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A stereoconvergent synthesis of the C(19)–C(31) fragment of scytophycin C†

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Abstract—The C(19)–C(31) fragment of the anti-tumor macrolide, scytophycin C, was realized in a stereoconvergent manner utilizing a desymmetrization approach to create eight contiguous asymmetric centers from a common precursor.

Moore et al. in 1986[1] first reported the isolation of a novel class of polyoxygenated 22-membered macrolides, scytophycins A–E from the cultured terrestrial blue-green alga *Scytonema pseudohofmanni* (Fig. 1). Structurally, scytophycins are closely related to swinholides, a group of 44-membered dimeric macrolides from *Theonella swinhoei*.[2] They have exhibited potent cytotoxicity against a variety of human carcinoma cell lines, as well as broad-spectrum antifungal activity. They act as cytotoxic agents by microfilament depolymerization[3a] and have been shown to circumvent P-glycoprotein medicated multi drug resistance in tumor cells,[3b] which gives them therapeutic potential for cancer patients.

To date, an elegant total synthesis of scytophycin C has been reported by Paterson.[4] Other approaches deal with selective syntheses of important fragments.[5]

As a part of our ongoing interest in the synthesis of biologically active molecules, especially anti-tumor agents,[6] our attention was drawn towards synthetic studies of this novel class of macrolide (Scheme 1)

The details of our approach towards the synthesis of scytophycin C are depicted in Scheme 1. A closer survey reveals two major fragments C(1)–C(18) and C(19)–C(31). Herein we report a stereoconvergent synthesis of the C(19)–C(31) fragment. This fragment is further broken into two smaller fragments, i.e. C(19)–C(25) and C(26)–C(31). They can be derived from a common precursor **7** which in turn is easily synthesized.[6a,c] The relative stereochemistry at C(2) and C(4) of the precursor **7** can be correlated to C(22), C(24), C(28) and C(30) of scytophycin C. The bicyclic compound **7** has five stereogenic centers and two prostereogenic sp^2 sites

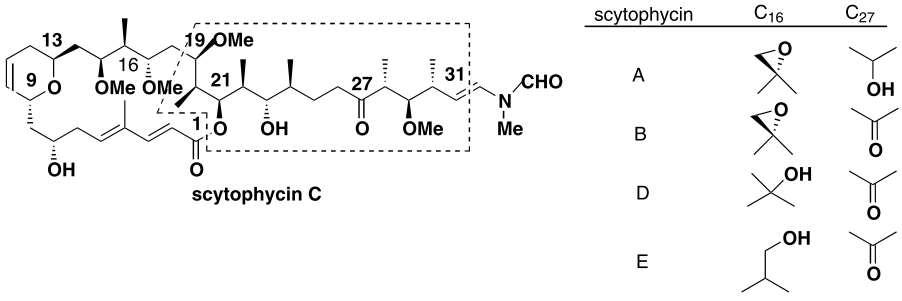

Figure 1.

Keywords: scytophycin C; common precursor; desymmetrization; stereoconvergent.

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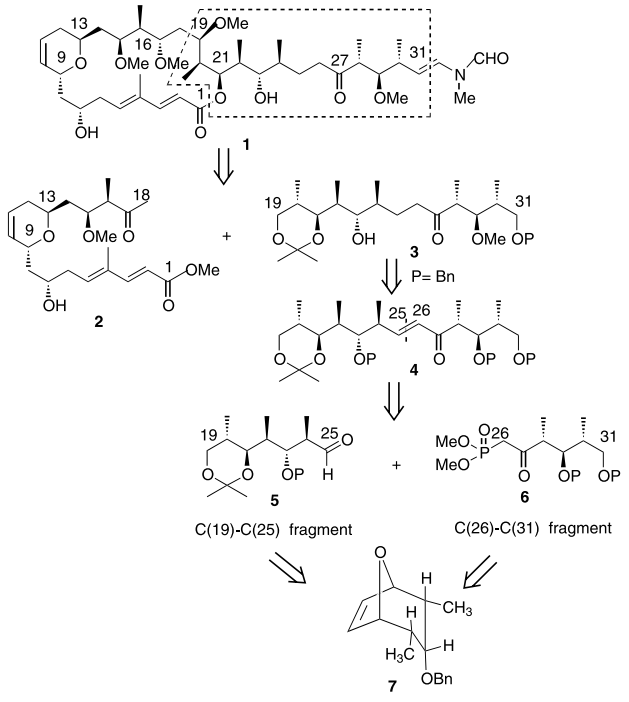
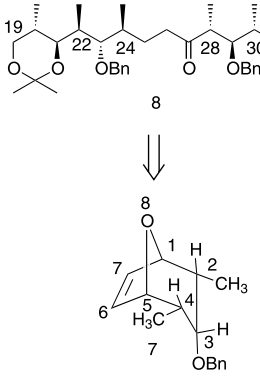


Scheme 1.

which can be used for further functionalization (Scheme 2).

