Reductive Cyclization

Deutsche Ausgabe: DOI: 10.1002/ange.201503442
Internationale Ausgabe: DOI: 10.1002/anie.201503442

Toward Naphthocyclinones: Doubly Connected Octaketide Dimers with a Bicyclo[3.2.1]octadienone Core by Thiolate-Mediated Cyclization**

Yoshio Ando, Subaru Hori, Takumi Fukazawa, Ken Ohmori, and Keisuke Suzuki**

Abstract: *A viable method is reported for the synthesis of the bicyclo[3.2.1]octadienone scaffold in naturally occurring octaketide dimers. The procedure employs a reductive cyclization reaction mediated by an unusual ethanedithiol monosodium salt.*

Dimerization is one of nature's strategies to increase molecular diversity and complexity.[1] A good example is the dimeric pyranonaphthoquinone antibiotics which are derived from type II polyketide biosynthesis (Figure 1).[2] After assembly of octaketide **1**, cyclization forms a monomer, specifically nanaomycin (**2**).[3] Oxidative dimerization to form a single connection (bond I) gives actinorhodin (**3**),[4] whereas dual connection (bonds I and II) leads to β-naphthocyclinone (**4**).[5] In view of the potential biological relevance and the synthetic challenge of the unusual bicyclo[3.2.1]octadienone core[6] in **4**, we sought the chemical realization of such dimerization reactions.

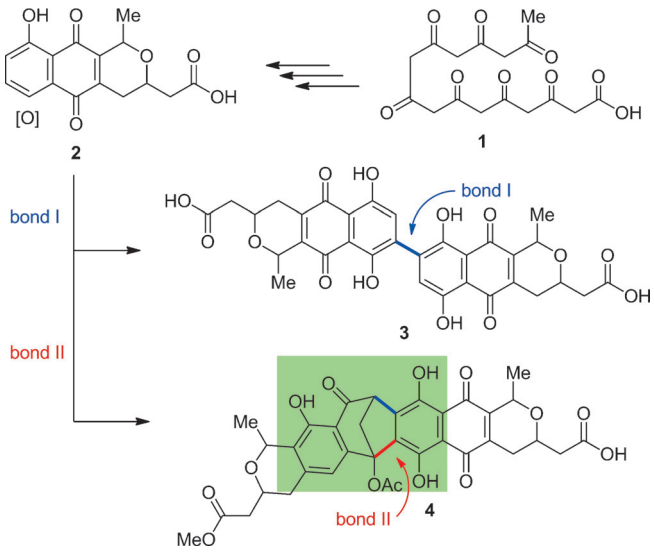
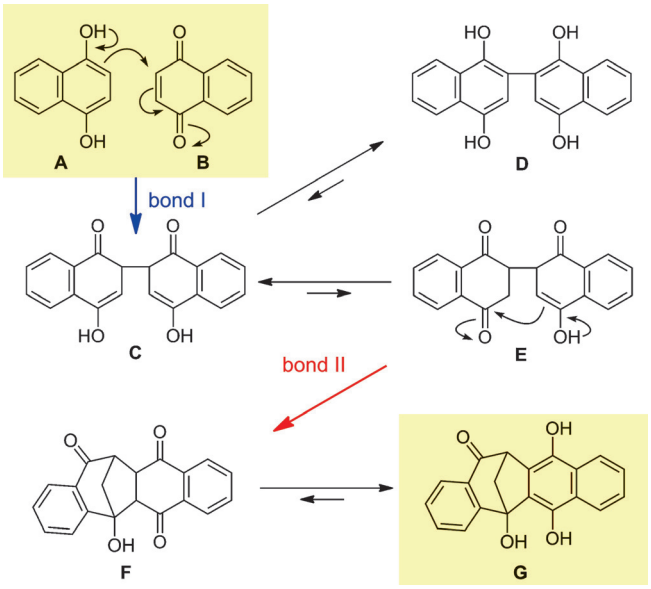


Figure 1. One- and two-bond dimerization reactions.

Our working hypothesis to obtain doubly connected octaketides is shown in Scheme 1. Given that one of the starting naphthoquinones was reduced as in **A**, 1,4-addition of



Scheme 1. Working hypothesis to obtain doubly connected compounds.

A to **B** would give adduct **C** (forming bond I), which would tautomerize into bishydroquinone **D**. Importantly, tautomer **E**, possibly a minor species, provides an opportunity for the second C–C bond formation (bond II) by intramolecular aldol reaction to give aldol **F** and its tautomer **G**.[7] This hypothesis is a simplistic view, as complications may arise from various equilibria by quinone–hydroquinone redox and keto–enol tautomerism. A particular concern is the presumably low concentration of tautomer **E** needed to achieve the key aldolization.

