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The first total synthesis and structural determination of TMC-264

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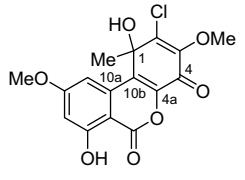
Abstract

The first total synthesis and structural determination of TMC-264 has been accomplished. Regioselective bromination, regioselective methoxymethylation, and nickel(0)-Lewis acid-mediated cyclization afforded multi-functionalized 1-methyl-dibenzo[*b*,*d*]-pyran skeleton.

Keywords: Total synthesis; Absolute configuration; TMC-264; Antiallergic agent; Regioselective methoxymethylation; Biaryl coupling

TMC-264 (**1**) was isolated as an inhibitor of IL-4 signaling from the fermentation broth of a fungus *Phoma* sp. TC 1674 by Tanabe Seiyaku group in 2003.[1] This compound has been found to inhibit selectively both tyrosine phosphorylation of STAT6 and the complex formation of phosphorylated STAT6 with its recognition sequence. TMC-264 has been expected as an antiallergic agent.[1,2] The structure of TMC-264 was elucidated to be the tricyclic structure including chloro-1*H*-dibenzo[*b*,*d*]pyran-4,6-dione skeleton (Fig. 1). However, the absolute configuration has not been determined yet. The unique structure and remarkable bioactivity stimulated us to synthesize TMC-264 (**1**).



TMC-264 (**1**)

Fig. 1. Structure of TMC-264 (**1**).

The synthetic plan of TMC-264 (**1**) is shown in Scheme 1. Compound **1** would be synthesized from bis(aryl halide) **2** by intramolecular aryl–aryl coupling followed by oxidation. Compound **2** should be provided by esterification with **3** and **4**. The per-substituted phenol **3** might be derived from the commercially available **5** by successive regioselective functionalization.

Regioselective synthesis of **3** was achieved as shown in Scheme 2 and Table 1. Selective de-O-methylation of **5** to afford **6** was realized in high yield by the treatment of **5** with 1 equiv of boron tribromide. Regioselective bromination of **6** was accomplished with *N*-bromosuccinimide, which promoted the reaction to give C6-brominated product predominantly. The structure of the resulting monobromide **7** was determined by the observation of NOE between H4 and OMe. It is quite interesting that bromination proceeded at C6 position superior to C4, although the electron density of C4 carbon was higher than C6 by ^{13}C NMR (δ_{C4} 104.0, δ_{C6} 109.2, Fig. 2). Catechol **7** was chlorinated to afford **8**. The next regioselective methoxymethylation to yield **3** was problematic. The normal conditions including methoxymethyl chloride and Hünig base promoted non-selective methoxymethylation (Table 1, entries 1 and 2). The structure of **3** was confirmed by NOE between C3–O*Me* and CH_2 in MOM ether, while **9** showed NOE between C3–O*Me* and OH (Fig. 3). After numerous examinations, we found that the addition of zinc(II) salt

