Arabian Journal of Chemistry (2019) **12**, 151–167

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Cr(II)-promoted internal cyclization of acyclic enediynes fused to benzo[*b*]thiophene core: Macrocycles *versus* 2-methylenecycloalkan-1-ols formation

A.E. Kulyashova [a], A.V. Ponomarev [a], S.I. Selivanov [a], A.F. Khlebnikov [a], V.V. Popik [b,*], I.A. Balova [a,*]

[a] *Saint Petersburg University, 7/9 Universitetskaya nab., St. Petersburg 199034, Russia*
[b] *Department of Chemistry, University of Georgia, Athens, GA 30602, USA*

Received 9 January 2018; accepted 9 May 2018
Available online 18 May 2018

KEYWORDS

Enediynes;
Diacetylenes;
Iodocyclization;
Intramolecular Nozaki-Hiyama-Kishi reactions;
Benzothiophene;
Allylic alcohols

Abstract The utility of the intramolecular Nozaki-type coupling for the synthesis of macrocyclic benzo[*b*]thiophene-fused enediynes has been explored. The starting acyclic enediynes were prepared by the iodocyclization of 2-(buta-1,3-diynyl)thioanisoles followed by the Sonogashira cross-coupling of the resulting iodo-substituted benzo[*b*]thiophene with corresponding acetylenes. We found that Cr(II)-promoted intramolecular cyclization of 7-[2-(iodoethynyl)benzo[*b*]thiophen-3-yl]hept-6-ynal and 7-[3-(iodoethynyl)benzo-[*b*]thiophen-2-yl]hept-6-ynal resulted in the formation of 11-membered macrocyclic enediynes, while both expected 10-membered enediynes cannot be produced under the Nozaki-type reaction from corresponding 6-[3-(iodoethynyl)benzo[*b*]thiophen-2-yl]hex-5-ynal and 6-[2-(iodoethynyl)benzo[*b*]thiophen-3-yl]hex-5-ynal. In the case the reaction was catalyzed by Ni(II), the attack on a proximal triple bond led to the formation of 2-methylenecycloalkane-1-ol fragments, instead of macrocyclization. The DFT analysis of the ring strain in the benzo[*b*]thiophene-fused 10- and 11-membered enediyne-containing cycle provides the plausible explanation of the observed regioselectivity.

1. Introduction

Macrocyclic enediynes are the key part of powerful natural antitumor antibiotics (Galm et al., 2005; Hamann et al., 2011; Maretina and Trofimov, 2006; Minto and Blacklock, 2008; Nicolaou et al., 1992a; Siddiq and Dembitsky, 2008; Smith and Nicolaou, 1996). All members of this class of natural products have characteristic structural fragments

* Corresponding authors.
E-mail addresses: vpopik@uga.edu (V.V. Popik), i.balova@spbu.ru (I.A. Balova).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.arabjc.2018.05.005
1878-5352

containing two triple bonds conjugated to a double bond in a *Z*-configuration. Depending on the structural features, the enediynes undergo either Bergman (Bergman, 1973) (as in the case of the most of natural enediynes (Nicolaou et al., 1993a), for example: dynemicin, (Konishi et al., 1990; Nicolaou and Smith, 1992) calicheamicin (Lee et al., 1991, 1987; Thorson et al., 2000)) or Myers-Saito (Myers, 1987; Nagata et al., 1989) (for example, neocarzinostatin (Goldberg, 1991)) cyclization to yield a benzenoid biradical (Wang and Sondheimer, 1980). The biradical then abstracts two hydrogen atoms from the dDNA carbohydrate-phosphate backbone, resulting in the dDNA double strand cleavage (De Voss et al., 1990; Lee et al., 1987; Sugiura et al., 1991, 1990; Wolkenberg and Boger, 2002; Zein et al., 1988). It is known that the rate of enediyne cyclization correlates with the ring size. For biomedical applications, the intramolecular Bergman cyclization (BC) should proceed spontaneously around the human body temperature. This can be achieved by incorporating the enediyne scaffold into 9-membered or 10-membered ring structure, as in the case of naturally occurring enediynes (Advani et al., 2010; Nicolaou et al., 1988, 1993a; Nicolaou and Dai, 1991). It is known that about 70% of marketed antibiotics are derived from natural products, although in some times their mode of action remained unclear and is still under investigations (Keohane et al., 2018). Despite the mechanism of action of enediyne antibiotics has been well studied, their clinical use is limited due to the complex structure of enediyne natural products as well as low selectivity along with remarkable biological activity (Nicolaou et al., 1992a, 1992b, 1992c, 1993b; Siddiq and Dembitsky, 2008; Smith and Nicolaou, 1996; Zein et al., 1988). Thus, designing new enediyne structures with the goal of taming DNA-cleaving activity of this class of antibiotics remains the important goal of modern medicinal chemistry (Chari et al., 2014; Joshi and Rawat, 2012; Kraka et al., 2008; Mohamed et al., 2013; Nicolaou et al., 2015; Oku et al., 2003; Poloukhtine et al., 2010).

The fusion of the enediynes moiety to a heterocyclic core (Choy et al., 2000; Kim and Russel, 1999, 1998; Kim et al., 2000, 1999; Zhao et al., 2005, 2004) allows not only for the modulation of the cycloaromatization rate, but also permits to explore the additional DNA-binding affinity. Our group has previously reported a new efficient and facile strategy for the preparation of heterocyclic enediynes, which is based on the cyclization of ortho-functionalized butadiynylheteroarenes (Danilkina et al., 2014, 2011; Vinogradova et al., 2011). This strategy provides an efficient method for the introduction of various functional groups at the termini of the (*Z*)-3-en-1,5-diyne fragment fused to heteroindenes, allowing for the use of various macrocyclization techniques. Thus, we have recently reported the synthesis of macrocyclic enediynes fused to benzothiophene and indole using ring-closing metathesis (Danilkina et al., 2012, 2015, 2014) or the Nicholas-type macrocyclization (Lyapunova et al., 2016, 2018).

Nozaki-Hiyama-Kishi reaction (NHK) (Jin et al., 1986; Takai et al., 1986) is a useful tool for the intramolecular construction the new C—C bond between sp^2-sp^2 (Bolte et al., 2015; Iwamoto et al., 2004; LeClair et al., 2010; Lubineau and Billault, 1998; Mi and Maleczka, 2001; Mohapatra et al., 2010; Muller et al., 1998; Pilli et al., 2000; Pilli and Victor, 1998; Takao et al., 2009; Wang et al., 2016) and sp-sp^2 carbon atoms (Boddenmann and Keese, 1993; Crévisy and Beau, 1991; Dai et al., 2001; Sandoval et al., 2002; Yamaguchi et al., 2012). This reaction is very selective and tolerant to various functional groups (ester, amide, alkene, etc.) (Furstner and Shi, 1996; Jin et al., 1986). A large number of 10- and 11-membered macrocyclic enediynes have been synthesized using NHK reaction as key step (Ban and Guanti, 2000; Banfi and Guanti, 2002a, 2002b; Brandstetter and Maier, 1994; Choy et al., 2000; Comanita et al., 2000; Crévisy and Beau, 1991; Dancy et al., 1995; Karpov et al., 2008; Karpov and Popik, 2007; Maier and Brandstetter, 1992; Nicolaou et al., 1992b; Nishikawa et al., 1994; Poloukhtine and Popik, 2005; Py et al., 1998; Semmelhack et al., 2002; Yamaguchi et al., 2012). We have also successfully applied Nozaki coupling in the synthesis of 10-membered macrocyclic cinnoline-fused endiyne (Vinogradova et al., 2011). It is important to note, that cinnolinemoiety quadruples the rate of cycloaromatization over the benzannulated analogue.

In this report we explore the scope and limitations of the intramolecular Nozaki reaction for the synthesis of 10- and 11- membered macrocyclic enediynes fused to benzothiophene.

2. Experimental section

2.1. General information and methods

Solvents and reagents were purchased from commercial suppliers and used without further purification, unless otherwise noticed. Solvents were dried and distilled using standard procedures. Starting compounds **6a-c**, **7a-c**, **9a**,**b**, **10a**,**b** **11a**,**b** were prepared using previously reported procedures (Danilkina et al., 2014; Jones et al., 1987; Kulyashova et al., 2013). All reactions were carried out under argon atmosphere in flame-dried glassware. Evaporation of solvents and concentration of reaction mixtures were performed in vacuo at 30–40 °C on a rotary evaporator. Preparative chromatography was conducted using silica gel 60. Melting points (mp) are uncorrected. Differential scanning calorimetry (DSC) experiments were carried out with 0.11 mg of samples using crucibles with pierced caps under nitrogen atmosphere at a heating/cooling rate of 20 °C min^{-1} from a temperature of 20 °C up to 395 °C, followed by cooling to 20 °C and heating to 395 °C for the second time. ^{1}H NMR and ^{13}C NMR spectra were recorded using 300 MHz spec (for **9b**) or 400 MHz instrument (for all other compounds) in $CDCl_3$ with TMS as the internal standard or in $CDCl_3$ without the internal standard (for **4b**, **16a**), or in DMSO d_6. The ^{1}H NMR data are reported as the chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (*J*, are given in Hz) and number of protons. The ^{13}C NMR data are reported as the chemical shift (δ) and type of carbon, determined from DEPT 135 experiments). Chemical shifts are referenced to residual solvent (δ = 7.26 ppm for ^{1}H in $CDCl_3$, δ = 77.00 ppm for ^{13}C in $CDCl_3$, δ = 2.50 ppm for ^{1}H in DMSO d_6, δ = 39.50 ppm for ^{13}C in DMSO d_6). High-resolution mass spectra (HRMS) were measured using FAB or ESI. The single-crystal X-ray diffraction studies were carried out at 100.0 K using Cu Kα radiation (λ = 1.54184 Å).

2.2. General procedure for synthesis ***9c, 10c***

*2.2.1. 2-[4-(Trimethylsilyl)buta-1,3-diynyl]thioanisole (**9c**) (Danilkina et al., 2014)*

$PdCl_2(PPh_3)_2$ (0.440 mmol, 5 mol.%), PPh_3 (0.890 mmol, 0.231 g, 10 mol.%), 4-(trimethylsilyl)buta-1,3-diyne **7c** were added to a solution of 2-iodothioanisole **8** (8.80 mmol, 2.20 g,) in triethylamine (90 mL) at room temperature. In 5 min CuI (1.32 mmol, 0.251 g, 15 mol.%) was added, and reaction mixture was stirred at 40 °C for 2.5 h (TLC control). The reaction mixture was cooled, diluted with EtOAc (70.0 mL) and washed with a saturated aqueous solution of NH_4Cl (2 × 70.0 mL), water (50.0 mL) and brine (50.0 mL). The combined aqueous layers were extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with a saturated aqueous solution of NH_4Cl (50.0 mL), water (50.0 mL), brine (50.0 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, crude product was purified by Isolera™ prime flash-chromatography system eluting with acetone/hexane system (gradient from 1% to 5% of acetone) to give product as yellow oil (1.81 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.44 (dd, J = 7.7 Hz, J = 1.2 Hz, 1H), 7.31 (td, J = 8.0 Hz, J = 1.4 Hz, 1H), 7.16 (d, J = 7.9 Hz, 1H), 7.07 (td, J = 7.6 Hz, J = 0.9 Hz, 1H), 2.49 (s, 3H), 0.24 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 143.5, 133.8, 129.6, 124.5, 124.3, 119.6, 92.5, 87.6, 80.2, 74.0, 15.2, −0.42.

*2.2.2. 3-Iodo-2-(2-trimethylsilylethynyl)benzo[b]thiophene (**10c**) (Danilkina et al., 2014)*

A solution of iodine (40.9 mmol, 1.04 g) in DCM (21.0 mL) was added dropwise to a degassed solution of 2-[4-(trimethylsilyl)buta-1,3-diynyl]thioanisole **9c** (4.09 mmol, 1.00 g) in DCM (21.0 mL) under argon atmosphere at rt. Reaction was stirred at room temperature for 1.5 h (TLC control). The reaction mixture was diluted with DCM (30.0 mL) and washed with a saturated aqueous solution of $Na_2S_2O_3$ (30.0 mL). The aqueous layer was extracted with DCM (2 × 15.0 mL). Combined organic layers were washed with brine (50.0 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, crude product was purified by flash chromatography on silica gel eluting with pentane to give crystalline cream solid. Mp. = 61–62 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.73–7.69 (m, 2H), 7.46–7.39 (m, 2H), 0.32 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 140.4, 138.9, 126.6, 126.3, 125.7, 124.8, 122.1, 105.5, 98.3, 88.7, −0.24.

2.3. General procedure for synthesis of enediynes ***11c,d***

A solution of 3-iodo-2-(2-trimethylsilylethynyl)benzo[*b*]thiophene **10c** (1.00 mmol, 0.356 g) and corresponding alkyn-1-ol (2.5 mmol) in dry DCM (5.0 mL) were added to a degassed suspension of $PdCl_2(PPh_3)_2$ (0.05 mmol, 0.035 g, 5 mol.%) and CuI (0.1 mmol, 0.019 g, 10 mol.%) in anhydrous triethylamine (5.0 mL). The reaction mixture was stirred at room temperature for 24 h (TLC control). The mixture was filtered through a shot pad of silica gel using EtOAc as an eluent. The solvent was removed under reduced pressure, crude product was purified by column chromatography on silica gel.

*2.3.1. 6-{2-[(Trimethylsilyl)ethynyl]benzo[b]thiophen-3-yl} hex-5-yn-1-ol (**11c**)*

The compound **11c** was synthesized following the standard procedure from **10c** (1.60 mmol, 0.570 g) and hex-5-yn-1-ol (4.00 mmol, 0.393 g) in triethylamine (8.0 mL) and DCM (8.0 mL). Purification of crude product by column chromatography using hexane/ethyl acetate (3:1) as the eluent gave 0.461 g (88%) of **11c** as a reddish-yellow oil. R_f = 0.41 (hexane/ethyl acetate (1:1)). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.86–7.81 (m, 1H), 7.72–7.69 (m, 1H), 7.42–7.36 (m, 2H), 3.75 (t, J = 6.0 Hz, 2H), 2.62 (t, J = 6.6 Hz, 2H), 1.89–1.74 (m, 4H), 1.40 (br. s, 1H), 0.30 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 138.7, 138.4, 126.2, 125.0, 124.9, 124.2, 123.5, 122.0, 105.0, 97.3, 97.2, 74.1, 62.4, 31.8, 25.0, 19.6, −0.1. HRMS ESI: $[M+Na]^+$ calculated for $C_{19}H_{22}NaOSSi^+$: 349.1053; found 349.1043.

