Natural Products Synthesis

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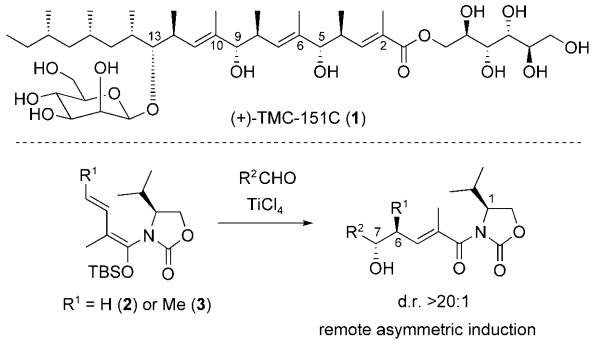
Convergent Total Synthesis of (+)-TMC-151C by a Vinylogous Mukaiyama Aldol Reaction and Ring-Closing Metathesis**

*Ryosuke Matsui, Kentaro Seto, Yuna Sato, Takahiro Suzuki, Atsuo Nakazaki, and Susumu Kobayashi**

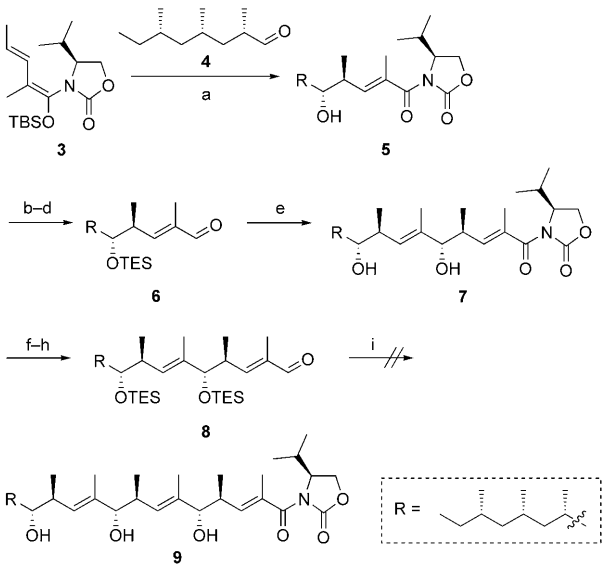
Antibiotic agents of the TMC-151 family were originally isolated from the fungus *Gliocladium catenulatum* Gilman & Abbott TC 1280 by a research group at the pharmaceutical company Tanabe Seiyaku in 1999 as novel polyketides containing β-D-mannoside and D-mannitol groups.[1] A related TMC-171 family of antibiotics and TMC-154 were also isolated.[2] Of these compounds, TMC-151C (**1**) shows the most significant cytotoxicity against a wide range of tumor cell lines, including HCT-116, B16, and HeLa cells. TMC-151C displays several interesting structural features. Notably, 1) the polyketide moiety contains three contiguous *anti* homoallylic alcohol motifs in the C1–C13 segment and three methyl-substituted asymmetric carbon centers in the C14–C20 segment, and 2) D-mannose is attached to the C13 hydroxy group as β-D-mannoside, which is still problematic in terms of chemical synthesis (Scheme 1). This combination of significant biological activity and structural complexity encouraged us to attempt the total synthesis of (+)-TMC-151C (**1**).



Scheme 1. Structure of (+)-TMC-151C and the vinylogous Mukaiyama aldol reaction (VMAR). TMC-151C contains three units that should be amenable to synthesis by the VMAR: C2–C5, C6–C9, and C10–C13. TBS = *tert*-butyldimethylsilyl.

We previously developed a highly stereoselective vinylogous Mukaiyama aldol reaction (VMAR) that enabled remarkable remote asymmetric induction by using the vinylketene silyl N,O-acetals **2** and **3** (Scheme 1).[3] From a synthetic point of view, this method can directly afford the *anti*-δ-hydroxy-α,γ-dimethyl α,β-unsaturated carbonyl unit which is present in many naturally occurring compounds. Indeed, the VMAR has been utilized successfully in natural product syntheses by many research groups,[4] including our own.[5] Given the presence of three *anti* homoallylic alcohol motifs (C2–C5, C6–C9, and C10–C13 units) in (+)-**1**, we reasoned that the total synthesis of **1** would provide a representative example of the VMAR. Herein, we report the first total synthesis of (+)-TMC-151C (**1**).

