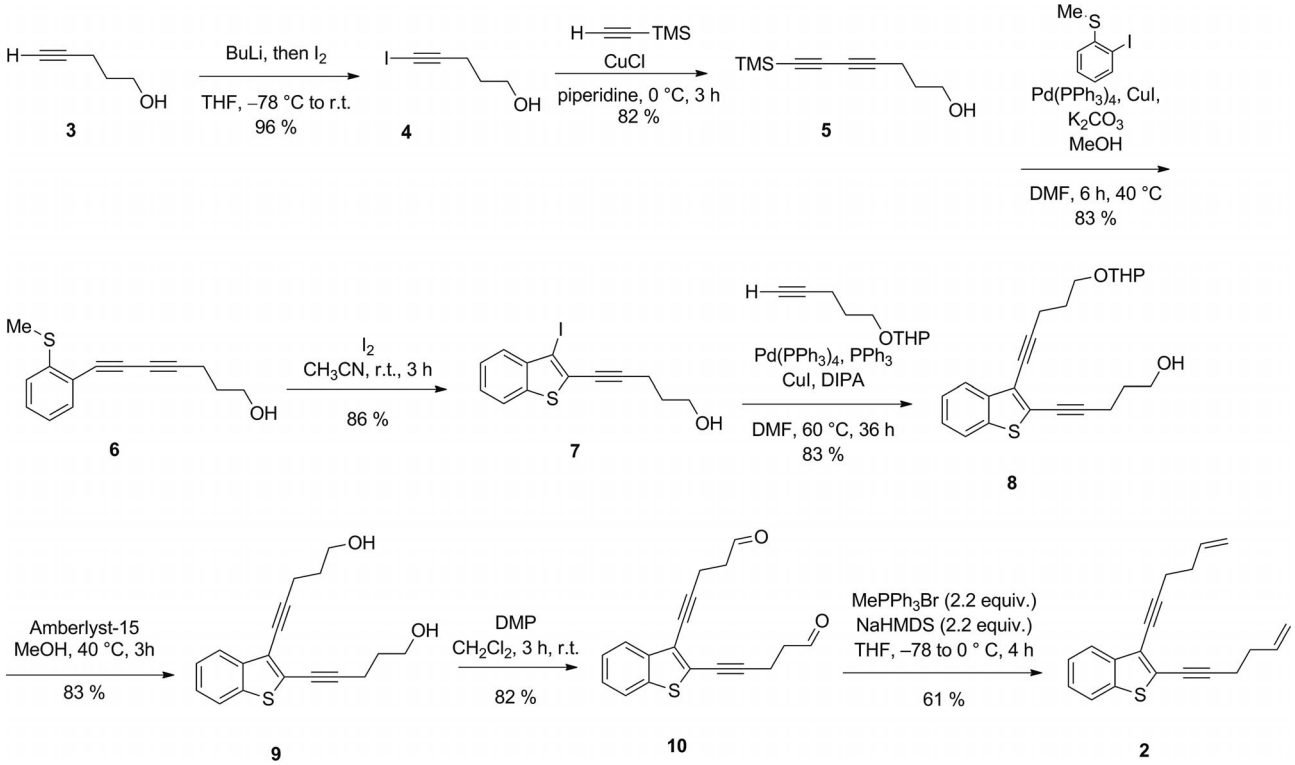


Scheme 2. Retrosynthesis of the 12-membered dienediyne.

method constituted the keystep in the multistage synthesis of dimethylene substrate **2** for the macrocyclization (Scheme 3).

The substrate for the electrophilic cyclization, *o*-(7-hydroxyhepta-1,3-diyn-1-yl)thioanisole (**6**), was synthesized in three steps (Scheme 3). Sonogashira coupling of *o*-iodothioanisole and trimethylsilyl-protected heptadiynol **5** was performed under known conditions, featuring one-pot removal of the TMS group.[15] Subsequent iodocyclization of thioanisole **6** in acetonitrile allowed iodoethynylbenzothiophene **7** to be obtained in 86% yield.

