An enantioselective synthesis of the C\textsubscript{24}–C\textsubscript{40} fragment of (-)-pulvomycin†

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The C\textsubscript{24}–C\textsubscript{40} fragment of (-)-pulvomycin was prepared in enantio-merically 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. In 1963, Akita et al. isolated a natural product from Streptomyces alboasporeus var. labilomyceticus, which they called labilomycin and which was later shown to be identical to pulvomycin. 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 C\textsubscript{32} and C\textsubscript{33}. 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).

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.

While synthetic reports on pulvomycin are scarce, the biosynthesis of the pulvomycin aglycone has been elucidated by labeling experiments. Our own interest in pulvomycin was triggered by our previous studies on the synthesis and antibi-otic activity 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. The synthesis of pulvomycin and pulvomycin analogues might consequently help to further investigate the many facets of EF-Tu activity. 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\textsubscript{24}–C\textsubscript{40} fragment 1 (Scheme 1) of pulvomycin.

Retrosynthetically, it was envisioned that ketone 1 (TBDPS = tert-butyldiphenylsilyle) could be derived from commercially available D-fucose (2), which shows the correct configuration at the stereogenic centers (C\textsubscript{30}–C\textsubscript{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\textsubscript{36}) 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\textsubscript{36} and C\textsubscript{37} of D-fucose.13

Regarding the C\textsubscript{24}–C\textsubscript{34} fragment, it seemed best to assemble the triene after the glycosylation step by an appropriate cross-coupling reaction, e.g. between C\textsubscript{29} and C\textsubscript{30}. The stereogenic center at C\textsubscript{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. Conversion to the required thioacetal 3 proceeded best in our hands with ethanethiol and BF$_3$-OEt$_2$ in CH$_2$Cl$_2$, which delivered depending on the reaction conditions and on the reaction scale variable amounts of separable $\alpha$/-$\beta$-isomers (see the ESI† for further details).

Since the relative configuration at the anomic center was irrelevant for the desired glycosylation reaction, the $\alpha$/-$\beta$-mixture of 3 was taken into the four-step procedure previously described for the selective preparation of alcohol $\beta$-$4^13$ and it furnished the desired product 4 as an $\alpha$/-$\beta$-mixture ($\alpha$/-$\beta$ = 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 C3$_a$ by a diastereoselective reaction induced by the adjacent stereogenic center at the carbon atom C$_\text{glycosyl}$. Surprisingly, the reduction of a (S)-lactate-derived, para-methoxybenzyl (PMB) protected alkyne 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 alkylated with TMS-acetylene under chelation control$^{18}$ yielding alcohol 7 and its epimer $\text{epi}$-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$^\ominus$-iodosuccinimide (NIS)$^{20}$ 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$_3$SnH$^{25}$ 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-ol was converted into the respective silyl ether 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-ol was converted into the respective silyl ether 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-ol was converted into the respective silyl ether 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-ol was converted into the respective silyl ether 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-ol was converted into the respective silyl ether 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-ol was converted into the respective silyl ether 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-ol was converted into the respective silyl ether 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-ol was converted into the respective silyl ether 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-ol was converted into the respective silyl ether 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-ol was converted into the respective silyl ether 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-ol was converted into the respective silyl ether 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-ol was converted into the respective silyl ether 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-ol was converted into the respective silyl ether 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-ol was converted into the respective silyl ether 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-ol was converted into the respective silyl ether 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-ol was converted into the respective silyl ether 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-ol was converted into the respective silyl ether 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-ol was converted into the respective silyl ether 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-ol was converted into the respective silyl ether 44% yield (Scheme 4). Iodide 14 was obtained from stannane 13 upon treatment with iodine in dichloromethane (85% yield).$^{26}$
(10 mol%) as the catalyst. 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 (λmax = 308 nm, ε = 28 035 M⁻¹ cm⁻¹ in MeCN), trienone 1 appears to be more stable than alcohol 17 (λmax = 271 nm, ε = 39 350 M⁻¹ cm⁻¹ in MeCN; shoulder at λmax = 282 nm, ε = 31 180 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, 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.

This project was supported by the Deutsche Forschungsgemeinschaft (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Deutsche Forschungsgemeinschaft (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemischen Industrie (Ba 1372-18/1), by the Fonds der Chemische