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[11] Crystal data for **1**: $[C_{16}H_{40}N_{32}Ni_6S_8][Cl]_4 \cdot 10\,MeOH$, $M = 1751.8$, monoclinic, space group $P2_1/c$ (no. 14), $a = 18.971(4)$, $b = 15.523(2)$, $c = 25.555(3)$ Å, $\beta = 104.03(2)^\circ$, $V = 7301(2)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.59\ g\,cm^{-3}$, $\mu Mo_{K\alpha} = 19.6\ cm^{-1}$, $F(000) = 3616$. A dark green rhomb of dimensions $0.83 \times 0.60 \times 0.47$ mm was used. **2**: $[C_{16}H_{40}N_{32}Ni_6S_8][Br]_4 \cdot 5\,MeOH \cdot Me_2CO$, $M = 1827.5$, monoclinic, space group $P2_1/c$ (no. 14), $a = 19.045(5)$, $b = 15.862(6)$, $c = 25.771(7)$ Å, $\beta = 103.88(2)^\circ$, $V = 7558(5)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.61\ g\,cm^{-3}$, $\mu Mo_{K\alpha} = 38.5\ cm^{-1}$, $F(000) = 3672$. A green platelike rhomb of dimensions $0.30 \times 0.13 \times 0.04$ mm was used. For **1**(**2**) 12800 (6955) independent reflections were measured at 203 K on a Siemens P4/PC diffractometer with graphite monochromated $Mo_{K\alpha}$ radiation and ω scans. The structures were solved by direct methods and were refined with full-matrix least squares based on F^2. In **1** all the major occupancy non-hydrogen atoms were refined anisotropically, but in **2**, due to a shortage of observed data, only the nickel, bromine, and sulfur atoms were refined anisotropically. In the case of **1**, a semiempirical absorption correction (based on ψ scans) was performed. The residuals in the final ΔF map were $R_1 = 0.047$ (0.093), $wR_2 = 0.097$ (0.193) for 9103 (3153) independent observed reflections $[|F_o| > 4\sigma(|F_o|), 2\theta \leq 50^\circ\ (40^\circ)]$ and 971 (444) parameters for **1** and **2** respectively. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101043. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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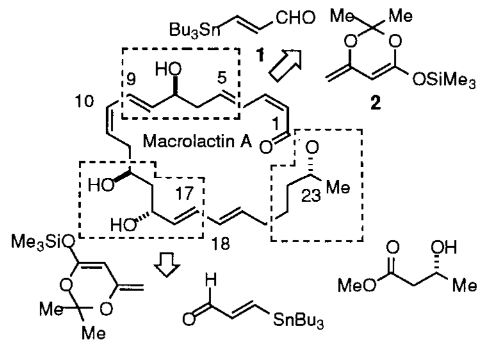
Total Synthesis of Macrolactin A with Versatile Catalytic, Enantioselective Dienolate Aldol Addition Reactions[**]

Yuntae Kim, Robert A. Singer, and Erick M. Carreira[*]

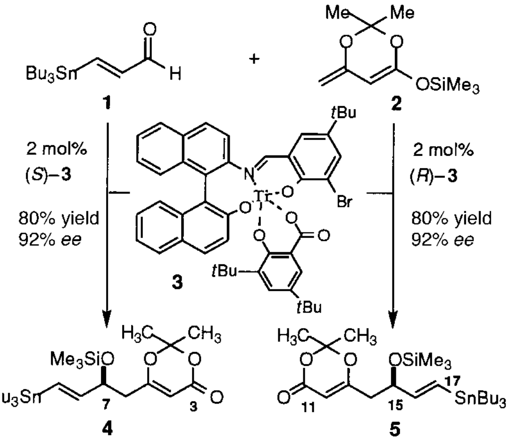
Polyene macrolide antibiotics form a diverse group of natural products that display a wide range of biological activities.[1] Impressive and elegant synthetic strategies have been used in their syntheses.[2–6] Recently, macrolactin A was isolated from a bacterium of unclassifed taxonomy, and in preliminary studies it was shown to inhibit HIV replication in T-lymphoblast cells (Scheme 1).[7] As the organism was isolated from deep-sea coring and is no longer readily available, further biological research must rely on de novo synthesis of macrolactin A. We report herein a total synthesis of macrolactin A that utilizes modern asymmetric catalytic C–C coupling methods in a highly convergent fashion.[8] A common enantioselective, catalytic dienolate addition reaction was used to synthesize two key fragments that contain most of the molecule's stereochemical complexity, and Pd^0 Stille coupling chemistry was used to assemble the principal fragments.



