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The first total synthesis and structural determination of YCM1008A

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Dedicated to the memory of the late Professor Yoshihiko Ito

Abstract—The first total synthesis and structural determination of YCM1008A, a Ca^{2+} signaling inhibitor, have been achieved. The *N*-methoxy pyrano-pyridone moiety was synthesized by successive O- and N-conjugate additions with diketoamide **15**. The absolute structure was determined to be (2*R*,3*R*,4*S*,8′*R*)-configuration.
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YCM1008A (**1**) was reported as Ca^{2+}-signaling inhibitor from *Fusarium* sp. by Kyowa Hakko Kogyo group in 2007.[1] The structure of **1** was determined as a *N*-methoxy pyrano-pyridone with an aliphatic side chain. Although the relative configuration of the pyran moiety was determined, the C8′ stereochemistry and the absolute configuration of **1** remained unknown. The striking structure as well as bioactivities embarked us to the total synthesis of this natural product. Herein, we present the first total synthesis and structural determination of YCM1008A (**1**).

To determine the absolute stereochemistry of **1** as well as establish synthesis of a functionalized pyrano-pyridone, the synthetic plan shown in Scheme 1 was set up. A diastereomeric mixture of **2a** (2*R*,3*R*,4*S*,8′*R*) and **2b** (2*S*,3*S*,4*R*,8′*R*), and another mixture of **2c** (2*R*,3*R*,4*S*,8′*S*) and **2d** (2*S*,3*S*,4*R*,8′*S*) would be synthesized apart. We anticipated that each mixture would be separated by attaching a chiral auxiliary at the hydroxyl group. Precursor **3** might be synthesized from β-ketoamide **5** via intermediary **4**, which could be submitted to two cyclization to construct the pyrano-pyridone skeleton. The conjugated enone **5** would be synthesized by connection of four components **6**, **7**, **8**, and **9**.

For maximum convergency, C5–C2′ unit **11** (Scheme 2) was synthesized to connect with C3′–C10′ unit **13** (Scheme 3). Carboxylic acid **7**[2] was coupled with β-ketoamide **6**[2] via acid chloride to obtain tricarbonyl **10** (Scheme 2).[3] Tricarbonyl **10** was readily subjected to Pd(0)-catalyzed de-allylation[4] accompanied with decarboxylation to give ketoamide **11**[2] in excellent yield.

Construction of carbon chain **15**, the precursor of pyrano-pyridone skeleton, was described in Scheme 3. (*R*)-2-Methyl-1-butanol (**12**)[5] was submitted to oxidation[5] and Takai reaction[6] to afford vinyl iodide **9**, which was subsequently connected with vinyl stannane **8**[7] by Stille coupling to obtain C3′–C10′ unit **13**.[8] Hornor–Wodsworth–Emmons reaction with aldehyde **13** and phosphonate **11** gave tetraenone **5**. Acylation of ketoamide **5** with dichloride **14**[9] yielded diketoamide **15**,[3] the precursor of cyclization to obtain pyrano-pyridone **3**.

Construction of pyrano-pyridone **3** and the total synthesis of YCM1008A to determine the absolute structure were accomplished as shown in Scheme 4. Treatment of diketoamide **15** with Amberlyst 15 gave a mixture of γ-pyrones **16** (2,3-*syn*:2,3-*anti* = 1:1) and **17**, a product by cyclization of O1 at C2 and a product by cyclization of 4-carbonyl oxygen at C7 position, respectively. The *syn*-isomers [(2*S*,3*S*,8′*R*) and (2*R*,3*R*,8′*R*)] of **16** were separated from *anti*-isomers by column

