HETEROCYCLES, Vol. 76, No. 1, 2008, pp. 699 - 713. © The Japan Institute of Heterocyclic Chemistry
Received, 28th March, 2008, Accepted, 16th April, 2008, Published online, 21st April, 2008. COM-08-S(N)67

TOTAL SYNTHESIS OF AN ENDOTHELIN CONVERTING ENZYME INHIBITOR, TMC-66

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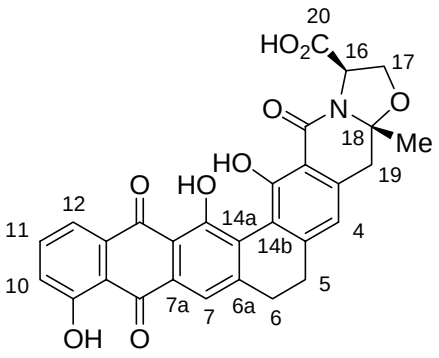
Dedicated to Professor Ryoji Noyori on the occation of his 70th birthday

Abstract – The first total synthesis and structural determination of TMC-66, an ECE inhibitor, was achieved in short steps by efficient construction of two tricyclic segments and coupling reactions. The oxidative coupling with phenols attaching to electron-withdrawing groups was realized with a novel copper (II) reagent.

INTRODUCTION

TMC-66 (**1**) was isolated as an endothelin converting enzyme (ECE) inhibitor by Tanabe Seiyaku group.[1] ECE inhibitors have been expected to be therapeutically useful chemicals for the treatment of diseases such as hypertension. The structure of TMC-66 (**1**) has been elucidated to contain the benzo[*a*]naphthacenequinone[2] skeleton fused with an amino acid component.[3] The relative stereochemistry of **1** was disclosed in 1999,[1] but the absolute stereochemistry remained unknown.



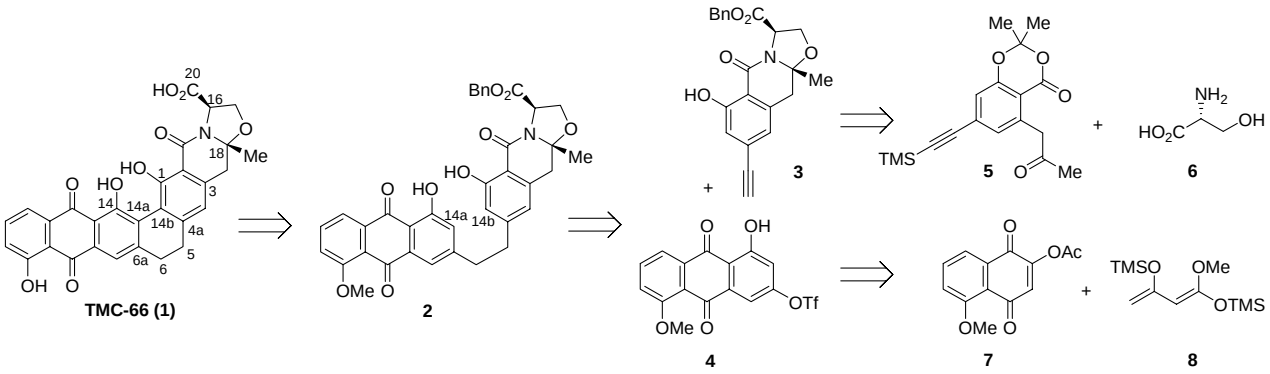
TMC-66 (**1**)

Figure 1. Structure of TMC-66 (**1**).

Although benzo[*a*]naphthacenequinones show a variety of bioactivities, few total syntheses have been accomplished.[4,5] Interested in the structure and bioactivities, we embarked on the enantioselective synthesis of TMC-66 (**1**). Herein, we present the first total synthesis and structural determination of TMC-66 (**1**).

RESULTS AND DISCUSSION

Our retrosynthetic analysis is shown in Scheme 1. The key step to construct the benzo[*a*]naphthacenequinone skeleton was intramolecular oxidative coupling between C14a and C14b of **2**, which possessed phenols with different electron-withdrawing groups. Oxidative coupling of phenols possessing electron-withdrawing groups is a challenging problem, including the control of regioselectivity. The precursor **2** should be constructed by Sonogashira coupling with similar-size segments **3** and **4**. Oxazolidine segment **3** would be afforded by condensation of ketoester **5** and D-serine (**6**). Anthraquinone **4** might be derived by Diels-Alder reaction of naphthoquinone **7** and diene **8**. Both segments, **3** and **4**, should be synthesized in short steps to establish efficiency and convergency.

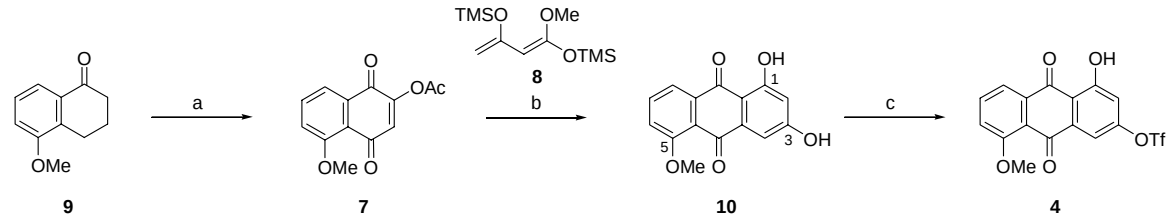


Scheme 1. Synthetic plan of TMC-66.

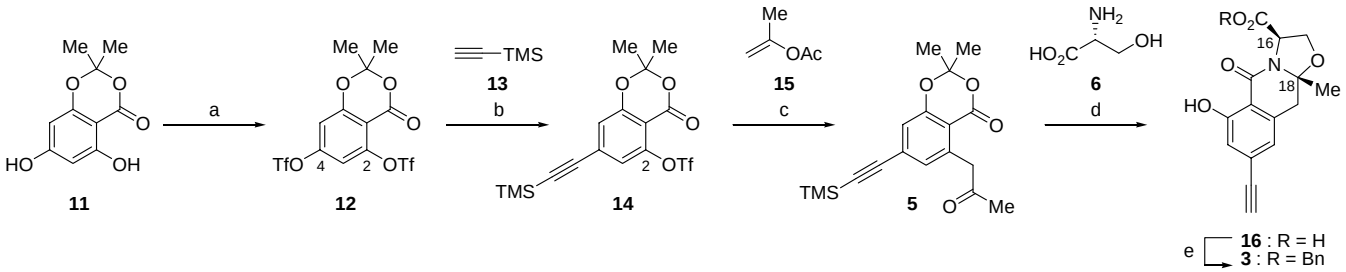
The anthraquinone segment **4** was constructed in three steps from a commercially available 5-methoxy-1-tetralone (**9**) (Scheme 2). The subsequent air oxidation[8] and acetylation gave naphthoquinone **7**. Diels-Alder reaction of **7** with **8** followed by aromatization with base afforded 1,3-dihydroxy-5-methoxyanthraquinone (**10**). Selective sulfonylation at O3 produced mono-triflate **4**, the anthraquinone segment.

