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Studies in Marine Macrolide Synthesis: A Stereocontrolled Synthesis of a C_{17}–C_{32} Subunit of Scytophycin C.

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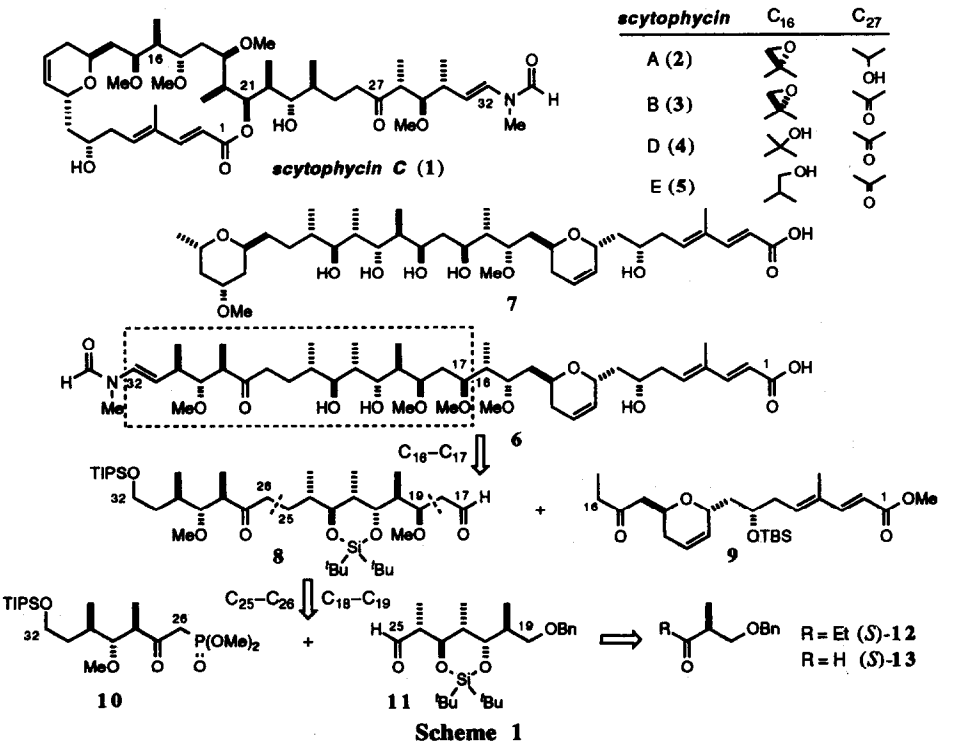
Abstract: The C_{17}–C_{32} subunit **8** of scytophycin C was prepared in 11 steps (19% yield, 83% ds) from (*S*)–**12**. Key features include the dipropionate aldol construction of the stereopentad **11**, the Brown asymmetric crotylboration leading to **10**, followed by their $Ba(OH)_2$-induced, Horner-Emmons coupling to give **23**, and the $BF_3{\cdot}OEt_2$-promoted allylation, **25** → **26**.

Scytophycins A–E, isolated from the blue green alga *Scytonema pseudohofmanni*, were first reported by Moore *et al.* in 1986.[1] They exhibit potent cytotoxicity against KB cells at 1 ng/ml and broad spectrum antifungal activity. Spectroscopic and X-ray crystallographic analysis indicated that the scytophycins were a novel series of 22-membered macrolides (**1**–**5** in **Scheme 1**), differing in substitution at C_{16} and C_{27}, with a C_{21} side-chain terminating in an *N*-methylformamide group. They have a close structural homology with the swinholides,[2] a group of 44-membered dimeric macrodiolides from *Theonella swinhoei*, as shown by comparing the secoacids **6** and **7** of scytophycin C and swinholide A, respectively.



Scheme 1

As part of our synthetic studies towards these bioactive marine macrolides,[3] we now report the enantiocontrolled synthesis of the C_{17}–C_{32} subunit **8** of the secoacid **6** of scytophycin C. In the accompanying Letter,[3c] we describe the synthesis of the corresponding C_1–C_{16} subunit **9**.

