# The Stereoselective Synthesis of the C6–C18 Fragment of Scytophycin C Employing a Novel Synthetic Methodology

Jhillu S. Yadav,* V. Sunitha, Basi V. Subba Reddy, E. Gyanchander

Division of Organic Chemistry-I, Indian Institute of Chemical Technology, Hyderabad 500007, India
Fax +91(40)27160512; E-mail: yadavpub@iict.res.in

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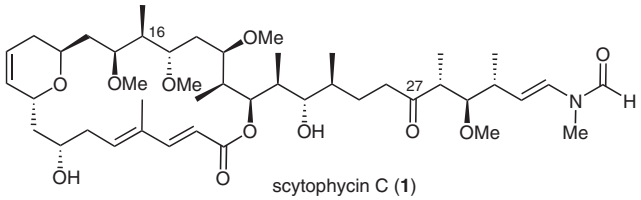
**Abstract:** A novel synthetic approach towards the stereoselective synthesis of the C6–C18 fragment of the biologically active antitumor agent scytophycin C is described. The synthesis involves Marouka allylation, base-catalyzed intramolecular conjugate addition, Wittig olefination, and a tandem allylation.

**Key words:** scytophycin, allylation, olefination, *trans*-2,6-disubstituted dihydropyran

The scytophycins, a group of highly functionalized polyoxygenated 22-membered macrolides isolated from the terrestrial blue-green algae *Scytonema pseudohofmanni*, were first reported by Moore et al. in 1986.[1] They exhibit potent cytotoxicity and antifungicidal activity.[2–4] Apart from scytophycin C (**1**), four related polyketide-derived[4] macrolides, scytophycins A, B, D, and E, were also isolated.[5] All the scytophycins (Figure 1) have a characteristic $C_{21}$ side chain terminating in an unusual *N*-methylformamide group, whereas scytophycins A–E differ from each other with regard to the substituents at C16 and C27. The potent cytotoxicity[6] associated with scytophycin C[7] and a closely related complex polyketide macrolide swinholide A[8] make these compounds attractive targets for synthetic organic chemists.

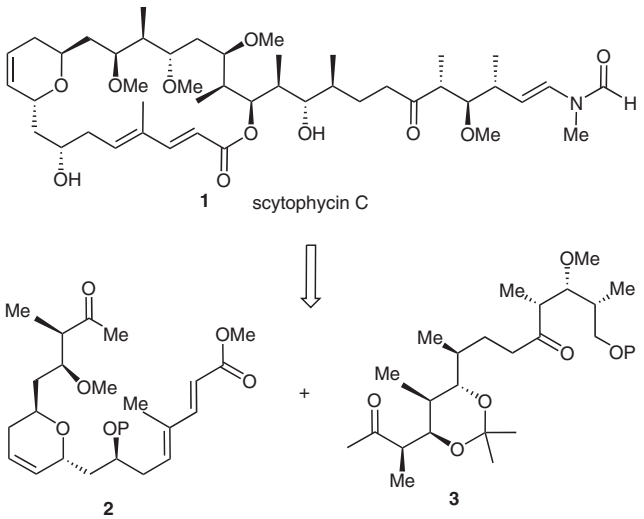



| Scytophycin | C16 | C 27 |
|---|---|---|
| A |  |  |
| B |  |  |
| D |  |  |
| E |  |  |

**Figure 1** Scytophycins A–E

Until now, an elegant total synthesis of scytophycin C has been reported by Paterson using stereoselective aldol reactions.[7a,9] The total synthesis of swinholide A has also been accomplished by Paterson and Nicolaou.[8a,10,11] The promising biological activity and its structural beauty make it an attractive synthetic target.

In continuation of our interest in the total synthesis of biologically active macrolide, scytophycin C,[12] we herein report a stereoselective synthesis of the C6–C18 fragment of scytophycin C. Retrosynthetic analysis of scytophycin C is outlined in Scheme 1.




**Scheme 1**

The natural product scytophycin C could be cleaved retrosynthetically into two fragments **2** and **3**. The synthesis of the C1–C18 fragment of scytophycin C **2** could be achieved via the stereoselective construction of a key intermediate **4**. The retrosynthesis of the C6–C18 fragment of scytophycin C **4** is depicted in Scheme 2.

The synthesis of fragment **4** began with the known aldehyde **9**, which was prepared using the literature procedure.[13] The aldehyde **9** was used as a precursor to introduce chirality at C15 by a catalytic asymmetric allylation. According to a recent report on the modified Keck allylation by Marouka et al., higher enantiomeric excess was observed.[14] Thus, the Marouka allylation of (*S*)-3-(benzyloxy)-2-methylpropanal (**9**) gave homoallylic alcohol **8**[15] in 78% yield with 95% de. Dihydroxylation of the alkene **8** and subsequent oxidation of the resulting diol