*2.3.2. 7-{2-[(Trimethylsilyl)ethynyl]benzo[b]thiophen-3-yl} hept-6-yn-1-ol (**11d**)*

The compound **11d** was synthesized following the standard procedure from **10c** (2.25 mmol, 0.800 g) and hept-6-yn-1-ol (5.61 mmol, 0.630 g) in trimethylamine (11.0 mL) and DCM (11.0 mL). Purification of the crude product by column chromatography using hexane/ethyl acetate (3:1) as the eluent gave 0.688 g (90%) of **11d** as a yellow oil. R_f = 0.51 (hexane/ethyl acetate (1:1)). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.86–7.82 (m, 1H), 7.72–7.68 (m, 1H), 7.42–7.36 (m, 2H), 3.69 (t, J = 6.3 Hz, 2H), 2.59 (t, J = 6.3 Hz, 2H), 1.77–1.69 (m, 2H), 1.68–1.59 (m, 4H), 1.41 (br. s, 1H), 0.30 (c, 1H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 138.8, 138.4, 126.2, 124.93, 124.88, 124.3, 123.5, 122.0, 104.9, 97.5, 97.2, 73.9, 62.8, 32.3, 28.6, 25.0, 19.8, −0.1. HRMS ESI: $[M+K]^+$ calculated for $C_{20}H_{24}KOSSi^+$: 379.0949; found 379.0943.

2.4. General procedure for the synthesis of terminal triple bond of enediynes 12a-d

Procedure A. TBAF hydrate (1.10 mmol, 287 mg) was added to a degassed solution of corresponding TMS-compound (1.00 mmol) in anhydrous THF (0.05 M, 20.0 mL) at 0 °C. The color of the solution changed from yellow to dark green. Reaction mixture was stirred for 15 min at 0 °C. The progress of the reaction was followed by TLC. The reaction mixture was poured into water (40 mL) and extracted with EtOAc (5 × 30 mL). Combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel.

Procedure B. K_2CO_3 (8.00 mmol, 1.11 g) was added to a degassed solution of corresponding TMS-compound (1.00 mmol) in methanol (0.1 M, 10.0 mL) under argon atmosphere at rt. Reaction was stirred for 3 h (TLC control), then diluted with EtOAc (10 mL) and washed with brine (10 mL). The aqueous layer extracted EtOAc (3 × 5 mL). Combined organic layers were washed with brine (10 mL) and dried under Na_2SO_4. The solvent was removed under reduced pressure, crude product was purified by column chromatography on silica gel.

*2.4.1. 6-(3-Ethynylbenzo[b]thiophen-2-yl)hex-5-yn-1-ol (**12a**)*

The enediyne alcohol **12a** was synthesized in accordance with typical procedure **A** from the enediyne alcohol **11a** (1.50 mmol, 490 mg) using a TBAF hydrate (1.65 mmol, 431 mg). Reaction time at room temperature – 15 min. Purification of the crude product by column chromatography using hexane/ethyl acetate (5:1) as the eluent gave 370 mg (96%) of **12a** as a red oil. R_f = 0.26. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.88–7.83 (m, 1H), 7.73–7.69 (m, 1H), 7.45–7.36 (m, 2H), 3.73 (t, J = 6.0 Hz, 2H), 3.53 (s, 1H), 2.60 (t, J = 6.5 Hz, 2H), 1.85–1.71 (m, 4H), 1.45 (br. s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 138.8, 137.9, 128.8, 126.0, 125.2, 123.1, 120.6, 101.3, 83.19, 83.15, 73.8, 62.4, 31.8, 24.7, 19.8, HRMS ESI: $[M+H]^+$ calculated for $C_{16}H_{15}OS^+$: 255.0838; found: 255.0838.

*2.4.2. 7-(3-Ethynylbenzo[b]thiophen-2-yl)hept-6-yn-1-ol (**12b**)*

The enediyne alcohol **12b** was synthesized in accordance with typical procedure from the enediyne alcohol **11b** (1.99 mmol, 650 mg) using a TBAF hydrate (2.19 mmol, 572 mg). Reaction time at room temperature – 15 min. Purification of the crude product by column chromatography using hexane/ethyl acetate (5:1) as the eluent gave 520 mg (97%) of **12b** as a dark red oil. R_f = 0.2. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.87–7.83 (m, 1H), 7.73–7.69 (m, 1H), 7.44–7.36 (m, 2H), 3.68 (t, J = 6.2 Hz, 2H), 3.54 (s, 1H), 2.57 (t, J = 6.9 Hz, 2H), 1.75–1.53 (m, 6H), 1.45 (br. s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 138.8, 137.9, 128.9, 125.9, 125.1, 123.1, 122.0, 120.5, 101.5 83.15, 83.12, 73.6, 62.8, 32.3, 28.1, 25.0, 20.0. HRMS ESI: $[M+H]^+$ calculated for $C_{17}H_{17}OS^+$: 269.0995; found: 269.1005.

*2.4.3. 6-(2-Ethynylbenzo[b]thiophen-3-yl)hex-5-yn-1-ol (**12c**)*

The enediyne alcohol **12c** was synthesized in accordance with procedure **B** from the enediyne alcohol **11c** (1.03 mmol, 350 mg) using a K_2CO_3 (8.22 mmol, 1.14 g). Purification of the crude product by column chromatography using hexane/ethyl acetate (3:1) as the eluent gave 251 mg (97%) of **12d** as a dark red oil. R_f = 0.36 (hexane/ethyl acetate (1:1)). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.87–7.83 (m, 1H), 7.74–7.69 (m, 1H), 7.45–7.38 (m, 2H), 3.75 (t, J = 6.1 Hz, 2H), 3.68 (s, 1H), 2.62 (t, J = 6.6 Hz, 2H), 1.88–1.74 (m, 4H), 1.50 (br. s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 138.7, 138.4, 126.4, 125.0, 124.8, 123.7, 123.6, 122.1, 97.5, 86.4, 76.8, 73.9, 62.4, 31.8, 25.0, 19.6 ppm. HRMS ESI: $[M+Na]^+$ calculated for $C_{16}H_{14}NaOS^+$: 277.0658; found 277.0650.

*2.4.4. 7-(2-Ethynylbenzo[b]thiophen-3-yl)hept-6-yn-1-ol (**12d**)*

The enediyne alcohol **12d** was synthesized in accordance with procedure **B** from the enediyne alcohol **11d** (0.429 mmol, 140 mg) using a K_2CO_3 (3.43 mmol, 474 mg). Purification of the crude product by column chromatography using hexane/ethyl acetate (3:1) as the eluent gave 97 mg (89%) of **12d** as a dark red oil. R_f = 0.36 (hexane/ethyl acetate (1:1)). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.88–7.84 (m, 1H), 7.74–7.70 (m, 1H), 7.45–7.38 (m, 2H), 3.71–3.68 (m, 3H), 2.59 (t, J = 6.9 Hz, 2H), 1.77–1.61 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 138.7, 138.4, 126.4, 125.1, 124.9, 123.61, 123.56, 122.1, 97.7, 86.4, 76.8, 73.7, 62.8, 32.3, 28.5, 25.0, 19.8. HRMS ESI: $[M+Na]^+$ calculated for $C_{17}H_{16}NaOS^+$: 291.0814; found 291.0807.

*2.5. General procedure for the iodination of terminal triple bond of enediynes **13a-d***

CuI (0.15 mmol, 28.6 mg) and *N*-iodomorpholine (Hein et al., 2009) (3.00 mmol, 1.02 g) were added to a degassed solution of starting material (1.00 mmol) in anhydrous THF (0.1 M, 10.0 mL) at rt. The progress of the reaction was checked by TLC. Upon completion the reaction mixture was washed with saturated aqueous solution of $Na_2S_2O_3$ (20 mL) and extracted with EtOAc (10 mL). Organic layer was washed with a saturated aqueous solution NH_4Cl (20 mL) and brine (20 mL). Combined water layers were extracted with EtOAc (3 × 10 mL). Combined organic layers were washed with a saturated aqueous solution of $Na_2S_2O_3$ (20 mL), NH_4Cl (20 mL), brine (20 mL) and dried over Na_2SO_4, concentrated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel.

*2.5.1. 6-[3-(Iodoethynyl)benzo[b]thiophen-2-yl]hex-5-yn-1-ol (**13a**)*

The enediyne alcohol **13a** was synthesized in accordance with typical procedure from the enediyne alcohol **12a** (2.71 mmol, 690 mg) using a CuI (0.407 mmol, 77.0 mg) and *N*-iodomorpholine (8.14 mmol, 2.77 g). Reaction time at room temperature – 1 h. Purification of the crude product by column chromatography using hexane/ethyl acetate (4:1) as the eluent gave 838 mg (82%) of **13a** as a light yellow crystals. R_f = 0.12, mp = 63–65 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.83 (dd, J = 6.8 Hz, J = 1.6 Hz, 1H), 7.70 (dd, J = 6.8 Hz, J = 1.6 Hz, 1H), 7.44–7.36 (m, 2H), 3.77 (t, J = 6.0 Hz, 2H), 2.62 (t, J = 6.5 Hz, 2H), 1.88–1.73 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 138.9, 137.7, 129.3, 126.0, 125.2, 123.1, 122.1, 122.0, 101.5 (C≡.)87.8, 73.9, 62.5, 31.9, 24.7, 19.9, 12.0. HRMS ESI: $[M+H]^+$ calculated for $C_{16}H_{14}IOS^+$: 380.9805; found: 380.9813.

*2.5.2. 7-[3-(Iodoethynyl)benzo[b]thiophen-2-yl]hept-6-yn-1-ol (**13b**)*

The enediyne alcohol **13b** was synthesized following the standard procedure from the enediyne alcohol **12b** (0.577 mmol, 155 mg) using a CuI (0.084 mmol, 22.0 mg) and *N*-iodomorpholine (1.67 mmol, 571 mg). Reaction time at room temperature – 1 h. Purification of the crude product by column chromatography using hexane/ethyl acetate (5:1) as the eluent gave 205 mg (90%) of **13b** as a light yellow crystals. R_f = 0.26, mp = 36–38 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.84–7.82 (m, 1H), 7.69 (d, J = 7.1 Hz, 1H), 7.43–7.36 (m, 2H), 3.71 (t, J = 7.1 Hz, 2H), 2.57 (t, J = 6.3 Hz, 2H), 1.74–1.55 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 138.9, 137.6, 129.3, 126.0, 125.1, 123.1, 122.0, 121.9, 101.7, 87.7, 73.7, 62.9, 32.3, 28.1, 25.0, 20.0, 12.0. HRMS ESI: $[M+H]^+$ calculated for $C_{17}H_{16}IOS^+$: 394.9961; found: 394.9965.

*2.5.3. 6-[2-(Iodoethynyl)benzo[b]thiophen-3-yl]hex-5-yn-1-ol (**13c**)*

The enediyne alcohol **13c** was synthesized following the standard procedure from the enediyne alcohol **12c** (0.944 mmol, 240 mg) using a CuI (0.142 mmol, 27.0 mg) and *N*-iodomorpholine (2.83 mmol, 965 mg). Reaction time at room temperature – 1.5 h. Purification of the crude product by

column chromatography using hexane/ethyl acetate (3:1) as the eluent gave 325 mg (91%) of **13c** as a dark brown oil. R_f = 0.3 (hexane/ethyl acetate (1:1)). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.86–7.82 (m, 1H), 7.73–7.68 (m, 1H), 7.44–7.37 (m, 2H), 3.77 (t, J = 6.1 Hz, 2H), 2.63 (t, J = 6.6 Hz, 2H), 1.89–1.76 (m, 4H), 1.49 (br. s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 138.1, 126.5, 125.1, 125.0, 123.6, 122.0, 97.6, 87.0, 73.9, 62.5, 31.8, 25.0, 19.6, 17.3. HRMS ESI: $[M+H]^+$ calculated for $C_{16}H_{14}IOS^+$: 380.9805; found 380.9813.

*2.5.4. 7-[2-(Iodoethynyl)benzo[b]thiophen-3-yl]hept-6-yn-1-ol (**13d**)*

The enediyne alcohol **13d** was synthesized following the standard procedure from the enediyne alcohol **12d** (1.64 mmol, 440 mg) using a CuI (0.246 mmol, 47.0 mg) and *N*-iodomorpholine (4.92 mmol, 1.68 g). Reaction time at room temperature – 1.5 h. Purification of the crude product by column chromatography using hexane/ethyl acetate (3:1) as the eluent gave 608 mg (94%) of **13d** as a dark brown oil. R_f = 0.27 (hexane/ethyl acetate (1:1)). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.86–7.82 (m, 1H), 7.72–7.69 (m, 1H), 7.44–7.38 (m, 2H), 3.72 (t, J = 6.2 Hz, 2H), 2.60 (t, J = 6.8 Hz, 2H), 1.77–1.59 (m, 6H) 1.43 (br. s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 138.4, 138.3, 126.5, 125.6, 123.6, 122.0, 97.8, 87.0, 73.7, 62.9, 32.2, 28.5, 25.0, 19.8, 17.2. HRMS ESI: $[M+Na]^+$ calculated for $C_{17}H_{15}NaIOS^+$: 416.9780; found 416.9796.

*2.6. General procedure for the oxidation of enediyne alcohols **14a-d***

DMP (3.00 mmol, 1.27 g) was added to a degassed solution of starting material (1.00 mmol) in freshly distilled DCM (0.1 M, 10.0 mL). The progress of the reaction was checked by TLC. Upon completion the reaction mixture was washed with saturated aqueous solution of Na_2CO_3 (20 mL) and extracted with EtOAc (10 mL). Organic layer was washed with saturated aqueous solution of NH_4Cl (20 mL) and brine (20 mL). Combined water layers were extracted with EtOAc (3 × 10 mL). Combined organic layers were washed with saturated aqueous solutions of $Na_2S_2O_3$ (20 mL), NH_4Cl (20 mL), brine (20 mL) and dried over Na_2SO_4, concentrated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel.