Scheme 1. Retrosynthetic analysis of macrolactin A.

Central to our retrosynthesis (Scheme 1) was the recognition of structural homology between the three different regions that contain the stereogenic centers found in macrolactin A. In this analysis the latent 1,3-oxygenation pattern of the acetogenic macrocycle guides the disconnection of the macrocycle into three key subunits of approximately equal complexity: C(2)–C(9), C(11)–C(17), and C(18)–C(24). We speculated that the first two of these could be constructed with their attendant hydroxy-substituted stereocenters by an acetoacetate aldol addition reaction; each subunit could then be joined pairwise by Pd^0-catalyzed sp^2–sp^2 coupling reactions. Importantly, implementation of this strategy was facilitated by our recently developed catalytic, enantioselective dienolate aldol addition.[9]

Fragments **4** and **5** were synthesized by a known strategy that started with aldehyde **1**, dienolate **2**, and the enantiomeric Ti^{IV} catalysts (*S*)- and (*R*)-**3** (Scheme 2). Treatment of propynal diethyl acetal with Bu$_3$SnH/BuLi/CuCN followed by mildly acidic workup conveniently provided 3-tributylstannyl-2-propenal.[10] In separate experiments with 2 mol% of (*S*)- and (*R*)- **3**, protected acetoacetate aldol adducts **4** and



Scheme 2.

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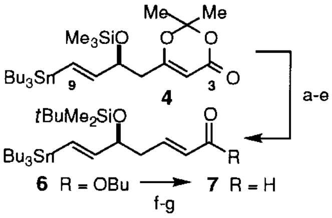
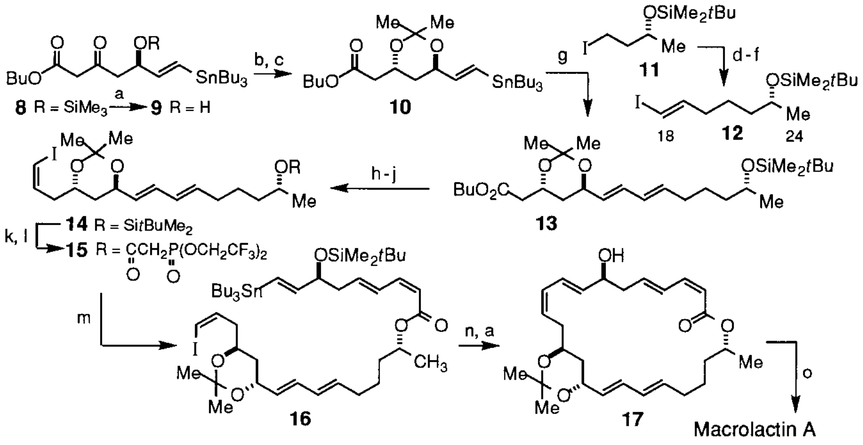
5 were each isolated in 80% yield and 92% *ee*, determined by derivatization as the (*S*)-(−)- and (*R*)-(+)- α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) esters and analysis of the ^{1}H NMR spectra.[11]