To address this issue, we focused our attention on bisacetal **6** as a model substrate in which bond I is already formed. We attempted to prepare **6** by hydrogenating bisenone **5**, which was met with failure (see below). These efforts, however, led us to discover a direct conversion of **5** into **7**, containing the targeted skeleton, by an unusual thiolate-mediated reductive cyclization [Eq. (1)], which will be described herein.

Early attempts to saturate bisenone **5**[8] to obtain **6** failed, giving mostly bisphenol **8**, resulting from the reductive opening of acetals and aromatization on both sides (Scheme 2).[9] As an indirect access to **6**, 1,4-addition of thiolates to **5** was investigated, with the hope that dithiodi-

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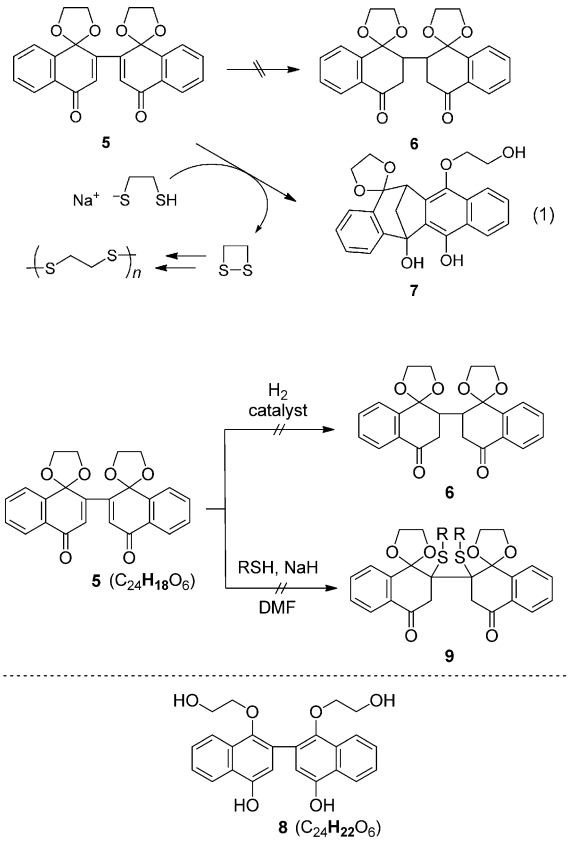
[**] This work was supported by a Grant-in-Aid for Specially Promoted Research from the JSPS (No. 23000006).
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201503442.



Scheme 2. Attempted preparation of model substrate. DMF = dimethylformamide.

ketone **9** may allow for the key aldol reaction. Again the attempts were fruitless,[10] giving mostly **8**. As this process corresponds to a four-electron reduction (see the elemental compositions of **8** relative to that of **5**), the thiolates served as a reductant.[11] This is not surprising in view of the highly conjugated π system in **5**.

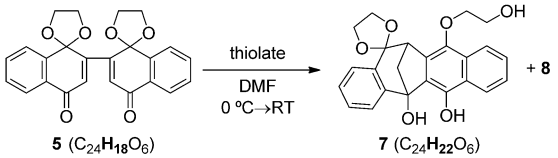
During further attempts, the reagent 1,2-ethanedithiol proved to be more successful. Use of its disodium salt EDT-2Na (**10**), generated from 1,2-ethanedithiol (6 equiv) and NaH (15 equiv), invariably gave **8** (Table 1, entry 1). However, the reaction of excess 1,2-ethanedithiol (6 equiv) with NaH (2 equiv) formed the reagent EDT-Na (**11**), whose application in the reaction led to the formation of acetal **7** with the target bicyclo[3.2.1]octadiene structure in 74 % yield (entry 2).[12]

The structure of **7** was carefully verified by extensive 2D NMR spectroscopy[13] and also by single-crystal X-ray diffraction analysis of ketone **12** (Figure 2), which was obtained by acid hydrolysis of **7** (1 M HCl, acetone, 92 % yield).[13,14]

Monitoring of the conversion of **5** into **7** by TLC suggested the presence of an intermediate, which was identified as ketoenone **13** by early quenching (10 min) [Eq. (2)]. **13** was shown to be an active intermediate, as resubjecting it to the same conditions led to the formation of product **7** in 82 % yield.

