Synthesis of the mycolactone core by ring-closing metathesis†

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The undecenolide core of mycolactone was synthesized by ring-closing metathesis and the structure confirmed using single-crystal X-ray diffraction techniques.

Mycobacterium ulcerans is the pathogen responsible for the disease Buruli ulcer, the third most prevalent mycobacterial infection after tuberculosis and leprosy.[1,2] The major secondary metabolite produced by *M. ulcerans* is mycolactone (**1**, Fig. 1),[3] from a family of polyketide toxins that contain a conserved 12-membered lactone with a variable polyunsaturated ester side chain. Mycolactone is both necessary and sufficient for causing the necrotic lesions characteristic of *M. ulcerans* infection *via* adipose cell apoptosis and concomitant immunomodulation.[4,5] Currently, standard treatment involves surgical removal of infected and surrounding tissue, often resulting in debilitating scars or amputation.[6] We are interested in developing synthetic constructs to study mycolactone biosynthesis and therefore have need of mycolactone and structural analogs.

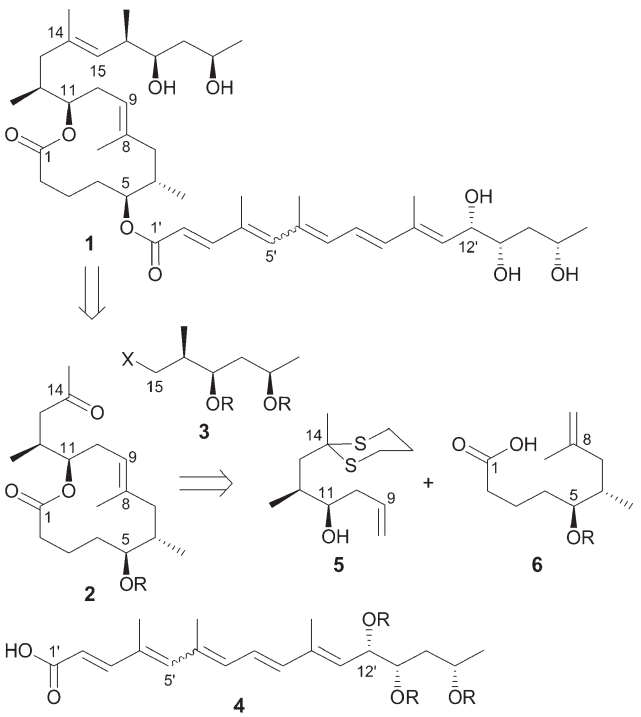

Fig. 1 Retrosynthetic analysis of RCM approach to mycolactone (**1**).[3] R = TBS; X = SO_2Ph or PPh_3.

The elegant total synthesis of mycolactone by Kishi *et al.* showcased a NMR database method for stereochemical assignment and established the absolute stereochemistry of the natural product.[7–9] While this route was well suited for selective isomer construction and NMR analysis, our purposes require a strategy that emphasizes rapid analog production. As shown in Fig. 1, mycolactone **1** may be divided into three main components: northern chain **3**, polyene side chain **4**, and lactone core **2**.[10] The macrocycle is derived from synthons **5** and **6** through a convergent route based on ring-closing metathesis (RCM) for formation of the lactone core. While any of the four building blocks **3–6** may be varied to produce analogs of mycolactone, our initial efforts are directed towards derivatives containing modifications in the side chains, based on the invariability of the lactone core in all known mycolactones.[11,12] Thus, compound **2** posseses significant potential for analog production, as panels of mycolactone congeners with variable northern chain (**3**) and fatty acid sidechain (**4**)[13] components could be derived from this single advanced intermediate. In this communication, we describe the synthesis of enantiomerically pure **2** from homoallylic alcohol **5** and acid **6**.

