Vic-Tricarbonyl Compounds: Synthesis of (±)-9-*epi*-Wailupemycin A

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Dedicated to Prof. R. W. Hoffmann on the occasion of his 80th birthday

Abstract: A synthesis of the 9-epimer of the marine natural product wailupemycin A is reported. The key reaction sequence consists of a diastereoselective enamine addition to a tricarbonyl monohydrate, the formation of an enol silyl acetal, and finally the stereocontrolled addition of the α-pyrone substructure.

Key words: vicinal tricarbonyl compound, enamine, α-pyrone, natural products, stereoselective synthesis

The use of vic-tricarbonyl compounds as polyelectrophiles in organic synthesis is mainly restricted to their reaction with O- and N-nucleophiles.[1,2] The stereocontrolled addition of C-nucleophiles has been studied with diethyl ketomalonate.[3] The crotylboration of vic-diketo amides and vic-diketo esters was possible with high diastereoselectivity and complementary regioselectivity.[4] A diastereoselective intramolecular aldol reaction of a vic-diketo ester has been achieved.[5] The asymmetric crotylboration of a vic-tricarbonyl compound was used as a key step in the total synthesis of awajanomycin.[6]

Wailupemycin A (**1**) and wailupemycin B (**2**) (Figure 1) are α-pyrone containing metabolites from the marine derived actinomycete BD-26T(20) isolated from sediments, which were collected at Wailupe beach south east of Hawai.[7] The structures of both compounds were determined by combined spectroscopic techniques. The wailupemycins were tested for antimicrobial activity against *Bacillus subtilis*, *Staphylococcus areus*, and *Escherica coli*. While wailupemycin B (**2**) was inactive, wailupemycin A (**1**) showed activity against *E. coli*.[7] The biosynthesis of the wailupemycins has been investigated and analogues have been prepared via mutasynthesis.[8] A total synthesis of enantiomerically pure wailupemycin B (**2**) has been reported by Bach and Kirsch.[9] Here, we present a synthesis of (±)-9-*epi*-wailupemycin A that focuses on the use of a vic-tricarbonyl compound as the key intermediate.

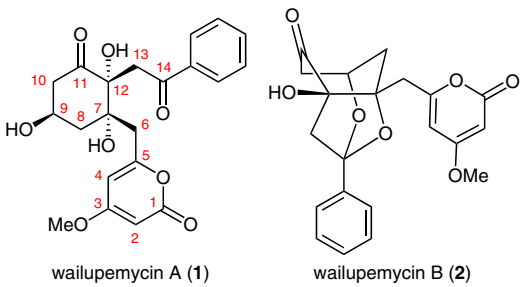
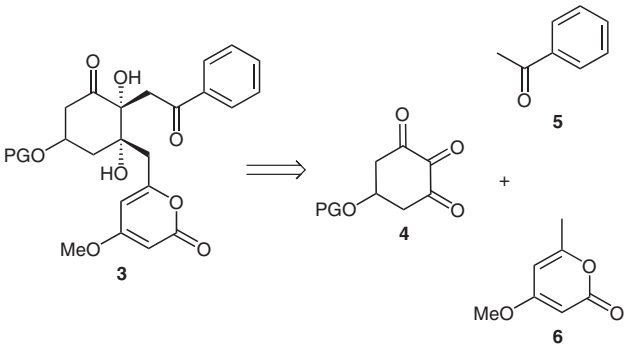


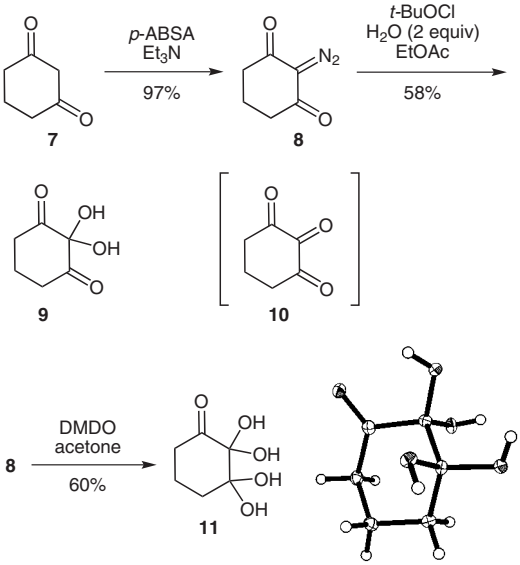
Figure 1 Structures of wailupemycin A (**1**) and wailupemycin B (**2**)

The retrosynthetic consideration of the wailupemycin A structure **3** leads to the vic-triketone **4**, acetophenone **5**, and the methyl-α-pyrone **6** (Scheme 1). A successive addition of enolates or enolate equivalents of **5** and **6** to the tricarbonyl substructure **4** could be used to assemble the target structure.



Scheme 1 Retrosynthetic analysis of wailupemycin A (**1**)

For initial studies, cyclohexane-1,2,3-trione (**10**) was chosen as test substrate for the addition of **5** and **6** (Scheme 2).



Scheme 2 Synthesis of cyclohexane-1,2,3-trione (**10**) and its hydrates **9** and **11**.

