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The first total synthesis and structural determination of epi-cochlioquinone A

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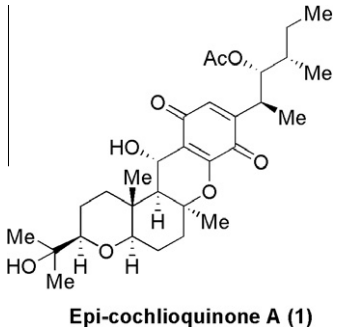
ABSTRACT

The first total synthesis of epi-cochlioquinone A has been achieved in a highly convergent manner via [3+3] cycloaddition of catechol **2** and oxadecalin **3** as the key reaction. The synthesis of the catechol segment, possessing the side chain with multi stereogenic centers, features the asymmetric vinylogous Mukaiyama aldol reaction, the stereoselective conjugate addition to the nitroalkene, the stereospecific nitro-Dieckmann condensation, and the transformation of 6-nitrocyclohex-2-enone into catechol **2**, using two new methodologies, such as (i) the hydrogen-transfer reaction to *o*-aminophenol and the subsequent auto-redox-catalysis to catechol and (ii) the direct oxidation of 6-nitrocyclohex-2-enone to *o*-quinone and the subsequent reduction. The oxadecalin segment was synthesized from a glycosyl cyanide by the [3+3] annulation with a ketone and an acetoacetate. These segments were connected by the [3+3] cyclization, and the resulting tetracyclic compound was subjected to a specific oxidation of the protected hydroquinone to provide epi-cochlioquinone A.

Epi-cochlioquinone A (**1**, Fig. 1) was isolated from the fermentation broth of *Stachybotrys bisbyi* as an inhibitor of acyl-CoA: cholesterol acyltransferase (ACAT) by Sankyo group in 1996.[1] Since ACAT plays a critical role both in cholesterol absorption in the intestine and in cholesterol ester formation in the liver and peripheral tissues,[2] ACAT inhibitors are expected to reduce serum cholesterol levels. The relative structure of epi-cochlioquinone A was determined by NMR spectrometric analysis and X-ray crystallographic analysis.[1] The cochlioquinone family has drawn attention due to its biological activities and the attractive structure;[3] however, the total synthesis of cochlioquinones has been unprecedented. Herein, we present the first total synthesis of epi-cochlioquinone A (**1**).

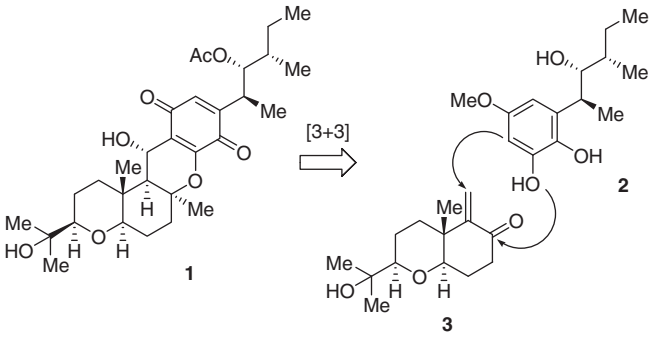


Epi-cochlioquinone A (1)

Figure 1. The structure of epi-cochlioquinone A (**1**).

In order to make the synthesis highly convergent, epi-cochlioquinone A (**1**) was divided into two segments (catechol **2** and oxadecalin **3**) in the retrosynthetic analysis (Scheme 1). The cochlioquinone skeleton would be synthesized by [3+3] cycloaddition with **2** and **3**. Therefore, the total synthesis started from the preparation of these segments.

The catechol **2** has been synthesized in a stereoselective manner (Scheme 2). The vinylogous Mukaiyama aldol reaction with the chiral dienol ether **4** and 2*S*-methylbutanal **5** afforded anti adduct



Scheme 1. The synthetic plan for epi-cochlioquinone A (**1**).

