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The first total synthesis and structural determination of (+)-BE-52440A

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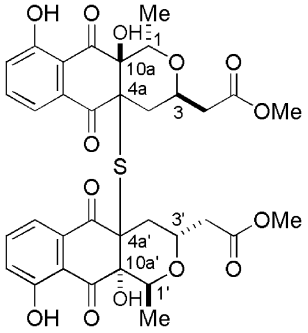
Abstract—The first total synthesis and structural determination of (+)-BE-52440A have been achieved by enantiodivergent synthesis. *S*-Bridging dimerization including S_N2 epoxy-opening reaction of tetrasubstituted epoxide **2** with sodium sulfide has been achieved in excellent yield with high regioselectivity. The structure of (+)-BE-52440A was determined to be the dimer of kalafungin type pyranonaphthoquinone.

Pyranonaphthoquinone antibiotics have drawn attention with their structures and potent antitumor activities.[1] In our laboratory, methodologies toward pyranonaphthoquinone antibiotics have been established and total syntheses of some of this family have been achieved.[2] The total syntheses of nanaomycin D and its enantiomer, kalafungin, were accomplished by the enantiodivergent strategies.[2a] (+)-BE-52440A [(+)-**1**] was reported as an antitumor agent from *Streptomyces* strain A52440 by Banyu group in 2000.[3] The structure of **1** was elucidated to be a dimer of nanaomycin derivatives bridged with sulfur (Fig. 1).[3] Although the relative configurations between C1, C3, and C10a, and between C1′, C3′, and C10a′ were determined, the relative stereochemistry of C4a and C4a′ as well as the absolute configuration of **1** remained unknown. The striking structure of *S*-bridged dimer **1** stimulated us to the total synthesis of the natural product. Herein, we present the first total synthesis and structural determination of (+)-BE-52440A [(+)-**1**].

Synthetic plan of nanaomycin type BE-52440A (**1**) is described in Scheme 1. We assumed that **1** would be biogenetically synthesized by epoxy-opening dimerization



BE-52440A (1)

Figure 1. The structure of BE-52440A (**1**) (relative stereochemistry only).

of OM-173 αE (**2**), a naturally occurring nanaomycin type antibiotic.[4] **2** might be obtained by stereospecific epoxidation of pyranonaphthoquinone **3**, which could be derived from lactone **4** and/or γ-hydroxyester **5**. Both lactone **4** and γ-hydroxyester **5** were obtained from lactol **6**, which was derived from L-rhamnoside **8** via enone **7**.[2] Kalafungin type BE-52440A (**1**) would be also synthesized from lactone **4** and/or γ-hydroxyester **5** by modification of our previous enantiodivergent syntheses of nanaomycins and kalafungins.[2,5]

Synthesis of both enantiomers of BE-52440A to determine the absolute configuration started with lactol **6** to