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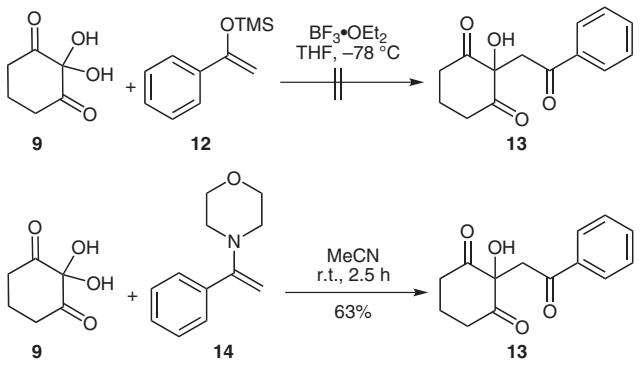
A Regitz diazo transfer using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) of the β-diketone **7** gave the α-diazo-β-dicarbonyl compound **8**.[10] Treatment of the latter with *tert*-butyl hypochlorite and 2 equivalents of water in ethyl acetate led to the monohydrate **9**.[4,11] Oxidation of **8** with an excess of dimethyl dioxirane (DMDO) in acetone gave the dihydrate **11** in good yield, which is in contrast to the earlier work demonstrating the formation of the monohydrate in the DMDO oxidation.[12] The structure of the dihydrate **11** was confirmed by X-ray crystallography.[13]

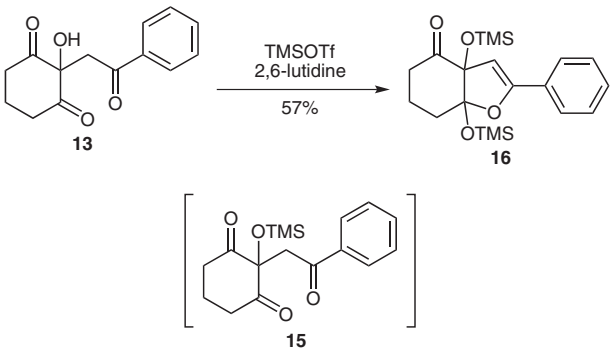
The addition of the acetophenone fragment to the central carbonyl group of the tricarbonyl compounds was investigated next. Attempts to dehydrate the monohydrate **9** with P_2O_5 or distillation and to use the purified triketone **10** failed probably due to the instability of the latter. Vic-tricarbonyl compounds can be generated in situ using $Et_2O{\cdot}BF_3$[4] but the integration of this method in a Mukaiyama aldol addition was unsuccessful (Scheme 3). The reaction of the monohydrate **9** with the silyl enol ether **12**[14] in the presence of $Et_2O{\cdot}BF_3$ did not lead to the aldol **13**, but to decomposition of the starting material. Schank et al. have shown that free cyclic vicinal triketones react with enamines.[15] For the present case, it was found, that the monohydrate **9** reacts with the morpholine enamine **14**[16] without any additive at room temperature to produce the desired aldol **13**.



Scheme 3 Reaction of monohydrate **9** with acetophenone enolate equivalents **12** and **14**

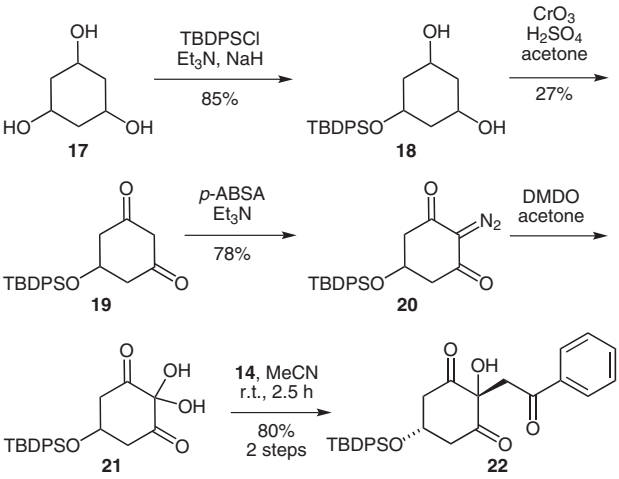
While trying to convert the aldol **13** into the TMS-protected compound **15**, the smooth formation of the enol silyl acetal **16** was observed (Scheme 4).

Having established the enamine-to-hydrate addition at the model system we turned our attention to wailupemycin A itself. Starting point for the synthesis was the triol **17** (*cis*/*trans* mixture), which was mono-TBDPS-protected to obtain the diol **18** (Scheme 5). Various oxidation conditions (DMP, IBX, PDC, PCC) were tested for the direct conversion of the diol **18** into the β-diketone **19**, but produced mainly monoxidation to the β-hydroxy ketone. Jones conditions[17] gave the best results for the desired dioxidation. Diazo transfer to the β-diketone **19** delivered the α-diazo-β-dicarbonyl compound **20** in very good yield. Oxidation of the diazo compound with DMDO in