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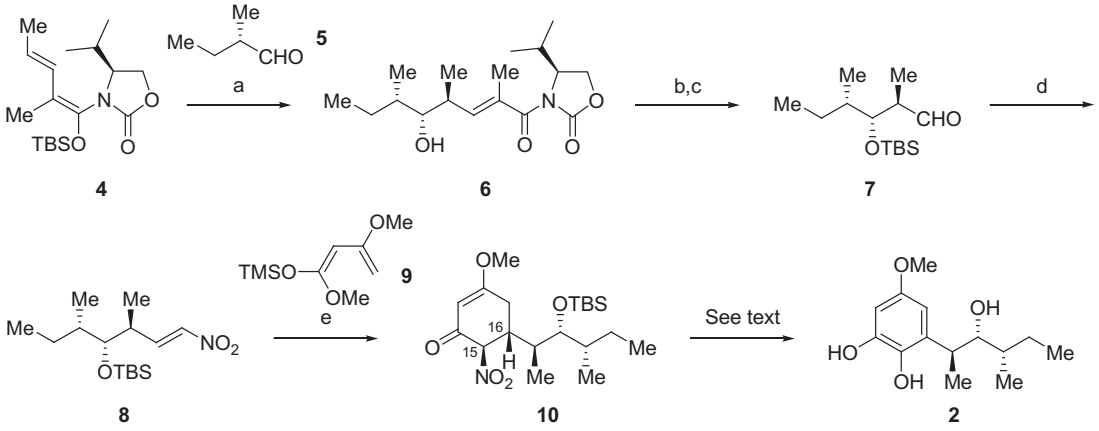
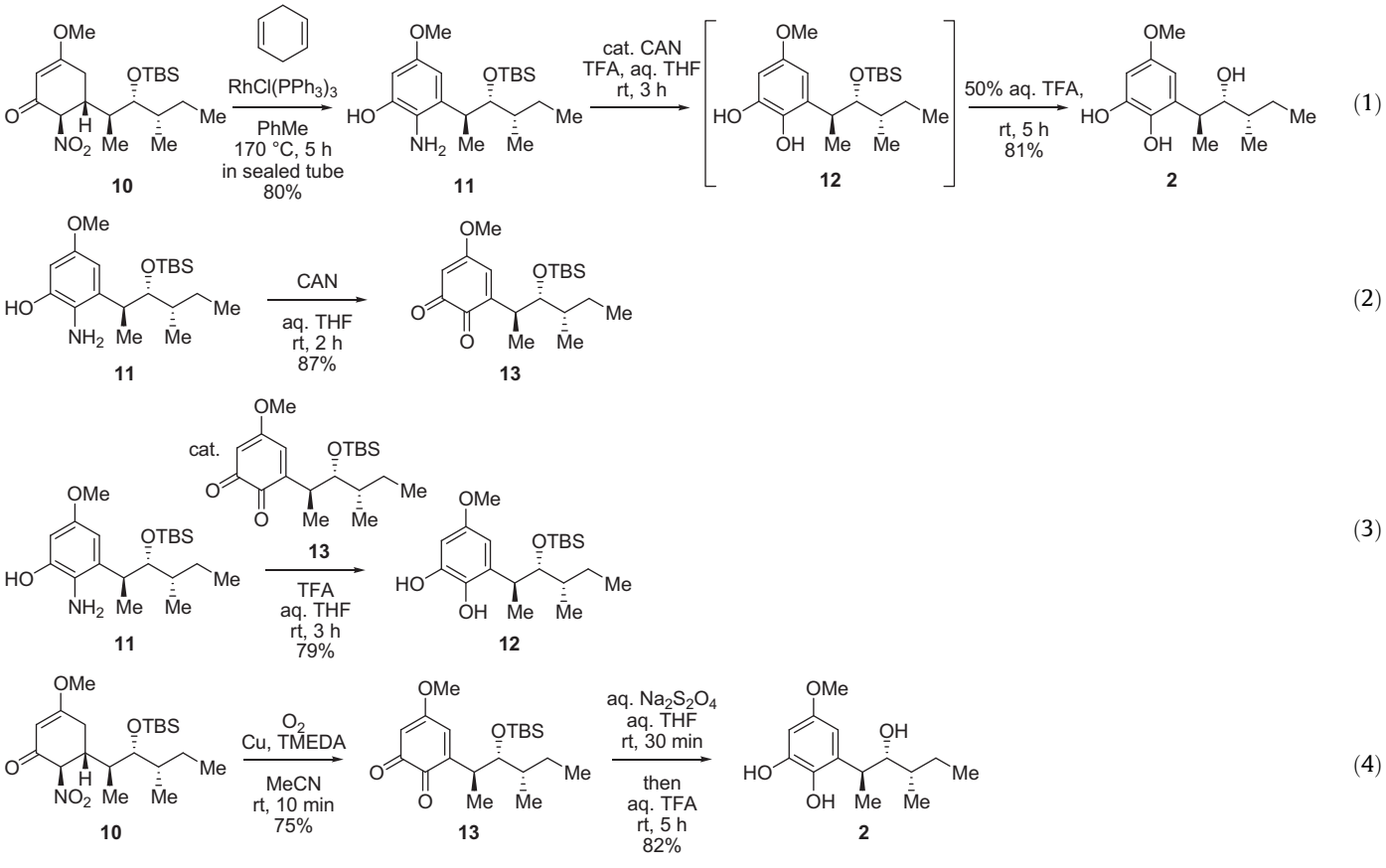


