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Model Studies toward the Synthesis of Macrolactin A: Organoiron Methodology for Introduction of the C1-C11 and C16-C24 Segments

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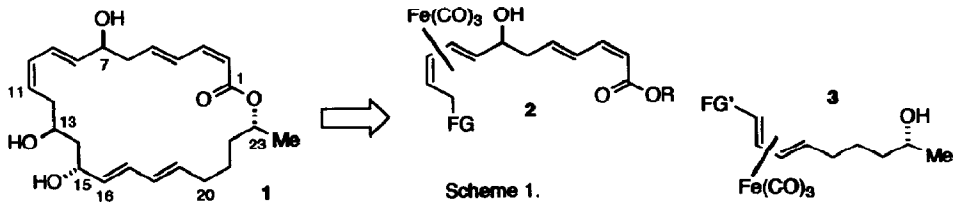
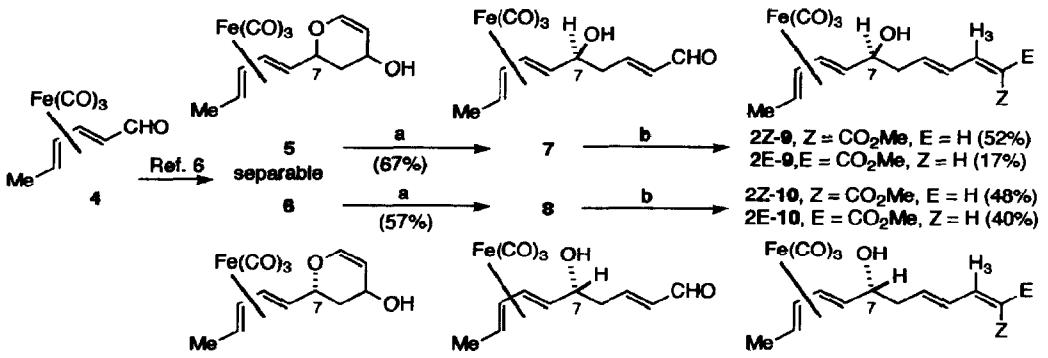
Abstract: Preparation of the Fe(CO)3 complexed C1-C11 and the C16-C24 segments of macrolactin A has been accomplished from (sorbaldehyde)Fe(CO)3 in 4 steps and 5 steps respectively.

Macrolactin A (**1**) is a 24-membered polyene macrolide isolated from a taxonomically-undefined deep sea bacterium.[1a] This compound inhibits B16-F10 murine melanoma cancer cells *in vitro* assays, inhibits Herpes Simplex I and II and protects T-lymphoblast cells against HIV replication. Its structure consists of 3 sets of conjugated dienes, whose stereochemistry was assigned on the basis of NMR spectroscopy.[1a] The relative and absolute stereochemistry of the four sp^3 centers adjacent and remote to the conjugated dienes was assigned by chemical degradation and synthesis of the fragments.[1b] Retrosynthetic analysis (Scheme 1) involves splitting the target molecule at the anti-1,3-diol functionality to generate two (diene)Fe(CO)3 fragments (**2**) and (**3**). We have previously reported methodology for the formation of E,Z-conjugated dienes by nucleophilic attack on (pentadienyl)$Fe(CO)_3^+$ cations.[2] Additionally, the Fe(CO)3 adjunct has been shown to facilitate diastereoselective C-C[3] or C-O[4] bond formation *adjacent* to conjugated dienes, and can act as a protecting group for the sensitive diene functionality. Herein, we report model studies for preparation of the C1-C11 and C16-C24 of macrolactin A in which one Fe(CO)3 adjunct controls the dienylic C7 stereocenter while a second controls the *remote* stereocenter at C23.



Scheme 1.