Synthesis of the C(19)–C(25) fragment

We initiated our synthesis from precursor **7**, which we had developed and utilized for a synthesis of rifamycin-S[6a] and (+)-discodermolide[6c] fragments wherein we had exploited the desymmetrization approach to create six stereogenic centers at once. For the synthesis of the C(19)–C(25) fragment of scytophycin C, we prepared the triol **9** by an earlier reported method.[6a] The stereocenters of the triol **9** were firmly established on the basis of our earlier report.[6a] The physical and spectroscopic data were found to be identical in all respects with those reported for the C(19)–C(27) fragment of rifamycin-S.[6a] The resultant triol **9** was converted with 2,2-dimethoxypropane–CSA (cat.) into acetonide **10** (92%) which constituted the main precursor for the C(19)–C(25) fragment. The alcohol **10** was oxidized to aldehyde **5**[7] (90%) using IBX in DMSO–THF, see Scheme 3.



Scheme 2.

Synthesis of the C(26)–C(31) fragment

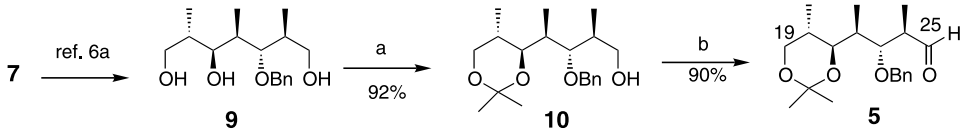
Asymmetric hydroboration of olefin **7** using (–)-diisopinocamphenylborane gave the optically pure alcohol **11** (96%). Using the two-step sequence (PCC, B.V. oxidation), alcohol **11** was converted into the lactone **12** (76%) in high optical purity.

The bicyclic lactone **12** was opened reductively with $LiAlH_4$ to give the triol **13** (92%), the stereocenters of the triol **13** were confirmed in the same way as for fragment **9**. Triol **13** was converted into the acetonide **14** (95%). The free hydroxyl moiety of **14** was protected as its benzyl ether using NaH and BnBr to give the benzyl ether **15** (98%). The acetonide protection of **15** was cleaved with 2N HCl in THF–H_2O to give the diol **16** (95%). The diol **16** was oxidatively cleaved by $RuCl_3{\cdot}3H_2O/NaIO_4$ and the resultant acid was esterified with diazomethane to yield the ester **17** (60%) over two steps. The ester **17** was converted into the phosphonate **6**[8] (70%) by treatment with dimethyl methane phosphonate and *n*-BuLi. With this we have completed the synthesis of the required β-ketophosphonate, i.e. the C(26)–C(31) fragment (Scheme 4).

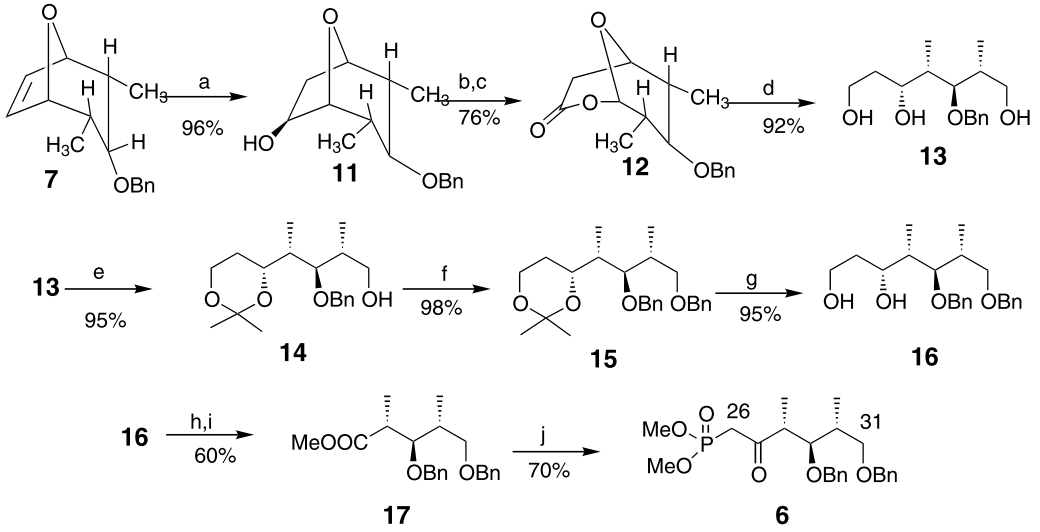
Barium hydroxide induced HWE reaction-synthesis of the C(19)–C(31) fragment

