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Total synthesis of mycestericin A

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Abstract

The first total synthesis of mycestericin A (**1**) starting from tartrates is described. The Overman rearrangement of an allylic trichloroacetimidate generated a tetra-substituted carbon with nitrogen, and subsequent stereoselective transformations afforded the highly functionalized vinyl iodide. The cross-coupling of the vinyl iodide with a chiral organozinc species under Negishi conditions, followed by deprotection, completed the total synthesis of **1**.

Keywords: Mycestericin A; Immunosuppressant; Total synthesis; Overman rearrangement; Negishi coupling

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Mycestericin A (**1**) is a member of mycestericins produced by *Mycelia sterilia* and reported to show a potent immunosuppressive activity.[1] A structural elucidation study revealed that the structure of mycestericin A is similar to that of myriocin, a well-known immunosuppressant,[2] but mycestericin A has another *E*-olefin between C-12 and C-13 and one distal (*R*)-allylic alcohol function at C-14.[1a] Due to the intriguing structures as well as potent biological properties, many reports on the total synthesis of natural products in this class, such as myriocin, sphingofungins E and F, mycestericins D, E, F, and G, and sulfamisterin have been described,[3,4] however, no synthetic approach to mycestericin A has appeared. In this Letter, we report the first total synthesis of mycestericin A starting from the tartrates.

Our previous success in the total synthesis of lactacystin,[5] myriocin,[3e,4h] and sphingofungin E[4h] starting from aldohexofuranoses suggested that the Overman rearrangement on chiral scaffolds would effectively generate the tetra-substituted carbon with nitrogen.[6] This idea involves disconnection of the carbon framework in **1** into the highly functionalized part, vinyl iodide **2** and the precursor of organometallic species, primary iodide **3**, possessing the (*E*,*R*)-allylic alcohol function (Fig. 1). The well-established Pd-catalyzed coupling reaction was expected to stereoselectively construct the carbon backbone in **1**. The vinyl iodide **2** was planned to be prepared from an alcohol with a tetra-substituted carbon **4**, which would be derived from the Overman rearrangement of an allylic trichloroacetimidate **5**. The imidate **5** was envisioned as arising from dimethyl L-tartrate. On the other hand, the counterpart **3** was planned to be synthesized from D-tartrate.

The synthesis of **2** commenced with the known acetonide **6**[7] prepared from dimethyl L-tartrate in a 3-step reaction in a 31% overall yield (Scheme 1).[4o] After protection of the primary hydroxy group in **6**, the *O*-benzyl group was removed to give **7** in 94% yield.[8] PCC oxidation of **7**, followed by Wittig reaction afforded **8** as the single *E*-isomer (93% for two steps). The reduction of **8** with DIBAL cleanly generated allyl alcohol **9** in 97% yield. The treatment of **9** with trichloroacetonitrile and DBU afforded trichloroacetimidate **5**, which, without isolation, was heated in xylene in the presence of K_2CO_3[9] in a sealed tube at 140 °C for 48 h that gave products due to the Overman

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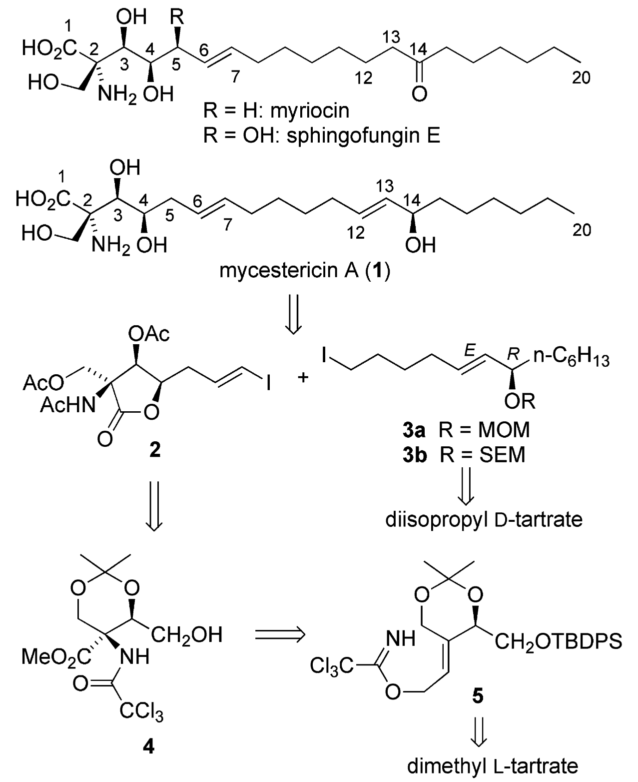
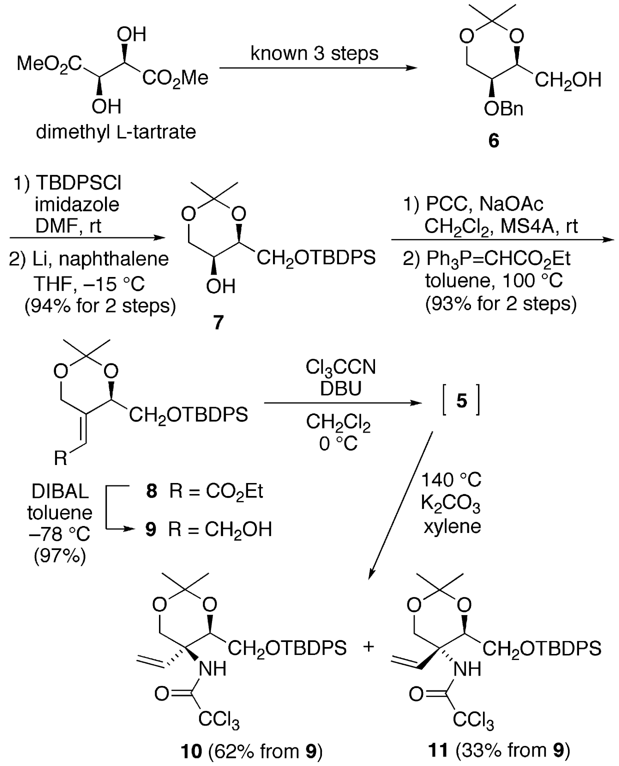