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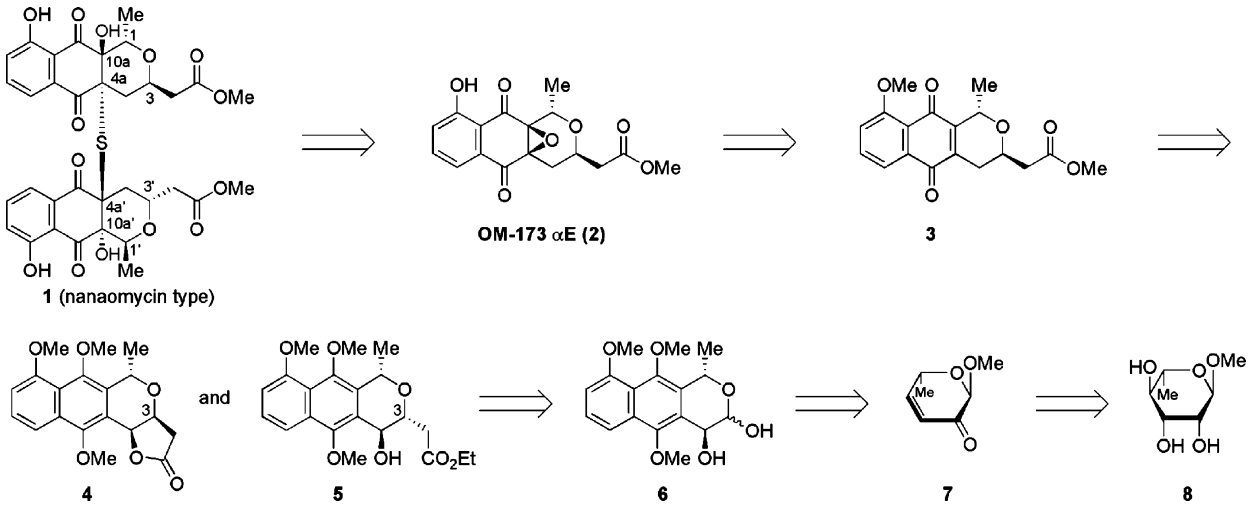
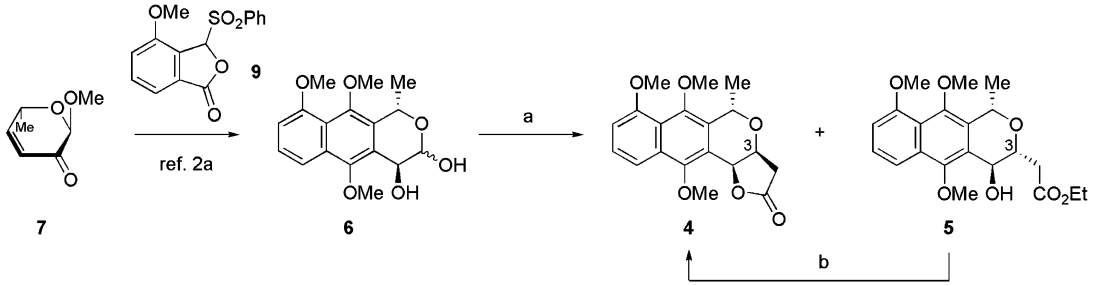


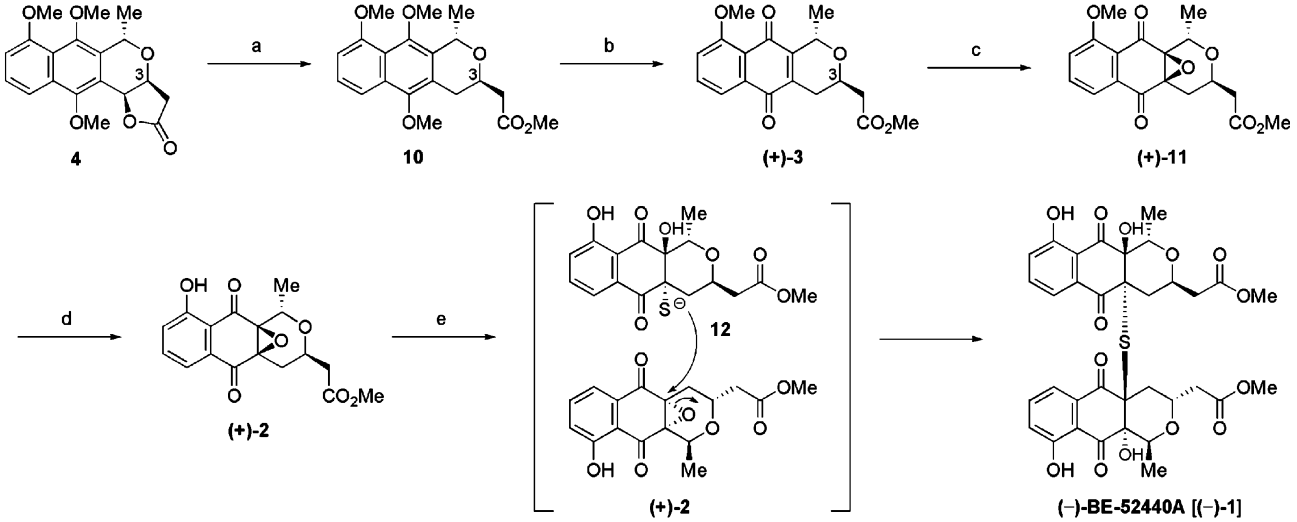
Scheme 1. Synthetic plan of nanaomycin type BE-52440A (**1**).

