

An enantioselective synthesis of the C₂₄–C₄₀ fragment of (–)-pulvomycin†

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The C₂₄–C₄₀ fragment of (–)-pulvomycin was prepared in enantiomerically pure form using a concise synthesis method (15 linear steps from D-fucose, 6.8% overall yield) featuring a diastereoselective addition to an aldehyde, a β -selective glycosylation and a Stille cross-coupling as the key steps.

The antibiotic pulvomycin was first isolated in 1957 from a *Streptomyces* species but due to the limited analytical data no structure was assigned to the compound.¹ In 1963, Akita *et al.* isolated a natural product from *Streptomyces albosporus* var. *labilomyceticus*,² which they called labilomycin and which was later shown to be identical to pulvomycin.³ Extensive analytical work by Smith *et al.* revealed the constitution of the natural product (Fig. 1) as well as the absolute and relative configuration at most stereogenic centers except for C₃₂ and C₃₃.⁴ The assignment was confirmed and the complete configuration was eventually proven by a crystal structure (1.4 Å resolution) of pulvomycin with the bacterial elongation factor Tu (EF-Tu).⁵ It is well established that pulvomycin is a potent inhibitor of EF-Tu and it therefore represents a promising lead compound for the development of new antibiotics.⁶

While synthetic reports on pulvomycin are scarce, the biosynthesis of the pulvomycin aglycone has been elucidated by labeling experiments.⁷ Our own interest in pulvomycin was triggered by our previous studies on the synthesis⁸ and antibiotic activity⁹ of thiazole peptides, such as the GE factors and the amythiamicins. It has been shown that the EF-Tu binding site of pulvomycin is in close proximity to the binding site of thiazole peptides.¹⁰ The synthesis of pulvomycin and pulvomycin analogues might consequently help to further investigate the many facets of EF-Tu activity.¹¹ Apart from its biological activity, pulvomycin presents itself as a formidable synthetic challenge due to its complex and labile structure. In this communication

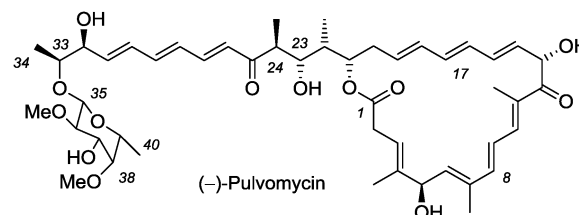
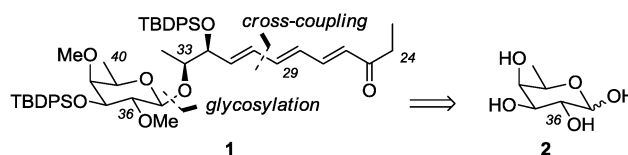


Fig. 1 Structure and compound numbering of (–)-pulvomycin.

Scheme 1 Retrosynthetic disconnection of the title compound **1** leading to D-fucose (**2**) as an appropriate carbohydrate substrate.

we disclose the enantioselective synthesis of a suitably protected C₂₄–C₄₀ fragment **1** (Scheme 1) of pulvomycin.

Retrosynthetically, it was envisioned that ketone **1** (TBDPS = *tert*-butyldiphenylsilyl) could be derived from commercially available D-fucose (**2**), which shows the correct configuration at the stereogenic centers (C₃₆–C₃₉) of the pyranose ring. In order to establish the desired β -configuration at the glycosidic center an appropriate neighbouring group, *e.g.* an acetate, was required (at carbon atom C₃₆)¹² and the methyl ether linkage was to be introduced after glycosylation. There was precedence for the differentiation of the two equatorial hydroxy groups at C₃₆ and C₃₇ of D-fucose.¹³

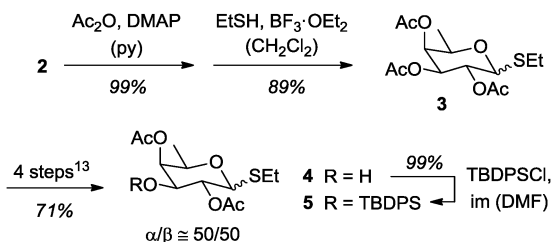
Regarding the C₂₄–C₃₄ fragment, it seemed best to assemble the triene¹⁴ after the glycosylation step by an appropriate cross-coupling reaction, *e.g.* between C₂₉ and C₃₀. The stereogenic center at C₃₃ appeared to be accessible from the chiral pool, *e.g.* from lactic acid, while the adjacent stereogenic center was to be introduced by a diastereoselective reaction.