Fig. 1. Structures of myriocin, sphingofungin E, and mycestericin A, and retrosynthetic route to mycestericin A. MOM = –CH_2OMe, SEM = –$CH_2OCH_2CH_2SiMe_3$, TBDPS = –$SiPh_2$(*t*-Bu).

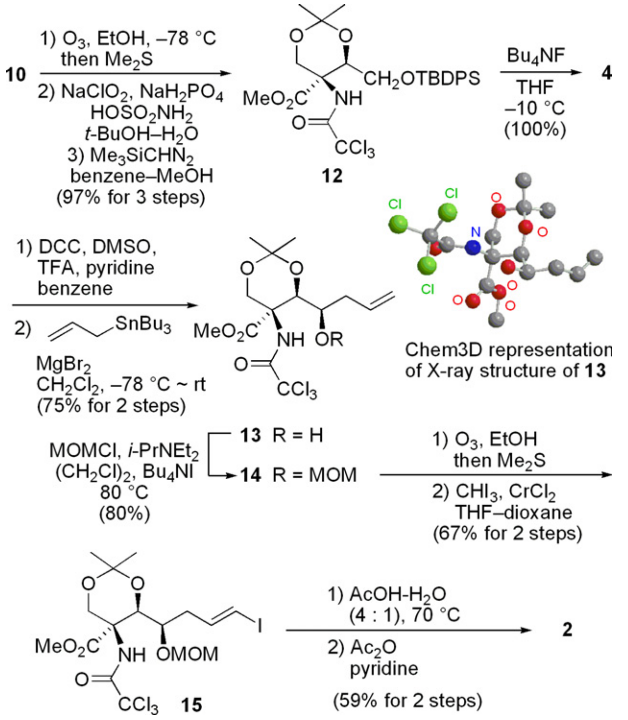


Scheme 1. Bn = –CH_2Ph, PCC = pyridinium chlorochromate, MS4A = molecular sieves 4A, DIBAL = $[(CH_3)_2CHCH_2]_2AlH$.

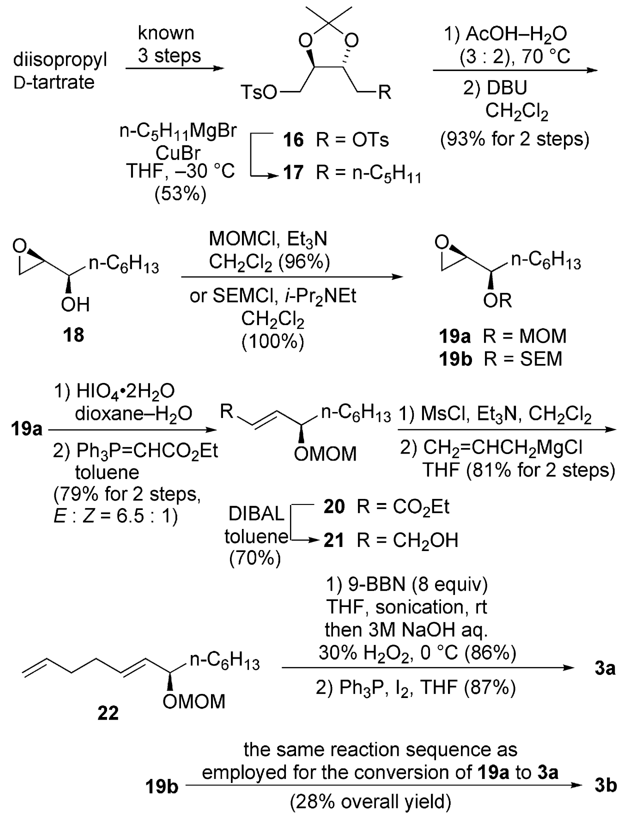
rearrangement, **10**[10] and its epimer **11**, in 62% and 33% isolated yields from **9**, respectively.