Scheme 4 Reaction of **13** with TMSOTf to the enol silyl acetal **16**

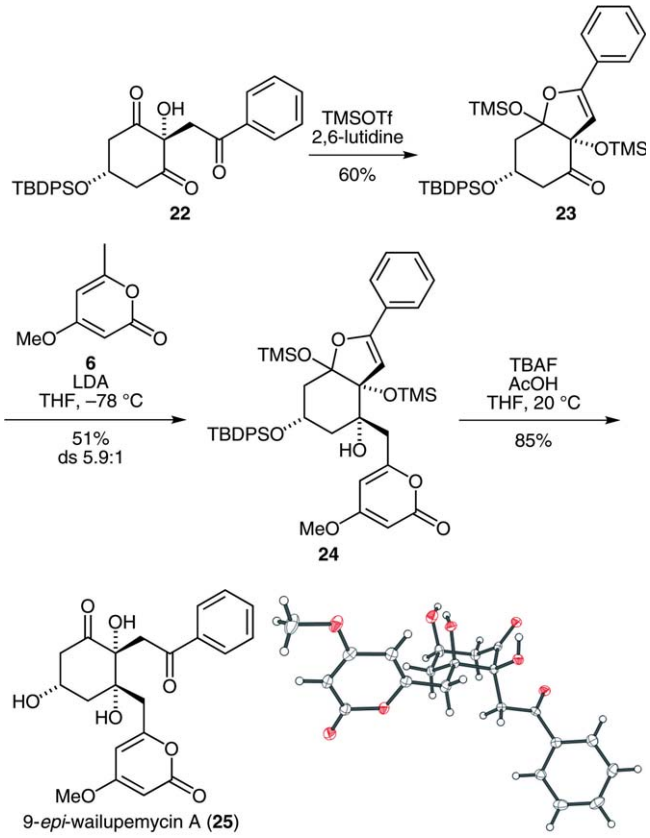
acetone gave the monohydrate **21**, which was used without chromatographic purification directly for the following enamine addition. The reaction with the morpholine enamine **14** resulted in the stereoselective formation of the aldol **22**. The enamine nucleophile had attacked the central carbonyl group of the in situ formed vic-triketone intermediate from the face opposite to the bulky TBDPS ether. The stereochemical outcome of the enamine addition opened the route to 9-*epi*-wailupemycin A. A Mitsunobu inversion at the 9-position could lead to wailupemycin A.



Scheme 5 Synthesis of the monohydrate **21** and its reaction with the enamine **14** to the aldol **22**

The final sequence for the construction of the wailupemycin skeleton used the differentiation of the three carbonyl groups in compound **22** by the formation of the enol silyl acetal, which was found for the model system **13** → **16**. Reaction of **22** with TMSOTf and 2,6-lutidine gave the enol silyl acetal **23** in good yield (Scheme 6). Compound **23** was formed as a single diastereomer; however, the relative configuration at the acetal stereocenter could not been identified without doubt. The addition of the α-pyrone substructure to the remaining carbonyl group was carried out with the methylpyrone **6**.[18] Lithiation at the methyl position of **6** with LDA[19] and addition of the ketone **23** resulted in the formation of the alcohol **24** with a 5.9:1 diastereoselectivity. After TBAF-mediated deprotection of the three silyl ethers in **24**, 9-*epi*-wailupemycine

A (**25**) was obtained in racemic form. The relative configuration of all three stereocenters was secured by X-ray crystallography of **25**.[20] Attempts to invert the C-9 stereocenter by a Mitsunobu inversion were unsuccessful.



Scheme 6 α-Pyrone addition and synthesis of racemic 9-*epi*-wailupemycin A (**25**) and X-ray structure of compound **25**

In conclusion, a diastereoselective synthesis of 9-*epi*-wailupemycin has been achieved. A vicinal tricarbonyl compound functioned as the key intermediate. It was used as monohydrate and gave a diastereoselective addition reaction with a morpholine enamine. Further key steps were the differentiation of the three keto groups in the aldol product via an enol silyl acetal and the stereocontrolled addition of a methylpyrone to the remaining keto group. The synthetic route developed here should be adaptable to further derivatives of the wailupemycines with potential bioactivities of interest.

All nonaqueous reactions were carried out using flame-dried glassware under argon atmosphere. All solvents were distilled by rotary evaporation. Solvents for nonaqueous reactions were dried as follows prior to use: THF was distilled from Na/benzophenone, and CH_2Cl_2 from CaH_2. MeCN was dried over molecular sieve (3 Å). All commercially available reagents and reactants were used without purification. 4-Methoxy-6-methyl-2-pyrone (**6**)[18] and α-(4-morpholino)styrene (**14**)[16] were prepared according to a literature procedure. Reactions were monitored by TLC using Merck Silica Gel 60 F_{245} plates and visualized by fluorescence quenching under UV light or by using a $KMnO_4$ stain. Chromatographic purification of products was performed on Macherey-Nagel Silica Gel 60 using a forced flow of eluents. Concentration under reduced pressure was performed by rotary evaporation at 40 °C and appropriate pressure. Yields refer to purified and spectroscopically pure products, unless otherwise noted. Melting points were measured with a Stuart SMP10 apparatus and are not corrected. IR spectra were recorded on a Bruker ALPHA FT-IR spectrometer (platinum ATR). The absorption bands are given in wavenumbers (cm^{-1}); intensities are reported using standard abbreviations. NMR spectra were recorded on a Bruker ARX300, DRX400, or DRX500 spectrometer at r.t. Chemical shifts are reported in ppm with the solvent resonance as internal standard (DMSO-d_6: $\delta_H = 2.50$, $\delta_C = 39.52$; $CDCl_3$: $\delta_H = 7.26$, $\delta_C = 77.16$; CD_2Cl_2: $\delta_H = 5.32$, $\delta_C = 53.84$; CD_3CN: $\delta_H = 1.94$, $\delta_C = 1.32$). Standard abbreviations were used for denoting the signal multiplicities. Mass spectra were recorded on a Finnigan LTQ-FT or MAT 95 spectrometer.

