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Total Synthesis of Pulvomycin D

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Abstract: A synthetic route to the pulvomycin class of natural products is presented, which culminated in the first synthesis of a pulvomycin, pulvomycin D. Key elements of the strategy include a pivotal aldol reaction which led to bond formation between the C24-C40 and the C8-C23 fragment. The remaining C1-C7 fragment was attached by a Yamaguchi esterifica- tion completing the assembly of the 40 carbon atoms within the main skeleton. Ring closure to the 22-membered lactone ring was achieved in the final stages of the synthesis by a Heck reaction. The completion of the synthesis required the removal of six silyl protecting groups in combination with olefin formation at C26-C27 by a Peterson elimination.

The history of the pulvomycin natural products dates back to the year 1957 when Zief et al. reported the isolation of a new antibiotic from an unidentified microbial strain.[1] In 1963, Akita et al. described an antibiotic from *Streptomyces albosporeus* var. *labilomyceticus*[2] which they named labilomycin „because of its labile nature." Pulvomycin and labilomycin were found to be identical by Schwartz et al. who isolated the compound from a bacterial culture.[3] Structural assignments remained cursory until a comprehensive NMR and MS study by Williams and co-workers revealed the correct constitution of the natural product which features a prominent 22-membered lactone ring and three triene units.[4] Eventually, a crystal structure analysis provided conclusive proof for the relative and absolute configuration of pulvomycin A as it is known today (Scheme 1).[5] Very recently, it was discovered by Moon et al. that three additional molecules with a related structure exist which were isolated from *Streptomyces sp.* HRS33. The compounds were called pulvomycins B–D with pulvomycin A (**1**) representing the original antibiotic.[6]

Pulvomycin A has been studied extensively due to its antibacterial activity, and its mode of action is well established.[7] Pulvomycin D (**2**) was found to show significant cytotoxicity against several cancer cell lines.[6] Biosynthetically, both compounds represent polyketides which are glycosylated after the C1-C34 carbon skeleton has been constructed.[6,8] The lability of the compounds against acid, base, oxygen, and light is likely associated with the conjugated triene units and the elimination prone hydroxy groups at C5 and C23.[9] Taking these
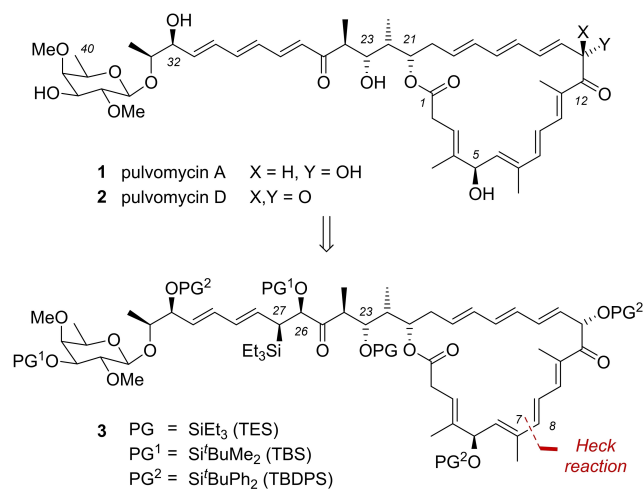
Scheme 1. Structure of pulvomycin A (**1**) and pulvomycin D (**2**) isolated from *Streptomyces* sp. and structure of a putative precursor **3** to the natural products. A late-stage Heck reaction was envisioned for ring closure of the 22-membered lactone ring, which was to be followed by a complete deprotection and a *syn*-stereospecific Peterson elimination at C26-C27.

facts into account, we devised a strategy towards the synthesis of pulvomycins A and D which aimed to mask the putatively most labile trienone (C25-C31) and to protect all hydroxy groups as silyl ethers. Compound **3** resulted as a potential precursor to pulvomycins A and D and was considered the prime target of our synthetic endeavor. In this contribution we report on the successful synthesis of compound **3** and on our attempts to achieve an unmasking of the C25-C31 trienone and a complete deprotection which eventually led to the synthesis and isolation of pulvomycin D (**2**).