Scheme 1 summarises our strategy for the synthesis of scytophycin C through **6**, involving an aldol coupling between the aldehyde **8** and the ethyl ketone **9** to form the C_{16}–C_{17} bond. An alternative strategy (not shown) is based on a C_{15}–C_{16} disconnection, *i.e.* reversing the aldehyde and ethyl ketone aldol components. These two interrelated approaches offer flexibility in the choice of a suitable diastereoselective aldol reaction for the final fragment coupling. The C_{17}–C_{32} segment **8** was anticipated to arise from a Horner-Emmons coupling between the ketophosphonate **10** and the aldehyde **11**. The latter should be attainable using our general synthetic approach[4] to such stereopentads[4b]; in this case, by starting from the ketone (*S*)-**12**. The ketophosphonate **10** should be available from the aldehyde (*S*)-**13** by an asymmetric crotylboration. These starting materials are prepared[4d,f] from the commercially available (*S*)-(+)-methyl 2-methyl-3-hydroxypropionate.

The synthesis of the C_{17}–C_{32} segment **8** from (*S*)-1-benzyloxy-2-methyl-3-pentanone (**12**)[4d,f] is shown in **Scheme 2** and outlined below. Aldol addition of the derived (*E*)-enol dicyclohexylborinate **14** to methacrolein gave the *anti-anti* adduct[4e] **15** in 81% yield and 98% ds. The ketone **15** was reduced with $Me_4NBH(OAc)_3$ to the corresponding 1,3-*anti* diol[5] **16** (94% ds), which was then converted to its di-*tert*-butylsilylene derivative **17**[6] by reaction with $^tBu_2Si(OTf)_2$/lutidine in 86% overall yield. The C_{24} stereocentre was next introduced by hydroboration of **17** using 9-BBN, followed by oxidative workup, to give **18**, $[\alpha]_D^{20}$ = –21.3° (*c* 0.6, $CHCl_3$), in 61% yield with 93% ds.[7] Hence, the required stereopentad **18** was readily prepared from (*S*)-**12**, *using only substrate-induced stereocontrol*, in 4 steps with 86% overall ds. Subsequent Swern oxidation of **18** then gave the aldehyde **11**, $[\alpha]_D^{20}$ = –56.9° (*c* 0.4, $CHCl_3$), in 92% yield.

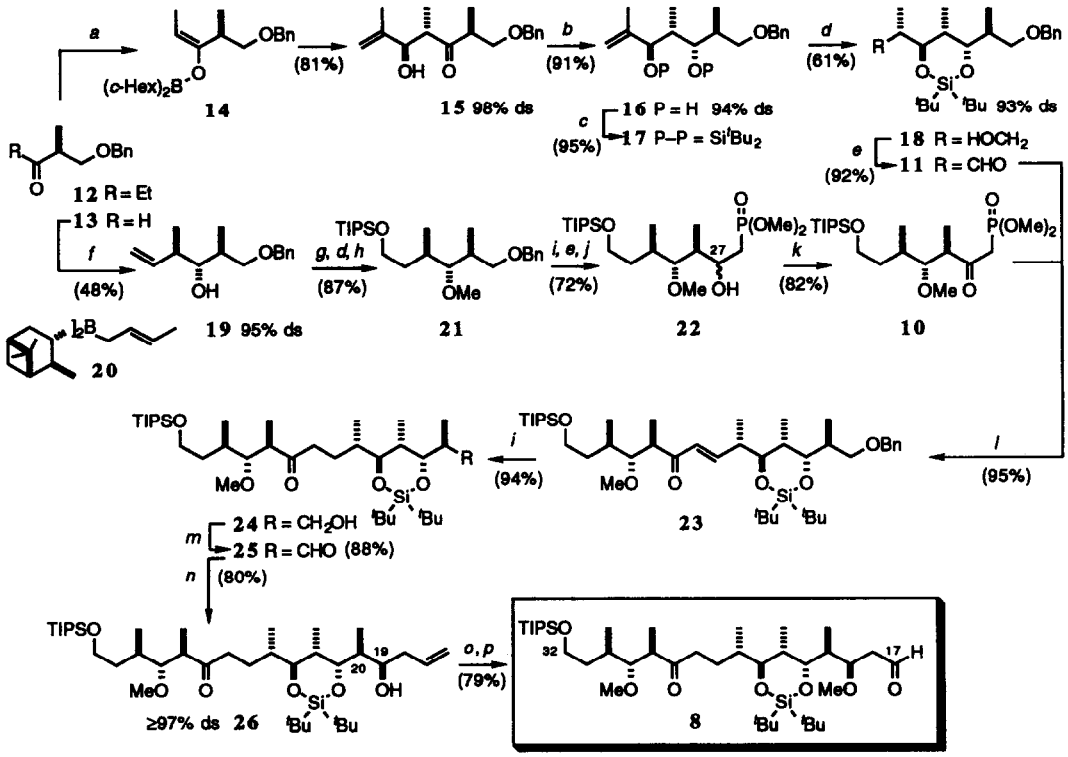
The *anti-anti* stereotriad spanning C_{27}–C_{31} in scytophycin C could be efficiently set up using Brown's asymmetric crotylboration reaction.[8] The homoallylic alcohol **19**,[8,9] synthesised with 95% ds by *anti* crotylboration of the aldehyde (*S*)-**13** with the (*E*)-crotyldiisopinocampheylborane **20**, was then further elaborated into the ketophosphonate **10**. *O*-Methylation, alkene hydroboration with oxidative workup, and *O*-silylation, first transformed **19** into the TIPS ether **21** in 87% yield. Debenzylation of **21**, followed by Swern oxidation, and addition of lithiated methyl dimethylphosphonate, then gave the β-hydroxyphosphonates **22** in 72% yield, as a 2:1 mixture of C_{27} epimers. Oxidation of **22** using PDC in DMF provided **10**, $[\alpha]_D^{20}$ = –59.5° (*c* 1.9, $CHCl_3$), in 82% yield.