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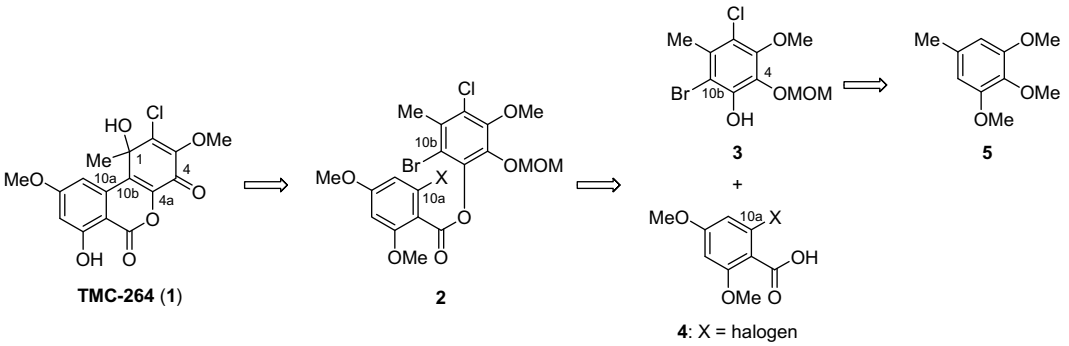
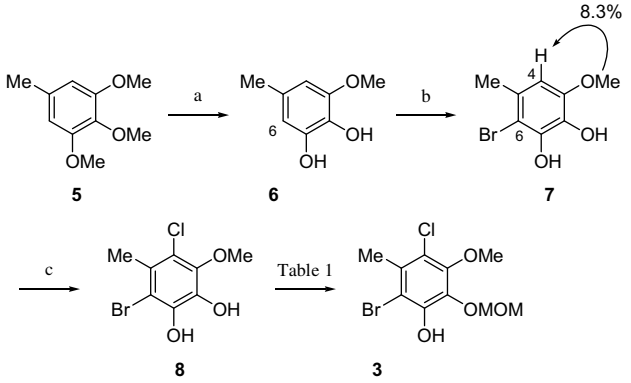


Scheme 1. Retrosynthetic analysis of TMC-264 (**1**).



Scheme 2. Reagents and conditions: (a) BBr_3, CH_2Cl_2, 0 °C, 5 min, 87%; (b) NBS, CCl_4, 0 °C, 1 day, 80% (**7**); (c) NCS, THF, rt, 1 h, 61%.

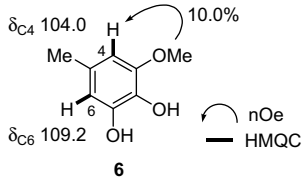


Fig. 2.

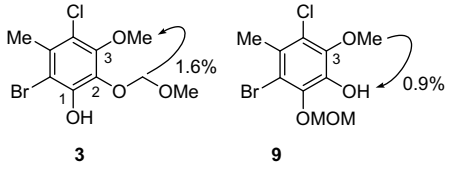
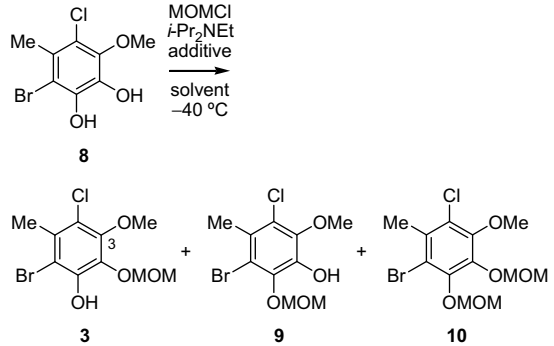


Fig. 3.

Table 1
Regioselective methoxymethylation with diol **8**

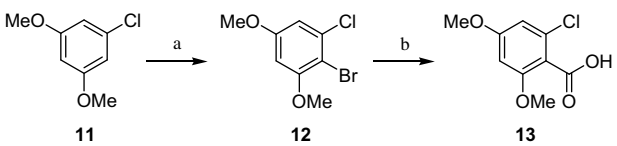


Entry	Additive (equiv)	Solvent	Isolated yield (%)		
			3	**9**	**10**
1	—	CH_2Cl_2	24	20	30
2	—	DMF	16	34	13
3	$Zn(OAc)_2{\cdot}2H_2O$ (1.0)	CH_2Cl_2	27	20	41
4	$Zn(OAc)_2{\cdot}2H_2O$ (1.0)	DMF	62	21	16
5	$ZnCl_2$(1.0)	DMF	83	13	2
6	$ZnCl_2$(0.2)	DMF	64	15	12

was effective for the regioselective alkylation. Zinc acetate preformed the regioselective methoxymethylation in DMF (entry 4). The best result was provided with 1 equiv of zinc chloride to give desired **3** in 83% yield (entry 5). Zinc chloride worked as catalyst to promote methoxymethylation in regioselective manner (entry 6), however, the isolated yield of **3** was decreased in comparison with the stoichiometric reaction. Therefore, per-substituted phenol **3** was synthesized in four steps from commercially available **5**.