*2.6.1. 6-[3-(Iodoethynyl)benzo[b]thiophen-2-yl]hex-5-ynal (**14a**)*

The aldehyde **14a** was synthesized following the standard l procedure from the enediyne alcohol **13a** (2.15 mmol, 820 mg) using a Dess-Martin periodinane (6.45 mmol, 2.73 g). Reaction time at room temperature – 3 h. Purification of the crude product by column chromatography using hexane/ethyl acetate (5:1) as the eluent gave 670 mg (82%) of **13a** as a light yellow crystals. R_f = 0.56, mp = 76–79 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 9.91 (s, 1H), 7.87–7.81 (m, 1H), 7.70 (dd, J = 6.4 Hz, J = 1.5 Hz, 1H), 7.46–7.35 (m, 2H), 2.77 (t, J = 7.2 Hz, 2H), 2.65 (t, J = 6.7 Hz, 2H), 2.05–1.95 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 201.5, 138.8, 137.7, 128.9, 126.1, 125.3, 123.1, 122.3, 122.2, 100.2, 87.8, 74.6, 42.7, 20.8, 19.4, 12.3. HRMS ESI: $[M+H]^+$ calculated for $C_{16}H_{12}IOS^+$: 378.9648 found: 378.9654.

*2.6.2. 7-[3-(Iodoethynyl)benzo[b]thiophen-2-yl]hept-6-ynal (**14b**)*

The aldehyde **14b** was synthesized following the standard procedure from the enediyne alcohol **13b** (1.32 mmol, 520 mg) using a Dess-Martin periodinane (3.96 mmol, 1.68 g). Reaction time at room temperature – 3 h. Purification of the crude product by column chromatography using hexane/ethyl acetate (5:1) as the eluent gave 360 mg (70%) of **14b** as a red oil. R_f = 0.41. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 9.83 (s, 1H), 7.83 (d, J = 7.3 Hz, 1H), 7.70 (d, J = 7.3 Hz,1H), 7.43–7.37 (m, 2H), 2.60 (t, J = 6.8 Hz, 2H, 2.57–2.53 (m, 2H), 1.93–1.86 (m, 2H), 1.75–1.67 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 202.1, 138.9, 137.7, 129.2, 129.1, 126.0, 125.2, 123.1, 122.0, 100.9, 87.7, 74.0, 43.4, 27.7, 21.3, 19.9, 12.1. HRMS ESI: $[M+H]^+$ calculated for $C_{17}H_{14}IOS$: 392.9805; found: 392.9817.

*2.6.3. 6-[2-(Iodoethynyl)benzo[b]thiophen-3-yl]hex-5-ynal (**14c**)*

The aldehyde **14c** was synthesized following the standard procedure from the enediyne alcohol **13c** (0.842 mmol, 320 mg) using a Dess-Martin periodinane (1.68 mmol, 714 mg). Reaction time at room temperature – 0.5 h. Purification of the crude product by column chromatography using hexane/ethyl acetate (10:1) as the eluent gave 219 mg (69%) of **14c** as a brown crystals. R_f = 0.36 (hexane/ethyl acetate (2:1)), mp = 61–62 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 9.91 (s, 1H) 7.84–7.80 (m, 1H), 7.74–7.68 (m, 1H), 7.44–7.39 (m, 2H), 2.79 (td, J = 6.1 Hz, J = 1.0 Hz, 2H), 2.67 (t, J = 6.8 Hz, 2H), 2.05–1.98 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 201.5, 138.3, 138.2, 126.5, 125.5, 125.2, 124.8, 123.5, 122.1, 96.3, 87.0, 74.7, 42.7, 21.1, 19.6, 17.4. HRMS ESI: $[M+H]^+$ calculated for $C_{16}H_{12}IOS^+$: 378.9648; found 378.9654.

*2.6.4. 7-[2-(Iodoethynyl)benzo[b]thiophen-3-yl]hex-6-ynal (**14d**)*

The aldehyde **14d** was synthesized following the standard procedure from the enediyne alcohol **13d** (0.254 mmol, 100 mg) using a Dess-Martin periodinane (0.507 mmol, 215 mg). Reaction time at room temperature – 0.5 h. Purification of the crude product by column chromatography using hexane/ethyl acetate (10:1) as the eluent gave 70 mg (70%) of **14d** as a dark brown oil. R_f = 0.34 (hexane/ethyl acetate (2:1)). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 9.83 (t, J = 1.7 Hz, 1H), 7.85–7.81 (m, 1H), 7.72–7.68 (m, 1H), 7.45–7.38 (m, 2H), 2.62 (t, J = 6.8 Hz, 2H), 2.55 (td, J = 7.2 Hz, J = 1.7 Hz, 2H), 1.97–1.89 (m, 2H), 1.78–1.71 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 202.3, 138.3, 126.5, 125.2, 125.1, 124.9, 123.5, 122.0, 97.0, 87.0, 74.1, 43.4, 28.0, 21.3, 19.6, 17.3. HRMS ESI: $[M+H]^+$ calculated for $C_{17}H_{14}IOS^+$: 392.9805; found 392.9817.

*2.7. General procedure for the synthesis of 2-methylenecycloalkan-1-ols **16a,b***

Anhydrous $NiCl_2$ (0.01 mmol, 1.27 mg) and anhydrous $CrCl_2$ (1.00 mmol, 0.121 g) were added to degassed mix of anhydrous solvents DMF (2.00 mL) and THF (4.00 mL). Argon was bubbled through the solution for 1 h. Solution of aldehyde (0.10 mmol) in THF (4.00 mL) was slowly added to the suspension via syringe pump under flue of argon within 80 min. Complete conversion of starting material to the product was

observed in 1.5 h (TLC control). Reaction mixture was diluted with Et_2O (10 mL) and washed with brine (3 × 10 mL). Combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure.

2.7.1. (E)-2-[(3-Ethynylbenzo[b]thiophen-2-yl)methylene] cyclopentanol (**16a**)

The alchohol **16a** was synthesized following the standard procedure from the aldehyde **14a** (0.634 mmol, 240 mg) using $NiCl_2$ (0.063 mmol, 8.22 mg) and anhydrous $CrCl_2$ (6.34 mmol, 0.780 g). Purification of the crude product by column chromatography on silica gel using hexane/ethyl acetate (3:1) as the eluent gave 140 mg (87%) of **16a** as a light yellow crystals. R_f = 0.30, mp = 100–103 °C. ^{1}H NMR (400 MHz, DMSO d_6), δ, ppm: 7.99 (d, J = 7.9 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.48 (t, J = 7.9 Hz, 1H), 7.41 (t, J = 7.9 Hz, 1H), 7.14–7.11 (m, 1H), 5.35 (d, J = 6.2 Hz, 1H), 4.52–4.44 (m, 1H), 3.36 (s, 1H), 2.71–2.55 (m, 2H), 1.99–1.81 (m, 2H), 1.75–1.59 (m, 1H), 1.52–1.44 (m, 1H). ^{13}C NMR (101 MHz, DMSO d_6), δ, ppm: 153.2, 146.2, 138.6, 137.3, 125.5, 125.4, 122.5, 122.0, 114.4, 113.4, 87.6, 76.9, 75.1, 34.5, 29.5, 21.2. HRMS FAB: $[M]^+$ calculated for $C_{16}H_{14}OS^+$: 254.0765; found: 254.0767. IR (KBr) (ν, cm^{-1}): 3292, 3058, 2960, 2860, 2097 (C≡C 1640, 1458, 1430, 1354, 1319, 1284, 1215, 1174, 1151, 1087, 1034, 1012, 946, 870, 831, 760, 730, 651, 632, 593.

Crystal of **16a** was fixed on a micro mount and placed on an Agilent Technologies Supernova Atlas diffractometer and measured at a temperature of 100 K using micro focused monochromated Cu Kα radiation. The unit cell parameters were refined by least square techniques using 27,670 reflections in the 2θ range of 7.6–152.74°. The structure have been solved by the direct methods and refined R_1 = 0.032 (wR_2 = 0.084) for 4646 unique reflections with $|F_o| \geq 4\sigma_F$ by means of the SHELXL–97 program[3] incorporated in the *OLEX2* program package[4]. The carbon-bound H atoms were placed in calculated positions and were included in the refinement in the 'riding' model approximation, with U_{iso}(H) set to 1.2U_{eq}(C) and C—H 0.97 Å for the CH_2 groups and U_{iso}(H) set to 1.5U_{eq}(N) and C—H 0.96 Å for the CH_3 groups. Empirical absorption correction was applied in CrysAlisPr[5] program complex using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.

16a: colorless crystals, ($C_{16}H_{14}OS$), M = 254.33, crystal size 0.14 × 0.11 × 0.09, monoclinic, space group $P21/a$, a = 8.4743(2) Å, b = 22.3793(3) Å, c = 13.9195(3) Å, V = 2570.91(8) Å3, Z = 8, ρ = 1.314 g cm^{-3}, μ = 2.092 mm^{-1}. 27,670 reflections, 5098 unique (R_{int} = 0.0320), 327 parameters, R1 ($|F_o| \geq 4\sigma_F$) 0.032, wR2 (all data) = 0.084, Gof = 0.937. Supplementary crystallographic data for this paper have been deposited at Cambridge Crystallographic Data Centre (CCDC 1479612) and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

2.7.2. (E)-2-[(3-Ethynylbenzo[b]thiophen-2-yl)methylene] cyclohexanol (**16b**)

The alchohol **16b** was synthesized in accordance with typical procedure from the enediyne **14b** (0.250 mmol, 100 mg) using anhydrous $NiCl_2$ (0.063 mmol, 8.22 mg) and anhydrous $CrCl_2$ (6.34 mmol, 0.780 g). Purification of the crude product by column chromatography using hexane/ethyl acetate (3:1) as the eluent gave 40 mg (58%) of **16b** as a yellowish crystals. R_f = 0.29, mp = 109–110 °C.

^{1}H NMR (400 MHz, DMSO d_6), δ, ppm: 7.87 (d, J = 7.9 Hz, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.40 (t, J = 7.9 Hz, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.11–7.01 (m, 1H), 4.30 (d, J = 6.2 Hz, 1H), 3.56 (s, 1H), 3.07–3.04 (m, 1H), 2.35–2.32 (m, 1H), 1.83–1.56 (m, 7H, water in solvent). ^{13}C NMR (101 MHz, DMSO d_6), δ, ppm: 148.6, 145.1, 139.4, 138.0, 125.3, 125.0, 122.8, 122.0, 116.3, 113.4, 84.2, 77.6, 74.0, 37.0, 28.9, 27.4, 23.3. HRMS FAB: $[M]^+$ calculated for $C_{17}H_{16}OS^+$: 268.0922; found: 268.0925.

2.8. Macrocyclic diol **4e**

Anhydrous $NiCl_2$ (0.005 mmol, 0.7 mg) and anhydrous $CrCl_2$ (0.211 mmol, 0.026 g) were added to degassed anhydrous THF (4 mL) at 0 °C. Argon was bubbled through the solution for 1 h. Solution of aldehyde (0.053 mmol, 20.0 mg) in THF (2 mL) was slowly added to the suspension via syringe pump under flue of argon within 80 min at 0 °C. Reaction was left to stir overnight. Complete conversion of starting material to the product was observed in 14 h (TLC control). Reaction mixture was diluted with Et_2O (10 mL) and washed with brine (3 × 10 mL). Combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure. Purification of the crude product by column chromatography on silica gel using hexane/ethyl acetate (3:1) as the eluent gave 6 mg (46%) dimerization product as a light yellow crystals. R_f = 0.30. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.80–7.76 (m, 2H), 7.70–7.68 (m, 2H), 7.42–7.35 (m, 4H), 5.14–5.10 (m, 1H), 4.88–4.84 (m, 1H), 2.71–2.64 (m, 3H), 2.17–1.85 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 138.6, 138.0, 127.5, 127.4, 125.97, 125.96, 125.86, 125.2, 125.1, 125.0, 123.2, 123.0, 122.3, 122.1, 121.7, 121.6, 100.7, 100.4, 96.4, 96.3, 78.6, 78.5, 75.0, 74.7, 32.0, 29.73, 29.69, 22.7. HRMS FAB: $[M]^+$ calculated for $C_{32}H_2NaO_2S_2^+$: 527.1110; found: 527.1123.

2.9. General procedure for the oxidation of enediyne alcohols **14a-d**

Anhydrous DMF (5.00 mL) was added in flask through the septum under argon atmosphere. Argon was bubbled through the solution for 15 min. The $CrCl_2$ (1.00 mmol, 0.123 g) was added to the solvent under argon. Solution of corresponding compound **14** (0.10 mmol) in anhydrous DMF (5.00 mL) had been simultaneously added. The reaction was stirred for 24–60 h. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL). The organic layer was washed with water (3 × 30 mL) and brine (30 mL). Combined water layers were extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water (30 mL), brine (30 mL) and dried over Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel.

2.9.1. 6,7,13,14-Tetradehydro-9,10,11,12-tetrahydro-8H-benzo[b]cycloundeca[d]thiophene-12-ol (**4b**)

The cyclic enediyne **4b** was synthesized in accordance with typical procedure from the enediyne aldehyde **14b** (0.076 mmol, 0.026 g) using a $CrCl_2$ (0.094 g, 0.765 mmol). Reaction time at room temperature – 24 h. Purification of the crude product by column chromatography on silica gel using hexane/ethyl

acetate (5:1) as the eluent gave 12 mg (60%) of **4b** as a light yellow crystals. R_f = 0.30 (hexane/ethyl acetate (5:1)), mp = 100–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.81–7.79 (m, 1H), 7.73–7.71 (m, 1H), 7.42–7.34 (m, 2H), 4.82 (dd, *J* = 8.1 Hz, *J* = 4.1 Hz, 1H), 2.64–2.60 (m, 2H), 2.19–2.02 (m, 3H), 2.00–1.85 (m, 2H), 1.81–1.64 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 137.7, 136.8, 130.4, 125.8, 125.2, 125.1, 122.7, 122.4, 102.7, 99.3, 80.8, 77.5, 64.1, 35.9, 24.7, 22.0, 18.7. HRMS ESI: $[M+Na]^+$ calculated for $C_{17}H_{14}NaOS^+$: 289.0658; found: 289.0652.

