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Enantioselective Synthesis of the C11-C24 Segment of Macrolactin A via Organoiron Methodology

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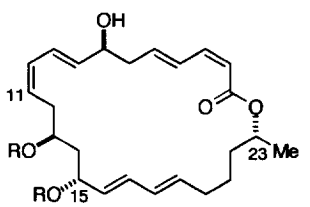
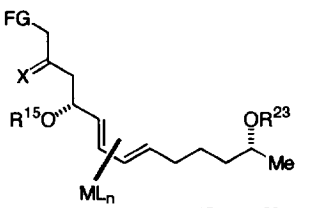
Abstract: The enantioselective synthesis of the $Fe(CO)_3$ complexed C11-C24 segment of macrolactin A has been accomplished from *rac*-(methyl 6-oxo-2,4-hexadienoate)$Fe(CO)_3$ in 11 steps (>50% ee).

Macrolactin A (**1a**) is a 24-membered polyene macrolide isolated from a taxonomically-undefined deep sea bacterium.[1a] The structure of **1a** was assigned on the basis of NMR spectroscopy,[1a] and by chemical degradation and synthesis of the fragments.[1b] This compound exhibits antiviral activity against Herpes Simplex I and II and against HIV. Unfortunately, the culturing of this bacterium has been "unreliable".[1b] The unique structure of **1a** coupled with its enticing biological activity and relative scarcity from natural sources has led to synthetic studies by several research groups.[2] Boyce and Pattenden have recently reported preparation of 13,15-dimethoxymacrolactin A (**1b**) using Stille Pd-coupling methodology for construction of the diene linkages.[3] The C11-C24 segment **2b** was a key intermediate in their synthesis. We here report on the preparation of a similar C11-C24 segment **2a** which relies on the *stereodirecting ability of an $Fe(CO)_3$ adjunct to control introduction of the remote asymmetric centers at C15 and C23*.

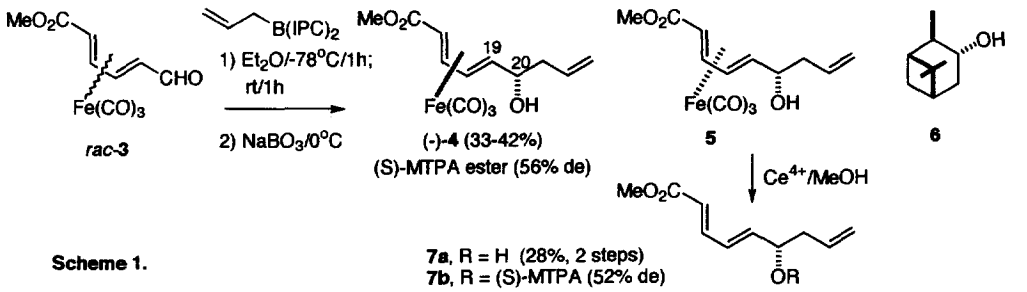


1a, R = H
1b, R = Me



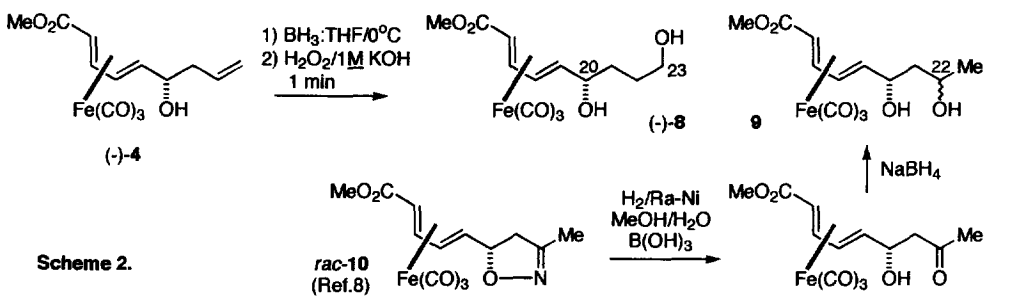
	FG	X	R^{15}	R^{23}	ML_n
2a	2-(1,3-dioxane)	O	H	OTBDMS	$Fe(CO)_3$
2b	CHO	OMe, H	Me	OAc	none