Scheme 2. Reagents and conditions: (a) $TiCl_4$, MS4A, CH_2Cl_2, −40 °C, 2 d, 89% dr 54:1; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 15 min; (c) O_3, CH_2Cl_2, −78 °C, 1 h, then Ph_3P, −78 °C, 30 min, 91% (in one pot); (d) $MeNO_2$, *n*-BuLi, THF, 0 °C, 2 d, then MsCl, Et_3N, 0 °C to rt, 2 h, 90%; (e) YbFOD (0.05 equiv), rt, 1 d, then K_2CO_3, EtOH, 70 °C, 2 d, 87%.

6 in high yield and excellent selectivity (dr 54:1, separable by column chromatography).[4] The protection of the hydroxy group as TBS ether was followed by ozonolysis in one pot to give aldehyde **7**[5] in high yield. Aldehyde **7** was converted to nitroalkene **8** by Henry aldol reaction[6] followed by the addition of mesyl chloride and triethylamine. The [4+2] cycloaddition reaction with **8** and dienol ether **9** proceeded stepwise to give cyclohexenone **10**. In the cycloaddition process, both the conjugate addition and the sequential nitro-Dieckmann reaction[7] proceeded in the stereoselective manner to give **10** as a single isomer (by 600 MHz ^{1}H NMR). The stereochemistry of cyclohexenone **10** was determined by X-ray crystallography (Fig. 2).[8,9]

Transformation of 6-nitrocyclohex-2-enone **10** into catechol **2** was achieved by two kinds of procedure. One involves the hydrogen transfer reaction and successive autocatalytic reaction (Eq. 1), and the other contains O_2 oxidation followed by reduction (Eq. 4).[10] In the former transformation (Eq. 1), de-hydrogenation of cyclohexenone and a concomitant reduction of the nitro group to amine were realized in the presence of Wilkinson catalyst and 1,4-cyclohexadiene at 170 °C, and the resulting *o*-aminophenol **11** was converted into catechol **2** with the catalytic amount (0.1 equiv) of oxidant under acidic conditions. The second step in Eq. 1 included an autocatalysis process, which was proven by the reactions shown in Eqs. 2 and 3. The equivalent amount of the oxi-



(1)

(2)

(3)

(4)

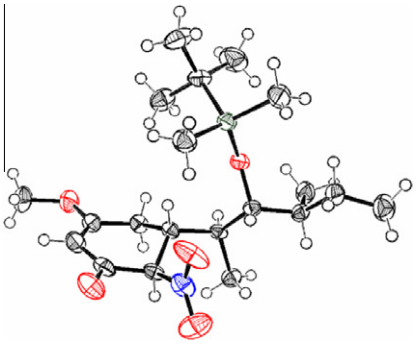
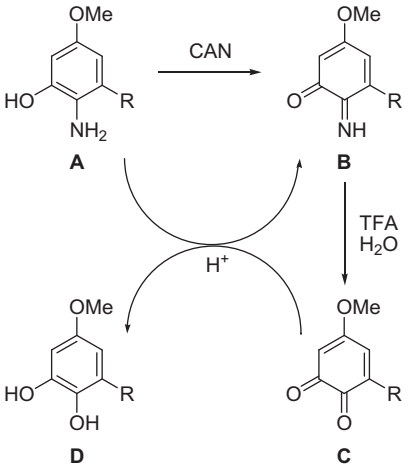


Figure 2. The ORTEP drawing of X-ray crystallography of **10**.

dant under the acidic conditions gave *ortho*-quinone **13** (Eq. 2). Treatment of aminophenol **11** with the catalytic amount (0.1 equiv) of quinone **13** in aqueous trifluoroacetic acid (TFA) gave catechol **12** (Eq. 3). Therefore, the mechanism of the transformation of *o*-aminophenol to catechol in Eq. 1 is presumed as Scheme 3. At first, aminophenol (**A**) should be oxidized to iminoquinone (**B**), which would receive the acid hydrolysis to give *o*-quinone (**C**). The resulting *o*-quinone (**C**) might work as an oxidant for aminophenol (**A**) to produce iminoquinone (**B**) and catechol (**D**). Therefore, this transformation contains the auto-redox-catalysis.