The acetylation of D-fucose (**2**) (Scheme 2) proceeded quantitatively delivering the tetraacetate as an α/β -mixture (α/β = 95/5)

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Scheme 2 Synthesis of the protected glycosyl donor **5** from D-fucose (**2**). DMAP = 4-(*N,N*-dimethylamino)pyridine, py = pyridine, im = imidazole.

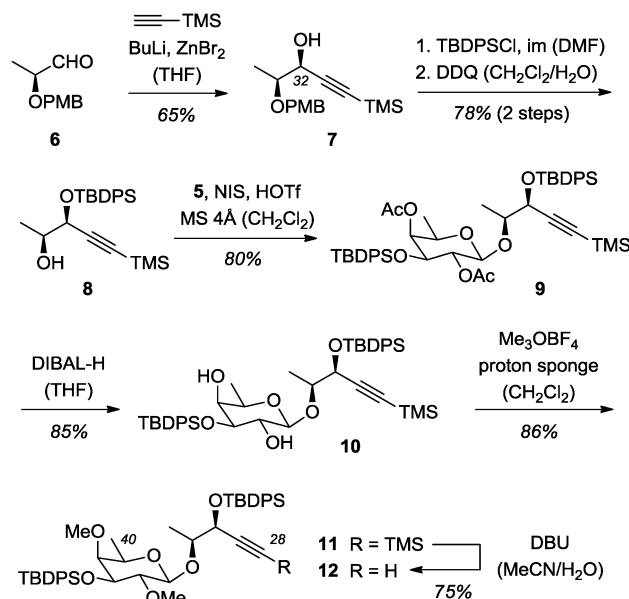
of anomers.¹³ Conversion to the required thioacetal **3** proceeded best in our hands with ethanethiol and BF₃·OEt₂ in CH₂Cl₂,¹⁵ which delivered depending on the reaction conditions and on the reaction scale variable amounts of separable α/β-isomers (see the ESI† for further details).

Since the relative configuration at the anomeric center was irrelevant for the desired glycosylation reaction, the α/β-mixture of **3** was taken into the four-step procedure previously described for the selective preparation of alcohol β-**4**¹³ and it furnished the desired product **4** as an α/β-mixture (α/β ≈ 50/50) in a total yield of 60% over six steps from D-fucose (**2**). Conversion of the equatorial alcohol **4** to silyl ether **5** required elevated temperature (60 °C) and a prolonged reaction time (3 d).

As mentioned above, it was planned to introduce the stereogenic center at C₃₂ by a diastereoselective reaction induced by the adjacent stereogenic center at the carbon atom C₃₃. Surprisingly, the reduction of a (*S*)-lactate-derived, *para*-methoxybenzyl (PMB) protected alkynyl ketone¹⁶ produced the desired alcohol **7** either in low yields or with insufficient diastereoselectivity (see the ESI† for further details). As an alternative approach, (*S*)-lactate-derived aldehyde **6**¹⁷ was alkynylated with TMS-acetylene under chelation control¹⁸ yielding alcohol **7** and its epimer *epi*-**7** in 81% yield and in a diastereomeric ratio (d.r.) of 87/13 (Scheme 3). The diastereomerically pure product **7** was isolated in 65% yield.