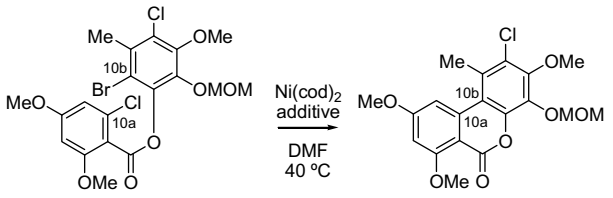
The halogenated carboxylic acid **4** was prepared in two steps from the commercially available **11** (Scheme 3). 5-Chloro-1,3-dimethoxybenzene (**11**) was brominated regioselectively to provide **12**, which was converted to carboxylic acid **13** (**4**: X = Cl) by lithiation followed by the addition of CO_2.

The first total synthesis of TMC-264 was accomplished as shown in Scheme 4. Carboxylic acid **13** was converted



Scheme 3. Reagents and conditions: (a) NBS, $(CH_2Cl_2)_2$, 60 °C, 5 h, 90%; (b) *s*-BuLi, PhMe, −78 °C, 10 min, then CO_2 (gas), rt, 30 min, 87%.

Table 2
Ni(0)-mediated cyclization with bis(arylhalide) **14**



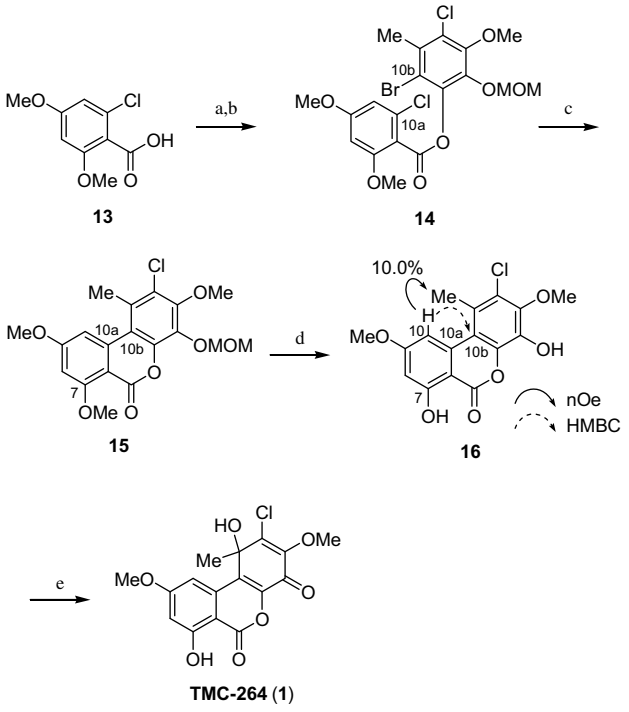
14 **15**

Entry	Additive	**14** (%)	**15** (%)	Time (h)
1	None	No reaction		18
2	Et_3Al	80	9	18
3	Et_2AlCl	68	23	18
4	$EtAlCl_2$	0	77	1