For achieving this unusual reaction of **5** to form **7**, EDT-Na (**11**) turned out to be uniquely effective. Even its one-carbon homologue, that is, the 1,3-propanedithiol monosodium salt, gave only a small amount of **7** (17 % yield) along

Table 1: Ethanedithiol salts for the conversion of **5** into **7** (and **8**).



Entry	thiolate	*t* [h]	yield [%] 7	8
1	NaS SNa EDT-2Na (**10**)	2	–	56
2	HS SNa EDT-Na (**11**)	3	74	8

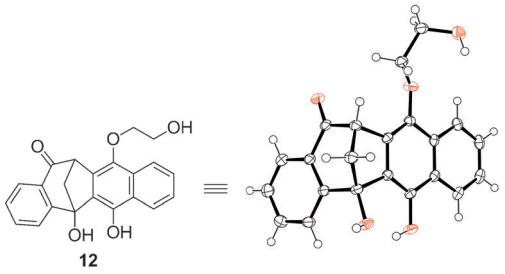
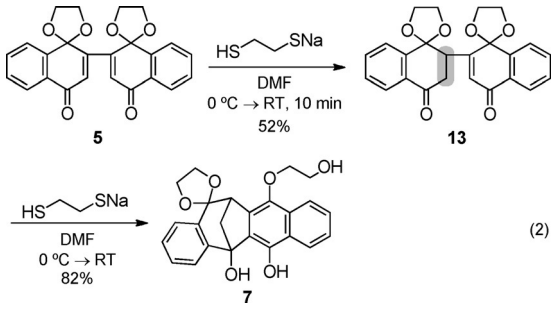


Figure 2. X-Ray structure of **12**.

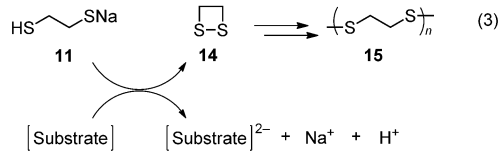


with bisnaphthol **8** (74 % yield). Other monoanions of dithiols led mostly to **8**.

Further information to explain the effectiveness of **11** was provided by the white precipitate formed in the reaction, which was identified as polyethylene disulfides **15**.[15] This suggested that EDT-Na (**11**) served as a two-electron reductant by forming an S–S bond to give 1,2-dithietane (**14**),[16] a putative species for the oxidation of ethanedithiol, that undergoes facile conversion into oligomer **15** [Eq. (3)].[17] This dithiol–disulfide redox system is reminiscent of some biological processes.[18]

The question remained as to why EDT-Na (**11**) is so efficient in the conversion of **5** into **7**, in contrast to other thiolates which convert **5** into **8**. It should be noted that both processes share a decrease of oxidation state of four electrons.

A known distinction between dithiols and monothiols is their enhanced acidity and electron affinity,[19] which is prominent with ethanedithiol (**I**; Figure 3). The higher acidity of **I** is attributed to the stabilization of the monoanion **II** by



a hydrogen bond. This stabilization also makes **II** less prone to a single-electron release to give radical **III**.

These dithiol properties led us to assume that EDT-Na (**11**) is particularly effective because, as a less basic anion, it serves as a good nucleophile for 1,4-addition rather than electron transfer. Indeed, the model reaction with enone **16** and **11** gave 1,4-adducts **17** with varying lengths of oligomeric disulfide chains [Eq. (4)], whereas the monosodium salt of 1,3-propanedithiol (not shown) gave mostly **18** (87%).

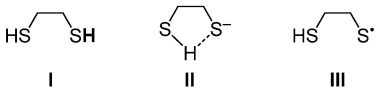
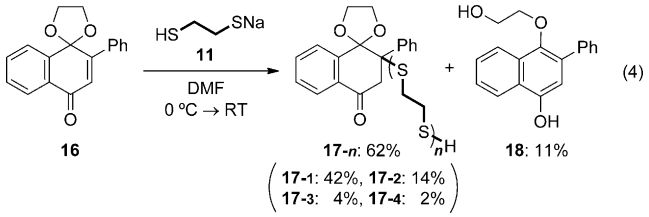


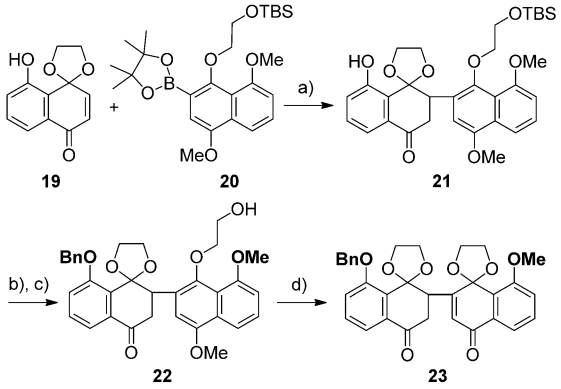
Figure 3. Ethanedithiol (**I**) and its monoanionic (**II**) and radical (**III**) forms. **II** is stabilized by hydrogen bonding.