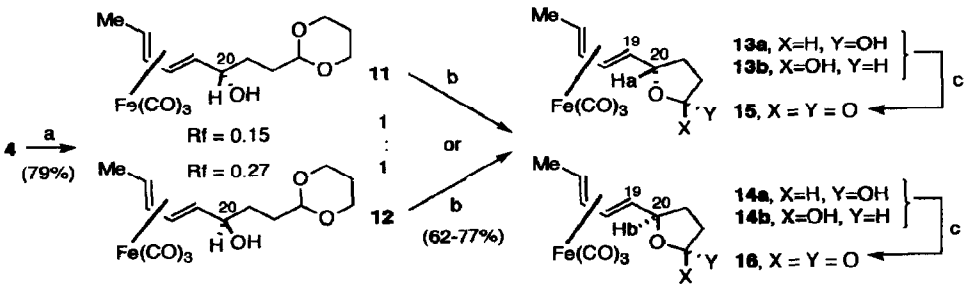
We have previously reported that cyclocondensation of (sorbaldehyde)Fe(CO)3 (**4**)[5] with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (CF_3CO_2H work-up) followed by reduction gives a separable mixture of diastereomeric dihydropyran alcohols **5** and **6** (Scheme 2).[6,7] Treatment of **5** with dilute $H_2SO_4/HgSO_4$ gave the ring-opened α,β-unsaturated aldehyde **7** (67%), while treatment of **6** under these conditions gave enal **8** (57%). Cis-selective olefination of **7** with methyl P,P-bis(trifluoroethyl)phosphonacetate[8]/K_2CO_3/18-crown-6 gave 2*Z*-**9** as the major product (52%) along with 2*E*-**9** (17%) readily separable by column chromatography. Olefination of **8** under similar conditions was not as selective, and gave a separable mixture of 2*Z*-**10** (48%) and 2*E*-**10** (40%). Notably, the ^1H NMR chemical shifts for H3 of both 2*Z*-**9**[9] and 2*Z*-**10** (δ 6.26 and 6.29 ppm respectively) are nearly identical with that reported for H3 of macrolactin A (δ 6.29 ppm).[1a]



Scheme 2. Reagents: a, $HgSO_4$/0.05M H_2SO_4/dioxane/acetone; b, $(CF_3CH_2O)_2P(O)CH_2CO_2Me/K_2CO_3$/18-crown-6.

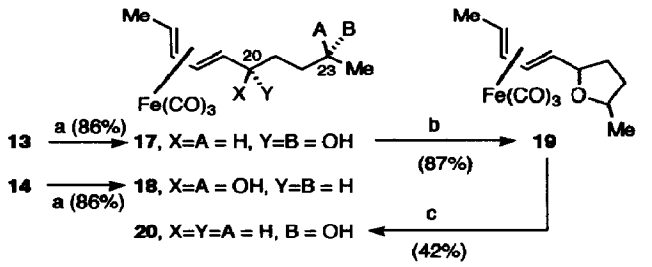
With methodology for construction of the C1-C11 segment of macrolactin in hand, attention was next focused on methodology for the construction of the C16-C24 segment. While it is well established that addition to unsaturated centers adjacent to a (diene)$Fe(CO)_3$ proceeds in a diastereoselective fashion,[3,4] reduction of ketones more remote occurs in a non-selective fashion.[10]

Addition of the Grignard reagent generated from 2-(2-bromoethyl)-1,3-dioxane to **4** gave a separable mixture of alcohols **11** and **12** (79%)[11] in nearly equimolar amounts (Scheme 3). While this lack of selectivity was initially disappointing, it was found that hydrolysis of either pure **11**, pure **12**, or a mixture of **11/12** gave a mixture of diastereomeric lactols **13a**, **13b**, **14a**, and **14b** (62-77%). This could be easily separated into a mixture of **13a/13b** and a mixture of **14a/14b** (**13**:**14**, ca. 3:1). Additionally, treatment of **13a/13b** or **14a/14b** under the hydrolysis conditions generates the same mixture of four diastereoisomers. *Thus the lack of diastereoselectivity for Grignard addition to 4 is of no consequence, since the C20 stereocenter (macrolactin numbering) is epimerized under the reaction conditions.* Oxidation of lactols **13a/13b** gave lactone **15**, while oxidation of lactols **14a/14b** gave lactone **16**, thus indicating that the lactols within each mixture (ie. **a**/**b**) are epimeric at the lactol carbon only. The relative stereochemistries of **15** and **16** (ψ-exo and ψ-endo respectively), are tentatively assigned on the basis of the relative chemical shifts of Ha and Hb (δ 4.12 and 4.38 ppm respectively).[12] Thus lactols **13** and **14** are also assigned the ψ-exo and ψ-endo relative stereochemistries (notably the diastereomer mixture **14** is less polar than diastereomer mixture **13**).[12] The equilibration of **13** and **14** may be rationalized by ionization of the C20 lactol C-O bond under the acidic conditions to generate the transoid pentadienyl cation. Rotation about the C19-C20 bond and attack of oxygen on the face opposite to iron effects epimerization.[13]



Scheme 3. Reagents: a, 2-(2-bromoethyl)-1,3-dioxane/Mg/THF; b, 0.05M H_2SO_4/acetone/reflux; c, PDC/CH_2Cl_2/3Å sieves.