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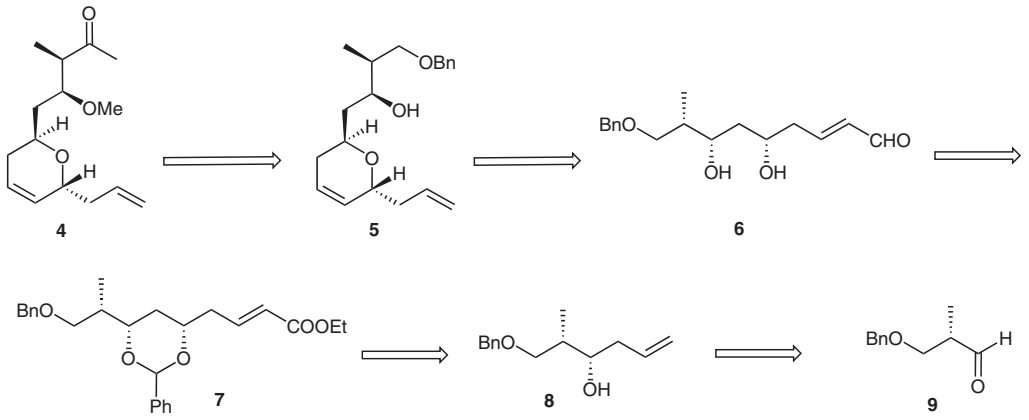


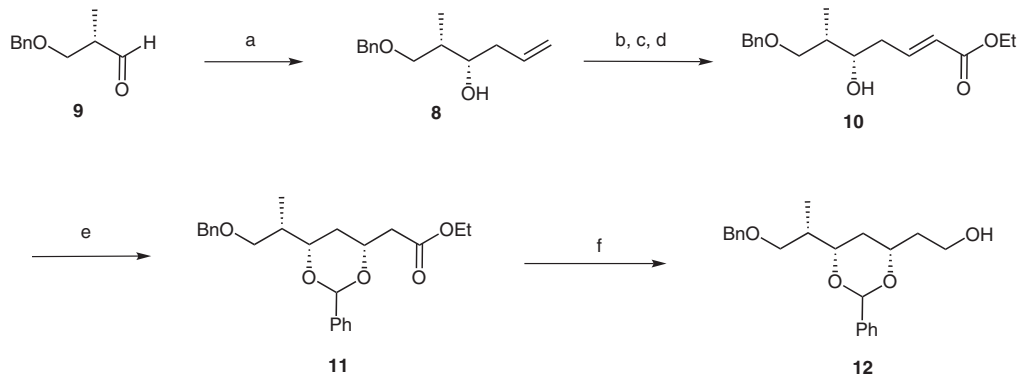

**Scheme 2**

with sodium periodate afforded a β-hydroxyaldehyde that was then subjected to Wittig olefination[16] with a stable ylide, (ethoxycarbonylmethylene)triphenylphosphorane, in benzene at room temperature to provide δ-hydroxy-α,β-unsaturated ester **10** (Scheme 3). Subsequent conversion of **10** into benzylidene acetal **11** was achieved in 70% yield with a diastereomeric ratio *syn*/*anti* 9:1 by base-catalyzed intramolecular conjugate addition[17] (oxy-Michael addition) using benzaldehyde and potassium *tert*-butoxide in tetrahydrofuran at 0 °C. The separation of the *syn*- and *anti*-isomers was achieved by column chromatography. The reduction of ester **11** with lithium aluminum hydride in tetrahydrofuran gave alcohol **12** in 90% yield (Scheme 3).

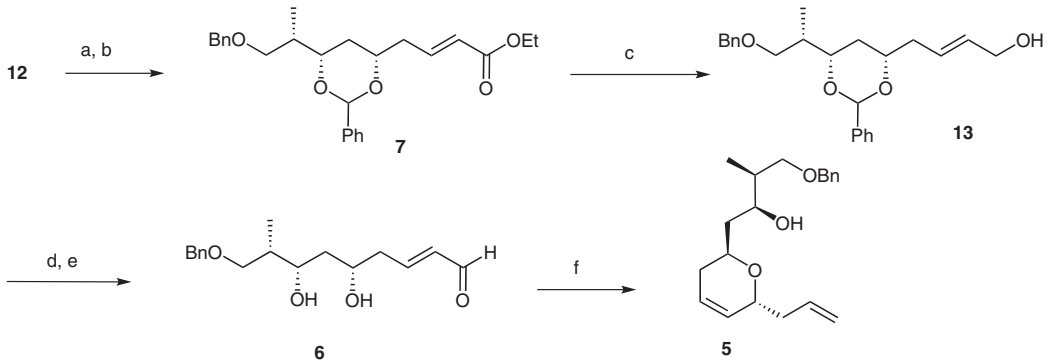
The alcohol **12** was oxidized with 2-iodoxybenzoic acid (IBX) in tetrahydrofuran–dimethyl sulfoxide at room temperature to give the corresponding aldehyde, which was treated with (ethoxycarbonylmethylene)triphenylphosphorane under Wittig conditions to afford the required (*E*)-ester derivative **7** in 92% yield. The ester **7** was reduced regioselectively to alcohol **13** using diisobutylaluminum hydride in dichloromethane at –78 °C. The hydrolysis of benzylidene acetal **13** using catalytic 4-toluenesulfonic acid in methanol gave the corresponding triol. The rate of hydrolysis of the benzylidene acetal was very slow and required a long reaction time. The regioselective oxidation of the triol using manganese(IV) oxide in dichloromethane gave the key intermediate **6**, a δ-hydroxy-α,β-unsaturated aldehyde, which was immediately converted into the *trans*-2,6-disubstituted 3,6-dihydropyran **5** using novel methodology recently developed in our laboratory (Scheme 4).[18]

