



Asymmetric total synthesis of MK8383: the iron-mediated coupling reaction is the only effective method for the construction of the (Z)-trisubstituted side-chain alkene

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ABSTRACT

The first asymmetric total synthesis of MK8383 through the iron-mediated coupling reaction is described. In this total synthesis, the key step was clearly the stereoselective construction of the (Z)-trisubstituted side-chain alkene. Although this problem was seemingly easy to resolve, in fact it presented us an opportunity to evaluate the coupling reactions reported to date, and the iron-mediated coupling reaction was found to be the only effective method for the stereoselective construction of the (Z)-trisubstituted side-chain alkene.

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MK8383 (Fig. 1) was isolated from *Phoma* sp. T2526 by a joint research group organized by Meiji Seika Kaishya, Ltd, and Mitsubishi Chemical Corporation.¹ This compound comprises a cis-fused dehydrodecalin ring with (*E,E*)-pentadienoic acid and a (*Z*)-trisubstituted alkene as characteristic substituents. The structure of MK8383 is almost the same as that of (+)-phomopsidin² (Fig. 1), except for the geometry of the alkene side chain.

MK8383 shows inhibitory activity against the assembly of microtubule proteins derived from the porcine brain at an IC₅₀ of 8.0 μM, which is comparable with that of (+)-phomopsidin (IC₅₀ of 5.7 μM).² MK8383 also exhibits antibacterial activities against a variety of phytopathogens (e.g., gray mold *Botrytis cinerea*).¹ Therefore, MK8383 and its derivatives are regarded as promising fungicides. Due to the above structures and biological activities, we are interested in the structure–activity relations of MK8383 and (+)-phomopsidin.

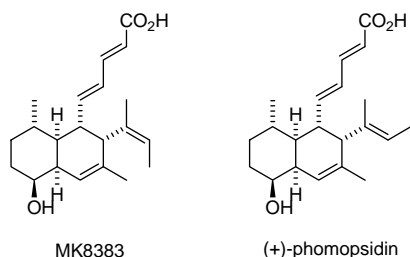


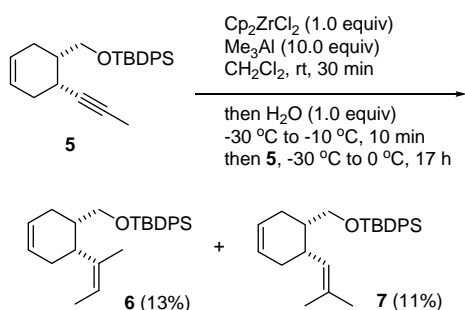
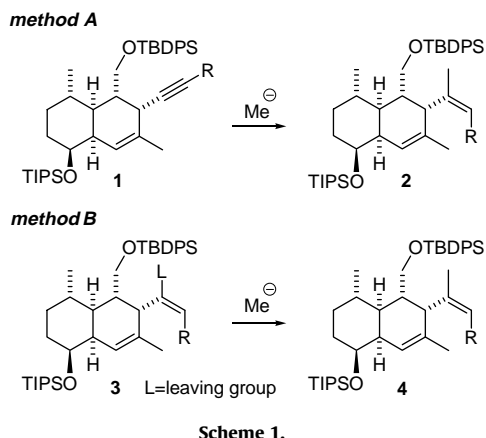
Figure 1. Respective structures of MK8383 and (+)-phomopsidin.

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We reported the first total synthesis of (+)-phomopsidin based on the construction of the cis-fused dehydrodecaline skeleton by a stereoselective transannular Diels–Alder (TADA) reaction.³ Accordingly, we started to investigate the asymmetric total synthesis of MK8383 through the stereoselective construction of the (*Z*)-trisubstituted alkenyl side chain. However, although the construction of the (*Z*)-trisubstituted alkenyl side chain was considered easy since many methods for the stereoselective construction of (*Z*)-trisubstituted alkenes have been reported to date, this seemingly easy challenge presented us an opportunity to evaluate the coupling reactions reported so far. We herein report the first asymmetric total synthesis of MK8383 based on the iron-mediated coupling reaction, which was the only effective method for the construction of the (*Z*)-trisubstituted alkene side chain.