Scheme 3 shows a proposed mechanism consisting of two stages. The first stage begins with the 1,4-addition of **11** to enone **5**, generating enolate **A**. Protonation gives thiolate **B**, which is converted into dienolate **C** by expelling 1,2-dithietane (**14**).[16,18a] Protonation of dienolate **C** by ethanedithiol present in excess gives semireduced product **13** as an intermediate. The second 1,4-addition of **11** to enone **13** gives enolate **D**, which undergoes the key aldol reaction, giving aldolate **E** with a bicyclo[3.2.1]octene skeleton. Finally,

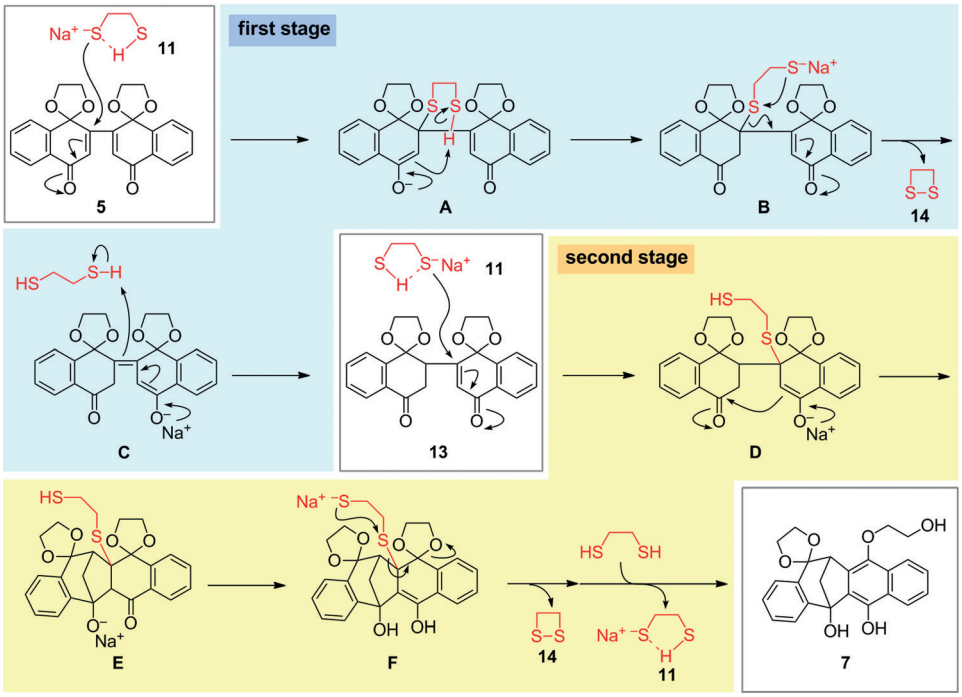


tautomerization to **F** and aromatization by opening of the cyclic acetal gives product **7**.

The synthetic implications of this intriguing reaction were subsequently addressed. We wondered whether we could use the process to access unsymmetrical dimers with different substitution patterns. To address this issue, model compound **23** was prepared (Scheme 4).[8] Quinone monoacetal **19** and



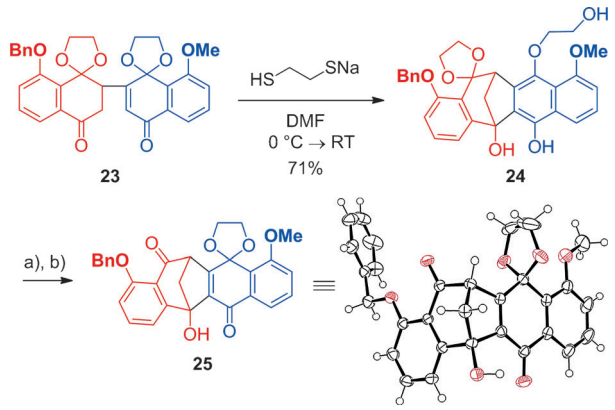
Scheme 4. Preparation of keto-enone **23**. a) [{RhCl(cod)}$_2$], Et_3N, 1,4-dioxane, H_2O, 91%; b) benzyl bromide, K_2CO_3, DMF; c) HF·pyridine, pyridine; d) cerium(IV) ammonium nitrate, 1,4-dioxane, H_2O, 60% (3 steps). cod = 1,5-cyclooctadiene. TBS = *tert*-butyldimethylsilyl.