The formation of the *trans*-2,6-disubstituted dihydropyran ring is the key step, which typically involves the Lewis acid catalyzed and nucleophile-induced tandem cyclization of a δ-hydroxy-α,β-unsaturated aldehyde. This tandem approach was utilized to introduce chirality at C9. Accordingly, treatment of δ-hydroxy-α,β-unsaturated aldehyde **6** with allyltrimethylsilane in the presence of 10 mol% of indium(III) bromide in dichloromethane at room temperature gave *trans*-2,6-disubstituted dihydropyran **5** in 83% yield with a diastereomeric ratio *cis*/*trans* 2:8. The separation of the *cis*- and *trans*-isomers was achieved by column chromatography. $^1$H NMR spectra revealed the presence of olefinic protons at δ = 5.94–5.69 and 5.21–5.01 as multiplets. A signal for the C9 proton appeared at δ = 4.32–4.24 as multiplet and also a signal for the C13 proton appeared at δ = 4.01–3.88 as a multiplet. The presence of allylic protons between δ = 2.54–1.97 confirmed the structure of compound **5**.

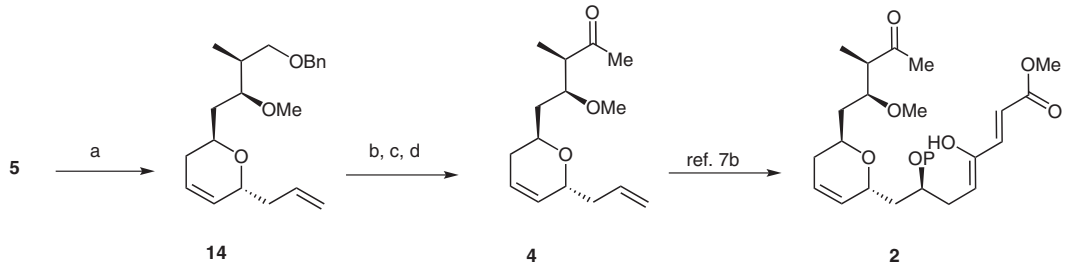
The secondary hydroxy group in compound **5** was protected as its methyl ether using sodium hydride and methyl iodide in dry tetrahydrofuran to give **14** in 92% yield. Deprotection of the benzyl group in **14** using lithium and




**Scheme 3** *Reagents and conditions*: (a) $TiCl_4$, $Ti(O\textit{i}\text{-}Pr)_4$, (*R*)-BINOL, $Ag_2O$, 12 h, –15 to 0 °C, 78%, 95% de; (b) $OsO_4$, NMO, acetone–$H_2O$; (c) $NaIO_4$, THF, $H_2O$, r.t.; (d) $Ph_3P{=}CHCO_2Et$, benzene, r.t., 4 h, 85%; (e) PhCHO, *t*-BuOK, 0 °C, 2 h, 70%; (f) $LiAlH_4$, THF, 0 °C, 90%.




**Scheme 4** *Reagents and conditions*: (a) IBX, DMSO, THF, r.t., 89%; (b) $Ph_3P{=}CHCO_2Et$, benzene, r.t., 92%; (c) DIBAL-H, $CH_2Cl_2$, –78 °C, 2 h, 87%; (d) PTSA, MeOH, r.t., 12 h., 76%; (e) $MnO_2$, $CH_2Cl_2$, r.t., 3 h, 87%; (f) allyltrimethylsilane, $InBr_3$, $CH_2Cl_2$, r.t., 1 h, 83%.




**Scheme 5** *Reagents conditions*: (a) NaH, MeI, THF, 0 °C, 92%; (b) Li, naphthalene, THF, –78 °C, 83%; (c) DMP, $CH_2Cl_2$, r.t., 1 h, 90%; (d) ref. 7b.

naphthalene followed by oxidation of the alcohol gave an aldehyde, which was further subjected to methylation using cerium(III) chloride and methyllithium in tetrahydrofuran furnished the target intermediate **4** by the route outlined in Scheme 5. The structure of the fragment **4** was established with the aid of spectral data, which was found to be identical in all respects with the reported values.[7b]

In conclusion, the synthesis of the C6–C18 fragment of scytophycin C has been achieved in a stereocontrolled manner employing a sequence of reactions that include Marouka allylation, base-catalyzed intramolecular oxy-Michael reaction, and a nucleophile-induced tandem cyclization. This synthetic sequence provides easy access to the construction of a key fragment of scytophycin C. Further work towards the total synthesis of scytophycin C by employing fragment **4** is in progress.

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. $^1$H NMR spectra were recorded on Varian-unity 300 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

**(2*S*,3*S*)-1-(Benzyloxy)-2-methylhex-5-en-3-ol (8)**

To a stirred soln of 1 M $TiCl_4$ in $CH_2Cl_2$ (1.4 mmol) in anhyd $CH_2Cl_2$ was added Ti(O*i*-Pr)$_4$ (4.2 mmol) at 0 °C and the mixture was stirred at r.t. for 1 h. The round-bottomed flask was wrapped with carbon paper and added $Ag_2O$ (2.8 mmol) was added at 25 °C and the mixture was allowed to stir at r.t. for 5 h. Then (*R*,*R*)-BINOL (5.6 mmol) was added to the mixture at 25 °C and it was stirred for 2 h. The mixture was cooled to –15 °C and freshly prepared **9** (28 mmol) in anhyd $CH_2Cl_2$ (15 mL) was added slowly dropwise and this was followed by the addition of allyltributylstannane (36.4 mmol) and the mixture was then stirred at –15 °C for 30 min. The mixture was allowed to warm to 0 °C and stirred at this temperature for 12 h. When the reaction was complete, it was quenched with sat. $NaHCO_3$ soln and $Et_2O$ was added. The organic layer was separated and the aqueous layer was extracted with $Et_2O$ (3 × 50 mL). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue was further purified by column chromatography (silica gel, 8% EtOAc–hexane) to give **8** (78% yield) as a pale yellow oil.