Acetoacetate adduct **4** was elaborated into the C(3) – C(9) subunit by a short, high-yielding reaction sequence (Scheme 3): hydrolysis of the acetonide protecting group afforded the corresponding β-keto ester (*n*BuOH, 80°C, 99%), which was reduced with $NaBH_4$ to provide a diastereomeric (1:1) mixture of β-hydroxy esters. The unpurified reaction mixture was treated with MsCl and Et_3N to form the corresponding α,β-unsaturated ester (71%, two steps), and after hydrolysis of the Me_3Si-ether the resulting 2° alcohol was protected as its *t*$BuMe_2Si$-ether to give **6**. Reduction of **6** to the primary alcohol and Swern oxidation yielded aldehyde **7** (80%, two steps), a structural subunit that later forms the C(3) – C(9) fragment of macrolactin A.[12]



Scheme 3. a) *n*BuOH, 80°C, 99%; b) $NaBH_4$, MeOH, 0°C; c) MsCl, Et_3N, 23°C, 71% over two steps; d) HF · py, THF, 23°C; e) *t*$BuMe_2SiCl$, DMAP, CH_2Cl_2, Et_3N, 90% over two steps; f) DIBAL-H, THF, −78°C; g) Swern oxidation, 80% over two steps. Ms = methane sulfonyl; py = pyridine; DMAP = 4-dimethylaminopyridine; DIBAL-H = diisobutylaluminium hydride.

With the synthesis of the C(3) – C(9) fragment complete, we proceeded to elaborate dienolate adduct **5**. Treatment of **5** with *n*BuOH (80°C) afforded keto ester **8**, which yielded δ-hydroxy-β-keto ester **9** with HF · py (96%, two steps, Scheme 4). Selective reduction of **9** with $Me_4NBH(OAc)_3$ converted **9** into the corresponding 1,3-*anti*-diol in 87% yield and 14:1 diastereoselectivity, determined by ^{1}H NMR spectroscopy of the unpurified diol product.[13] This 1,3-*anti*-diol was protected ($Me_2C(OMe)_2$, PPTS, 23°C) as acetonide **10** (89%). Synthesis of the C(18) – C(24) fragment **12** was achieved with iodide **11**, prepared from commercially available ethyl 3-(*R*)-hydroxybutyrate.[14] Enolization of acetaldehyde *N,N*-dimethylhydrazone (LiN*i*Pr_2, THF) and alkylation with **11** provided the corresponding alkylated hydrazone (75%). Ozonolytic cleavage of this hydrazone afforded 5-(*R*)-*tert*-butyldimethylsilyloxyhexanal, which was subjected to the Takai olefination (CHI_3, $CrCl_2$, THF) without purification to yield (*E*)-iodoalkene **12** (68%, two steps).[15, 16]



Scheme 4. a) HF · py, THF, 23°C, 96% (from 5); b) $Me_4NBH(OAc)_3$, MeCN, −10°C, 87%; c) $Me_2C(OMe)_2$, PPTS, 23°C, 89%; d) $MeC(H)NNMe_2$, LDA, THF, 0°C, 75%; e) O_3, CH_2Cl_2, −78°C; f) CHI_3, $CrCl_2$, THF, 68% over two steps; g) $Pd_2(dba)_3$, $CdCl_2$, *i*Pr_2NEt, 69%; h) DIBAL-H, −78°C, THF, 80%; i) Swern oxidation; j) $Ph_3PCH_2I_2$, KHMDS, THF, −78°C, 78% over two steps; k) HF · py, THF, 23°C, 80%; l) $(CF_3CH_2O)_2POCH_2COCl$, DMAP, CH_2Cl_2, 90%; m) **7**, KHMDS, 18-C-6, THF, 60%; n) $[Pd_2(dba)_3]$, *N*-Me-pyrrolidinone, 58%; o) Dowex-H^+, 23°C, MeOH, 60%. PPTS = pyridinium-*p*-toluene sulfonate; LDA = lithium diisopropylamide; dba = dibenzylidene acetone; KHMDS = potassium bis(trimethylsilyl)amide.