Our initial plan for the synthesis of compound **3** rested on the construction of an acyclic precursor as ω-hydroxycarboxylic acid which would undergo macrolactonization[10] to the desired 22-membered lactone ring in one of the final steps. A pivotal intermediate representing the C12-C40 segment of pulvomycin had been previously prepared by a diastereoselective aldol reaction linking carbon atoms C23 and C24.[11] Although this intermediate could be further processed to the required precursor, the macrolactonization failed, most likely due to

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steric hindrance by the TES-protected hydroxy group at C23.[11b,12] Among many alternative routes toward a possible ring closure, the Heck reaction turned out to be the superior C—C bond forming event which eventually gave access to the desired compound.

Besides the Heck disconnection, the other two major disconnection steps of our retrosynthesis included ester bond formation at the C21 hydroxy group and the previously established aldol reaction.[11c,13] Application of this strategy led to three main building blocks containing carbon atoms C1-C7, C8-C23, and C24-C40. Maximum convergence was achieved by attaching the diene fragment C8-C11 early to a chiral protected glycerin aldehyde. Indeed, the synthetic sequence commenced with the preparation of this building block which was obtained by Sharpless dihydroxylation (97% ee)[14] of protected allylic alcohol 4 (Scheme 2).
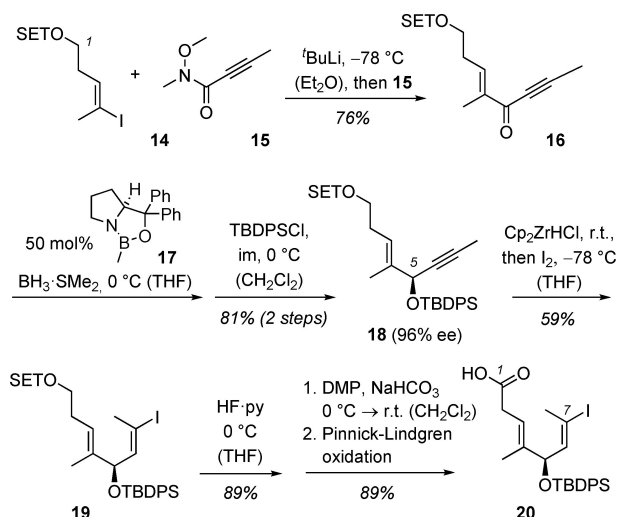
The primary hydroxy group at C12 was liberated by a two-fold protection and selective deprotection at C12.[15] Alcohol 5 was routinely obtained on a scale of 10–20 g and served as the precursor to the above-mentioned aldehyde which was generated by oxidation with the Dess-Martin periodinane (DMP).[16] Nozaki-Hiyama coupling[17] with iodide 6 delivered the desired C8-C14 fragment 7 as a mixture of diastereoisomers. Since the relative configuration at C12 is inconsequential for the synthesis, the diastereoisomers were not separated. Rather, the compound was processed as a mixture of diastereoisomers. Iodide 6 was obtained from literature known (E)-4-iodopent-3-enol[18] by mesylate formation and subsequent elimination with KOtBu.[19] Protection of the secondary hydroxy group and deprotection of the primary hydroxy group at C14 gave alcohol 8. The subsequent reaction sequence followed earlier work in which a truncated fragment had been employed for the synthesis of the C11-C23 segment.[11c] Diene formation was achieved by a vinylogous Horner-Wadsworth-Emmons

reaction[20] and aldehyde 9 was linked to the chiral 5-sulfonyl tetrazole 10[11c] in an (E)-selective Julia-Kocieński olefination.[21] The pivaloyl (Piv) protecting group was released by reduction with Dibal-H and aldehyde 11 was obtained by oxidation of the resulting alcohol. The ensuing aldol reaction had been optimized in earlier work, in which a synthetic route to ketone 12 had also been developed.[11c] After enolization to the O-(E)-enolate a transmetalation to a chiral boron residue guarantees control of the facial and simple diastereoselectivity.[11,13] Bond formation at positions C23 and C24 generates both stereogenic centers with the required relative configuration. The primary product of the aldol reaction was treated with 8-hydroxyquinoline in dichloromethane/methanol[22] to hydrolyze the boron fragment and the temporary protecting group at 21 was released with HF·py at low temperature.[23] The desired product 13 was obtained in 26% yield over three steps and 29% of ketone 12 were recovered. Aldehyde 11, which was used in excess, was partially reduced by the Ipc₂B reagent[24] and the respective alcohol was isolated (63% yield). Since the configuration at C22 was not compromised, the alcohol could be taken directly into the oxidation step to deliver aldehyde 11. From previous work, it was known that the hydroxy group at C21 is significantly more reactive than the C23 hydroxy group. The installation of the C1-C7 fragment by esterification was hence expected to occur with high selectivity. The stereoselective synthesis of the required acid commenced by acylation of an alkenyl lithium reagent generated from known TES-protected (E)-4-iodopent-3-enol (see above)[18] (14) with Weinreb amide 15 (Scheme 3).[25]