*2.9.2. 6,7,13,14-Tetradehydro-9,10,11,12-tetrahydro-8H-benzo[b]cycloundeca[d]thiophen-8-ol (**4d**)*

The cyclic enediyne **4d** was synthesized in accordance with typical procedure from the enediyne aldehyde **14d** (0.204 mmol, 80.0 mg) using a $CrCl_2$ (2.04 mmol, 251 mg). Reaction time at room temperature – 60 h. Purification of the crude product by column chromatography using hexane/ethyl acetate (10:1) as the eluent gave 36 mg (66%) of **4d** as a reddish-white crystals. R_f = 0.29 (hexane/ethyl acetate (2:1)), mp = 121–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.84–7.79 (m, 1H), 7.76–7.71 (m, 1H), 7.43–7.36 (m, 2H), 4.82 (t, *J* = 8.2 Hz, *J* = 4.2 Hz, 1H), 2.62 (t, *J* = 6.5 Hz, 2H), 2.22–2.03 (m, 2H), 2.01–1.85 (m, 3H), 1.82–1.67 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 138.4, 136.8, 128.1, 126.9, 126.1, 125.0, 123.1, 122.5, 102.0, 99.5, 80.8, 77.7, 64.1, 35.7, 25.0, 22.0, 18.6. HRMS ESI: $[M+H]^+$ calculated for $C_{17}H_{15}OS^+$: 267.0838; found 267.0832.

*2.9.3. 7-(3-Ethynylbenzo[b]thiophen-2-yl)hex-5-ynal (**17a**)*

The aldehyde **17a** was recognized in the mix with **14a** according to NMR and HRMS as product of the deiodination of the latter. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 9.86 (s, 1H), 7.86 (dd, *J* = 6.8 Hz, *J* = 1.8 Hz, 1H), 7.72 (dd, *J* = 6.9 Hz, *J* = 1.7 Hz, 1H), 7.41 (qd, *J* = 7.2 Hz, *J* = 3.6 Hz, 2H), 3.53 (s, 1H), 2.73 (td, *J* = 7.2 Hz, *J* = 0.9 Hz, 2H), 2.64 (t, *J* = 6.8 Hz, 2H), 1.99 (p, *J* = 7.0 Hz, 2H). HRMS ESI: $[M+NH_4]^+$ calculated for $C_{16}H_{16}NOS^+$: 270.0947; found: 270.1764.

*2.9.4. 7-(3-ethynylbenzo[b]thiophen-2-yl)hept-6-ynal (**17b**)*

The aldehyde **17b** was isolated by column chromatography using hexane/ethyl acetate (10:1) as the eluent gave 14 mg (27%) of **17b** as a yellow oil. R_f = 0.33. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 9.80 (s, 1H), 7.85 (d, *J* = 7.3 Hz, 1H), 7.71 (d, *J* = 7.3 Hz, 1H), 7.44–7.37 (m, 2H), 3.54 (s, 1H), 2.59 (t, *J* = 6.8 Hz, 2H), 2.53 (t, *J* = 6.8 Hz, 2H), 1.91–1.83 (m, 2H), 1.74–1.62 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 202.2, 138.7, 137.8, 128.6, 126.0, 125.1, 123.1, 122.0, 120.6, 100.7, 83.3, 76.9, 73.9, 43.3, 27.6, 21.2, 19.8. HRMS FAB: $[M]^+$ calculated for $C_{17}H_{14}OS^+$: 266.0760; found: 266.0764.

*2.9.5. 6-(2-ethynylbenzo[b]thiophen-3-yl)hex-5-ynal (**17c**)*

The aldehyde **17c** was isolated by column chromatography using hexane/ethyl acetate (10:1) as the eluent gave 48 mg (60%) of **17c** as a brown oil. R_f = 0.36 (hexane/ethyl acetate (2:1)). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 9.87 (s, 1H), 7.86–7.81 (m, 1H), 7.74–7.70 (m, 1H), 7.45–7.39 (m, 2H), 3.69 (s, 1H), 2.76 (td, *J* = 7.2 Hz, *J* = 1.1 Hz, 2H), 2.66 (t, *J* = 6.8 Hz, 2H), 2.02 (p, *J* = 7.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 201.7, 138.5, 138.4, 126.4, 125.1, 124.4, 124.1, 123.5, 122.1, 96.2, 86.6, 76.7, 74.6, 42.7, 21.1, 19.2. HRMS ESI: $[M+Na]^+$ calculated for $C_{16}H_{12}NaOS^+$: 275.0501; found 275.0502.

*2.9.6. 7-(2-ethynylbenzo[b]thiophen-3-yl]hex-6-ynal (**17d**)*

The aldehyde **17d** was isolated by column chromatography using hexane/ethyl acetate (10:1) as the eluent gave 14 mg (26%) of **17d** as a brown oil. R_f = 0.38 (hexane/ethyl acetate (2:1)). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 9.82 (t, *J* = 1.6 Hz, 1H), 7.87–7.84 (m, 1H), 7.74–7.70 (m, 1H), 7.45–7.39 (m, 2H), 3.68 (s, 1H), 2.62 (t, *J* = 6.9 Hz, 2H), 2.54 (td, *J* = 7.3 Hz, *J* = 1.6 Hz, 2H), 1.96–1.88 (m, 2H), 1.78–1.71 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 202.2, 138.6, 138.4, 126.4, 125.1, 124.6, 123.8, 123.5, 122.1, 96.9, 86.5, 76.7, 74.0, 43.3, 28.0, 21.2, 19.5. HRMS ESI: $[M+Na]^+$ calculated for $C_{17}H_{14}NaOS^+$: 289.0658; found 289.0662.

3. Results and discussion

3.1. Preliminary calculations of enediynes activity in the Bergman cyclization

Before the synthesis of macrocyclic enediynes, the DFT calculations were performed to predict their activity in the Bergman cyclization. As was mentioned above, BC proceeds via the formation of *p*-benzyne biradicals. Therefore, we have calculated the relative activation energy for the formation of these intermediates for known 10-membered macrocyclic enediynes **1**–**3** and 9-membered macrocyclic enediynes **5** and compared these values with 10-,11-membered benzothiophene fused enediynes **4a**,**c**,**d** (Fig. 1). Geometry optimizations of reactants and transition stated were performed using B3LYP functional with the 6-31G++(d,p) basis set. Because of the open shell nature of the transition-state and product, calculations on these structures were performed using BS-UB3LYP (broken-spin-symmetry, unrestricted) calculations. Values calculated are the same for enediyne **4a** and isomeric macrocycle **4c**.

We found out that calculation data related to the 10-membered enediynes fused with benzo- and cinnoline core correlate with the experimental data obtained before (Vinogradova et al., 2011) and predicted macrocyclic enediynes annulated with benzothiophene to be more reactive in this series. It should be noted, that only the precursor of the most reactive nine-membered enediyne **5** with one triple bond masked as a cyclopropenone was obtained under Nozaki-Hiyama-Kishi conditions, and after photochemical decarbonylation 4,5-benzocyclonona-2,6-diyn-1-ol (**5**) underwent spontaneous Bergman cyclization (Pandithavidana et al., 2009). Thus 10-membered enediyne **4a** and isomeric macrocycle **4c** which could be obtained by NHK cyclization became synthetic targets of the research whereas 11-membered enediynes **4b,d** were selected for test NHK reaction (Fig. 2).

3.2. Synthesis of starting materials

For the synthesis of 10- and 11-membered macrocycles enediynes fused to benzo[*b*]thiophene **4a-d** by the NHK-cyclization, two regioisomers of the starting acyclic enediynes **11a-d** were

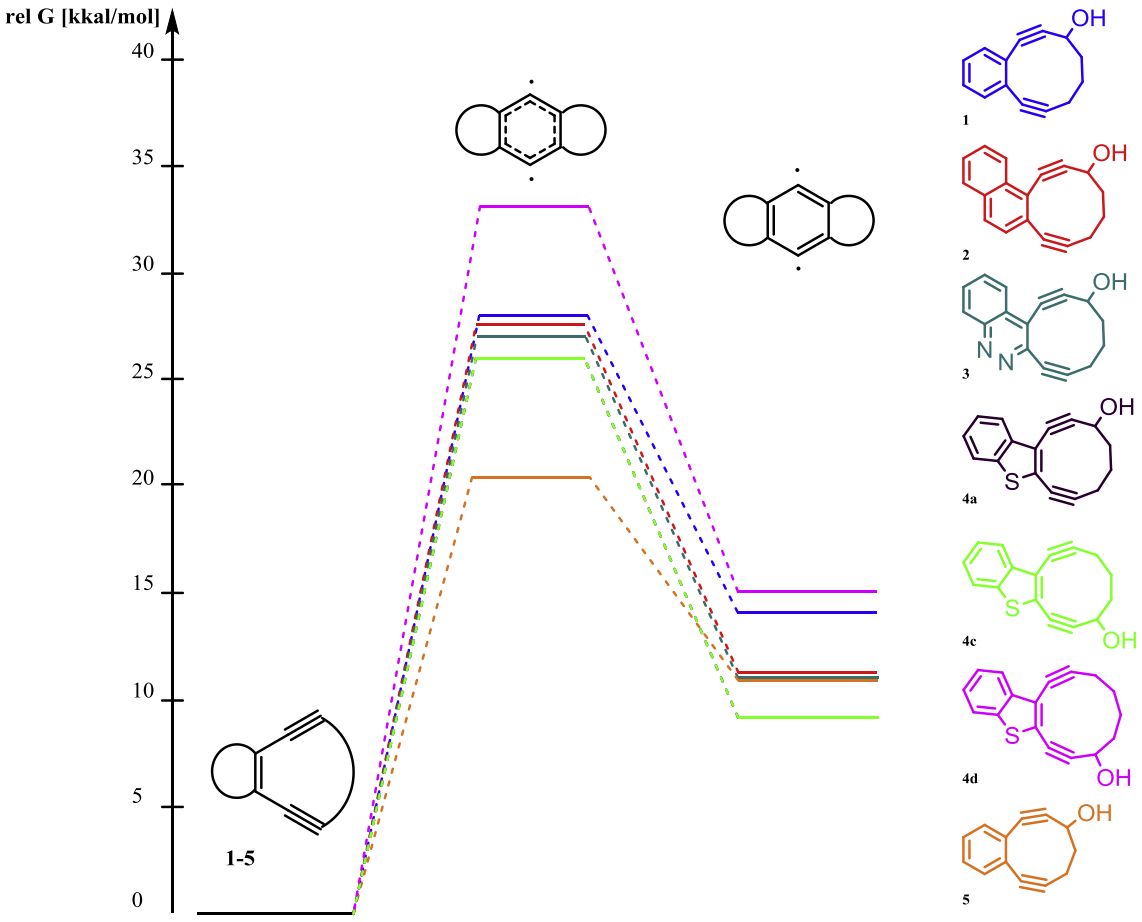


Fig. 1 Relative activation energy and relative stability of biradical intermediates of Bergman cyclization.

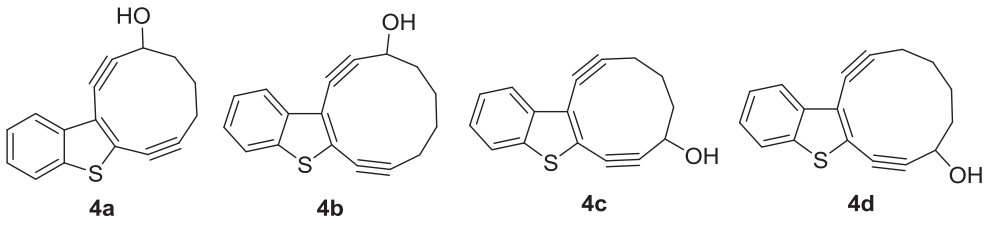


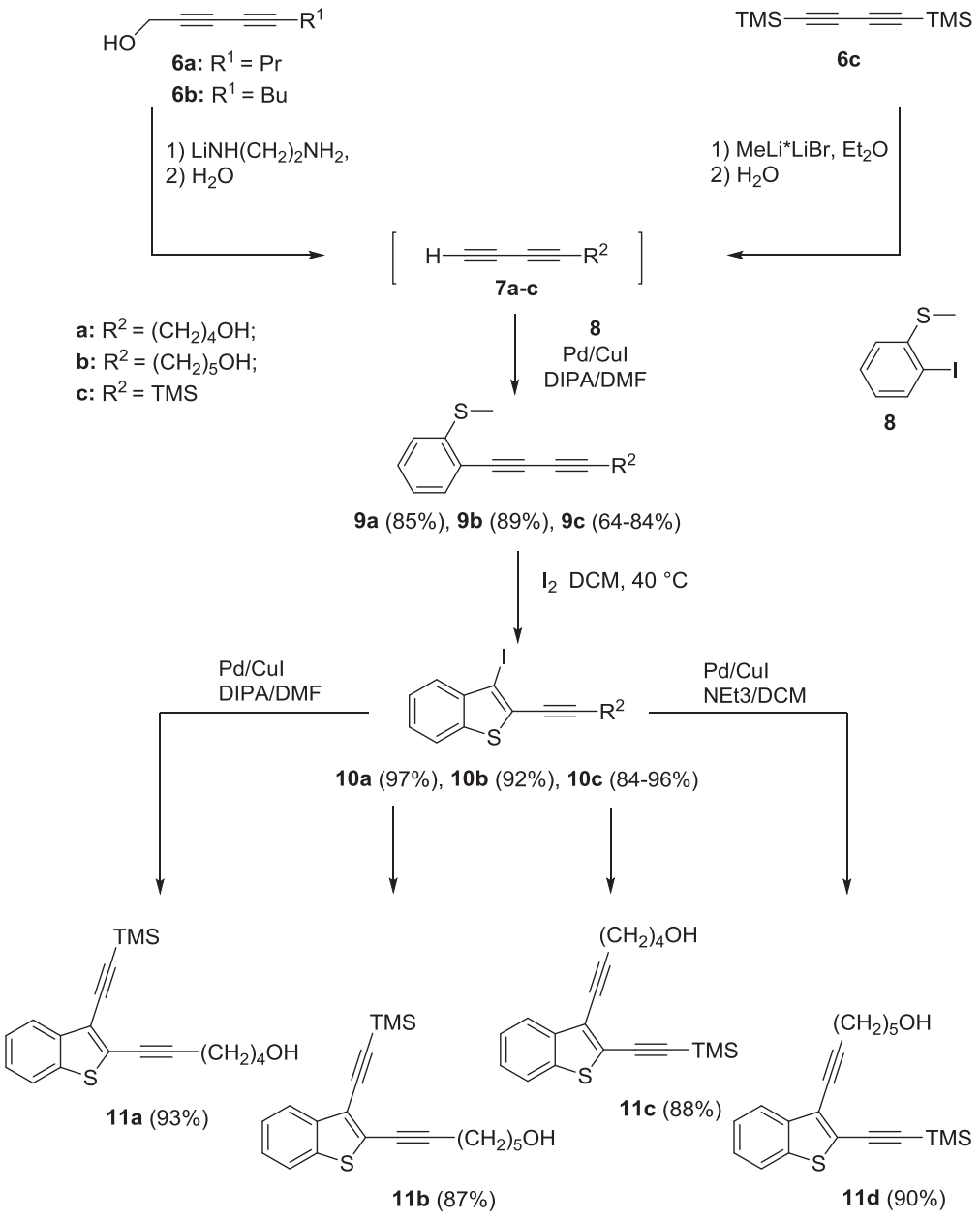
Fig. 2 Targets of research.

produced by varying initial diacetylene derivatives for iodocyclization (Scheme 1).