Scheme 3. The presumed reaction mechanism of the autocatalytic reaction to give catechol.

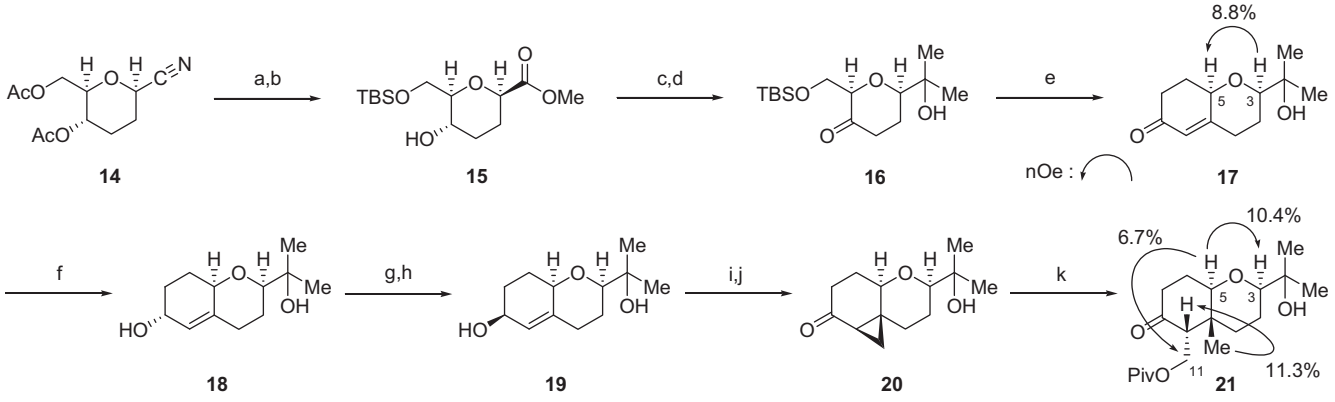
The other procedure to give catechol **2** from 6-nitrocyclohex-2-enone **10** is shown in Eq. 4. The α-proton (*CH*–NO_2) of **10** was absorbed under the mild basic conditions and oxidized[11] to provide *o*-quinone **13** in 75% yield. The reduction of quinone **13** followed by the addition of aqueous TFA gave de-O-silylated **2**.

Both these methodologies (Eqs. 1 and 4) are new methods to synthesize catechols. The method in Eq. 1 is applicable to not only catechol but also *o*-aminophenol, and features auto-redox-catalysis from *o*-aminophenol to catechol. On the other hand, the method in Eq. 4 contains the direct transformation of 6-nitrocyclohex-2-enone to *o*-quinone.

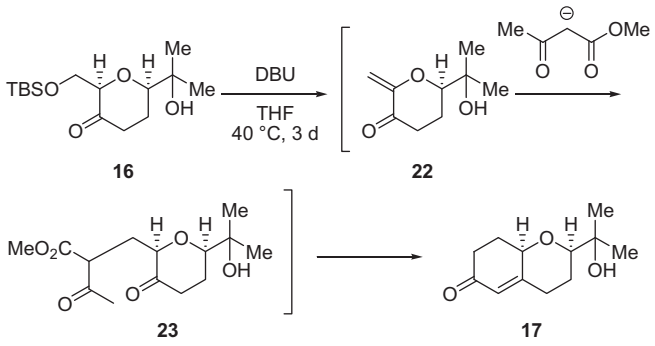
The synthesis of the oxadecalin moiety (**21**, the precursor of enone **3**) is disclosed in Scheme 4. The glycosyl cyanide **14**[12] was subjected to methanolysis of cyanide and acetate, which was followed by the selective silylation to afford **15**. Grignard reaction of ester **15** with excess amount of methylmagnesium bromide and the subsequent oxidation gave ketone **16**. Treatment of ketone **16** with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in the presence of methyl acetoacetate at 40 °C gave oxadecalin **17** in the manner of [3+3] cycloaddition reaction. The mechanism is proposed as Scheme 5, which involves β-elimination to afford enone **22**, conjugate addition of acetoacetate to give diketone **23**, and condensation with a concomitant de-carboxylation by the nucleophilic attack of eliminated H_2O to yield oxadecalin **17**. The stereochemistry of the C5 position was determined by NOE (8.8%) between H3 and H5.