deliver lactone **4** and ester **5**, the intermediates in nanaomycin D and kalafungin synthesis, respectively (Scheme 2).[2] Enone **7** and lactone **9** were coupled by subsequent Michael–Dieckmann reactions to deliver **6**. Wittig reaction with lactol **6** provided lactone **4** and ester **5** as almost 1:1 mixture.[2] Ester **5** was converted to lactone **4** under basic conditions.

Lactone **4** was converted to BE-52440A (**1**: nanaomycin type) via (+)-OM-173 αE [(+)-**2**] (Scheme 3). Hydrogeno-



Scheme 2. Synthesis of pyranonaphthalene structure. Reagents and conditions: (a) $Ph_3P{=}CHCO_2Et$, PhMe, 105 °C, 30 h, **4**: 53%, **5**: 41%; (b) K_2CO_3, 18-crown-6, DMF, 100 °C, 10 h, 60%.



Scheme 3. Synthesis of **1** (nanaomycin type) [(−)-BE-52440A]. Reagents and conditions: (a) H_2, Pd–C, MeOH, 25 °C, 9 h, then HCl, MeOH, 25 °C, 6 h, 92%; (b) AgO, 3 N $HClO_4$, 1,4-dioxane, 25 °C, 20 min, 94%; (c) TBHP, *t*-BuOK, THF, −45 to 25 °C, 4 h, 71%; (d) BCl_3, CH_2Cl_2, 0 °C, 30 min, 92%; (e) Na_2S, 1,4-dioxane, 25 °C, 30 min, 98%.

lysis of **4** followed by esterification gave methyl ester **10**. Trimethoxynaphthalene **10** was oxidized with AgO under the acidic conditions to obtain unstable quinone (+)-**3**, which was identical in all aspect with the known nanaomycin derivative.[1b] Exposure of quinone (+)-**3** to *tert*-butyl hydrogen peroxide (TBHP) in the presence of potassium *tert*-butoxide afforded epoxide (+)-**11** in high stereoselectivity (ds = 10:1), which was followed by de-O-methylation to provide (+)-OM-173 αE [(+)-**2**]. The structure of synthetic (+)-**2** was confirmed by X-ray crystallography (Fig. 2).

The stage of the key reaction sequence, regioselective epoxy-opening dimerization, which should include S_N2 reaction between *tert*-thiolate **12** and tetrasubstituted epoxide (+)-**2**, was set up. By treatment of epoxide (+)-**2** with Na_2S, the reaction proceeded smoothly at room temperature and the desired adduct BE-52440A (**1**: nanaomycin type) was obtained within half an hour in almost quantitative yield. The intermediary *tert*-thiolate **12** was so reactive that the corresponding thiol was not observed by monitoring TLC during the bridging reaction to produce the thioether sandwiched with two quaternary carbons. Product **1** (nanaomycin type) was identical to the natural product in all aspects except the optical rotation [**1** (nanaomycin type): $[\alpha]_D^{28}$ −242 (*c* 1.00, DMSO), the natural product $[\alpha]_D^{20}$ +252 (*c* 1.0, DMSO)]. X-ray crystallography of the product confirmed the stereochemistry of *S*-bridged **1** (nanaomycin type).[6] Thus, **1** (nanaomycin type) was determined as (−)-BE-52440A.