Terminal alkadiynols **7a,b** were readily obtained by the treatment of the corresponding internal diacetylenes **6a,b** with lithium 2-aminoethylamide (LAETA) («diacetylene zipper reaction») (Kulyashova et al., 2013). TMS-buta-1,3-diyne **7c** was synthesized according to the reported procedure (Danilkina et al., 2014). Both isomers of terminal diacetylenes were used in the next step without purification. The Sonogashira coupling of ortho-iodothioanisole **8** with terminal diacetylenes **7a-c** opened access to the compounds **9a-c**. Iodocyclization of thioanisoles **9a-c** followed by the Sonogashira cross-coupling (Scheme 1) with corresponding acetylenes led to acyclic enediynes fused to *S*-heteroindene **11a-d** as key intermediates.

While Pd/Cu-promoted coupling of compounds **10a,b** with TMS-acetylene using diisopropanolamine (DIPA) as a base in DMF gave products **11a,b** in high yields, the synthesis of **11c,d** under the same conditions led to the formation of products in moderate yields (~40%) due to a visible decomposition of reaction mixtures. Meanwhile, the coupling of 2-(2-trimethylsilyl)ethynyl-3-iodobenzo[*b*]thiophene (**10c**) with hex-5-yn-1-ol or hept-6-yn-1-ol was carried out successfully in the presence of less active base (NEt_3) in DCM.

Precursors for NHK macrocyclization have to contain iodo- and aldehyde moieties at opposite termini of (*Z*)-3-ene-1,5-diyne system. These compounds were obtained in several steps from enediynes **11a-d** (Scheme 2). Compounds **12a-d** were synthesized from TMS derivatives **11a-d** upon treatment with TBAF hydrate. Next, the reaction with iodine-



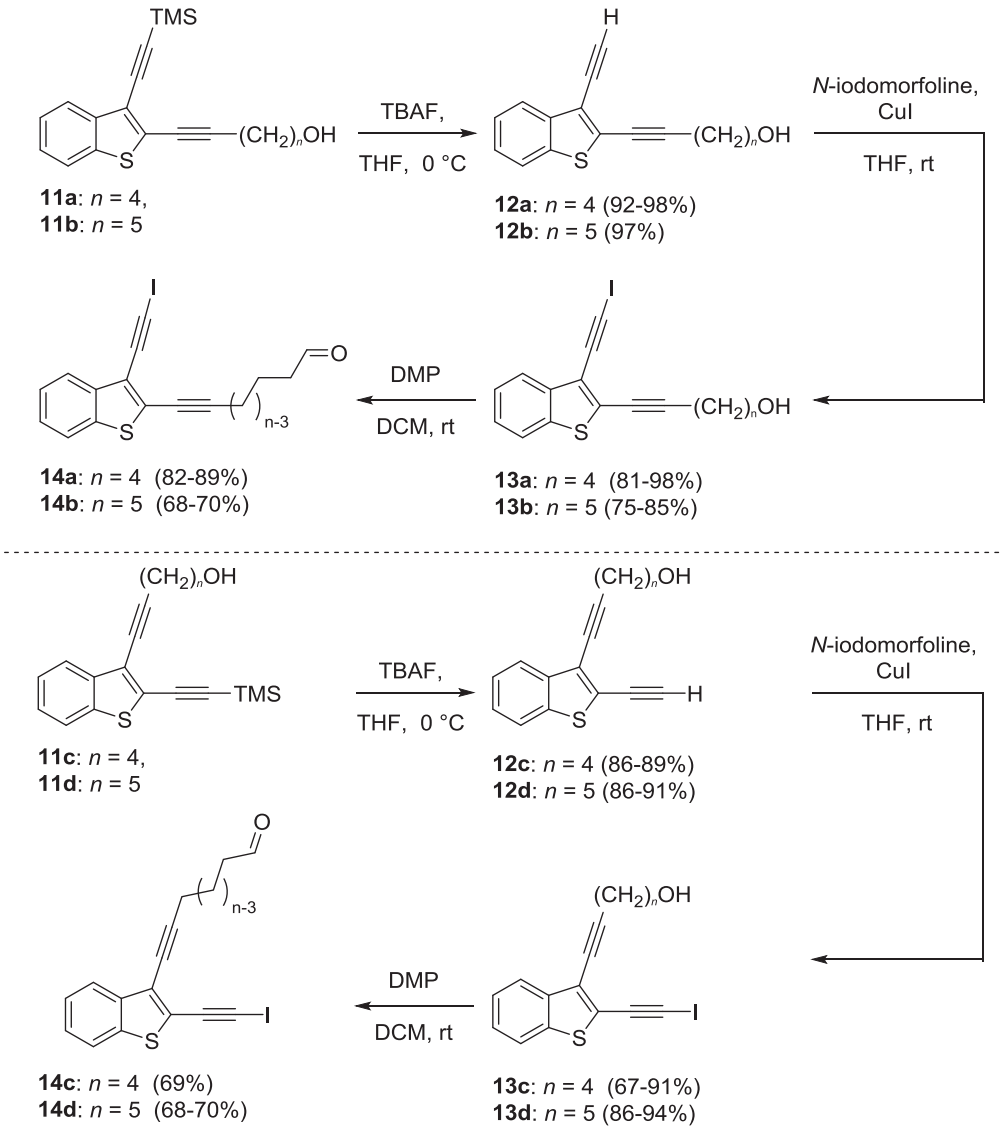
Scheme 1 Synthesis of two regioisomers of starting acyclic enediynes **11a-d**.

morpholine complex in presence of CuI (Hein et al., 2009) gave iodides **13a-d**, which were then oxidized using Dess-Martin periodinane to give starting materials for Nozaki reaction 14**a-d**.

3.3. Investigation of Cr(II)-promoted cyclizations

Intramolecular macrocyclization under NHK conditions has several features: (1) diluted solutions in polar solvents like DMF (Takai et al., 1986), DMSO (Jin et al., 1986), THF and their mixtures (Panek et al., 2000) are used to avoid intermolecular processes; (2) a mixture of anhydrous $CrCl_2$ as a reagent and $NiCl_2$ as a catalyst, has been found as the more effective combination for NHK reaction (Takai et al., 1986); (3) excess of $CrCl_2$ are required due to the formation of chromium (III) alcoholates as the by-products; (4) inert atmosphere and absence of moisture are needed (Jin et al., 1986; Takai et al., 1986) to avoid oxidation and decomposition of chromium salts and intermediates (Takai et al., 1983). Therefore, all experiments were carried out at 10^{-2}–10^{-3} M concentration of the starting material using 4–20-fold excess of $CrCl_2$ under argon.

According to Vinogradova et al. (2011), a facile intramolecular NHK reaction of acyclic enediyne fused with cinnoline gave desired 10-membered macrocycle using $CrCl_2$–$NiCl_2$ mixture in DMF (0.01 M concentration of starting material) at 0 °C. Therefore, these conditions were initially tested for the cyclization of benzo[*b*]thiophenes **14a**. However, instead of cyclization, compound **14a** underwent partial convertiion into the product of deiodination **17a** (Entry 1, Table 1). Exploring



Scheme 2 Synthesis of precursors for Nozaki-reaction.

of DMSO and THF as solvents with different concentrations has revealed the fast formation of complicated mixture of oligomers (Entries 2–4, Table 1). When the concentration of starting aldehyde **14a** was increased from 0.001 M to 0.01 M under the action of 4-fold excess of $CrCl_2$ in the presence of catalytic amount of $NiCl_2$ (Entry 5, Table 1, Scheme 3), only a dimeric product was isolated from the reaction mixture in low yield.

NMR ^1H spectra of dimer showed signals of two diastereomers namely two individual signals (multiplicity-triplet) of stereocentres at hydroxyl group in spectra. In addition, double set of signals had been detected in NMR ^{13}C (see SI).

Then intramolecular cyclization of substrates **14a**,**b** has been investigated in the THF/DMF mixture. No reaction was observed for the compound **14a** when tenfold access of $CrCl_2$ was used in THF/DMF (3:1) (Panek et al., 2000) at 0 °C (Entry 6, Table 1). When 20 equivalents of $CrCl_2$ were employed at room temperature, a single product has been formed from both starting aldehydes **14a** and **14b** (Entry 7, 8, Table 1). NMR ^1H spectra of new product did not show the signal of an aldehyde group, but rather presented characteristic signals CH-OH group.

HRMS ESI spectra contain signals of molecular ions at 254.0763 and 268.0925 *m*/*z*. This masses corresponds to the chemical formulae $C_{16}H_{14}OS^+$ and $C_{17}H_{16}OS^+$ respectively, which agrees with the structure of the Bergman cyclization products **15a** and **15b** (Scheme 4, route A).

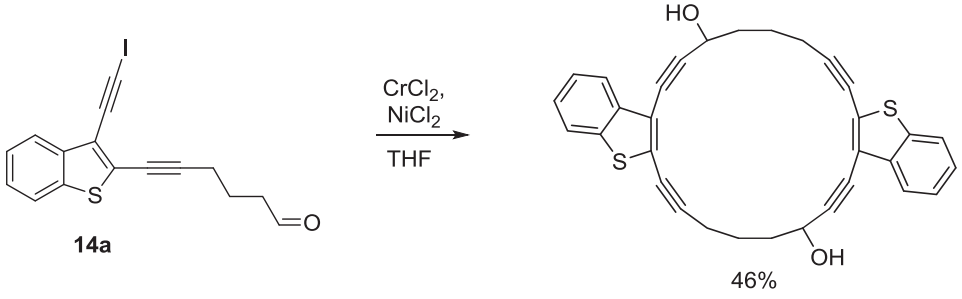
Therefore, we have initially suggested a reaction sequence involving intramolecular NHK reaction followed by the *in situ* cycloaromatization. However, the analysis of spectral data, including IR, NMR ^1H, ^{13}C (in $CDCl_3$ and DMSO d_6) revealed the presence of only one triple bond and a new double bond in the products.

The analysis of the spectral data, including NOESY, allowed us to establish the structure of the unexpected products of the intramolecular cyclization as vinyl cyclopentanol **16a,b** with *E*-configuration of double bond (Scheme 4, route B). In addition, the structure of **16a** has been established by single-crystal X-ray analysis (Fig. 3). Compounds **16a,b** are the apparent products of the electrophilic addition of acetylene

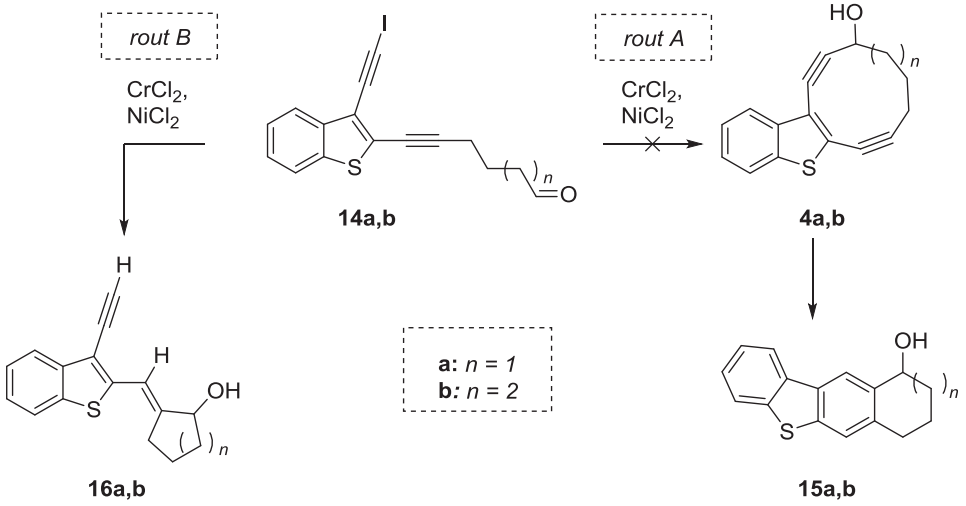
Table 1 Investigation of intramolecular NHK reaction of compounds **14a-d**.