To enone **17** were introduced a methyl group and an acyloxymethyl group regio- and stereoselectively by the following sequence. Luche reduction gave allyl alcohol **18**, of which the stereochemistry of the hydroxy group was inverted by Mitsunobu reaction to afford **19**. Simmons–Smith reaction[13] proceeded in the stereospecific manner to give the cyclopropane, which was oxidized to ketone **20**. The structure of **20** was determined by X-ray crystallography (Fig. 3).[9] Birch reduction with lithium naphthalenide opened the cyclopropane ring and the resulting enolate was alkylated with iodomethyl pivalate to yield oxadecalin **21**.

The total synthesis of epi-cochlioquinone A (**1**) was accomplished as Scheme 6. Treatment of ketone **21** with alumina in dichloromethane afforded enone **3** (Scheme 1), which was reacted with catechol **2** in the presence of boron trifluoride in one pot to give cyclized **24** as expected in our synthetic plan. Both the phenol and the secondary alcohol of **24** were acetylated, and the tertiary alcohol was protected as trimethylsilyl ether **25**. Epoxidation of the enol ether was followed by epoxide-opening methylation by



Scheme 4. Reagents and conditions: (a) HCl, MeOH, 50 °C, 12 h, 90%; (b) TBSCl, imidazole, DMF, −30 °C, 3 h, 90%; (c) MeMgBr, THF, −10 °C, 1 h, 91%; (d) IBX, Py, PhMe–DMSO, 50 °C, 12 h, 90%; (e) methyl acetoacetate, DBU, THF (degassed), 40 °C, 3 d, 42%; (f) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C, 1 h, 89%; (g) DEAD, Ph_3P, HCO_2H, PhMe, rt, 30 min, 79% **19**:**18** = 5:1; (h) 0.5 M Et_3N, MeOH, rt, 2 h, 91%; (i) Et_2Zn, CH_2I_2, TFA, CH_2Cl_2, 0 °C, 1 h, 83%; (j) PDC, MS4A, CH_2Cl_2, 0 °C, 1 h, 89%; (k) Li, naphthalene, THF, −78 °C, 15 min, then, ICH_2OPiv, −78 to −30 °C, 1 h, 60%.



Scheme 5. The mechanism of production of enone **17**.

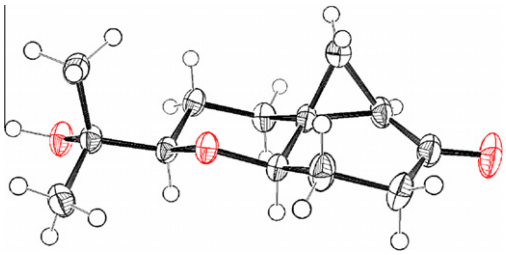


Figure 3. The ORTEP drawing of X-ray crystallography of **20**.

addition of trimethylaluminum to give tertiary alcohol **26** as a single isomer. De-hydration of **26** with thionyl chloride accompanied with de-O-silylation, and the sequential hydrogenation proceeded stereoselectively to give **27**. The stereochemistry of the C8 and C9 positions of **27** was determined by NOESY showing correlations between H5 and H9, H9 and H20, H20 and H11α, and H11β and H19. Oxidation of the protected hydroquinone **27** with cerium ammonium nitrate (CAN) introduced the hydroxy group at the benzylic position at first in the stereoselective manner (rt, 30 min) and then converted to quinone (rt, 1 day) to give epi-cochlioquinone A (**1**). This direct oxidation from **27** to **1** proceeded in 88% yield. Observation of NOE between H11 and H19 of the product **1** confirmed the stereochemistry of C11. The synthetic **1** was identical in all respects with the natural product including the optical rotation (synthetic **1**: $[\alpha]_D^{25}$ +42.2 (*c* 0.90, EtOH), natural: $[\alpha]_D^{25}$ +43.2 (*c* 0.95, EtOH)). Thus, the absolute structure of epi-cochlioquinone A (**1**) was determined as shown in Figure 1.

In conclusion, the first total synthesis and the structural determination of epi-cochlioquinone A (**1**) were achieved by [3+3] cycloaddition reaction with catechol **2** and enone **3**. Catechol **2** was synthesized from 6-nitrocyclohex-2-enone **10** by two kinds of methodologies including the hydrogen transfer reaction followed by the auto-redox-catalytic reaction converting o-aminophenol to catechol and oxidation of 6-nitrocyclohex-2-enone to *o*-quinone followed by reduction. Oxadecalin **21** was derived from glycosyl cyanide **14** by [3+3] cycloaddition reaction with ketone **16** and reductive alkylation with cyclopropylketone **20**. The absolute structure of epi-cochlioquinone A (**1**) was determined as shown in Figure 1.

