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Synthetic studies on macrolactin A by using a (diene)Fe(CO)$_3$ complex

Akihiro Fukuda,[a] Yusuke Kobayashi,[a] Tetsutaro Kimachi[b] and Yoshiji Takemoto[a,*]

[a]*Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan*
[b]*Faculty of Pharmaceutical Sciences, Mukogawa Women's University, 11-68 Koshien Kyuban-cho, Nishinomiya 663-8179, Japan*

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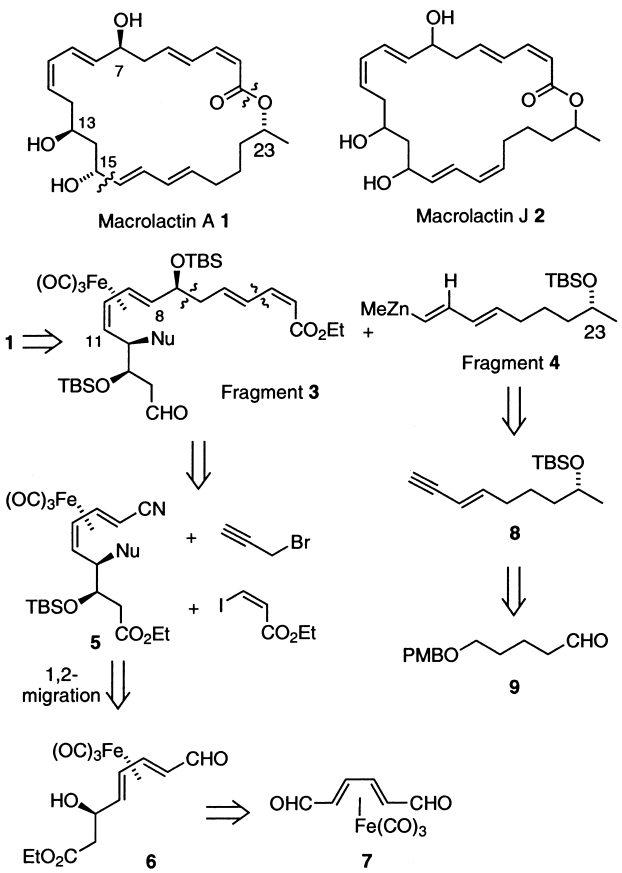
Abstract—The stereoselective synthesis of the two segments **3** and **4** of macrolactin A **1** is described. Macrolactin A is a 24-membered polyene macrolide antibiotic, which is of interest due to a strong activity against B16–F10 murine tumor cell and HIV-1 virus. The key step of the synthesis is the 1,2-migration reaction of a (diene)Fe(CO)$_3$ complex with a introduction of the thiol group to construct the unstable (*E*,*Z*)-conjugated dienic moiety (C8–C11).

1. Introduction

Macrolactin A **1** was isolated from a deep sea marine bacterium in 1989 as a 24-membered polyene macrolide antibiotic.[1] This compound possesses three sets of (*E*,*E*) and (*E*,*Z*) conjugated dienes and four stereogenic centers in the molecule, and exhibits a broad spectrum of activity with significant antiviral and cancer cell cytotoxic properties including inhibition of B16–F10 murine melanoma cell replication.[2,3] Because of unreliable supply from cell culture as well as its structural uniqueness and broad therapeutic potential, macrolactin A has been an attractive target for asymmetric synthesis. Although, thus far, three total synthesis[4] and novel synthetic studies[5] have been developed, systematic examination of the structure–activity relationship of macrolactins such as **1** and **2** have not yet been carried out to reveal the mechanism of their biological activities. With an expectation of preparing macrolactin A–M and other analogues, we have started to develop a flexible synthetic strategy for synthesizing structural analogues bearing the (8*E*,10*E*)- and (16*E*,18*Z*)-dienic moieties (Scheme 1). We report herein a novel synthetic strategy of key subunit **3** for macrolactin A that utilize the (diene)Fe(CO)$_3$ complex as a mobile chiral auxiliary for constructing C7–C13 fragment.

2. Results and discussion

The synthetic plan of total synthesis of macrolactin A



Scheme 1. Macrolactin A and its retrosynthetic analysis.

Keywords: macrolactin; iron–tricarbonyl complex; antibiotics; antivirus; synthesis.
* Corresponding author. Tel.: +81-75-753-4528; fax: +81-75-753-4569; e-mail: takemoto@pharm.kyoto-u.ac.jp

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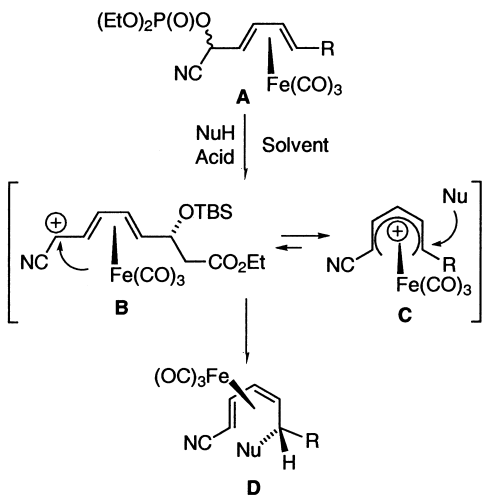
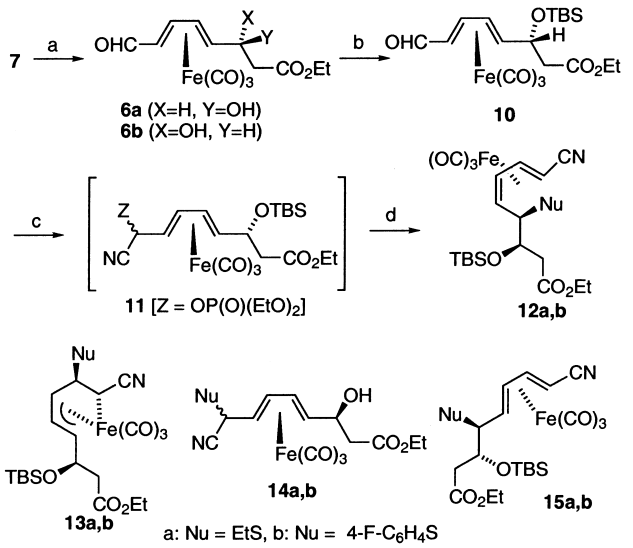
involves assembly of two fragments **3** and **4** by diastereoselective alkenylation[6] and macrolactonization[7] (Scheme 1). The (diene)$Fe(CO)_3$ complex in **3** plays a central role in our strategy, serving not only as a chiral auxiliary for constructing the two chiral centers (C7 and C13), but also as a protecting group of the unstable (*E*,*Z*)-conjugated dienic moiety (C8–C11).[8] We have already reported that treatment of (*E*,*E*)-cyanophosphate complex A with Lewis acid such as BF_3·etherate and $LiClO_4$ in the presence of a nucleophile gave the (*E*,*Z*)-nitrile complex D as a major isomer via the intermediates B and C (Scheme 2).[9] In this way, the 1,2-migration reaction provided the protected (*E*,*Z*)-dienic product stereoselectively. We anticipated that this compound **3** could be prepared from meso-dialdehyde $Fe(CO)_3$ complex **7**[10] by aldol condensation of achiral or chiral acetate (**7**→**6**), 1,2-migration of the $Fe(CO)_3$ complex along with a hydride introduction (**6**→**5**), and subsequent diastereoselective alkylation, followed by Pd-catalyzed cross-coupling reaction (**5**→**3**). On the other hand, **4** could be derived from enyne **8**, which would be synthesized from aldehyde **9** in two steps, by hydrozirconation with Cp_2ZrHCl and subsequent transmetallation with dimethylzinc.[6]



Scheme 2. 1,2-Migration of phosphate **A** for synthesis of (*E*,*Z*)-diene $Fe(CO)_3$ complex **D**.

Synthesis of the fragment **3** commenced from aldehyde **7**. Aldol condensation of **7** with the lithium enolate of ethyl acetate gave the desired alcohol **6b** in 60% yield as a major product (**6a/6b**=1/4) (Scheme 3). After protecting the hydroxyl group of **6b** (**10**, 95% yield), cyanophosphate **11** was obtained as a mixture of diastereoisomers by the usual manner.[11] Having the desired starting material at hand, we first investigated the key 1,2-migration of **11** in the presence of several hydride reagents such as triethylsilane and sodium cyanoborohydride.[12] Although we have tried the reaction of **11** under various reaction conditions, unfortunately, the aimed migration product could not be obtained at all. Our focus was then directed to the 1,2-migration in the presence of thiol as a nucleophile. Unexpectedly, subjection of **11** to a typical 1,2-migration reaction (5 equiv. of EtSH and 0.1 equiv. of BF_3·Et_2O in THF at room temperature) only furnished the undesired (alkenediyl)iron complex **13a**[13] in 58% yield and we could not identified the desired product **12a** in the reaction mixture. We next examined



Scheme 3. (a) AcOEt, LDA, 60% (**6a/6b**=1/4); (b) TBSOTf, 95%; (c) $(EtO)_2P(O)CN$, LiCN; (d) NuH, Acid, Solvent (see Table 1).

