Total Synthesis

Total Synthesis and Structural Elucidation of (−)-Delactonmycin**

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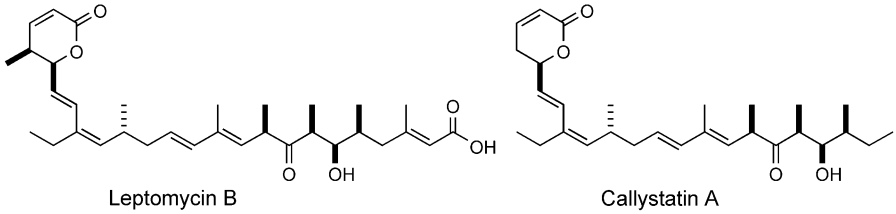
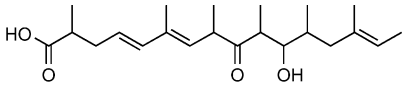
Dedicated to Professor Albert J. Kascheres on the occasion of his 60th birthday

In recent years, a number of highly cytotoxic polyketides with similar chemical structures, including the leptomycins, kazusamycins, anguinomycins, and leptolstatins, were isolated as secondary metabolites from *Streptomyces* strains.[1] In 1997, Wang et al. identified two novel polyketides, named delactonmycin and dilactonmycin, in the extracts from *Streptomyces* strain A92-308902 with very potent inhibitory activity of the nucleo-cytoplasmic translocation of the HIV-1 regulatory protein Rev.[2] The planar structure of delactonmycin was established by spectroscopic methods, but its relative as well as its absolute configuration remained unknown. In our synthetic studies towards the elucidation of the relative configuration of delactonmycin (**1**), we were led to presume that it is the same as that of leptomycin B and callystatin A—a structurally related polyketide isolated from the marine sponge *Callyspongia truncata*[3]—whose relative and absolute configurations were established by spectroscopic methods and total synthesis.[4,5]





Delactonmycin (**1**)

Our interest in the synthesis of delactonmycin stemmed from its greater structural simplicity relative to that of other members of this class, which renders it an interesting model compound for structure–activity studies.[6] Additionally, the implementation of a successful approach to **1** would pave the way to the total synthesis of other polyketides whose structures have not yet been confirmed by total synthesis. Herein, we disclose our approach and results toward the first total synthesis and structural elucidation of (−)-delactonmycin (**1**, Scheme 1).

The installation of the C4–C5 bond through *E*-selective Wittig olefination between aldehyde **2** and phosphonium bromide **3** was left to a late stage of the synthesis in our retrosynthetic analysis. In turn, **3** could be obtained from a Wittig olefination of aldehyde **4** with ethyl triphenylphosphoranylidene propionate. It was envisaged that aldehyde **4** could be prepared from the *syn* aldol adduct obtained from the reaction between ethyl ketone **5** and γ,δ-unsaturated aldehyde **6**. The fragments **2**, **5**, and **6** are available from the methyl (*R*)- and (*S*)-3-hydroxy-2-methylpropionates, which we have already used in the total synthesis of the aglycon of the macrolide antibiotic 10-deoxymethymycin.[7]

Aldehyde **6** was readily obtained through the sequence shown in Scheme 2. A palladium-catalyzed cross-coupling reaction between the chiral zinc homoenolate **8**[8,9] and *cis*-2-bromo-2-butene (both commercially available) led to the formation of **11**, which was carefully reduced with diisobutylaluminum hydride at −90 °C to afford **6** in 86% overall yield. Ketone **5** was prepared as described by Paterson et al.[10] in three steps and 57% overall yield. Conversion of (*R*)-**7** into the Weinreb amide **9** was followed by protection as its *p*-methoxybenzyl ether **10**. Subsequent addition of ethyl magnesium bromide provided ethyl ketone **5**. Treatment of **5** with stannous triflate and Et_3N at −78 °C in CH_2Cl_2 generated the corresponding *Z* enolate, which reacted with the γ,δ-unsaturated aldehyde **6** to afford the *syn* aldol adduct **12** in 75% yield (92% based on consumed starting material) and 96:4 diastereomeric ratio. The stereochemical control observed in the formation of **12** is ultimately derived from the tin(II) enolate of ketone **5**.[11]

As depicted in Scheme 1, we planned to postpone the installation of the ketone at C9 to a late stage in our synthetic sequence in order to carry out the requisite functional-group manipulation and chain extension. The stereoselective formation of 1,3-diol **13** was explored using metal-chelation control and intermolecular hydride transfer. The best 1,3-*syn* diastereofacial selectivity (d.r. 95:5) was achieved in the reduction of β-hydroxyketone **12** with DIBAL-H at −78 °C (Scheme 3).[12] The diastereomeric ratio was determined by GC/MS analysis of acetonide **14**.