Another segment **3** was synthesized from commercially available **11** (Scheme 3). Acetonide **11** was converted to bistriflate **12**, which was submitted to the regioselective Sonogashira coupling[7] with trimethylsilylacetylene (**13**) to afford monotriflate **14** in quantitative yield. The C2 position of the triflate **14** was substituted smoothly with the acetonyl group by Migita's procedure[8] in the presence of LiCl[9] and Buchwald ligand[10] to give ketoester **5**. Treatment of **5** with a mixture of D-serine (**6**, 1.2 eq.) and NaOMe (1.0 eq.) in MeOH at 60 °C provided tricyclic **16** as a single isomer. Trimethylsilyl group of **5** was quickly removed under these conditions to give *exo*-acetylene moiety. The resulting carboxylic acid **16**

was benzylated to give ester **3**, the oxazolidine segment. The methyl group of **3** was found *cis* to the ester group, indicating the stereochemistry of the C18 position as (*R*)-configuration, by nOe experiment (Figure 2). The mode of cyclization was determined by means of equations 1 and 2. Benzoisopyranone **17**, obtained by treatment of **5** with base, was submitted to the conditions of condensation of **5** and **6** (eq.1).[11] Although the product **16** was obtained, the reaction proceeded more slowly than that with ketoester **5**. Accordingly, benzoisopyranone **17** was not the intermediate of the transformation shown in Scheme 3. On the other hand, lactone **18**, missing the ketone moiety, did not react with serine (**6**) (eq. 2). Therefore, the mode of cyclization and construction of the C18 stereochemistry was explained as Scheme 4. Amino group of serine (**6**) attacked to ketone of **5** followed by lactam formation and dehydration to produce cationic intermediate **19**, which cyclized to give oxazolidine **16**. The preferred cyclization proceeded via **21** to avoid electrostatic repulsion between carboxylate group and the lactam carbonyl of conformer **20**.



Scheme 2. Synthesis of anthraquinone **4**. Reagents and conditions: (a) O_2, *t*-BuOK, *t*-BuOH, rt, 45 min, then Ac_2O, rt, 2 h, 47%; (b) **8**, toluene, 110 °C, 23 h, then pyridine, DMAP, 110 °C, 1.5 h, 70%; (c) TfCl, NaHMDS, HMPA, THF, 0 °C, 5 min, 74%.



Scheme 3. Synthesis of oxazolidine **3**. Reagents and conditions: (a) Tf_2O, pyridine, 0 °C, 5 min, 95%; (b) $PdCl_2(PPh_3)_2$, CuI, *i*-Pr_2NH, toluene, rt, 5 min, quant.; (c) *n*-Bu_3SnOMe, $Pd_2(dba)_3{\cdot}CHCl_3$, 2-diphenylphosphino-2'-(*N,N*-dimethylamino)biphenyl, LiCl, toluene, 110 °C, 5 min, 83 %; (d) NaOMe, MeOH, 60 °C, 1 d; (e) BnBr, Cs_2CO_3, HMPA, rt, 12 h, 72% in 2 steps.

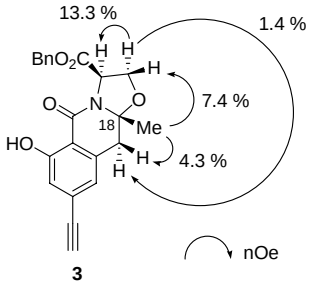
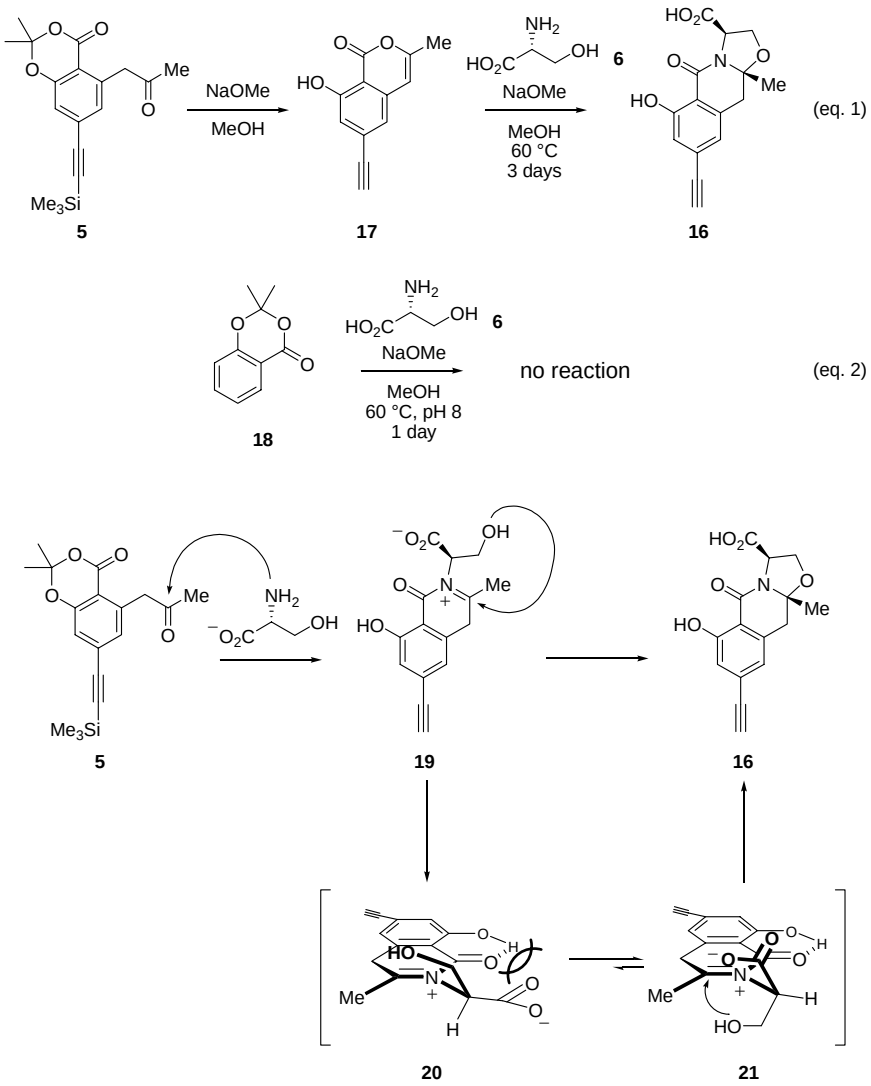


