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The first total synthesis and structural determination of TMC-66

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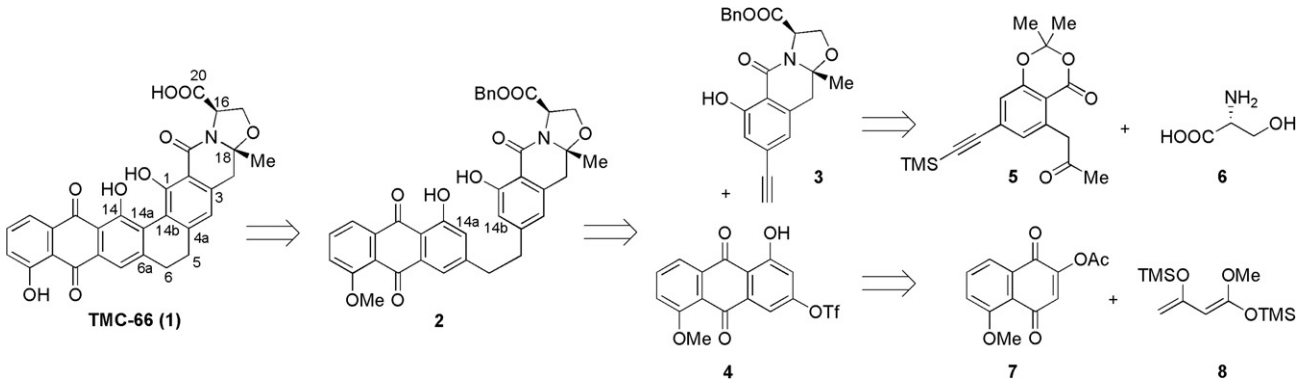
Abstract—The first total synthesis and structural determination of TMC-66, an ECE inhibitor, was achieved in short steps by efficient construction and coupling of segments. The oxidative coupling with phenols attaching to electron-withdrawing groups was realized with a novel copper(II) reagent.

TMC-66 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. TMC-66 has the benzo[*a*]naphthacenequinone[2,3] skeleton fused with an amino acid component. 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**).

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 included phenols attaching to different electron-withdrawing groups. Oxidative coupling with phenols possessing strongly electron-withdrawing groups is a challenging problem as well as control of regioselectivity. Precursor **2** should be constructed by Sonogashira coupling with same size segments **3** and **4**. Tricyclic **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. Retrosynthetic analysis of TMC-66.

Keywords: Total synthesis; Structural determination; TMC-66; Oxidative coupling; ECE inhibitor.
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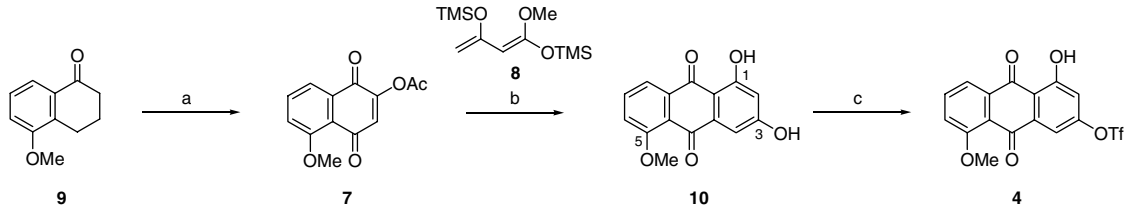
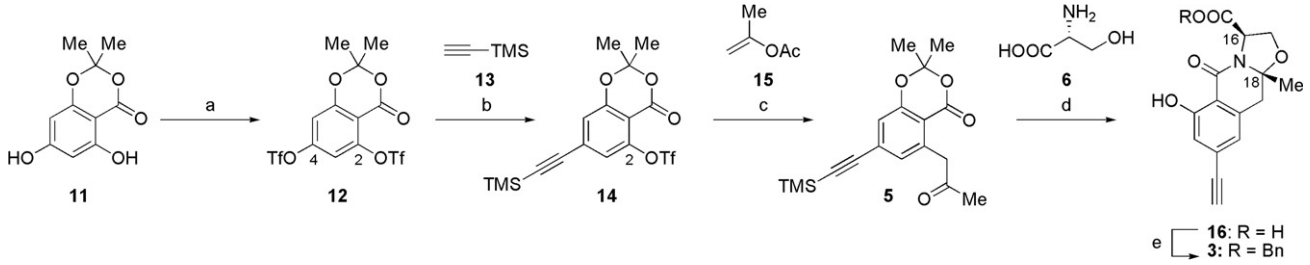


Scheme 2. Synthesis of anthraquinone **4**. Reagents and conditions: (a) O_2, *t*-BuOK, *t*-BuOH, rt, 45 min, then Ac_2O, rt, 2 h, 47%; (b) **8**, toluene, 110 °C, 23 h, then pyridine, DMAP, 110 °C, 1.5 h, 70%; (c) TfCl, NaHMDS, HMPA, THF, 0 °C, 5 min, 74%.