$[\alpha]_D^{20}$ +5.74 (*c* 1.05, $CHCl_3$).

IR (KBr): 3449, 2921, 2857, 1640, 1454, 1363, 1094, 913, 740, 698 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.9 Hz, 3 H), 1.85 (dq, *J* = 4.5, 6.9, 11.5, 13.9 Hz, 1 H), 2.09–2.21 (m, 1 H), 2.26–2.37 (m, 1 H), 2.98 (d, *J* = 3.5 Hz, 1 H, OH), 3.44 (dd, *J* = 6.7, 9.0 Hz, 1 H), 3.56 (dd, *J* = 6.7, 9.0 Hz, 2 H), 4.5 (s, 2 H), 5.03–5.12 (m, 2 H), 5.77–5.94 (m, 1 H), 7.21–7.35 (m, 5 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 13.8, 37.9, 39.3, 73.4, 74.7, 74.9, 117.2, 127.6, 127.7, 128.4, 135.2, 137.8.

MS (EI): *m*/*z* = 243 [M + Na]$^+$, 220 [M]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{20}O_2Na$: 243.1360. Found: 243.1366.

**Ethyl (*E*)-(5*S*,6*S*)-7-(Benzyloxy)-5-hydroxy-6-methylhept-2-enoate (10)**

To a stirred suspension of NMO (34.0 mmol) in acetone (16 mL) and $H_2O$ (4 mL), was added $OsO_4$ (5 mg, 1.02 mmol) in THF (100 mL) followed by addition of a soln of **8** (20.4 mmol) in acetone at 25 °C. The mixture was stirred for 3 h then solid $Na_2S$ was added and the mixture was stirred for 30 min. The acetone was evaporated under reduced pressure and $H_2O$ was added to the residue and this was stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The com-

bined organic layers were washed with brine, dried ($Na_2SO_4$), and concentrated under reduced pressure to afford the diol as a colorless oil, which was used for next step without purification. To a soln of the diol (16.5 mmol) in THF (24 mL) and $H_2O$ (6 mL) at 0 °C was added $NaIO_4$ (33.0 mmol) and the mixture was stirred at 25 °C for 30 min. When the reaction was complete, THF was added and the mixture was filtered through a pad of Celite with the aid of EtOAc. The resulting filtrate was extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with brine, dried ($Na_2SO_4$), and concentrated in vacuo to give the aldehyde. The crude aldehyde (15.3 mmol) was taken up in anhyd benzene (40 mL) and to this was added $Ph_3P{=}CHCO_2Et$ (30.6 mmol) and the mixture was stirred at r.t. for 4 h. The solvent was removed and the resulting crude product was further purified by column chromatography (silica gel, EtOAc–hexane, 1:9) to give **10** (85% yield over 3 steps) as a colorless oil.

$[\alpha]_D^{20}$ +11.9 (*c* 1.0, $CHCl_3$).

IR (KBr): 3446, 2968, 2920, 2858, 1734, 1631, 1453, 1257, 1100, 1023, 757, 698 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.9 Hz, 3 H), 1.29 (t, *J* = 6.7 Hz, 3 H), 1.86 (dq, *J* = 3.7, 6.9, 11.3, 14.3 Hz, 1 H), 2.21–2.45 (m, 2 H), 3.30 (d, *J* = 3.7 Hz, 1 H), 3.43 (dd, *J* = 3.7, 9.0 Hz, 1 H), 3.59 (dd, *J* = 7.5, 9.0 Hz, 1 H), 3.65 (m, 1 H), 4.16 (q, *J* = 7.5,15.8 Hz, 2 H), 4.5 (s, 2 H), 5.84 (d, *J* = 15.8 Hz, 1 H), 6.99 (dt, *J* = 7.5, 15.8 Hz, 1 H), 7.23–7.36 (m, 5 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 13.8, 14.2, 37.7, 37.9, 60.1, 65.2, 73.5, 74.8, 74.9, 123.4, 127.8, 128.5, 128.9, 137.5, 145.7, 166.3.

MS (EI): *m*/*z* = 315 $[M + Na]^+$, 292 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{24}O_4Na$: 315.1572. Found: 315.1578.;

**Ethyl {(4*R*,6*S*)-6-[(*S*)-2-(Benzyloxy)-1-methylethyl]-2-phenyl-1,3-dioxan-4-yl}acetate (11)**

To a well-stirred soln of **10** (13.6 mmol) in THF (30 mL) at 0 °C was added *t*-BuOK (4.1 mmol) in THF (2 mL) followed by freshly distilled benzaldehyde (41.0 mmol) and the resulting yellow soln was stirred at 0 °C for 15 min. This addition sequence was repeated (2 ×) and the mixture was quenched with pH 7 phosphate buffer (10 mL). $Et_2O$ was added to the mixture, the layers were separated, and the aqueous layer was extracted with $Et_2O$ (3 × 50 mL). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue was further purified by column chromatography (silica gel, EtOAc–hexane, 1:9) to give **11** (70% yield) as a colorless liquid.