Entry	Solvent	t °C	Time, h	$C_{M,}$ mol/L	$CrCl_2/NiCl_2$	Product (Yield, %)[a]
1 (**14a**)	DMF	r.t.	14	0.01	4/0.1	**17a**[b]
2 (**14a**)	DMSO	r.t.	14	0.01	4/0.1	Mixture of oligomers
3 (**14a**)	THF	0 °C → r.t.	14	0.005	4/0.1	Mixture of oligomers
4 (**14a**)	THF	0 °C → r.t.	14	0.001	4/0.1	Mixture of oligomers
5 (**14a**)	THF	0 °C → r.t.	14	0.01	4/0.1	Dimer **4e** (46)
6 (**14a**)	THF/DMF (3 : 1)	0 °C → r.t.	14	0.01	10/0.1	–
7 (**14a**)	THF/DMF (3 : 1)	r.t.	1	0.01	20/0.1	**16a** (56–67)
8 (**14b**)	THF/DMF (3 : 1)	r.t.	1	0.01	20/0.1	**16b** (58)
9 (**14a**)	THF/DMF (4 : 1)	r.t.	1.5	0.007	10/0.1	**16a** (87)
10[c] (**14b**)	THF/DMF (1 : 4)	r.t.	18	0.002	10/0	**4b** (33), 17b (27)
11[c] (**14b**)	THF/DMF (1 : 4)	r.t.	24	0.005	10/0	**4b** (47), 17b (29)
12[c] (**14b**)	THF/DMF (1 : 4)	r.t.	24	0.01	10/0	**4b** (47), 17b (47)
13[c] (**14b**)	DMF	r.t.	48	0.01	10/0	**4b** (60)
14[c] (**14a**)	DMF	r.t.	48	0.01	10/0	**17a**[b]
15[c] (**14c**)	DMF	r.t.	48	0.01	10/0	**17c** (60)
16[c] (**14d**)	DMF	r.t.	48	0.01	10/0	**4d** (51–66) **17d** (13–26)

[a] Isolated yields.
[b] In the mix with **14a** according to NMR and HRMS.
[c] Reactions were carried out in absence of $NiCl_2$.



Scheme 3 Synthesis of the macrocyclic diol.



Scheme 4 Synthesis of 2-methylenecycloalkan-1-ols as alternative way of Nozaki reaction.

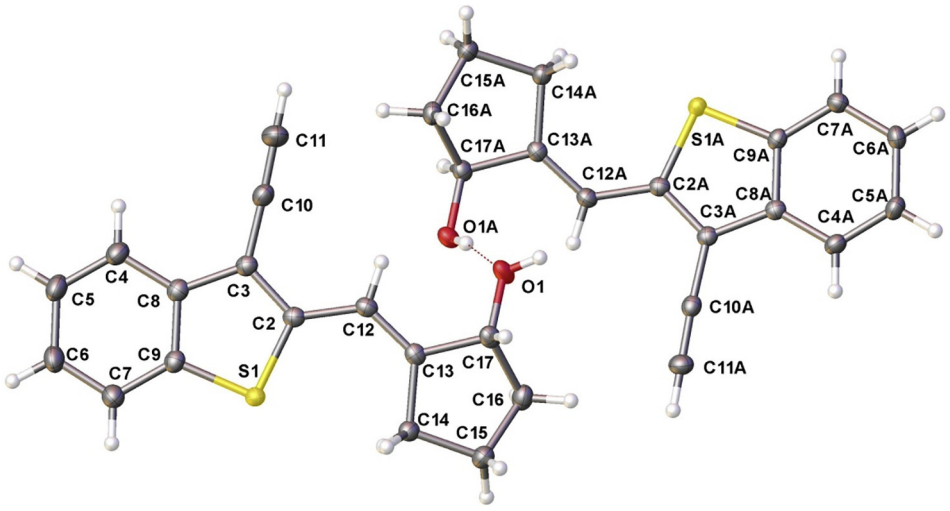


Fig. 3 Molecular structure of compound **16a** according to X-ray data.

to Cr (II) – activated aldehyde. The dilution of a reaction mixture by THF (ratio of THF:DMF was changed from 3:1 to 4:1) and reduction of excess of $CrCl_2$ to10 equivalents have led to the formation of cyclic allylic alcohol **16a** in a good yield (Entry 9, Table 1).

The authors know only one other example of the similar intramolecular formation of allylic alcohol under NHK conditions (Boddenmann and Keese, 1993). At the same time, the nickel-catalyzed intermolecular formation of 2-methylenecyclopentane-1-ol and 2-methylenecyclohexane-1-ol from derivatives of hex-5yn-1-al and hept-6-yn-1al has been reported previously (Malik et al., 2010; McCarren et al., 2009; Montgomery, 2004; Oblinger and Montgomery, 1997; Tang and Montgomery, 1999). Apparently nickel coordination in THF activates both the triple bond and the carbonyl group (Hodgson and Wells, 1994). Therefore, we decided to elucidate the influence of $NiCl_2$ on the cyclization.

In the absence of $NiCl_2$ aldehyde **14b** under the action of 10-fold excess of $CrCl_2$ in the mixture THF/DMF in ratio 1:4 produces the target 11-membered enediyne **4b** (Scheme 5, entry 10–12, Table 1) along with the product of reduction of iodoacetylene **14b** to terminal alkyne **17b**.

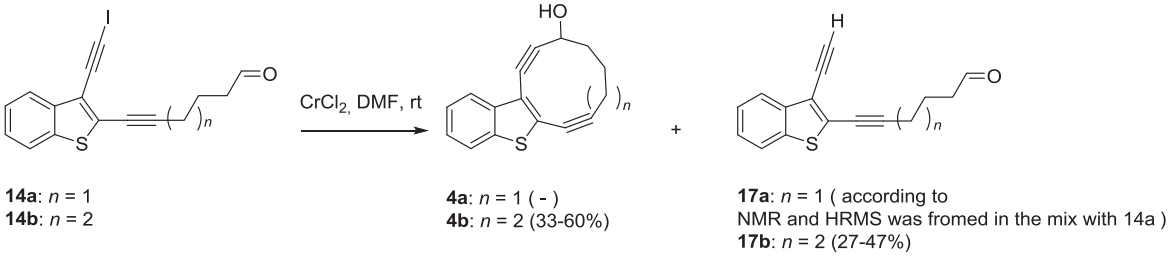
The best yield of **4b** (60%) without the traces of byproduct **17b** has been obtained under the action of 10-fold access of $CrCl_2$ in DMF (0.01 M) at ambient temperature (Entry 13, Table 1). These results suggest that the formation of by-product **17** can be minimized by avoiding $NiCl_2$ and THF. The cyclization of aldehyde **14a** to 10-membered macrocycle **4a** under the same conditions failed (Entry 14, Table 1). Purification and separation of a crude reaction mixture allowed to yield only product of deiodination in mixture with starting material (80% of starting material was recovered).

The cycloaromatization of enediyne **4b** has been studied by DSC, which is commonly used to characterize the efficiency of the enediyne cycloaromatization (Basak et al., 2004; Danilkina et al., 2016, 2015, 2014; Hickenboth et al., 2008; König and Rütters, 1994). The onset of the cycloaromatization was recorded at 172 °C, which agrees well with the calculated activation energy of 33.1 kcal/mol and previous experimental data (Danilkina et al., 2016).

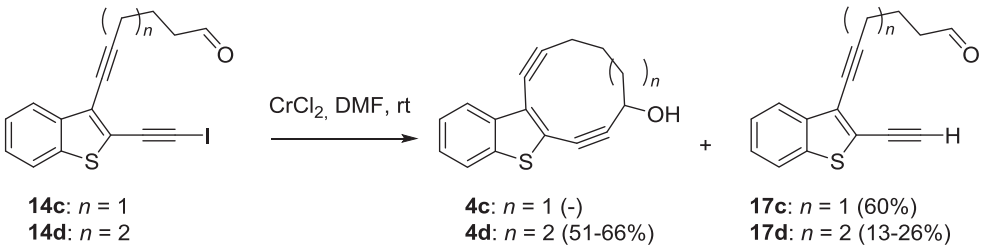
The treatment of isomeric compounds **14c,d** under NHK conditions showed very similar results. While the macrocyclization of acyclic enediyne **14d** in the prence of Cr(II) in DMF (no $NiCl_2$) produced good yield of 11-membered **4d** (Entry 16, Table 1, Scheme 6), all attempts of cyclization of **14c** resulted in the formation of the deiodination product **17c** (Entry 15, Table 1) or complex mixture of oligomeric products.

In order to explain the difference in reactivity between **14a,c** and **14b,d**, the DFT analysis of the ring strain in the target cyclic systems has been carried out. The relative strain energies of structures **1**–**5** were calculated at B3LYP/6-31G + + (d,p) level using isodesmic reactions and benzannulated 10-membered ring enediyne as a reference (Fig. 4).

There is virtually no difference in the ring strain between **1** and **2, 3**, **4d** and all of these compounds have been successfully prepared using Nozki cyclization (e.g., Vinogradova et al., 2011). On the other hand, ring strain in macrocycles **4a,c** is about 2 kcal/mol higher than in **1**. Apparently, this additional



Scheme 5 Cr(II)-promoted reaction of compounds **14a,b**.



Scheme 6 Cr(II)-promoted reaction of compounds **14c,d**.

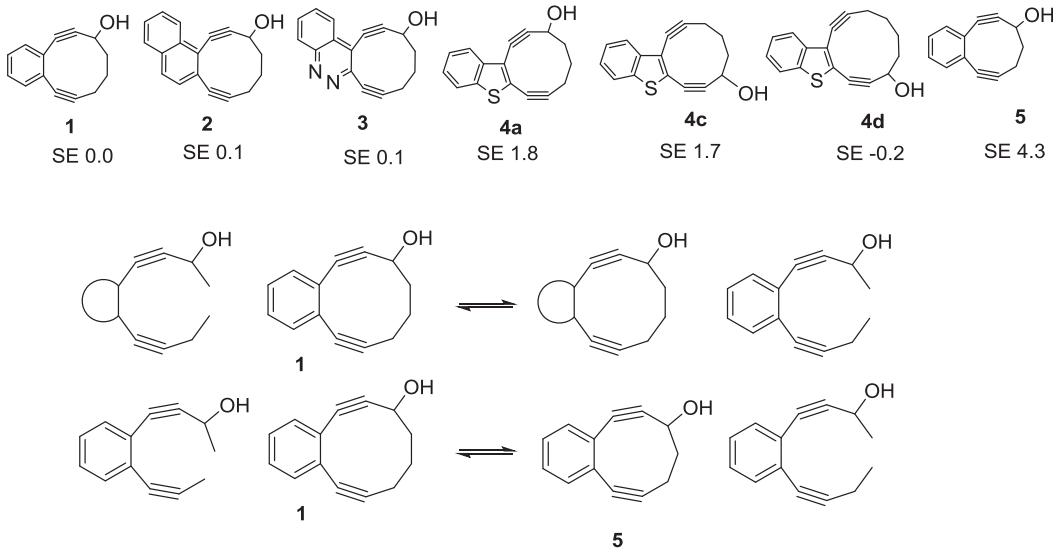


Fig. 4 Scheme of calculation of relative SE (kcal) for enediyne macrocycles, the strain energy of molecule **1** was admitted as zero.

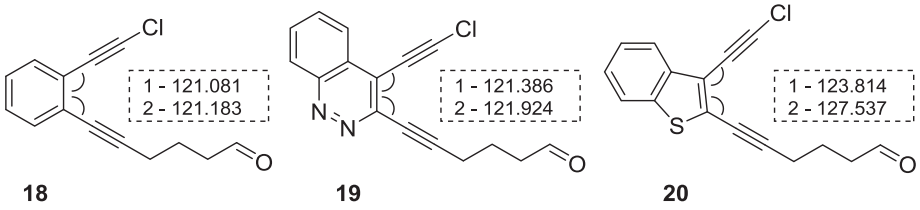


Fig. 5 Values of angles 1 and 2 calculated of model substrates for NHK-cyclization.

ring strain prevents macrocyclization of acyclic enediynes **14a, c**. The cycle **5** with the highest ring strain calculated was obtained under Nozaki-Hiyama-Kishi only with one triple bond masked as a cyclopropenone (Pandithavidana et al., 2009).

Another possible cause of the inefficient cyclization **14a,c** is an increased distance between reacting groups due to the lager angles between substituents attached to the 5-membered rings in comparison to the 6-membered analogs. Compounds **18**–**20** containing chlorine as halogen were used in DFT calculations as models of precursors for NHK reaction. A noticeable increase in the angles 1 and 2 in compound **20** over **18**, **19** is observed, supporting this suggestion (Fig. 5). Consequently, NHK intramolecular cyclization producing 10-membered enediyne cycle conjugated with benzothiophene is forbidden.

4. Conclusion

The investigation of intramolecular Nozaki-type coupling of acyclic enediynes fused to benzo[*b*]thiophene elucidated that geometry and structure of starting material as well as nature of catalytic system influence dramatically on the reaction results. We found, that two different metal (chromium and nickel) commonly employed in this reaction, expand the number of coordination sites and might lead to the formation of different types of cycles. Thus, in the presence of Ni(II) NHK coupling of the compounds discussed in the present manuscript instead of a macrocycle formation gives the product of nucleophilic addition of the triple bond to the carbonyl group within the same fragment. Cyclic allylic alcohols were obtained as the result of *exo*-cyclization under the action of

Cr^{2+}/Ni^{2+} system in THF/DMF in the case of 6-[3-(iodoethynyl)benzo[*b*]thiophen-2-yl]hex-5-ynal and 7-[3-(iodoethynyl)benzo[*b*]thiophen-2-yl]hept-6-ynal. The use of $CrCl_2$ without $NiCl_2$ co-catalyst in DMF (0.01 M) led to the formation of 11-membered enediyne macrocycles. The formation of more strained 10-membered benzotiophene-fussed enediynes by Nozaki cyclization is restricted probably due to the high values of activation energy barrier which correlates with the ring strain. Thus, our findings demonstrated both limitations of NHK reaction in the synthesis of 10-membered macrocyclic enediynes and intriguing challenge for study of cheap $NiCl_2$–catalyzed intramolecular cyclization of easily formed hex-5-ynal and hept-6-ynal fragments as facile and universal approach to the synthesis of important cyclic allylic alchohols.

Acknowledgment

This study was supported by Saint Petersburg University - Russia (SPbU) (grant numbers 12.40.515.2017). A.E.K. is grateful to RFBR (grant numbers 16-33-00817, mol-a). A.E. K. and V. V. P. are thankful to NIH (Award #R01-CA175480). Scientific research was performed at the Center for Magnetic Resonance, the Center for Chemical Analysis and Materials Research, the Thermogravimetric and Calorimetric Research Centre and the Center for X-ray Diffraction Methods of Research park of St. Petersburg State University.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.arabjc.2018.05.005.

