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ARTICLE TYPE

Enantioselective synthesis of the C_{24}-C_{40} fragment of (–)-pulvomycin

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The C_{24}-C_{40} fragment of (–)-pulvomycin was prepared in enantiomerically pure form by a concise synthesis (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 key steps.

The antibiotic pulvomycin was first isolated in 1957 from *Streptomyces* species but due to the limited analytical data no structure was assigned to the compound.[1] In 1963, Umezawa et al. isolated a natural product from *Streptomyces albosporeus* var. *labilomyceticus*,[2] which they called labilomycin and which was later shown to be identical to pulvomycin.[3] Extensive analytical work by Williams et al. revealed the constitution of the natural product (figure 1) as well as the absolute and relative configuration at most stereogenic centers except for C_{32} and C_{33}.[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]

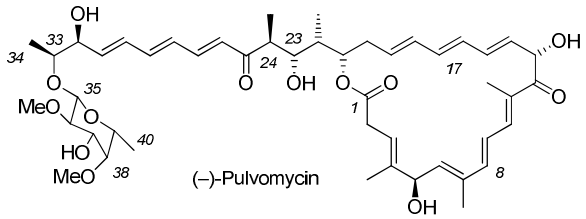
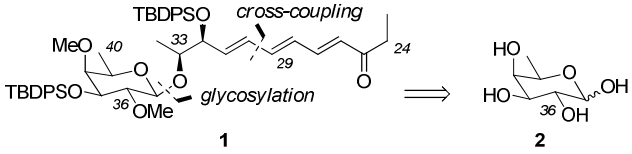


Figure 1 Structure and compound numbering of (–)-pulvomycin

While synthetic reports on pulvomycin are scarce, the biosynthesis of the pulvomycin aglycon has been elucidated by labeling experiments.[7] Our own interest in pulvomycin was triggered by our previous studies on the synthesis[8] and antibiotic acitivity[9] 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 we disclose the enantioselective synthesis of a suitably protected C_{24}-C_{40} fragment **1** (scheme 1) of pulvomycin.

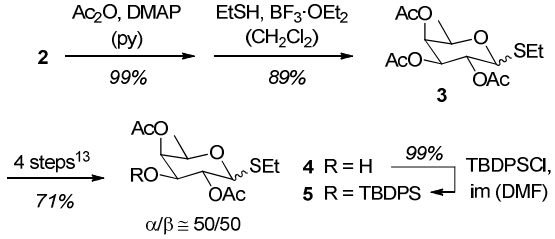
Retrosynthetically, it was envisioned that ketone **1** (TBDPS = *tert*-butyldiphenylsilyl) could be derived from commercially available D-fucose (**2**), which shows the correct configuration at the stereogenic centers (C_{36}-C_{39}) of the pyranose ring. In order to establish the desired β-configuration at the glycosidic center an appropriate neighbouring group, e.g. an acetate, was required (at carbon atom C_{36})[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 C_{36} and C_{37} of D-fucose.[13]



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

Regarding the C_{24}-C_{34} fragment, it seemed best to assemble the triene[14] after the glycosylation step by an appropriate cross-coupling reaction, e.g. between C_{29} and C_{30}. The stereogenic center at C_{33} 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.