Scheme 3. Proposed reaction mechanism (isolated compounds are shown in gray squares).

borane **20** were combined in the presence of a rhodium catalyst to give 1,4-adduct **21** (91% yield).[20] Subsequent benzylation, desilylation, and oxidation gave keto-enone **23**. Note that the protecting groups for the two rings are different (methyl versus benzyl).

Exposure of keto-enone **23** to the key cyclization conditions gave **24** as the single product (Scheme 5), whose structure was unambiguously assigned by an extensive 2D NMR spectroscopic study.[13] Although our focus was on whether any scrambling to the isomeric product happened or not, the reaction gave only **24**. Acid hydrolysis of **24** and oxidation gave quinone monoacetal **25**, the structure of which



Scheme 5. Reductive cyclization of **23** and X-ray structure of **25**. a) Aqueous HCl (1 M), acetone, 80%; b) $PhI(OCOCF_3)_2$, CH_3CN, 89%.

was confirmed by single-crystal X-ray diffraction analysis (Scheme 5).[14]

In conclusion, we have discovered a method for constructing the bicyclo[3.2.1]octadienone structure which serves as the core unit in the naphthocyclinone class of dimeric natural products. Further studies are in progress.

Experimental Section

Synthesis of acetal **7**: To a solution of 1,2-ethanedithiol (38 µL) in DMF (750 µL) was added NaH (63% dispersion in oil, 6 mg) at 0°C. After stirring for 15 min at RT, the mixture was cooled to 0°C, to which was added bis-enone **5** (29.5 mg). After stirring for 3 h at RT, the reaction was quenched using phosphate buffer (pH 7, 0°C). The reaction mixture was extracted using EtOAc (×3) and purified twice by preparative TLC (using a mixture of toluene:acetone, 2/1 v/v) to give **7** (22.0 mg, 74%) as a colorless oil and **8** (2.3 mg, 8%) as a white solid.

Keywords: cyclization · dimerization · dithiol reagents · quinones · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 9650–9653
Angew. Chem. **2015**, *127*, 9786–9789

[1] a) G. Lian, B. Yu, *Chem. Biodiversity* **2010**, *7*, 2660–2691; b) J. Sperry, P. Bachu, M. A. Brimble, *Nat. Prod. Rep.* **2008**, *25*, 376–400.

[2] a) T. Taguchi, M. Yabe, H. Odaki, M. Shinozaki, M. Metsä-Ketelä, T. Arai, S. Okamoto, K. Ichinose, *Chem. Biol.* **2013**, *20*, 510–520; b) K. Schröder, H. G. Floss, *J. Org. Chem.* **1978**, *43*, 1438–1441; c) B. Krone, A. Zeeck, H. G. Floss, *J. Org. Chem.* **1982**, *47*, 4721–4724.

[3] a) S. Omura, H. Tanaka, Y. Koyama, R. Oiwa, M. Katagiri, J. Awaya, T. Nagai, T. Hata, *J. Antibiot.* **1974**, *27*, 363–365; b) H. Tanaka, Y. Koyama, J. Awaya, H. Marumo, R. Oiwa, M. Katagiri, T. Nagai, S. Omura, *J. Antibiot.* **1975**, *28*, 860–867; c) H. Tanaka, Y. Koyama, T. Nagai, H. Marumo, S. Omura, *J. Antibiot.* **1975**, *28*, 868–875.

[4] a) H. Brockmann, H. Pini, O. Plotho, *Chem. Ber.* **1950**, *83*, 161–167; b) H. Brockmann, A. Zeeck, K. van der Merwe, W. Müller, *Justus Liebigs Ann. Chem.* **1966**, *698*, 209–229; c) A. Zeeck, P. Christiansen, *Justus Liebigs Ann. Chem.* **1969**, *724*, 172–182.