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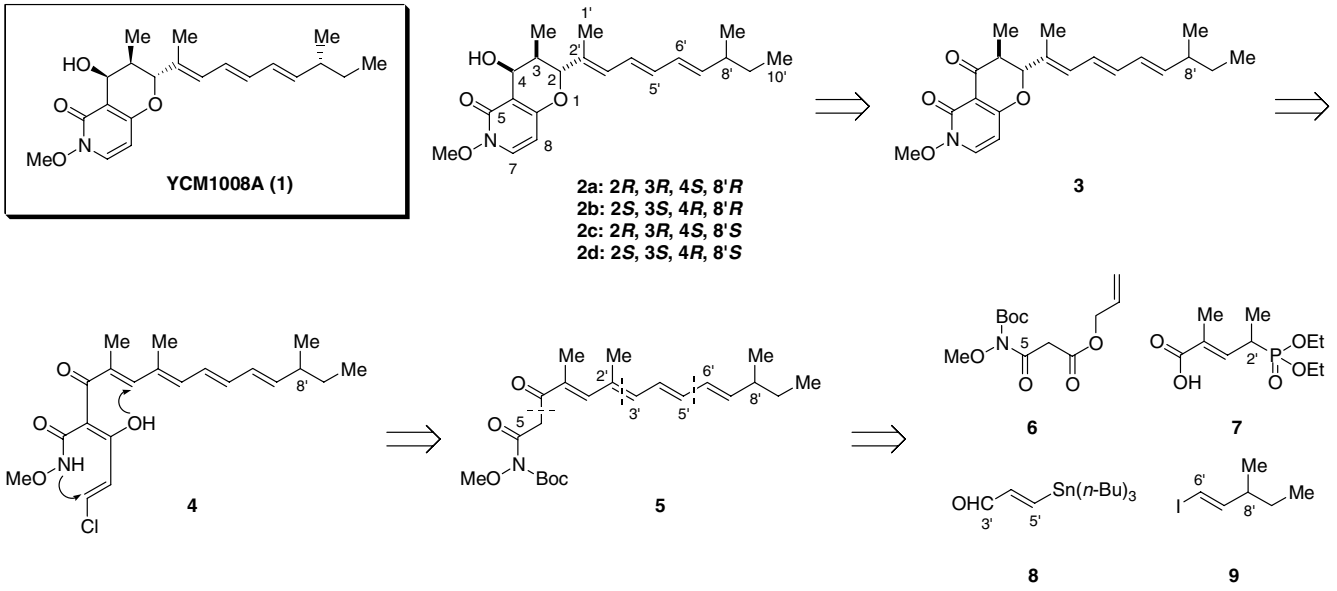
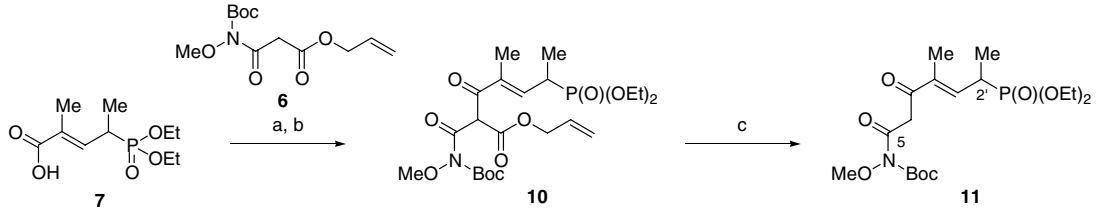
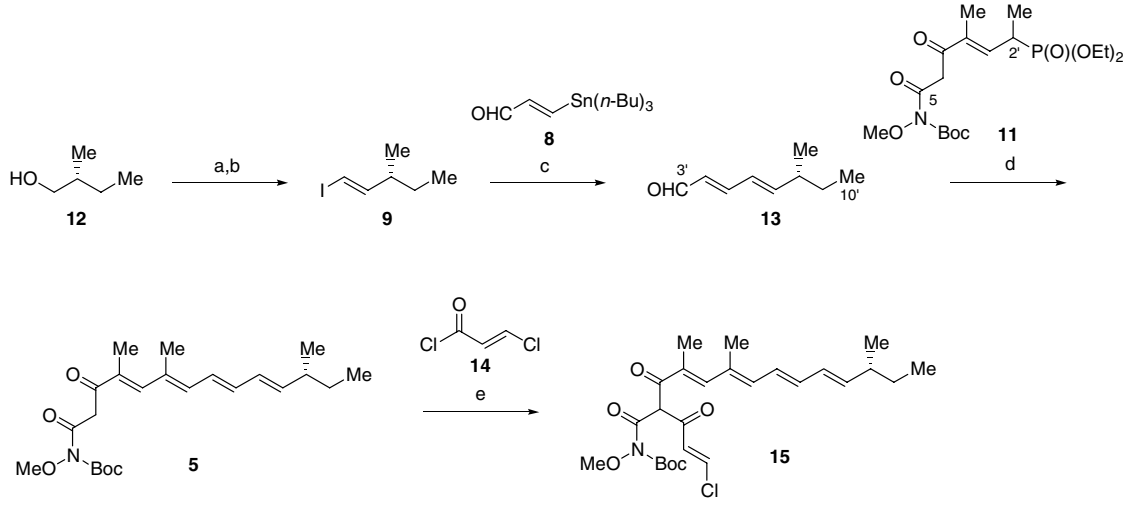


Scheme 1. Synthetic plan of YCM1008A.

