Total Synthesis of Polyketides

Total Synthesis of (+)-Wailupemycin B**

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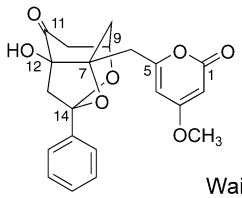
Dedicated to Professor Reinhard W. Hoffmann on the occasion of his 70th birthday

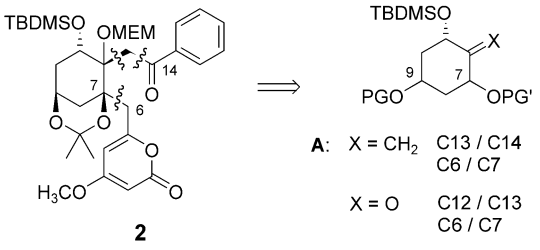
Wailupemycin B (**1**), an α-pyrone-containing metabolite, was isolated together with two structurally related compounds (wailupemycin A and C) by Davidson and co-workers from



Wailupemycin B (**1**)

Streptomyces maritimus. The organism was found at Wailupe Beach Park along the southeast coast of Oahu (Hawaii).[1] Because of the limited supply from natural sources, the antiinfective potential of the natural product has not been fully evaluated. Owing to its unique structural features, wailupemycin B was considered an attractive target for synthesis, not only because of its novel structure, but because a flexible de novo approach would allow a variation of the peripheral cyclic substituents. The natural product is a polyketide-derived cyclohexanone structure characterized by a high density of functional groups. Although the biosynthesis of the wailupemycins has been studied intensively, no total synthesis of any wailupemycin has, to our knowledge, been reported.[2] Herein, we describe the first total synthesis of (+)-wailupemycin B.

Wailupemycin B (**1**) is the cyclic acetal of a ketone (C14) and a *cis*-1,3-cyclohexanediol (C7, C9). Davidson and co-workers already mentioned its lability to acids.[1] We planned to postpone the oxidation at C11 to the final step of the synthesis. This strategy avoids chemoselectivity problems that could arise from a possible competitive oxidation at C9. We reckoned that the hydroxy group at C11 would have to adopt an axial position to allow smooth and selective acetal formation. Along this retrosynthetic analysis we considered cyclohexane **2** (Scheme 1; TBDMS = *tert*-butyldimethylsilyl, MEM = methoxyethoxymethyl) as a key intermediate that



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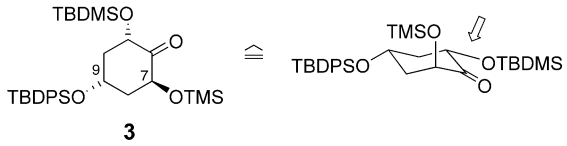
Scheme 1. Retrosynthetic disconnection of key intermediate **2**. PG, PG′ = protecting groups.

contains all stereogenic centers with the correct configuration. We further envisioned a flexible strategy for the introduction of the peripheral substituents which should establish the stereogenic centers with high stereoselectivity. Cyclohexanes of type **A**, derived from carvone,[3] could conveniently be used as key building blocks.

Powerful nucleophiles are required to create the C13–C14 bond by reaction with an epoxide derived from **A** (X = CH_2) or to form the C12–C13 bond by addition to a ketone **A** (X = O). To avoid the risk of competing attack at the α-pyrone (Scheme 1), the formation of the C6–C7 bond was postponed to a later stage of the synthesis. Another approach was based on the formation of the C4–C5 bond followed by cyclization and was a possible alternative for the introduction of the α-pyrone moiety.[4]

Preliminary studies also suggested that the presence of a dithiane-protected ketone at C14, which was obtained by opening of an epoxide ring, inhibits addition to C7 and C5 carbonyl groups. We consequently decided to establish the relevant bonds starting from ketone **A** (X = O) in the sequence C12–C13 and C6–C7. Further preliminary experiments indicated that the configuration at C7 and C9 has a significant effect on the facial diastereoselectivity of the C12–C13 bond formation. Bulky groups at C9 and C11 effectively lock the molecule into a chair conformation. Sufficiently large nucleophiles attack cyclohexanone derivatives **3** (TBDPS = *tert*-butyldiphenylsilyl, TMS = trimethylsilyl) in an equatorial



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fashion, as represented schematically. Epimers of compound **3** with the desired absolute configuration at C9 either showed worse diastereoselectivities or did not react at all.