Acid fragment **6** was synthesized in nine steps from known aldehyde **7** (Scheme 1).[14] A high yielding and stereoselective aldol reaction[15,16] was used to provide the Evans *syn* diastereomer as the only detectable stereoisomer in 93% yield after protection of the newly formed secondary alcohol as a TBS ether. The chiral auxiliary in **8** was cleaved with $LiBH_4$ and the resulting alcohol was oxidized using Swern conditions[17] to afford aldehyde **9** in 70% yield over the two steps. The aldehyde was treated with 2-propenylmagnesium bromide, and the resulting magnesium alkoxide product was trapped *in situ* with acetic anhydride and pyridine to deliver a diastereomeric mixture of allylic acetates **10** in 89% yield. Palladium-catalyzed hydrogenolysis with ammonium formate and tributylphosphine according to a modification of the Tsuji protocol[18] provided terminal olefin **11** in an 88% yield with no detectable internal olefin regioisomer. The primary TBDPS ether was removed in the presence of the secondary TBS group in 96% yield by heating at reflux in MeOH with 5 N NaOH.[19] The resulting alcohol was oxidized to the aldehyde using Swern conditions.[17] The crude aldehyde was further oxidized to the carboxylic acid under Kraus' conditions[20] with sodium chlorite and 2-methyl-2-butene as chlorine scavenger to generate acid **6** in 85% yield over the two steps.

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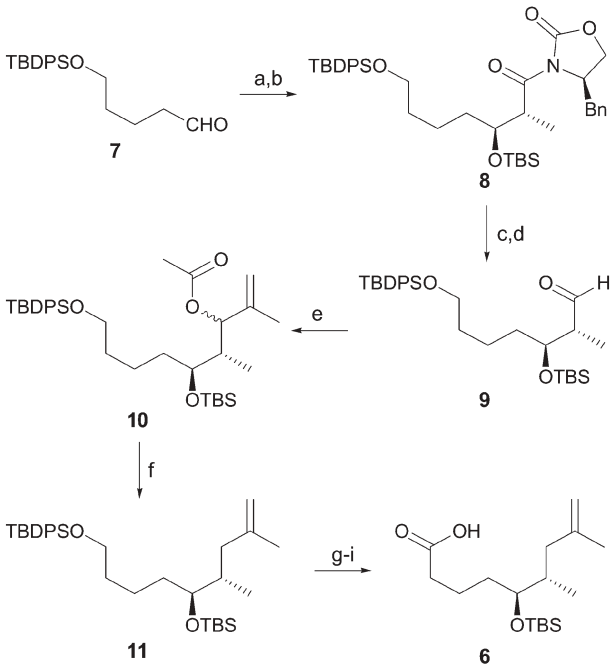
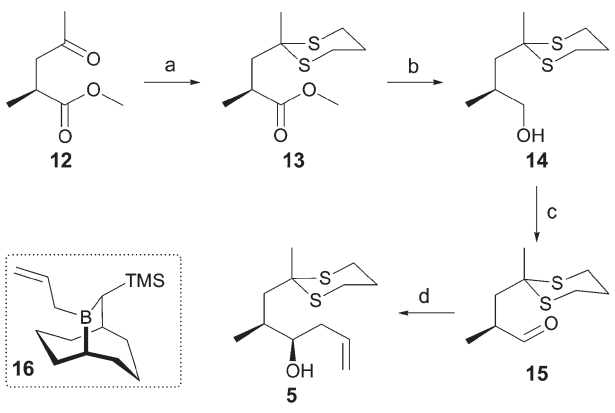