2-Diazocyclohexane-1,3-dione (8)

Cyclohexane-1,3-dione (**7**; 5.00 g, 43.3 mmol) and *p*-acetamidobenzenesulfonyl azide (10.7 g, 43.3 mmol) were dissolved in MeCN (216 mL), and Et_3N (6.60 mL, 47.6 mmol) was slowly added. The reaction mixture was stirred for 12 h at r.t. and filtered through a silica gel pad with CH_2Cl_2 (500 mL) as the eluent. The solvent was removed under reduced pressure and the crude product purified by flash chromatography on silica gel (CH_2Cl_2) to give **8** (5.77 g, 41.8 mmol, 97%) as a yellow solid; $R_f = 0.55$ (EtOAc).

IR (ATR, neat): 2958 (w), 2897 (w), 2198 (w), 2131 (m), 1625 (s), 1460 (w), 1414 (w), 1324 (m), 1282 (s), 1236 (m), 1172 (m), 1130 (m), 1086 (m), 1067 (w), 1038 (w), 995 (m), 902 (w), 860 (m), 750 (w), 684 (m), 630 (m), 597 (m), 568 (m), 495 (w), 454 (w), 401 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.56 (t, J = 6.4 Hz, 4 H), 2.10–1.97 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.4 (2 C), 84.9, 37.0 (2 C), 18.7.

HRMS (ESI): *m*/*z* calcd for $C_6H_6N_2O_2$ + Na $[M + Na]^+$: 161.0321; found: 161.0324.

2,2-Dihydroxycyclohexane-1,3-dione (9)

α-Diazo-β-dicarbonyl compound **8** (0.50 g, 3.62 mmol) was dissolved in EtOAc (17 mL) and H_2O (0.13 mL, 7.24 mmol) was added. The reaction mixture was cooled to 0 °C and *tert*-butyl hypochlorite (0.45 mL, 3.98 mmol) was added dropwise. The mixture was warmed up to r.t. and stirred for 15 min. The mixture was poured into pentane (100 mL), cooled to 4 °C for 1 h, and warmed up to r.t. The precipitate was collected by filtration and dried under reduced pressure to give **9** (0.31 g, 2.12 mmol, 58%) as a white solid; $R_f = 0.28$ (EtOAc).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.02 (s, 2 H), 2.70–2.63 (m, 4 H), 1.82–1.71 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 204.4 (2 C), 96.4, 36.8 (2 C), 17.3.

HRMS (ESI): *m*/*z* calcd for $C_6H_8O_4$ + Na $[M + Na]^+$: 167.0315; found: 167.0315.

2,2,3,3-Tetrahydroxycyclohexanone (11)

α-Diazo-β-dicarbonyl compound **8** (0.50 g, 3.62 mmol) was dissolved in a DMDO solution in acetone (77.5 mL, 5.43 mmol) and was stirred for 12 h at r.t. The solvent was removed under reduced pressure and the crude product was washed with CH_2Cl_2 (20 mL) and EtOAc (10 mL). Upon storage in an open flask at r.t. for 3 d, the dihydrate **11** (0.35 g, 2.15 mmol, 60%) solidified as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.83 (s, 2 H), 5.32 (s, 2 H), 2.38 (t, J = 6.8 Hz, 2 H), 1.87–1.77 (m, 2 H), 1.64–1.52 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 207.8, 97.1, 95.6, 36.1, 33.6, 19.2.

HRMS (ESI): *m*/*z* calcd for $C_6H_{10}O_5$ + Na $[M + Na]^+$: 185.0420; found: 185.0421.

2-Hydroxy-2-(2-oxo-2-phenylethyl)cyclohexane-1,3-dione (13)
Monohydrate **9** (274 mg, 1.90 mmol) was dissolved in anhydrous MeCN (10 mL) and α-(4-morpholino)styrene (**14**;[16] 511 mg, 2.69 mmol) in anhydrous MeCN (10 mL) was slowly added. The reaction mixture was stirred at r.t. for 2.5 h. Aq HCl (0.2 M, 40 mL) was added to the mixture and the aqueous layer was extracted with CH_2Cl_2 (6 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give **13** (297 mg, 1.21 mmol, 63%) as an orange oil; R_f = 0.66 (EtOAc). It was not possible to separate the product from acetophenone, so the yield was calculated by NMR analysis.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99–7.91 (m, 2 H), 7.65–7.57 (m, 1 H), 7.52–7.43 (m, 2 H), 4.90 (s, 1 H,), 3.61 (s, 2 H), 3.13–2.99 (m, 2 H), 2.84–2.72 (m, 2 H), 1.92 (quint, J = 7.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.1 (2 C), 198.5, 136.3, 134.1, 128.8 (2 C), 128.6 (C), 87.6, 42.1, 36.9 (2 C), 18.9.