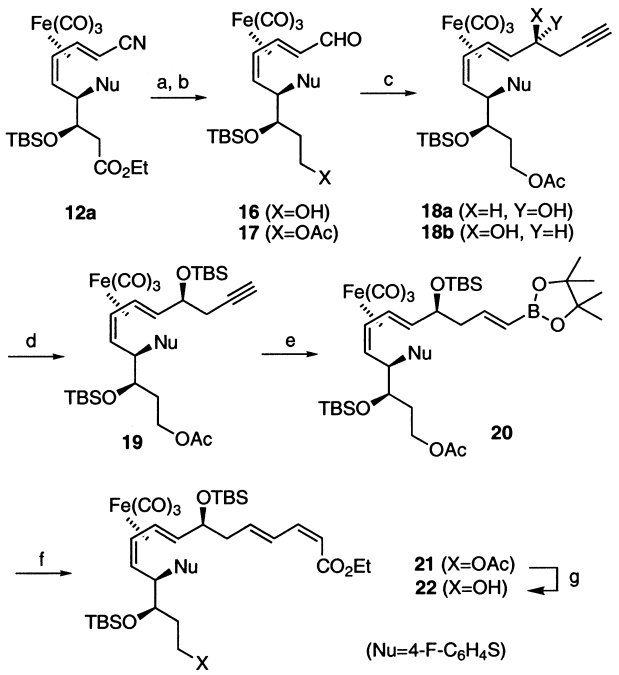
several acidic catalysts and solvents in the presence of 4-fluorobenzenethiol, a weaker nucleophile than ethyl thiol (Table 1). These results indicate that the solvent employed have a significant effect on the ratio of the products **12b**–**15b**. Although use of THF as a solvent gave (alkenediyl)iron complex **13b** as a major product, the same reaction of **11** in CH_2Cl_2 at −40°C provided non-migrated product **14b** predominantly. In contrast, the desired product **12b** was obtained in moderate yield by the same treatment of **11** in dioxane. Furthermore, employing HBF_4 as an acid in dioxane at room temperature led to the best yield of **12b** together with the (*E*,*E*)-migrated product **15b**. We have no reasonable explanation of the solvent effect that determined the predominant product at this stage.

Table 1. 1,2-Migration of phosphate **11** in the presence of 4-fluorobenzene thiol

Entry	Acid	Solvent	Yield (%)			
			12	**13**	**14**	**15**
1	BF_3·OEt_2	THF	10	35	–[a]	–[a]
2	BF_3·OEt_2	CH_2Cl_2	18	–[a]	46	–[a]
3	BF_3·OEt_2	1,4-Dioxane	27	–[a]	–[a]	16
4	HBF_4	1,4-Dioxane	46	–[a]	–[a]	8

[a] The product was not identified.

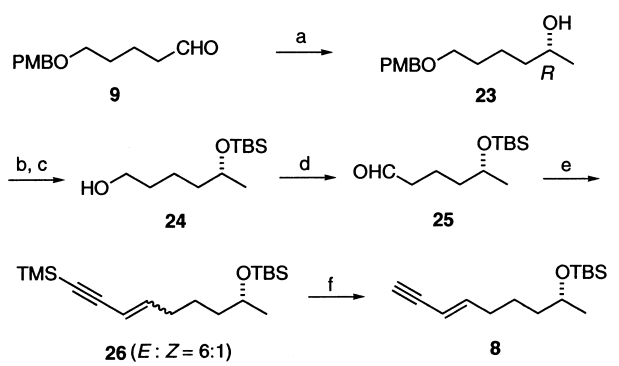
Having established the synthesis of the desired (*E*,*Z*)-dienyl sulfide $Fe(CO)_3$ complex **12b**, we next investigated an efficient introduction of the (2*Z*,4*E*)-hexadienoic acid moiety into **12b** (Scheme 4). This nitrile **12b** was first subjected to hydride-reduction using an excess of DIBAL-H (**16**, 77% yield), and the desired acetate **17** was obtained in 98% yield after protection with acetic anhydride in pyridine. Although we expected the subsequent Reformatsky reaction of **17** proceeded diastereoselectively by utilizing the chirality of the (diene)$Fe(CO)_3$ moiety, the propargylation of the resulting aldehyde **17** with propargyl bromide and zinc in the presence of NH_4Cl[14] furnished secondary alcohols **18a** and **18b** as a 1/1 mixture. Several experiments with indium (0) and aluminum (0) could not improve the



Scheme 4. (a) DIBAL-H, 77%; (b) Ac_2O, 98%; (c) propargyl bromide, Zn, NH_4Cl, 88% (**12a**/**12b**=1/1); (d) TBSOTf, 50%; (e) pinacolborane, Rh(CO)$(PPh_3)_2Cl$, 27%; (f) Ethyl (*Z*)-3-iodopropenate, $Pd(PPh_3)_4$, 10% TlOH, 43% (**21**), 24% (**22**); (g) K_2CO_3, EtOH, 85%.

diastereoselectivity of **18a** and **18b**. Configuration of the products **18a** and **18b** was elucidated by comparison of their R_f values according to the literature.[15] Fortunately, protection of a mixture of **18a** and **18b** with TBSOTf only gave the desired product **19** in 50% yield along with recovery of undesired diastereomer **18a**. Hydroboration of **19** with pinacolborane (27% yield),[16] followed by Pd-catalyzed cross-coupling reaction with ethyl (*Z*)-3-iodopropenoate,[17] produced a mixture of acetate **21** and alcohol **22** in 46 and 20% yields, respectively. The acetate **21** was easily transformed into **22** by the hydrolysis with K_2CO_3 in EtOH.

With the half building block now accessible, we undertook the synthesis of the other fragment **8**, which involved the catalytic asymmetric methylation of **9** with dimethylzinc. Synthesis of **8** began with PMB aldehyde **9** derived from 1,5-pentanediol in two steps (Scheme 5). The asymmetric methylation of **9** with Me_2Zn and Ti(O-*i*-Pr)$_4$[18] was first examined in the presence of several chiral ligands **E**–**G**

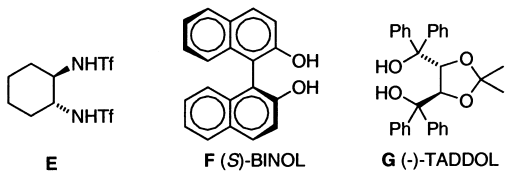


Scheme 5. (a) Me_2Zn Ti(O-*i*-Pr)$_4$, (+)-TADDOL, 99% (95% ee); (b) TBSCl, imidazole, 93%; (c) DDQ; $NaBH_4$, quant; (d) IBX, 76%; (e) TMSCCCH=PPh_3, 84%; (f) TBAF, 94%.

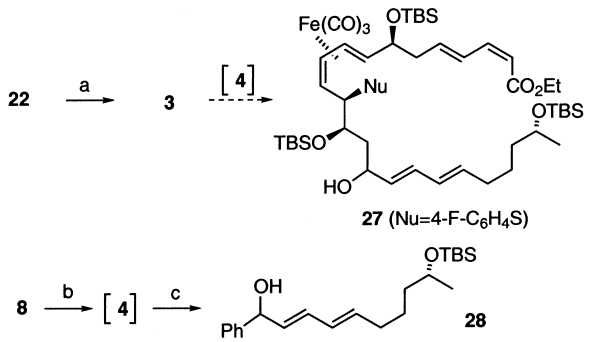
Table 2. Asymmetric methylation of aldehyde **9** in the presence of several chiral ligands to synthesize **23**

Entry	Ligand (equiv.)	Me_2Zn (equiv.)	Ti(O-*i*-Pr)$_4$ (equiv.)	Temperature (°C)	Yield (%)	ee (%)
1	**E** (0.06)	1.5	1.5	−25	27	68
2	**F** (0.1)	3.0	1.2	0	22	22
3	**G** (0.2)	2.0	2.2	−25	99	96

(Table 2). The reactions with bis-sulfonamide **E**[18a] and (*S*)-BINOL **F**[18b] gave rise to the desired alcohol **23** in low to moderate enantioselectivity. However, **23** was obtained in 99% yield with high enantioselectivity (96% ee) under Seebach's conditions [Me_2Zn and Ti(O-*i*-Pr)$_4$ in the presence of (+)-TADDOL **G** (20 mol%)].[18c] The resulting alcohol **23** was protected as a TBS ether before removal of the terminal PMB ether to furnish primary alcohol **24**. Oxidation of **24** to an aldehyde, followed by exposure to Corey's reagent,[19] produced (*E*)-enyne **26** as a major product [*E*/*Z*=6/1]. After separation of undesired (*Z*)-enyne by column chromatography, deprotection of the TMS group in **26** gave the desired product **8**.