Reduction of alkynyl ketone 16 with chiral oxazaborolidine 17 in a Corey-Bakshi-Shibata (CBS) reaction[27] delivered the respective alcohol with high enantioselectivity (96% ee). The absolute configuration at the stereogenic center C5 was proven by comparison with known material (see the Supporting
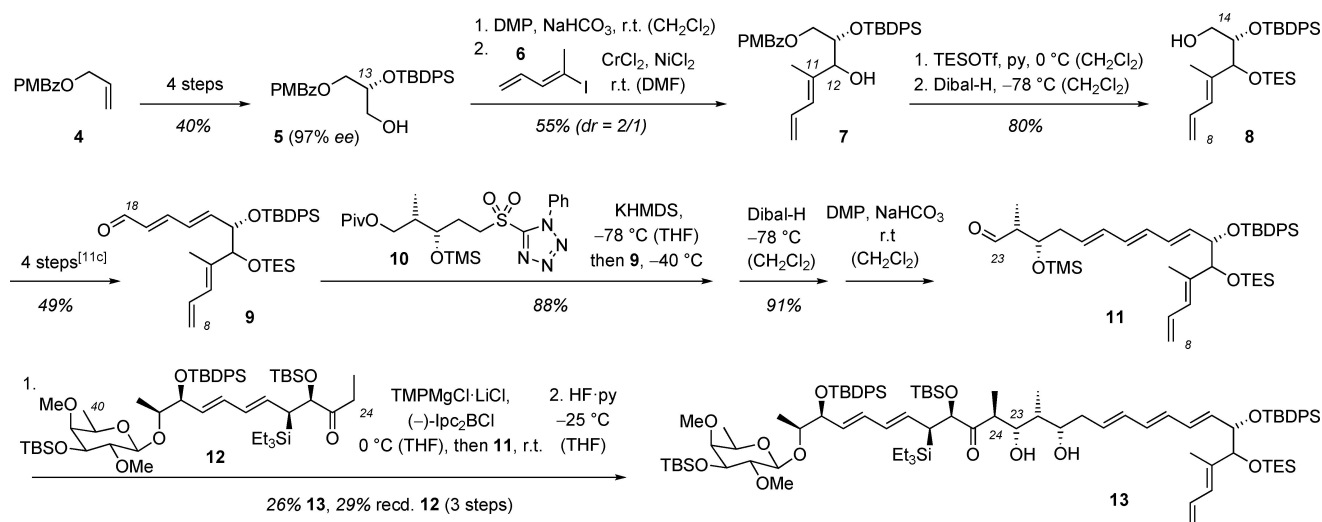
Scheme 2. Synthesis of the C8-C23 aldehyde 11 from product 5 of a Sharpless dihydroxylation employing a Nozaki-Hiyama coupling and a Julia-Kocieński olefination as key steps. The C8-C40 fragment 13 of pulvomycin D was assembled by an aldol reaction of ketone 12[11a] and aldehyde 11 (abbreviations: Dibal-H = diisobutylaluminium hydride, DMP = Dess-Martin periodinane, Ipc = isopinocampheyl, KHMDS = potassium hexamethyldisilazide, Piv = pivaloyl, PMBz = 4-methoxybenzoyl, py = pyridine, recd. = recovered, Tf = trifluoromethanesulfonyl, TMP = tetramethylpiperidinyl, TMS = trimethylsilyl).