Sonogashira coupling[16] was used for the synthesis of enediynediol **9**. An attempt to diminish the number of steps by using unprotected substrates in the Sonogashira coupling gave diol **9** in poor yield (36%). On the other hand, working with both *O*-THP-protected **7** and pent-4-yn-1-ol (**3**) failed due to the close retention times of the desired product and the THP-protected deca-4,6-diyne-1,10-diol, which was an expected byproduct of the Sonogashira coupling.[17] It was found that the best starting materials for the synthesis of enediynediol **9** are THP-protected pent-4-

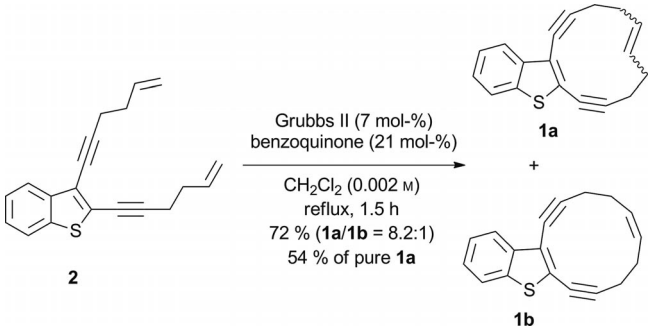


Scheme 3. Synthesis of 2,3-di(hex-5-en-1-yn-1-yl)benzo[*b*]thiophene (**2**).

yn-1-ol and benzothiophene **7**, which has a free hydroxy group. With the Sonogashira reaction of these substrates, enediyne **8** was obtained in excellent yield (83%). Deprotection of compound **8** in the presence of Amberlyst-15 in methanol gave desired diol **9** (83%).

To convert endiynediol **9** into dimethylene compound **2**, a sequence involving Dess–Martin periodinane mediated oxidation followed by methylenation was found to be suitable. Whereas the first reaction proceeded smoothly, a recently developed rhodium-catalyzed methylenation of aldehydes with trimethylsilyldiazomethane in the presence of the Wilkinson catalyst developed by Lebel et al.[18] was ineffective for the substrate **10** (only 9% yield). Hence, we proceeded with a classical Wittig olefination. In this case, the nature of the base utilized proved to be crucial: thus, the use of BuLi led to compound **2** in a lower yield (18%), whereas NaHMDS gave bismethylenated substrate **2** for the RCM in satisfactory yield (61%).

Gratifyingly, RCM macrocyclization of compound **2** proceeded smoothly in refluxing dichloromethane with the Grubbs II catalyst (7 mol-%) and benzoquinone[19] to prevent double-bond migration (Scheme 4). The macrocyclic dienediyne was prepared as a mixture of (*E*)/(*Z*) isomers (i.e., **1a**/**1b** = 8.2:1 according to ^{1}H NMR spectroscopy) in 72% overall yield. It was also possible to isolate pure (*E*) isomer **1a** by column chromatography in 54% yield.



Scheme 4. Ring-closing metathesis of dimethylene compound **2**.

The (*E*) configuration of the metathesis-formed double bond was established by X-ray analysis (Figure 1)[20] and confirmed by ^{1}H NMR spectroscopy with selective decoupling from both the CH_2(12) and CH_2(15) hydrogen atoms.[21]

The X-ray data showed that compound **1a** represents a class of macrocycles with planar chirality, where the chiral plane is the plane of the double bond and exists in crystals as two enantiomers (*p*S/*p*R = 55:45 or vice versa). It is known that such types of systems might be configurationally stable in solution if the double bond is unable to switch through the macrocycle [(*E*)-cyclooctene,[22a,22b] (*E*)-silacycloheptene[22c]]. On the other hand, decreased hindrance to rotation of the ethylenic linkage [such as increasing the ring size, as in (*E*)-cyclononene or (*E*)-cyclodecene[22d]] would reduce the configurational stability of the cycloolefins. In the case of compound **1a**, the conversion of two enantiomers was expected to proceed easily in solution at room