Protection of the secondary alcohol proceeded smoothly at ambient temperature and the PMB group was cleaved oxidatively with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)¹⁹ to deliver alcohol **8**. The enantiomeric excess (ee) of alcohol **8** was established by chiral HPLC analysis and comparison with a racemic sample (see the ESI† for further details). Gratifyingly, the glycosylation reaction, when performed with *N*-iodosuccinimide (NIS) and trifluoromethanesulfonic acid (HOTf) as activating agents,²⁰ delivered a single diastereomerically pure product **9**, which was shown to have the desired β-configuration.²¹ Reductive removal of the acetyl groups with diisobutylaluminum hydride (DIBAL-H)²² produced 1,3-diol **10**, which was converted into the respective dimethylether **11** upon treatment with an excess (10 equiv.) of Meerwein salt and proton sponge [1,8-bis(dimethylamino)-naphthalene].²³ Less electrophilic methylating reagents (MeOTf, MeI) in combination with appropriate bases failed to react or led to substrate decomposition. Selective desilylation of the alkyne was achieved with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).²⁴

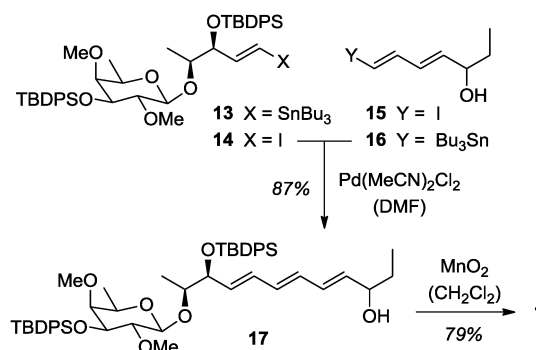
With alkyne **12** in hand, various approaches to potential cross-coupling substrates were pursued. It was found that the



Scheme 3 Assembly of the C₂₈-C₄₀ fragment via glycosylation of enantiomerically pure (≥98% ee) alcohol **8** with glycosyl donor **5**.

Pd-catalyzed hydrostannylation with Bu₃SnH²⁵ can be successfully performed with alkyne **12** delivering stannane **13** in 44% yield (Scheme 4). Iodide **14** was obtained from stannane **13** upon treatment with iodine in dichloromethane (85% yield).²⁶ The alkyne hept-3-en-1-yne-5-ol²⁷ seemed to be the most suitable precursor for iodide **15** and stannane **16**. The compound was available from bis-1,4-(trimethylsilyl)buta-1,3-diyne in four steps and an overall yield of 53% (see the ESI† for further details). Stannylation of hept-3-en-1-yne-5-ol with Bu₃SnH was readily achieved employing the Cu-based protocol of Betzer *et al.*²⁸ to deliver stannane **16** in 79% yield. As for **14**, iodide **15** was generated by iodo-de-stannylation employing iodine in dichloromethane (79% yield).

While attempted Stille cross-coupling reactions²⁹ of stannane **13** and iodide **15** failed, the desired C-C bond formation proceeded smoothly, when performed with the carbohydrate building block as the electrophile. Iodide **14** and stannane **16** underwent a clean cross-coupling employing Pd(MeCN)₂Cl₂



Scheme 4 Stille cross-coupling of building blocks **13** and **15** as key step for the assembly of the title compound.



(10 mol%) as the catalyst.³⁰ Alcohol **17** was obtained in 87% yield and was immediately further oxidized to the desired ketone by treatment with an excess (30 equiv.) of MnO₂. Despite a pronounced long wavelength absorption ($\lambda_{\text{max}} = 308 \text{ nm}$, $\epsilon = 28\,035 \text{ M}^{-1} \text{ cm}^{-1}$ in MeCN), trienone **1** appears to be more stable than alcohol **17** ($\lambda_{\text{max}} = 271 \text{ nm}$, $\epsilon = 39\,350 \text{ M}^{-1} \text{ cm}^{-1}$ in MeCN; shoulder at $\lambda_{\text{max}} = 282 \text{ nm}$, $\epsilon = 31\,180 \text{ M}^{-1} \text{ cm}^{-1}$) and could be stored for one week at -25°C in the dark.

In summary, the enantiomerically pure western fragment **1** of (–)-pulsomycin was synthesized in 15 linear steps. The fragment comprises the carbohydrate part (labilose, C₃₅–C₄₀) of the natural product and one of its three triene components (C₂₄–C₃₄). Should an aldol-type reaction of fragment **1** with a suitable Eastern fragment not be successful, stannane **13** and iodide **14** offer suitable options to connect the protected glycoside fragment to the rest of the molecule.

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