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Scheme 3. Synthesis of the C1–C7 fragment **20** of pulvomycin D from iodide **14** and Weinreb amide **15**. Conditions for the Pinnick-Lindgren oxidation:[26] NaOCl, NaH$_2$PO$_4$, 2-methyl-2-butene, r.t. (*tert*-butanol/H$_2$O = 1/1).

Information for details). Conversion of the secondary alcohol to silyl ether **18** set the stage for a *syn*-specific, regioselective hydrometalation which was favorably performed with the Schwartz reagent[28] at ambient temperature. Subsequent iodo-de-zirconation[29] at −78 °C delivered the desired (*E*)-iodide **19** which required only an adjustment of its oxidation state at C1. Selective removal of the TES protecting group gave a primary alcohol which was stepwise oxidized to the carboxylic acid **20** thus completing the preparation of the C1–C7 fragment.

Gratifyingly, the regioselectivity of the esterification between acid **20** and 1,3-diol **13** met our expectations and proceeded with high site selectivity (Scheme 4). Under Yamaguchi conditions,[10,30] the acyl group was exclusively attached to the hydroxy group at C21. Ester **21** was isolated in 62% yield and 16% of the valuable alcohol **13** could be recovered. Performing the reaction at −30 °C proved to be crucial to avoid elimination of the sensitive alcohol. Being aware of the sterically

encumbered situation at C23 we chose to protect the secondary alcohol with the comparably small TES group. The silyl ether at this position was sufficiently stable to resist the conditions chosen for removal of the TES group at the allylic alcohol site C12.[31] The purity of this alcohol played a crucial role in the subsequent reactions and clean material was generated by adding the silyl ether to the HF·py mixture pre-cooled to −20 °C. Under these conditions, the deprotection was reproducible on a scale of 250 mg and delivered the product as a colorless foam. Oxidation of this alcohol delivered ketone **22** which had in preliminary experiments turned out to be the best substrate for an intramolecular Heck reaction.[32,33] Without going into further details regarding the optimization of the reaction conditions, the best yields were obtained in the absence of phosphane ligands (Jeffery conditions) and with a combination of potassium phosphate and triethylamine as base.[34] Given the low molar quantities of precursor **22**, the palladium source was used in stoichiometric amounts (1.3 equiv.). For the isolation, it was found beneficial to remove the metal by an appropriate scavenger (e.g. QuadraPure™ TU)[35] and to filter the reaction solution through Celite™ before solvent removal and purification by column chromatography. DMF was removed at room temperature under high vacuum, to reduce thermal stress on the heat-sensitive compound. Product **3** was reasonably stable and could be fully characterized. Although we had probed the protecting group removal and the Peterson elimination[36] on several intermediates en route to compound **3**, it turned out that the simultaneous release of six silyl protecting groups and the concomitant Peterson elimination could not be pursued in a single reaction step. The situation was particularly delicate because the high lability of the final product excluded typical basic or acidic silyl deprotection conditions (e.g. TBAF in THF, BF$_3$ in CH$_2$Cl$_2$, or HF in MeCN).[37] We had recognized in fragment deprotection reactions that a TBDPS group at the C37 alcohol[11] was extremely robust and it was already decided at the design stage to change it to a TBS group (Scheme 1). The search for optimal deprotection conditions was greatly facilitated by ESI-MS analysis with which the successive removal of the protective
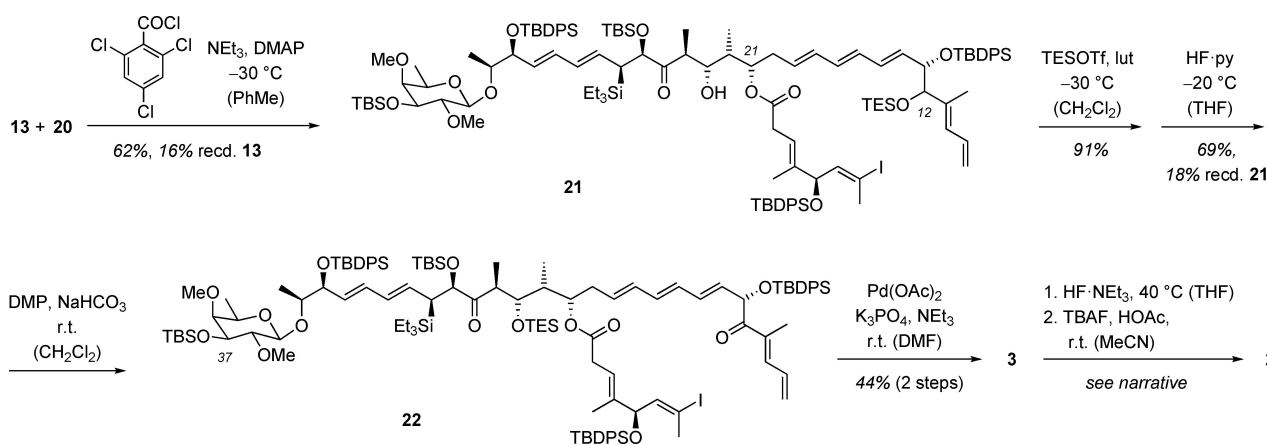
Scheme 4. Completion of the synthesis of pulvomycin D (**2**) by esterification of carboxylic acid **20** and by an intramolecular Heck reaction (**22**→**3**) as the key step (abbreviations: Ac = acetyl, DMAP = 4-(dimethylamino)pyridine, lut = 2,6-lutidine, TBAF = tetrabutylammonium fluoride).