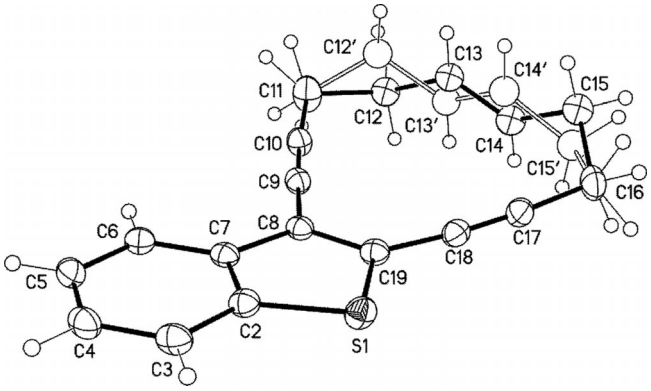
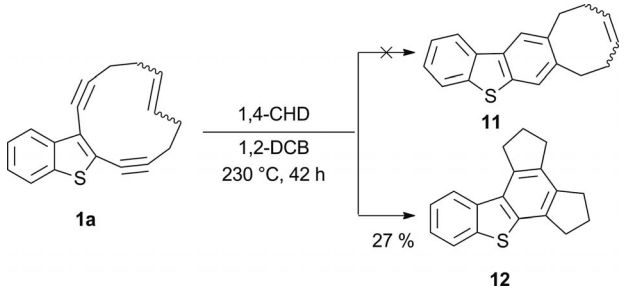


Figure 1. Molecular structure of **1a** showing the 55:45 disorder (displacement parameters are drawn at the 50% probability level).

temperature due to the degree of conformational flexibility possible in the dodecadienediyne system, which was confirmed by ^{1}H NMR spectroscopy.[23]

It has been shown that in order for the Bergman cyclization of 12-membered and large enediynes to proceed at moderate temperature, some special structural features are essential.[1j,1k,24] We supposed that inclusion of the (*E*) double bond in the 12-membered ring might reduce the high temperature required for the cyclization of enediynes with large rings.[1g,7] Finally, to determine the reactivity of dienediyne **1a** in the Bergman cyclization, several experiments were carried out (Scheme 5).



Scheme 5. Cycloaromatization of dienediyne **1a**.

Cyclic dienediyne derivative **1a** was heated in a sealed argon-flushed vial in three different solvents (24 h each): *i*PrOH (130 °C), toluene (130 °C), and 1,4-dichlorobenzene (DCB, 230 °C). In the two last entries, 1,4-cyclohexadiene (60 equiv.) was used as a potential source of hydrogen. As demonstrated by GC–MS monitoring,[25] no reaction occurred in *i*PrOH and toluene, whereas a reaction product with *m*/*z* = 264.1, which corresponds to the addition of two hydrogen atoms to starting material **1a**, alongside starting material **1a** in ca. 1:1 ratio was observed in the case of DCB. After 42 h heating in DCB, this compound was isolated as the main product of the reaction (GC–MS). Surprisingly, the obtained compound was determined to be indacene derivative **12** (*m*/*z* = 264.1) instead of the expected product of Bergman cyclization (i.e., **11**; *m*/*z* = 264.1). It should be noted that (*Z*)-tribenzo[*c*,*g*,*k*]-1,2,5,6-tetradehydro[12]-annulene cyclized to the corresponding (*Z*)-cyclooctene with a conversion of about 50% at 250 °C, whereas ind-

acene derivatives have been formed only under AuCl-catalyzed cycloaromatization conditions.[12a]

To compare the abilities of cyclic enediyne **1a** and acyclic enediynes **2**, **9**, and **10** to undergo Bergman cyclization, we turned to differential scanning calorimetry (DCS) studies.[1j,26] The obtained data[27] reveals that there is no significant difference between acyclic (i.e., **2**, **9**, and **10**) and cyclic 12-membered (i.e., **1a**) enediyne systems. Thus, the exothermic peaks at 280 (for **9**), 259 (for **10**), 254 (for **2**), and 264 °C (for **1a**) obviously illustrate the Bergman cyclization of the corresponding enediynes. Additional evidence suggesting that irreversible Bergman cyclization took place is the fact that neither endothermic nor exothermic features were observed during the scanning of the thermolyzed sample for the second time.