Finally, treatment of alcohol **22** with IBX[20] gave rise to the desired product **3** (Scheme 6). Therefore, we next examined the coupling reaction of aldehyde **3** and enyne **8** using the Wipf's protocol[6] [hydrozirconation and Me_2Zn-mediated nucleophilic addition]. Although the coupling reaction of **3** and **4** was carried out under various reaction conditions (even in the presence of chiral amino alcohol as a promoter), we could obtained no desired product **27** at all. To secure the formation of alkenylzinc species **4** from **8**, the reaction of **4** with benzaldehyde was conducted, giving the corresponding alcohol **28** in 50% yield. From these results, the failure of coupling of **3** with **4** seems to be attributed to the poor reactivity of the aldehyde **3**.



Scheme 6. (a) IBX; (b) $Cp_2Zr(H)Cl$; Me_2Zn; (c) benzaldehyde, 50%.

3. Conclusion

We have succeeded in the synthesis of (*Z*,*E*,*E*,*Z*)-tetraene complex **22** by the 1,2-migration reaction of the $Fe(CO)_3$ group and also chiral enyne **8** by the catalytic asymmetric methylation with Me_2Zn, while the final coupling reaction

of **3** and **8** has not yet been achieved. We are now investigating alternative strategy for total synthesis of macrolactin A.

4. Experimental

4.1. General information

Melting points are uncorrected. IR spectra were obtained using a JASCO FTIR-410 spectrometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125.7 MHz) spectra were obtained using a JEOL JNM-LA-500 spectrometer using TMS as an internal standard. Optical rotations were measured with a JASCO DIP-360 polarimeter. Nominal (MS) and high-resolution (HRMS) mass spectra were measured with a JEOL JMS-01SG-2 or JMS-HX/HX 110A mass spectrometer. Column chromatography was carried out using Merck Kieselgel 60. Enantiomeric excess was determined by chiral HPLC using a Shimadzu SPD-10A with Daicel Chiralpak AD (0.46 cm×25 cm), Chiralpak OD (0.46 cm×25 cm), or Chiralpak OD-H (0.46 cm×25 cm). Dry solvents purchased from Kanto Chemicals were used in all reactions.

4.1.1. Ethyl (3*RS*,4*RS*,4*E*,6*E*)-tricarbonyliron[(η^4-4-7)-7-formyl-3-hydroxyhepta-4,6-dienoate] (6b). A solution of AcOEt (352 mg, 4.00 mmol) in 4.0 ml THF was added to a LDA solution, which was prepared with *n*-BuLi (1.59 M in hexane, 3.0 ml, 4.80 mmol) and *i*-Pr_2NH (0.67 ml, 4.80 mmol) in THF (5.6 ml), at −78°C under an argon atmosphere. After 30 min, the resulting solution was slowly added to a stirred solution of **7** (1.00 g, 4.00 mmol) in THF (25 ml) at −78°C. The mixture was stirred for 30 min at −78°C and a saturated $NaHCO_3$ solution was added to the whole mixture. The resulting mixture was allowed to warm up to room temperature, and extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane/AcOEt=2/1) to give **6a** (201 mg, 15%) and **6b** (812 mg, 60%).

Compound **6b**. Yellow crystals: mp 151.5–152°C (AcOEt); R_f=0.50 (hexane/AcOEt=1/1); ^{1}H NMR ($CDCl_3$) δ: 1.30 (dd, 1H, *J*=4.0, 7.6 Hz), 1.30 (t, 3H, *J*=7.0 Hz), 1.50 (dd, 1H, *J*=7.0, 8.5 Hz), 2.59 (dd, 1H, *J*=8.5, 16.8 Hz), 2.71 (dd, 1H, *J*=3.1, 16.8 Hz), 3.50 (d, 1H, *J*=4.3 Hz), 4.00 (dddd, 1H *J*=3.1, 4.3, 7.0, 8.5 Hz), 4.21 (q, 2H, *J*=7.0 Hz), 5.65 (dd, 1H, *J*=5.2, 8.5 Hz), 5.86 (dd, 1H, *J*=5.2, 7.6 Hz), 9.33 (d, 1H, *J*=4.0 Hz); ^{13}C NMR ($CDCl_3$) δ: 14.2, 42.3, 54.9, 61.2, 65.2, 69.1, 82.5, 86.3, 172.3, 196.1; IR ($CHCl_3$): 3528, 2065, 2006, 1716, 1680 cm^{-1}; MS (FAB) *m*/*z* 339 (MH^+, 37), 321 (40), 283 (21), 254 (90), 237 (95), 154 (100). Anal. calcd for $C_{13}H_{14}FeO_7$: C, 46.18; H, 4.17. Found: C, 46.24; H, 4.26.

Compound **6a**. Yellow crystals: mp 68–69°C ($CHCl_3$/hexane); R_f=0.40 (hexane/AcOEt=1/1); ^{1}H NMR ($CDCl_3$) δ: 1.22 (dd, 1H, *J*=4.0, 8.2 Hz), 1.30 (t, 3H, *J*=7.0 Hz), 1.52 (dd, 1H, *J*=5.8, 8.9 Hz), 2.53 (dd, 1H, *J*=9.5, 16.8 Hz), 2.69 (dd, 1H, *J*=3.1, 16.8 Hz), 3.31 (s, 1H), 4.18–4.23 (m, 1H), 4.20 (t, 2H, J=7.0 Hz), 5.58 (dd, 1H, *J*=5.2, 8.9 Hz), 5.83 (dd, 1H, *J*=5.2, 8.2 Hz), 9.32 (d, 1H, *J*=4.0 Hz); ^{13}C NMR ($CDCl_3$) δ: 14.1, 43.6, 54.4, 61.1, 68.2, 68.2, 81.4, 85.0, 172.0, 196.1; IR ($CHCl_3$): 3539, 2065, 2004, 1717, 1678 cm^{-1}; MS (FAB) *m*/*z* 339 (MH^+, 37), 321 (8), 254 (96), 237 (100). Anal. calcd for $C_{13}H_{14}FeO_7$: C, 46.18; H, 4.17. Found: C, 46.00; H, 4.18.

4.1.2. Ethyl (3*RS*,4*RS*,4*E*,6*E*)-tricarbonyliron[(η^4-4-7)-3-(*tert*-butyldimethylsilyloxy)-7-formylhepta-4,6-dienoate] (10). To a stirred solution of **6b** (150 mg, 0.444 mmol) in THF (14 ml) were successively added 2,6-lutidine (0.16 ml, 1.33 mmol) and TBSOTf (*tert*-butyldimethylsilyl trifluoromethanesulfonate) (0.15 ml, 0.666 mmol) at −40°C. The mixtures was stirred at −40°C for 1 h, before being quenched with aqueous ammonium chloride solution. The aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane/AcOEt=10/1) to give **10** (190 mg, 95%). a yellow oil; ^{1}H NMR ($CDCl_3$) δ: 0.09 (s, 3H), 0.13 (s, 3H), 0.86 (s, 9H), 1.27 (t, 3H, *J*=7.0 Hz), 1.40 (dd, 1H, *J*=3.4, 7.9 Hz), 1.69 (dd, 1H, *J*=8.2, 8.5 Hz), 2.61 (dd, 1H, *J*=4.0, 15.0 Hz), 2.68 (dd, 1H, *J*=7.6, 15.0 Hz), 3.97 (ddd, 1H, *J*=4.0, 7.6, 8.5 Hz), 4.12–4.17 (m, 2H), 5.42 (dd, 1H, *J*=5.2, 8.2 Hz), 5.83 (dd, 1H, *J*=5.2, 7.9 Hz), 9.35 (d, 1H, *J*=3.4 Hz); ^{13}C NMR ($CDCl_3$) δ: −4.6, −4.0, 14.1, 18.0, 25.6, 44.5, 55.2, 60.6, 66.7, 71.9, 82.2, 87.4, 170.2, 195.7; IR ($CHCl_3$): 2956, 2858, 2065, 2007, 1731, 1679 cm^{-1}; MS (FAB) *m*/*z* 452 (M^+, 82), 424 (96), 368 (53), 236 (81), 153 (100); HRMS (FAB) *m*/*z* calcd for $C_{19}H_{28}FeO_7Si$ (M^+) 452.0954. Found: 452.0956.