The first of the Pd^0-coupling reactions, which links stannane **10** with vinyl iodide **12**, was effected with $[Pd_2(dba)_3]$, *i*Pr_2NEt, and $CdCl_2$ to provide diene **13** (69%).[17] Homologation of **13** to (*Z*)-vinyl iodide **14** as a single diastereomer (determined by ^{1}H NMR spectroscopy) was effected in 78% yield by treatment of the aldehyde derived from **13** with $Ph_3PCH_2I_2$ under conditions developed by Stork.[18] Deprotection of the silyl ether in **14** provided a secondary alcohol, which was acylated with *O,O*-bis-(2,2,2-trifluoroethyl)phosphonoacetyl chloride to give **15** (90%).[19, 20] Condensation of **15** with fragment **7** yielded hexaene **16**, an intermediate that incorporates the complete carbon skeleton and all the concomitant stereocenters found in the target macrolactin A. An intramolecular Pd^0-mediated coupling reaction afforded the macrocyclic lactone, which, without purification, was treated with HF · py to give macrolactin A acetonide **17**. Hydrolysis of this acetonide with Dowex resin yielded macrolactin A, which proved to be identical in all respects with the data reported for the material isolated from natural sources.[21]

We have described an enantioselective total synthesis of macrolactin A, a rare polyene macrolide antibiotic that inhibits HIV replication in T-lymphoblast cells. Our synthetic strategy utilizes our recently developed catalytic, enantioselective dienolate addition methodology to introduce key stereocenters. The availability of both enantiomeric forms of the Ti^{IV} catalyst allows ready access to two of the three fragments in macrolactin A, and constitutes the first application of enantioselective dienolate addition reactions to natural product synthesis. This highly convergent route, in which the longest linear sequence is 16 steps with an average yield of 86% per step, can provide 1.1 g of bioactive, but otherwise inaccessible, macrolactin A from as little as 15 g of the commercially available 3-(*R*)-hydroxybutyrate.

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Redox-Active Nanotubes of Vanadium Oxide

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Martin Müller, F. Krumeich, and Hans U. Nissen

Dedicated to Professor Roald Hoffmann on the occasion of his 60th birthday

Nanoporous materials (nanostructures), which are considered as intermediates between classical molecular scale and microsized entities, constitute a rapidly growing field of scientific interest and industrial applications. Well-defined structures of this length scale are difficult to obtain because neither typical physical tailoring techniques nor planned chemical syntheses are very applicable in this size domain. Since chemical reactivity and physical properties in the nanoregion are strongly dependent on the size of the structures, such materials are very interesting in many respects, particularly for the production of highly functional, finely dispersable, and resource-saving base materials for "nanodevices". Nanoparticles may be of quite different shapes such as spheroids, mushrooms,[1] platelets, rods, or tubes; the form adopted plays a large role in determining the basic properties, for example, isotropic or anisotropic behavior and region-dependent surface reactivity.

The tubular form is particularly attractive since it provides access to three different contact regions: inner and outer surface as well as the tube ends. Carbon nanotubes[2, 3] establish such singly or multiwalled entities that consist of graphite-like sheets depending on the synthesis conditions.[4, 5] They have already attracted a great deal of interest because they might turn out to become very useful in future nanodevice technology. Another very interesting family are the nanoporous MCM-aluminosilicates[6, 7] with continous framework structures that have tunnel dimensions between 3 and 10 nm, extending the range of zeolite-like materials. The synthesis of these mesostructured molecular sieves relies on surfactant micelles or liquid-crystal arrays of micelles as structure-directing agents for the assembly and subsequent polymerization of inorganic alumosilicate precursors at the surfactant-solution interface. The application of complementary electrostatic interactions between surfactant molecules and charged or polarized metal oxy precursors as the inorganic component has opened a way to new metastable modifications of metal oxides.[8] Quite recently it has been shown that hydrogen bonding[9] or real coordinative interactions[10–12] between the ligand liquid crystal template and the metal center offer new perspectives for the controlled synthesis of surfactant-based periodic inorganic structures.

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