With the desired rearranged product **10** in hand, its transformation into **2** was examined (Scheme 2). Ozonolysis of **10**, followed by further oxidation and esterification afforded **12** in 97% yield. Removal of the *O*-silyl protecting group provided **4** (100%). Pfitzner–Moffatt oxidation of **4** gave an aldehyde, which, without purification, was reacted with allyl tributyltin in the presence of $MgBr_2$ in CH_2Cl_2[11] to stereoselectively afford homoallyl alcohol **13**, whose structure was unambiguously confirmed by a single crystal X-ray analysis,[12] in 75% yield from **4**. The hydroxy group in **13** was protected as a methoxymethyl ether to give **14** (80% yield), whose ozonolysis, followed by the Takai reaction[13] with CHI_3 in the presence of $CrCl_2$ in THF/1,4-dioxane provided (*E*)-vinyl iodide **15** in 67% yield along with its *Z*-isomer (8%) from **14**. The treatment of **15** with aqueous acetic acid at 70 °C removed all the protecting groups including the *N*-trichloroacetyl moiety, to give the γ-lactone **2** in 59% yield after acetylation.

The counterparts for the coupling reaction, **3a** and **3b**, were synthesized from D-tartrate (Scheme 3). The known di-*O*-tosylate[14] **16**, prepared from diisopropyl D-tartrate in an 86% overall yield, was treated with pentylmagnesium bromide in the presence of CuBr to afford **17** in 53% yield. After deprotection of the acetonide group, the product was converted into epoxide **18**, whose hydroxy group was protected as a MOM or a SEM ether to give **19a** (89% yield from **17**) or **19b** (93% yield from **17**). Oxidative cleavage of the epoxide function in **19a** with HIO_4[15] afforded the corresponding aldehyde, which was then reacted with the



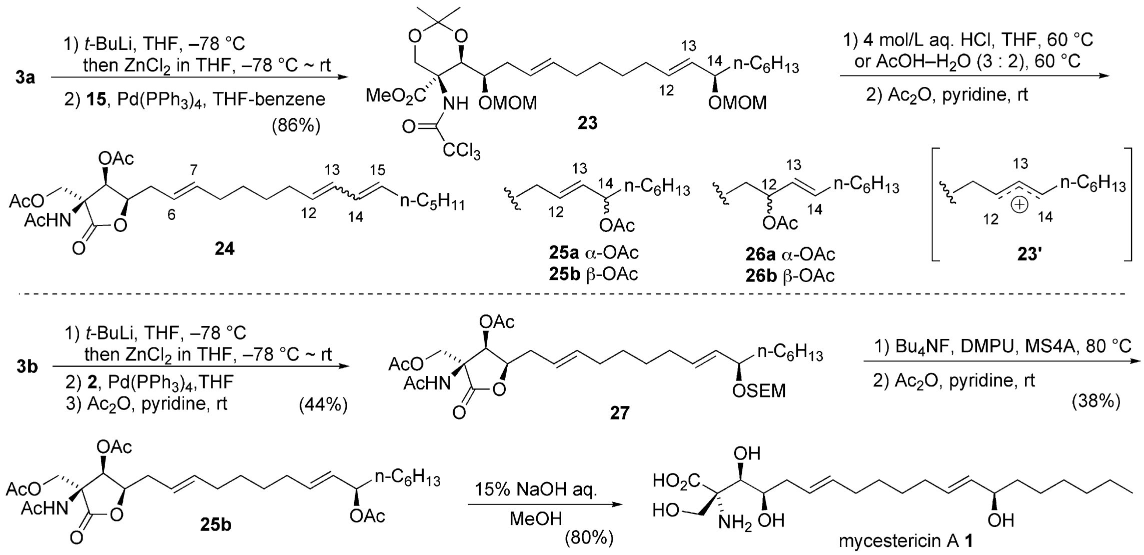
Scheme 2. DCC = *N*,*N*′-dicyclohexylcarbodiimide, TFA = CF_3CO_2H.