$[\alpha]_D^{20}$ –19.2 (*c* 1.0, $CHCl_3$).

IR (KBr): 2920, 2854, 1735, 1454, 1346, 1212, 1100, 1023, 751, 698 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 6.9 Hz, 3 H), 1.27 (d, *J* = 7.5 Hz, 3 H), 1.45 (t, *J* = 11.3 Hz, 2 H), 2.01 (m, 1 H), 2.45 (dd, *J* = 6.0, 15.1 Hz, 1 H), 2.69 (dd, *J* = 6.0, 15.1 Hz, 1 H), 3.52 (d, *J* = 5.2 Hz, 2 H), 3.85 (dddd, *J* = 2.2, 7.5, 9.8, 11.3 Hz, 1 H), 4.16 (q, *J* = 7.5, 14.3 Hz, 2 H), 4.26 (m, 1 H), 4.49 (s, 2 H), 5.50 (s, 1 H), 7.21–7.33 (m, 8 H), 7.34–7.41 (m, 2 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 30.8, 32.2, 37.3, 39.1, 67.4, 72.4, 117.0, 124.4, 125.9, 128.5, 128.6, 29.4, 135.3, 142.5.

MS (EI): *m*/*z* = 421 $[M + Na]^+$, 398 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{30}O_5Na$: 421.1990. Found: 421.2000

**2-{(4*S*,6*S*)-6-[(*S*)-2-(Benzyloxy)-1-methylethyl]-2-phenyl-1,3-dioxan-4-yl}ethanol (12)**

To a well-stirred suspension of $LiAlH_4$ (13.1 mmol) in THF (30 mL) was added **11** (3.5 g, 8.79 mmol) in THF (20 mL) at 0 °C. The mixture was allowed to come up to 25 °C and it was stirred at r.t. for 4 h then cooled to 0 °C and quenched by the dropwise addition of sat. $Na_2SO_4$ soln, stirred for 1 h, and filtered through Celite. To the filtrate was added $H_2O$, the organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, 15% EtOAc–hexane) to give **12** (90% yield) as a colorless oil.

$[\alpha]_D^{20}$ –17.5 (*c* 1.0, $CHCl_3$).

IR (KBr): 3424, 3032, 2915, 2860, 1453, 1345, 1103, 1023, 752, 699 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 7.5 Hz, 3 H), 1.46–1.58 (t, *J* = 7.5 Hz, 2 H), 1.71–1.90 (m, 2 H), 1.92–2.05 (m, 1 H), 3.49 (d, *J* = 5.28 Hz, 2 H), 3.73–3.85 (m, 3 H), 3.97–4.07 (m, 1 H), 4.48 (s, 2 H), 5.49 (s, 1 H), 7.19–7.40 (m, 10 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 12.9, 14.2, 33.6, 38.1, 38.4, 60.4, 71.5, 73.0, 100.5, 126.0, 127.5, 128.2, 128.3, 128.6, 138.6.

MS (EI): *m*/*z* = 379 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{28}O_4Na$: 379.1885. Found: 379.1881.

**Ethyl (*E*)-4-{(4*S*,6*S*)-6-[(*S*)-2-(Benzyloxy)-1-methylethyl]-2-phenyl-1,3-dioxan-4-yl}but-2-enoate (7)**

To a suspension of IBX (10.9 mmol) in DMSO (5 mL) at 0 °C was added dropwise a soln of **12** (7.3 mmol) in THF (25 mL) and the mixture was stirred 25 °C for 2 h. When the reaction was complete, the mixture was poured into $Et_2O$ and filtered through Celite. The resulting filtrate was washed with sat. $NaHCO_3$ soln (3 ×) and extracted with $Et_2O$ (3 × 20 mL). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and concentrated under reduced pressure to yield the aldehyde as yellow oil in 89% yield, which was used in the next step without purification. The crude aldehyde (5.6 mmol) was taken up in anhyd benzene (30 mL) and to this was added $Ph_3P{=}CHCO_2Et$ (11.2 mmol) and the mixture was stirred at 25 °C for 4 h. The solvent was removed and the resulting crude product was further purified by column chromatography (silica gel, EtOAc–hexane, 1:9) to give **7** (92% yield) as a colorless oil.

$[\alpha]_D^{20}$ –6.36 (*c* 1.1, $CHCl_3$).

IR (KBr): 2920, 2852, 1717, 1655, 1454, 1316, 1269, 1105 1024, 754, 699 $cm^{-1}$.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 7.3 Hz, 3 H), 1.29 (t, *J* = 7.3 Hz, 3 H), 1.42 (t, *J* = 6.5 Hz, 1 H), 1.56 (tt, *J* = 6.5, 12.4 Hz, 1 H), 1.99 (m, 1 H), 2.32–2.67 (m, 2 H), 3.50 (d, *J* = 5.1 Hz, 2 H), 3.72–4.01 (m, 2 H), 4.18 (q, *J* = 7.3, 14.6 Hz, 2 H), 4.48 (s, 2 H), 5.46 (s, 1 H), 5.88 (d, *J* = 15.3 Hz, 1 H), 6.85–7.06 (m, 1 H), 7.19–7.44 (m, 10 H).