Scheme 3. Synthesis of oxazolidine **3**. Reagents and conditions: (a) Tf_2O, pyridine, 0 °C, 5 min, 91%; (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 two steps.

The anthraquinone segment **4** was constructed in three steps from a commercially available 5-methoxy-1-tetralone (**9**) (Scheme 2). The subsequent air oxidation[4] and acetylation gave naphthoquinone **7**. Diels–Alder reaction of **7** with **8** followed by aromatization 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[5] with trimethylsilylacetylene (**13**) to afford monotriflate **14** in quantitative yield. The C2 position of triflate **14** was substituted smoothly with the acetonyl group by Migita's procedure[6] in the presence of LiCl[7] and Buchwald ligand[8] to give keto-ester **5**. Treatment of **5** with a mixture of D-serine (**6**, 1.2 equiv) and NaOMe (1.0 equiv) in MeOH at 60 °C provided tricyclic **16** as single isomer. Trimethylsilyl group of **5** was removed quickly under these conditions to give *exo*-acetylene moiety. The resulting carboxylic acid **16** was benzylated to give ester **3**, the counter part of anthraquinone **4**. Methyl group of **3** was found cis to the ester group by NOE experiment (Fig. 1). Thus, the stereochemistry of the C18 position was determined as (*R*)-configuration.

Connection of fragments **3** and **4**, and completion of total synthesis of TMC-66 are shown in Scheme 4. Sonogashira coupling of **3** with **4** proceeded to give hexacyclic **17**, which was reduced selectively at acetylene moiety without cleavage of benzyl group to afford **2**. The next intramolecular oxidative coupling was problematic. Among a variety of known oxidants,[9] only Koga's reagent [CuCl(OH)·(TMEDA)][10] gave the desired heptacyclic **18**, but in low yield (~20%). After a number

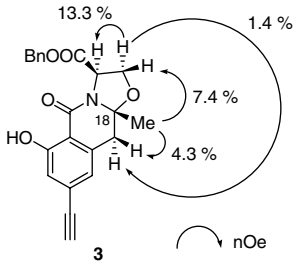
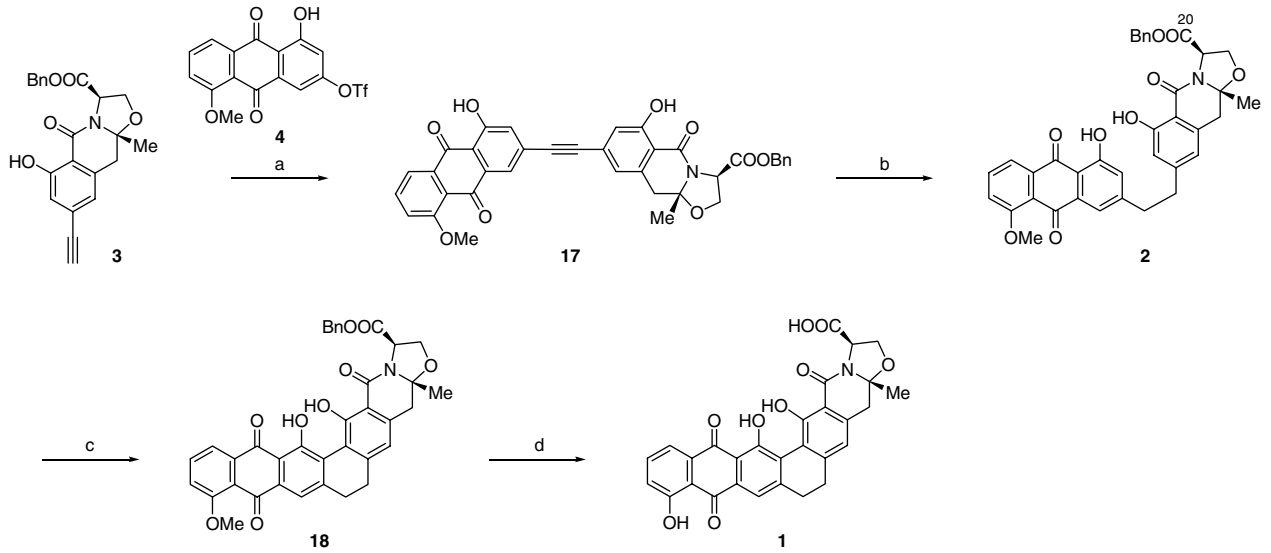