Having secured the diastereoselective preparation of *syn*-diol **13**, we proceeded to its oxidative conversion with DDQ

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author (spectroscopic and analytical data for compounds (−)-**13**, (−)-**20**, and (−)-**1**, including a CD curve for (−)-**1**).

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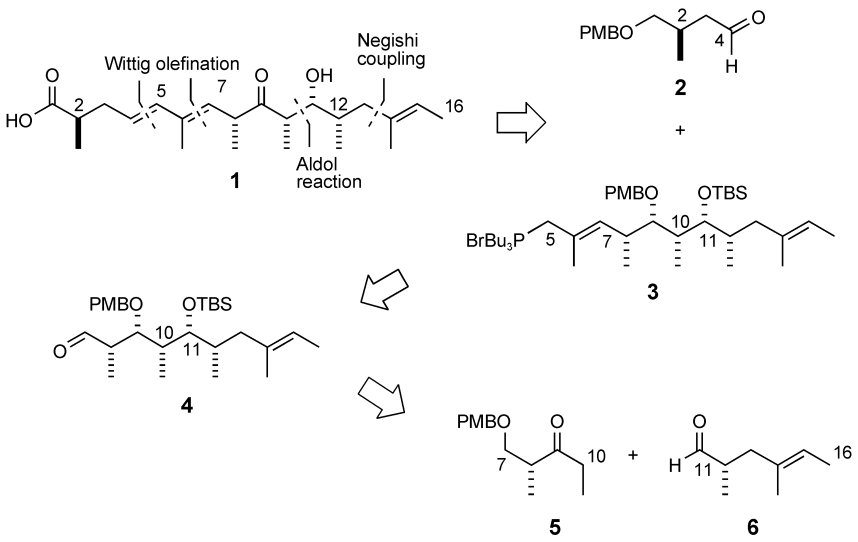
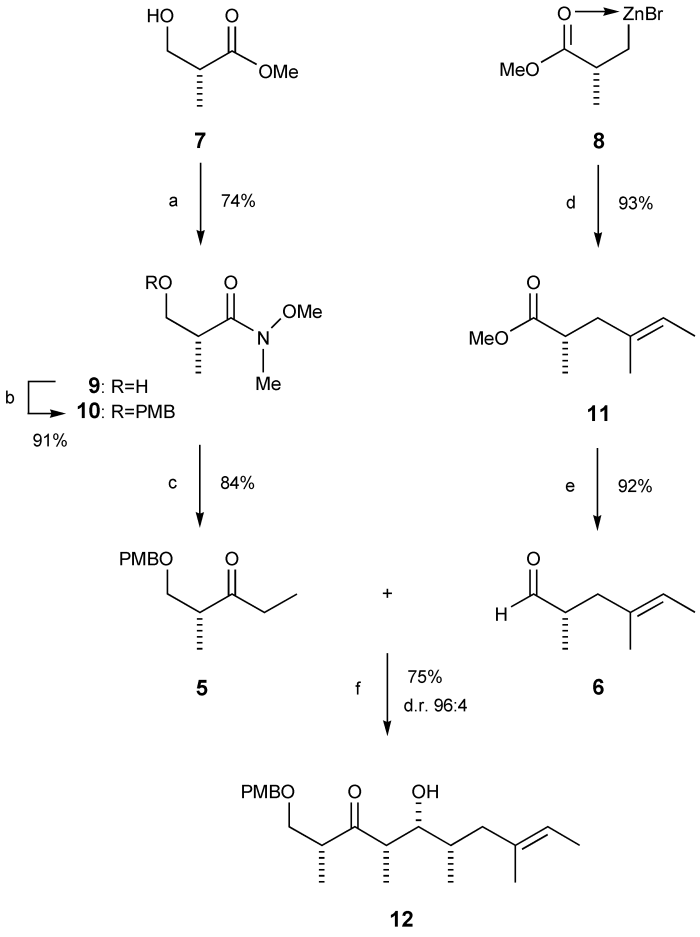


Scheme 1. Retrosynthetic analysis of the putative stereostructure of delactonmycin.