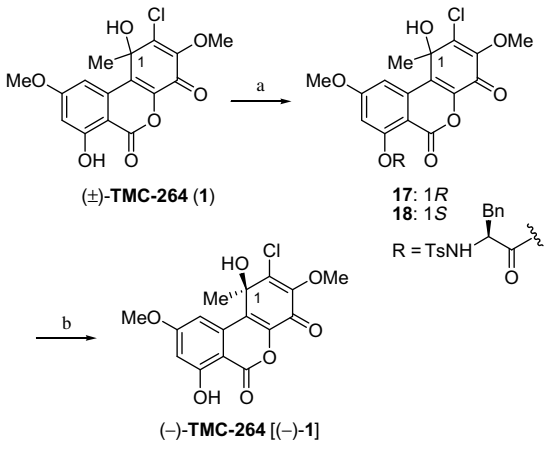
to acid chloride to promote esterification with phenol **3**. 10a-Chloro-10b-bromoester **14** was submitted to Ni(0)-mediated cyclization (Table 2). Treatment of **14** with $Ni(cod)_2$ at 40 °C resulted in no reaction (entry 1).[3] After numerous experiments, we found that aluminum reagents were effective for the coupling reaction (entries 2–4). Triethylaluminum, known as reductant for Ni(II) species,[4] afforded the desired product in low yield, and 80% of starting material was recovered (entry 2). Diethylaluminum chloride also worked to give **15**, but the reaction proceeded slowly yet (entry 3).[5] The best result was obtained by using ethylaluminum dichloride, which dramatically promoted the cyclization to afford **15** in high yield (entry 4). Therefore, the role of aluminum reagents was not as reductant but as Lewis acid to promote the oxidative addition of nickel(0) in this reaction. Eventually, Ni(0)-Lewis acid-mediated cyclization and successive selective de-O-methylation at C7 concomitant with de-O-methoxymethylation of the crude **15** gave biphenol **16** in 70% yield (Scheme 4). The tricyclic structure was confirmed with **16** by NOE between H10 and Me as well as HMBC between H10 and C10b. Finally, oxidation in the presence of [bis-(salicylidene)ethylenediamine]cobalt (salcomine) under oxygen atmosphere afforded (±)-TMC-264 (**1**).[6] The synthetic **1** was identical with natural product in all spectrometric aspects including ^1H and ^{13}C NMR, IR, and MS, completing the first total synthesis.

The absolute stereochemistry of (−)-TMC-264 [(−)-(**1**)], the natural form, was determined by optical resolution and X-ray crystallography (Scheme 5). Racemic TMC-264 [(±)-(**1**)] was submitted to esterification with *N*-Ts-L-phenylalanyl chloride. The resulting diastereo-mixture, including L-phenylalanates **17** and **18**, was separated by silica gel column chromatography. Treatment of each diastereomer with 4-dimethylaminopyridine in pyridine containing 5% water provided optically pure TMC-264. Recrystallization of optically pure (−)-(**1**) from toluene gave single crystals ($[\alpha]_D^{22}$ −40.9 (*c* 0.66, $CHCl_3$) [natural $[\alpha]_D^{25}$ −43.8 (*c* 0.5, $CHCl_3$)]), which were suitable to perform X-ray crystallography (Fig. 4).[7] The Flack parameter[8] obtained for structure **1** was 0.01(2). Therefore, the natural form (−)-TMC-264 was determined as 1*R* configuration. Optically pure (+)-(**1**) also provided single crystals to be determined as 1*S* configuration by X-ray crystallography.[7–9]

In conclusion, the first total synthesis of TMC-264 was accomplished and the structural determination of (−)-TMC-264 was achieved. Subsequent regioselective transformation of phenols including de-O-methylation, bromination, and O-methoxymethylation gave per-substituted phenol **3** in short steps. Intramolecular Ni(0)-medi-



Scheme 4. Reagents and conditions: (a) $(COCl)_2$, DMF, CH_2Cl_2, 40 °C, 5 h, (b) **3**, Py, 50 °C, 16 h, 82% (two steps), (c) $Ni(cod)_2$, $EtAlCl_2$, DMF, 40 °C, 1 h; (d) BCl_3, CH_2Cl_2, −15 °C, 5 min, 70% (2 steps); (e) O_2, salcomine, MeCN, rt, 2.5 h, 62%.



Scheme 5. Reagents and conditions: (a) *N*-tosyl-L-phenylalanyl chloride, pyridine, CH_2Cl_2, rt, 10 h, 58% (**17**:**18** = 1:1); (b) DMAP, pyridine, rt, 1 day, 91% for (−)-**1**, 89% for (+)-**1**.