Conclusions

For the first time, the RCM reaction has been demonstrated for the synthesis of a macrocyclic dienediyne system. The combination of the electrophilic cyclization of *ortho*-functionalized buta-1,3-diynylarenes with RCM may open a simple synthetic route towards other dienediyne systems of variable ring size and nature of the fused heterocycle. The obtained 12-membered dienediyne represents a polyenyne macrocycle with interesting interconvertible planar chirality.

The DSC experiment showed that Bergman cyclization of 12-membered dienediyne **1a** as well as that of acyclic enediynes requires high temperatures (250–280 °C). The scope and limitations of the synthetic strategy described herein for the synthesis of 11- and 10-membered dienediynes, which are expected to be more reactive than **1a** in Bergman cyclization, are under investigation.

Experimental Section

RCM Procedure for the Preparation of (9*E*)-Benzo[*b*]thieno[4,3-*b*]-cyclododeca-3,9-diene-1,5-diyne (1a): To a solution of compound **2** (121 mg, 0.438 mmol) in dry CH_2Cl_2 (200 mL, thoroughly flushed with argon) was added 1,4-benzoquinone (10.0 mg, 0.0920 mmol, 21 mol-%), followed by Grubbs II catalyst (26.0 mg, 0.0310 mmol, 7 mol-%). The reaction mixture was then heated at reflux for 1.5 h. After cooling, ethylvinyl ether (0.200 mL) was added to the reaction mixture, and the solvent was evaporated under reduced pressure to yield the crude product. Purification by column chromatography on silica gel (pentane) delivered pure (*E*)-**1a** (62.0 mg, 54%) as a white solid and a mixture of (*E*)-**1a**/(*Z*)-**1b** isomers (20.0 mg, 17% *E*/*Z* = 1.22: 1[28]) as colorless crystals. Total yield of the mixture (**1a**/**1b** = 8.2:1) was calculated as 72%. Data for **1a**: M.p. 156–158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36–2.40 (m, 4 H), 2.67–2.71 (m, 4 H), 5.50–5.61 (m, 2 H), 7.33–7.40 (m, 2 H), 7.68–7.70 (m, 1 H), 7.81–7.83 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.75, 19.95, 30.83, 31.02, 76.41 (one C_{sp} signal is under the $CDCl_3$ triplet), 96.43, 100.11, 122.12, 123.00, 124.32, 124.80, 125.67, 127.18, 130.89, 131.37, 137.83, 138.17 ppm. IR (neat): $\tilde{\nu}$ = 2922 (CH), 2899 (CH), 2838 (CH), 2212 (both C≡C), 1459, 1428, 1366, 1317, 1213, 1158, 1131, 1116, 1064, 1013, 981, 957, 901, 854, 822, 764, 730, 714, 642 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 262.1 (11.1) $[M]^+$, 247.1 (1.8) $[M - CH_3]^+$, 234.1 (1.6) $[M - CH_2CH_2]^+$, 221.1 (1.0), 208.0 (7.6), 163.1 (2.5), 58.1 (25.6), 43.0 (100.0). HRMS (EI): calcd. for $C_{18}H_{14}S$ $[M]^+$ 262.0816; found 262.0817. $C_{18}H_{14}S$ (262.37): calcd. C 82.40, H 5.38, S 12.22; found C 82.43, H 5.31, S 12.47.

Supporting Information (see footnote on the first page of this article): Experimental procedures, copies of the ^{1}H NMR and ^{13}C NMR spectra for all compounds, GC–MS chromatograms and DCS thermograms.

Acknowledgments

We are thankful to Prof. Michael A. Meier (Karlsruhe Institute of Technology) for providing the equipment for DSC measurements. I.B. and N.D. acknowledge Saint-Petersburg State University for a research grant (12.38.14.2011). N.D. acknowledges the Center for Functional Nanostructures (CFN) for financial support.