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groups could be nicely followed. The use of TBAF in acetonitrile, buffered with an equimolar amount of acetic acid, turned out to be the reagent of choice for most silyl cleavage reactions.[38] Protective group removal under these conditions was found to occur in the order C13, C32 > C26-C27 (Peterson elimination) > C23 > C5. Unfortunately, the reaction progress was accompanied by increasing decomposition. Furthermore, no deprotection of the TBS group at the C37 alcohol was observed under the buffered TBAF conditions.

A literature report from Paterson and co-workers suggested the use of a large excess of HF·py in THF to remove the TBS group at the C37 hydroxy group.[39] Indeed, treatment of ketone fragment **12** with a 250-fold excess of HF·py looked promising. However, when applied to the macrocyclic product **3**, the conditions proved to be unsuitable to allow for a rapid deprotection of the remaining silyl groups and – even more severely – significant decomposition set in with prolonged reaction times. Switching from HF·py to the less common HF·NEt$_3$ reagent[40] significantly decreased the amount of decomposition.

Stirring the reaction mixture for five days at 40 °C with an excess of HF·NEt$_3$ led to removal of the silyl protecting groups at positions C13, C23, C32, and C37. Only the masked olefin at C26-C27 and the silyl ether at C5 remained intact. Subsequent treatment of the intermediate with buffered TBAF at ambient temperature induced the final deprotection steps within 18 h. Due to its high polarity, the isolation of the final product was performed by reversed-phase HPLC. Surprisingly, its retention time did not match an authentic sample of pulvomycin A. High resolution MS (HRMS) analysis revealed an exact mass of $m/z = 859.4241$ [M + Na$^+$] for the final product, which suggested the formation of pulvomycin D ($m/z = 859.4245$ for [M + Na$^+$]). Oxidation reactions have been observed to occur in the presence of TBAF[41] and we could verify the identity of the final product by comparison of its ^{1}H NMR data with the spectrum of pulvomycin D. Additional analytical data were also in agreement with this assignment (see the Supporting Information for more details). Regrettably, the lability of the compound precluded recording a ^{13}C NMR spectrum. Typically, ca. 0.5 mg material were obtained from deprotecting 10 mg of compound **3** (12% yield) which was not sufficient to record ^{13}C NMR spectra with short acquisition times (≤ 1 h). After longer times the material deteriorated and attempts to immediately store the small quantities at low temperature and combine samples remained futile.

In summary, we have synthesized for the first time a representative of the pulvomycin class of natural products. The longest linear sequence starting from protected allylic alcohol **4** comprised 22 steps to reach Heck coupling product **3** in a total yield of 0.23% (average of 76% per step). The synthetic strategy is applicable also to the preparation of fragments or analogues of the natural product which will hopefully display an improved stability but retain the interesting biological properties of the pulvomycins.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: aldol reactions · Heck reactions · protecting groups · polyketides · total synthesis

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