4.1.3. Ethyl (3*RS*,4*SR*,5*SR*,5*Z*,7*E*)-tricarbonyliron[(η^4-5-8)-3-(*tert*-butyldimethylsilyloxy)-8-cyano-4-(4-fluorophenysulphanyl)octa-5,7-dienoate] (12). To a stirred solution of **10** (490 mg, 1.08 mmol) in THF (11 ml) were added diethyl phosphorocyanidate (0.18 ml, 1.2 mmol) and LiCN (11 mg, 0.32 mmol) at 0°C under an argon atmosphere. After 30 min, a saturated $NaHCO_3$ solution was added to the mixture, and the resulting mixture was extracted with AcOEt. The extracts were washed with brine, dried over $MgSO_4$, and then concentrated in vacuo to give **11** (757 mg, 100%) as a crude product, which was used without further purification for next reaction [entry 1 in Table 1]. To a stirred solution of **11** (25 mg, 0.038 mmol) in THF (0.38 ml) were added 4-fluorobenzenethiol (0.082 ml, 0.77 mmol) and $BF_3{\cdot}OEt_2$ (0.010 ml, 0.079 mmol) at 0°C under an argon atmosphere. After 1 h, a saturated $NaHCO_3$ solution was added to the reaction mixture, and the resulting mixture was extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane/AcOEt=12/1) to give **12** (2.3 mg, 10%) and **13** (7.7 mg, 35%) [entry 2 in Table 1]. To a stirred solution of **11** (25 mg, 0.038 mmol) in CH_2Cl_2 (0.38 ml) were added 4-fluorobenzenethiol (0.082 ml, 0.77 mmol) and $BF_3{\cdot}OEt_2$ (0.010 ml, 0.079 mmol) at −40°C under an argon atmosphere. After 1 h, a saturated $NaHCO_3$ solution was added to the reaction mixture, and the resulting mixture was extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2,

hexane/AcOEt=12:1) to give **12** (4.0 mg, 18%) and **14** (8.4 mg, 46%, 2/1 diastereomixture) [entry 3 in Table 1]. To a stirred solution of **11** (18 mg, 0.028 mmol) in 1,4-dioxane (0.28 ml) were added 4-fluorobenzenethiol (0.061 ml, 0.57 mmol) and $BF_3{\cdot}OEt_2$ (0.010 ml, 0.079 mmol) at room temperature under an argon atmosphere. After 1 h, another $BF_3{\cdot}OEt_2$ (0.010 ml, 0.079 mmol) was added to the reaction mixture at room temperature. After 1 h, a saturated $NaHCO_3$ solution was added to the reaction mixture, and the resulting mixture was extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane/AcOEt=12/1) to give **12** (4.5 mg, 27%) and **15** (2.7 mg, 16%) [entry 4 in Table 1]. To a stirred solution of **11** (88.0 mg, 0.132 mmol) in 1,4-dioxane (1.3 ml) were added 4-fluorobenzenethiol (0.14 ml, 1.3 mmol) and HBF_4 (54% ether solution, 0.022 ml, 0.16 mmol) at 20°C under an argon atmosphere. After 1 h, a saturated $NaHCO_3$ solution was added to the reaction mixture, and the resulting mixture was extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane/AcOEt=12/1) to give **12** (35.8 mg, 46%) and **15** (6.2 mg, 8%).

Compound **12**. A yellow oil; ^{1}H NMR ($CDCl_3$) δ: 0.16 (s, 3H), 0.19 (s, 3H), 0.93 (s, 9H), 1.30 (dd, 3H, J=7.0, 7.3 Hz), 1.38 (d, 1H, J=7.6 Hz), 2.58 (dd, 1H, J=3.7, 16.2 Hz), 2.61 (d, 1H, J=11.9 Hz), 3.11 (dd, 1H, J=10.1, 16.2 Hz), 3.30 (dd, 1H, J=7.9, 11.9 Hz), 4.14–4.20 (m, 2H), 4.44 (dd, 1H, J=3.7, 10.1 Hz), 4.98 (dd, 1H, J=5.2, 7.9 Hz), 5.31 (dd, 1H, J=5.2, 7.6 Hz), 7.00–7.04 (m, 2H), 7.26–7.29 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 4.8, −4.2, 14.2, 18.0, 25.2, 25.6, 40.1, 58.5, 60.9, 63.2, 71.5, 82.8, 92.0, 116.3 (J=21.7 Hz), 121.4, 129.7, 136.6 (J=8.3 Hz), 162.8 (J=248.2 Hz), 171.1; IR ($CHCl_3$): 2956, 2931, 2858, 2223, 2066, 2005, 1721, 1490 cm^{-1}; MS (FAB) m/z 590 (MH^+, 4.7), 561 (3.3), 379 (26), 378 (100). Anal. calcd for $C_{26}H_{32}FFeNO_6SSi$: C, 52.97; H, 5.47; N, 2.38. Found: C, 52.68; H, 5.54; N, 2.37.

Compound **13**. A yellow oil; ^{1}H NMR ($CDCl_3$) δ: 0.16 (s, 3H), 0.16 (s, 3H), 0.15 (d, 1H, J=8.2 Hz), 0.92 (s, 9H), 1.30 (dd, 3H, J=7.0, 7.0 Hz), 2.74 (dd, 1H, J=6.1, 15.3 Hz), 2.90 (dd, 1H, J=5.8, 15.3 Hz), 3.51 (dd, 1H, J=5.8, 11.3 Hz), 4.02 (dd, 1H, J=7.6, 8.2 Hz), 4.17–4.23 (m, 2H), 4.44 (ddd, 1H, J=5.8, 5.8, 6.1 Hz), 4.46 (dd, 1H, J=7.0, 7.6 Hz), 4.73 (dd, 1H, J=7.0, 11.3 Hz), 7.03 (dd, 2H, J=8.5, 8.5 Hz), 7.39–7.42 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: −4.9, −4.5, −3.9, 14.2, 18.1, 25.8, 44.9, 50.0, 57.7, 60.9, 71.9, 82.5, 97.4, 116.5 (J=21.7 Hz), 126.6, 127.3 (J=3.0 Hz), 135.7 (J=8.3 Hz), 163.0 (J=249.0 Hz), 170.2, 202.5, 208.5, 209.5; IR ($CHCl_3$): 2956, 2932, 2859, 2205, 2074, 2018, 1729, 1489 cm^{-1}; MS (FAB) m/z 590 (MH^+, 1.1), 462 (26), 378 (100); HRMS (FAB) m/z calcd for $C_{26}H_{33}FFeNO_6SSi$ (MH^+) 590.1131. Found: 590.1151.

Compound **14**. A yellow oil; ^{1}H NMR ($CDCl_3$) δ: Major isomer: 0.87 (dd, 1H, J=7.6, 9.8 Hz), 1.11 (dd, 1H, J=8.9, 9.5 Hz), 1.29 (t, 3H, J=7.0 Hz), 2.60 (dd, 1H, J=9.2, 15.9 Hz), 2.70 (dd, 1H, J=4.0, 15.9 Hz), 3.09–3.15 (m, 1H), 3.53 (d, 1H, J=9.8 Hz), 4.21 (q, 2H, J=7.0 Hz), 4.84 (dd, 1H, J=5.2, 8.9 Hz), 5.11 (dd, 1H, J=5.2, 7.6 Hz), 7.06–7.10 (m, 2H), 7.48 (dd, 2H, J=5.5, 8.2 Hz), Minor isomer: 0.94 (dd, 1H, J=7.0, 7.9 Hz), 1.17 (dd, 1H, J=8.9, 10.1 Hz), 1.31 (t, 3H, J=7.0 Hz), 2.59–2.64 (m, 1H), 2.71–2.75 (m, 1H), 3.09–3.15 (m, 1H), 3.64 (d, 1H, J=7.0 Hz), 4.22 (q, 2H, J=7.0 Hz), 4.73 (dd, 1H, J=5.2, 8.9 Hz), 5.02 (dd, 1H, J=5.2, 7.9 Hz), 7.06–7.10 (m, 2H), 7.48 (dd, 2H, J=5.5, 8.2 Hz); IR ($CHCl_3$): 3540, 2058, 1996, 1731, 1490 cm^{-1}; MS (FAB) m/z 475 (M^+, 2.8), 458 (8), 374 (100); HRMS (FAB) m/z calcd for $C_{20}H_{17}FFeNO_5S$ ($M-OH^+$) 458.0161. Found: 458.0142.