The Horner-Emmons coupling[10] between **10** and **11** was investigated under a range of conditions. The use of strong bases like NaH led to competing epimerisation and elimination, while the milder Masamune-Roush[11a]/Rathke[11b] protocols (*e.g.* LiCl, $^iPr_2NEt$ or Et_3N, MeCN) either gave little or no reaction, or induced β-elimination in the aldehyde **11**. In contrast, $Ba(OH)_2{\cdot}8H_2O$ (0.8 equiv),[12] used with equimolar amounts of **10** and **11** in aqueous THF (20 °C, 3 h), promoted a clean Horner-Emmons reaction to give exclusively the (*E*)-enone **23**, $[\alpha]_D^{20}$ = –38.7° (*c* 0.7, $CHCl_3$), in 95% yield. Barium hydroxide appears to be generally useful[13] in promoting efficient Horner-Emmons reactions between complex, epimerisable aldehydes and ketophosphonates. We have since made use of these novel conditions in several demanding situations in macrolide and polyether fragment assembly.[14]

Catalytic hydrogenation of **23**, in the presence of 10% Pd/C, led to debenzylation and 1,4-reduction of the enone to give the alcohol **24**. Dess-Martin oxidation[15] of **24** then gave the aldehyde **25**, $[\alpha]_D^{20}$ = –58.3° (*c* 1.0, $CHCl_3$), in 88% yield, which was our pivotal intermediate for the synthesis of **8**. The remaining C_{19} stereocentre was set up by Lewis acid-promoted allylation of this aldehyde with Felkin-Anh control. The reaction of **25** with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$ gave the desired 19,20-*syn* adduct **26**, $[\alpha]_D^{20}$ = –28.9° (*c* 1.7, $CHCl_3$), with ≥97% ds in 80% yield. In contrast, the use of $TiCl_4$ led to much poorer diastereoselectivity, producing a 2:1 mixture of C_{19} epimers. *O*-Methylation of **26** with MeOTf/2,6-di-*tert*-butylpyridine[16] and ozonolysis finally afforded the desired aldehyde **8**,[6] $[\alpha]_D^{20}$ = –27.4° (*c* 0.6, $CHCl_3$), in 79% yield.

In summary, the C_{17}-C_{32} subunit **8** of scytophycin C has been synthesised in enantiomerically pure form by a highly convergent route in 11 steps (19% yield, 83% ds) from (*S*)-**12**. Five of the seven newly created stereocentres were installed by a series of substrate-controlled reactions: (*i*) the boron-mediated aldol

reaction, **12** → **15**, (*ii*) the reduction, **15** → **16**, (*iii*) the hydroboration, **17** → **18**, and (*iv*) the allylation, **25** → **26**; the remaining two relied on a single reagent-controlled reaction: the crotylboration, **13** + **20** → **19**. This work further demonstrates the general applicability of our systematic approach[4] to the stereocontrolled synthesis of polypropionate natural products. Further studies directed towards the total synthesis of scytophycin C *via* the aldol coupling of subunits **8** and **9**[3c] are underway.