References

Advani, A., Coiffier, B., Czuczman, M.S., Dreyling, M., Foran, J., Gine, E., Gisselbrecht, C., Ketterer, N., Nasta, S., Rohatiner, A., Schmidt-Wolf, I.G.H., Schuler, M., Sierra, J., Smith, M.R., Verhoef, G., Winter, J.N., Boni, J., Vandendries, E., Shapiro, M., Fayad, L., 2010. Safety, pharmacokinetics, and preliminary clinical activity of inotuzumab ozogamicin, a novel immunoconjugate for the treatment of B-cell non-Hodgkin's lymphoma: results of a phase I study. J. Clin. Oncol. 28, 2085–2093. https://doi.org/10.1200/JCO.2009.25.1900.

Ban, L., Guanti, G., 2000. Synthesis of a methoxy-substituted lactenediyne. Tetrahedron Lett. 41, 6523–6526. https://doi.org/10.1016/S0040-4039(00)01072-8.

Banfi, L., Guanti, G., 2002a. Synthesis of a new lactenediyne scaffold equipped with three handles. Tetrahedron Lett. 43, 7427–7429. https://doi.org/10.1016/S0040-4039(02)01603-9.

Banfi, L., Guanti, G., 2002b. Synthesis of intramolecularly activated lactenediynes and evaluation of their activity against plasmid DNA. Eur. J. Org. Chem. 2002, 3745–3755. https://doi.org/10.1002/1099-0690(200211)2002:22<3745::AID-EJOC3745>3.0.CO;2-C.

Basak, A., Bag, S.S., Majumder, P.A., Das, A.K., Bertolasi, V., 2004. Effect of remote trigonal carbons on the kinetics of bergman cyclization: synthesis and chemical reactivity of pyridazinedione-based enediynes. J. Org. Chem. 69, 6927–6930. https://doi.org/10.1021/jo049396d.

Bergman, R.G., 1973. Reactive 1,4-dehydroaromatics. Acc. Chem. Res. 6, 25–31. https://doi.org/10.1021/ar50061a004.

Boddenmann, B., Keese, R., 1993. Synthesis of cyclododeca-2,8-diyne-1,7-dione. Tetrahedron Lett. 34, 1467–1470. https://doi.org/10.1016/S0040-4039(00)60320-9.

Bolte, B., Basutto, J.A., Bryan, C.S., Garson, M.J., Banwell, M.G., Ward, J.S., 2015. Modular total syntheses of the marine-derived resorcylic acid lactones cochliomycins A and B Using a late-stage Nozaki-Hiyama-Kishi macrocyclization reaction. J. Org. Chem. 80, 460–470. https://doi.org/10.1021/jo5024602.

Brandstetter, T., Maier, M.E., 1994. Synthesis and oxidative activation of an oxabicyclo[7.2.1]enediyne. Tetrahedron 50, 1435–1448. https://doi.org/10.1016/S0040-4020(01)80628-1.

Chari, R.V.J., Miller, M.L., Widdison, W.C., 2014. Antibody-drug conjugates: an emerging concept in cancer therapy. Angew. Chemie - Int. Ed. 53, 3796–3827. https://doi.org/10.1002/anie.201307628.

Choy, N., Blanco, B., Wen, J., Krishan, a., Russell, K.C., 2000. Photochemical and thermal bergman cyclization of a pyrimidine enediynol and enediynone. Org. Lett. 2, 3761–3764. https://doi.org/10.1021/ol006061j.

Comanita, B.M., Heuft, M.A., Rietveld, T., Fallis, A.G., 2000. A mild route to α-alkoxyacetylenes mediated by Lewis Acids and synthetic routes to 10–11- and 12-membered ring enediyne carbocycles. Isr. J. Chem. 40, 241–253. https://onlinelibrary.wiley.com/doi/abs/10.1560/7J4F-D8BG-3FQR-E3TD.

Crévisy, C., Beau, J., 1991. The esperamicin- calicheamicin aglycones: ring closure of a simple strained system mediated by chromium(II)-nickel(II) salts. Tetrahedron Lett. 32, 3171–3174. https://doi.org/10.1016/S0040-4039(00)79714-0.

Dai, W.M., Wu, A., Hamaguchi, W., 2001. Intramolecular Nozaki-Hiyama-Kishi reactions and Ln(III)-catalyzed allylic rearrangement as the key steps towards 10-membered ring enediynes. Tetrahedron Lett. 42, 4211–4214. https://doi.org/10.1016/S0040-4039(01)00707-9.

Dancy, I., Skrydstrup, T., Crevisy, C., Beau, J.-M., 1995. Synthetic studies related to the esperamicin/calicheamicin aglycone: efficient construction of a homochiral oxabicyclo [7:3:1] analogue from D-xylose. J. Chem. Soc. Chem. Commun. 3, 799–800. https://doi.org/10.1039/C39950000799.

Danilkina, N.A., Bräse, S., Balova, I.A., 2011. Electrophilic cyclization of buta-1,3-diynylarenes: synthesis of precursors of (z)-3-ene-1,5-diyne systems fused to heterocycles. Synlett 517–520. https://doi.org/10.1055/s-0030-1259547.

Danilkina, N.A., Gurskaya, L.Y., Vasilyev, A.V., Balova, I.A., 2016. Towards isocoumarin-fused enediyne systems through the electrophilic cyclization of methyl o -(Buta-1,3-diynyl)benzoates. Eur. J. Org. Chem. 2016, 739–747. https://doi.org/10.1002/ejoc.201501262.

Danilkina, N.A., Kulyashova, A.E., Khlebnikov, A.F., Bräse, S., Balova, I.A., 2014. Electrophilic cyclization of aryldiacetylenes in the synthesis of functionalized enediynes fused to a heterocyclic core. J. Org. Chem. 79, 9018–9045. https://doi.org/10.1021/jo501396s.

Danilkina, N.A., Lyapunova, A.G., Khlebnikov, A.F., Starova, G.L., Bräse, S., Balova, I.A., 2015. Ring-closing metathesis of Co2(CO) 6–alkyne complexes for the synthesis of 11-membered dienediynes: overcoming thermodynamic barriers. J. Org. Chem. 80, 5546–5555. https://doi.org/10.1021/acs.joc.5b00409.

Danilkina, N., Nieger, M., Selivanov, S., Bräse, S., Balova, I., 2012. Electrophilic cyclization and ring-closing metathesis as key steps in the synthesis of a 12-membered cyclic enediyne. Eur. J. Org. Chem. 5660–5664. https://doi.org/10.1002/ejoc.201200881.

De Voss, J.J., Hangeland, J.J., Townsend, C.A., 1990. Characterization of the in vitro cyclization chemistry of calicheamicin and its relation to DNA cleavage. J. Am. Chem. Soc. 112, 4554–4556. https://doi.org/10.1021/ja00167a069.

Furstner, a., Shi, N., 1996. Nozaki - Hiyama - Kishi Reactions catalytic in chromium. J. Am. Chem. Soc. 118, 12349–12357. https://doi.org/10.1021/ja9625236.

Galm, U., Hager, M.H., Van Lanen, S.G., Ju, J., Thorson, J.S., Shen, B., 2005. Antitumor antibiotics: Bleomycin, enediynes, and mitomycin. Chem. Rev. 105, 739–758. https://doi.org/10.1021/cr030117g.

Goldberg, I.H., 1991. Mechanism of neocarzinostatin action: role of DNA microstructure in determination of chemistry of bistranded oxidative damage. Acc. Chem. Res. 24, 191–198. https://doi.org/10.1021/ar00007a001.

Hamann, P.R., Upeslacis, J., Borders, D.B., 2011. Enediynes. In: Cragg, G.M., Kingston, D.G.I., Newman, D.J. (Eds.), Anticancer Agents from Natural Products, Boca Raton, pp. 575−621.

Hein, J.E., Tripp, J.C., Krasnova, L.B., Sharpless, K.B., Fokin, V.V., 2009. Copper(I)-catalyzed cycloaddition of organic azides and 1-iodoalkynes. Angew. Chemie - Int. Ed. 48, 8018–8021. https://doi.org/10.1002/anie.200903558.

Hickenboth, C.R., Rule, J.D., Moore, J.S., 2008. Preparation of enediyne-crosslinked networks and their reactivity under thermal and mechanical conditions. Tetrahedron 64, 8435–8448. https://doi.org/10.1016/j.tet.2008.04.106.

Hodgson, D.M., Wells, C., 1994. Chromium(II)-mediated nickel(II)-catalysed cyclisations of (iodoaryl)-substituted alkynes and alkynals. Tetrahedron Lett. 35, 1601–1604. https://doi.org/10.1016/S0040-4039(00)76769-4.

Iwamoto, M., Miyano, M., Utsugi, M., Kawada, H., Nakada, M., 2004. Synthetic studies on the seven- and eight-membered rings by the intramolecular Nozaki-Hiyama reaction of the allylic phosphates. Tetrahedron Lett. 45, 8653–8657. https://doi.org/10.1016/j.tetlet.2004.09.142.

Jin, H., Uenishi, J., Christ, W.J., Kishi, Y., 1986. Catalytic effect of nickel(II) chloride and palladium(II) acetate on chromium(II)-mediated coupling reaction of iodo olefins with aldehydes. J. Am. Chem. Soc. 108, 5644–5646. https://doi.org/10.1021/ja00278a057.

Jones, G.E., Kendrick, D.A., Holmes, A.B., 1987. 1,4-BIS(TRIMETHYLSILYL)BUTA-1,3-DIYNE. Org. Synth. 65, 52 https://doi.org/10.15227/orgsyn.065.0052.

Joshi, M.C., Rawat, D.S., 2012. Recent developments in enediyne chemistry. Chem. Biodivers. 9, 459–498. https://doi.org/10.1002/cbdv.201100047.

Karpov, G., Kuzmin, A., Popik, V.V., 2008. Enhancement of the reactivity of photochemically generated enediynes via keto-enol tautomerization. J. Am. Chem. Soc. 130, 11771–11777. https://doi.org/10.1021/ja802688c.

Karpov, G.V., Popik, V.V., 2007. Triggering of the bergman cyclization by photochemical ring contraction. Facile cycloaromatization of benzannulated cyclodeca-3,7-diene-1,5-diynes. J. Am. Chem. Soc. 129, 3792–3793. https://doi.org/10.1021/ja064470q.

Keohane, C.E., Steele, A.D., Fetzer, C., Khowsathit, J., Van Tyne, D., Moynié, L., Gilmore, M.S., Karanicolas, J., Sieber, S.A., Wuest, W. M., 2018. Promysalin elicits species-selective inhibition of pseudomonas aeruginosa by targeting succinate dehydrogenase. J. Am. Chem. Soc. 140, 1774–1782. https://doi.org/10.1021/jacs.7b11212.

Kim, C.S., Russel, K.C., 1999. Solvent dependent Bergman cyclization of 2,3-diethynylquinoxaline. Tetrahedron Lett. 40, 3835–3838. https://doi.org/10.1016/S0040-4039(99)00634-6.

Kim, C., Diez, C., Russell, K., 2000. Tautomer-dependent Bergman cyclization of novel uracil-enediyne chimeras. Chem. - A Eur. J. 6, 1555–1558. https://doi.org/10.1002/(SICI)1521-3765(20000502)6:9<1555::AID-CHEM1555>3.0.CO;2-M.

Kim, C.S., Russell, K.C., 1998. Rapid Bergman cyclization of 1,2-diethynylheteroarenes. J. Org. Chem. 63, 8229–8234. https://doi.org/10.1021/jo980879p.

Kim, G., Kang, S., Ryu, Y., Keum, G., Seo, M.J., 1999. A Pd-catalyzed double coupling reaction to 4,5-disubstituted imidazole alkynes. Synth. Commun. 29, 507–512. https://doi.org/10.1080/00397919908085793.

König, B., Rütters, H., 1994. Synthesis and reactivity of the first bis (crown ether) enediyne. Tetrahedron Lett. 35, 3501–3504. https://doi.org/10.1016/S0040-4039(00)73220-5.

Konishi, M., Ohkuma, H., Tsuno, T., Oki, T., VanDuyne, G.D., Clardy, J., 1990. Crystal and molecular structure of dynemicin A: a novel 1,5-diyn-3-ene antitumor antibiotic. J. Am. Chem. Soc. 112, 3715–3716. https://doi.org/10.1021/ja00165a097.

Kraka, E., Tuttle, T., Cremer, D., 2008. Design of a new warhead for the natural enediyne dynemicin A. An increase of biological activity. J. Phys. Chem. B 112, 2661–2670. https://doi.org/10.1021/jp0773536.

Kulyashova, A.E., Sorokoumov, V.N., Popik, V.V., Balova, I.A., 2013. An acetylene zipper-Sonogashira reaction sequence for the efficient synthesis of conjugated arylalkadiynols. Tetrahedron Lett. 54, 2235–2238. https://doi.org/10.1016/j.tetlet.2013.02.066.

LeClair, C.A., Boxer, M.B., Thomas, C.J., Maloney, D.J., 2010. Total synthesis of LL-Z1640-2 utilizing a late-stage intramolecular Nozaki–Hiyama–Kishi reaction. Tetrahedron Lett. 51, 6852–6855. https://doi.org/10.1016/j.tetlet.2010.10.092.

Lee, M.D., Dunne, T.S., Chang, C.C., Ellestad, G.A., Siegel, M.M., Morton, G.O., McGahren, W.J., Borders, D.B., 1987. Calichemicins, a novel family of antitumor antibiotics. 2. Chemistry and structure of calichemicin.gamma. 1I. J. Am. Chem. Soc. 109, 3466–3468. https://doi.org/10.1021/ja00245a051.

Lee, M.D., Ellestad, G.A., Borders, D.B., 1991. Calicheamicins: discovery, structure, chemistry, and interaction with DNA. Acc. Chem. Res. 24, 235–243. https://doi.org/10.1021/ar00008a003.

Lubineau, A., Billault, I., 1998. New access to unsaturated keto carba sugars (gabosines) using an intramolecular nozaki-kishi reaction as the key step. J. Org. Chem. 63, 5668–5671. https://doi.org/10.1021/jo980309p.

Lyapunova, A.G., Danilkina, N.A., Khlebnikov, A.F., Köberle, B., Bräse, S., Balova, I.A., 2016. Oxaenediynes through the Nicholas-Type Macrocyclization Approach. European J. Org. Chem. 28, 4842–4851. https://doi.org/10.1002/ejoc.201600767.

