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An 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 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 albosporeus* 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 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]

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 synthesis[8] and antibiotic activity[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.

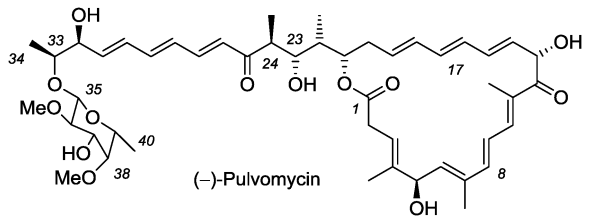
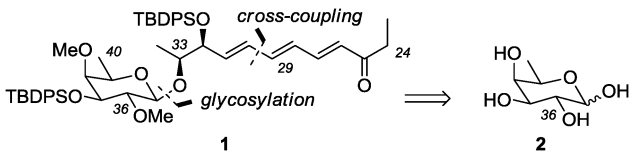


Fig. 1 Structure and compound numbering of (–)-pulvomycin.



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

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]

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)

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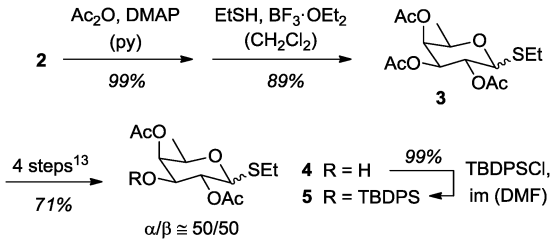


Scheme 2 Synthesis of the protected glycosyl donor **5** from D-fucose (**2**). DMAP = 4-(*N*,*N*-dimethylamino)pyridine, py = pyridine, im = imidazole.

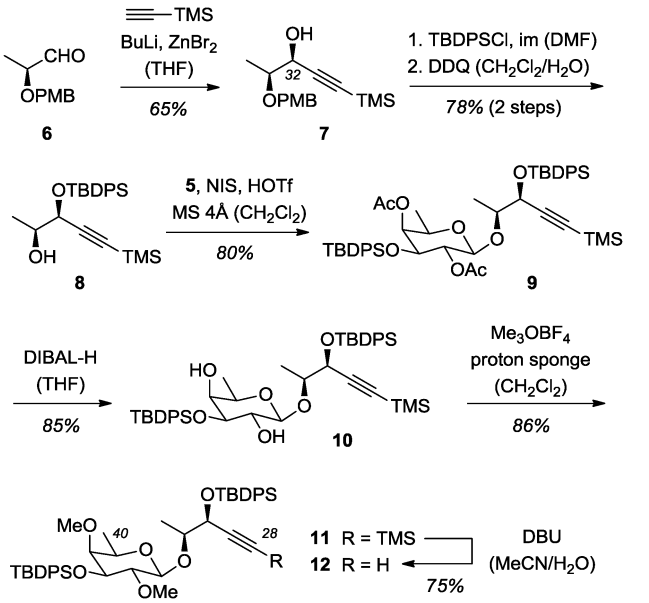
of anomers.[13] Conversion to the required thioacetal **3** proceeded best in our hands with ethanethiol and $BF_3{\cdot}OEt_2$ in CH_2Cl_2,[15] which delivered depending on the reaction conditions and on the reaction scale variable amounts of separable α/β-isomers (see the ESI† for further details).

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 ($\alpha/\beta \cong 50/50$) 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 the 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). 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-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]

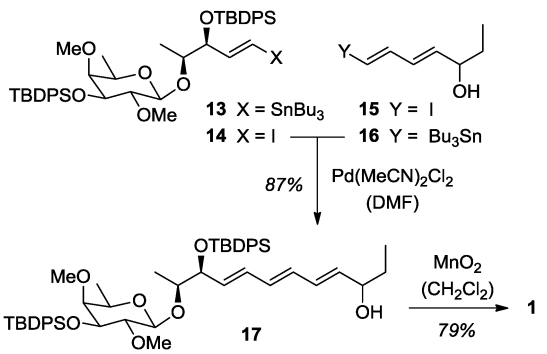
With alkyne **12** in hand, various approaches to potential cross-coupling substrates were pursued. It was found that the



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

Pd-catalyzed hydrostannylation with Bu_3SnH[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[27] 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 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).