Scheme 2 (*a*) (*c*-C_6H_{11})$_2$BCl, Et_3N, Et_2O, –15 °C, 2 h; H_2C=C(Me)CHO, 2 h; H_2O_2, MeOH-pH7 buffer; (*b*) $Me_4NBH(OAc)_3$, 1:1 MeCN-AcOH, –40 → –20 °C, 16 h; (*c*) ^{t}Bu$_2$Si(OTf)$_2$, 2,6-lutidine, CH_2Cl_2, 20 °C, 15 h; (*d*) 9-BBN, THF, 20 °C, 5–16h; H_2O_2/NaOH, 3 h; (*e*) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1 h; Et_3N, –78 → –25 °C, 1–2 h; (*f*) **20**, THF, –78 °C, 4 h; H_2O_2/NaOH, reflux, 18 h; (*g*) MeI, NaH, THF, 20 °C, 17 h; (*h*) TIPSCl, imidazole, CH_2Cl_2, 20 °C, 90 min; (*i*) H_2, Pd/C, EtOH, 20 °C, 3–6 h; (*j*) $(MeO)_2P(O)Me$, ^{n}BuLi, THF, –78 °C, 7 min; (*k*) PDC, DMF, 30 °C, 1 h; (*l*) $Ba(OH)_2$•$8H_2O$, 40:1 THF/H_2O, 20 °C, 3 h; (*m*) Dess-Martin periodinane, CH_2Cl_2, 20 °C, 35 min; (*n*) Me_3SiCH_2CH=CH_2, BF_3•Et_2O, CH_2Cl_2, –90 → –78 °C, 90 min; (*o*) MeOTf/2,6-di-*tert*-butylpyridine, $CHCl_3$, reflux, 2 h; (*p*) O_3, $NaHCO_3$, 3:1 CH_2Cl_2/MeOH, –78 °C; Me_2S, –78 → 20 °C, 3 h.