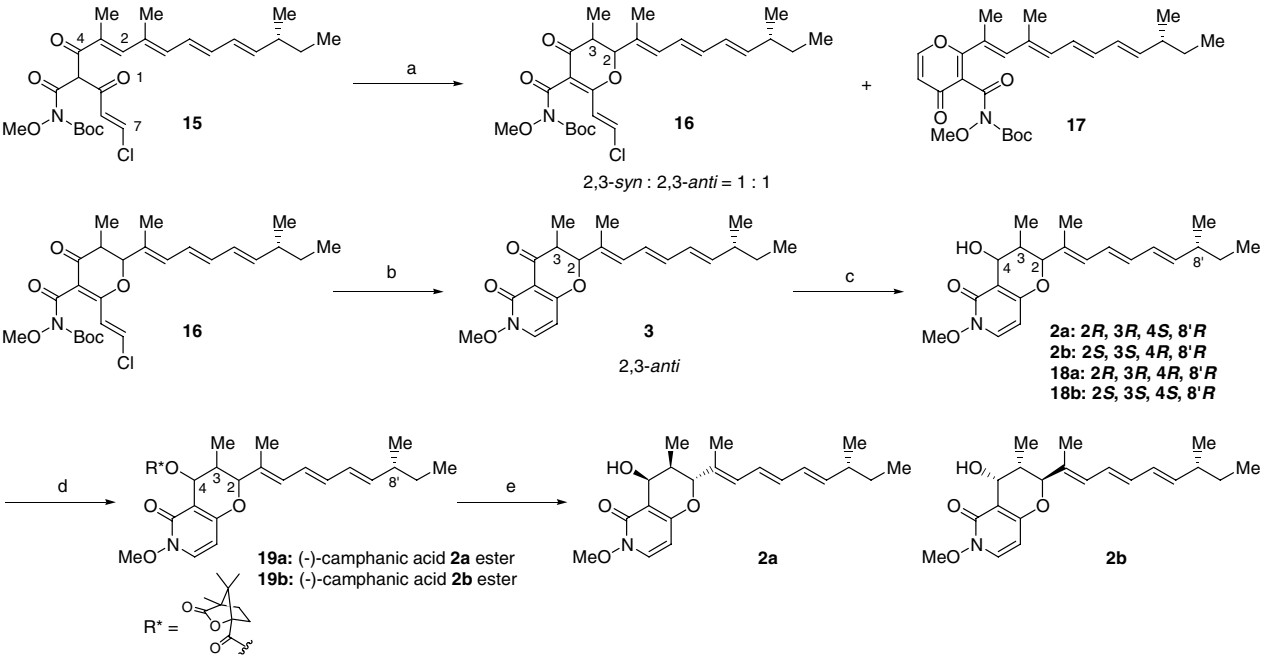


Scheme 2. Reagents and conditions: (a) $(COCl)_2$, DMF, CH_2Cl_2, rt, 2 h; (b) *i*-Pr_2NEt, $MgCl_2$, THF, 0 °C to rt, 12 h, 74% in 2 steps; (c) $Pd(PPh_3)_4$, HCO_2H, Et_3N, THF, 0 °C, 20 min, 87%.