HRMS (ESI): m/z calcd for $C_{14}H_{14}O_4$ + Na $[M + Na]^+$: 269.0784; found: 269.0782.

2-Phenyl-3a,7a-bis(trimethylsilyloxy)-5,6,7,7a-tetrahydrobenzofuran-4(3a*H*)-one (16)
Aldol **13** (93.0 mg, 0.38 mmol) was dissolved in anhydrous CH_2Cl_2 (8.1 mL) and cooled to 0 °C. First 2,6-lutidine (0.18 mL, 1.51 mmol) and then Me_3SiOTf (0.14 mL, 0.75 mmol) were dropwise added to the cooled solution. The reaction mixture was warmed up to r.t. and was stirred for 12 h. Sat. aq $NaHCO_3$ (20 mL) was added and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (pentane–EtOAc, 100:3) to give **16** (84.0 mg, 0.22 mmol, 57%) as a colorless oil; R_f = 0.26 (pentane–EtOAc, 98:2).

^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.67–7.59 (m, 2 H), 7.44–7.37 (m, 3 H), 5.26 (s, 1 H), 2.62–2.49 (m, 1 H), 2.47–2.34 (m, 1 H), 2.30–2.19 (m, 1 H), 1.92–1.68 (m, 3 H), 0.23 (s, 9 H), 0.17 (s, 9 H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ = 208.1, 159.3, 130.2, 130.0, 128.9 (2 C), 126.1 (2 C), 112.0, 99.4, 91.0, 38.2, 37.2, 16.7, 2.6 (3 C), 1.7 (3 C).

HRMS (ESI): m/z calcd for $C_{20}H_{30}O_4Si_2$ + Na $[M + Na]^+$: 413.1575; found: 413.1577.

5-(*tert*-Butyldiphenylsilyloxy)cyclohexane-1,3-diol (18)
tert-Butyldiphenylsilyl chloride (9.16 mL, 34.5 mmol) and Et_3N (4.78 mL, 34.5 mmol) were added to a suspension of cyclohexane-1,3,5-triol (**17**; 4.00 g, 28.7 mmol) in anhydrous THF (80 mL). The mixture was stirred for 30 min at r.t. and then treated with NaH (60% dispersion in mineral oil, 1.49 g, 37.4 mmol). At the end of the H_2 development, the mixture was stirred at 45 °C for 48 h. The mixture was cooled to 10 °C and was filtered through Celite with THF (60 mL) as the eluent. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (EtOAc) to give **18** (9.04 g, 24.4 mmol, 85%) as a white solid; mp 94 °C; R_f = 0.42 (EtOAc).

IR (ATR, neat): 3275 (w), 2939 (w), 2891 (w), 2858 (w), 1465 (w), 1426 (w), 1367 (w), 1322 (w), 1274 (w), 1107 (m), 1038 (s), 1013 (m), 931 (w), 868 (w), 813 (w), 769 (w), 738 (m), 698 (s), 613 (m), 497 cm^{-1} (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ (isomer 1) = 7.70–7.65 (m, 4 H), 7.48–7.35 (m, 6 H), 4.45–4.38 (m, 1 H), 4.31–4.25 (m, 1 H), 4.14–4.07 (m, 1 H), 2.14–2.06 (m, 1 H), 1.95–1.84 (m, 2 H), 1.65–1.59 (m, 1 H), 1.55–1.45 (m, 2 H), 1.42–1.31 (m, 2 H), 1.08 (s, 9 H); δ (isomer 2) = 7.70–7.65 (m, 4 H), 7.48–7.35 (m, 6 H), 3.74–3.67 (m, 1 H), 3.56–3.49 (m, 2 H), 2.11–2.06 (m, 1 H), 2.06–2.00 (m, 2 H), 1.53–1.45 (m, 2 H), 1.43–1.34 (m, 1 H), 1.06 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (isomer 1) = 136.0 (2 C), 135.9 (2 C), 133.4, 133.3, 130.2, 130.2, 127.9 (2 C), 127.9 (2 C), 70.4, 68.0, 64.7, 42.5, 41.7, 38.8, 27.1 (3 C), 19.2; δ (isomer 2) = 135.9 (4 C), 134.0 (2 C), 129.9 (2 C), 127.8 (4 C), 67.6 (2 C), 66.1, 43.5, 43.4, 27.1 (3 C), 19.2.

HRMS (ESI): m/z calcd for $C_{22}H_{30}O_3Si$ + Na $[M + Na]^+$: 393.1856; found: 393.1855.

5-(*tert*-Butyldiphenylsilyloxy)cyclohexane-1,3-dione (19)
Concd H_2SO_4 (1.47 mL, 27.6 mmol) was slowly added to a solution of CrO_3 (1.69 g, 16.9 mmol) in H_2O (4.90 mL, 272 mmol) to give the Jones reagent (2.65 M). The Jones reagent was slowly added to a solution of diol **18** (1.00 g, 2.70 mmol) in acetone (20 mL) at 0 °C. The reaction mixture was stirred for 20 min at r.t. and was then cooled to 0 °C. *i*-PrOH (20 mL) was added to the cooled suspension and after 5 min, H_2O (5 mL) was added. The aqueous layer was extracted with Et_2O (4 × 50 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (pentane–EtOAc, 2:1 to EtOAc) to give **19** (0.27 g, 0.74 mmol, 27%) as a white foam; R_f = 0.66 (EtOAc).