13C NMR (75 MHz, $CDCl_3$): δ = 12.8, 14.1, 33.3, 38.4, 38.6, 60.1, 71.3, 72.9, 75.2, 76.5, 100.3, 123.6, 125.9, 127.3, 127.4, 128.2, 128.4, 138.5, 144.1, 166.2.

MS (EI): *m*/*z* = 447 $[M + Na]^+$, 424 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{32}O_5Na$: 447.2147. Found: 447.2167.

**(*E*)-4-{(4*S*,6*S*)-6-[(*S*)-2-(Benzyloxy)-1-methylethyl]-2-phenyl-1,3-dioxan-4-yl}but-2-en-1-ol (13)**

A soln of **7** (4.22 mmol) in anhyd $CH_2Cl_2$ (30 mL) was stirred and cooled to –78 °C and then 20% DIBAL-H soln (5.07 mmol) was added dropwise over a period of 15 min. The mixture was stirred for 30 min at this temperature and then quenched with sat. sodium potassium tartrate soln and stirred for 1 h. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue

was purified by column chromatography (silica gel, EtOAc–hexane, 1:9) to give **13** (87% yield) as a colorless oil.

$[\alpha]_D^{20}$ –35.3 (*c* 1.25, $CHCl_3$).

IR (KBr): 3416, 3032, 2922, 2854, 1689, 1453, 1345, 1211, 1105, 1021, 974, 753, 699 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.6 Hz, 3 H), 1.21–1.63 (m, 2 H), 1.86–2.07 (m, 1 H), 2.17–2.51 (m, 2 H), 3.50 (d, *J* = 5.1 Hz, 2 H), 3.72–3.88 (m, 2 H), 4.06 (d, *J* = 4.4 Hz, 2 H), 4.2 (br, 1 H), 4.48 (s, 2 H), 5.44 (s, 1 H), 5.68–5.76 (m, 2 H), 7.21–7.44 (m, 10 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 13.1, 33.5, 38.7, 39.0, 63.7, 71.8, 73.2, 76.6, 78.0, 100.6, 126.2, 127.6, 127.7, 128.3, 128.7, 132.0, 138.9, 139.0.

MS (EI): *m*/*z* = 405 $[M + Na]^+$, 228 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{30}O_4Na$: 405.2041. Found: 405.2049.

**(*E*)-(5*S*,7*S*,8*S*)-9-(Benzyloxy)-5,7-dihydroxy-8-methylnon-2-enal (6)**

To a soln of **13** (3.4 mmol) in MeOH (20 mL) at 25 °C was added catalytic PTSA (5 mol%) and the mixture was stirred for 12 h. When the reaction was complete, the solvent was removed in vacuo and the crude product was washed with $NaHCO_3$ and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and concentrated under reduced to afford the triol (76% yield), which was used in the next step without purification. To a soln of triol (2.5 mmol) in anhyd $CH_2Cl_2$ (20 mL) at 25 °C was added activated $MnO_2$ (5 mmol) and the mixture was allowed to stir for 2 h. When the reaction was complete, the solvent was removed under reduced pressure at low temperature and the crude product was purified by flash column chromatography (EtOAc–hexane, 3:7) to give pure aldehyde **6** (87% yield) as a colorless oil.

$[\alpha]_D^{20}$ –59.3 (*c* 0.65, $CHCl_3$).

IR (KBr): 3423, 2920, 2858, 1722, 1685, 1454, 1381, 1067, 740, 698 $cm^{-1}$.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 7.0 Hz, 3 H), 1.36–1.73 (m, 2 H), 1.74–1.94 (m, 1 H), 2.36–2.58 (m, 2 H), 3.42 (t, *J* = 4.0 Hz, 1 H), 3.63 (dd, *J* = 4.0, 9.1 Hz, 1 H), 3.69–3.84 (m, 1 H), 3.92–4.10 (m, 1 H), 4.25 (br s, 2 H), 4.51 (s, 2 H), 6.12 (dd, *J* = 7.8, 15.6 Hz, 1 H,), 6.92 (m, 1 H), 7.20–7.40 (m, 5 H), 9.5 (d, *J* = 7.8 Hz, 1 H, CHO).

MS (EI): *m*/*z* = 315 $[M + Na]^+$, 292 $[M]^+$.

**(2*S*,3*S*)-1-[(2*S*,6*R*)-6-Allyl-3,6-dihydro-2*H*-pyran-2-yl]-4-(benzyloxy)-3-methylbutan-2-ol (5)**

To a soln of a mixture of **6** (2.12 mmol) in $CH_2Cl_2$ (20 mL) was added allyltrimethylsilane (2.12 mmol) followed by addition of a catalytic amount of $InBr_3$ (5 mol%) and the mixture was stirred at 25 °C for 1 h. When the reaction was complete (TLC), the mixture was diluted with $H_2O$ (10 mL) and extracted with $CH_2Cl_2$ (2 × 15 mL). The organic layers were dried (anhyd $Na_2SO_4$) and purified by column chromatography (silica gel, EtOAc–hexane, 1:9) to afford pure **5** (83% yield) as a oil.

$[\alpha]_D^{20}$ –81.2 (*c* 1.6, $CHCl_3$).