[1] a) N. Ishida, K. Miyamki, K. Kumagai, M. Rikimaru, *J. Antibiot.* **1965**, *18*, 68–76; b) M. Konishi, H. Ohkuma, K. Saitoh, H. Kawaguchi, J. Golik, G. Dubay, G. Groenewold, B. Krishnan, T. W. Doyle, *J. Antibiot.* **1985**, *38*, 16051609; c) J. Golik, J. Clardy, G. Dubay, G. Groenewold, H. Kawaguchi, M. Konishi, B. Krishnan, H. Ohkuma, K. Saitoh, T. W. Doyle, *J. Am. Chem. Soc.* **1987**, *109*, 3461–3462; d) J. Golik, G. Dubay, G. Groenewold, H. Kawaguchi, M. Konishi, B. Krishnan, H. Ohkuma, K. Saitoh, T. W. Doyle, *J. Am. Chem. Soc.* **1987**, *109*, 3462–3464; e) M. D. Lee, T. S. Dunne, M. M. Siegel, C. C. Chang, G. O. Morton, D. B. Borders, *J. Am. Chem. Soc.* **1987**, *109*, 3464–3466; f) M. D. Lee, T. S. Dunne, C. C. Chang, G. A. Ellestad, M. M. Siegel, G. O. Morton, W. J. McGahren, D. B. Borders, *J. Am. Chem. Soc.* **1987**, *109*, 3466–3468; g) K. C. Nicolaou, G. Zuccarello, C. Riemer, V. A. Estevez, W.-M. Dai, *J. Am. Chem. Soc.* **1992**, *114*, 7360–7371; h) A. L. Smith, K. C. Nicolaou, *J. Med. Chem.* **1996**, *39*, 2103–2117; i) I. A. Maretina, B. A. Trofimov, *Russ. Chem. Rev.* **2006**, *75*, 825–845; j) M. C. Joshi, D. S. Rawat, *Chem. Biodiversity* **2012**, *9*, 459–498; k) A. Basak, S. Mandal, S. S. Bag, *Chem. Rev.* **2003**, *103*, 4077–4094.

[2] a) R. R. Jones, R. G. Bergman, *J. Am. Chem. Soc.* **1972**, *94*, 660–661; b) R. Nagata, H. Yamanaka, E. Okazaki, I. Saito, *Tetrahedron Lett.* **1989**, *30*, 4995–4998; c) A. G. Myers, E. Y. Kuo, N. S. Finney, *J. Am. Chem. Soc.* **1989**, *111*, 8057–8059.

[3] a) B. H. Long, J. Golik, S. Forenza, B. Ward, R. Rehfuss, J. C. Dabrowiak, J. J. Catino, S. T. Musial, K. W. Brookshire, T. W. Doylet, *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 2–6; b) N. Zein, M. Poncin, R. Nilakantan, G. A. Ellestad, *Science* **1989**, *244*, 697–699; c) A. G. Myers, *Tetrahedron Lett.* **1987**, *28*, 4493–4496.

[4] a) K. C. Nicolaou, G. Zuccarello, Y. Ogawa, E. J. Schweiger, T. Kumazawa, *J. Am. Chem. Soc.* **1988**, *110*, 4866–4868; b) K. C. Nicolaou, A. L. Smith, *Acc. Chem. Res.* **1992**, *25*, 497–503.

[5] a) C.-S. Kim, K. C. Russel, *J. Org. Chem.* **1998**, *63*, 8229–8234; b) O. V. Vinogradova, I. A. Balova, V. V. Popic, *J. Org. Chem.* **2011**, *76*, 6937–6941; c) I. V. Alabugin, M. Manoharan, S. V. Kovalenko, *Org. Lett.* **2002**, *4*, 1119–1122; d) G. B. Jones, P. M. Warner, *J. Am. Chem. Soc.* **2001**, *123*, 2134–2145; e) N. Choy, C.-S. Kim, C. Ballestero, L. Artigas, C. Diez, F. Lichtenberger, J. Shapiro, K. C. Russell, *Tetrahedron Lett.* **2000**, *41*, 6955–9658.