We initially attempted a straightforward linear approach consisting of three iterative VMARs (Scheme 2). The carbohydrate units would then be combined at a later stage in the synthesis. According to the established protocol, the first VMAR of the known chiral aldehyde **4**[6] with the vinylketene silyl N,O-acetal **3** in the presence of $TiCl_4$ afforded the



Scheme 2. Attempted linear approach: a) $TiCl_4$ (1.0 equiv), aldehyde **4** (1.5 equiv), CH_2Cl_2, −78→−40 °C, 91% (d.r. > 20:1); b) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, quantitative; c) $LiBH_4$, MeOH, Et_2O, 0 °C, 98%; d) MnO_2, CH_2Cl_2, room temperature, 99%; e) $TiCl_4$ (4.0 equiv), **3** (5.0 equiv), CH_2Cl_2, −78→−20 °C, 51% (d.r. 13:1); f) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 93%; g) $LiBH_4$, MeOH, Et_2O, 0 °C, 94%; h) MnO_2, CH_2Cl_2, room temperature, quantitative; i) $TiCl_4$ (5.0 equiv), **3** (5.0 equiv), CH_2Cl_2, −78→−20 °C, complex mixture. TES = triethylsilyl, Tf = trifluoromethanesulfonyl.

[*] R. Matsui, K. Seto, Y. Sato, Dr. T. Suzuki, Dr. A. Nakazaki, Prof. Dr. S. Kobayashi
Faculty of Pharmaceutical Sciences, Tokyo University of Science
2641 Yamazaki, Noda-shi, Chiba 278-8510 (Japan)
Fax: (+81) 4-7121-3671
E-mail: kobayash@rs.noda.tus.ac.jp
Homepage: http://www.rs.noda.tus.ac.jp/kobalab/index.html

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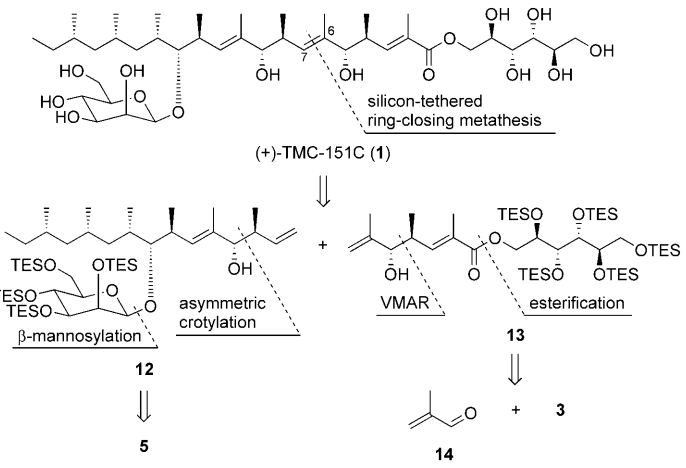
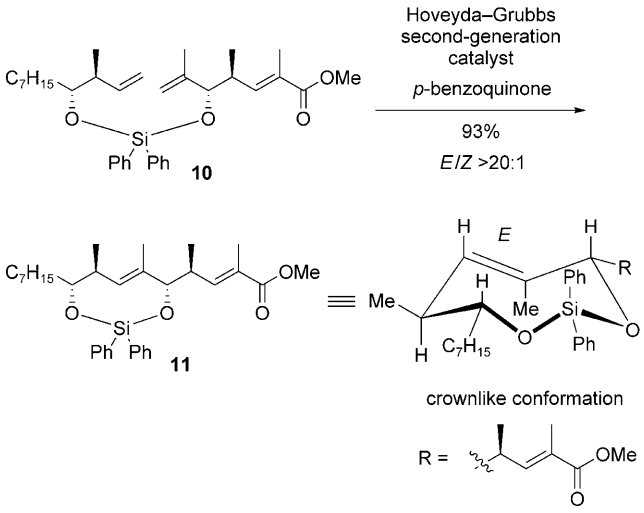
corresponding C12–C13 *anti* aldol adduct **5** in 91% yield with high diastereoselectivity. TES protection of the secondary alcohol, reductive removal of the chiral auxiliary with $LiBH_4$, and oxidation of the resulting primary alcohol with MnO_2 provided the second VMAR substrate **6**. An excess amount of $TiCl_4$ and the N,O-acetal **3** were required for this second VMAR owing to the low reactivity of enal **6**. Under these conditions, the desired aldol adduct **7** was formed in 51% yield with good diastereoselectivity (d.r. 13:1; the minor diastereomer was could be separated from **7** by preparative TLC). The aldol adduct **7** was transformed into enal **8** by the same sequence of reactions used for the conversion of **5** into **6**. However, despite repeated efforts, the desired third VMAR product **9** could not be obtained from **8**. In each case, a complex mixture of products was generated, probably as a result of the Lewis acidity of $TiCl_4$.