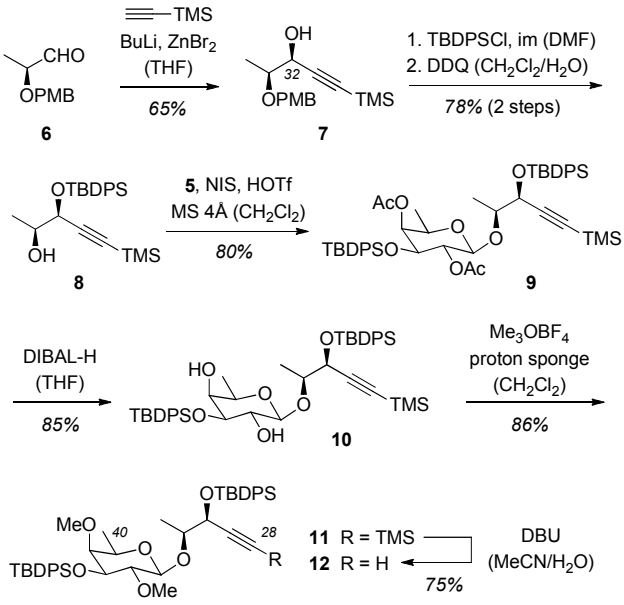
The acetylation of D-fucose (**2**) (scheme 2) proceeded quantitatively delivering the tetraacetate as an α/β-mixture (α/β = 95/5) of anomers.[13] Conversion to the required thioacetal **3** proceeded in our hands best with ethanethiol and $BF_3 \cdot OEt_2$ in CH_2Cl_2,[15] which delivered depending on the reaction conditions and on the reaction scale variable amounts of separable α/β-isomers (see the ESI for further details).



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

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).

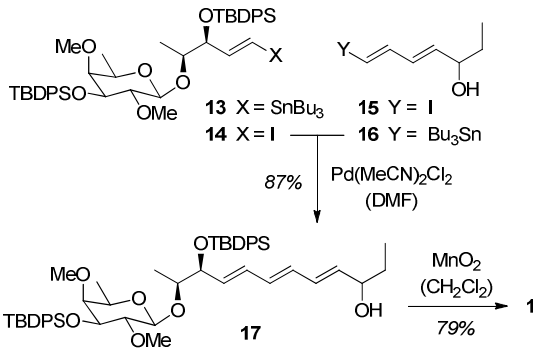
As mentioned above, it was planned to introduce the stereogenic center at C_{32} by a diastereoselective reaction induced by the adjacent stereogenic center at carbon atom C_{33}. Surprisingly, the reduction of a (*S*)-lactate-derived, *para*-methoxybenzyl(PMB) protected alkynyl ketone[16] produced the 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 control[18] yielding alcohol **7** and its epimer *epi*-**7** in 81% yield and in a diastereomeric ratio (d.r.) of 87/13 (scheme 3). Diastereomerically pure product **7** was isolated in 65% yield.



Scheme 3 Assembly of the C_{28}-C_{40} fragment via glycosylation of enantiomerially pure (≥98% *ee*) alcohol **8** with glycosyl donor **5**

Protection of the secondary alcohol proceeded smoothly at ambient temperature and the PMB group was cleaved oxidatively with 2,3-dicloro-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 diisobutylaluminium 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 Pd-catalyzed hydrostannylation with Bu_3SnH[25] can be performed with alkyne **12** delivering stannane **13** in 44% yield. Iodide **14** was obtained from stannane **13** upon treatment with iodine in dichloromethane (85% yield).[26] The alkyne hept-3-en-1-yne-5-ol[27] seemed to be the most suitable precursor for iodide **15** and stannane **16**. The compound was available from bis-1,4-(trimethysilyl)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 Bu_3SnH 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).



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

While attempted Stille cross-coupling reactions[29] of stannane **13** and iodide **15** failed, the desired C-C bond formation proceeded smoothly, if performed with the carbohydrate building block as electrophile. Iodide **14** and stannane **16** underwent a clean cross-coupling employing $Pd(MeCN)_2Cl_2$ (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 MnO_2. Despite a pronounced long wavelength absorption (λ_{max} = 308 nm, ε = 28035 M^{-1} cm^{-1} in MeCN), trienone **1** appears to be more stable than alcohol **17** (λ_{max} = 271 nm, ε = 39350 M^{-1} cm^{-1} in MeCN; shoulder at λ_{max} = 282 nm, ε = 31180 M^{-1} cm^{-1}) and could be stored for one week at −25 °C in the dark.

In summary, the enantiomerically pure Western fragment **1** of (−)-pulvomycin was synthesized in 15 linear steps. The fragment comprises the carbohydrate part (labilose, C_{35}-C_{40}) of the natural product and one of its three triene components (C_{24}-C_{34}). 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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