Acknowledgments

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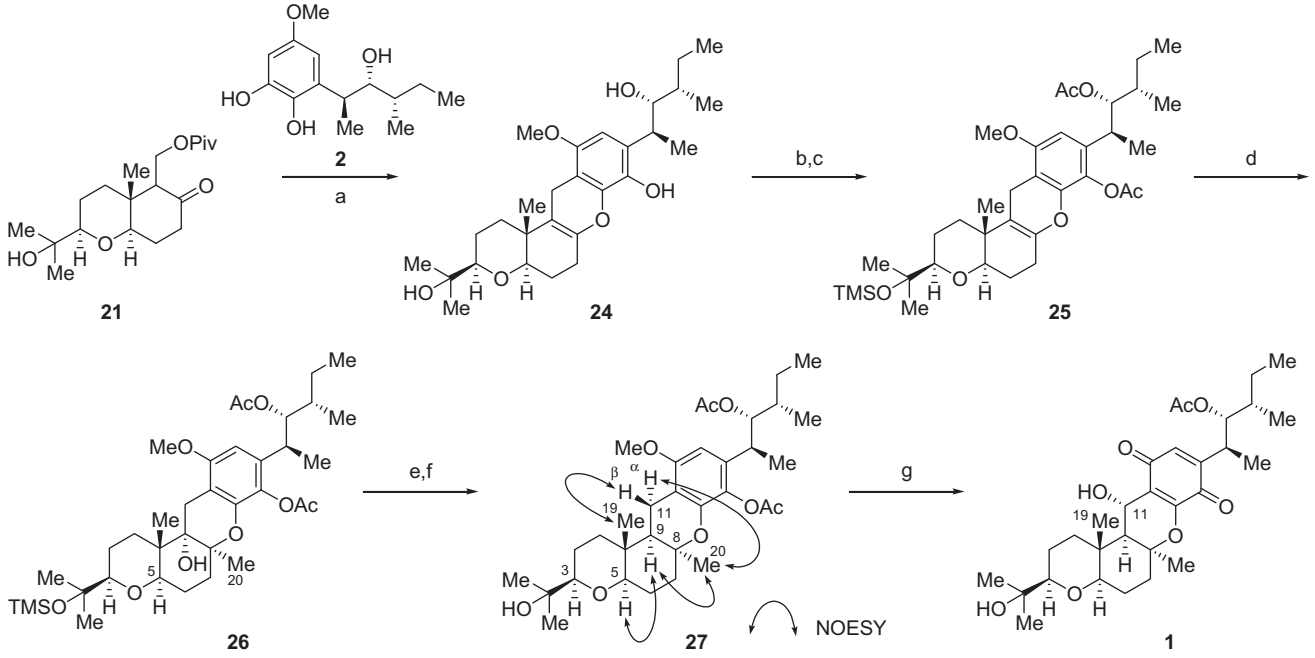
Supplementary data

Supplementary data (the spectrum data of compounds **2**, **6**, **7**, **8**, **10**, **11**, **13**, **16**, **17**, **20**, **21**, **24**, **26**, **27,** and synthetic epi-cochlioquinone A (**1**), and ^{1}H NMR spectrum (600 MHz in $CDCl_3$) and ^{13}C NMR spectrum (150 MHz in $CDCl_3$) of synthetic epi-cochlioquinone A (**1**)



Scheme 6. Reagents and conditions: (a) Al_2O_3 ,CH_2Cl_2, rt, 3 h, then $BF_3{\cdot}Et_2O$, −78 °C, then 0 °C, 2 h, 80%; (b) Ac_2O, pyridine, 50 °C, 6 h, 88%; (c) TMSOTf, 2,6-lutidine, CH_2Cl_2, rt, 30 min, 92%; (d) *m*CPBA, CH_2Cl_2, 0 °C, 15 min, then Me_3Al, 0 °C, 30 min, 81%; (e) $SOCl_2$, pyridine, rt, 30 min; (f) H_2, 10% Pd–C, EtOH, rt, 12 h, 84% in two steps; (g) CAN, aq CH_3CN, rt, 1 d, 88%.

associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.153.

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