Advanced intermediate **4** (Scheme 2) was readily generated in 42% overall yield from commercially available (*S*)-(+)-carvone according to literature procedures.[5] Ozonolytic cleavage of the exocyclic C–C double bond and reductive workup resulted in the formation of the orthogonally protected ketone **3**, which was treated with allylmagnesium bromide (whose use is justified below). The reaction proceeded with good diastereoselectivity (d.r. = 90:10). Protection of the tertiary hydroxy group at C12 as a MEM ether

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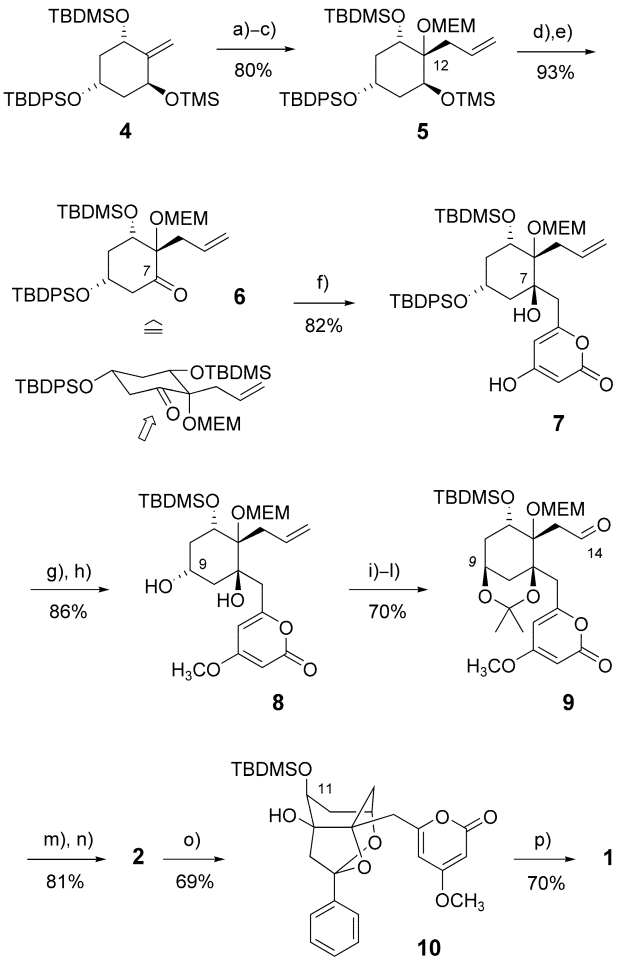

Scheme 2. Total synthesis of (+)-wailupemycin B (**1**). Yields refer to isolated, purified, and fully characterized compounds. a) O_3, MeOH in CH_2Cl_2, −78 °C; then Me_2S, −78 °C→RT, quant.; b) CH_2CHCH_2MgBr (1.5 equiv) in THF, −20 °C, 1 h, quant. (d.r. = 90:10); c) MEMCl (2.0 equiv), Et*N*iPr_2 (3.0 equiv) in DCE, 70 °C, 4 h, 80% (d.r. = > 95:5); d) K_2CO_3 in MeOH (3% w/v), room temperature, 12 h, 95%; e) IBX (2.0 equiv) in DMSO, room temperature, 5 h, 98%; f) 4-hydroxy-6-methylpyran-2-one (2.5 equiv), *t*BuLi (5.3 equiv) in THF, −85 °C→0 °C; then **6** in THF, −85 °C, 2 d, 82%; g) dimethyl sulfate (2.0 equiv), K_2CO_3 (10.0 equiv) in acetone, room temperature, 6 h, 92% (d.r. = > 95:5); h) HF·py in THF, 0 °C→RT, 12 h, 94%; i) IBX (1.5 equiv) in DMSO, room temperature, 4 h, 96%; j) L-Selectride (1.0 equiv) in THF, −78 °C, 1 h, 97%; k) 2-methoxypropene (2.0 equiv), PPTS (cat.) in DCE, room temperature, 3 h, 90%; l) OsO_4 (0.2 equiv), $NaIO_4$ (2.4 equiv), NaOAc (24.0 equiv) in THF/H_2O (1:1 v/v), room temperature, 4 h, 83%; m) PhMgBr (1.5 equiv) in THF, −78 °C, 1 h, 89%; n) DMP (2.0 equiv), $NaHCO_3$ (14.0 equiv) in CH_2Cl_2, room temperature, 3 h, 91%; o) TFA/HOAc/H_2O/THF (1:2:2:4 v/v), room temperature; 1.5 h, 69%; p) 1) TBAF (1.0 equiv) in THF, 0 °C, 25 min; 2) IBX (5.0 equiv) in EtOAc, 77 °C, 4 h, 70%. Abbreviations not defined in text: DMSO = dimethyl sulfoxide, *t*BuLi = *tert*-butyllithium, L-Selectride = lithium tri(*sec*-butyl)borohydride, PPTS = pyridinium *p*-toluenesulfonate, TBAF = tetrabutylammonium fluoride.