The reaction of (methyl 6-oxo-2,4-hexadienoate)$Fe(CO)_3$ (*rac*-**3**)[4] with *B*-allyldiisopinocampheylborane (prepared from (-)-$(IPC)_2BOMe$),[5] followed by brief oxidative work up with $NaBO_3$, gave a mixture of alcohols (-)-**4**, **5** and isopinocampheol **6** (Scheme 1). After chromatographic separation, the desired (-)-**4** was assigned the 19S,20S stereochemistry (54% ee, macrolactin A numbering) by comparison of its optical rotation with that of the previously reported[6] R,R enantiomer. The (S)-Mosher's ester of (-)-**4** was determined to be 56% de by ^1H NMR spectroscopy. While (-)-**4** was readily separable, the diastereomeric alcohol **5** could not be easily separated from **6**. However, treatment of a mixture of **5** and **6** with $(NH_4)_2Ce(NO_3)_6$ gave the free ligand **7a**, which was easily separable from **6**. The derived (S)-MTPA ester **7b** was determined to be 52% de by ^1H NMR spectroscopy.



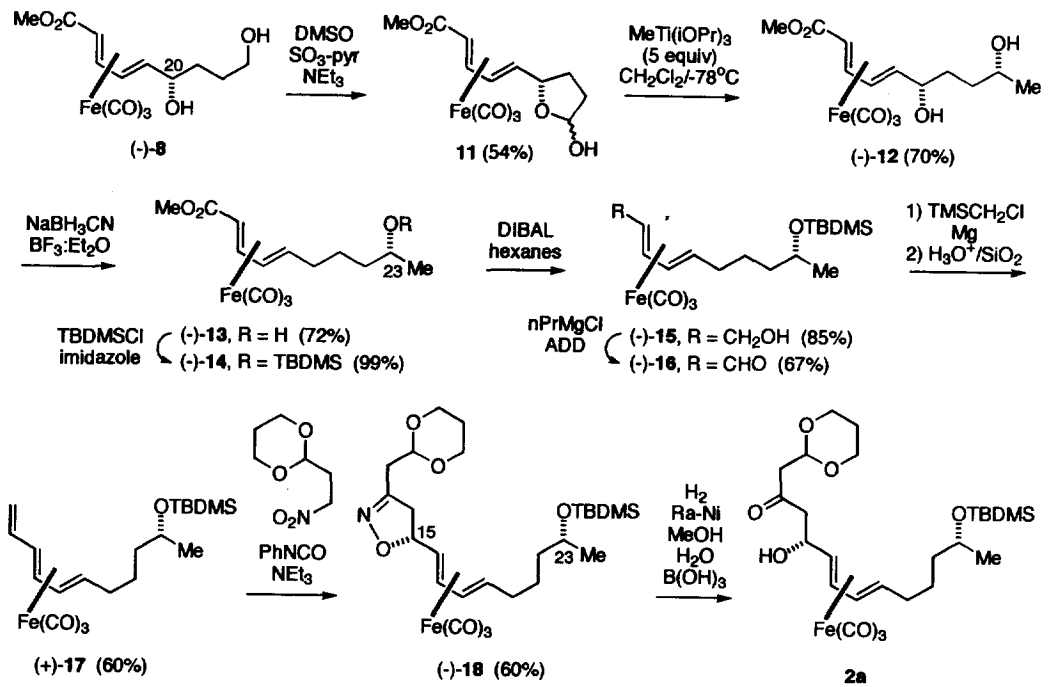
Scheme 1.

The hydroboration-oxidation of **4** has been previously reported[7] to afford only the 1,4-diol **8** (91%). In our hands, treatment of (-)-**4** by the literature procedure gave a separable mixture of (-)-**8** (57%) *and* 1,3-diol diastereomers **9** (35%). The identity of **9** was established by comparison to a racemic sample prepared by independent synthesis (Scheme 2). Reductive hydrolysis of the known[8] isoxazoline *rac*-**10**, followed by reduction of the resultant hydroxyketone gave *rac*-**9** as a mixture of C22 epimers. The formation of significant amounts of product resulting from Markovnikov addition in the hydroboration of 4-hydroxy-1-alkenes has been previously noted.[9] The 23-TBDPS ether-20-(S)-MTPA ester of (-)-**8** was determined to be 57% de by ^{1}H NMR spectroscopy.



Scheme 2.