Treatment of **13** with MeTi(iPrO)3[14] gave the diol **17**[15] as a *single* diastereomer (Scheme 4, 86%). The relative stereochemistries at C20 (ψ-exo) and C23 (syn) were established by single crystal X-ray diffraction analysis (Figure 1),[16] thus also corroborating the ψ-exo assignments for **13** and **15**. Notably, the ψ-exo stereochemistry at C20 positions the hydroxyl appropriately for ionization with assistance from the metal center (*vide infra*). Similarly, treatment of **14** with MeTi(iPrO)3 gave a single diol product (**18**, 86%) which was assigned the syn relative stereochemistry by analogy. Thus the C23 stereocenter can be efficiently introduced in a diastereospecific fashion with respect to the (diene)FeCO)3 functionality by chirality transfer.



Scheme 4. Reagents: a, MeTi(OiPr)3/CH_2Cl_2; b, pTsOH/C_6H_6/3Å sieves; c, $NaBH_3CN/BF_3{\cdot}Et_2O$/THF

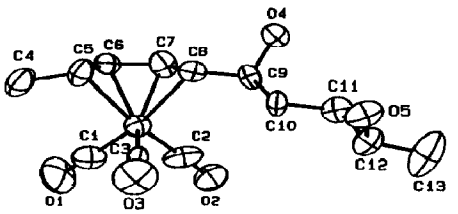


Figure 1. ORTEP of **17**.

Removal of the C20 hydroxyl group proved challenging. Attempts at selective protection of either the C20 or C23 hydroxyls of **17** were unsuccessful. Furthermore, attempts at ionic reduction[17] of the C20 hydroxyl led predominantly to formation of the tetrahydrofuran complex **19**. Compound **19** could most efficiently be prepared by dehydration of **17** (pTsOH, C_6H_6, 3Å sieves, 87%).[18] Ionic reduction of **19**, via the trans-pentadienyl cation ($NaBH_3CN$, $BF_3{\cdot}Et_2O$, 42%), gave **20** as a single diastereomer (Scheme 4).[19]

In summary, methodology for generation of the functionality present in the C1-C11 and the C16-C24 segments of macrolactin A has been presented. The (diene)Fe(CO)3 controls the stereochemistry at C7 via cyclocondensation, while a second (diene)Fe(CO)3 controls the remote C23 stereocenter via chirality transfer. We will report on our efforts toward the enantioselective synthesis of macrolactin A in due course.

Acknowledgment. Financial support for this work was provided by the National Institutes of Health (GM-42641) and the Marquette University Committee-on-Research. High resolution mass-spectral determinations were made at the Midwest Center for Mass Spectrometry with partial support by the National Science Foundation, Biology Division (Grant No. DIR9017262). P.T.B. thanks the Department of Education for a Fellowship (T200A90035-90, 1990-93) and Marquette University for an Arthur J. Schmitt Fellowship (1993-94).

References and Notes

(1) (a) Gustafson, K.; Roman, R.; Fenical, W. *J. Am. Chem. Soc.*.**1989**, *111*, 7519-24; (b) Rychnovsky, S.D.; Skalitzky, D.J.; Pathirana, C.; Jenson, P.R.; Fenical, W. *J. Am. Chem. Soc.* **1992**, *114*, 671-7.

(2) (a) Tao, C.; Donaldson, W.A. *J. Org. Chem.* **1993**, *58*, 2134-43; (b) Donaldson, W.A.; Ramaswamy, M. *Tetrahedron Lett.* **1989**, *30*, 1339-42.