proceeded smoothly only at elevated temperature in 1,2-dichloroethane (DCE) as the solvent.[6,7] Selective deprotection of the secondary TMS ether, followed by oxidation with 2-iodoxybenzoic acid (IBX)[8–10] yielded ketone **6**. Introduction of the pyrone fragment was achieved with the dianion[11] derived from 4-hydroxy-6-methylpyran-2-one. The addition of the dianion to the carbonyl group at C7 in **6** proceeded with very good facial diastereoselectivity. The preferential formation of the desired diastereoisomer can be understood by an equatorial approach of the dianion to a chairlike conformation of ketone **6** (Scheme 2). This result confirmed our retrosynthetic considerations concerning the configuration of intermediate **3** and the choice of protecting groups. Subsequent *O*-methylation of the resulting hydroxypyrone with dimethyl sulfate followed by selective cleavage of the TBDPS ether with HF·py (py = pyridine) furnished alcohol **8**. The high chemoselectivity of desilylation was to be expected as the TBDMS ether at C11 is highly shielded. In fact, removal of the TBDMS protecting group could only be effected after cleavage of the MEM group.

The inversion of the C9 stereogenic center was achieved by oxidation and subsequent reduction. As expected, the hydride reagent approached the conformationally locked substrate equatorially. This sequence was followed by simultaneous protection of the free hydroxy groups as an isopropylidene acetal and subsequent introduction of the phenyl group at C14. At first sight, the late introduction of the phenyl group is surprising, and a direct addition of 2-phenylpropenylmagnesium bromide to **3** in step b) (Scheme 2) might appear to be a more direct alternative. Our decision to introduce the allyl group instead was driven by the desire to gain flexibility for the installation of other substituents at C14 at the end of the synthesis. Furthermore, the bulky phenyl group retards or prevents simple reactions at the densely functionalized cyclohexanone framework. Lemieux–Johnson oxidation[12] gave the corresponding aldehyde **9**, which was then treated with phenylmagnesium bromide at low temperature to provide the two C14 epimers. Surprisingly, but in line with the above-mentioned reactivity associated with the sterically demanding phenyl group, exposure of a mixture of C14 epimers to several standard oxidation reactions either resulted in no reaction or gave rise to a series of uncharacterizable products. In this respect, we were delighted to find that key intermediate **2** was readily accessed upon treatment with Dess–Martin periodinane (DMP)[13] in the presence of sodium bicarbonate.[14] The following step involved removal of the MEM protecting group, hydrolytic cleavage of the acetonide ring, and conversion into the internal ketal **10**, an objective which was accomplished by exposing **2** to a mixture of TFA (trifluoroacetic acid), acetic acid, water, and THF (1:2:2:4). Finally, precursor **10** was converted into wailupemycin B (**1**) by initial deprotection of the secondary silyl ether followed by oxidation with IBX without isolation of the intermediate unstable axial alcohol. Based on spectroscopic data[16] the synthetic material was identical to natural wailupemycin B. The absolute configuration of wailupemycin B was proven by comparison of the optical rotations ($[\alpha]_D^{20} = +79.0$ ($c = 0.09$, MeOH), natural product[1]: $[\alpha]_D^{24} = +77.7$ ($c = 0.07$, MeOH)), which also confirmed the absolute configuration proposed by Davidson and co-workers.