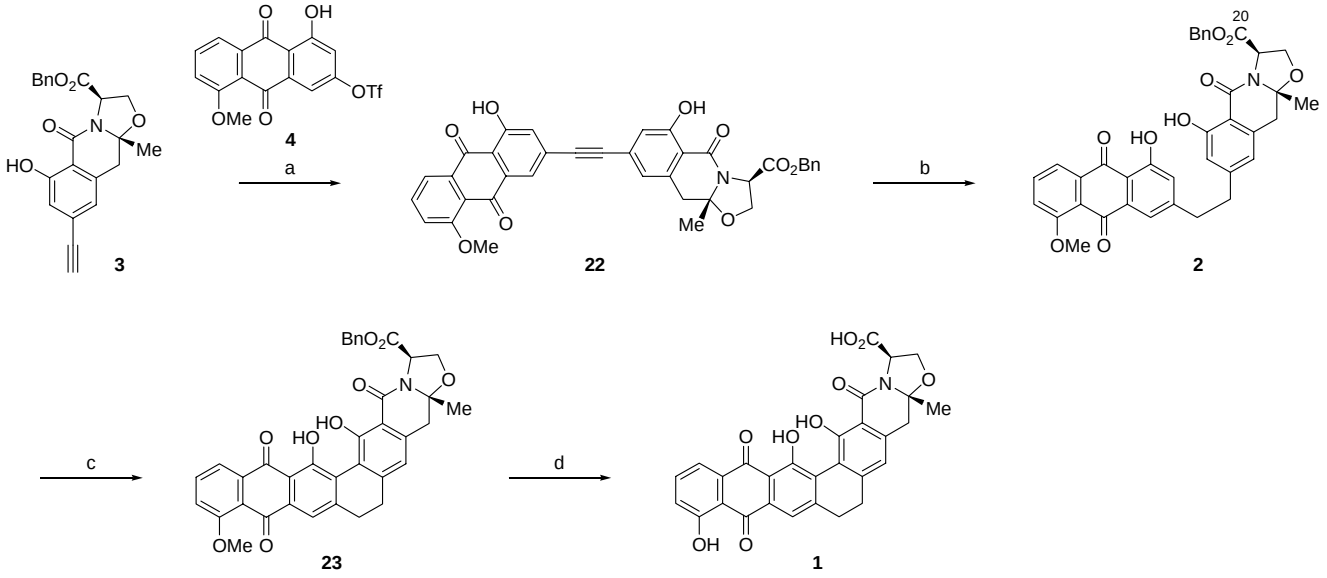
Figure 2. The structural determination of tricyclic **3**.



Scheme 4. The stereoselective construction of tricycle **16**.

Completion of the total synthesis of TMC-66 is shown in Scheme 5. Sonogashira coupling of **3** with **4** proceeded to give hexacycle **22**, which was selectively reduced at the acetylene moiety without cleavage of benzyl group to afford **2**. The next intramolecular oxidative coupling was problematic. Among a variety of known oxidants,[12] only Koga's reagent [CuCl(OH)·(TMEDA)][13] gave the desired heptacycle **23**, but in low yield (~20%). After a number of experiments, we found that the conditions including copper-*N*-methylimidazole (Cu-NMI) complex, prepared from CuCl and *N*-methylimidazole by Koga's procedure,[13] in refluxing DMF were effective to promote the oxidative coupling. The reaction proceeded regioselectively to afford **23** in 89% yield. Protection of the carboxylic acid of **2** was essential to the intramolecular oxidative coupling. The carboxylic acid derivative of **2** decomposed under various conditions of oxidative coupling and did not provide the corresponding heptacyclic product. The structure of **23** was confirmed by nOe and HMBC as shown in Figure 3. Correlations between H7 and C8, H12 and C13, and H4 and C19 were observed. Additionally, nOe was observed between H4 and H19. Thus,

oxidative coupling product **23** should possess the TMC-66 skeleton. Finally, de-O-methylation accompanied by the de-O-benzylation was realized by treatment of **23** with BBr_3 to give TMC-66 (**1**). The spectral data of the synthetic **1** were identical with those of the natural TMC-66. The reddish orange solution of the synthetic TMC-66 (**1**) was levorotatory, $[\alpha]_D^{26}$ –73° (*c* 0.09, $CHCl_3$), as that of brown sample of the natural product ($[\alpha]_D^{24}$ –327° (*c* 0.01, $CHCl_3$)).[1] Therefore, the total synthesis of TMC-66 was accomplished to determine its absolute configuration as (16*R*,18*R*)-configuration.



Scheme 5. Total synthesis of TMC-66 (**1**). Reagents and conditions: (a) $Pd(OAc)_2$, PPh_3, CuCl, *i*-Pr_2NH-DMF (1 : 5), rt, 5 min, 78%; (b) H_2, $RhCl(PPh_3)_3$, xylene, 120 °C, 50 min, 81%; (c) Cu-NMI complex, DMF, reflux, 1.75 h, 89%; (d) BBr_3, CH_2Cl_2, –78 °C, 30 min, 70%. NMI = *N*-methylimidazole.

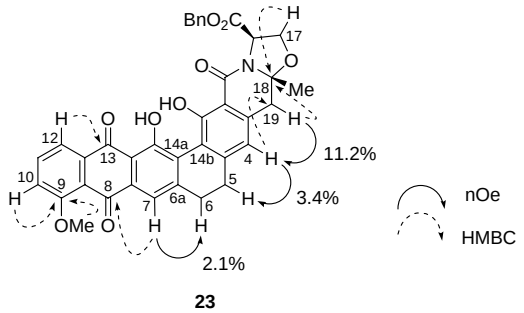


Figure 3. The structural determination of heptacyclic **23**.

The optical purity of the synthetic **1** was confirmed with a chiral 1,2-diphenylethane-1,2-diamine[14] by ^1H NMR (Figure 4). Racemic TMC-66 was synthesized from *dl*-serine as above. The spectrum A is ^1H NMR spectrum of a mixture of racemic TMC-66 and (1*R*, 2*R*)-1,2-diphenylethane-1,2-diamine in the ratio of 2:1, while the spectrum B is that of a mixture of synthetic (–)-TMC-66 (**1**) and (1*R*, 2*R*)-1,2-diphenylethane-1,2-diamine. The spectrum A shows that (+)- and (–)-TMC-66 are distinguishable in the presence of a chiral 1,2-diphenylethane-1,2-diamine. The protons around the chiral