While oxidation of (-)-**8** with PDC or QDC occurred predominantly at the C20 pseudo-benzylic hydroxyl group, it was found that Moffat oxidation gave predominantly **11** as a mixture of lactol epimers (54%, Scheme 3).[10] Reaction of **11** with MeTi(iPrO)$_3$[11] gave a *single* diastereomeric diol, (-)-**12** (70%),[12] which was tentatively assigned the syn-1,4 stereochemistry on the basis of literature precedent[11] and by analogy to our previous model compound studies.[2c] Selective ionic reduction[2b,c,13] of the C20 alcohol group of (-)-**12** gave the known[2b] (-)-**13** (72% yield, 53% ee by $[\alpha]_D$).[14] The absolute stereochemistry of (-)-**13** (ie. 23R) was assigned on the basis of the relative chemical shifts of the C24 methyl groups of the corresponding (R)- and (S)-MTPA esters (δ 1.35 and 1.27 ppm respectively).[15] Conversion of (-)-**13** to the aldehyde (-)-**16** (TBDMSCl/imidazole/ DMAP, 99%; DIBAL/hexanes, 85%; nPrMgCl/1,1'-(azodicarbonyl)dipiperidine, 67%) followed the method of Grée, *et al.*[2b] The enantiomeric excess of (-)-**16** was assayed by treatment with (1S,2S)-N,N'-dimethyl-1,2-diphenylethylenediamine/molecular sieves to generate the diastereomeric imidazolidines.[16] Integration of the diastereomeric methyl groups of the crude product (δ 2.54 and 2.19 ppm vs δ 2.35 and 2.25 ppm) indicated these to be 55% de. Peterson methenylation of (-)-**16** gave the complexed triene (+)-**17** (60%).



Scheme 3.

With successful installation of the C23 stereocenter relative to the (diene)$Fe(CO)_3$ group, attention was focused on introduction of the C15 stereocenter. It was anticipated, on the basis of literature precedent,[8] that nitrile-oxide cycloaddition to (+)-**17** would occur on the *s-trans* rotamer on the face opposite to the bulky tricarbonyl iron adjunct. In the event, reaction of (+)-**17** with 2-(2'-nitroethyl)-1,3-dioxane in the presence of phenylisocyanate and triethylamine led to the isolation of (-)-**18** (Scheme 3). The relative stereochemistry of isoxazoline (-)-**18** was assigned as Ψ-exo by comparison of its ^1H NMR spectral data[17] to that of a model compound of known relative stereochemistry. In particular, for (-)-**18**, the signals for the C15 methine proton and the diastereotopic C14 protons appear at δ 4.26 (q), 3.18 (dd) and 2.86 (dd) ppm respectively, while the corresponding signals for the Ψ-exo [3-methyl-5-(1,3-pentadienyl)-isoxazoline]$Fe(CO)_3$[8,13] appear at δ 4.24 (q), 3.09 (dd) and 2.74 (dd) ppm respectively. In this fashion, the relative stereochemistries at two centers (C15 and C23) *which are 9 carbons separated,* was controlled by use of the $Fe(CO)_3$ adjunct. Reductive hydrolysis of (-)-**18** (H_2, Ra-Ni, MeOH/H_2O, $B(OH)_3$, 5h) gave the β-hydroxy ketone **2a** in modest yields.[18] Further processing of **2a** was precluded due to a dearth of material, however it is anticipated that the desired C13,C15 anti-diol stereochemistry could be established by reduction of **2** with $Me_4NBH(OAc)_3$.[2f,19]

In summary, the C11-C24 segment of macrolactin A has been prepared in an optically active form using organoiron methodology. The (diene)$Fe(CO)_3$ functionality controls both C23 stereocenter via a chirality relay strategy and the C15 stereocenter via a highly diastereoselective nitrile oxide-olefin cycloaddition.

Acknowledgment. Financial support for this work was provided by the National Institutes of Health (GM-42641). High resolution mass-spectral determinations were made at the Nebraska Center for Mass Spectrometry and the Washington University Resource for Biomedical and Bio-organic Mass Spectrometry. The authors thank Ms. Zhi Wang for the preparation of a racemic sample of **11**, Mr. Bireshwar Dasgupta for preparation of 2-(2'-nitroethyl)-1,3-dioxane, and Dr. René Grée for generously providing spectral data and optical rotations for **13-16**.