In conclusion, we have described an expedient, stereocontrolled synthesis of wailupemycin B (16 steps, 14% overall yield from **4**). The stereogenic centers were formed with high facially diastereoselective control. Furthermore, our flexible

approach should provide access to a variety of new analogues by incorporating different substituents at the periphery. Applications of the newly developed synthetic strategy and investigations into the biological activity of wailupemycin B and its derivatives are currently underway.

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Keywords: antibiotics · asymmetric synthesis · ketones · polyketides · total synthesis

[1] N. Sitachitta, M. Gadepalli, B. S. Davidson, *Tetrahedron* **1996**, *52*, 8073 – 8080.

[2] a) B. S. Moore, C. Hertweck, *Nat. Prod. Rep.* **2002**, *19*, 70 – 99; b) L. Xiang, J. A. Kalaitzis, G. Nilsen, L. Chen, B. S. Moore, *Org. Lett.* **2002**, *4*, 957 – 960; c) J. Piel, C. Hertweck, P. R. Shipley, D. M. Hunt, M. S. Newman, B. S. Moore, *Chem. Biol.* **2000**, *7*, 943 – 955; d) C. Hertweck, B. S. Moore, *Tetrahedron* **2000**, *56*, 9115 – 9120; e) J. Piel, K. Hoang, B. S. Moore, *J. Am. Chem. Soc.* **2000**, *122*, 5415 – 5416.

[3] a) J. Wang, R. Busson, N. Blaton, J. Rozenski, P. Herdewijn, *J. Org. Chem.* **1998**, *63*, 3051 – 3058; b) S. Hatakeyama, H. Numata, K. Osanai, S. Takano, *J. Org. Chem.* **1989**, *54*, 3515 – 3517; c) K. A. Parker, A. Dermatakis, *J. Org. Chem.* **1997**, *62*, 6692 – 6696.

[4] T. Bach, S. Kirsch, *Synlett* **2001**, 1974 – 1976.

[5] Starting from (*S*)-(+)-carvone, we mostly followed the procedures given in reference [3b]. Reduction to the desired diastereoisomer was achieved with $NaBH_4/CeCl_3$ according to reference [3b], footnote 13.

[6] E. J. Corey, J.-L. Gras, P. Ulrich, *Tetrahedron Lett.* **1976**, 809 – 812.

[7] For examples of the use of 1,2-dichloroethane at elevated temperatures, see: a) H. Paulsen, B. Mielke, *Liebigs Ann. Chem.* **1990**, 169 – 180; b) D. A. Clark, F. De Riccardis, K. C. Nicolaou, *Tetrahedron* **1994**, *50*, 11391 – 11426; c) P. A. Procopiou, E. J. Bailey, C. Chan, G. G. A. Inglis, M. G. Lester, A. R. P. Srikantha, P. J. Sidebottom, N. S. Watson, *J. Chem. Soc. Perkin Trans. 1* **1995**, 1341 – 1348.

[8] For the synthesis of IBX, see: a) C. Hartmann, V. Meyer, *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 1727 – 1732; b) M. Frigerio, M. Santagostino, S. Sputore, *J. Org. Chem.* **1999**, *64*, 4537 – 4538.

[9] a) M. Frigerio, M. Santagostino, *Tetrahedron Lett.* **1994**, *35*, 8019 – 8022; b) S. De Munari, M. Frigerio, M. Santagostino, *J. Org. Chem.* **1996**, *61*, 9272 – 9279; c) J. D. More, N. S. Finney, *Org. Lett.* **2002**, *4*, 3001 – 3003.

[10] For a review on IBX oxidations, see: T. Wirth, Angew. Chem. **2001**, *113*, 2893 – 2895; *Angew. Chem. Int. Ed.* **2001**, *40*, 2812 – 2814.