(3) (a) Laabassi, M.; Grée, R. *Tetrahedron Lett.* **1988**, *29*, 611-4; (b) Nunn, K.; Mosset, P.; Grée, R.; Saalfrank, R. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1188-9; (c) Benvegnu, T.; Martelli, J.; Grée, R. *Tetrahedron Lett.* **1990**, *31*, 3145-8; (d) Donaldson, W.A.; Craig, R.A.; Spanton, S. *Tetrahedron Lett.* **1992**, *33*, 3967-8.

(4) (a) Giguo, A.; Lellouche, J.-P.; Beaucourt, J.-P.; Toupet, L.; Grée, R. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 755-7; (b) Le Gall, T.; Lellouche, J.-P.; Toupet, L.; Beaucourt, J.-P. *Tetrahedron Lett.* **1989**, *30*, 6517-20; (c) Franck-Neumann, M.; Colson, P.-J. *Synlett* **1991**, 891-4.

(5) All compounds described are racemic mixtures of enantiomers. Only one enantiomer has been diagrammed for clarity. Resolution of (diene)Fe(CO)3 complexes has been accomplished (cf.

Donaldson, W.A.; Shang, W.; Rogers, R.D. *Organometallics* **1994**, *13*, 6-7; and *references therein*), thus in principle this work could readily be applied to asymmetric synthesis.

(6) The cyclocondensation diastereomeric ratio varies from 3.8:1 to 1:3 depending upon the Lewis acid: Donaldson, W.A.; Tao, C.; Bennett, D.W.; Grubisha, D.S. *J. Org. Chem.* **1991**, *56*, 4563-6.

(7) (Sorbaldehyde)Fe(CO)3 was chosen for the model studies due to its ready availability and due to the anticipated spectral simplicity. The synthesis of fragment **2** would require cyclocondensation of a 2E,4Z-dienal complex with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene. We have previously demonstrated this type of reaction.[2a]

(8) Still, W.C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405-8.

(9) 2Z-**9**: R_f 0.65 (hexanes-ethyl acetate (7:3)); ^{1}H NMR (C_6D_6) δ 7.81 (ddd, *J* = 1.1, 11.2, 15.4 Hz, 1H), 6.26 (t, *J* = 11.2 Hz, 1H), 5.77 (dt, *J* = 15.4, 7.6 Hz, 1H), 5.63 (d, *J* = 11.2 Hz, 1H), 4.50 (dd, *J* = 4.9, 8.9 Hz, 1H), 4.37 (dd, *J* = 4.9, 8.8 Hz, 1H), 3.37 (s, 3H), 3.22 (dq, *J* = 3.7, 6.7 Hz, 1H), 2.12 (m, 2H), 1.32 (d, *J* = 3.8 Hz, 1H), 1.03 (d, *J* = 6.1 Hz, 3H), 0.68-0.57 (m, 2H); ^{13}C NMR (C_6D_6) δ 212.3, 166.5, 144.9, 140.4, 129.8, 116.6, 85.2, 80.7, 72.9, 67.7, 57.6, 50.7, 43.7, 18.8; IR (CH_2Cl_2) 3489, 2039, 1973, 1713, 1640, 1202 cm^{-1}; HRMS *m/z* 306.0547 [calcd for $C_{14}H_{18}O_4Fe$ (M-2CO) *m/z* 306.0552].

(10) Nunn, K.; Mosset, P.; Grée, R.; Saalfrank, R.W. *J. Org. Chem.* **1992**, *57*, 3359-64.