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(10) **11** (mixture of lactol epimers): IR (KBr, cm^{-1}) 3374, 2066, 1973, 1715; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 5.1, 8.1 Hz, 1H), 5.58 (m, 0.5H), 5.48 (t, *J* = 4.1 Hz, 0.5H), 5.43 (m, 1H), 4.03 (q, *J* = 7.8 Hz, 0.5H), 3.84 (q, *J* = 8.3 Hz, 0.5H), 3.67 (s, 3H), 2.56 (br s, 1H), 2.3-1.7 (m, 4H), 1.33 (t, *J* = 8.3 Hz, 0.5H), 1.17 (m, 1H), 1.10 (d, *J* = 8.7 Hz, 0.5H); ^{13}C NMR ($CDCl_3$, diastereomeric signals in parentheses) δ 172.4 (172.3), 99.4 (99.2), 86.1 (86.0), 85.0 (84.8), 82.8 (80.0), 65.5 (63.0), 51.7, 46.6 (46.5), 34.5 (33.6), 32.1 (31.3); HRMS (EI) *m/z* 338.0079 (calcd for $C_{13}H_{14}O_7Fe$ (M^+) 338.0093); Anal. Calcd for $C_{13}H_{14}O_7Fe$: C, 46.18; H, 4.17. Found: C, 46.42; H, 4.17.

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(12) (-)-**12**: mp 108-111°C; $[\alpha]_D$ -110° (c 0.16, MeOH); ^1H NMR ($CDCl_3$) δ 5.83 (dd, *J* = 5.1, 8.1 Hz, 1H), 5.50 (dd, *J* = 5.1, 8.7 Hz, 1H), 3.88 (m, 1H), 3.66 (s, 3H), 3.57 (m, 1H), 1.92-1.82 (m, 1H), 1.76-1.50 (m, 5H), 1.33 (t, *J* = 7.8 Hz, 1H), 1.23 (d, *J* = 6.3 Hz, 1H), 1.04 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.6, 85.5, 83.9, 73.4, 68.2, 67.2, 51.7, 46.0, 35.5, 35.3, 23.7; HRMS (FAB) *m/z* 355.0468 (calcd for $C_{14}H_{19}O_7Fe$ $(M+H)^+$ 355.0480); Anal. Calcd for $C_{33}H_{41}NO_5Si$: C, 48.04; H, 5.25. Found: C, 47.48; H, 5.12.

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(14) (-)-**13**: $[\alpha]_D$ -120° (c 0.16, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (dd, *J* = 5.1, 8.1 Hz, 1H), 5.22 (dd, *J* = 5.1, 8.7 Hz, 1H), 3.80 (m, 1H), 3.65 (s, 3H), 1.76-1.30 (m, 7H), 1.20 (d, *J* = 6.3 Hz, 3H), 0.97 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 172.6, 87.2, 83.0, 67.7, 65.3, 51.6, 45.6, 38.6, 34.1, 28.2, 23.6. This NMR spectral data matches that kindly provided by Dr. René Grée.

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(17) (-)-**18**: $[\alpha]_D$ -36° (c 0.16, MeOH); IR ($CDCl_3$, cm^{-1}) 2047, 1979; ^1H NMR (300 MHz, $CDCl_3$) δ 5.23 (dd, *J* = 4.9, 8.2 Hz, 1H), 5.08 (dd, *J* = 5.0, 8.8 Hz, 1H), 4.74 (t, *J* = 4.8 Hz, 1H), 4.26 (q, *J* = 9.3 Hz, 1H), 4.11 (m, 3H), 3.76 (m, 4H), 3.18 (dd, *J* = 10.3, 17.6 Hz, 1H), 2.86 (dd, *J* = 8.6, 17.6 Hz, 1H), 2.64 (t, *J* = 3.9 Hz, 2H), 2.07 (m, 1H), 1.73-1.20 (m, 7H), 1.10 (d, *J* = 6.0 Hz, 3H), 1.02 (t, *J* = 8.9 Hz, 1H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.0, 99.4, 86.3, 83.5, 83.0, 68.2, 66.8, 65.8, 59.6, 45.0, 39.1, 34.3, 33.6, 28.2, 25.8, 25.4, 23.7, 18.0, -4.5, -4.8; HRMS (FAB) *m/z* 564.2072 (calcd for $C_{26}H_{42}O_7NSiFe$ $(M+H)^+$ 564.2079).

(18) Attempted reductive hydrolysis of (-)-**18** over *48 h* resulted in loss of the $Fe(CO)_3$ adjunct, reduction of the conjugated diene, and reduction of the ketone functionality.

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