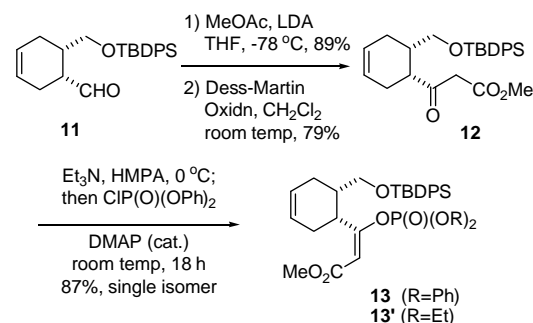
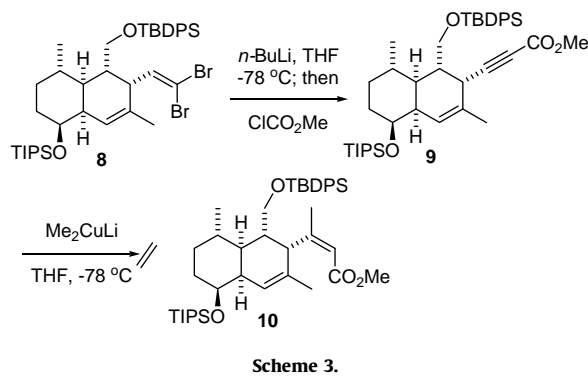
Clearly, the stereoselective construction of the (*Z*)-trisubstituted alkene side chain presented a problem in the total synthesis of MK8383, as we reported the synthesis of the cis-fused dehydrodecaline skeleton. Among various methods, the cis-addition of organometallic reagents to alkynes^{4a,5} and the coupling reaction of alkenes incorporating a leaving group with organometallic reagents^{4b} have been employed in the synthesis of natural products due to their wide applicability. Therefore, a carbometallation–protonation sequence of the alkyne **1** (*R* = Me) affording the product **2** and a transition-metal catalyzed coupling reaction of the alkene **3** incorporating a leaving group with an organometallic reagent (*method B*) affording the product **4** were promising methods for this purpose (Scheme 1).

First, we conceived that a carbometallation–protonation sequence of alkyne **1** (*R* = Me) would be a straight-forward method; hence, we first examined the reaction using the model compound **5** (Scheme 2). However, the carbometallation of the alkyne **5** gave the products **6** and **7** in low yield with almost no regioselectivity,



suggesting that this protocol would be unsuitable for the synthesis of the side chain.

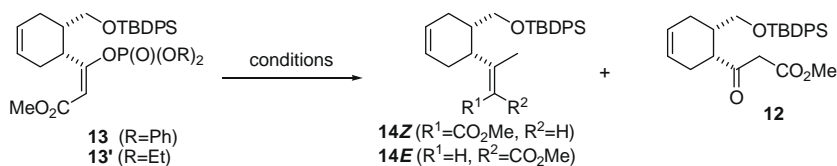
Therefore, although transformations of the functional group after the coupling reaction would be inevitable, we examined the *cis*-addition of a cuprate⁶ with the alkyne **9** incorporating an ester group at the alkyne terminal, which was readily prepared from the known alkenyl dibromide **8**³ (Scheme 3) by the Corey–Fuchs protocol.⁷ To our surprise, however, no products were formed in the reaction of the alkyne **9** with lithium dimethyl cuprate.