Compound **15**. A yellow oil; ^{1}H NMR ($CDCl_3$) δ: 0.08 (s, 3H), 0.12 (s, 3H), 0.43 (d, 1H, J=7.9 Hz), 0.90 (s, 9H), 1.09 (dd, 1H, J=8.5, 10.1 Hz), 1.28 (dd, 3H, J=7.0, 7.3 Hz), 2.61 (dd, 1H, J=4.0, 15.9 Hz), 2.71 (dd, 1H, J=8.5, 15.9 Hz), 3.02 (dd, 1H, J=2.1, 10.1 Hz), 4.10–4.19 (m, 2H), 4.45 (ddd, 1H, J=2.1, 4.0, 8.5 Hz), 4.58 (dd, 1H, J=4.9, 8.5 Hz), 5.41 (dd, 1H, J=4.9, 7.9 Hz), 7.08 (dd, 2H, J=8.2, 8.5 Hz), 7.43 (dd, 2H, J=5.5, 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ: −5.0, −4.7, 14.1, 18.0, 24.8, 25.7, 38.7, 60.8, 61.4, 61.8, 72.2, 81.5, 86.8, 116.6 (J=21.7 Hz), 120.8, 128.7 (J=3.1 Hz), 137.3 (J=8.3 Hz), 163.1 (J=249.0 Hz), 170.7; IR ($CHCl_3$): 2955, 2932, 2858, 2223, 2068, 2011, 1731, 1489 cm^{-1}; MS (FAB) m/z: 590 (MH^+, 1.3), 307 (39), 154 (100); HRMS (FAB) m/z calcd for $C_{26}H_{33}FFeNO_6SSi$ (MH^+) 590.1131. Found: 590.1110.

4.1.4. (2*SR*,6*SR*,7*RS*,2*E*,4*Z*)-Tricarbonyliron[(η^4-2-5)-7-(*tert*-butyldimethylsilyloxy)-6-(4-fluorophenysulphanyl)-9-hydroxynona-2,4-dienal] (16). To a stirred solution of **12** (88.0 mg, 0.149 mmol) in toluene (1.5 ml) were added DIBAL-H (1.0 M in toluene, 0.89 ml, 0.89 mmol) at −78°C under an argon atmosphere. The mixture was stirred at 0°C for 2 h and then quenched with aqueous ammonium chloride solution. The resulting mixture was filtrated through a pad of Celite and washed with AcOEt. The combined filtrates were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane/AcOEt=5/1) to give **16** (63.5 mg, 77%). A yellow oil; ^{1}H NMR ($CDCl_3$) δ: 0.15 (s, 3H), 0.18 (s, 3H), 0.95 (s, 9H),1.70–1.80 (s, 1H), 1.83–1.87 (m, 1H), 2.12 (dd, 1H, J=4.3, 8.9 Hz), 2.27–2.34 (m, 1H), 2.86 (d, 1H, J=11.9 Hz), 3.44 (dd, 1H, J=7.9, 11.9 Hz), 3.78–3.89 (m, 2H), 4.33 (dd, 1H, J=4.0, 8.9 Hz), 5.00 (dd, 1H, J=5.5, 7.9 Hz), 5.53 (dd, 1H, J=5.5, 8.9 Hz), 6.97 (dd, 2H, J=8.5, 8.5 Hz), 7.33–7.36 (m, 2H), 9.12 (d, 1H, J=4.3 Hz); ^{13}C NMR ($CDCl_3$) δ: −4.7, −3.9, 18.2, 25.8, 37.7, 54.8, 59.6, 59.9, 65.5, 74.5, 82.9, 91.7, 116.0 (J=21.7 Hz), 130.2, 136.6 (J=8.3 Hz), 162.7 (J=248.0 Hz), 197.0; IR ($CHCl_3$): 3427, 2955, 2931, 2858, 2061, 1998, 1678, 1489 cm^{-1}; MS (FAB) m/z 551 (MH^+, 1.9), 522 (3.0), 423 (15), 339 (27), 73 (100); HRMS (FAB) m/z calcd for $C_{24}H_{32}FFeO_6SSi$ (MH^+) 551.1022. Found: 551.1035.

4.1.5. (2*SR*,6*SR*,7*RS*,2*E*,4*Z*)-Tricarbonyliron[(η^4-2-5)-9-acetoxy-7-(*tert*-butyldimethylsilyloxy)-6-(4-fluorophenysulphanyl)nona-2,4-dienal] (17). To a stirred solution of **16** (88.7 mg, 0.161 mmol) in pyridine (1.6 ml) were added Ac_2O (23 μl, 0.24 mmol) and (dimethylamino)pyridine (2.0 mg, 0.016 mmol) at 0°C. The mixture was stirred at room temperature for 2 h, and then quenched with a saturated $NaHCO_3$ solution. The resulting mixture was extracted with AcOEt. The extract was washed with brine,

dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane/AcOEt=7/1) to give **17** (93.6 mg, 98%). A yellow oil; ^{1}H NMR ($CDCl_3$) δ: 0.16 (s, 3H), 0.18 (s, 3H), 0.95 (s, 9H), 1.93 (dd, 1H, J=3.7, 8.5 Hz), 2.08–2.12 (m, 1H), 2.10 (s, 3H), 2.22–2.30 (m, 1H), 2.57 (d, 1H, J=11.6 Hz), 3.40 (dd, 1H, J=8.2, 11.6 Hz), 4.13–4.17 (m, 1H), 4.23–4.30 (m, 2H), 5.04 (dd, 1H, J=5.2, 8.2 Hz), 5.56 (dd, 1H, J=5.2, 8.5 Hz), 7.00 (dd, 2H, J=8.2, 8.5 Hz), 7.32–7.35 (m, 2H), 9.17 (d, 1H, J=3.7 Hz); ^{13}C NMR ($CDCl_3$) δ: −4.6, −4.0, 18.2, 20.9, 25.8, 35.0, 54.6, 58.9, 61.1, 64.3, 72.4, 82.9, 91.4, 116.2 (J=21.7 Hz), 129.7, 137.0 (J=8.3 Hz), 162.9 (J=249.0 Hz), 171.1, 196.1; IR ($CHCl_3$): 2956, 2932, 2858, 2062, 1998, 1736, 1684, 1489 cm^{-1}; MS (FAB) m/z 593 (MH^+, 16), 508 (26), 381 (100); HRMS (FAB) m/z calcd for $C_{26}H_{34}FFeO_7SSi$ (MH^+) 593.1128. Found: 593.1119.

4.1.6. (4*SR*,5*SR*,9*SR*,10*RS*,5*E*,7*Z*)-Tricarbonyliron[(η^4-5-8)-12-acetoxy-10-(*tert*-butyldimethylsilyloxy)-9-(4-fluorophenysulphanyl)dodeca-5,7-dieneyne-4-ol] (18b). To a mixture of **17** (435 mg, 0.734 mmol), NH_4Cl (47 mg, 0.88 mmol), and zinc dust (58 mg, 0.88 mmol) in THF (7.3 ml) was added propargyl bromide (0.083 ml, 1.10 mmol) at room temperature under an argon atmosphere. The resulting mixture was stirred for 1 h and then quenched with an aqueous ammonium chloride solution. The mixture was extracted with ether and the combined extracts were washed with aqueous ammonium chloride solution and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane/AcOEt=7/1) to give a mixture of **18a** and **18b** (**18a**/**18b**=1/1.2) (409 mg, 88%).

Compound **18a**. A yellow oil; R_f=0.30 (hexane/AcOEt=5/1); ^{1}H NMR ($CDCl_3$) δ: 0.16 (s, 3H), 0.20 (s, 3H), 0.95 (s, 9H), 1.86 (dd, 1H, J=8.2, 9.2 Hz), 2.01–2.09 (m, 1H), 2.09 (s, 3H), 2.16 (dd, 1H, J=2.4, 2.4 Hz), 2.21–2.29 (m, 1H), 2.36–2.39 (m, 2H), 2.60 (d, 1H, J=11.9 Hz), 3.14 (dd, 1H, J=7.9, 11.9 Hz), 3.34–3.39 (m, 1H), 3.97–4.01 (m, 1H), 4.21 (dd, 1H, J=4.6, 9.2 Hz), 4.31–4.36 (m, 1H), 4.83 (dd, 1H, J=5.5, 7.9 Hz), 4.99 (dd, 1H, J=5.5, 9.2 Hz), 6.99–7.03 (m, 2H), 7.32–7.37 (m, 2H).

