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Synthesis of the C23–C32 fragment of spirangien

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Abstract—The synthesis of the C23–C32 fragment of spirangien A is reported using Evans' alkylation, Evans–Metternich aldol reaction and a substrate controlled stereoselective reduction.

1. Introduction

Myxcobacteria are a valuable source for the isolation of structurally diverse biologically active natural products. Among the various strains isolated from *Sorangium cellulosum*, strain So ce90 produces important antibiotic and cytotoxic compounds such as epothilone. Spirangien A (**1**) and B (**2**) (Fig. 1) were isolated from the same strain[1] and have been tested for their biological activity. They show high activity against yeast and fungi (e.g., diameters of inhibition zones: *Pichia membranaefaciens* 24 mm, *Rhodotorula glutins* 19 mm, *Botrytis cinerea* 11 mm).[1] Additionally, high cytotoxicity of **1** against L929 mouse fibroblast cell line ($IC_{50} = 0.7$ ng/mL^{-1}) and for **3** ($IC_{50} = 7$ ng/mL^{-1}) (Fig. 2) has been observed.[1]

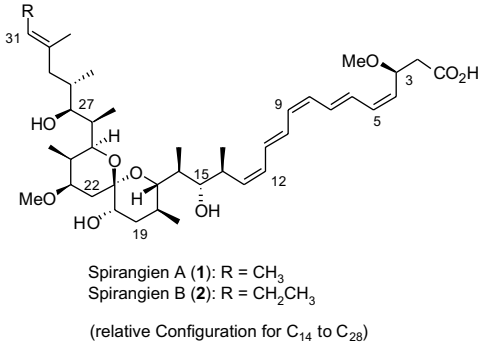

Figure 1. Spirangien A (**1**) and B (**2**).

Höfle and co-workers elucidated the structures of these two spirangiens A (**1**) and B (**2**) by NMR spectroscopy and mass spectrometry. They contain a highly functionalised spiroketal core structure, a side chain bearing a pentaene chromophore, a terminal carboxyl group and a total of 14 stereocentres. Through a cross metathesis reaction **1** was shortened to segment **3** of which X-ray

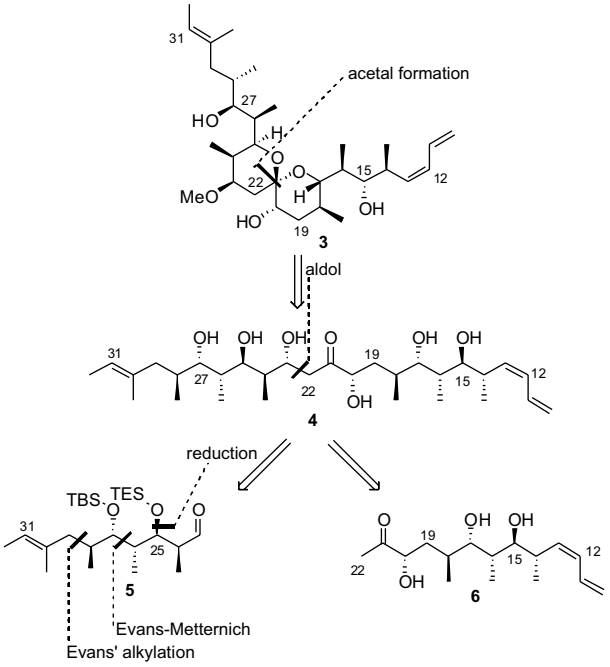

Figure 2. Retrosynthesis of **3**.

Keywords: Evans alkylation; Substrate controlled stereoselective reduction; Evans–Metternich aldol.
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analysis was utilised to determine the relative configuration.