Scheme 3. 9-BBN = 9-borabicyclo[3.3.1]nonane.

Wittig reagent to afford an inseparable mixture of *E*-olefin **20** and its *Z*-isomer (79% combined yield, *E*:*Z* = 6.5:1). DIBAL reduction of the mixture, followed by chromatographic separation gave geometrically pure *E*-allyl alcohol **21** in 70% isolated yield. The primary hydroxy group in **21** was transformed into *O*-mesylate, which was then reacted with allylmagnesium chloride to provide **22** in 81% yield. Hydroboration of **22** with excess (8 equiv to **22**) 9-BBN, followed by oxidation provided a primary alcohol, whose hydroxy function was replaced with iodide to afford **3a**,[10] a precursor for the coupling reaction, in 75% yield. The same reaction sequence as employed for the conversion of **19a** to **3a** was applied to **19b** to provide **3b**[10] in 28% overall yield from **19b**.

Having established the procedure for the preparation of both counterparts for the coupling reaction, we then explored the Negishi cross-coupling[16,17] conditions, which had been utilized for the total synthesis of myriocin and sphingofungin F by Ham et al.[3f,4i] The treatment of the iodide **3a** with *t*-BuLi at −78 °C, followed by treatment with $ZnCl_2$ generated an alkyl zinc species, which was then reacted with vinyl iodide **15** in the presence of $Pd(PPh_3)_4$ to provide coupling product **23** in 86% yield (Scheme 4). The treatment of **23** with aqueous HCl at 60 °C removed all the protecting groups, however, the concomitant elimination of a methoxymethyloxy or hydroxy function at C-14 also took place, and after acetylation, γ-lactone-diene **24** was obtained.[18] On the other hand, the reaction of **23** with aqueous acetic acid, followed by acetylation afforded γ-lactone, that is expected to possess the structure of **25b** in 49% yield. The ^1H NMR data of the synthetic γ-lactone were very close to those reported for the lactone **25b** derived from natural mycestericin A,[1a] and the FAB-MS data also supported its structure. However, in the ^{13}C NMR of the synthetic γ-lactone, in addition to a set of four signals (δ 123.2, 128.6, 134.0, and 135.0 ppm) due to olefinic carbons whose chemical shifts are in good agreement with those of the authentic **25b**, extra four signals (δ 123.1, 128.1, 134.4, and 134.6 ppm) of olefinic carbons, whose intensities were almost the same as those of the former four signals, were observed. These results revealed that the synthetic γ-lactone is an inseparable mixture of diastereomers. The plausible products of the acid hydrolysis of **23**, followed by acetylation, are **25a**,**b** and/or **26a**,**b**, which would be formed via an allyl cation



Scheme 4. DMPU = *N*,*N*-dimethyl propylene urea.

intermediate **23′**. The attempted deprotection of **23** with TMSBr, which was reported to be effective for the clean deprotection of an allylic MOM ether,[19] also resulted in the formation of a mixture of **25a**,**b** and/or **26a**,**b**. These results clearly showed that the allylic alcohol moiety in **23** is unexpectedly labile under the acidic conditions.

To avoid the formation of the allyl cation **23′**, the coupling reaction of substrates possessing protecting groups, which could be removed under basic conditions, was next investigated. To our delight, the Negishi coupling of an alkyl zinc derived from the SEM-ether **3b** with γ-lactone **2**, followed by acetylation, successfully provided **27** in 44% yield. The treatment of **27** with anhydrous Bu_4NF and MS4A in DMPU[20] at 80 °C, followed by acetylation, provided **25b** as a single isomer in 38% yield.[21] The spectral data (^{1}H and ^{13}C NMR) as well as the $[\alpha]_D$ value of the synthetic **25b** were completely identical with those already reported.[1a] Finally, alkaline hydrolysis of **25b** furnished mycestericin A (**1**) in 80% yield. The $[\alpha]_D$ value $\{[\alpha]_D^{28}$ −9.1 (*c* 0.16, MeOH); lit.[1a] $[\alpha]_D$ −8.5 (*c* 0.50, MeOH)$\}$ as well as spectroscopic data showed a good agreement with those reported for the natural product.[1a]

In summary, the first total synthesis of mycestericin A (**1**) starting from tartrates has been accomplished. This synthesis fully confirmed the proposed absolute structure of the natural product, and provided a new synthetic pathway to highly oxygenated α-substituted α-amino acid derivatives showing potent biological activities starting from readily available tartrates.

Acknowledgment

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Supplementary data

The spectrum data and ^{1}H and ^{13}C NMR spectra of compounds **9**, **10**, **11**, **4**, **13**, **15**, **2**, **3a**, **3b**, **23**, **27**, **25b**, and **1**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.105.

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