Compound **18b**. A yellow oil; R_f=0.25 (hexane/AcOEt=5/1); ^{1}H NMR ($CDCl_3$) δ: 0.16 (s, 3H), 0.19 (s, 3H), 0.94 (s, 9H), 1.70 (dd, 1H, J=7.9, 8.9 Hz), 2.01–2.09 (m, 1H), 2.06 (s, 3H), 2.23–2.29 (m, 1H), 2.29 (dd, 1H, J=2.4, 2.4 Hz), 2.33–2.39 (m, 1H), 2.46–2.53 (m, 1H), 2.52 (d, 1H, J=11.6 Hz), 3.22 (dd, 1H, J=7.9, 11.6 Hz), 3.46–3.51 (m, 1H), 4.12 (dd, 2H, J=6.1, 7.0 Hz), 4.25 (dd, 1H, J=5.2, 8.9 Hz), 4.87 (dd, 1H, J=5.2, 7.9 Hz), 5.13 (dd, 1H, J=5.2, 8.9 Hz), 6.99–7.03 (m, 2H), 7.32–7.37 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: −4.7, −4.6, −4.0, −4.0, 18.1, 18.2, 20.9, 21.1, 25.8, 25.8, 28.7, 29.9, 35.4, 35.5, 57.8, 59.0, 60.7, 61.0, 62.5, 63.5, 66.3, 71.6, 71.7, 71.8, 72.1, 72.4, 72.6, 78.8, 79.6, 79.8, 80.0, 90.7, 91.6, 115.9 (J=21.7 Hz), 116.0 (J=21.7 Hz), 130.2 (J=4.1 Hz), 130.3 (J=3.0 Hz), 136.7 (J=8.2 Hz), 137.1 (J=8.3 Hz), 162.7 (J=248.0 Hz), 162.8 (J=249.2 Hz), 171.2, 171.9; IR ($CHCl_3$): 3567, 3305, 2956, 2932, 2893, 2858, 2047, 1982, 1732, 1489 cm^{-1}; MS (FAB) m/z 631 ($M-H^+$, 15), 604 (27), 547 (68), 267 (82), 127 (100); HRMS (FAB) m/z calcd for $C_{29}H_{36}FFeO_7SSi$ ($M-H^+$) 631.1284. Found: 631.1322.

4.1.7. (4*SR*,5*SR*,9*SR*,10*RS*,5*E*,7*Z*)-Tricarbonyliron[(η^4-5-8)-12-acetoxy-4,10-bis(*tert*-butyldimethylsilyloxy)-9-(4-fluorophenysulphanyl)dodeca-5,7-dieneyne] (19). To a stirred solution of a mixture of **18a** and **18b** (117 mg, 0.185 mmol) in pyridine (0.67 ml) was added TBSOTf (0.085 ml, 0.37 mmol) at 0°C under an argon atmosphere. The mixture was stirred for 30 min, before being quenched with aqueous saturated sodium chloride solution. The mixture was extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane/AcOEt=20/1) to give **19** (68.9 mg, 50%) and **18a** (55.6 mg, 48%).

Compound **19**. A yellow oil; ^{1}H NMR ($CDCl_3$) δ: 0.01 (s, 3H), 0.06 (s, 3H), 0.16 (s, 3H), 0.20 (s, 3H), 0.88 (s, 9H), 0.95 (s, 9H), 2.06 (s, 3H), 1.97–2.09 (m, 2H), 2.19 (dd, 1H, J=2.4, 2.7 Hz), 2.23–2.30 (m, 1H), 2.33 (ddd, 1H, J=2.7, 5.5, 16.8 Hz), 2.40–2.45 (m, 1H), 2.56 (d, 1H, J=11.9 Hz), 3.17 (dd, 1H, J=7.9, 11.9 Hz), 3.47 (m, 1H), 4.07–4.16 (m, 2H), 4.29 (dd, 1H, J=5.2, 7.6 Hz), 4.87 (dd, 1H, J=5.2, 7.9 Hz), 5.07 (dd, 1H, J=5.2, 8.9 Hz), 6.98 (dd, 2H, J=8.5, 8.5 Hz), 7.34–7.37 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: −4.5, −4.4, −4.3, −4.0, 18.1, 18.2, 21.0, 25.8, 25.9, 29.1, 35.5, 59.0, 61.2, 63.5, 64.2, 71.6, 72.8, 73.1, 79.5, 80.1, 92.6, 116.0 (J=21.6 Hz), 130.1, 136.7 (J=8.3 Hz), 162.6 (J=248.0 Hz), 171.1; IR ($CHCl_3$): 3306, 2956, 2932, 2891, 2858, 2046, 1980, 1734, 1489 cm^{-1}; MS (CI) m/z (relative intensity) 747 (MH^+, 0.49), 289 (73), 157 (100), 133 (100); HRMS (CI) m/z calcd for $C_{35}H_{52}FFeO_7SSi_2$ (MH^+) 747.2305. Found: 747.2269.

4.1.8. Ethyl (7*SR*,8*SR*,12*SR*,13*RS*,2*Z*,4*E*,8*E*,10*Z*)-tricarbonyliron[(η^4-8-11)-7,13-bis(*tert*-butyldimethylsilyloxy)-12-(4-fluorophenylsulphanyl)-15-hydroxypentadeca-2,4,8,10-tetraenoate] (22). A solution of pinacolborane (0.230 ml, 0.230 mmol), freshly prepared according to the literature,[16] was slowly added to a stirred solution of **19** (85.2 mg, 0.114 mmol) and $Rh(CO)(PPh_3)_2Cl$ (4.8 mg, 0.0072 mmol) in CH_2Cl_2 (0.60 ml) at 0°C under an argon atmosphere. After being stirred at room temperature for 1 h, the reaction mixture was quenched with water and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane/AcOEt=20/1) to give **19** (17.7 mg, 21%) and **20** (26.8 mg, 27%). In a flask, a solution of ethyl (*Z*)-3-iodopropenoate (27.6 mg, 0.122 mmol) and tetrakis(triphenylphosphine)palladium (28.2 mg, 0.0244 mmol) in THF (0.67 ml) was stirred for 30 min under an argon atmosphere. In a second flask, to a stirred solution of **20** (26.8 mg, 0.0306 mmol) in THF (0.67 ml) was added 10% thallium hydroxide solution (0.27 ml) at 0°C under an argon atmosphere. The mixture was stirred at room temperature for 2 min, and the content of the first flask (0.34 ml) was then transferred into this boronate solution at 0°C. After being stirred at room temperature for 1 h, the mixture was quenched with water and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane/AcOEt=15/1) to give **21** (11.0 mg, 43%) and **22** (5.8 mg, 24%). To a stirred solution of **21** (11.0 mg, 0.0130 mmol) in ethanol (0.5 ml) was added

K_2CO_3 (10 mg, 0.072 mmol) at 0°C. After being stirred at room temperature for 6 h, the mixture was evaporated and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane/AcOEt=15/1) to give **22** (8.9 mg, 85%).

Compound **22**. A yellow oil; ^{1}H NMR ($CDCl_3$) δ: 0.00 (s, 3H), 0.02 (s, 3H), 0.14 (s, 3H), 0.18 (s, 3H), 0.88 (s, 9H), 0.93 (s, 9H), 1.30 (t, 3H, J=7.0 Hz), 1.79 (dd, 1H, J=8.2, 8.9 Hz), 1.80–1.86 (m, 1H), 2.04–2.14 (m, 2H), 2.46 (ddd, 1H, J=3.7, 8.5, 14.6 Hz), 2.48 (ddd, 1H, J=4.9, 5.2, 14.6 Hz), 2.59 (d, 1H, J=11.9 Hz), 3.19 (dd, 1H, J=7.9, 11.9 Hz), 3.51 (ddd, 1H, J=3.7, 4.9, 8.2 Hz), 3.58–3.66 (m, 2H), 4.19 (q, 2H, J=7.0 Hz), 4.29 (dd, 1H, J=4.6, 7.9 Hz), 4.83 (dd, 1H, J=5.2, 7.9 Hz), 5.06 (dd, 1H, J=5.2, 8.9 Hz), 5.65 (d, 1H, J=11.3 Hz), 6.12 (ddd, 1H, J=5.2, 8.5, 15.0 Hz), 6.60 (dd, 1H, J=11.3, 11.9 Hz), 6.94 (dd, 2H, J=8.5, 8.5 Hz), 7.28–7.31 (m, 2H), 7.45 (dd, 1H, J=11.9, 15.0 Hz); ^{13}C NMR ($CDCl_3$) δ: −4.6, −4.4, −4.2, −3.9, 14.3, 18.1, 18.2, 25.8, 25.9, 38.6, 41.5, 59.4, 59.5, 60.2, 64.8, 65.0, 73.8, 74.2, 80.0, 93.5, 115.9 (J=21.6 Hz), 116.4, 129.3, 130.4 (J=3.1 Hz), 136.4 (J=8.3 Hz), 140.5, 144.9, 162.5 (J=246.9 Hz), 166.9; IR ($CHCl_3$): 3514, 2955, 2931, 2890, 2858, 2044, 1976, 1702, 1637, 1595, 1489 cm^{-1}; MS (FAB) m/z 805 (MH^+, 0.31), 677 (10), 431 (100), 73 (100); HRMS (CI) m/z calcd for $C_{32}H_{53}FeO_8Si_2$ ($M-C_6H_4FS^+$) 677.2628. Found: 677.2647.