[6] a) P. Magnus, S. Fortt, T. Pitterna, J. P. Snyder, *J. Am. Chem. Soc.* **1990**, *112*, 4986–4987; b) J. P. Snyder, *J. Am. Chem. Soc.* **1990**, *112*, 5367–5369; c) P. R. Schreiner, *Chem. Commun.* **1998**, 483–484.

[7] a) Z. Zhao, Y. Peng, N. K. Dalley, J. F. Cannon, M. A. Peterson, *Tetrahedron Lett.* **2004**, *45*, 3621–3624; b) J. Kaiser, B. C. J. van Esseveldt, M. J. A. Segers, F. L. van Delft, J. M. M.

Smits, S. Butterworth, F. P. J. T. Rutjes, *Org. Biomol. Chem.* **2009**, *7*, 695–705.
[8] a) A. Siddiq, V. Dembitsky, *Anti-Cancer Agents Med. Chem.* **2008**, *8*, 132–170; b) R.-G. Shao, *Curr. Mol. Pharmacol.* **2008**, *1*, 50–60; c) G. B. Jones, F. S. Fouad, *Curr. Pharm. Des.* **2002**, *8*, 2415–2440.
[9] a) N. A. Danilkina, A. E. Kulyashova, I. A. Balova, *Chem. Heterocycl. Compd.* **2012**, *48*, 95–106; b) O. V. Vinogradova, V. N. Sorokoumov, I. A. Balova, *Tetrahedron Lett.* **2009**, *50*, 6358–6360; c) N. A. Danilkina, S. Bräse, I. A. Balova, *Synlett* **2011**, 517–520.
[10] a) N. L. Snyder, K. W. Graepel in *Name Reactions for Carbocyclic Ring Formations* (Eds.: J. J. Li), John Wiley & Sons, Hoboken, New Jersey, **2010**, pp. 489–577; b) for the only precedent regarding the use of RCM in the synthesis of enediyne systems, see D. W. Klosowski, S. Burke, G. B. Jones, 243rd ACS National Meeting & Exposition, San Diego, CA, March 25–29, **2012**.
[11] a) L. Banfi, G. Guanti, *Tetrahedron Lett.* **2002**, *43*, 7427–7429; b) L. Banfi, G. Guanti, *Eur. J. Org. Chem.* **2002**, 3745–3755; c) M. F. Semmelhack, M. Jaskowski, R. Sarpong, D. M. Ho, *Tetrahedron Lett.* **2002**, *43*, 4947–4950; d) L. Banfi, G. Guanti, *Tetrahedron Lett.* **2000**, *41*, 6523–6526; e) C. R. Hickenboth, J. D. Rule, J. S. Moore, *Tetrahedron* **2008**, *64*, 8435–8448; f) N. Choy, B. Blanco, J. Wen, A. Krishan, K. C. Russel, *Org. Lett.* **2000**, *2*, 3761–3764; g) S. Py, C. W. Harwig, S. Banerjee, D. L. Brown, A. G. Fallis, *Tetrahedron Lett.* **1998**, *39*, 6139–6142; h) G. Karpov, A. Kuzmin, V. V. Popik, *J. Am. Chem. Soc.* **2008**, *130*, 11771–11777; i) A. Poloukhtine, V. V. Popik, *J. Org. Chem.* **2006**, *71*, 7417–7421; j) D. R. Pandithavidana, A. Polouchtine, V. V. Popik, *J. Am. Chem. Soc.* **2009**, *131*, 351–356.
[12] a) M. Iyoda, K. Fuchigami, A. Kusaka, T. Yoshida, M. Yoshida, H. Matsuyama, Y. Kuwatani, *Chem. Lett.* **2000**, *29*, 860–861; b) M. Eckhard, R. Brückner, *Angew. Chem.* **1996**, *108*, 1185; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1093–1096; c) M. Rucker, R. Brückner, *Tetrahedron Lett.* **1997**, *38*, 7353–7356; d) E. Rank, R. Brückner, *Eur. J. Org. Chem.* **1998**, 1045–1053.
[13] X. Cao, Y. Yang, X. Wang, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2485–2489.
[14] H. N. C. Wong, F. Sondheimer, *Tetrahedron Lett.* **1980**, *21*, 217–220.
[15] V. Fiandanese, D. Bottalico, G. Marchese, A. Punzi, *Tetrahedron* **2006**, *62*, 5126–5132.