The lack of success with the third VMAR in the linear approach prompted us to investigate an alternative synthetic route. In this context, we recently developed an unusually *E*-selective silicon-tethered ring-closing metathesis (RCM) of silylene acetal **10**, prepared from an allylic alcohol and a homoallylic alcohol (Scheme 3).[7] Our novel convergent strategy, which is based on this methodology, is outlined in Scheme 4. (+)-TMC-151C (**1**) was divided at the C6–C7 olefin into two fragments: the left-hand fragment **12** and the right-hand fragment **13**. We envisaged that **12** and **13** could be connected by using this *E*-selective silicon-tethered RCM methodology. We reasoned that the use of this methodology could result in a short and convergent synthetic route. The left-hand fragment **12** was synthesized from the VMAR product **5** by β-mannosylation followed by asymmetric crotylation. To dispense with the protection–deprotection steps, we introduced a β-mannosyl group into **5**. Although β-mannoside formation is often regarded as one of the most difficult glycosylation reactions, several excellent methodologies have been developed to facilitate this transformation.[8] The right-hand fragment **13** was synthesized by a VMAR with methacrolein (**14**) and esterification with a D-mannitol derivative.

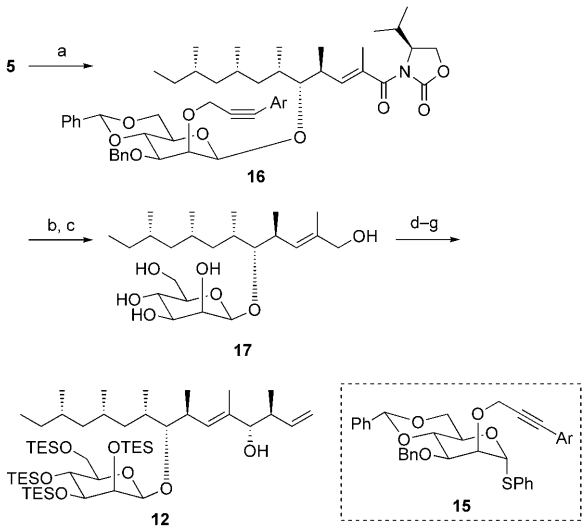


Scheme 4. Convergent retrosynthetic analysis based on the VMAR and RCM.



Scheme 3. Formation of an eight-membered ring by *E*-selective silicon-tethered ring-closing metathesis (RCM).