4.1.9. 5-(4-Methoxybenzyloxy)pentanal (9). To a suspension of sodium hydride (1.9 g, 48 mmol) in DMF (100 ml) was added 1,5-pentandiol (5.0 g, 48 mmol) at 0°C under an argon atmosphere, and the mixture was stirred at room temperature for 30 min. To the mixture was slowly added a solution of 4-methoxybenzyl chloride (6.5 ml, 48 mmol) at −20°C, and the whole was stirred at 0°C for 12 h. After being quenched with water, the mixture was extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane/AcOEt=2/1) to give the PMB ether (5.2 g, 48%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ: 1.37 (br, 1H), 1.41–1.47 (m, 2H), 1.55–1.66 (m, 4H), 3.45 (t, 2H, J=6.4 Hz), 3.64 (t, 2H, J=6.1 Hz), 3.80 (s, 3H), 4.43 (s, 2H), 6.88 (d, 2H, J=8.5 Hz), 7.26 (d, 2H, J=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ: 22.3, 29.3, 32.3, 55.1, 62.4, 69.9, 72.5, 113.6, 129.2, 130.5, 159.0; IR ($CHCl_3$): 3430, 1612, 1513, 1464 cm^{-1}; MS (EI) m/z (relative intensity) 224 (M^+, 8.4), 223 (6.0), 137 (56), 121 (100); HRMS (EI) m/z calcd for $C_{13}H_{20}O_3$ (M^+) 224.1412. Found 224.1413. To a solution of oxalyl chloride (1.7 ml, 20 mmol) in CH_2Cl_2 (45 ml) was added a solution of DMSO (1.5 ml, 21 mmol) in CH_2Cl_2 (10 ml) at −60°C. The mixture was stirred for 2 min, and then cooled to −78°C. To the mixture was added dropwise a solution of the PMB ether (3.0 g, 13 mmol) in CH_2Cl_2 (14 ml) and the resulting mixture was stirred at −78°C for 1.5 h. After triethylamine (9.3 ml) was added to the mixture at −78°C, the resulting mixture was warmed to 0°C. The mixture was quenched with water at 0°C and extracted with ethyl acetate. The extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane/AcOEt=5/1) to give **9** (2.7 g, 90%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ: 1.60–1.66 (m, 2H), 1.70–1.76 (m, 2H), 2.45 (dt, 2H, J=1.8, 7.2 Hz), 3.46 (t, 2H, J=6.1 Hz), 3.80 (s, 3H), 4.42 (s, 2H), 6.88 (d, 2H, J=8.5 Hz), 7.25 (d, 2H, J=8.5 Hz), 9.76 (t, 1H, J=1.8 Hz); ^{13}C NMR ($CDCl_3$) δ: 18.9, 29.1, 43.5, 55.2, 69.3, 72.5, 113.7, 129.2, 130.5, 159.1, 202.5; IR ($CHCl_3$): 1722, 1612, 1513, 1464 cm^{-1}; MS (EI) m/z (relative intensity) 222 (M^+, 6.8), 137 (20), 121 (100); HRMS (EI) calcud. for $C_{13}H_{18}O_3$ (M^+) 222.1256. Found 222.1251.

4.1.10. (2*R*)-6-(4-Methoxybenzyloxy)hexan-2-ol (23). Entry 1 in Table 2. A catalyst **E** (8.17 mg, 0.022 mmol) was placed in a dried round-bottom flask under an argon atmosphere. To this, were added degassed toluene (1.0 ml) and Ti(O-*i*-Pr)$_4$ (0.16 ml, 0.54 mmol), and the mixture was stirred at −40°C for 20 min. After being cooled to −78°C, a 1.0 M solution of Me_2Zn (0.54 ml, 0.54 mmol) in hexane was added to the mixture. To the whole mixture was added a solution of **9** (80 mg, 0.36 mmol) in toluene (1 ml). The mixture was warmed to −25°C, and stirring was continued at that temperature for 2 h. The mixture was quenched with 2N HCl and extracted with ether. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane/AcOEt=2/1) to furnish **23** (34.2 mg, 27%, 68%ee). Entry 2 in Table 2: (*S*)-BINOL **F** (10.2 mg, 0.0356 mmol) was placed in a dry flask under an argon atmosphere. To this were added degassed toluene (0.8 ml) and Ti(O-*i*-Pr)$_4$ (0.12 ml, 0.42 mmol), and the mixture was stirred at room temperature for 60 min. A solution of **9** (80 mg, 0.36 mmol) in toluene (0.8 ml) and a 1.0 M solution of Me_2Zn (1.07 ml, 1.07 mmol) were added to the mixture at 0°C. After being stirred at 0°C for 2 h, the reaction mixture was quenched with 1N HCl. The mixture was treated by the same procedure described above to give **23** (18.5 mg, 22%, 22% ee). Entry 3 in Table 2: (+)-TADDOL **G** (1.18 g, 2.52 mmol) was placed in a dry Schlenk tube under an argon atmosphere. To this were added Ti(O-*i*-Pr)$_4$ (0.89 ml, 3.02 mmol) and toluene (19 ml). After being stirred at room temperature for 5 h, toluene and 2-propanol was removed in vacuo. A solution of Ti(O-*i*-Pr)$_4$ (7.4 ml, 25 mmol) in toluene (9.4 ml) was added to the yellow solid residue at room temperature, and the mixture was cooled to −25°C. To the reaction mixture was successively added a solution of **9** (2.80 g, 12.6 mmol) in toluene (28 ml) and then Me_2Zn (25.2 ml, 1.0 M solution in *n*-hexane, 25.2 mmol). After being quenched with a NH_4Cl solution, the mixture was filtrated through a pad of Celite and washed with ether. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane/AcOEt=2/1) to furnish **23** (2.96 g, 99%, 96% ee). The enantiomeric excess of **23** was determined by chiral HPLC analysis (DAICEL Chiralcel OD, 3% 2-propanol in hexane, 1.2 ml/min, retention times: (*R*) (major) 20.9 min, (*S*) (minor) 22.1 min.

Compound **23**. A colorless oil; $[\alpha]_D^{20}$=−2.75 (c=1.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.18 (d, 3H, J=6.1 Hz), 1.36 (br, 1H), 1.39–1.52 (m, 4H), 1.59–1.67 (m, 2H), 3.45 (t, 2H, J=6.4 Hz), 3.80 (s, 3H), 3.80 (m, 1H), 4.43 (s, 2H), 6.88 (d, 2H, J=8.5 Hz), 7.26 (d, 2H, J=8.5 Hz); ^{13}C NMR

($CDCl_3$) δ: 22.4, 23.4, 29.6, 39.0, 55.2, 67.9, 69.9, 72.5, 113.7, 129.2, 130.6, 159.1; IR ($CHCl_3$): 3445, 1612, 1513, 1464 cm^{-1}; MS (EI) *m/z* (relative intensity) 238 (M^+, 6.8), 137 (47), 121 (100); HRMS (EI) calcd for $C_{14}H_{22}O_3$ (M^+) 238.1569. Found 238.1576.