The key factor in realizing the successful synthesis of the C(19)–C(31) fragment was to achieve an efficient Horner–Wadsworth–Emmons coupling between the sterically hindered aldehyde **5** and the β-ketophosphonate **6**, as reported by Paterson.[9] Accordingly β-ketophosphonate **6** was treated with activated $Ba(OH)_2$ in THF followed by addition of the aldehyde **5** in wet THF, to realize the desired (*E*)-enone **4** in a 95% yield.[10] The double bond in (*E*)-enone **4** was selectively reduced by $LiAlH_4$/CuI in THF as reported by Ashby[11] to furnish the desired C(19) to C(31) fragment **8** (80%)[12] (Scheme 5).

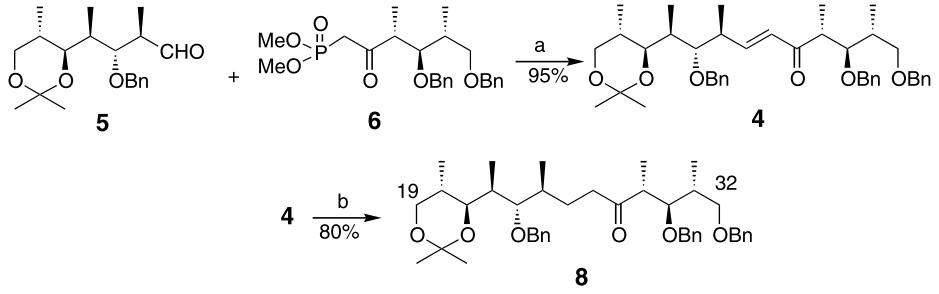
In conclusion, this highly stereospecific synthesis of the C(19)–C(31) fragment illustrates the dynamic utility of the precursor **7**, and the desymmetrization approach to control the eight required stereocenters to yet another



Scheme 3. *Reagents and conditions*: (a) 2,2-DMP, CSA (cat.), CH_2Cl_2, 25°C, 1 h; (b) IBX, DMSO–THF, 25°C, 2 h.



Scheme 4. *Reagents and conditions*: (a) (–)-Ipc_2BH, –23°C, 24 h, 3N NaOH, 30% H_2O_2, 25°C, 6 h; (b) PCC, CH_2Cl_2, 25°C, 3 h; (c) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 25°C, 10 h; (d) $LiAlH_4$, THF, 0→25°C, 4 h; (e) 2,2-DMP, CSA (cat.), CH_2Cl_2, 25°C, 1 h; (f) NaH, BnBr, THF, reflux, 3 h; (g) 2N HCl, THF/H_2O, 25°C, 1 h; (h) $RuCl_3{\cdot}3H_2O$, $NaIO_4$, 1:1:3 CH_3CN:CCl_4:H_2O, 25°C, 1 h; (i) CH_2N_2 in ether, 0°C, 15 min; (j) $(MeO)_2$ P(O)Me, *n*-BuLi, THF, –78°C, 1 h.



Scheme 5. *Reagents and conditions*: (a) $Ba(OH)_2{\cdot}8H_2O$, 40:1 THF/H_2O, 25°C, 1 h; (b) $LiAlH_4$/CuI, THF, 0→25°C, 30 min.

important fragment of a biologically active molecule. Further studies towards the preparation of the C(1)–C(18) fragment of scytophycin C, leading to its total synthesis are on-going.