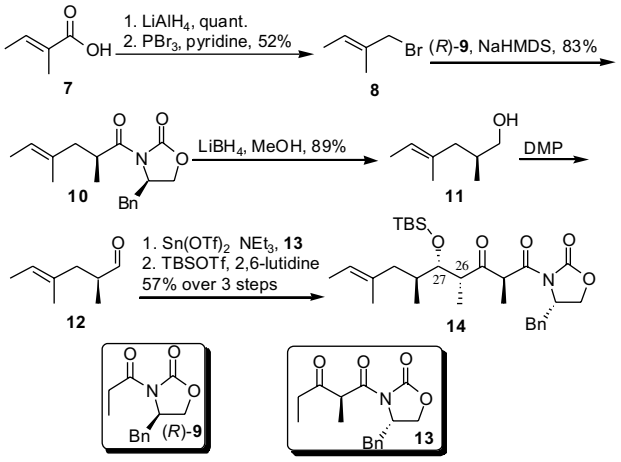
Our retrosynthetic analysis dissects **3** at the spiroketal moiety to the open chain fragment **4** (Fig. 2). This in turn can be assembled by an aldol addition of ketone **6** to aldehyde **5** (Fig. 2). Here, we report the synthesis of the C23–C32 fragment **5** of spirangien.

The synthesis of aldehyde **5** (Scheme 1) starts with the commercially available tiglic acid (**7**) which is reduced[2] quantitatively to the corresponding alcohol with $LiAlH_4$ and subsequently transformed into bromide **8** using PBr_3 and pyridine for buffering the reaction mixture.[3]

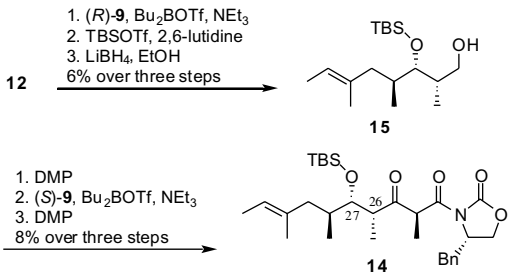
Bromide **8** is then employed in an Evans' alkylation[2] using oxazolidinone **9**. Deprotonation with NaHMDS as the base results in high yields and stereoselectivity to provide **10**. Reductive cleavage of the Evans auxiliary with $LiBH_4$ in methanol[4] followed by oxidation with DMP leads to aldehyde **12** (Scheme 1). Next, a *syn* selective Evans–Metternich aldol[5] reaction with auxiliary **13**, in the presence of freshly prepared $Sn(OTf)_2$ and NEt_3 yields the product in a diastereomeric ratio of 1.7:1 in favour of the desired product. A similar highly *syn* selective aldol addition using tin enolates was described by Evans and co-workers.[5] TBS protection allowed separation of the diastereomers of ketone **14** cleanly (Scheme 1). This protocol generates **14** in a very good yield over three steps starting from DMP oxidation of **11**.

The stereochemistry at C26 and C27 was confirmed by the synthesis of **14** via two *syn* selective Evans aldol reactions[6] and TBS-protection of the free alcohol (Scheme 2) followed by comparison of optical rotations and NMR spectroscopy of a mixture of **14** which were synthesised through two different routes (Schemes 1 and 2). Nevertheless, the previous route via the Evans–Metternich aldol reaction was identified advantageous due to the poor yields in the two subsequent Evans aldol reactions.

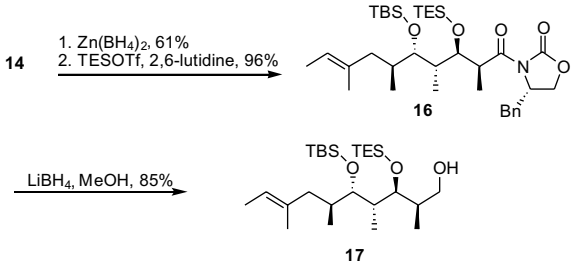
A stereoselective substrate controlled reduction of ketone **14** at C25 can be achieved by using freshly pre-



Scheme 1. Synthesis of ketone **14**.



Scheme 2. Alternative route to synthesise **14**.