[16] K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467–4470.
[17] A. Elangovan, Y.-H. Wang, T.-I. Ho, *Org. Lett.* **2003**, *5*, 1841–1844.
[18] H. Lebel, V. Paquet, *J. Am. Chem. Soc.* **2004**, *126*, 320–328.
[19] S. H. Hong, D. P. Sanders, C. W. Lee, R. H. Grubbs, *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161.
[20] CCDC-873723 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[21] Selective decoupling of the hydrogen atoms of both the CH_2(12) and CH_2(15) groups (see the Supporting Information) breaks down the strongly coupled system and allows the measurement of the coupling constant ^3J[C(13)H,C(14)H] = 15.2 Hz, which is in good accordance with the (*E*) configuration of the double bond.
[22] a) A. C. Cope, B. A. Pawson, *J. Am. Chem. Soc.* **1965**, *87*, 3649–3651; b) M. Royzen, G. P. A. Yap, J. M. Fox, *J. Am. Chem. Soc.* **2008**, *130*, 3760–3761; c) A. Krebs, K.-I. Proff, W. Raffay, B. Thökle, W. A. König, I. Hardt, R. Boese, *Angew. Chem.* **1997**, *109*, 159; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 159–160; d) A. C. Cope, K. Banholzer, H. Keller, B. A. Pawson, J. J. Whang, H. J. S. Winkler, *J. Am. Chem. Soc.* **1965**, *87*, 3644–3649.
[23] The signals of the hydrogen atoms of CH_2(11) and CH_2(16) appear as two triplets (J = 6.3 Hz) in the normal ^{1}H NMR spectrum and as two singlets in a spectrum with selective decoupling from both CH_2(12) and CH_2(15) (see the Supporting Information). This is evidence for the magnetic equivalency of both hydrogen atoms at C(11), as well as those at C(16), which may be observed in the case of fast (on the NMR timescale) switching of the double bond through the macrocycle. On the other hand, another reason for such an NMR spectrum might be the degeneracy of the AB systems of the hydrogen atoms at C(11) and C(16) as a result of the close chemical shifts of each hydrogen atom. This explanation should not be ruled out until additional spectra at lower temperature and higher resonance frequency are measured.
[24] a) A. Basak, S. K. Roy, S. Mandal, *Angew. Chem.* **2005**, *117*, 134; *Angew. Chem. Int. Ed.* **2005**, *44*, 132–135; b) S. Bhattacharyya, A. E. Clark, M. Pink, J. M. Zaleski, *Chem. Commun.* **2003**, 1156–1157; c) A. Basak, J. C. Shain, U. K. Khamrai, K. R. Rudra, A. Basak, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1955–1964.
[25] For all GC–MS chromatograms, see the Supporting Information.
[26] a) R. H. Grubbs, D. Kratz, *Chem. Ber.* **1993**, *126*, 149–157; b) B. König, H. Rütters, *Tetrahedron Lett.* **1994**, *35*, 3501–3504; c) B. P. Warner, S. P. Millar, R. D. Broene, S. L. Buchwald, *Science* **1995**, *269*, 814–816.
[27] For all DSC thermograms, see the Supporting Information.
[28] The **1a/1b** ratio was calculated from the ^{1}H NMR spectrum of the obtained mixture. For the ^{1}H NMR spectrum and GC–MS chromatogram of this mixture, see the Supporting Information.

Received: July 3, 2012
Published Online: September 3. 2012