IR (ATR, neat): 3067 (w), 2932 (w), 2895 (w), 2858 (w), 1577 (m), 1467 (w), 1423 (w), 1393 (w), 1341 (w), 1307 (w), 1219 (m), 1155 (w), 1105 (s), 1082 (s), 991 (w), 904 (w), 824 (w), 791 (w), 736 (m), 702 (s), 611 (m), 505 (m), 437 cm^{-1} (w).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.58 (m, 4 H), 7.50–7.37 (m, 6 H), 4.45–4.39 (m, 1 H), 3.56 (dt, J = 18.2, 1.7 Hz, 1 H), 3.38 (d, J = 18.2 Hz, 1 H), 2.81–2.70 (m, 2 H), 2.58–2.46 (m, 2 H), 1.00 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.9 (2 C), 135.9 (4 C), 132.8 (2 C), 130.3 (2 C), 128.1 (4 C), 65.3, 57.7, 47.9 (2 C), 26.9 (3 C), 19.2.

HRMS (ESI): m/z calcd for $C_{22}H_{26}O_3Si$ + Na $[M + Na]^+$: 389.1543; found: 389.1540.

5-(*tert*-Butyldiphenylsilyloxy)-2-diazocyclohexane-1,3-dione (20)
β-Diketone **19** (1.49 g, 4.05 mmol) and *p*-ABSA (1.20 g, 4.86 mmol) were dissolved in MeCN (22 mL), and Et_3N (0.73 mL, 5.27 mmol) was slowly added. The reaction mixture was stirred for 12 h at r.t. and filtered through a silica gel pad with CH_2Cl_2 (100 mL) as the eluent. The solvent was removed under reduced pressure and the crude product purified by flash chromatography on silica gel (pentane–EtOAc, 4:1) to give **20** (1.25 g, 3.18 mmol, 78%) as a yellow solid; mp 112 °C; R_f = 0.33 (pentane–EtOAc, 4:1).

IR (ATR, neat): 2934 (w), 2860 (w), 2143 (m), 1683 (w), 1648 (s), 1467 (w), 1423 (w), 1356 (w), 1291 (s), 1207 (w), 1146 (w), 1106 (m), 1076 (s), 1004 (m), 976 (m), 941 (w), 891 (w), 822 (m), 745 (w), 705 (s), 630 (w), 605 (s), 513 (s), 485 (s), 428 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64–7.59 (m, 4 H), 7.50–7.36 (m, 6 H), 4.29–4.23 (m, 1 H), 2.71 (dd, J = 16.6, 5.0 Hz, 2 H), 2.55 (dd, J = 16.6, 3.1 Hz, 2 H), 1.03 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.4 (2 C), 135.8 (4 C), 132.9 (2 C), 130.3 (2 C), 128.1 (4 C), 84.4, 65.2, 45.4 (2 C), 26.9 (3 C), 19.2.

HRMS (ESI): m/z calcd for $C_{22}H_{24}N_2O_3Si$ + Na $[M + Na]^+$: 415.1448; found: 415.1457.

5-(*tert*-Butyldiphenylsilyloxy)-2-hydroxy-2-(2-oxo-2-phenylethyl)cyclohexane-1,3-dione (22)
The α-diazo-β-dicarbonyl compound **20** (100 mg, 255 μmol) was dissolved in a DMDO solution (DMDO in acetone) (9.10 mL, 637 μmol) and stirred for 12 h at r.t. The solvent was removed and the product dried for 24 h under reduced pressure to give the crude hydrate **21** as a pink foam. Hydrate **21** was dissolved in anhydrous MeCN (2 mL) and α-(4-morpholino)styrene (**14**;[16] 74.8 mg, 395 μmol) in anhydrous MeCN (1.5 mL) was slowly added. The reaction mixture was stirred at r.t. for 2.5 h. Aq HCl (0.2 M, 20 mL)

was added to the mixture and the aqueous layer was extracted with Et_2O (4 × 10 mL). The combined organic layers were washed with brine (20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give **22** (102 mg, 203 μmol, 80%) as an orange oil. The yield was calculated by NMR analysis; R_f = 0.66 (pentane–EtOAc, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93–7.87 (m, 2 H), 7.75–7.61 (m, 7 H), 7.47–7.32 (m, 6 H), 4.52 (s, 1 H), 4.42–4.36 (m, 1 H), 3.65 (s, 2 H), 3.01 (dd, *J* = 14.1, 2.9 Hz, 2 H), 2.92 (dd, *J* = 14.1, 3.7 Hz, 2 H), 1.00 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.4 (2 C), 196.8, 136.3, 135.9 (4 C), 134.0, 132.5 (2 C), 130.3 (2 C), 128.8 (2 C), 128.8 (2 C), 128.0 (4 C), 86.3, 65.3, 45.7 (2 C), 45.2, 26.8 (3 C), 19.2.

HRMS (ESI): *m*/*z* calcd for $C_{30}H_{32}O_5Si$ + Na $[M + Na]^+$: 523.1911; found: 523.1909.