While attempted Stille cross-coupling reactions[29] 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 $Pd(MeCN)_2Cl_2$



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 MnO_2. Despite a pronounced long wavelength absorption (λ_{max} = 308 nm, ε = 28 035 M^{-1} cm^{-1} in MeCN), trienone **1** appears to be more stable than alcohol **17** (λ_{max} = 271 nm, ε = 39 350 M^{-1} cm^{-1} in MeCN; shoulder at λ_{max} = 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, 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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Notes and references

1 M. Zief, R. Woodside and H. Schmitz, *Antibiot. Chemother.*, 1957, **7**, 384–386.
2 (*a*) E. Akita, K. Maeda and H. Umezawa, *J. Antibiot., Ser. A*, 1963, **16**, 147–151; (*b*) E. Akita, K. Maeda and H. Umezawa, *J. Antibiot., Ser. A*, 1964, **17**, 200–217.
3 J. L. Schwartz, M. Tishler, B. H. Arison, H. M. Shafer and S. Omura, *J. Antibiot.*, 1976, **29**, 236–241.
4 R. J. Smith, D. H. Williams, J. C. J. Barna, I. R. McDermott, K. Haegele, F. Piriou, J. Wagner and W. Higgins, *J. Am. Chem. Soc.*, 1985, **107**, 2849–2857.
5 A. Parmeggiani, I. M. Krab, S. Okamura, R. C. Nielsen, J. Nyborg and P. Nissen, *Biochemistry*, 2006, **45**, 6846–6857.
6 For a recent review, see: K. M. G. O'Connell, J. T. Hodgkinson, H. F. Sore, M. Welch, G. P. C. Salmond and D. R. Spring, *Angew. Chem., Int. Ed.*, 2013, **52**, 10706–10733.
7 N. D. Priestley and S. Gröger, *J. Org. Chem.*, 1995, **60**, 4951–4953.
8 (*a*) O. Delgado, H. M. Müller and T. Bach, *Chem. – Eur. J.*, 2008, **14**, 2322–2339; (*b*) C. Ammer and T. Bach, *Chem. – Eur. J.*, 2010, **16**, 14083–14093.
9 S. Gross, F. Nguyen, M. Bierschenk, D. Sohmen, T. Menzel, I. Antes, D. N. Wilson and T. Bach, *ChemMedChem*, 2013, **8**, 1954–1962.
10 A. Parmeggiani, I. M. Krab, S. Okamura, R. C. Nielsen, J. Nyborg and P. Nissen, *Biochemistry*, 2006, **45**, 6846–6857.
11 Reviews: (*a*) R. Berisio, A. Ruggiero and L. Vitagliano, *Isr. J. Chem.*, 2010, **50**, 71–79; (*b*) A. Parmeggiani and P. Nissen, *FEBS Lett.*, 2006, **580**, 4576–4581.
12 (*a*) R. U. Lemieux and J.-I. Hayami, *Can. J. Chem.*, 1965, **43**, 2162–2173; (*b*) G.-J. Boons, *Contemp. Org. Synth.*, 1996, **3**, 173–200; (*c*) T. K. Lindhorst, *Essentials of Carbohydrate Chemistry and Biochemistry*, Wiley-VCH, Weinheim, 3rd edn, 2007, pp. 157–208.
13 D. Comegna, E. Bedini and M. Parrilli, *Tetrahedron*, 2008, **64**, 3381–3391.
14 For selected recent total syntheses of naturally occurring conjugated (*E*,*E*,*E*)-trienes, see: (*a*) D. J. Del Valle and M. J. Krische, *J. Am. Chem. Soc.*, 2013, **135**, 10986–10989; (*b*) C. Jahns, T. Hoffmann, S. Müller, K. Gerth, P. Washausen, G. Höfle, H. Reichenbach, M. Kalesse and R. Müller, *Angew. Chem., Int. Ed.*, 2012, **51**, 5239–5243; (*c*) M. Yoshino, K. Eto, K. Takahashi, J. Ishihara and S. Hatakeyama, *Org. Biomol. Chem.*, 2012, **10**, 8164–8174; (*d*) P. G. E. Craven and R. J. K. Taylor, *Tetrahedron Lett.*, 2012, **53**, 5422–5425; (*e*) H. J. Jessen, A. Schumacher, F. Schmid, A. Pfaltz and K. Gademann, *Org. Lett.*, 2011, **13**, 4368–4370; (*f*) D. Amans, V. Bellosta and J. Cossy, *Chem. – Eur. J.*, 2009, **15**, 3457–3473; (*g*) M. T. Crimmins, H. S. Christie, A. Long and K. Chaudhary, *Org. Lett.*, 2009, **11**, 831–834; (*h*) I. S. Mitchell, G. Pattenden and J. Stonehouse, *Org. Biomol. Chem.*, 2005, **3**, 4412–4431.