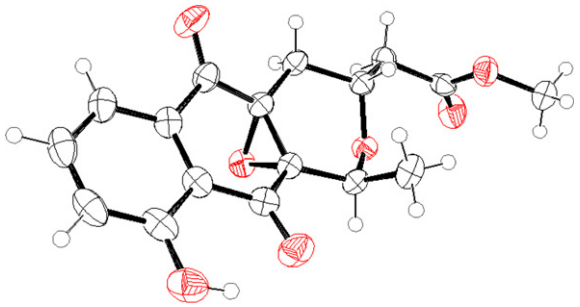
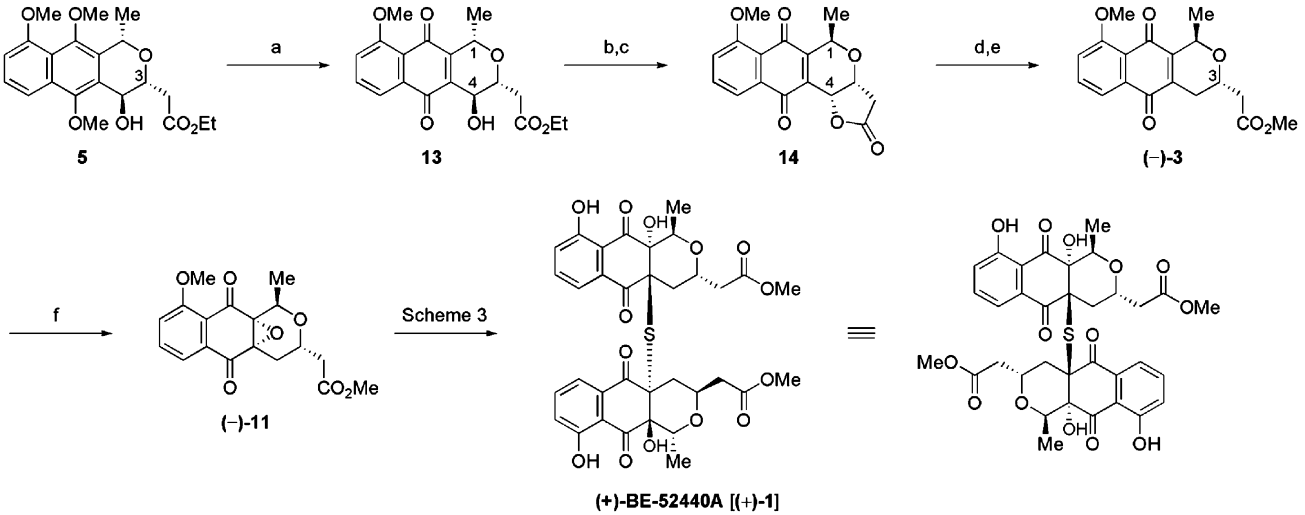


Figure 2. ORTEP drawing of (+)-OM-173 αE [(+)-**2**].

The total synthesis of (+)-BE-52440A [(+)-**1**: kalafungin type], the natural form, was accomplished by methodologies based on the enantiodivergent synthesis starting with lactone **4** and γ-hydroxyl ester **5** (Scheme 4 and 5). First of all, pyranonaphthalene **5** was oxidized to naphthoquinone **13**. Treatment of **13** with sulfuric acid promoted epimerization at C1 and C4 positions followed by lactonization to give lactone **14**. Hydrogenolysis at C4 position accompanied with reduction of the quinone to the hydroquinone, which was submitted to successive oxidation and esterification to afford quinone (−)-**3**. Unstable quinone (−)-**3** was immediately converted to the corresponding epoxide (−)-**11**, which was confirmed to be the enantiomer of epoxide (+)-**11** [$[\alpha]_D^{26}$ −18.1 (*c* 0.75, $CHCl_3$)]. Further manipulation for quinone (−)-**11** as same as for epoxide (+)-**11** provided (+)-BE-52440A [(+)-**1**]. Synthetic (+)-BE-52440A [(+)-**1**] was identical to the natural product in all aspects including the optical rotation [synthetic (+)-**1**: $[\alpha]_D^{27}$ +249 (*c* 0.80, DMSO)], indicating that natural (+)-BE-52440A possessed (1*R*,3*R*,4a*R*,10a*S*, 1′*R*,3′*R*,4a′*R*,10a′*S*)-configuration. X-ray crystallography of synthetic (+)-BE-52440A [(+)-**1**] confirmed the stereochemistry as shown in Figure 3.[6]