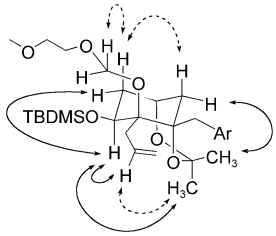
[11] a) M. P. Wachter, T. M. Harris, *Tetrahedron* **1970**, *26*, 1685 – 1694; b) G. A. Poulton, T. D. Cyr, *Can. J. Chem.* **1982**, *60*, 2821 – 2829; c) W. C. Groutas, M. A. Stanga, M. J. Brubaker, T. L. Huang, M. K. Moi, R. T. Carroll, *J. Med. Chem.* **1985**, *28*, 1106 – 1109.

[12] a) R. Pappo, D. S. Allen, R. U. Lemieux, W. S. Johnson, *J. Org. Chem.* **1956**, *21*, 478 – 479; b) C.-Y. Chen, D. J. Hart, *J. Org. Chem.* **1993**, *58*, 3840 – 3849; c) P. Wipf, Y. Kim, D. M. Goldstein, *J. Am. Chem. Soc.* **1995**, *117*, 11106 – 11112.

[13] a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155 – 4156; b) D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277 – 7287; c) R. K. Boeckman, Jr., P. Shao, J. J. Mullins, *Org. Synth.* **1999**, *77*, 141 – 149.

[14] For examples of Dess–Martin oxidations in the presence of sodium bicarbonate, see: a) T. I. Richardson, S. D. Rychnovsky, *Tetrahedron* **1999**, *55*, 8977 – 8996; b) K. C. Nicolaou, J. Jung, W. H. Yoon, K. C. Fong, H.-S. Choi, Y. He, Y.-L. Zhong, P. S. Baran, *J. Am. Chem. Soc.* **2002**, *124*, 2183 – 2189.

[15] The relative configurations and conformations of various intermediates were been determined throughout the synthesis by NOESY experiments. The rigid precursor to compound **2**, which already contains all stereogenic centers of the natural product, offered a chance to check the relative configuration. The most important NOE data (----- = medium, —— = strong) are given in the illustration (Ar = 4-methoxy-6-oxopyran-2-yl).



[16] Spectroscopic data for **1**: ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.62 (d, ^2J = 13.3 Hz, 1H; $H_{8a}H_b$), 2.41 (ddd, ^2J = 13.3 Hz, ^3J = 5.0 Hz, ^4J = 2.6 Hz, 1H; H_aH_{8b}), 2.55 (d, ^2J = 13.6 Hz, 1H; $H_{13a}H_b$), 2.74 (dd, ^2J = 18.7 Hz, ^3J = 5.3 Hz, 1H; $H_{10a}H_b$), 2.76 (d, ^2J = 13.6 Hz, 1H; H_aH_{13b}), 2.85 (d, ^2J = 14.9 Hz, 1H; H_6H_b), 3.03 (d, ^2J = 14.9 Hz, 1H; H_aH_{6b}), 3.14 (br d, ^2J = 18.7 Hz, 1H; H_aH_{10b}), 3.80 (s, 3H; OCH_3), 4.01 (br s, 1H; OH), 4.76 (virt. t, ^3J = 5.0 Hz, 1H; H_9), 5.43 (d, ^4J = 2.0 Hz, 1H; H_2), 6.02 (d, ^4J = 2.0 Hz, 1H; H_4), 7.36–7.41 (m, 3H; CH_{ar}), 7.59 ppm (d, ^3J = 7.0 Hz, 2H; CH_{ar}); ^{13}C NMR (90 MHz, $CDCl_3$, 25 °C): δ = 36.1, 38.7, 43.7, 54.7, 55.8, 69.0, 85.0, 85.4, 88.2, 103.2, 105.9, 125.0, 128.3, 128.9, 138.5, 160.5, 164.3, 171.0, 208.9 ppm; MS (EI, 70 eV): *m*/*z* (%): 384 (18) [M^+], 356 (48), 209 (51), 140 (100), 125 (50), 105 (92), 77 (33).