15 P. Sjölin, S. K. George, K.-E. Bergquist, S. Roy, A. Svensson and J. Kihlberg, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1731–1742.
16 The ketone was prepared from literature known Weinreb amide (V. Convertino, P. Manini, W. B. Schweizer and F. Diederich, *Org. Biomol. Chem.*, 2006, **4**, 1206–1208) by substitution with the respective magnesium acetylide (see the ESI† for further details).
17 W. Yu, Y. Zhang and Z. Jin, *Org. Lett.*, 2001, **3**, 1447–1450.
18 K. T. Mead, *Tetrahedron Lett.*, 1987, **28**, 1019–1022.
19 Y. Oikawa, T. Yoshioka and O. Yonemitsu, *Tetrahedron Lett.*, 1982, **23**, 885–888.
20 (*a*) G. H. Veeneman, S. H. van Leeuwen and J. H. van Boom, *Tetrahedron Lett.*, 1990, **31**, 1331–1334; (*b*) P. Konradsson, U. E. Udodong and B. Fraser-Reid, *Tetrahedron Lett.*, 1990, **31**, 4313–4316.
21 ^{1}H-NMR data of glycoside **9** (500 MHz, $CDCl_3$): δ (ppm) = 0.09 [s, 9H; $Si(CH_3)_3$], 0.97 [s, 9H; $C(CH_3)_3$], 0.96–0.99 (m, 3H; H_3-40), 1.05 [s, 9H; $C(CH_3)_3$], 1.30 (d, ^3J = 6.3 Hz, 3H; H_3-34), 1.46 (s, 3H; $C(O)CH_3$-36), 2.12 [s, 3H; $C(O)CH_3$-38], 3.05 (q, ^3J = 6.4 Hz, 1H; H-39), 3.41 (qd, ^3J = 6.3, 3.9 Hz, 1 H; H-33), 3.44 (d, ^3J = 8.1 Hz, 1 H; H^{β}-35), 3.60 (dd, ^3J = 9.8, 3.3 Hz, 1H; H-37), 4.19 (d, ^3J = 3.9 Hz, 1H; H-32), 4.79 (d, ^3J = 3.3 Hz, 1H; H-38), 5.06 (dd, ^3J = 9.8, 8.1 Hz, 1H; H-36), 7.23–7.27 (m, 4H; H_{arom}), 7.30–7.48 (m, 10H; H_{arom}), 7.55–7.58 (m, 2H; H_{arom}), 7.60–7.65 (m, 4H; H_{arom}), 7.69–7.73 (m, 2H; H_{arom}).
22 F. E. McDonald and M. Wu, *Org. Lett.*, 2002, **4**, 3979–3981.
23 B. Wang, T. M. Hansen, T. Wang, D. Wu, L. Weyer, L. Ying, M. M. Engler, M. Sanville, C. Leitheiser, M. Christmann, Y. Lu, J. Chen, N. Zunker, R. D. Cink, F. Ahmed, C.-S. Lee and C. J. Forsyth, *J. Am. Chem. Soc.*, 2010, **133**, 1484–1505.
24 C.-E. Yeom, M. J. Kim, W. Choi and B. M. Kim, *Synlett*, 2008, 565–568.
25 (*a*) H. X. Zhang, F. Guibe and G. Balavoine, *J. Org. Chem.*, 1990, **55**, 1857–1867; (*b*) J. R. Frost, C. M. Pearson, T. N. Snaddon, R. A. Booth and S. V. Ley, *Angew. Chem., Int. Ed.*, 2012, **51**, 9366–9371.
26 R. Alvarez, M. Herrero, S. López and A. R. de Lera, *Tetrahedron*, 1998, **54**, 6793–6810.
27 K. Green, J. W. Keeping and V. Thaller, *J. Chem. Res., Synop.*, 1985, 103; K. Green, J. W. Keeping and V. Thaller, *J. Chem. Res., Miniprint*, 1985, 1260–1267.
28 J.-F. Betzer, F. Delaloge, B. Muller, A. Pancrazi and J. Prunet, *J. Org. Chem.*, 1997, **62**, 7768–7780.
29 Reviews: (*a*) J. K. Stille, *Angew. Chem., Int. Ed.*, 1986, **25**, 508–524; (*b*) T. N. Mitchell, *Synthesis*, 1992, 803–815; (*c*) V. Farina, V. Krishnamurthy and W. J. Scott, *Org. React.*, 1997, **50**, 1–652.
30 J. K. Stille and B. L. Groh, *J. Am. Chem. Soc.*, 1987, **109**, 813–817.