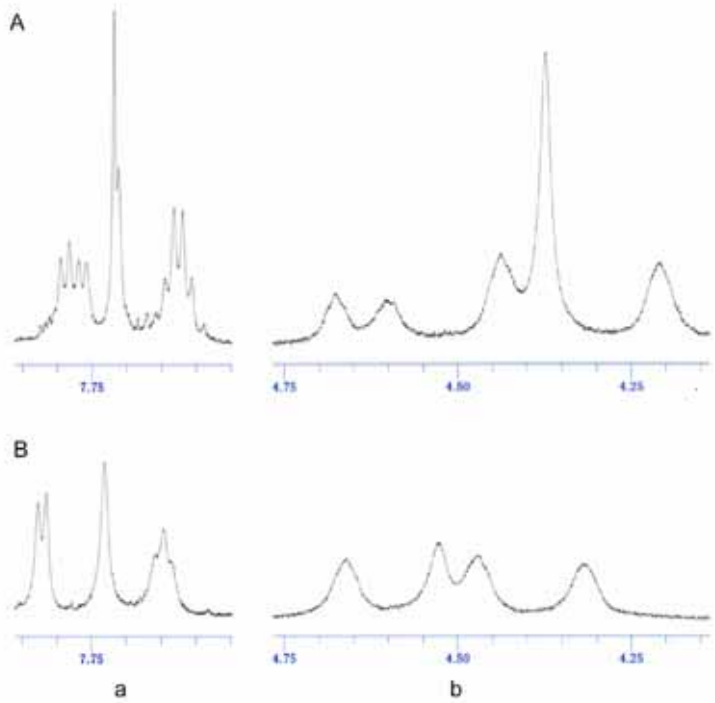


Figure 4. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C) spectra of (**A**): 2:1 mixture of racemic TMC-66 + (1*R*, 2*R*)-1,2-diphenylethane-1,2-diamine and (**B**): 2:1 mixture of synthetic (–)-TMC-66 (**1**) + (1*R*, 2*R*)-1,2-diphenylethane-1,2-diamine. (FromLeft side) a: H12, H7, H11, b: H16, C<u>H</u>-NH_2 of diamine, H17a, and H17b.

centers, including H16 and H17, and C*H*-N of the chiral amine were observed between 4.15 and 4.75 ppm. Although they are broadened, these spectra are obviously discerned. The peaks around δ 7.75 ppm are corresponding to H12, H7, and H11. Even these protons are far from the chiral centers (C16 and C18) of TMC-66, they are also distinguishable between (+)- and (–)-TMC-66 with spectrum A. Obviously, the spectrum B is that of highly optical pure TMC-66 (**1**). Therefore, the difference of the value of the optical rotation was due to the inherent color of TMC-66 (**1**).

In conclusion, the first total synthesis and structural determination of TMC-66 (**1**) have been achieved. The regioselective intramolecular oxidative coupling of **2** was realized in high yield using Cu-NMI complex as an oxidant. The efficient and stereoselective route to the benzo[*a*]naphthacenequinone fused with an oxazolidine ring possessing stereogenic centers has been established.

EXPERIMENTAL

General Methods

^{1}H NMR spectra were recorded at 600 MHz with Bruker AVANCE 600 instrument. Coupling constants (*J*) are reported in Hz. ^{13}C NMR spectra were recorded at 150 MHz with Bruker AVANCE 600 instrument. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to the residual

solvent peak. Melting point (mp) determinations were performed by using a Yanako MP-S3 instrument. FT-IR spectra were recorded at JEOL JIR-WINSPEC 50. HR-MS and MS were obtained with a JEOL JMS-SX102A. Optical rotations were measured with a JASCO DIP-370. Analytical thin layer chromatography was performed on 0.25 mm E. Merck silica gel plates ($60F_{254}$).

Syntheses

Proton numbering is corresponding to that of TMC-66 (Figure 1).

Quinone **7**

The following reaction was carried out under an oxygen atmosphere. A solution of compound **9** (10.1 mg, 57.3 μmol) in *t*-BuOH (500 μL) was stirred for 15 min, then potassium *tert*-butoxide (32.2 mg, 287 μmol) was added and the mixture was stirred at rt. After stirring for 45 min, acetic anhydride (500 μL) was added and the resulting mixture was stirred at rt for 2 h. After evaporation in vacuo, the crude residue was purified by flash column chromatography (hexane-EtOAc 2:1) to yield the quinone **7** as a yellow solid (6.6 mg, 26.8 μmol, 47%).

R_f = 0.38 (hexane-EtOAc 1 : 1). HR-MS (FAB+): calcd. for $C_{13}H_{11}O_5$: 247.0607, found 247.0605 $[M+H]^+$. mp 136.5-140.5 °C (decomp.) IR (cm^{-1}): 1770, 1658, 1587, 1184. ^1H NMR ($CDCl_3$, 600 MHz at 25 °C) δ (ppm): 2.37 (3H, s, Me of Ac), 4.01 (3H, s, OMe), 6.66 (1H, s, H-7a), 7.34 (1H, dd, J = 8.5 & 1.0 Hz, H-10), 7.69 (1H, dd, J = 8.5 & 7.5 Hz, H-11), 7.78 (1H, dd, J = 7.5 & 1.0 Hz, H-12). ^{13}C NMR ($CDCl_3$, 150 MHz at 25 °C) δ (ppm): 20.5, 56.6 118.6, 119.5, 119.8, 128.0, 133.2, 135.0, 152.3, 159.7, 167.7, 178.9, 183.7.

Tricycle **10**

To a solution of compound **7** (29.3 mg, 119 μmol) in toluene (476 μL) was added diene (**8**) (93.0 μL, 357 μmol) under an argon atmosphere and the mixture was heated at 110 °C for 23 h. To the reaction mixture was added pyridine (11.5 mL, 143 μmol) and *N*,*N*-dimethylaminopyridine (6.7 mg, 59.5 μmol) and stirred at 110 °C for 1.5 h. After evaporation in vacuo, acetone (400 μL) was added and the resulting precipitates were collected by filtration and dried in vacuo to yield the compound **10** as a yellow solid (22.5 mg, 83.3 μmol, 70%). R_f = 0.34 (toluene-EtOAc 2 : 1). HR-MS (FAB+): calcd. for $C_{15}H_{11}O_5$: 271.0607, found 271.0598 $[M+H]^+$. mp >300 °C. IR (cm^{-1}): 1627, 1340, 1288, 1160. ^1H NMR (DMSO-d_6, 600 MHz at 25 °C) δ (ppm): 3.91 (3H, s, OMe), 6.50 (1H, d, J = 2.5 Hz, H-14a), 7.00 (1H, d, J = 2.5 Hz, H-7), 7.53 (1H, dd, J = 8.5 Hz & 1.0 Hz, H-10), 7.77 (1H, dd, J = 7.5 Hz & 1.0 Hz, H-12), 7.80 (1H, dd, J = 8.5 Hz & 7.5 Hz, H-11), 11.23 (1H, s, HO-6a), 12.62 (1H, s, HO-14). ^{13}C NMR (DMSO-d_6, 150 MHz at 25 °C) δ (ppm): 56.6, 106.8, 108.1, 109.1, 118.8 119.3, 120.5, 135.1, 135.8, 136.8, 160.3, 164.5, 165.7, 180.5,

185.9.