Then, we turned our attention to *method B* in Scheme 1. Although the stereoselective preparation of compound **3** (R = Me), incorporating an energetically unfavorable alkene, was thought to be difficult, compound **3** (R = ester) was expected to be readily obtainable from the corresponding β -keto ester. For example, the stereoselective preparation of both geometrical isomers of enol phosphates from the corresponding β -keto esters has been reported.⁸

We prepared the (*E*)-enol phosphate **13** (R = Ph) as the model compound in order to examine the coupling reaction (Scheme 4). The aldol reaction of the aldehyde **11** with the lithium enolate of methyl acetate afforded the desired product (89%), followed by

Table 1
Coupling reaction of enol phosphates **13** and **13'**



Entry	Substrate	Reagents (equiv)	Solvent	Temperature (°C)	Time (h)	Yield ^a (%)		
						13	14Z	12
1	13	Ni(acac) ₂ (0.9), Me ₃ Al (6.0)	THF	0	1.5	0	26 ^b	0
2	13	Me ₂ CuMgCl (8.0)	THF	0	3.5	— ^c	— ^c	— ^c
3	13	Me ₃ FeLi (3.0)	THF	0	1.5	26	0	60
4	13	Me ₃ FeLi (3.0)	THF/NMP = 20/1	0	1.5	2	0	52
5	13	Fe(acac) ₃ (0.6), MeMgCl ^d (9.0)	THF/NMP = 20/1	0	1	0	88	12
6	13'	Pd(PPh ₃) ₄ (0.3), Me ₃ Al (6.0)	(CH ₂ Cl) ₂	80	16	0 ^e	25	37
7	13'	Fe(acac) ₃ (0.9), MeMgCl ^d (12)	THF/NMP = 20/1	0	2	0 ^e	65	28

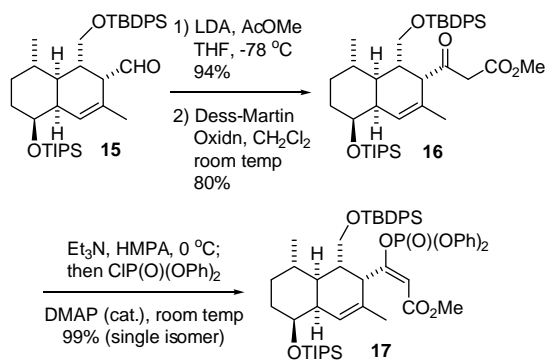
^a Isolated yields.

^b 30% of **14E** was formed.

^c No reaction.

^d THF solution was used.

^e Recovered yield of **13**.



Scheme 5.

Dess–Martin oxidation⁹ to give the β -keto ester **12** (79%), which was treated with $\text{ClP}(\text{O})(\text{OPh})_2$ in the presence of triethylamine, providing the enol phosphate **13** ($\text{R} = \text{Ph}$), stereoselectively (87%). The enol phosphate **13'** ($\text{R} = \text{Et}$) was also prepared by the same method as the single isomer (89%).

The coupling reaction of the enol phosphate **13** ($\text{R} = \text{Ph}$) with Me_3Al in the presence of $\text{Ni}(\text{acac})_2$ ¹⁰ produced a geometrical mixture of compounds **14E** and **14Z** (Table 1, entry 1). The reaction with Me_2CuMgCl ¹¹ gave no products (entry 2). Although Corey and Seibel reported the reaction of an enol phosphate with lithium trimethyl ferrate,¹² the reaction of the enol phosphate **13** afforded the β -keto ester **12** (entries 3 and 4). On the other hand, the reaction of MeMgCl in the presence of a catalytic amount of $\text{Fe}(\text{acac})_3$ in the mixed solvent system ($\text{THF}/\text{NMP} = 20/1$)¹³ successfully provided the desired product **14Z** in 88% yield without the formation of its isomer, **14E**, and the β -keto ester **12** was formed in only 12% yield (entry 5). The reaction of the enol phosphate **13'** ($\text{R} = \text{Et}$) with Me_3Al in the presence of a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ gave compound **14Z** in low yield (25%, entry 6), and the iron-mediated

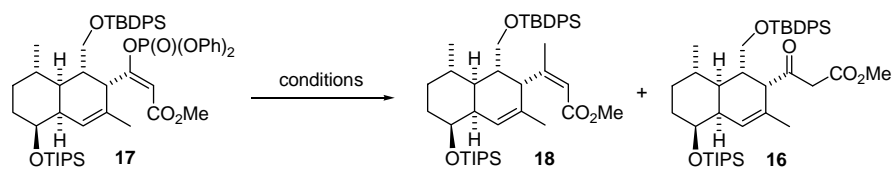
reaction provided compound **14Z** in 65% yield (entry 7). The yield obtained by using the enol phosphate **13** ($\text{R} = \text{Ph}$) was higher, and therefore we decided to employ the iron-mediated coupling reaction of the diphenyl enol phosphate in order to pursue the effective and stereoselective construction of the side chain in MK8383.