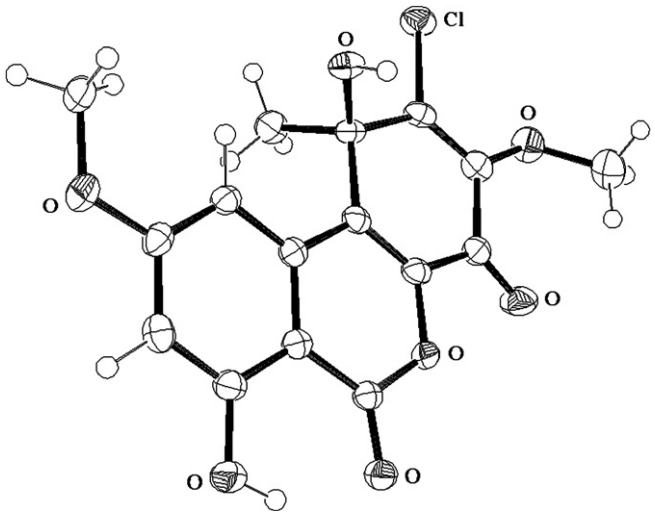


Fig. 4. ORTEP drawing of (−)-TMC-264 (**1**), the natural form.

ated biaryl coupling was achieved with 10a-chloro-10b-bromoester **14** in the presence of ethylaluminum dichloride. X-ray crystallography of each optically active TMC-264 confirmed the absolute structure of the natural product to be 1*R* configuration.

Acknowledgments

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Supplementary data

The spectrum data of compounds **3**, **6**, **7**, **13**, **14**, **16**–**18**, (−)- **1** and (+)-**1**, ^{1}H NMR spectrum (400 MHz in $CDCl_3$), and ^{13}C NMR (100 MHz in $CDCl_3$) spectrum of synthetic (±)-TMC-264 (**1**) are provided. The experimental procedures of selective de-O-methylation to yield **6**, selective methoxymethylation to afford **3**, and Ni(0)-Lewis acid-mediated biaryl coupling followed by deprotection to give **16** were also disclosed. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.074.

References and notes

1. (a) Sakurai, M.; Nishio, M.; Yamamoto, K.; Okuda, T.; Kawano, K.; Ohnuki, T. *J. Antibiot.* **2003**, *56*, 513–519; (b) Sakurai, M.; Nishio, M.; Yamamoto, K.; Okuda, T.; Kawano, K.; Ohnuki, T. *Org. Lett.* **2003**, *5*, 1083–1085.
2. Arai, M.; Tomoda, H.; Matsumoto, A.; Takahashi, Y.; Woodruff, B. H.; Ishiguro, N.; Kobayashi, S.; Omura, S. *J. Antibiot.* **2001**, *54*, 554–561.
3. (a) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 7547–7560; (b) Semmelhack, M. F.; Helquist, P.; Jones, L. D.; Keller, L.; Mendelson, L.; Ryono, L. S.; Smith, J. G.; Stauffer, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 6460–6471.
4. (a) Yamamoto, T.; Yamamoto, A. *J. Organomet. Chem.* **1973**, *57*, 127–137; (b) Fischer, K.; Jonas, K.; Misbach, P.; Stabba, R.; Wilke, G. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 943–1026.
5. Et_2AlCl and $EtAlCl_2$ were reported to promote the reductive elimination of dialkylnickel. Pennington, B. T.; Howell, J. E. *J. Organomet. Chem.* **1977**, *136*, 95–102.
6. Bozell, J. J.; Hames, B. R. *J. Org. Chem.* **1995**, *60*, 2398–2404.
7. Crystallographic data (excluding structure factors) for the structures of (−)-**1** and (+)-**1** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 680809 for (−)-**1** and 680810 for (+)-**1**.
8. Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39* , 876–881.
9. The Flack parameter of (+)-**1**, obtained for the structure of the enantiomer of **1**, was 0.03(5).