Triflate **4**

To a cooled (0 °C) solution of compound **10** (1.02 g, 3.77 mmol) in THF (20 mL) and HMPA (2 mL) was added NaHMDS (1.90M, 2.19 mL, 4.15 mmol) under an argon atmosphere, and the mixture was stirred at 0 °C. After stirring for 15 min, trifluoromethanesulfonyl chloride (456 μL, 4.34 mmol) was added and stirred for 45 min at 0 °C. The reaction mixture was quenched with 1M HCl (5 mL) and the mixture was evaporated in vacuo. Then H_2O (10 mL) was added, and the mixture was extracted with EtOAc (2×30 mL). The combined extracts were evaporated in vacuo. The crude residue was purified by flash column chromatography (toluene-EtOAc 20:1) to yield the compound **4** as a yellow solid (1.11 g, 2.77 mmol, 74%). R_f = 0.45 (toluene-EtOAc 5 : 1). HR-MS (FAB+): calcd. for $C_{16}H_{10}F_3O_7S$: 403.0099, found 403.0076 $[M+H]^+$. mp 154.0-155.0 °C. IR (cm^{-1}): 3085, 1672, 1645, 1241, 1209. ^1H NMR ($CDCl_3$, 600 MHz at 25 °C) δ (ppm): 4.07 (3H, s, OMe), 7.15 (1H, d, J = 2.5 Hz, H-14a), 7.41 (1H, dd, J = 8.5 & 1.0 Hz, H-10), 7.65 (1H, d, J = 2.5 Hz, H-7), 7.79 (1H, dd, J = 8.5 & 7.5 Hz, H-11), 7.99 (1H, dd, J = 7.5 & 1.0 Hz, H-12), 12.60 (1H, s, HO-14). ^{13}C NMR ($CDCl_3$, 150 MHz at 25 °C) δ (ppm): 56.7, 112.1, 115.2, 115.5, 118.6 (q, J = 321 Hz, Tf), 119.0, 119.8, 120.8, 134.8, 135.8, 137.2, 154.5, 160.9, 163.6, 179.6, 187.7.

Bistriflate **12**

The following reaction was carried out under an argon atmosphere. To a cooled (0 °C) solution of compound **11** (40.7 mg, 194 μmol) in pyridine (400 μL) was added trifluoromethanesulfonic anhydride (81.5 μL, 484 mmol) and the mixture was stirred for 5 min. The reaction mixture was quenched with sat. aq. $NaHCO_3$ (200 μL) and extracted with EtOAc (3×600 μL). The combined extracts were evaporated in vacuo. The crude residue was purified by flash column chromatography (hexane-EtOAc 4:1) to yield the bistriflate **12** as a colorless solid (87.2 mg, 184 μmol, 95%). R_f = 0.74 (hexane-EtOAc 2 : 1). HR-MS (FAB+): calcd. for $C_{12}H_9F_6O_9S_2$: 474.9592, found 474.9572 $[M+H]^+$. mp 95.1-95.6 °C. IR (cm^{-1}): 1752, 1621, 1429, 1211, 1135. ^1H NMR ($CDCl_3$, 600 MHz at 25 °C) δ (ppm): 1.80 (6H, s, C<u>Me</u>$_2$), 6.93 (1H, d, J = 2.5 Hz, H-4), 7.04 (1H, d, J = 2.5 Hz, H-14b). ^{13}C NMR ($CDCl_3$, 150 MHz at 25 °C) δ (ppm): 25.5, 107.8, 108.2, 110.7, 111.2, 118.5 (q, J = 321 Hz, Tf), 118.7 (q, J = 321 Hz, Tf), 149.6, 153.2, 155.8, 158.3.

Acetylene **14**

To a solution of compound **12** (59.9 mg, 126 μmol) in toluene (1.2 mL) was added diisopropylamine (25.0 μL, 253 μmol), $PdCl_2(PPh_3)_2$ (8.9 mg, 12.6 μmol), and CuI (2.4 mg, 12.6 μmol) under an argon

atmosphere. The mixture was stirred at rt for 5 min, then trimethylsilylacetylene (**13**) (19.6 μL, 139 μmol) was added. After stirring for 5 min, the reaction mixture was evaporated in vacuo. The crude residue was purified by flash column chromatography (hexane-EtOAc 3:1) to yield the compound **14** as a colorless solid (53.4 mg, 126 μmol, quant.). R_f = 0.60 (hexane-EtOAc 3 : 1). HR-MS (FAB+): calcd. for $C_{16}H_{18}F_3O_6SSi$: 423.0545, found 423.0527 $[M+H]^+$. mp 94.4-96.0 °C. IR (cm^{-1}): 1751, 1621, 1558, 1207, 1139. ^1H NMR ($CDCl_3$, 600 MHz at 25 °C) δ (ppm): 0.27 (9H, s, Si$\underline{Me}_3$), 1.75 (6H, s, C$\underline{Me}_2$), 7.02 (1H, d, J = 1.5 Hz, H-4), 7.10 (1H, d, J = 1.5 Hz, H-14b). ^{13}C NMR ($CDCl_3$, 150 MHz at 25 °C) δ (ppm): –0.5, 25.5, 101.1, 102.4, 107.0, 107.9, 118.7 (q, J = 322 Hz, Tf), 119.6, 120.8, 131.5, 148.4, 156.7, 157.1.

Ketoester **5**

To a solution of isopropenyl acetate (1.07 mL, 9.72 mmol) in toluene (1.2 mL) was added tributyltin methoxide (1.96 mL, 6.81 mmol) under an argon atmosphere, and the mixture was heated at 110 °C for 20 min. After cooling to ambient temperature, to the mixture were added $Pd_2(dba)_3$•$CHCl_3$ (152 mg, 166 μmol), 2-diphenylphosphino-2'-(*N,N*-dimethylamino)biphenyl (381 mg, 999 μmol), and LiCl (282 mg, 6.66 mmol). After heating at 110 °C for 5 min, a solution of compound **14** (703 mg, 1.66 mmol) in toluene (2.4 mL) was added. After 5 min at the elevated temperature, the reaction mixture was evaporated in vacuo. The crude residue was purified by flash column chromatography (hexane-EtOAc 7:1) to yield the compound **5** as a colorless solid (456 mg, 1.38 mmol, 83%). R_f = 0.45 (hexane-EtOAc 2 : 1). HR-MS (FAB+): calcd. for $C_{18}H_{23}O_4Si$: 331.1366, found 331.1357 $[M+H]^+$. mp 102.0-103.3 °C. IR (cm^{-1}): 2962, 2161, 1733, 1612, 1284, 844. ^1H NMR ($CDCl_3$, 600 MHz at 25 °C) δ (ppm): 0.25 (9H, s, Si$\underline{Me}_3$), 1.71 (6H, s, C$\underline{Me}_2$), 2.30 (3H, s, Me-21), 4.14 (2H, s, H-19), 6.92 (1H, d, J = 1.5 Hz, H-4), 6.99 (1H, d, J = 1.5 Hz, H-14b). ^{13}C NMR ($CDCl_3$, 150 MHz at 25 °C) δ (ppm): –0.3, 25.6, 30.2, 48.8, 99.3, 102.9, 105.9, 112.6, 119.6, 129.6, 130.1, 138.8, 156.7, 160.6, 204.7.

Oxazolidine **3**

The following reaction was carried out under an argon atmosphere. To a solution of D-serine (**6**) (2.0 mg, 19 μmol) in MeOH (100 μL) was added sodium methoxide (5.2 mg, 16 μmol), and the mixture was stirred at 0 °C for 10 min. Then compound **5** (5.2 mg, 16 μmol) was added, and the mixture was heated at 60 °C. After stirring for 1 day, the reaction mixture was evaporated in vacuo to give the crude tricycle **16** as single isomer, which was used in the next step without further purification.