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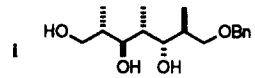
6. All new compounds gave spectroscopic data in agreement with the assigned structures. **23** had ^{1}H NMR δ (400 MHz, $CDCl_3$) 7.34-7.26 (5H, m, Ph), 7.00 (1H, dd, *J* = 15.9, 8.2 Hz, 25-CH), 6.17 (1H, d, *J* = 15.9 Hz, 26-CH), 4.52-4.43 (2H, ABq, $C\underline{H}_2Ph$), 3.87 (1H, dd, *J* = 9.6, 3.2 Hz, 21-CH), 3.79-3.62 (4H, m, 19-CH_A, 23-CH, 32-CH_2), 3.45 (1H, dd, *J* = 8.5, 6.9 Hz, 19-CH_B), 3.36 (1H, dd, *J* = 9.3, 2.0 Hz, 29-CH), 3.25 (3H, s, OMe), 3.10 (1H, qd, *J* = 9.3, 7.0 Hz, 28-CH), 2.50-2.42 (1H, m, 24-CH), 1.96-1.82 (3H, m, 20-CH, 22-CH, 30-CH), 1.73-1.65 (1H, m, 31-CH_A), 1.36-1.27 (1H, m, 31-CH_B), 1.11 (3H, d, *J* = 6.7 Hz, 24-CMe), 1.15-0.85 (3H, m, $(Me_2C\underline{H})_3Si$), 1.07-0.97 (6H, buried d's, 28-CMe, 30-CMe), 1.04 (18H, d, *J* = 4.3 Hz, $(\underline{Me}_2CH)_3Si$), 1.02 (9H, s, ^{t}BuSi), 0.99 (9H, s, ^{t}BuSi), 0.94 (3H, d, *J* = 7.0 Hz, 20-CMe or 22-CMe), 0.89 (3H, d, *J* = 6.8 Hz, 20-CMe or 22-CMe); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 204.0, 149.1, 138.8, 130.8, 128.2, 127.6, 127.3, 88.0, 82.1, 73.4, 73.1, 72.5, 61.3, 60.7, 45.5, 43.8, 36.9, 36.5, 33.1, 30.9, 28.2, 27.7, 22.1, 21.8, 18.0, 17.0, 16.2, 14.1, 13.8, 13.5, 11.9; HRMS (CI, NH_3) $(M+H)^+$ found 761.5570, $C_{44}H_{81}O_6Si_2$ requires 761.5571. **8** had ^{1}H NMR δ (400 MHz, $CDCl_3$) 9.84 (1H, t, *J* = 2.5 Hz, CHO), 4.36 (1H, m, 19-CH), 4.09 (1H, dd, *J* = 9.9, 2.5 Hz, 21-CH), 3.79-3.74 (1H, m, 32-CH_A), 3.69-3.63 (1H, m, 32-CH_B), 3.56 (1H, dd, *J* = 6.6, 2.4 Hz, 23-CH), 3.36-3.25 (1H, dd, 29-CH), 3.29 (3H, s, COMe), 3.28 (3H, s, COMe), 2.88-2.81 (1H, m, 28-CH), 2.88-2.76 (1H, m, 18-CH_A), 2.64-2.41 (3H, m, 18-CH_B, 26-CH_2), 1.96-1.60 (5H, m, 22-CH, 24-CH, 25-CH_A, 30-CH, 31-CH_A), 1.58-1.46 (2H, m, 20-CH, 25-CH_B), 1.38-1.25 (1H, m, 31-CH_B), 1.11-1.05 (3H, m, $(Me_2C\underline{H})_3Si$), 1.04 (18H, br s, ^{t}BuSi), 1.03 (18H, d, *J* = 5.2 Hz, $(\underline{Me}_2CH)_3Si$), 1.00 (3H, d, *J* = 6.9 Hz, $\underline{Me}CH$), 0.99 (3H, d, *J* = 7.1 Hz, $\underline{Me}CH$), 0.93 (3H, d, *J* = 7.0 Hz, $\underline{Me}CH$) 0.88 (3H, d, *J* = 6.6 Hz, $\underline{Me}CH$) 0.78 (3H, d, *J* = 6.8 Hz, $\underline{Me}CH$); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 214.8, 201.5, 88.5, 83.3, 73.9, 72.7, 61.3, 60.7, 57.1, 48.3, 46.8, 41.6, 41.4, 39.1, 35.2, 33.4, 31.0, 28.5, 27.6, 25.4, 22.2, 21.8, 18.0, 17.1, 15.6, 14.0, 13.7, 12.0, 8.8; HRMS (CI, NH_3) $(M+H)^+$ found 729.5520, $C_{40}H_{81}O_7Si_2$ requires 729.5521.

7. Removal of the silylene group in **19** gave the same major triol **i** as previously prepared (ref. 4b) by direct hydroboration of **16** with (+)-Ipc_2BH.



i

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9. The ^{13}C NMR and optical rotation, $[\alpha]_D^{20} = -12.2°$ (*c* 1.6, MeOH), of homoallylic alcohol **18** matched with those reported in ref. 8 by Brown *et al.*

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12. A mixture of ketophosphonate **10** (115.3 mg, 255 μmol) and $Ba(OH)_2.8H_2O$ (64.3 mg, 204 μmol) in THF (5 ml) was stirred at 20 °C for 30 min. A solution of aldehyde **11** (100.1 mg, 230 μmol) in wet THF (3 ml, 40:1 THF/H_2O) was then added. After 3 h, the reaction mixture was diluted with CH_2Cl_2 (30 ml), washed first with $NaHCO_3$ solution (10 ml, sat. aq.) and then brine (10 ml). The organic extracts were dried ($MgSO_4$) and the solvent evaporated *in vacuo*. Purification by flash chromatography (20% Et_2O/hexane) gave **23** (note 6) as a colourless oil (165.5 mg, 95%). This procedure was adapted from that described by: Alvarez-Ibarra, C.; Arias, S.; Banon, G.; Fernandez, M. J.; Rodriguez, M.; Sinisterra, V. *J. Chem. Soc., Chem. Commun.* **1987**, 1509.

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