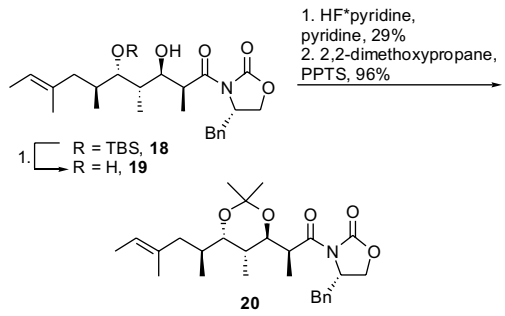


Scheme 3. Final steps for the synthesis of **17**.

pared $Zn(BH_4)_2$ to furnish β-hydroxy ketone **18** in moderate yields (Scheme 4).[7] The reducing reagent is ideally suited for a highly coordinating transition state. The two oxygens in this α-methyl-β-ketoamide are coordinated by $Zn(BH_4)_2$ such that the hydride attacks from the side opposite to the α-methyl group. This yields the desired *syn* product as described by Oishi, Evans and co-workers.[8] TES-protection of the alcohol at C25 and reductive cleavage of the Evans auxiliary with $LiBH_4$ in methanol yield alcohol **17** (Scheme 3).

In order to additionally confirm the relative configuration of the diol at C25 and C27 TBS deprotection of **18** to produce diol **19** followed by acetonide formation utilising 2,2-dimethoxypropane[9] results in the formation of **20** which shows indicative ^{13}C NMR shifts for the methyl groups and the quaternary carbon at $\delta = 24.6$, 25.7 and 102.1 ppm, respectively (Scheme 4) confirming the expected 1,3-*anti* configuration of the diol.

In summary, we have achieved the efficient and selective synthesis of the C23–C32 segment of spirangien with an Evans–Metternich aldol and a substrate controlled



Scheme 4. Synthesis of acetal **20** to confirm the relative configuration at C25 and C27.

stereoselective reduction using $Zn(BH_4)_2$ in the key steps. The C23–C32 segment will serve as the pivotal substrate for completing the synthesis of this natural product and to provide analogues for detailed SAR studies.

2. Experimental

2.1. Acetal 20

To a solution of **19** (7.0 mg, 16.8 μmol) in CH_2Cl_2 (1 mL) 2,2-dimethoxypropane (55 μL, 425 μmol) and PPTS (0.5 mg, cat.) were added at 0 °C. The mixture was stirred for 16 h and satd aq $NaHCO_3$-solution was added. The aqueous layer was extracted with CH_2Cl_2 and the organic layer was washed with water, dried over $MgSO_4$ and concentrated in vacuo. Purification via flash chromatography (EtOAc/hexanes 1:5) yielded **20** as a colourless oil (7 mg, 16.2 μmol, 96%). $R_f = 0.22$ (EtOAc/hexanes 1:5); $[\alpha]_{589}^{20}$ +39.6 (*c* 0.70 $CHCl_3$); ^1H NMR (400 MHz, CD_3OD) $\delta = 7.26$–7.38 (m, 5H), 5.23 (q, $J = 6.6$ Hz, 1H), 4.71–4.77 (m, 1H), 4.28–4.35 (m, 2H), 4.03–4.09 (m, 1H), 3.66 (dd, $J = 5.9$, 5.6 Hz, 1H), 3.38 (dd, $J = 10.3$, 3.8 Hz, 1H), 3.18 (dd, $J = 13.4$, 3.2 Hz, 1H), 3.01 (dd, $J = 13.5$, 8.2 Hz, 1H), 2.58 (d, $J = 13.2$ Hz, 1H), 1.98–2.04 (m, 1H), 1.65–1.72 (m, 1H), 1.62 (d, $J = 6.5$ Hz, 3H), 1.59 (s, 3H), 1.49 (dd, $J = 13.1$, 10.9 Hz, 1H), 1.35 (s, 3H), 1.33 (s, 3H), 1.29 (d, $J = 6.9$ Hz, 3H), 0.98 (d, $J = 6.8$ Hz, 3H), 0.74 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) $\delta = 176.6$, 155.4, 137.2, 135.9, 131.0, 130.1, 128.5, 121.3, 102.1, 77.7, 75.5, 67.9, 57.1, 45.2, 43.0, 38.6, 36.9, 32.3, 27.5, 25.7, 24.6, 15.9, 14.9, 13.8, 12.8; HRMS (ESI, $C_{27}H_{40}O_5N$ $[M+H^+]$) calculated: 458.2906; found: 458.2901.