Figure 1. The structural determination of tricyclic **3**.

of experiments, we found that the conditions including $CuCl(OH){\cdot}(NMI)_2$ in refluxing DMF were effective to promote the oxidative coupling. The reaction proceeded regioselectively to afford **18** in 89% yield. Protection of the carboxylic acid group 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 **18** was confirmed by NOE and HMBC as shown in Figure 2. Correlation 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 **18** should possess the TMC-66 skeleton. Finally, de-O-methylation accompanied with de-O-benzylation was realized by treatment of **18** with BBr_3 to give TMC-66 (**1**). The spectral data of synthetic **1** was identical with that of the natural TMC-66. The reddish orange solution of the synthetic TMC-66 (**1**) shows the optical rotation $[\alpha]_D^{26}$ −73.3 (*c* 0.09, $CHCl_3$), levorotatory as the brown sample of the natural product ($[\alpha]_D^{24}$ −327 (*c* 0.01, $CHCl_3$)).[1] Thus, the total synthesis of TMC-66 was accomplished to determine its absolute configuration as (16*R*,18*R*)-configuration.



Scheme 4. 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) $CuCl(OH)\cdot(NMI)_2$, DMF, reflux, 1.75 h, 89%; (d) BBr_3, CH_2Cl_2, −78 °C, 30 min, 70%. NMI = *N*-methylimidazole.

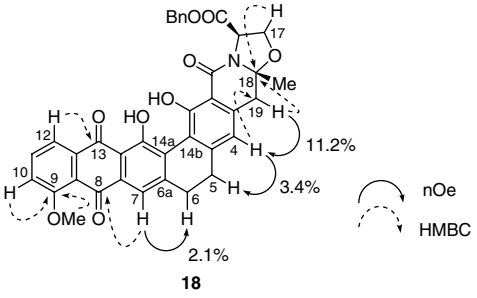


Figure 2. The structural determination of heptacyclic **18**.

The optical purity of synthetic **1** was confirmed with a chiral 1,2-diphenylethane-1,2-diamine[11] by ^1H NMR (Fig. 3). The spectrum A is that of a mixture of racemic TMC-66[12] and (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine, while spectrum B is that of a mixture of synthetic (−)-TMC-66 (**1**) and (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine. The peaks around δ 7.75 ppm were corresponding to H12, H7, and H11, and those of δ 4.50 ppm were corresponding to H16, H17 (two protons), and CH–N of the chiral diamine. The spectrum A shows that (+)- and (−)-TMC-66 are distinguishable in the presence of a chiral 1,2-diphenylethane-1,2-diamine. Obviously, spectrum B is that of highly optical pure TMC-66 (**1**). Thus, 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 $CuCl(OH)\cdot(NMI)_2$ as an oxidant. The efficient and stereoselective route to the benzo[*a*]naphthacenequinone fused with an oxazolidine ring possessing stereogenic centers has been established.

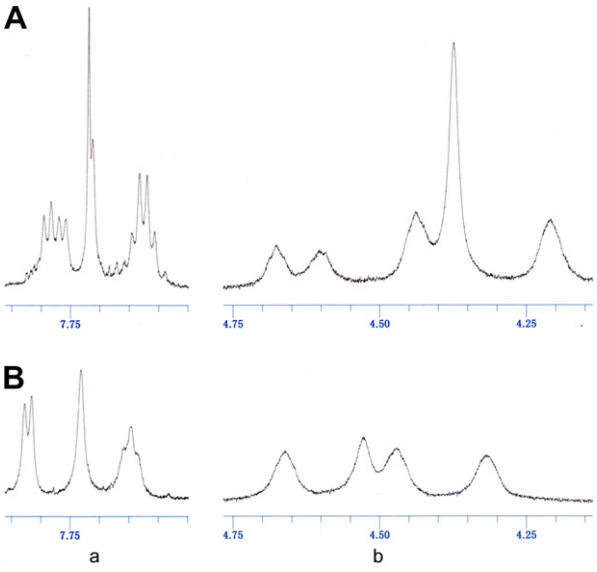


Figure 3. ^1H NMR (600 MHz, $CDCl_3$, 25 °C) spectra of (**A**): 2:1 mixture of racemic TMC-66 + (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine and (**B**): 2:1 mixture of synthetic (−)-TMC-66 (**1**) + (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine. (From left side) (a) H12, H7, H11; (b) H16, C*H*–NH_2 of diamine, H17a, and H17b.