We prepared the requisite enol phosphate **17** as shown in Scheme 5 starting from the aldol reaction of the known aldehyde **15**³ with an enolate of methyl acetate (94%). The resultant alcohol was subjected to the Dess–Martin oxidation to provide the β -keto ester **16** (80%), which was successfully converted into the enol phosphate **17**, stereoselectively (99%), under the conditions described in Scheme 5.

The coupling reactions of the enol phosphate **17** are summarized in Table 2. The reaction of the enol phosphate **17** with MeMgCl (5.0 equiv) in the presence of a catalytic amount of $\text{Fe}(\text{acac})_3$ (0.2 equiv) in the mixed solvent system ($\text{THF}/\text{NMP} = 20/1$) afforded the desired product in only 12% yield, the β -keto ester **16** was formed in 22% yield, and a certain amount of the enol phosphate **17** remained (64%, entry 1). Interestingly, compared with the successful coupling reaction of the model compound **13** under the catalytic conditions (Table 1, entry 5), the reaction with 10 equiv of MeMgCl in the presence of 1 equiv $\text{Fe}(\text{acac})_3$ did not improve the results (entry 2). However, the reaction with 30 equiv of MeMgCl and 3 equiv of $\text{Fe}(\text{acac})_3$ provided the desired product **18** in 26% yield (entry 3). Therefore, large amounts of the reagents were used for this reaction, and 60 equiv of MeMgCl and 5 equiv of $\text{Fe}(\text{acac})_3$ were found to effectively afford product **18** in 82% yield (entry 4).¹⁴ In this case, the starting material **17** disappeared, and the β -keto ester **16** was not formed.

In addition to the iron-mediated reaction, we surveyed other frequently used reagents for this type of coupling reaction. However, organocopper reagents (entries 5 and 6) and palladium-mediated reactions (entries 7–9) yielded disappointing results, and nickel-mediated reactions (entries 11, 12, and 15) afforded product **17** in low yield.

Table 2
Coupling reaction of enol phosphates **17**



Entry	Reagents (equiv)	Solvent	Temperature ^a (°C)	Time ^a (h)	Yield ^b (%)		
					17	18	16
1	$\text{Fe}(\text{acac})_3$ (0.2), MeMgCl^c (5.0)	$\text{THF}/\text{NMP} = 20/1$	0	1	64	12	22
2	$\text{Fe}(\text{acac})_3$ (1.0), MeMgCl^c (10)	$\text{THF}/\text{NMP} = 20/1$	0	1	76	5	16
3	$\text{Fe}(\text{acac})_3$ (3.0), MeMgCl^c (30)	$\text{THF}/\text{NMP} = 20/1$	0	1	61	26	10
4	$\text{Fe}(\text{acac})_3$ (5.0), MeMgCl^c (60)	$\text{THF}/\text{NMP} = 20/1$	0	1	—	82	—
5	Me_2CuMgCl (3.0)	THF	−30, 0, rt	2, 1, 1	87	—	11
6	$\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2$ (4.0)	THF	−30, 0, rt	2, 1, 1	21	—	55
7	$\text{Pd}(\text{PPh}_3)_4$ (0.1), Me_3Al (2.0)	$(\text{CH}_2\text{Cl})_2$	rt, 50, 80	1, 1, 1	57	—	12
8	$\text{Pd}(\text{PPh}_3)_4$ (1.0), Me_3Al (10)	$(\text{CH}_2\text{Cl})_2$	rt, 50, 80	1, 1, 1	9	Trace	—
9	$\text{Pd}(\text{PPh}_3)_4$ (5.0), Me_3Al (60)	$(\text{CH}_2\text{Cl})_2$	rt, 50	1, 1	— ^d	— ^d	— ^d
10	$\text{Ni}(\text{acac})_2$ (0.1), MeMgCl^c (2.5)	Et_2O	0, rt	1, 1	67	—	Trace
11	$\text{Ni}(\text{acac})_2$ (1.0), MeMgCl^c (10)	Et_2O	0, rt	1, 1	63	12	20
12	$\text{Ni}(\text{acac})_2$ (5.0), MeMgCl^c (60)	Et_2O	0	1	—	20	10
13	$\text{NiCl}_2(\text{dppe})$ (0.1), MeZnCl (2.5)	Benzene	rt	1	NR ^e	0	0
14	$\text{NiCl}_2(\text{dppe})$ (1.0), MeZnCl (10)	Benzene	rt	1	93	—	Trace
15	$\text{NiCl}_2(\text{dppe})$ (5.0), MeZnCl (60)	Benzene	rt	1	31	19	Trace