To a solution of the crude tricyclic **16** in HMPA (100 μL) was added Cs_2CO_3 (10 mg, 32 μmol) and BnBr (3.8 μL, 32 μmol) under an argon atmosphere, and the mixture was stirred at rt for 12 h. The reaction mixture was quenched with H_2O (100 μL) and extracted with toluene (3×200 μL). The combined extracts were evaporated in vacuo. The crude residue was purified by flash column chromatography

(hexane-EtOAc 4:1) to yield the compound **3** as a colorless solid (4.4 mg, 12 μmol, 72%). R_f = 0.50 (hexane-EtOAc 2 : 1). HR-MS (FAB+): calcd. for $C_{22}H_{20}NO_5$: 378.1341, found 378.1361 $[M+H]^+$. $[\alpha]_D^{28}$ –48.7° (*c* 1.02, $CHCl_3$). mp 107.9-108.6 °C. IR (cm^{-1}): 3282, 2958, 2111, 1749, 1641, 1465, 1189. ^1H NMR ($CDCl_3$, 600 MHz at 25 °C) δ (ppm): 1.46 (3H, d, *J* = 1.0 Hz, Me-21), 3.05 (1H, d, *J* = 15.0 Hz, H-19), 3.11 (1H, dq, *J* = 15.0 Hz & 1.0 Hz, H-19), 3.18 (1H, s, H-6), 4.16 (1H, dd, *J* = 9.0 & 7.0 Hz, H-17), 4.50 (1H, dd, *J* = 9.0 & 8.5 Hz, H-17), 4.83 (1H, dd, *J* = 8.5 & 7.0 Hz, H-16), 5.25 (1H, d, *J* = 12.5 Hz, O-C$\underline{H}_2$-Ph), 5.27 (1H, d, *J* = 12.5 Hz, O-C$\underline{H}_2$-Ph), 6.82 (1H, br s, H-4), 6.98 (1H, br s, H-14b), 7.32-7.43 (5H, m, Ph) , 11.51 (1H, s, HO-1). ^{13}C NMR ($CDCl_3$, 150 MHz at 25 °C) δ (ppm): 22.6, 40.6, 56.4, 67.5, 67.7, 79.8, 82.4, 94.3, 110.6, 120.1, 122.4, 128.1, 128.3, 128.6, 128.7, 134.9, 135.9, 160.8, 164.3, 169.3.

Enlactone **17**

To a solution of compound **5** (29.6 mg, 89.6 μmol) in methanol (890 μL) was added sodium methoxide (4.8 mg, 89.6 μmol) under an argon atmosphere, and the mixture was stirred at 60 °C. After stirring for 7 h, the reaction mixture was evaporated in vacuo. Then H_2O (250 μL) and sat. aq. $KHSO_4$ (20 μL) were added, and the products were extracted with EtOAc (500 μL, then 300 μL). The combined extracts were evaporated in vacuo. The crude residue was purified by flash column chromatography (hexane-EtOAc 3:1) to yield **17** as a colorless solid (15.5 mg, 77.4 μmol, 86 %). R_f = 0.45 (hexane-EtOAc 2 : 1). FAB-MS: 201 $[M+H]^+$. ^1H NMR ($CDCl_3$, 400MHz at 25 °C) δ (ppm): 2.28 (3H, br s, Me), 3.26 (1H, s, H-6), 6.21 (1H, br s, H-19), 6.90 (1H, br s, H-14b), 7.00 (1H, br s, H-4), 10.95 (1H, s, OH). H-6, H-14b, and H-19 are interchangeable. ^{13}C NMR ($CDCl_3$, 400MHz at 25 °C) δ (ppm): 19.4, 80.9, 82.2, 104.2, 105.7, 117.8, 118.7, 130.9, 137.9, 154.7, 161.3, 166.3.

Hexacycle **22**

To a solution of the compound **4** (20.5 mg, 50.9 μmol) in DMF (400μL) and diisopropylamine (100μL) were added $Pd(OAc)_2$ (2.4mg, 10.2μmol), PPh_3 (8.0 mg, 30.5 μmol), and CuCl (5.0 mg, 50.9μmol) under an argon atmosphere. The mixture was stirred at rt for 5 min. A solution of compound **3** (19.2 mg, 50.9 μmol) in DMF (400μL) was added at rt. After stirring for 5 min, the reaction mixture was quenched with sat. aq. $KHSO_4$ (100 μL) and extracted with toluene (3×400 μL). The combined extracts were evaporated in vacuo. The crude residue was purified by flash column chromatography (toluene-EtOAc 7:1) to yield the hexacycle **22** as a yellow solid (25.0 mg, 39.7 μmol, 78%). R_f = 0.42 (toluene-EtOAc 3 : 1). HR-MS (FAB+): calcd. for $C_{37}H_{28}NO_9$: 630.1764, found 630.1768 $[M+H]^+$. $[\alpha]_D^{26}$ –43.2° (*c* 0.99, $CHCl_3$). mp 230.3-237.4 °C (dec.). IR (cm^{-1}): 2923, 2210, 1749, 1670, 1635, 1284, 709. ^1H NMR ($CDCl_3$, 600 MHz at 25 °C) δ (ppm): 1.49 (3H, s, Me-21), 3.11 (1H, d, *J* = 15.0 Hz, H-19), 3.15 (1H, d, *J* = 15.0 Hz, H-19),

4.07 (3H, s, OMe), 4.18 (1H, dd, *J* = 9.0 & 7.0 Hz, H-17), 4.51 (1H, dd, *J* = 9.0 & 8.5 Hz, H-17), 4.85 (1H, dd, *J* = 8.5 & 7.0 Hz, H-16), 5.26 (1H, d, *J* = 13.0 Hz, O-C$\underline{H}_2$-Ph), 5.28 (1H, d, *J* = 13.0 Hz, O-C$\underline{H}_2$-Ph), 6.92 (1H, s, H-4), 7.06 (1H, s, H-14b), 7.35 (1H, d, *J* = 1.5 Hz, H-14a), 7.33-7.43 (6H, m, H-10 & Ph), 7.76 (1H, dd, *J* = 8.0 & 8.0 Hz, H-11), 7.87 (1H, d, *J* = 1.5 Hz, H-7), 7.98 (1H, dd, *J* = 8.0 & 1.0 Hz, H-12), 11.60 (1H, s, HO-1), 12.46 (1H, s, HO-14). ^{13}C NMR ($CDCl_3$, 150 MHz at 25 °C) δ (ppm): 22.6, 40.6, 56.5, 56.7, 67.5, 67.7, 90.3, 92.9, 94.3, 110.9, 115.4, 118.7, 119.6, 119.8, 121.3, 122.2, 122.5, 125.1, 128.1, 128.3, 128.6, 128.7, 131.2, 135.0, 135.0, 135.3, 135.3, 136.1, 160.7, 160.9, 161.8, 164.3, 169.3, 181.0, 188.0.