Acknowledgments

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Supplementary data

The spectrum data of compounds **2**, **3**, **4**, **5**, **17**, **18**, and synthetic **1**, and ^{1}H and ^{13}C NMR spectra (600 MHz in $CDCl_3$ and in DMSO-d_6) of synthetic **1**, ^{1}H NMR spectra of a 2:1 mixture of racemic **1** and (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine, and those of a 2:1 mixture of synthetic **1** and (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine are presented in the Supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.037.

References and notes

1. Asai, Y.; Nonaka, N.; Suzuki, S.; Nishio, M.; Takahashi, K.; Shima, H.; Ohmori, K.; Ohnuki, T.; Komatsubara, S. *J. Antibiot.* **1999**, *52*, 607–612.
2. Related natural products: (a) Ōmura, S.; Nakagawa, A. *J. Am. Chem. Soc.* **1986**, *108*, 6088–6089; (b) Takeuchi, T.; Hara, T.; Naganawa, H.; Okada, M.; Hamada, M.; Umezawa, H.; Gomi, S.; Sezaki, M.; Kondo, S. *J. Antibiot.* **1988**, *41*, 807–811; (c) Oki, T.; Konishi, M.; Tomatsu, K.; Tomita, K.; Saitoh, K.; Tsunakawa, M.; Nishio, M.; Miyaki, T.; Kawaguchi, H. *J. Antibiot.* **1988**, *41*, 1701–1704; (d) Tsurumi, Y.; Ohhata, N.; Iwamoto, T.; Shigematsu, N.; Sakamoto, K.; Nishikawa, M.; Kiyoto, S.; Okuhara, M. *J. Antibiot.* **1994**, *47*, 619–630; (e) Ritzau, M.; Vettermann, R.; Fleck, W. F.; Gutsche, W.; Dornberger, K.; Gräfe, U. *J. Antibiot.* **1997**, *50*, 791–793; (f) Kondo, S.; Ikeda, Y.; Ikeda, D. *J. Antibiot.* **1998**, *51*, 232–234; (g) Tsukamoto, M.; Nakajima, S.; Arakawa, H.; Sugiura, Y.; Suzuki, H.; Hirayama, M.; Kamiya, S.; Teshima, Y.; Kondo, H.; Kojiri, K.; Suda, H. *J. Antibiot.* **1998**, *51*, 908–914; (h) Sontag, B.; Müller, J. G.; Hansske, F. G. *J. Antibiot.* **2004**, *57*, 823–828.
3. For total synthesis of natural products possessing the related structure; (±)-cervinomycins: (a) Kelly, T. R.; Jagoe, C. T.; Li, Q. *J. Am. Chem. Soc.* **1989**, *111*, 4522–4524; (b) Rao, A. V. R.; Yadav, J. S.; Reddy, K. K.; Upender, V. *Tetrahedron Lett.* **1991**, *32*, 5199–5202; (c) Mehta, G.; Shah, S. R.; Venkateswarlu, Y. *Tetrahedron* **1994**, *50*, 11729–11742; (+)-Benanomicin B: (d) Ohmori, K.; Tamiya, M.; Kitamura, M.; Kato, H.; Oorui, M.; Suzuki, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3871–3874.
4. (a) Hocquaux, M.; Jacquet, B.; Vidril-Robert, D.; Maurette, M.-T.; Oliveros, E. *Tetrahedron Lett.* **1984**, *25*, 533–536; (b) Ameer, F.; Giles, R. G. F.; Green, I. R.; Pearce, R. *Synth. Commun.* **2004**, *34*, 1247–1258.
5. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.
6. (a) Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 242–246; (b) Kosugi, M.; Hagiwara, I.; Migita, T. *Chem. Lett.* **1983**, 839–840.
7. Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630–4632.
8. (a) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360–1370; (b) Gaertzen, O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465–475; (c) Liu, P., ; Lanza, T. J., Jr.; Jewell, J. P.; Jones, C. P.; Hagmann, W. K.; Lin, L. S. *Tetrahedron Lett.* **2003**, *44*, 8869–8871.
9. Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469.
10. Noji, M.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1994**, *35*, 7983–7984.
11. Fulwood, R.; Parker, D. *J. Chem. Soc., Perkin Trans. 2* **1994**, 57–64; For a review on NMR determination of enantiomeric purity, see: Parker, D. *Chem. Rev.* **1991**, *91*, 1441–1457.
12. Racemic TMC-66 was synthesized from racemic serine by disclosed procedure.