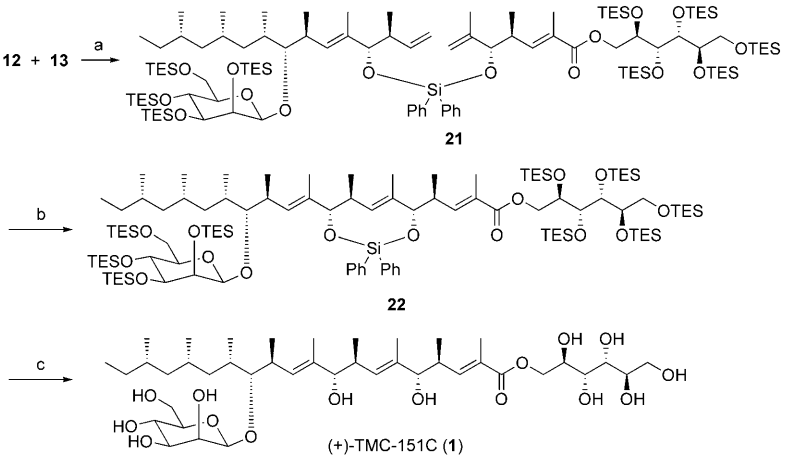
The synthesis of the left-hand fragment **12** began with a β-selective mannosylation of **5** (Scheme 5). After extensive studies in which we examined a variety of different approaches, we found that β-mannosylation of **5** with the mannosyl donor **15** by the method developed recently by Crich and Karatholuvhu[8g] afforded the desired product **16** in 82% yield almost as a single isomer. The stereostructure of **16** was determined by NOE experiments.[9] Reductive removal of the chiral auxiliary in **16** with $LiBH_4$, followed by the



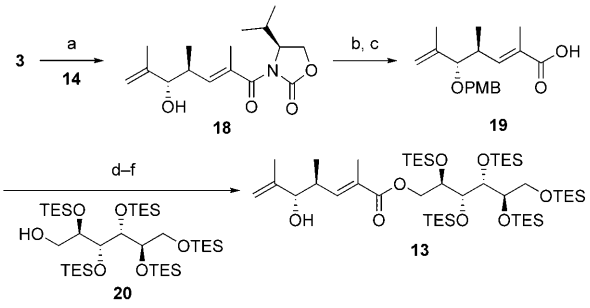
Scheme 5. Synthesis of the left-hand fragment **12**: a) **15** (Ar = *p*-$CF_3C_6H_4$), BSP, Tf_2O, TTBP, 4Å M.S., CH_2Cl_2, −60 °C, 82% (β:α > 20:1); b) $LiBH_4$, MeOH, Et_2O, 0 °C, 97%; c) Na, liquid NH_3, THF–*t*BuOH, −70 → −20 °C, 75%; d) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, quantitative; e) AcOH–H_2O, THF, room temperature, 47% (89% based on recovered starting material); f) MnO_2, CH_2Cl_2, room temperature, 97%; g) (*E*)-(*R*,*R*)-crotyl boronate, 4Å M.S., toluene, −78 °C, 89% (d.r. 4.7:1). Bn = benzyl, BSP = 1-benzenesulfinylpiperidine, M.S. = molecular sieves, TTBP = 2,4,6-tri-*tert*-butylpyrimidine.

removal of all protecting groups under Birch conditions,[8g] provided the pentaol **17**. Following the protection of all five hydroxy groups of **17** as their TES ethers, selective cleavage of the primary allylic TES ether with AcOH–H_2O–THF afforded the corresponding allylic alcohol, which was oxidized with MnO_2 in 97% yield. A Roush asymmetric *anti* crotylation[10] then gave the desired left-hand fragment **12** in 89% yield with d.r. 4.7:1 (the minor diastereomer was separated by silica-gel column chromatography).

Next, we focused on the synthesis of the right-hand fragment **13** (Scheme 6). The synthesis commenced with a VMAR between the N,O-acetal **3** and methacrolein (**14**). Under standard conditions ($TiCl_4$ in CH_2Cl_2, 2.0 equivalents of **14**), the aldol adduct **18** was formed in low yield (23%), presumably as a result of polymerization of **14**. During an extensive survey of reaction conditions, we improved the yield of



Scheme 7. Completion of the total synthesis of (+)-TMC-151C (**1**): a) **13** (1.5 equiv), Et_2NPh_2SiCl, Et_3N, DMAP (cat.), then **12**, DMAP, CH_2Cl_2, 0°C→RT, 54% (81% from **12** on the basis of recovered starting material); b) Hoveyda–Grubbs second-generation catalyst (20 mol%), *p*-benzoquinone, xylene, reflux, 87% (*E*/*Z* > 20:1); c) HF–pyridine, pyridine, then aqueous HF, THF–MeCN, 0°C→RT, 54%.