6-(*tert*-Butyldiphenylsilyloxy)-2-phenyl-3a,7a-bis(trimethylsilyloxy)-5,6,7,7a-tetrahydrobenzofuran-4(3a*H*)-one (23)

Aldol **22** (116 mg, 232 μmol) was dissolved in anhydrous CH_2Cl_2 (5 mL) and cooled to 0 °C. First 2,6-lutidine (110 μL, 926 μmol) and then Me_3SiOTf (80.0 μL, 463 μmol) were added dropwise to the cooled solution. The reaction mixture was warmed up to r.t. and stirred for 12 h. Sat. aq $NaHCO_3$ (20 mL) was added and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (20 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (pentane–EtOAc, 100:3) to give **23** (89.0 mg, 138 μmol, 60%) as a white foam; R_f = 0.22 (pentane–EtOAc, 100:2).

IR (ATR, neat): 3066 (w), 2957 (w), 2898 (w), 2859 (w), 1723 (m), 1642 (w), 1583 (w), 1452 (w), 1426 (w), 1386 (w), 1311 (w), 1251 (m), 1197 (m), 1133 (m), 1084 (s), 1053 (m), 995 (w), 919 (s), 896 (m), 839 (s), 736 (s), 698 (s), 612 (w), 503 (m), 400 cm^{-1} (w).

^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.60–7.57 (m, 2 H), 7.56–7.52 (m, 2 H), 7.41–7.37 (m, 2 H), 7.36–7.32 (m, 5 H), 7.31–7.24 (m, 4 H), 5.00 (s, 1 H), 4.17–4.10 (m, 1 H), 2.82 (ddd, *J* = 18.0, 7.0, 2.0 Hz, 1 H), 2.50–2.44 (m, 2 H), 1.98 (dd, *J* = 13.3, 11.3 Hz, 1 H), 1.03 (s, 9 H), 0.16 (s, 9 H), 0.15 (s, 9 H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ = 206.2, 158.8, 136.1 (2 C), 136.0 (2 C), 134.0, 133.9, 130.3, 130.2, 130.2, 129.5, 128.8 (2 C), 128.1 (2 C), 128.0 (2 C), 126.2 (2 C), 108.9, 98.5, 90.6, 63.6, 48.0 (2 C), 47.7 (2 C), 27.1 (3 C), 19.3, 2.6 (3 C), 1.7 (3 C).

HRMS (EI): *m*/*z* calcd for $C_{36}H_{48}O_5Si_3$ $[M]^+$: 644.2810; found: 644.2796.

6-[(6-(*tert*-Butyldiphenylsilyloxy)-4-hydroxy-2-phenyl-3a,7a-bis(trimethylsilyloxy)-3a,4,5,6,7,7a-hexahydrobenzofuran-4-yl)methyl]-4-methoxy-2*H*-pyran-2-one (24)

LDA was prepared freshly by slowly adding *n*-BuLi (1.6 M in THF) (1.61 mL, 2.57 mmol) to a solution of *i*-Pr_2NH (0.41 mL, 2.92 mmol) in anhydrous THF (8.5 mL) at –78 °C. The solution was stirred 15 min at –78 °C and then 5 min at r.t., and then cooled to –78 °C. Methylpyrone **6**[18] (369 mg, 2.63 mmol) in anhydrous THF (10 mL) was slowly added to the LDA solution at –78 °C. The reaction mixture was stirred 25 min at –78 °C. A solution of enol silyl acetal **23** (404 mg, 0.63 mmol) in anhydrous THF (8.5 mL) was slowly added to the mixture at –78 °C and stirred for 20 min at this temperature. Sat. aq NH_4Cl (20 mL) was added to the mixture with subsequent stirring for 5 min at r.t. The aqueous layer was extracted with CH_2Cl_2 (5 × 15 mL) and the combined organic layers were washed with brine (25 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product purified by flash chromatography on silica gel (pentane–EtOAc, 3:1 to 2:1) to give **24** (254 mg, 322 μmol, 51%) with a dr of 5.9:1 as a white foam; R_f = 0.69 (pentane–EtOAc, 1:1).

IR (ATR, neat): 3066 (w), 2957 (w), 2897 (w), 2859 (w), 1724 (m), 1646 (w), 1569 (w), 1454 (w), 1420 (w), 1314 (w), 1250 (m), 1196 (w), 1135 (w), 1102 (m), 997 (w), 919 (m), 897 (m), 842 (s), 740 (m), 699 (s), 613 (w), 545 (w), 505 (w), 405 cm^{-1} (w).