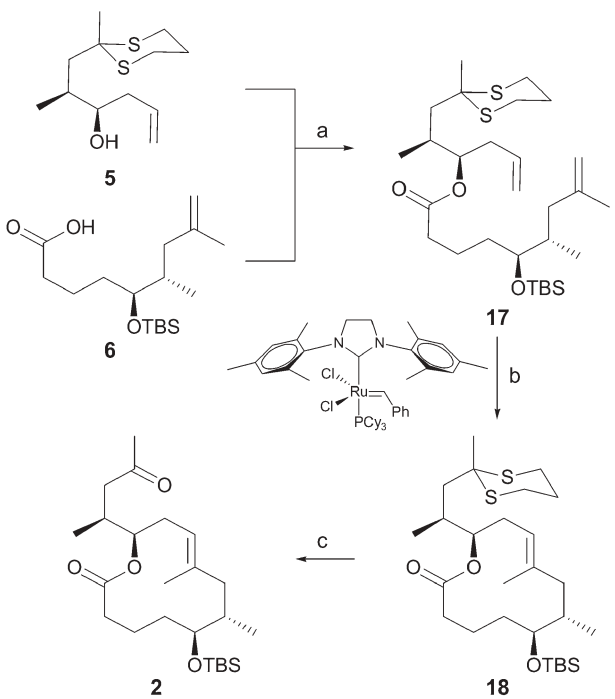
Scheme 1 (a) (*R*)-3-(1-Oxopropyl)-4-(phenylmethyl)-2-oxazolidinone, Et_3N, Bu_2BOTf, CH_2Cl_2, −78 → 0 → −78 °C, then **7**, −78 → 0 °C, 95%; (b) TBSOTf, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 98%; (c) $LiBH_4$, MeOH, THF, 0 °C, 74%; (d) i. $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; ii. Et_3N, −78 → 20 °C, 95%; (e) i. 2-propenylmagnesium bromide, THF, 0 °C, add **9**; ii. Ac_2O, pyridine, DMAP (cat.), 89%; (f) HCO_2NH_4, $Pd(PPh_3)_4$, PBu_3, dioxane, reflux, 88%; (g) 5 N NaOH, MeOH, reflux, 96%; (h) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; ii. Et_3N, −78 → 20 °C, 97%; (i) sodium chlorite, 2-methyl-2-butene, *t*-BuOH, NaH_2PO_4, 88%.

The γ-keto ester **12** (Scheme 2) was prepared from *tert*-butyl acetoacetate and methyl L-lactate according to the one-pot procedure of Hoffman and Kim (see ESI†).[21] The ketone in **12** was protected as the dithiane, **13**, in 96% yield through reaction with 1,3-propanedithiol and $BF_3{\cdot}Et_2O$. Reduction of the methyl ester directly to the aldehyde with DIBAL-H proved to be ineffective, as variable mixtures of methyl ester starting material, desired aldehyde, and over-reduced alcohol were routinely observed. Therefore, a two step sequence was employed, where the methyl ester was fully reduced to the alcohol with lithium aluminium hydride and oxidized back to the aldehyde **15** with TPAP.[22] This process proceeded in 79% yield over the two steps. Asymmetric allylboration was effected using the 9-BBN-derived reagent **16**, recently developed by Soderquist *et al.*[23] The stereochemistry in **5** requires a high level of reagent control in the addition to the aldehyde **15**[24] because **5** is the anti-Felkin product and represents the mismatched case[25] for allylboration. Nonetheless, **16** shows excellent facial selectivity in addition to aldehydes. The *R*-isomer of **16** added exclusively to the *re* face of **15** to provide homoallylic alcohol **5** in 88% yield as the only observable diastereomer in the ^{1}H-NMR spectrum.

The completion of compound **2** was carried out as shown in Scheme 3. Acid **6** and secondary alcohol **5** were coupled in 96% yield using Keck's modification of the Steglich esterification.[26,27] The RCM reaction was carried out using Grubb's second generation catalyst **16** under standard conditions (5 mol% catalyst loading).[28,29] Undecenolide **18** was obtained in 60% yield after flash chromatography to remove acyclic dimer and benzylidene adduct side products (see ESI†). The RCM reaction was exceptionally stereoselective and a single isomer of ring olefin was observed in the ^{13}C-NMR spectrum. Fortunately, NOE experiments with **18** suggested it was the *E*-stereoisomer that had formed, based on a lack of NOE correlation between the C(9) proton and C(8) methyl group.[30] A clean removal of the dithiane group in **18** was achieved using *N*-chlorosuccinimide and silver nitrate to give ketone **2** in 81% yield.[31] Upon purification by flash chromatography, an amorphous solid was obtained that formed crystalline needles from hexanes.[32] The crystal structure of **2** (Fig. 2) confirmed the absolute stereochemistry of all four stereocenters and the *E* configuration of the ring double bond. This structure has the same stereochemical configuration as that of the natural product as determined by Kishi.[8,9]



Scheme 2 (a) 1,3-Propanedithiol, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −10 °C, 96%; (b) $LiAlH_4$, THF, 0 → 20 °C, 98%; (c) TPAP, 4 Å sieves, NMO, CH_2Cl_2, 81%; (d) **16**, Et_2O, −78 °C, add **15**, 88%.