Hexacycle **2**

To a solution of the compound **22** (101 mg, 160 μmol) in xylene (2.0 mL) was added $RhCl(PPh_3)_3$ (57.0 mg, 61.6 μmol), and the mixture was heated at 120 °C for 50 min under hydrogen atmosphere. After cooling to ambient temperature, the reaction mixture was directly purified by flash column chromatography (toluene-EtOAc 7:1) to yield the compound **2** as a yellow solid (82.5 mg, 130 μmol, 81%). R_f = 0.37 (toluene-EtOAc 3 : 1). HR-MS (FAB+): calcd. for $C_{37}H_{32}NO_9$: 634.2077, found 634.2088 $[M+H]^+$. $[\alpha]_D^{27}$ –32.8° (*c* 1.02, $CHCl_3$). mp 200.8-203.6 °C. IR (cm^{-1}): 2923, 1749, 1670, 1635, 1278, 796. ^{1}H NMR ($CDCl_3$, 600 MHz at 25 °C) δ (ppm): 1.46 (3H, s, Me-21), 2.90-2.95 (2H, m, H-5 & H-6), 2.98-3.05 (3H, m, H-5, H-6, & H-19), 3.10 (1H, d, *J* = 15.0 Hz, H-19), 4.05 (3H, s, OMe), 4.16 (1H, dd, *J* = 9.0 & 7.0 Hz, H-17), 4.48 (1H, dd, *J* = 9.0 & 8.5 Hz, H-17), 4.82 (1H, dd, *J* = 8.5 & 7.0 Hz, H-16), 5.25 (1H, d, *J* = 12.5 Hz, O-C$\underline{H}_2$-Ph), 5.27 (1H, d, *J* = 12.5 Hz, O-C$\underline{H}_2$-Ph), 6.51 (1H, s, H-4), 6.70 (1H, s, H-14b), 7.02 (1H, d, *J* = 1.5 Hz, H-14a), 7.32-7.42 (6H, m, H-10 & Ph) , 7.62 (1H, d, *J* = 1.5 Hz, H-7), 7.74 (1H, dd, *J* = 8.0 & 7.5 Hz, H-11), 7.97 (1H, dd, *J* = 7.5 & 1.0 Hz, H-12), 11.43 (1H, s, HO-1), 12.42 (1H, s, HO-14). ^{13}C NMR ($CDCl_3$, 150 MHz at 25 °C) δ (ppm): 22.7, 36.7, 37.4, 40.8, 56.4, 56.6, 67.5, 67.6, 94.4, 108.6, 114.0, 116.1, 118.4, 119.4, 119.4, 119.7, 121.6, 122.3, 128.3, 128.6, 128.7, 135.0, 135.1, 135.1, 135.5, 136.0, 148.2, 151.5, 160.6, 161.3, 162.2, 164.7, 169.5, 181.9, 188.0.

Heptacycle **23**

Preparation of copper-N-methylimidazole complex

The following reaction was carried out under an oxygen atmosphere. To a solution of CuCl (496 mg, 5.01 mmol) in 95% aq. MeOH was added *N*-methylimidazole (1.60 mL, 20.0 mmol), and the mixture was stirred at rt for 1 h. The resulting precipitates were collected by filtration, washed with acetone, and dried in vacuo to give the desired copper-*N*-methylimidazole complex as a dark green powder (1.29 g). mp 149.7-151.3 °C (decomp.)

Synthesis of compound ***23***

The following reaction was carried out under air. To a solution of the compound **2** (6.0 mg, 9.5 μmol) in DMF (300 μL) was added Cu-NMI complex (8.0 mg, 29 μmol), and the mixture was heated at 155 °C for 1.75 h. After cooling to 0 °C, the reaction mixture was quenched with sat. aq. $KHSO_4$ (100 μL) and extracted with EtOAc (3×300 μL). The combined extracts were evaporated in vacuo. The crude residue was purified by flash column chromatography (toluene-EtOAc 7:1) to yield the heptacycle **23** as an orange solid (5.3 mg, 8.4 μmol, 89%). R_f = 0.32 (toluene-EtOAc 3 : 1). HR-MS (FAB+): calcd. for $C_{37}H_{30}NO_9$: 632.1921, found 632.1931 $[M+H]^+$. $[\alpha]_D^{25}$ –115.5° (*c* 1.08, $CHCl_3$). mp 143.4-152.2 °C. IR (cm^{-1}): 2946, 1749, 1662, 1627, 1272, 750. ^1H NMR ($CDCl_3$, 600 MHz at 25 °C) δ (ppm): 1.54 (3H, s, Me-21), 2.61-3.03 (4H, m, H-5 & H-6), 3.11 (1H, d, *J* = 15.0 Hz, H-19), 3.18 (1H, d, *J* = 15.0 Hz, H-19), 4.06 (3H, s, OMe), 4.20 (1H, dd, *J* = 9.0 & 7.0 Hz, H-17), 4.50 (1H, dd, *J* = 9.0 & 8.0 Hz, H-17), 4.86 (1H, dd, *J* = 8.0 & 7.0 Hz, H-16), 5.26 (1H, d, *J* = 12.0 Hz, O-C$\underline{H}_2$-Ph), 5.29 (1H, d, *J* = 12.0 Hz, O-C$\underline{H}_2$-Ph), 6.68 (1H, s, H-4), 7.35 (1H, dd, *J* = 8.5 & 1.0 Hz, H-10), 7.32-7.45 (5H, m, Ph) , 7.70 (1H, s, H-7), 7.73 (1H, dd, *J* = 8.5 & 8.0 Hz, H-11), 8.01 (1H, dd, *J* = 8.0 & 1.0 Hz, H-12), 12.58 (1H, br s, HO-1), 13.48 (1H, br s, HO-14). ^{13}C NMR ($CDCl_3$, 150 MHz at 25 °C) δ (ppm): 22.8, 30.3, 30.7, 40.7, 56.6, 56.7, 67.6, 67.7, 94.2, 109.4, 114.8, 117.8, 118.0, 118.2, 119.5, 121.5, 126.3, 128.3, 128.6, 128.7, 133.4, 135.0, 135.1, 135.8, 136.0, 147.6, 149.6, 159.5, 159.5, 160.4, 165.3, 169.5, 182.0, 188.5. ^1H NMR ($CDCl_3$, 600 MHz at 50 °C) δ (ppm): 1.53 (3H, s, Me-21), 2.65-2.95 (4H, m, H-5 & H-6), 3.08 (1H, d, *J* = 15.0 Hz, H-19), 3.17 (1H, d, *J* = 15.0 Hz, H-19), 4.04 (3H, s, OMe), 4.20 (1H, dd, *J* = 9.0 & 6.5 Hz, H-17), 4.47 (1H, dd, *J* = 9.0 & 8.5 Hz, H-17), 4.86 (1H, dd, *J* = 8.5 & 6.5 Hz, H-16), 5.26 (1H, d, *J* = 12.0 Hz, O-C$\underline{H}_2$-Ph), 5.28 (1H, d, *J* = 12.0 Hz, O-C$\underline{H}_2$-Ph), 6.65 (1H, s, H-4), 7.33 (1H, dd, *J* = 8.5 & 1.0 Hz, H-10), 7.30-7.43 (5H, m, Ph) , 7.68 (1H, s, H-7), 7.71 (1H, dd, *J* = 8.5 & 7.5 Hz, H-11), 8.01 (1H, dd, *J* = 7.5 & 1.0 Hz, H-12), 12.46 (1H, br s, HO-1), 13.36 (1H, br s, HO-14). ^{13}C NMR ($CDCl_3$, 150 MHz at 50 °C) δ (ppm): 23.0, 30.4, 30.8, 40.9, 56.6, 56.8, 67.7, 67.7, 94.3, 109.6, 114.9, 117.7, 117.9, 118.5, 119.2, 119.6, 121.9, 126.5, 128.3, 128.5, 128.7, 133.6, 134.9, 135.3, 136.0, 136.1, 147.6, 149.6, 159.4, 159.7, 160.5, 165.3, 169.5, 181.9, 188.5.