IR (KBr): 3445, 2924, 2855, 1455, 1218, 1075, 701 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 6.9 Hz, 3 H), 1.44–1.69 (m, 2 H), 1.85–1.96 (m, 1 H), 1.97–2.04 (m, 2 H), 2.26–2.38 (m, 1 H), 2.41–2.54 (m, 1 H), 3.36–3.60 (m, 2 H), 3.72–3.84 (m, 1 H), 3.88–4.01 (m, 1 H), 4.26 (br s, 1 H), 4.23–4.32 (m, 1 H) 4.53 (s, 2 H), 5.10–5.21 (m, 2 H), 5.69–5.94 (m, 3 H), 7.24–7.37 (m, 5 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 14.0, 30.9, 31.9, 38.7, 39.9, 64.5, 71.5, 72.5, 73.3, 74.2, 116.8, 124.5, 127.5, 128.3, 128.9, 135.3, 138.1.

MS (EI): *m*/*z* = 339 $[M + Na]^+$, 317 $[M + 1]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{28}O_3Na$: 339.1936. Found: 339.1946.

**(2*S*,6*R*)-6-Allyl-2-[(2*S*,3*S*)-4-(benzyloxy)-2-methoxy-3-methylbutyl]-3,6-dihydro-2*H*-pyran (14)**

To a soln of **5** (1.7 mmol) in anhyd THF (20 mL), NaH (60% dispersion in mineral oil, 6.1 mmol) was added at 0 °C and the mixture was stirred at this temperature for 15 min. Then MeI (2.5 mmol) was added dropwise followed by a catalytic amount of TBAI and the mixture was stirred at 25 °C for 4 h. The mixture was quenched with aq $NH_4Cl$ soln and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 5% EtOAc–hexane) to give **14** (92% yield) as a pale yellow oil.

$[\alpha]_D^{20}$ –62.5 (*c* 1.15, $CHCl_3$).

IR (KBr): 2924, 2854, 1641, 1456, 1368, 1090, 912, 737, 700 $cm^{-1}$.

$^1H$ NMR (200 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.5 Hz, 3 H), 1.45–1.62 (m, 3 H), 1.89–2.02 (m, 2 H), 2.19–2.42 (m, 2 H), 3.30 (s, 3 H), 3.34–3.38 (m, 1 H), 3.44–3.57 (m, 2 H), 3.66–3.76 (m, 1 H), 4.16–4.21 (m, 1 H), 4.50 (s, 2 H), 4.97–5.13 (m, 2 H), 5.69–5.90 (m, 3 H), 7.32–7.36 (m, 5 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 11.3, 31.7, 35.4, 36.2, 38.6, 57.5, 65.2, 71.1, 72.3, 73.6, 78.2, 116.0, 124.3, 127.2, 127.5, 128.1, 129.3, 135.6, 138.9.

MS (EI): *m*/*z* = 353 $[M + Na]^+$, 330 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{30}O_3Na$: 353.2092. Found: 353.2096.

**(3*R*,4*S*)-5-[(2*S*,6*R*)-6-Allyl-3,6-dihydro-2*H*-pyran-2-yl]-4-methoxy-3-methylpentan-2-one (4)**

To a stirred soln of naphthalene (7.5 mmol) in anhyd THF, was added Li (7.5 mmol) at 25 °C and the mixture was stirred for 30 min. After the mixture turned a dark green color, compound **14** (1.5 mmol) was added dropwise at –78 °C, and the mixture was stirred for 2 h at the same temperature. When the reaction was complete, the reaction was quenched with sat. $NH_4Cl$ soln and extracted with $Et_2O$ (3 × 10 mL). The organic layer was washed with brine, dried ($Na_2SO_4$), and concentrated under reduced pressure to afford the primary alcohol (83% yield). The crude alcohol (1.16 mmol) in anhyd $CH_2Cl_2$ (10 mL) was added DMP (1.39 mmol) at r.t. and the mixture was stirred for 10 min. The solid materials were filtered through a sintered funnel. The resulting filtrate was washed with hypo solution ($Na_2S_2O_3 \cdot 5H_2O$) and sat. $NaHCO_3$ soln and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and concentrated under reduced pressure to obtain the aldehyde. To a suspension of $CeCl_3$ (0.84 mmol) in THF (10 mL) was added 1.04 M MeLi in $Et_2O$ (0.84 mmol) at –78 °C and the mixture was stirred for 30 min at this temperature. The crude aldehyde (0.84 mmol) in THF (5 mL) was added dropwise and the mixture was stirred at –78 °C for 1 h. Sat. $NH_4Cl$ was added and the mixture was filtered through Celite and the aqueous layer was extracted with $Et_2O$ (5 × 20 mL). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and concentrated in vacuo to obtain the crude alcohol. To a soln of the alcohol (0.47 mmol) in anhyd $CH_2Cl_2$ (20 mL) was added DMP (0.56 mmol) at r.t. and the mixture was stirred for 10 min. The mixture was filtered through Celite. The filtrate was washed with hypo solution and sat. $NaHCO_3$ soln and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were washed with brine, dried

($Na_2SO_4$), and concentrated under reduced pressure to yield the ketone, which was further purified by column chromatography (silica gel, EtOAc–hexane, 1:9) to afford **4** (90% yield) as a yellow oil.

$[\alpha]_D^{20}$ –98 (*c* 0.5, $CHCl_3$).