On the other hand, lactone **4** (Scheme 2) was also converted to (+)-BE-52440A [(+)-**1**] (Scheme 5). Methyl ester **10**, the derivative of lactone **4** (Scheme 3), was submitted to epimerization at C3 position in the presence of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) to afford ester **15**.[1d,2e] After oxidation to quinone **16**, epimerization at C1 position was realized by treatment with acid to give quinone (−)-**3**, the intermediary of (+)-BE-52440A [(+)-**1**]. Therefore, both lactone **4** and ester **5** were



Scheme 4. Synthesis of kalafungin type BE-52440A [(+)-**1**]. Reagents and conditions: (a) AgO, 3 N $HClO_4$, 1,4-dioxane, 25 °C, 5 min, 89%; (b) H_2SO_4, PhH, 0 °C, 30 min; (c) PhMe, reflux, 11 h, 73% in two steps; (d) H_2, Pd-Black, MeOH, 25 °C, 2 h; (e) O_2, $CHCl_3$–MeOH, 25 °C, 30 min, then Me_3SiCHN_2, −78 °C, 1.5 h, 76% in three steps; (f) TBHP, *t*-BuOK, THF, −45 to 25 °C, 4 h, 71%.

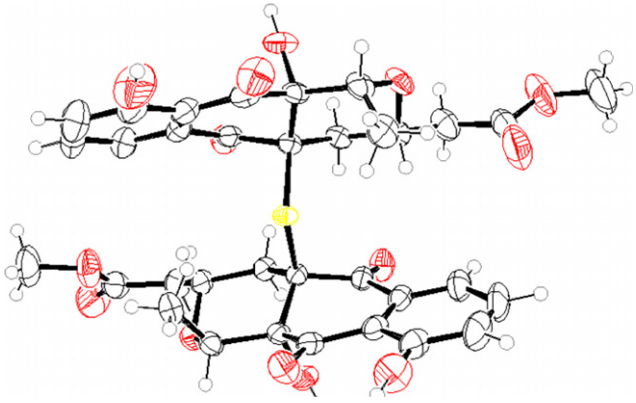
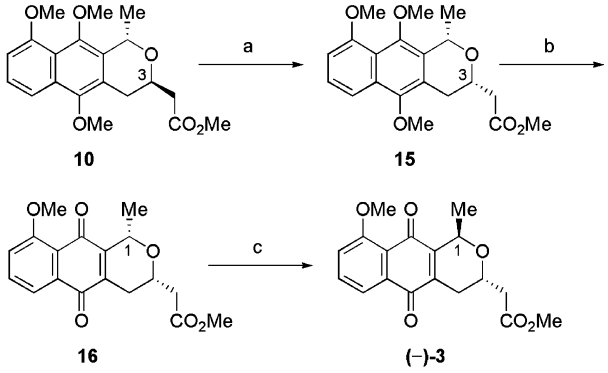


Figure 3. ORTEP drawing of (+)-BE-52440A [(+)-**1**].



Scheme 5. Transformation of pyranonaphthalene **10** to quinone (−)-**3**. Reagents and conditions: (a) DBU, DMF, 140 °C, 16 h, 53%, recovery of **10**, 31%; (b) AgO, 3 N $HClO_4$, 1,4-dioxane, 25 °C, 10 min, 91%; (c) H_2SO_4, PhMe, −25 °C, 9 h, 65%, recovery of **16**, 14%.

derived to (+)-BE-52440A [(+)-**1**], and in turn, lactol **6** was converted to (+)- and (−)-BE-52440A enantiodivergently.