[5] a) A. Zeeck, M. Mardin, *Justus Liebigs Ann. Chem.* **1974**, 1063–1099; b) A. Zeeck, H. Zähner, M. Mardin, *Justus Liebigs Ann. Chem.* **1974**, 1100–1125; c) B. Krone, A. Zeeck, *Liebigs Ann. Chem.* **1983**, 471–502; d) E. Egert, M. Noltemeyer, G. M. Sheldrick, W. Saenger, H. Brand, A. Zeeck, *Liebigs Ann. Chem.* **1983**, 503–509; e) B. Krone, A. Zeeck, *Liebigs Ann. Chem.* **1983**, 510–518.

[6] For the synthesis of bicyclo[3.2.1]octadienone skeletons, see: a) W. R. Vaughan, M. V. Andersen, Jr., R. Q. Little, Jr., *J. Am. Chem. Soc.* **1954**, *76*, 1748–1752; b) S. J. Cristol, F. P. Parungo, D. E. Plorde, *J. Am. Chem. Soc.* **1965**, *87*, 2870–2879; c) H. Y. Elnagar, K. H. Chow, A. T. Johnson, R. Somanathan, P. Nunez, M. J. Watson, C. S. Parsons, E. J. Grubbs, *Tetrahedron* **1986**, *42*, 5841–5848.

[7] Recently, biomimetic synthesis of a related natural product based on this sequence was reported, see: H. Yang, J. Feng, Y. Li, Y. Tang, *Org. Lett.* **2015**, *17*, 1441–1444.

[8] For the substrate preparation, see the Supporting Information.

[9] Pd/C, Rh/C, and Wilkinson's catalysts were studied.

[10] Thiolates derived from PhSH, EtSH, and $C_{12}H_{25}SH$ were examined.

[11] For thiolates as reducing agents, see: a) M. J. Gibian, D. V. Winkelman, *Tetrahedron Lett.* **1969**, *10*, 3901–3904; b) H. Bayley, D. N. Standring, J. R. Knowles, *Tetrahedron Lett.* **1978**, *19*, 3633–3634; c) H. E. Fried, E. T. Kaiser, *J. Am. Chem. Soc.* **1981**, *103*, 182–184.

[12] Other base/solvent combinations were demonstrated to be ineffective: KH, CaH_2, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), *n*BuLi, and *i*PrMgCl; THF, CH_2Cl_2, toluene, *N*-methyl-2-pyrrolidone (NMP), *N*,*N*-dimethylacetamide (DMA), 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one (DMPU), and dimethylsulfoxide (DMSO).

[13] See the Supporting Information.

[14] CCDC-873993 (**12**) and 1051963 (**25**) contain 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.

[15] In the Raman spectrum, bands at 505 cm^{-1} (S–S bond) and 726 cm^{-1} (C–S bond) were detected, and in the EI mass spectrum fragmentation signals were found from the mono-, di-, tri-, and tetramers. For polyethylene disulfide, see: a) J. G. Affleck, G. Dougherty, *J. Org. Chem.* **1950**, *15*, 865–868; b) N. Kobayashi, A. Osawa, T. Fujisawa, *J. Polym. Sci. B* **1973**, *11*, 225–228; c) E. I. Stout, B. S. Shasha, W. M. Doane, *J. Org. Chem.* **1974**, *39*, 562–563.

[16] For 1,2-dithietane, see: a) M. Platen, E. Steckhan, *Chem. Ber.* **1984**, *117*, 1679–1694; b) K. C. Nicolaou, S. A. DeFrees, C.-K. Hwang, N. Stylianides, P. J. Carroll, J. P. Snyder, *J. Am. Chem. Soc.* **1990**, *112*, 3029–3039; c) A. S. Kiselyov, L. Strekowski, V. V. Semenov, *Tetrahedron* **1993**, *49*, 2151–2158.

[17] Under basic conditions, thiols are oxidized to the corresponding disulfide by O_2. Even under degassed conditions, formation of polyethylene disulfide and compound **7** were detected, suggesting dienone **5** worked as the oxidizing agent for the thiol.

[18] a) K. Inaba, Y. Takahashi, K. Ito, S. Hayashi, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 287–292; b) K. Inaba, S. Murakami, M. Suzuki, A. Nakagawa, E. Yamashita, K. Okada, K. Ito, *Cell* **2006**, *127*, 789–801.

[19] J. M. Karty, Y. Wu, J. I. Brauman, *J. Am. Chem. Soc.* **2001**, *123*, 9800–9805.

[20] N. Tokunaga, T. Hayashi, *Adv. Synth. Catal.* **2007**, *349*, 513–516, and references therein.

Received: April 16, 2015
Revised: May 2, 2015
Published online: June 26, 2015