(11) **11**: R_f 0.15 (hexanes-ethyl acetate (7:3)); ^{1}H NMR ($CDCl_3$) δ 5.23 (dd, *J* = 4.9, 8.3 Hz, 1H), 5.04 (dd, *J* = 5.0, 8.8 Hz, 1H), 4.58 (t, *J* = 4.6 Hz, 1H), 4.08 (dd, *J* = 4.1, 11.2 Hz, 2H), 3.75 (dd, *J* = 2.4, 11.9 Hz, 2H), 3.43 (m, 4H), 3.01 (d, *J* = 4.6 Hz, 1H), 2.05 (m, 2H), 1.9-1.5 (m, 4H), 1.40 (d, *J* = 6.4 Hz, 3H), 1.20 (m, 1H), 0.95 (t, *J* = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 212.0, 101.9, 86.3, 82.4, 73.4, 66.9, 64.7, 58.1, 32.5, 31.0, 25.5, 19.1; IR (KBr) 3421, 2041, 1969, 1146 cm^{-1}; Anal. Calcd for $C_{17}H_{20}O_5Fe$: C, 51.60; H, 5.72. Found: C, 51.10; H, 5.81. **12**: R_f 0.27 (hexanes-ethyl acetate (7:3)); ^{1}H NMR ($CDCl_3$) δ 5.16 (dd, *J* = 4.8, 8.3 Hz, 1H), 5.03 (dd, *J* = 4.9, 8.8 Hz, 1H), 4.57 (t, *J* = 4.4 Hz, 1H), 4.10 (dd, *J* = 4.5, 11.2 Hz, 2H), 3.76 (dt, *J* = 2.4, 12.2 Hz, 2H), 3.53 (m, 4H), 2.46 (d, *J* = 3.2 Hz, 1H), 2.06 (m, 2H), 1.8-1.6 (m, 4H), 1.40 (d, *J* = 6.4 Hz, 3H), 1.11 (dq, *J* = 8.3, 6.4 Hz, 1H), 1.02 (t, *J* = 8.0, 1H); ^{13}C NMR ($CDCl_3$) δ 101.8, 85.1, 80.7, 73.3, 68.4, 66.9, 57.6, 34.1, 31.7, 25.5, 19.1; IR (KBr) 3468, 2047, 1962, 1134 cm^{-1}; Anal. Calcd for $C_{17}H_{20}O_5Fe$: C, 51.60; H, 5.72. Found: C, 51.33; H, 5.83.

(12) For a discussion of the empirical trends in NMR chemical shifts and chromatographic mobility of the ψ-exo and ψ-endo isomers see Ref 2a.

(13) Epimerization of this type, under acidic conditions, has previously been observed: Grée, D.; Grée, R.; Lowinger, T.B.; Martelli, J.; Negri, J.T.; Paquette, L.A. *J. Am. Chem. Soc.* **1992**, *114*, 8841-6.

(14) Tomooka, K.; Okinaga, T.; Suzuki, K.; Tsuchihashi, G.*Tetrahedron Lett.*, **1987**, *28*, 6335-8.

(15) **17**: mp 118-125 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.23 (dd, *J* = 4.6, 8.8, 1H), 5.07 (dd, *J* = 4.6, 8.8, 1H), 3.85 (m, 1H), 3.43 (td, *J* = 8.1, 2.7, 1H), 2.40 (br s, 1H), 1.85 and 1.7-1.5 (m, 4H), 1.59 (s, 1H), 1.42 (d, *J* =6.4, 3H), 1.25 (m, 1H,), 1.22 (d, J=6.3, 3H), 0.99 (t, *J* = 8.1, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.0, 86.4, 82.2, 74.5, 68.3, 64.7, 58.4, 35.4, 35.2, 23.8, 19.2; Anal. Calcd for $C_{13}H_{18}O_5Fe$: C, 50.35; H, 5.85. Found: C, 50.25; H, 5.66.

(16) Compound **17** crystallizes in the orthorhombic space group $Pca2_1$ with the following unit cell dimensions: *a* = 7.4855(18) Å, *b* = 10.086(3) Å, *c* = 20.270(3) Å, V = 1530.3(6) Å^3, and d_{calc} = 1.346 g cm^{-3} for z = 4.

(17) Ionic hydrogenation of (hydroxymethylene-1,3-butadiene)Fe(CO)3 complexes has been reported: Kappes, D.; Gerlach, H.; Zbinden, P.; Dobler, M. *Helv. Chim. Acta* **1990**, *73*, 2136-46; Schio, L. Doctoral Dissertation, University of Rennes, **1990**.

(18) Tetrahydrofuran formation of this type has previously been observed.[8]

(19) **20**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99 (d, *J* = 8.1 Hz, 2H), 3.80 (m, 1H), 1.7-1.4 (m, 5H), 1.38 (d, *J* = 6.1 Hz, 3H), 1.19 (d, *J* = 6.1, 3H), 1.10 (quintet, *J* = 6.3 Hz, 1H), 1.01 (q, *J* = 7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.0, 85.1, 83.7, 67.9, 63.3, 57.2, 38.8, 34.2, 28.3, 23.6, 19.1; HRMS *m/z* 294.0537 [calcd for $C_{13}H_{18}O_4Fe$, *m/z* 294.0557].

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