^a The reaction was carried out at the indicated temperatures for the indicated times.

^b Isolated yields.

^c THF solution was used.

^d Decomposition occurred.

^e No reaction.

In the case of the enol phosphate **13** (Table 1, entry 5), the reaction was completed by use of a catalytic amount of $\text{Fe}(\text{acac})_3$ (0.6 equiv), although the amount was relatively large. On the other hand, the reaction of the enol phosphate **17** required a large excess of the reagents. This can be attributed to the steric hindrance derived from the two adjacent substituents (a *tert*-butyldiphenylsilyloxymethyl group and a methyl group), which were placed at both sides of the enol phosphate substituent. That is, the steric hindrance retarded the coupling reaction, and therefore large amounts of the reagents were required. Furthermore, the reactive species generated in the reaction mixture to provide product **18** were not clear, although it could be possible to exclude the ironate complex since Me_3FeLi provided no coupling products in the reaction with the enol phosphate **13** (Table 1, entries 3 and 4).

After we had established the synthetic route to compound **18**, we examined its transformation into MK8383 (Scheme 6). The ester **18** was reduced by DIBAL to provide the allylic alcohol (97%), which was subjected to bromination. Although a mixture of the geometrical isomers was formed by the use of PPh_3 and CBr_4 , no isomerization was observed when PBr_3 was used. The allylic bromide **19** thus obtained was subjected to a reaction with LiAlH_4 (71%, two steps), followed by treatment with TBAF to provide the diol **20** (quant). The primary and secondary hydroxyls of the diol were protected as a TBS ether (89%) and a benzoate (96%), respectively, and product **21** was treated with TBAF to give the alcohol (99%), which was oxidized with Dess–Martin periodinane⁹ to provide the aldehyde **22** (98%). The Horner–Wadsworth–Emmons reaction of the aldehyde **22** with the phosphonate **23** successfully afforded the (*E,E*)-dienoate **24** (94%) as a single isomer, which was subjected to the hydrolysis under basic conditions to accomplish the total synthesis of MK8383 (83%). The synthetic MK8383 was

spectroscopically identical in all respects with the naturally occurring MK8383,¹ thereby confirming the asymmetric total synthesis of MK8383.