2.2. Alcohol 17

To a solution of the diprotected alcohol **16** (21 mg, 32.5 μmol) in THF (1 mL) methanol (500 μL) and $LiBH_4$ (2 M in THF, 49 μL, 97.6 μmol) were added dropwise at 0 °C. The mixture was warmed to rt and stirred for 2 h. The solution was then cooled to 0 °C and another portion of $LiBH_4$ (2 M in THF, 49 μL, 97.6 μmol) was added. After stirring for additional 2 h at rt aq NaOH-solution (2 M) was added. The organic layer was extracted with CH_2Cl_2, washed with satd aq $NaHCO_3$-solution, brine, dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:25) yielded alcohol **17** (13 mg, 27.5 μmol, 85%). $R_f = 0.28$ (EtOAc/hexanes 1:25); $[\alpha]_{589}^{20}$ −7.32 (*c* 1.1 $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) $\delta = 5.18$ (q, $J = 6.3$ Hz, 1H), 3.77 (dd, $J = 6.3$, 0.5 Hz, 1H), 3.57 (t, $J = 3.1$ Hz, 1H), 3.44–3.52 (m, 2H), 2.11 (q, $J = 9.1$ Hz, 1H), 1.81–1.85 (m, 2H), 1.71–1.80 (m, 2H), 1.59 (s, 3H), 1.57 (s, 3H), 1.25–1.28 (m, 1H), 0.97 (t, $J = 8.0$ Hz, 9H), 0.91 (s, 9H), 0.89 (d, $J = 3.8$ Hz, 3H), 0.87 (d, $J = 3.4$ Hz, 3H), 0.78 (d, $J = 6.1$ Hz, 3H), 0.63 (q, $J = 8.0$ Hz, 6H), 0.07 (d, $J = 3.4$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 134.3$, 119.9, 74.6, 67.1, 41.9, 41.2, 37.9, 36.9, 26.2, 18.6, 15.7, 15.5, 13.4, 12.0, 11.1, 7.1, 5.6, −3.5, −3.6; HRMS (ESI, $C_{26}H_{57}O_3$ $[M+H^+]$) calculated: 473.3768; found: 473.3875.

References and notes

1. Niggemann, J.; Bedorf, N.; Flörke, U.; Steinmetz, H.; Gerth, K.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **2005**, 5013–5018.
2. Clive, D. L. J.; Murthy, K. S. K.; Wee, A. G. H.; Prasad, J. S.; da Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Evans, C. F.; Haugen, R. D.; Heerze, L. D.; Barrie, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 3018–3028.
3. Lauchenauer, A.; Schinz, H. *Helv. Chim. Acta* **1951**, *183*, 1514–1523.
4. Pilli, R. A.; Russowsky, D. *J. Org. Chem.* **1996**, *61*, 3187–3190.
5. (a) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866–868; (b) Evans, D. A.; Kim, A.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 5921–5942; (c) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757–6761.
6. Evans, D. A.; Palniaszek, R. P.; DeVries, K. M.; Guinn, D. E.; Mathre, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 7613–7630.
7. (a) Evans, D. A.; Trenkle, W. C.; Zhang, J.; Burch, J. D. *Org. Lett.* **2005**, *7*, 3335–3338; (b) Paquette, L. A. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons: NY, 1995; Vol. 8, 5536.
8. (a) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338–344; (b) Evans, D. A.; Ennis, M. D.; Le, T. *J. Am. Chem. Soc.* **1984**, *106*, 1154, and references cited therein.
9. (a) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9; (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099–7100; (c) Patterson, I.; Temal-Laib, T. *Org. Lett.* **2002**, *15*, 1273–2476.