Scheme 6. Synthesis of the right-hand fragment **13**: a) $TiCl_4$, methacrolein (**14**; 4.0 equiv), toluene, −78→−50°C, 65% (d.r. > 20:1); b) PMBOC(NH)CCl_3, CSA (cat.), CH_2Cl_2, 0°C→RT, 68%; c) LiOH·H_2O, H_2O_2, THF–H_2O, 0°C, 83%; d) Piv_2O, Et_3N, CH_2Cl_2, 0°C; e) **20**, DMAP, toluene, room temperature, 60% (over 2 steps); f) DDQ, CH_2Cl_2–buffer (pH 7.5), 0°C, 93%. PMB = *p*-methoxybenzyl, CSA = camphorsulfonic acid, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = *N*,*N*-4-dimethylaminopyridine, Piv = pivaloyl.

18 to 65% with greater than 20:1 diastereoselectivity by using toluene as the solvent and 4.0 equivalents of **14**. The major by-products were
1,4-addition adducts (15% yield) as a mixture of diastereomers. After protection of the secondary alcohol with PMBOC(NH)CCl_3, the chiral auxiliary was removed with LiOH and H_2O_2 to provide the carboxylic acid **19**. Esterification of the unsaturated acid **19** (as the mixed anhydride formed by treatment with Piv_2O) with the alcohol **20**[9] afforded the corresponding ester in 60% overall yield for the two steps. Cleavage of the PMB ether gave the right-hand fragment **13**.

With both fragments in hand, we proceeded to the final stage of the total synthesis of (+)-**1** (Scheme 7). Our silicon-tethering method with Et_2NPh_2SiCl/Et_3N/DMAP[7] was used successfully for the connection of **12** and **13** to afford silylene acetal **21** in 54% yield (81% from **12** as calculated on the basis of recovered starting material). The crucial silicon-tethered RCM[11,12] of **21** under the previously reported conditions[7] (with the Hoveyda–Grubbs second-generation catalyst[13] in the presence of *p*-benzoquinone[14] in xylene at reflux) provided the desired *E* olefin **22** in 87% yield with high stereoselectivity (*E*/*Z* > 20:1). The configuration of the *E* olefin **22** was determined by NOE experiments.[9] Finally, desilylation by the sequential treatment of **22** with HF·pyridine and aqueous HF completed the total synthesis of (+)-TMC-151C.[15] The spectroscopic data (^{1}H NMR, ^{13}C NMR, and IR spectra, HRMS) of synthetic (+)-**1** were identical to those of natural (+)-**1**.[1a]

In conclusion, we have completed the first total synthesis of (+)-TMC-151C by a highly convergent synthetic route. Characteristic features of the present synthesis include the construction of the C1–C5 and C9–C13 units by vinylogous Mukaiyama aldol reactions and the use of a silicon-tethered diene for the stereoselective formation of the C6–C7 double bond by our recently developed *E*-selective RCM reaction to give an eight-membered ring. This synthetic strategy should provide efficient access to a range of related naturally occurring polyketides containing pent-2-ene-1,5-diol units.

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[15] Although the $[\alpha]_D$ value of synthetic (+)-**1** ($+4.4\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$, $c = 1.3 \times 10^{-3}\ \mathrm{g\,cm^{-3}}$ in MeOH) was lower than that of natural (+)-**1** ($+27\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$, $c = 1.0 \times 10^{-3}\ \mathrm{g\,cm^{-3}}$ in MeOH), the stereostructure and the purity of synthetic (+)-**1** were confirmed by NMR spectroscopy.