Scheme 3. Reagents and conditions: (a) TEMPO, NaOCl, KBr, $NaHCO_3$, aq CH_2Cl_2, 0 °C, 30 min; (b) $CrCl_3$, $LiAlH_4$, CHI_3, THF, 0 °C to rt, 5 h, 33% in 2 steps; (c) $Pd(PPh_3)_2Cl_2$, CuI, DMF, rt, 12 h, 60%; (d) NaH, THF, rt, 4 h, 25%; (e) *i*-Pr_2NEt, $MgCl_2$, THF, 0 °C, 1.5 h. TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl.

chromatography. Both isomers of **16** were transformed to 2,3-*anti*-pyridones **3** [(2*S*,3*R*,8′*R*) and (2*R*,3*S*,8′*R*)] in the presence of TiCl(O-*i*-Pr)$_3$ by successive reactions including removal of Boc group and N-Michael addition–elimination reaction, in which *anti*-isomers of **16** gave pyridones **3** in 75% yield and *syn*-isomers also gave predominantly *anti*-pyridones **3** in 34% yield by epimerization at C3 under the reaction conditions. The relative stereochemistry at C2 and C3 of the pyrone moiety was confirmed to be *anti* with pyridones **3** by ^{1}H NMR to



Scheme 4. Reagents and conditions: (a) Amberlyst 15, CH_2Cl_2, rt, 16 h, **16**: 34% and **17**: 11% in 2 steps; (b) $TiCl(O\textit{i}\text{-}Pr)_3$, $Cl(CH_2)_2Cl$, rt, 12 h 75% from *anti*-**16** and 34% from *syn*-**16**; (c) DIBAL-H, CH_2Cl_2, −78 °C, 2 h, **2a** + **2b**: 40% and **18a** + **18b**: 27%; (d) (−)-camphanic chloride, pyridine, CH_2Cl_2, rt, 12 h, separation, **19a**: 49% and **19b**: 48%; (e) NaOMe, MeOH, rt, 12 h, **2a**: 79% and **2b**: 76%.

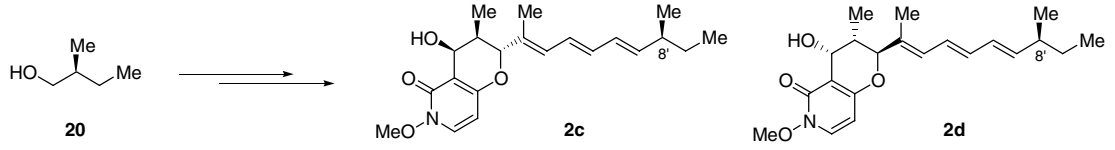
give large coupling constants ($J = 12.5$ Hz) between H2 and H3. The reduction of **3** with DIBAL-H in CH_2Cl_2 gave a mixture of 4 stereoisomers including **2a**, **2b**, **18a**, and **18b**. Although two major isomers were unable to be separated each other, a mixture of major isomers was separated from a mixture of two minor isomers by column chromatography.

The major isomers were determined to be **2a** and **2b** by ^{1}H NMR to give the coupling constant between H3 and H4 to be 3.7 Hz, while **18a** and **18b** showed 9.2 Hz and hydrogen bonding of the hydroxyl proton to the pyridone carbonyl oxygen. Additionally, ^{1}H NMR spectrum of the mixture of **2a** and **2b** showed that one of these isomers possessed the relative configuration identical with that of the natural YCM1008A. Minor isomers, **18a** and **18b**, were submitted to Dess–Martin oxidation to reuse as ketone **3** in quantitative yield. The mixture of **2a** and **2b** was esterified with (−)-camphanic chloride to afford diastereomeric esters **19a** and **19b**, which were separated by column chromatography. Esters **19a** and **19b** were submitted to hydrolysis to obtain alcohols **2a** and **2b**, respectively. The absolute stereochemistry of **2a** was determined to be (2*R*,3*R*,4*S*)-configuration by Mosher's method[10] with (*R*)- and (*S*)-MTPA esters of **2a**.[2]

Isomers **2c** (2*R*,3*R*,4*S*,8′*S*) and **2d** (2*S*,3*S*,4*R*,8′*S*) were also synthesized by the same procedures as Scheme 3 and 4 from (*S*)-2-methyl-1-butanol (**20**) (Scheme 5).