Scheme 3 (a) DCC, DMAP, CSA, CH_2Cl_2, 95%; (b) CH_2Cl_2, reflux, 60%; (c) *N*-chlorosuccinimide, $AgNO_3$, 4 : 1 CH_3CN–H_2O, 81%.

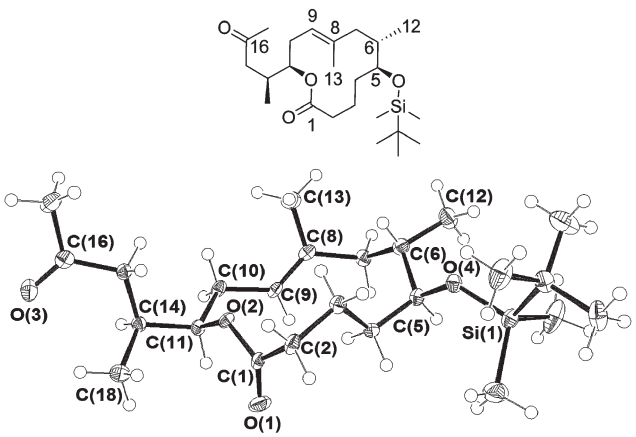


Fig. 2 ORTEP diagram of the X-ray crystal structure of compound **2** (ellipsoids are at the 50% probability level and numbering differs from **1**).

Here we have shown a convergent route to macrocyclic ketone **2**, a potential building block for mycolactone. The longest linear sequence is 14 steps with an overall yield of 19%. The preparation of **1** and its derivatives from common intermediate **2** is currently under investigation.

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3 Mycolactones A and B, depicted here as **1**, are 4′*Z*- and 4′*E*-isomers, respectively. The TBS-protected fatty acid side chain, **4**, was previously synthesized by Kishi as a mixture of 4′-olefin geometries.[7] Recently, separate syntheses of the protected fatty acid sidechains of mycolactones A and B were reported by Negishi.[13] In this route, the 12′-OH is protected as a MOM ether instead of a TBS ether.

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30 Compound **18** in $CDCl_3$ was selectively irradiated at the frequency corresponding to 1.67 ppm, and no enhancement of the signal at 5.01 ppm was observed.

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32 A colorless needle 0.20 × 0.07 × 0.07 mm in size was mounted on a cryoloop with Paratone® oil. Data was collected in a nitrogen gas stream at −173 °C. Crystal-to-detector distance was 60 mm and exposure time was 40 seconds per frame using a scan width of 0.5°. Data collection was 99.8% complete to 25° in θ. A total of 4449 reflections were collected covering the indices, $h = -14$ to 14, $k = -19$ to 28, $l = -18$ to 19. All 4449 reflections were found to be symmetry independent, with an R_{int} of 0.0523 indicating that the data set was of better than average quality (average = 0.07). Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $P2_12_12_1$ (No. 19). The data were integrated using the Bruker SAINT software program and scaled using the Bruker SADABS software program. Solution by direct methods (SIR-2004) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed using a riding model and their positions constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97. **Crystal data**. $C_{24}H_{44}O_4Si$, $M = 424.68$, orthorhombic, $a = 7.6150(9)$, $b = 13.9000(17)$, $c = 23.912(3)$ Å, $U = 2531.0(5)$ Å^3, $T = 100$ K, space group $P2_12_12_1$ (No. 19), $Z = 4$, μ(Mo-Kα) = 0.117 mm^{-1}, 4449 reflections measured, 4449 unique (R_{int} = 0.0523). The final R indices [$I > 2\sigma(I)$] $R1 = 0.0604$, $wR2 = 0.1021$, R indices (all data) $R1 = 0.0658$, $wR2 = 0.1037$. CCDC 613942. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b609408b.