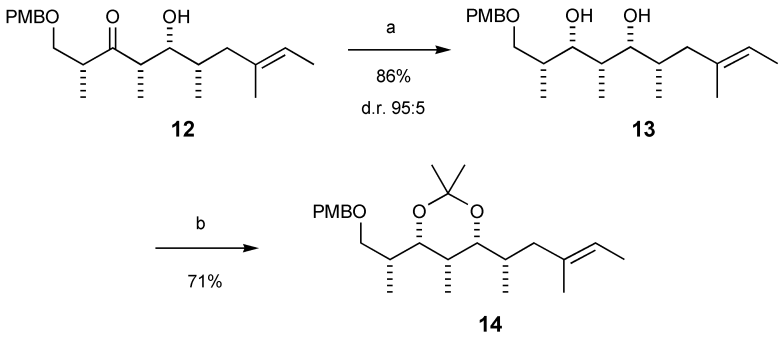


Scheme 2. Synthesis of **12**. Reagents and conditions: a) MeONHMe·HCl, $AlMe_3$, CH_2Cl_2, 0 °C→RT, 18 h; b) PMBOC(=NH)CCl_3, CSA, CH_2Cl_2, room temperature, 18 h; c) EtMgBr, Et_2O, 0 °C, 1 h; d) *cis*-2-bromo-2-butene, [$PdCl_2(PPh_3)_2$], THF, 0 °C→RT, 24 h; e) DIBAL-H, hexane, −90 °C, 1 h; f) $Sn(OTf)_2$, Et_3N, CH_2Cl_2, −78 °C; then **5**, 2 h; then **6**, −78 °C, 2 h and −50 °C, 1 h. PMB = *p*-methoxybenzyl, CSA = camphor-10-sulfonic acid, Tf = trifluoromethanesulfonyl. DIBAL-H = diisobutylaluminium hydride.

into the corresponding *p*-methoxybenzylidene acetal **15** under anhydrous conditions[14] and protection of the secondary hydroxy group at C11 as the *tert*-butyldimethylsilyl ether **16** (Scheme 4). Regioselective cleavage of the PMP acetal[14] efficiently provided the primary alcohol **17**, and its subsequent oxidation with Dess–Martin periodinane led to the aldehyde **4**. An *E*-selective Wittig olefination of **4** with $Ph_3P{=}C(Me)CO_2Et$ in toluene afforded α,β-unsaturated ester **18** as the only product. Reduction of the ester moiety in **18** with DIBAL-H provided the allylic alcohol **19**, which was converted with CBr_4 and PPh_3 in the presence of 2,6-lutidine into the corresponding bromide **20** in 31% overall yield from β-hydroxyketone **12**. The *all-syn* configuration in bromide **20** was established after analysis of the ^1H and ^{13}C NMR spectra and NOESY experiments carried out with acetonide **14** and *p*-methoxybenzylidene acetal **15** (Figure 1).