Lyapunova, A.G., Danilkina, N.A., Rumyantsev, A.M., Khlebnikov, A.F., Chislov, M.V., Starova, G.L., Sambuk, E.V., Govdi, A.I., Bräse, S., Balova, I.A., 2018. Relative reactivity of benzothiophene-fused enediynes in the bergman cyclization. J Org Chem. 83, 2788–2801. https://doi.org/10.1021/acs.joc.7b03258.

Maier, M.E., Brandstetter, T., 1992. Synthesis of an oxabicyclo[7.2.1] enediyne from a furanoside derivative. Tetrahedron Lett. 33, 7511–7514. https://doi.org/10.1016/S0040-4039(00)60810-9.

Malik, H.A., Sormunen, G.J., Montgomery, J., 2010. A general strategy for regiocontrol in nickel-catalyzed reductive couplings of aldehydes and alkynes. J. Am. Chem. Soc. 132, 6304–6305. https://doi.org/10.1021/ja102262v.

Maretina, I., Trofimov, B., 2006. Enediyne antibiotics and their models: new potential of acetylene chemistry. Russ. Chem. Rev. 75, 825–845. https://doi.org/10.1070/RC2006v075n09ABEH002479.

McCarren, P.R., Liu, P., Cheong, P.H.Y., Jamison, T.F., Houk, K.N., 2009. Mechanism and transition-state structures for nickel-catalyzed reductive alkyne-aldehyde coupling reactions. J. Am. Chem. Soc. 131, 6654–6655. https://doi.org/10.1021/ja900701g.

Mi, B., Maleczka, R.E., 2001. A Nozaki−Hiyama−Kishi Ni(II)/Cr(II) coupling approach to the phomactins. Org. Lett. 3, 1491–1494. https://doi.org/10.1021/ol015807q.

Minto, R.E., Blacklock, B.J., 2008. Biosynthesis and function of polyacetylenes and allied natural products. Prog. Lipid Res. 47, 233–306. https://doi.org/10.1016/j.plipres.2008.02.002.

Mohamed, R.K., Peterson, P.W., Alabugin, I.V., 2013. Concerted reactions that produce diradicals and zwitterions: electronic, steric, conformational, and kinetic control of cycloaromatization processes. Chem. Rev. 113, 7089–7129. https://doi.org/10.1021/cr4000682.

Mohapatra, D.K., Das, P.P., Pattanayak, M.R., Gayatri, G., Sastry, G.N., Yadav, J.S., 2010. Protecting-group directed stereoselective intramolecular Nozaki-Hiyama-Kishi reaction: a concise and efficient total synthesis of amphidinolactone A. Eur. J. Org. Chem. 2010, 4775–4784. https://doi.org/10.1002/ejoc.201000565.

Montgomery, J., 2004. Nickel-catalyzed reductive cyclizations and couplings. Angew. Chemie - Int. Ed. 43, 3890–3908. https://doi.org/10.1002/anie.200300634.

Muller, B., Lallemand, J., Panerazi, A., Prunet, J., 1998. ''Ab normal'' Eight - Membered Ring Formation through SN2' intramolecular Nozaki/Kishi reaction in a synthetic approach to a taxane precursor Benoit Muller, Jean-Pierre F6r6zou*, Jean-Yves Lallemand, Ange Panerazi, Jo∼lle Pru. Tetrahedron Lett. 39, 279–282. https://doi.org/10.1016/S0040-4039(97)10512-3.

Myers, A.G., 1987. Proposed structure of the neocarzinostatin chromophore-methyl thioglycolate adduct; A mechanism for the nucleophilic activation of neocarzinostatin. Tetrahedron Lett. 28, 4493–4496. https://doi.org/10.1016/S0040-4039(00)96545-6.

Nagata, R., Yamanaka, H., Okazaki, E., Saito, I., 1989. Biradical formation from acyclic conjugated eneyne-allene system related to neocarzinostatin and esperamicin-calichemicin. Tetrahedron Lett. 30, 4995–4998. https://doi.org/10.1016/S0040-4039(01)80564-5.

Nicolaou, K.C., Zuccarello, G., Ogawa, Y., Schweiger, E.J., Kumazawa, T., 1988. J. Am. Chem. Soc. 110, 4868–4869. https://doi.org/10.1021/ja00222a077.

Nicolaou, K., Dai, W., 1991. Chemistry and biology of the enediyne anticancer antibiotics. Angew. Chemie - Int. Ed. 30, 1387–1416. https://doi.org/10.1002/anie.199113873.

Nicolaou, K.C., Dai, W.-M., Tsay, S.-C., Estevez, V.A., Wrasidlo, W., 1992a. Designed enediynes: a new class of DNA-cleaving molecules with potent and selective anticancer activity. Science 80 (256), 1172–1178. https://doi.org/10.1126/science.256.5060.1172.

Nicolaou, K.C., Dai, W.-M., Tsay, S.-C., Wrasidlo, W., 1992b. On the mechanism of activation of designed enediynes with selective cytotoxicity. Bioorg. Med. Chem. Lett. 2, 1155–1160. https://doi.org/10.1016/S0960-894X(00)80638-1.

Nicolaou, K.C., Liu, A., Zeng, Z., McComb, S., 1992c. Redox-controlled Bergman cycloaromatizations. Designed enediynes with DNA-cleaving properties and antitumor activity. J. Am. Chem. Soc. 114, 9279–9282. https://doi.org/10.1021/ja00050a006.

Nicolaou, K.C., Lu, Z., Li, R., Woods, J.R., Sohn, T., 2015. Total synthesis of Shishijimicin A. J. Am. Chem. Soc. 137, 8716–8719. https://doi.org/10.1021/jacs.5b05575.

Nicolaou, K.C., Smith, A.L., 1992. Molecular design, chemical synthesis, and biological action of enediynes. Acc. Chem. Res. 25, 497–503. https://doi.org/10.1021/ar00023a003.

Nicolaou, K.C., Smith, a.L., Yue, E.W., 1993a. Chemistry and biology of natural and designed enediynes. Proc. Natl. Acad. Sci. 90, 5881–5888. https://doi.org/10.1073/pnas.90.13.5881.

Nicolaou, K.C., Stabila, P., Esmaeli-Azad, B., Wrasidlo, W., Hiatt, A., 1993b. Cell-specific regulation of apoptosis by designed enediynes. Proc. Natl. Acad. Sci. 90, 3142–3146. https://doi.org/10.1073/pnas.90.8.3142.

Nishikawa, T., Shibuya, S., Hosokawa, S., Isobe, M., 1994. One pot synthesis of haloacetylenes from trimethylsilylacetylenes. Synlett 1994, 485–486. https://doi.org/10.1055/s-1994-22897.

Oblinger, E., Montgomery, J., 1997. A new stereoselective method for the preparation of allylic alcohols. J. Am. Chem. Soc. 119, 9065–9066. https://doi.org/10.1021/ja9719182.

Oku, N., Matsunaga, S., Fusetani, N., 2003. Shishijimicins A-C, novel enediyne antitumor antibiotics from the ascidian Didemnum proliferum. J. Am. Chem. Soc. 125, 2044–2045. https://doi.org/10.1021/ja0296780.

Pandithavidana, D.R., Poloukhtine, A., Popik, V.V., 2009. Photochemical generation and reversible cycloaromatization of a nine-membered ring cyclic enediyne. J. Am. Chem. Soc. 131, 351–356. https://doi.org/10.1021/ja8077076.

Panek, J.S., Liu, P., June, R.V., 2000. Total synthesis of the actin-depolymerizing agent (-) -Mycalolide A: application of chiral silane-based bond construction methodology. J. Am. Chem. Soc. 122, 11090–11097.

Pilli, R.A., Victor, M.M., 1998. Total synthesis of (−)-decarestrictine D through a stereoselective intramolecular Nozaki-Hiyama-Kishi reaction. Tetrahedron Lett. 39, 4421–4424. https://doi.org/10.1016/S0040-4039(98)00837-5.

Pilli, R.A., Victor, M.M., de Meijere, A., 2000. First Total Synthesis of Aspinolide B, a New Pentaketide Produced by Aspergillus o chraceus. J. Org. Chem. 65, 5910–5916. https://doi.org/10.1021/jo000327i.

Poloukhtine, A., Popik, V.V., 2005. Application of photochemical decarbonylation of cyclopropenones for the in situ generation of reactive enediynes. construction of a cyclopropenone-containing enediyne precursor by using a cyclopropenone acetal building block. J. Org. Chem. 70, 1297–1305. https://doi.org/10.1021/jo048065y.

Poloukhtine, A., Rassadin, V., Kuzmin, A., Popik, V.V., 2010. Nucleophilic cycloaromatization of ynamide-terminated enediynes. J. Org. Chem. 75, 5953–5962. https://doi.org/10.1021/jo101238x.

Py, S., Harwig, C.W., Banerjee, S., Brown, D.L., Fallis, A.G., 1998. Taxamycin studies: Synthesis of taxoid-calicheamicin hybrids. Tetrahedron Lett. 39, 6139–6142. https://doi.org/10.1016/S0040-4039(98)01297-0.

Sandoval, C., Redero, E., Mateos-Timoneda, M.A., Bermejo, F.A., 2002. Suitable entry to a 10-membered ring with eleutheside functionality through Nozaki-Hiyama condensation. Tetrahedron Lett. 43, 6521–6524. https://doi.org/10.1016/S0040-4039(02)01475-2.

Semmelhack, M.F., Jaskowski, M., Sarpong, R., Ho, D.M., 2002. A simple synthesis and evaluation of the bicyclo[8.3.0] enediyne framework. Tetrahedron Lett. 43, 4947–4950. https://doi.org/10.1016/S0040-4039(02)00940-1.

Siddiq, A., Dembitsky, V., 2008. Acetylenic anticancer agents. Anticancer. Agents Med. Chem. 8, 132–170.

Smith, A.L., Nicolaou, K.C., 1996. The enediyne antibiotics. J. Med. Chem. 39, 2103–2117. https://doi.org/10.1021/jm9600398.

Sugiura, Y., Arakawa, T., Uesugi, M., Shiraki, T., Ohkuma, H., Konishi, M., 1991. Reductive and nucleophilic activation products of dynemicin A with methyl thioglycolate. A rational mechanism for DNA cleavage of the thiol-activated dynemicin A. Biochemistry 30, 2989–2992. https://doi.org/10.1021/bi00226a001.

Sugiura, Y., Shiraki, T., Konishi, M., Oki, T., 1990. DNA intercalation and cleavage of an antitumor antibiotic dynemicin that contains anthracycline and enediyne cores. Proc. Natl. Acad. Sci. 87, 3831–3835. https://doi.org/10.1073/pnas.87.10.3831.

Takai, K., Kimura, K., Kuroda, T., Hiyama, T., Nozaki, H., 1983. Selective grignard-type carbonyl addition of alkenyl halides mediated by chromium(II) chloride. Tetrahedron Lett. 24, 5281–5284. https://doi.org/10.1016/S0040-4039(00)88417-8.

Takai, K., Tagashira, M., Kuroda, T., Oshima, K., Utimoto, K., Nozaki, H., 1986. Reactions of alkenylchromium reagents prepared from alkenyl trifluoromethanesulfonates (triflates) with chromium (II) chloride under nickel catalysis. J. Am. Chem. Soc. 108, 6048–6050. https://doi.org/10.1021/ja00279a068.

Takao, K.I., Hayakawa, N., Yamada, R., Yamaguchi, T., Saegusa, H., Uchida, M., Samejima, S., Tadano, K.I., 2009. Total syntheses of (+)- and (-)-pestalotiopsin A. J. Org. Chem. 74, 6452–6461. https://doi.org/10.1021/jo9012546.

Tang, X.Q., Montgomery, J., 1999. Nickel catalysis in the stereoselective preparation of quinolizidine, pyrrolizidine, and indolizidine alkaloids: total synthesis of (+)- allopumiliotoxin 267A. J. Am. Chem. Soc. 121, 6098–6099. https://doi.org/10.1021/ja990997+.

Thorson, J., Sievers, E., Ahlert, J., Shepard, E., Whitwam, R., Onwueme, K., Ruppen, M., 2000. Understanding and exploiting natures chemical arsenal: the past, present and future of calicheamicin research. Curr. Pharm. Des. 6, 1841–1879. https://doi.org/10.2174/1381612003398564.

Vinogradova, O.V., Balova, I.A., Popik, V.V., 2011. Synthesis and reactivity of cinnoline-fused cyclic enediyne. J. Org. Chem. 76, 6937–6941. https://doi.org/10.1021/jo201148h.

Wang, H.-Y., Kato, A., Kinami, K., Li, Y.-X., Fleet, G.W.J., Yu, C.-Y., 2016. Concise synthesis of calystegines B 2 and B 3 via

intramolecular Nozaki–Hiyama–Kishi reaction. Org. Biomol. Chem. 14, 4885–4896. https://doi.org/10.1039/C6OB00697C.

Wang, H.N.C., Sondheimer, F., 1980. TSOCH, TsOCH2. Tetrahedron Lett. 21, 217–220.

Wolkenberg, S.E., Boger, D.L., 2002. Mechanisms of in situ activation for DNA-targeting antitumor agents. Chem. Rev. 102, 2477–2496. https://doi.org/10.1021/cr010046q.

Yamaguchi, S., Tanaka, H., Yamada, R., Kawauchi, S., Takahashi, T., 2012. Synthetic study of the angular tetracyclic core skeleton of landmycine a via Masamune-Bergman cyclization. Synlett 23, 1327–1330. https://doi.org/10.1055/s-0031-1290937.

Zein, N., Sinha, A., McGahren, W., Ellestad, G., 1988. Calicheamicin gamma 1I: an antitumor antibiotic that cleaves double-stranded DNA site specifically. Science 80 (240), 1198–1201. https://doi.org/10.1126/science.3240341.

Zhao, Z., Peacock, J.G., Gubler, D.A., Peterson, M.A., 2005. Photoinduced Bergman cycloaromatization of imidazole-fused enediynes. Tetrahedron Lett. 46, 1373–1375. https://doi.org/10.1016/j.tetlet.2004.12.136.

Zhao, Z., Peng, Y., Dalley, N.K., Cannon, J.F., Peterson, M.A., 2004. Bergman cycloaromatization of imidazole-fused enediynes: the remarkable effect of N-aryl substitution. Tetrahedron Lett. 45, 3621–3624. https://doi.org/10.1016/j.tetlet.2004.02.152.