4.1.11. Determination of the absolute configuration of 23. Absolute configuration was determined by ^1H NMR methods previously described by Mosher et al.[21] ^1H NMR of (+) or (−)-MTPA esters of **23** are as follows: (+)-MTPA ester: ^1H NMR ($CDCl_3$) δ: 1.32 (d, 3H, *J*=6.1 Hz), 1.48–1.67 (m, 6H), 3.35 (t, 2H, *J*=6.4 Hz), 3.56 (s, 3H), 3.80 (s, 3H), 4.40 (s, 2H), 5.14 (m, 1H), 6.87 (d, 2H, *J*=8.5 Hz), 7.23 (d, 2H, *J*=8.5 Hz), 7.37 (m, 3H), 7.53 (m, 2H). (−)-MTPA ester: ^1H NMR ($CDCl_3$) δ: 1.24 (d, 3H, *J*=6.1 Hz), 1.33–1.48 (m, 6H), 3.42 (t, 2H, *J*=6.4 Hz), 3.53 (s, 3H), 3.80 (s, 3H), 4.41 (s, 2H), 5.14 (m, 1H), 6.87 (d, 2H, *J*=8.5 Hz), 7.23 (d, 2H, *J*=8.5 Hz), 7.37 (m, 3H), 7.53 (m, 2H).

4.1.12. (5*R*)-5-(*tert*-Butyldimethylsilyloxy)hexan-1-ol (24). To a solution of alcohol **23** (1.00 g, 4.20 mmol) in DMF (20 ml) was successively added imidazole (857 mg, 12.6 mmol) and TBSCl (1260 mg, 8.40 mmol) at room temperature. The whole was stirred at room temperature for 2 h, before quenching with a saturated $NaHCO_3$ solution. The mixture was extracted with ether and the extract was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane/AcOEt=20/1) to give the TBS ether (1.38 g, 93%) as a colorless oil; $[\alpha]_D^{20}=-4.83$ (*c*=1.35, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 0.04 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 1.18 (d, 3H, *J*=5.8 Hz), 1.33–1.45 (m, 4H), 1.55–1.62 (m, 2H), 3.45 (t, 2H, *J*=6.4 Hz), 3.74–3.79 (m, 1H), 3.80 (s, 3H), 4.43 (s, 2H), 6.88 (d, 2H, *J*=8.5 Hz), 7.26 (d, 2H, *J*=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ: −4.8, −4.5, 18.1, 22.3, 23.7, 25.9, 30.0, 39.5, 55.1, 68.5, 70.0, 72.4, 113.7, 129.1, 130.1, 159.0; IR ($CHCl_3$): 1612, 1513, 1464, 1250 cm^{-1}; MS (CI) *m/z* (relative intensity) 353 (MH^+, 1.7), 351 (1.2), 121 (100); HRMS (CI) calcd for $C_{20}H_{37}O_3Si$ (MH^+) 353.2519. Found 353.2502. To a solution of the TBS ether (1.2 g, 3.4 mmol) in a mixture of CH_2Cl_2 (34 ml) and H_2O (2 ml) was added DDQ (85 mg, 3.7 mmol) at 0°C. The mixture was stirred at room temperature for 60 min, before being addition of methanol (30 ml). To reduce *p*-anisaldehyde produced in the reaction, several portions of $NaBH_4$ were added to the mixture at 0°C until *p*-anisaldehyde had disappeared on the TLC. After being quenched with saturated $NaHCO_3$ solution, the mixture was diluted with ether and filtered through a pad of Celite. The combined filtrates were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane/AcOEt=5/1) to furnish **24** (790 mg, quant.) as a colorless oil; $[\alpha]_D^{22}=-6.87$ (*c*=1.53, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 0.05 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 1.12 (d, 3H, *J*=6.1 Hz), 1.26 (br, 1H), 1.32–1.50 (m, 4H), 1.54–1.60 (m, 2H), 3.62–3.67 (m, 2H), 3.76–3.83 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: −4.7, −4.4, 18.1, 21.8, 23.8, 25.9, 32.8, 39.4, 63.0, 68.5; IR ($CHCl_3$): 3442, 1255 cm^{-1}; MS (CI) *m/z* (relative intensity) 233 (MH^+, 22), 101 (13), 57 (100); HRMS (CI) calcd for $C_{12}H_{29}O_2Si$ (MH^+) 233.1937. Found 233.1933.

4.1.13. (5*R*)-5-(*tert*-Butyldimethylsilyloxy)hexanal (25). To a solution of **24** (455 mg, 1.91 mmol) in 19 ml of a mixture of DMSO and THF (2/1) was added IBX (697 mg, 2.49 mmol), and the mixture was stirred at room temperature for 30 min. After being poured into a saturated $NaHCO_3$ solution, the aqueous layer was extracted with diethyl ether, and combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane/AcOEt=5/1) to give **25** (335 mg, 76%) as a colorless oil; $[\alpha]_D^{22}=-8.90$ (*c*=1.28, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 0.05 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 1.13 (d, 3H, *J*=6.1 Hz), 1.38–1.49 (m, 2H), 1.58–1.66 (m, 1H), 1.68–1.77 (m, 1H), 2.43 (m, 2H), 3.78–3.84 (m, 1H), 9.76 (t, 1H, *J*=1.8 Hz); ^{13}C NMR ($CDCl_3$) δ: −4.8, −4.4, 18.1, 18.3, 23.7, 25.8, 38.9, 43.9, 68.1, 202.6; IR ($CHCl_3$): 1722, 1255 cm^{-1}; MS (CI) *m/z* (relative intensity) 231 (MH^+, 9.1), 99 (100); HRMS (CI) calcd for $C_{12}H_{27}O_2Si$ (MH^+) 231.1780. Found 231.1785.

4.1.14. (8*R*,3*E*)-8-(*tert*-Butyldimethylsilyloxy)-1-(trimethylsilyl)non-3-en-1-yne (27). To a suspension of triphenyl-(3-trimethylsilylprop-2-ynyl)phosphonium bromide (400 mg, 0.882 mmol) in 4.4 ml of THF was added a 1.58 M solution of *n*-butyllithum (0.56 ml, 0.882 mmol) at −78°C, and the mixture was stirred at −40°C for 30 min. A solution of **25** (135 mg, 0.588 mmol) in THF (1 ml) was added to the mixture at −78°C. The whole was stirred at −78°C for 1 h and then allowed to warm to ambient temperature. After being stirred for 4 h, the mixture was quenched with water and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane/AcOEt=200/1) to furnish **27** (161 mg, 84%) and *Z*-isomer (26 mg, 14%). **27**: a colorless oil; $[\alpha]_D^{20}=-5.75$ (*c*=1.57, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 0.04 (s, 3H), 0.04 (s, 3H), 0.18 (s, 9H), 0.88 (s, 9H), 1.11 (d, 3H, *J*=6.1 Hz), 1.32–1.52 (m, 4H), 2.07–2.11 (m, 2H), 3.73–3.80 (m, 1H), 5.50 (d, 1H, *J*=15.9 Hz), 6.18–6.24 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: −4.7, −4.4, 0.0, 18.1, 23.9, 24.8, 25.9, 33.1, 39.1, 68.3, 92.4, 104.2, 109.7, 146.2; IR ($CHCl_3$): 2958, 2931, 2858, 2131, 1626, 1254, 844 cm^{-1}; MS (CI) *m/z* (relative intensity) 325 (MH^+, 11), 309 (100), 267 (27), 193 (70); HRMS (CI) calcd for $C_{18}H_{37}OSi_2$ (MH^+) 325.2383. Found 325.2375.

4.1.15. (8*R*,3*E*)-8-(*tert*-Butyldimethylsilylloxy)non-3-en-1-yne (8). To a stirred solution of **27** (52 mg, 0.16 mmol) in THF (0.87 ml) was added a 1.0 M solution of tetra-*n*-butylammonium fluoride (0.23 ml, 0.23 mmol) in THF at 0°C. After 1 h, the mixture was quenched with brine and extracted with diethyl ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexane/AcOEt=100/1) to give **8** (38 mg, 94%) as a colorless oil; $[\alpha]_D^{21}=-7.56$ (*c*=1.59, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 0.04 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 1.11 (d, 3H, *J*=5.8 Hz), 1.35–1.53 (m, 4H), 2.09–2.13 (m, 2H), 2.78 (d, 1H, *J*=1.8 Hz), 3.75–3.80 (m, 1H), 5.46 (dd, 1H, *J*=1.8, 15.9 Hz), 6.24 (dt, 1H, *J*=7.0, 15.9 Hz); ^{13}C NMR ($CDCl_3$) δ: −4.7, −4.4, 18.1, 23.8, 24.7, 25.9, 33.0, 39.0, 68.3, 75.6, 82.5, 108.5, 146.8; IR ($CHCl_3$): 3306, 2954, 2931, 2858, 2102, 1629, 1255, 835 cm^{-1}; MS (CI) *m/z*

(relative intensity) 253 (MH^+,43), 237 (30), 195 (37), 121 (51), 19 (100); HRMS (CI) calcd for $C_{15}H_{29}OSi$ (MH^+) 253.1988. Found 253.1992.

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