Acknowledgements

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7. Data for compound **5**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.70 (3H, d, $J=6.67$ Hz), 0.81 (3H, d, $J=6.67$ Hz), 1.1 (3H, d, $J=6.67$ Hz), 1.30 (6H, s), 1.79–2.01 (3H, m), 2.62–2.75 (1H, m), 3.40–3.52 (1H, m), 3.62–3.79 (2H, m), 4.59 (2H, ABq), 7.29 (5H, m), 9.79 (1H, s); $[\alpha]_D^{25}$ +2.89 (*c* 1.8, $CHCl_3$); IR (liquid film) 2825, 1735 cm^{-1}; FABMS *m*/*z* 335 (M^++H). Anal. calcd for $C_{20}H_{30}O_4$: calcd: C, 71.82; H, 9.04. Found: C, 71.93; H, 9.19%.
8. Data for compound **6**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.05 (3H, d, $J=6.33$ Hz), 1.1 (3H, d, $J=6.33$ Hz), 1.7 (1H, m), 2.1 (1H, m), 2.9–3.05 (1H, m), 3.15–3.3 (1H, m), 3.4 (1H, m), 3.6 (1H, buried m's), 3.65 (3H, s), 3.7 (3H, s), 3.75 (1H, buried m's), 4.42 (2H, buried ABq), 4.5 (2H, s), 7.25 (10H, m); $[\alpha]_D^{20}$ −28.34 (*c* 0.6, $CHCl_3$); IR (liquid film): 1720, 1417, 1269, 1035 cm^{-1}; FABMS *m*/*z* 471 (M^++Na), 341 (M^+−107). Anal. calcd for $C_{24}H_{33}O_6P$: calcd: C, 64.27; H, 7.42. Found: C, 64.35; H, 7.43%.
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10. Data for compound **4**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.58 (3H, d, $J=6.9$ Hz), 0.67 (3H, d, $J=6.9$ Hz), 0.85 (3H, d, $J=6.9$ Hz), 1.05 (3H, d, $J=6.9$ Hz), 1.12 (3H, d, $J=6.9$ Hz), 1.3 (6H, s), 1.5–1.7 (3H, m), 2.02–2.19 (1H, m), 2.5–2.7 (1H, m), 3.19–3.33 (1H, m), 3.35–3.5 (3H, m), 3.59–3.79 (2H, m), 3.8–3.9 (1H, m), 4.4–4.62 (6H, m), 6.2 (1H, d, $J=15.4$ Hz), 7.0 (1H, dd, $J=7.69$, 15.38 Hz), 7.19–7.39 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.13, 148.69, 139.02, 138.79, 138.73, 130.31, 128.31, 128.23, 128.14, 127.74, 127.66, 127.52, 127.45, 127.34, 127.29, 126.98, 126.87, 126.84, 126.78, 97.98, 84.59, 84.43, 83.35, 73.39, 73.23, 73.12, 72.03, 66.23, 39.93, 37.65, 36.89, 36.19, 36.04, 30.18, 19.54, 17.60, 13.95, 12.41, 12.34, 11.42; $[\alpha]_D^{25}$ −31.34 (*c* 0.6, $CHCl_3$); IR (liquid film): 1685, 1670, 1630, 1005 cm^{-1}; FABMS *m*/*z* 657 (M^++H). Anal. calcd for $C_{42}H_{56}O_6$: calcd: C, 76.79; H, 8.59. Found: C, 76.75; H, 8.63%.
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12. Data for compound **8**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.65 (3H, d, $J=6.4$ Hz), 0.8 (3H, d, $J=6.1$ Hz), 0.85 (3H, d, $J=6.1$ Hz), 1.05 (3H, d, $J=6.4$ Hz), 1.22 (3H, d, $J=6.4$ Hz), 1.17–1.28 (2H, overlapping m's), 1.3 (6H, s), 1.8–196 (3H, m), 2.0–2.1 (1H, m), 2.3–2.45 (1H, m), 2.6–2.8 (1H, m), 2.85–2.96 (1H, m), 3.3–3.5 (5H, m), 3.55–3.7 (1H, m), 3.8–3.95 (1H, m), 4.45–4.65 (6H, m), 7.2–7.39 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.14, 139.25, 138.99, 138.87, 128.45, 128.36, 128.24, 127.89, 127.67, 127.63, 127.55, 127.39, 127.21, 126.88, 126.76, 126.71, 126.68, 97.78, 84.51, 84.33, 83.25, 74.39, 73.23, 73.17, 73.09, 70.13, 45.29, 38.33, 37.87, 36.89, 36.29, 36.04, 32.49, 30.27, 19.45, 18.66, 14.37, 13.95, 12.13, 10.95; $[\alpha]_D^{25}$ −29.31 (*c* 1.3, $CHCl_3$); IR (liquid film): 1720, 1455, 1096 cm^{-1}; FABMS *m*/*z* 659 (M^++H). Anal. calcd for $C_{42}H_{58}O_6$: calcd: C, 76.56; H, 8.87. Found: C, 76.67; H, 8.69%.