In conclusion, the first total synthesis and structural determination of (+)-BE-52440A have been achieved via (−)-OM-173 αE [(−)-**2**]. The enantiodivergent methodology gave both enantiomers of BE-52440A [(+)- and (−)-**1**] stereoselectively from the same intermediary **6** derived from L-rhamnose. Epoxy-opening dimerization of tetrasubstituted epoxide **2** proceeded smoothly and regioselectively under the mild conditions. The natural (+)-BE-52440A was determined to be the dimer of kalafungin type pyranonaphthoquinone.

Acknowledgments

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Supplementary data

The spectrum data of compounds (+)-**1**, (+)-**2**, (−)-**3**, and (+)-**11**, and ^1H NMR spectra (600 MHz in $CDCl_3$) of synthetic (+)-BE-52440A [(+)-**1**] and (+)-OM-173 αE [(+)-**2**] are presented. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.039.

References and notes

1. (a) Ōmura, S.; Tanaka, H.; Koyama, Y.; Ōiwa, R.; Katagiri, M.; Awaya, J.; Nagai, T.; Hata, T. *J. Antibiot.* **1974**, *27*, 363–365; (b) Tanaka, H.; Koyama, Y.; Nagai, T.; Marumo, H.; Ōmura, S. *J. Antibiot.* **1975**, *28*, 868–875; (c) Moore, H. W. *Science* **1977**, *197*, 527–532; (d) Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1197–1202; (e) Uno, H. *J. Org. Chem.* **1986**, *51*, 350–358.
2. (a) Tatsuta, K.; Akimoto, K.; Annaka, M.; Ohno, Y.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1699–1706; (b) Tatsuta, K.; Akimoto, K.; Annaka, M.; Ohno, Y.; Kinoshita, M. *J. Antibiot.* **1985**, *38*, 680–682; (c) Tatsuta, K.; Ozeki, H.; Yamaguchi, M.; Tanaka, M.; Okui, T. *Tetrahedron Lett.* **1990**, *31*, 5495–5498; (d) Tatsuta, K.; Ozeki, H.; Yamaguchi, M.; Tanaka, M.; Okui, T.; Nakata, M. *J. Antibiot.* **1991**, *44*, 901–902; (e) Tatsuta, K.; Hirabayashi, T.; Kojima, M.; Suzuki, Y.; Ogura, T. *J. Antibiot.* **2004**, *57*, 291–297.
3. Tsukamoto, M.; Nakajima, S.; Murooka, K.; Naito, M.; Suzuki, H.; Hirayama, M.; Hirano, K.; Kojiri, K.; Suda, H. *J. Antibiot.* **2000**, *53*, 687–693.
4. (a) Iwai, Y.; Kimura, K.; Takahashi, Y.; Hinotozawa, K.; Shimizu, H.; Tanaka, H.; Ōmura, S. *J. Antibiot.* **1983**, *36*, 1268–1274, Naturally occurring 4a(10a)-epoxide derivatives of pyranonaphthoquinone antibiotics are known to be widespread; (b) Kasai, M.; Shirahata, K.; Ishii, S.; Mineura, K.; Marumo, H.; Tanaka, H.; Ōmura, S. *J. Antibiot.* **1979**, *32*, 442–445; (c) Ōmura, S.; Minami, S.; Tanaka, H. *J. Biochem.* **1981**, *90*, 291–293; (d) Okabe, T.; Nomoto, K.; Tanaka, N. *J. Antibiot.* **1986**, *39*, 1–5; (e) Hara, M.; Soga, S.; Shono, K.; Eishima, J.; Mizukami, T. *J. Antibiot.* **2001**, *54*, 182–186.
5. (a) Ōmura, S.; Tanaka, H.; Okada, Y.; Marumo, H. *J. Chem. Soc., Chem. Commun.* **1976**, 320–321; (b) Bergy, M. E. *J. Antibiot.* **1968**, *21*, 454–457; (c) Hoeksema, H.; Krueger, W. C. *J. Antibiot.* **1976**, *29*, 704–709.
6. Crystallographic data (excluding structure factors) for the structures of (+)-**1**, (−)-**1**, and (+)-**2** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Nos. CCDC 656350, 656349, and 656348 for (+)-**1**, (−)-**1**, and (+)-**2**, respectively. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).