^{1}H NMR (300 MHz, CD_2Cl_2): δ (*cis*-isomer) = 7.59–7.55 (m, 2 H,), 7.55–7.52 (m, 2 H,), 7.38–7.23 (m, 11 H,), 5.94 (d, *J* = 2.3 Hz, 1 H), 5.42 (d, *J* = 2.3 Hz, 1 H), 5.07 (s, 1 H), 3.97–3.90 (m, 1 H), 3.82 (s, 3 H), 3.04 (d, *J* = 1.9 Hz, 1 H), 2.86 (d, *J* = 14.0 Hz, 1 H), 2.65 (t, *J* = 11.9 Hz, 1 H), 2.45 (d, *J* = 13.9 Hz, 1 H), 2.24 (dd, *J* = 12.2, 4.9 Hz, 1 H), 1.92 (ddd, *J* = 15.0, 8.4, 2.0 Hz, 1 H), 1.83 (dd, *J* = 15.0, 5.7 Hz, 1 H), 0.99 (s, 9 H), 0.17 (s, 9 H,), 0.11 (s, 9 H); δ (*trans*-isomer) = 7.68–7.59 (m, 4 H), 7.48–7.28 (m, 11 H), 5.80 (d, *J* = 2.2 Hz, 1 H), 5.40 (d, *J* = 2.2 Hz, 1 H), 5.35 (s, 1 H), 4.21–4.08 (m, 1 H), 3.80 (s, 3 H), 2.76 (d, *J* = 14.5 Hz, 1 H), 2.64 (d, *J* = 14.5 Hz, 1 H), 2.49 (dd, *J* = 13.8, 5.1 Hz, 1 H), 2.02–1.95 (m, 1 H), 1.95–1.76 (m, 2 H), 1.06 (s, 9 H), 0.16 (s, 9 H), 0.08 (s, 9 H).

^{13}C NMR (125 MHz, CD_2Cl_2): δ (*cis*-isomer) = 171.4, 164.9, 162.9, 158.5, 136.1 (2 C), 136.0 (2 C), 134.5, 134.3, 130.0 (2 C), 130.0, 129.9, 128.7 (2 C), 128.0 (2 C), 127.9 (2 C), 126.1 (2 C), 109.4, 103.1, 97.0, 88.1, 87.8, 78.2, 65.1, 56.3, 43.8, 43.1, 40.2, 27.1 (3 C), 19.3, 2.2 (3 C), 2.1 (3 C); δ (*trans*-isomer) = 171.3, 164.7, 163.2, 157.2, 136.2 (2 C), 136.1 (2 C), 134.8, 134.6, 130.3, 130.0, 130.0, 129.8, 128.7 (2 C), 128.0 (2 C), 127.9 (2 C), 125.9 (2 C), 109.6, 103.2, 99.0, 89.2, 88.0, 76.9, 65.4, 56.3, 43.9, 43.0, 39.7, 27.2 (3 C), 19.4, 2.4 (3 C), 2.1 (3 C).

HRMS (EI): *m*/*z* calcd for $C_{43}H_{56}O_8Si_3$ $[M]^+$: 784.3283; found: 784.3270.

9-*epi*-Wailupemycin A (25)

Alcohol **24** (25.0 mg, 32.0 μmol) was dissolved in THF (0.4 mL) and a solution of TBAF (1.0 M in THF, 0.19 mL, 191 μmol) and AcOH (0.04 mL, 732 μmol) were added dropwise. After stirring for 3 h at r.t., sat. aq NH_4Cl (20 mL) was added. The aqueous layer was extracted with $CHCl_3$ (5 × 10 mL) and the combined organic layers were washed with phosphate puffer (pH 7) and brine (10 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product purified by flash chromatography on silica gel (EtOAc) to give **25** (11.0 mg, 27.3 μmol, 85%) as a white solid; mp 175 °C; R_f = 0.29 (EtOAc).

IR (ATR, neat): 3355 (w), 2924 (w), 2853 (w), 1723 (m), 1687 (s), 1636 (m), 1557 (s), 1454 (m), 1411 (m), 1356 (w), 1319 (w), 1252 (s), 1206 (m), 1145 (m), 1093 (w), 1063 (w), 1033 (m), 996 (w), 939 (w), 906 (w), 862 (w), 819 (w), 747 (w), 686 (m), 640 (w), 600 (w), 548 (m), 493 (w), 409 cm^{-1} (w).

^{1}H NMR (500 MHz, CD_3CN): δ = 8.02–7.97 (m, 2 H), 7.66–7.61 (m, 1 H), 7.54–7.49 (m, 2 H), 6.00 (d, *J* = 2.2 Hz, 1 H), 5.46 (d, *J* = 2.2 Hz, 1 H), 4.38–4.32 (m, 2 H), 4.02 (d, *J* = 1.4 Hz, 1 H), 3.85 (d, *J* = 16.6 Hz, 1 H), 3.81 (s, 3 H), 3.73 (d, *J* = 7.8 Hz, 1 H), 3.49 (dd, *J* = 16.6, 1.1 Hz, 1 H), 3.12 (dd, *J* = 13.5, 4.5 Hz, 1 H), 2.92 (d, *J* = 14.2 Hz, 1 H), 2.81 (d, *J* = 14.2 Hz, 1 H), 2.65 (dt, *J* = 13.5, 2.6 Hz, 1 H), 2.29 (ddd, *J* = 15.6, 3.7, 1.5 Hz, 1 H), 2.20 (dt, *J* = 15.6, 2.6 Hz, 1 H).

^{13}C NMR (125 MHz, CD_3CN): δ = 209.0, 198.5, 172.2, 165.1, 162.6, 138.0, 134.6, 129.7 (2 C), 129.5 (2 C), 104.0, 88.6, 83.2, 82.9, 70.5, 57.0, 46.8, 43.9, 40.7, 38.0.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{22}O_8$ + Na $[M + Na]^+$: 425.1207; found: 425.1206.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(13) The crystal data of compound **11** has been deposited in the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 957231. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or by writing to the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk.
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(20) The crystal data of compound **25** has been deposited in the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 957232.

