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An enantioselective synthesis of the $C_{24}-C_{40}$ 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 crosscoupling 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 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 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

Regarding the C_{24} - C_{34} fragment, it seemed best to assemble the triene¹⁴ after the glycosylation step by an appropriate crosscoupling 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 ($\alpha/\beta = 95/5$)

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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 -4¹³ 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 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 TMSacetylene 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-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 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 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 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 ($\lambda_{max} = 308$ nm, $\varepsilon = 28035$ M⁻¹ cm⁻¹ in MeCN), trienone 1 appears to be more stable than alcohol 17 ($\lambda_{max} = 271$ nm, $\varepsilon = 39350$ M⁻¹ cm⁻¹ in MeCN; shoulder at $\lambda_{max} = 282$ nm, $\varepsilon = 31180$ 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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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.
- (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 ¹H-NMR data of glycoside **9** (500 MHz, CDCl₃): δ (ppm) = 0.09 [s, 9H; Si(CH₃)₃], 0.97 [s, 9H; C(CH₃)₃], 0.96–0.99 (m, 3H; H₃-40), 1.05 [s, 9H; C(CH₃)₃], 1.30 (d, ³*J* = 6.3 Hz, 3H; H₃-34), 1.46 (s, 3H; C(O)CH₃-36), 2.12 [s, 3H; C(O)CH₃-38], 3.05 (q, ³*J* = 6.4 Hz, 1H; H-39), 3.41 (qd, ³*J* = 6.3, 3.9 Hz, 1 H; H-33), 3.44 (d, ³*J* = 8.1 Hz, 1 H; H³-35), 3.60 (dd, ³*J* = 9.8, 3.3 Hz, 1H; H-37), 4.19 (d, ³*J* = 3.9 Hz, 1H; H-32), 4.79 (d, ³*J* = 3.3 Hz, 1H; H-38), 5.06 (dd, ³*J* = 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.