The four stereoisomers **2a**–**2d** were compared to the natural YCM1008A in spectral features. Although the stereocenter C8′ is far from C2, C3, and C4 carbons, ^{1}H NMR spectrum of **2a** (**2d**) is distinguishable from that of **2b** (**2c**) at the H7′ signals around δ 5.65 ppm (Fig. 1). ^{1}H and ^{13}C NMR spectra of **2a** and **2d** were identical with the spectra of the natural product, while NMR spectra of **2b** and **2c** were not superimposed with those of the natural product.[2] The optical rotation of **2a** and **2d** were $[\alpha]_D^{23}$ −76.0 (*c* 0.33, MeOH) and $[\alpha]_D^{23}$ +75.1 (*c* 0.33, MeOH), respectively, while the rotation of natural product was $[\alpha]_D^{23}$ −58.1 (*c* 0.03, MeOH).[1] Thus, isomer **2a** was identical with the natural product in all aspects including bioactivities and the stereochemistry of YCM1008A was determined to be (2*R*,3*R*,4*S*,8′*R*)-configuration.

In conclusion, the first total synthesis of YCM1008A (**1**) has been accomplished to determine the absolute structure to be (2*R*,3*R*,4*S*,8′*R*)-configuration. The method to construct a pyrano-pyridone skeleton has been established by coupling of β-ketoamide and



Scheme 5. Synthesis of **2c** and **2d**.

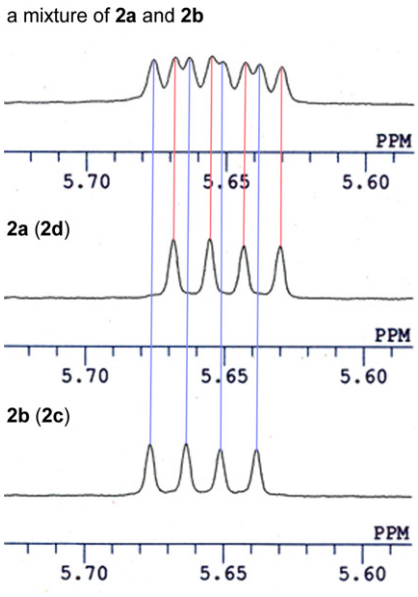


Figure 1. Comparison of ^{1}H NMR spectra on H7′ of a mixture of **2a** and **2b**, **2a** (**2d**), and **2b** (**2c**).

3-chloroacryloyl chloride (**14**) followed by successive O- and N-cyclizations.

Acknowledgments

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Supplementary data

The spectrum data of compounds **3**, **5**, **6**, **7**, **9**, **11**, **13**, **19a**, **19b**, (*R*)- and (*S*)-MTPA esters of **2a**, **2a**, and **2b**, and ^{1}H NMR spectra (600 MHz in $CDCl_3$) of **2a**, **2b**, mixture of **2a** and **2b**, and that of natural YCM1008A kindly provided by Drs. Y. Kanda and M. Ichimura, Kyowa Hakko Kogyo Co. Ltd, are presented as supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.074.

References and notes

1. Koizumi, F.; Fukumitsu, N.; Zhao, J.; Chanklan, R.; Miyakawa, T.; Kawahara, S.; Iwamoto, S.; Suzuki, M.; Kakita, S.; Rahayu, E. S.; Hosokawa, S.; Tatsuta, K.; Ichimura, M. *J. Antibiot.*, submitted for publication.
2. See Supplementary data.
3. Rathke, M. W.; Cowan, P. J. *J. Org. Chem.* **1985**, *50*, 2622–2624.
4. (a) Shimizu, I.; Tsuji, J. *J. Am. Chem. Soc.* **1982**, *104*, 5844–5846; (b) Tsuji, J.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1985**, *50*, 3416–3417; (c) Kanda, Y.; Arai, H.; Ashizawa, T.; Morimoto, M.; Kasai, M. *J. Med. Chem.* **1992**, *35*, 2781–2786.
5. Tyrrell, E.; Skinner, G. A.; Janes, J.; Milsom, G. *Synlett* **2002**, 1073–1076.
6. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.
7. Johnson, C. R.; Kadow, J. F. *J. Org. Chem.* **1987**, *52*, 1493–1500.
8. Goure, W. F.; Wright, M. E.; Davis, P. D.; Labadie, S. S.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 6417–6422.
9. Urdaneta, N. A.; Herrera, J. C.; Salazar, J.; López, S. E. *Synth. Commun.* **2002**, *32*, 3003–3009.
10. (a) Dale, J. A.; Mosher, H. *J. Am. Chem. Soc.* **1973**, *95*, 512–519; (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.