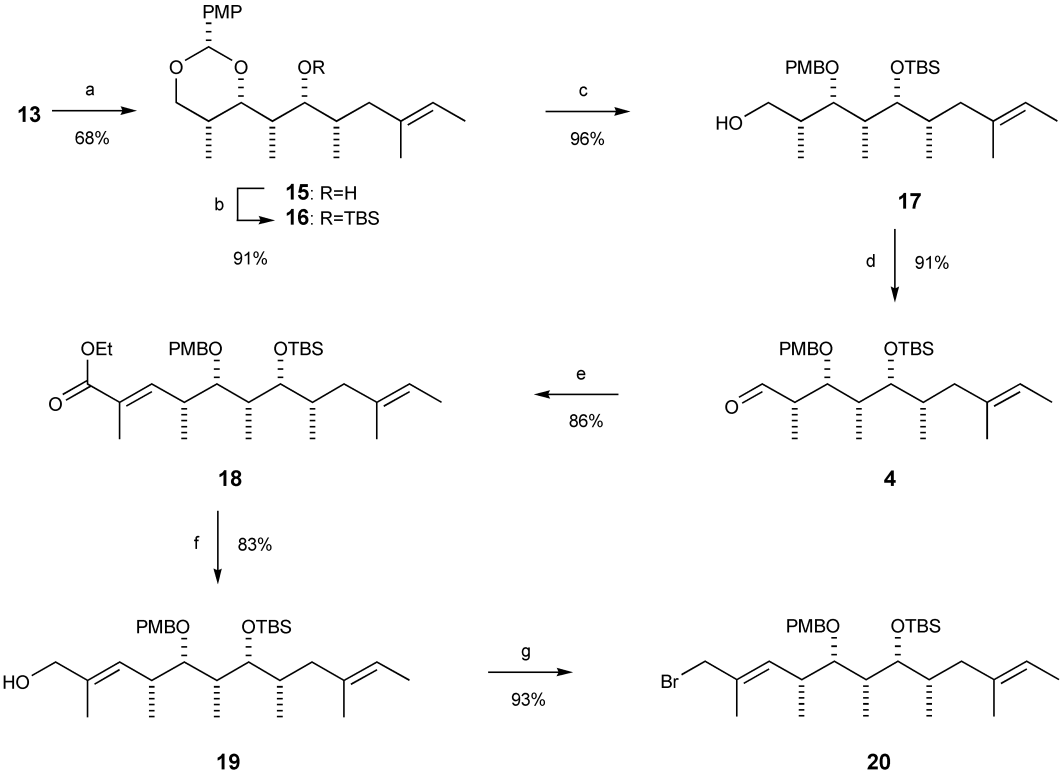
At this stage, a final Wittig olefination was used to join the known aldehyde **2**[15] and the tributylphosphonium salt derived from allylic bromide **20** (Scheme 5). The coupling was carried out under the conditions described by Tamura et al.[16] to provide **21** (d.r. *E*/*Z* 8:1). Next we sought the chemoselective deprotection of the PMB ethers at C1 and C9. Attempts to deprotect **21** with DDQ invariably gave complex reaction mixtures.[17] In fact, closer inspection of the literature revealed that several authors have been unable to remove methoxybenzyl groups in the presence of conjugated dienes.[18] Several alternative methods (hydrogenolysis, reduction with dissolved metal, as well as Lewis acid conditions)[19,20] were investigated for model compounds without much success. After extensive experimentation, the PMB group of **21** was selectively cleaved with TFA in CH_2Cl_2 to give diol **22**, albeit in low yield.[21]

The synthesis was completed with the double oxidation of **22** (oxidation with Dess–Martin periodinane[22] followed by Pinnick oxidation to the carboxylic acid[23]) and deprotection of the secondary TBS ether with HF/pyridine complex in THF. The spectroscopic data of the synthetic (−)-delac-



Scheme 3. Synthesis of **13** and determination of its d.r. Reagents and conditions: a) DIBAL-H, THF, −78 °C, 3 h; b) $Me_2C(OMe)_2$, PTSA, CH_2Cl_2, room temperature, 12 h. PTSA = *p*-toluenesulfonic acid.

tonmycin (**1**) (IR, HRMS, ^1H and ^{13}C NMR) nicely matched those reported for the natural product,[2] thus allowing us to confirm their identity and unambiguously establish its relative configuration. Unfortunately, the lack of a sample of natural delactonmycin (**1**) or its chiroptical data precluded the determination of its absolute configuration at this point. Studies directed towards the total synthesis of other members of this family of polyketides are now underway in our laboratory and will be reported in due course.



Scheme 4. Synthesis of **20**. Reagents and conditions: a) DDQ, molecular sieves (3 Å), CH_2Cl_2, room temperature, 30 min; b) TBSOTf, 2,6-lutidine, 0 °C→RT, 1 h; c) DIBAL-H, CH_2Cl_2, 0 °C→RT, 2 h; d) Dess–Martin periodinane, CH_2Cl_2/H_2O, room temperature, 15 min; e) $Ph_3P{=}C(Me)CO_2Et$, toluene, room temperature, 36 h; f) DIBAL-H, CH_2Cl_2, −78 °C, 1 h; g) CBr_4, PPh_3, 2,6-lutidine, CH_3CN, room temperature, 15 min. DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone, TBS = *tert*-butyldimethylsilyl, PMP = *p*-methoxyphenyl.