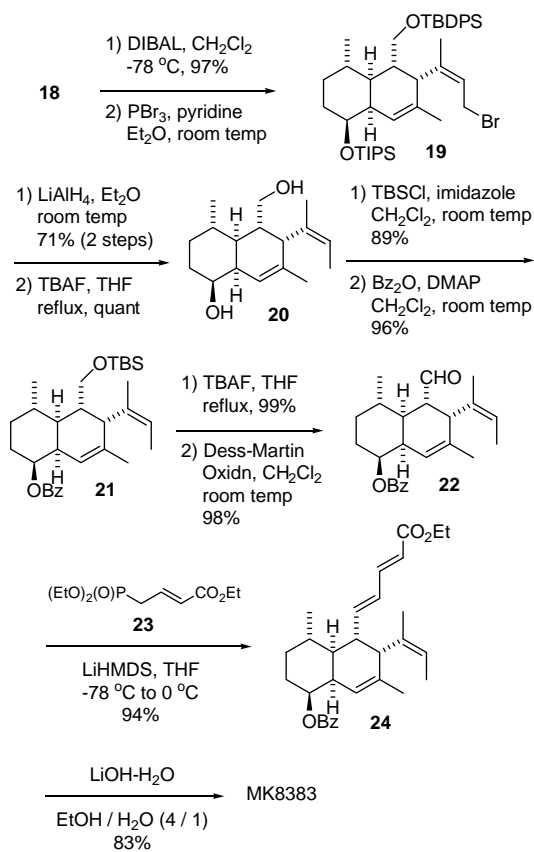
In conclusion, we accomplished the first asymmetric total synthesis of MK8383 by utilizing the iron-mediated coupling reaction. In this total synthesis, the problem with the synthesis was clearly the stereoselective construction of the (*Z*)-trisubstituted side-chain alkene. However, although this problem was seemingly easy to solve, in fact it presented us an opportunity to evaluate the coupling reactions reported to date, and the iron-mediated coupling reaction was found to be the only effective method for the stereoselective construction of the (*Z*)-trisubstituted side-chain alkene of MK8383. Although the iron-mediated coupling reaction has not been extensively applied to the synthesis of natural products,¹³ it is considered relatively more reliable than other coupling reactions, which failed to give the desired product as described above.

Acknowledgments

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- Preparation of compound 18:** To a stirred solution of the enol phosphonate **17** (0.0152 g, 0.0162 mmol) and $\text{Fe}(\text{acac})_3$ (0.0288 g, 0.0815 mmol) in a mixed solvent (THF/NMP = 20/1, 3.15 mL) was added MeMgCl (0.324 mL, 3.0 M in THF) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the aqueous layer was extracted with Et_2O (20 mL \times 3). The combined organic layer was dried over MgSO_4 , filtered, and evaporated. The residue was purified by silica gel chromatography (hexane/ethyl acetate = 50/1) to give the ester **18** (0.0093 g, 82%) as a colorless oil: R_f = 0.52 (hexane/ethyl acetate = 10/1); ^1H NMR (400 MHz, CDCl_3) δ 7.65–7.57 (4H, m), 7.44–7.39 (6H, m), 5.75 (1H, s), 5.65 (1H, s), 4.46–4.39 (1H, m), 3.75 (1H, ddd, J = 11.7, 4.4, 4.4 Hz), 3.70 (3H, s), 3.64 (1H, d, J = 9.8 Hz), 3.50 (1H, dd, J = 9.8, 5.4 Hz), 2.72–2.64 (1H, m), 2.56–2.47 (1H, m), 1.78–1.70 (1H, m), 1.68–1.60 (2H, m), 1.59 (3H, s), 1.52 (3H, s), 1.50–1.36 (1H, m), 1.13–0.94 (35H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 166.2, 161.7, 135.5, 135.4, 134.1, 133.8, 132.5, 129.5, 127.6, 127.5, 124.0, 118.9, 73.6, 63.3, 50.8, 42.1, 42.0, 40.7, 37.6, 33.8, 31.6, 28.2, 26.7, 23.0, 22.1, 19.2, 19.2, 18.2, 12.4; IR (neat) ν_{max} 2936, 2868, 1716, 1632, 1464, 1430, 1374, 1362, 1208, 1150, 1112, 1088, 1010, 998, 882, 862, 824, 762, 740, 702 cm^{-1} ; FAB-MS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{43}\text{H}_{67}\text{O}_4\text{Si}_2$: 703.4578, found: 703.4599; $[\alpha]_D^{18}$ +51.6 (c 0.4, CHCl_3).



Scheme 6.