TMC-66 (**1**)

The following reaction was carried out under an argon atmosphere. To a cooled (–78 °C) solution of the compound **23** (5.3 mg, 8.4 μmol) in CH_2Cl_2 (650 μL) was added boron tribromide (1.0 M in CH_2Cl_2, 42.0 μL, 42 μmol) and the mixture was stirred at –78 °C for 0.5 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ (100 μL) and stirred at 0 °C for 0.5 h. The mixture was added sat. aq. $KHSO_4$ (200 μL) and the mixture was extracted with EtOAc (2×650 μL). The combined extracts were evaporated in vacuo. The crude residue was purified by flash column chromatography (toluene-EtOAc 3:1 0.5% aq. TFA) to yield

the TMC-66 (**1**) as a red solid (3.1 mg, 5.9 μmol, 70%). R_f = 0.50 ($CHCl_3$-MeOH 3 : 1). HR-MS(FAB+): calcd. for $C_{29}H_{22}NO_9$: 528.1295, found 528.1289 $[M+H]^+$. $[\alpha]_D^{26}$ –60.0° (*c* 0.01, $CHCl_3$), $[\alpha]_D^{26}$ –73.3° (*c* 0.09, $CHCl_3$). mp 215-220 °C (dec.). IR (cm^{-1}): 3446, 2950, 1733, 1616, 1270, 754. ^{1}H NMR ($CDCl_3$, 600 MHz at 25 °C) δ (ppm): 1.52 (3H, s, Me-21), 2.59-3.08 (4H, m, H-5 & H-6), 3.17 (1H, d, *J* = 15.5 Hz, H-19), 3.25 (1H, d, *J* = 15.5 Hz, H-19), 4.56 (2H, d, *J* = 8.0 Hz, H-17), 4.88 (1H, t, *J* = 8.0 Hz, H-16), 6.73 (1H, s, H-4), 7.31 (1H, dd, *J* = 8.5 & 1.0 Hz, H-10), 7.68 (1H, dd, *J* = 8.5 & 7.5 Hz, H-11), 7.77 (1H, s, H-7), 7.87 (1H, dd, *J* = 7.5 & 1.0 Hz, H-12), 12.15 (1H, br s, HO-1), 12.68 (1H, s, HO-9), 13.68 (1H, br s, HO-14). ^{13}C NMR ($CDCl_3$, 150 MHz at 25 °C) δ (ppm): 22.7, 30.2, 30.4, 40.6, 56.7, 66.3, 94.2, 108.6, 115.2, 116.1, 117.9, 118.2, 119.2, 119.4, 124.7, 128.0, 131.5, 133.5, 136.5, 136.7, 148.7, 149.3, 159.4, 160.3, 162.6, 166.7, 170.3, 187.9, 187.9. ^{1}H NMR (DMSO-d_6, 600 MHz at 25 °C) δ (ppm): 1.43 (3H, s, Me-21), 2.55-3.11 (4H, m, H-5 & H-6), 3.18 (1H, d, *J* = 15.0 Hz, H-19), 3.25 (1H, d, *J* = 15.0 Hz, H-19), 4.15 (1H, dd, *J* = 9.0 & 7.0 Hz, H-17), 4.56 (1H, dd, *J* = 9.0 & 8.5 Hz, H-17), 4.71 (1H, dd, *J* = 8.5 & 7.5 Hz, H-16), 6.87 (1H, s, H-4), 7.40 (1H, dd, *J* = 8.0 & 1.0 Hz, H-10), 7.73 (1H, s, H-7), 7.78 (1H, dd, *J* = 7.5 & 1.0 Hz, H-12), 7.83 (1H, dd, *J* = 8.0 & 7.5 Hz, H-11), 12.52 (1H, s, HO-9), 12.81 (1H, s, HO-1 or HO-14), 13.37 (1H, br s, HO-1 or HO-14). ^{13}C NMR (DMSO-d_6, 150 MHz at 25 °C) δ (ppm): 22.4, 29.1, 29.6, 39.9, 56.3, 67.2, 93.5, 108.8, 114.5, 115.8, 117.6, 117.8, 117.8, 118.9, 124.4, 127.7, 130.8, 133.1, 137.0, 137.1, 147.3, 149.5, 158.3, 159.3, 161.5, 164.2, 170.8, 187.3, 187.4. ^{1}H NMR (DMSO-d_6, 600 MHz at 90 °C) δ (ppm): 1.45 (3H, s, Me-21), 2.65-3.00 (4H, m, H-5 & H-6), 3.17 (2H, s, H-19), 4.16 (1H, dd, *J* = 8.5 & 6.0 Hz, H-17), 4.50 (1H, dd, *J* = 8.5 & 8.0 Hz, H-17), 4.72 (1H, dd, *J* = 8.0 & 6.0 Hz, H-16), 6.82 (1H, s, H-4), 7.36 (1H, dd, *J* = 6.5 & 3.0 Hz, H-10), 7.72 (1H, s, H-7), 7.77-7.83 (2H, m, H-11 & H-12). ^{13}C NMR (DMSO-d_6, 150 MHz at 90 °C) δ (ppm): 22.4, 29.1, 29.6, 39.9, 56.3, 67.2, 93.5, 108.8, 114.5, 115.8, 117.6, 117.8, 117.8, 118.9, 124.4, 127.9, 130.8, 133.1, 137.0, 137.1, 147.3, 149.5, 158.4, 159.3, 161.5, 164.2, 170.8, 187.3, 187.4.

ACKNOWLEDGEMENTS

This work was financially supported by the 21COE program “Center for Practical Nano-Chemistry”, the Consolidated Research Institute for Advanced Science and Medical Care, the Global COE program “Center for Practical Chemical Wisdom”, and Scientific Research on Priority Area “Creation of Biologically Functional Molecules” from the Ministry of Education, Culture, Sports, Science and Technology.

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