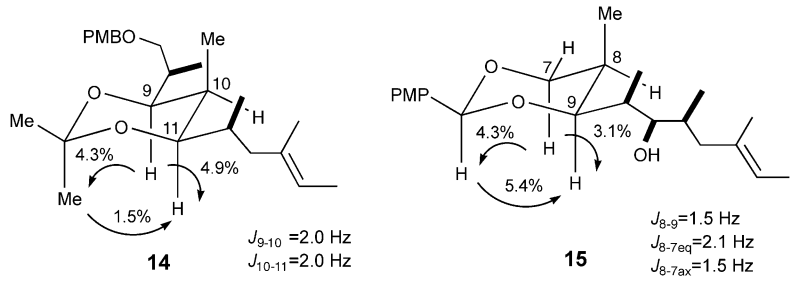


Figure 1. Configurational assignment of acetonide **14** and *p*-methoxybenzylidene acetal **15**.

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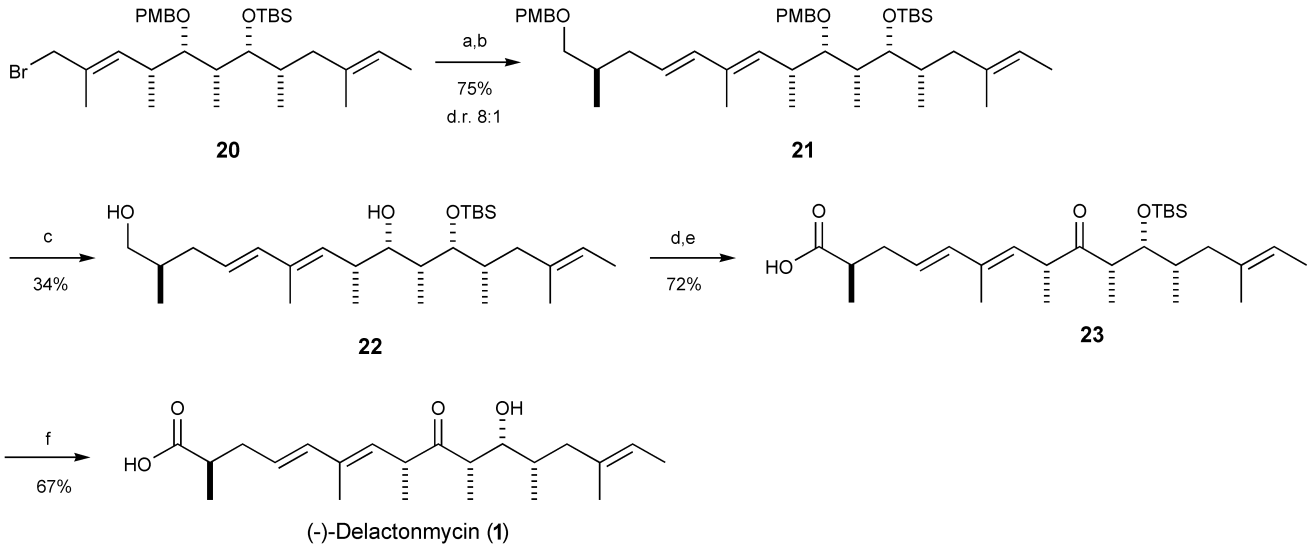

Scheme 5. Completion of **1**. Reagents and conditions: a) PBu_3, MeCN, room temperature, 2 h; b) **2**, KO*t*Bu, toluene, 0 °C, 2 h; c) TFA, CH_2Cl_2, room temperature, 20 min; d) Dess–Martin periodinane, CH_2Cl_2/H_2O, room temperature, 30 min; e) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH/H_2O, room temperature, 2 h; f) HF·pyridine, THF, room temperature, 64 h. TFA = trifluoroacetic acid.

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