IR (KBr): 2924, 2856, 1715, 1635, 1451, 1279, 1082, 765 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 7.0 Hz, 3 H), 1.20 (d, *J* = 7.0 Hz, 3 H), 1.35–1.65 (m, 2 H), 1.65–1.89 (m, 2 H), 1.91–2.23 (m, 2 H), 2.83 (m, 1 H), 3.48 (s, 3 H), 3.58–3.62 (m, 1 H), 3.85–3.93 (m, 1 H), 4.28 (br s, 1 H), 4.95–5.28 (m, 2 H), 5.68–5.97 (m, 3 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 10.8, 29.5, 30.8, 36.4, 37.9, 39.1, 49.8, 57.4, 64.7, 72.3, 78.4, 116.0, 124.4, 123.9, 128.5, 135.3, 210.7.

MS (EI): *m*/*z* = 275 $[M + Na]^+$, 252 $[M]^+$.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{24}O_3$: 252.1402. Found: 252.1411.

## References


(1) (a) Ishibashi, M.; Moore, R. E.; Patterson, G. M. L.; Xu, C.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5300. (b) Moore, R. E.; Patterson, G. M. L.; Mynderse, J. S.; Barchi, J. Jr.; Norton, T. R.; Furusawa, E.; Furusawa, S. *Pure Appl. Chem.* **1986**, *58*, 263.

(2) Moore, R. E.; Banaejee, S.; Bornemann, V.; Caplan, F. R.; Chen, J. L.; Corley, D. E.; Larsen, L. K.; Moore, B. S.; Patterson, G. M. L.; Paul, V. J.; Stewart, J. B.; Williams, D. E. *Pure Appl. Chem.* **1989**, *61*, 521.

(3) (a) Moore, R. E. In *Marine Natural Products Chemical and Biological Perspectives*, Vol. IV; Sheuer, P. J., Ed.; Academic Press: New York, **1981**, 1. (b) Carmeli, S.; Moore, R. E.; Patterson, G. M. L. *J. Nat. Prod.* **1990**, *53*, 1533. (c) Jung, J. H.; Moore, R. E.; Patterson, G. M. L. *Phytochemistry* **1991**, *30*, 3615.

(4) Carmeli, S.; Moore, R. E.; Patterson, G. M. L.; Yoshida, W. Y. *Tetrahedron Lett.* **1993**, *34*, 5571.

(5) Scytophycins isolated from other species of *Scytonema* and *Cylindrospermum musicola* see: refs. 3b and 3c.

(6) (a) Patterson, G. M. L.; Smith, C. D.; Kimura, L. H.; Brittern, B.; Carmeli, S. *Cell Motil. Cytoskeleton* **1993**, *24*, 39. (b) Smith, C. D.; Carmeli, S.; Moore, R. E.; Patterson, G. M. L. *Cancer Res.* **1993**, *53*, 1343.

(7) For a total synthesis of scytophycin C: (a) Paterson, I.; Watson, C.; Yeung, K. S.; Wallace, P. A.; Ward, R. A. *J. Org. Chem.* **1997**, *62*, 452. (b) Nakamura, R.; Tanino, K.; Miyashita, M. *Org. Lett.* **2003**, *5*, 3579. (c) Nakamura, R.; Tanino, K.; Miyashita, M. *Org. Lett.* **2003**, *5*, 3583.

(8) For syntheses of swinholide A, see: (a) Paterson, I.; Yeung, K. S.; Ward, R. A.; Smith, J. D.; Cumming, J. G.; Lamboley, S. *Tetrahedron* **1995**, *51*, 9467. (b) Paterson, I.; Yeung, K. S.; Ward, R. A.; Smith, J. D.; Cumming, J. G. *J. Am. Chem. Soc.* **1994**, *116*, 9391. (c) Nicolaou, K. C.; Ajito, K.; Patron, A. P.; Khatuya, H.; Richter, P. K.; Bertinato, P. J. *J. Am. Chem. Soc.* **1996**, *118*, 3059.

(9) (a) Paterson, I.; Yeung, K. S.; Wallace, P. A.; Ward, R. A. *Tetrahedron* **1998**, *54*, 11935. (b) Paterson, I.; Yeung, K. S.; Wallace, P. A.; Ward, R. A. *Tetrahedron* **1998**, *54*, 11955.

(10) Nicolaou, K. C.; Patron, A. P.; Ajito, K.; Richter, P. K.; Khatuya, H.; Bertinato, P.; Miller, R. A.; Tomaszewski, M. J. *Chem.–Eur. J.* **1996**, *2*, 847.

(11) The synthesis of preswinholide A has also been accomplished by Nakata and co-workers: Nagasawa, K.; Shimizu, I.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6885.

(12) Yadav, J. S.; Ahmed, M. M. *Tetrahedron Lett.* **2002**, *43*, 7147.

(13) Paquette, L. A.; Guevel, R.; Sakamoto, S.; Kim, I. H.; Crawford, J. *J. Org. Chem.* **2003**, *68*, 6096.

(14) (a) Hanawa, H.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 1708. (b) Keck, G. E.; Tarbet, H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467.

(15) Brown, C. H.; Krishna, S. B.; Ramnarayan, S. R. *J. Org. Chem.* **1989**, *54*, 1570.

(16) (a) Wittig, G.; Rieber, M. *Justus Liebigs Ann. Chem.* **1949**, *562*, 187. (b) Wittig, G.; Geissler, G. *Justus Liebigs Ann. Chem.* **1953**, *580*, 44. (c) Wittig, G.; Schollkopf, V. *Chem. Ber.* **1954**, *87*, 1318. (d) Gensle, W. J. *Chem. Rev.* **1957**, *57*, 191.

(17) Evans, D. A.; Gouchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446.

(18) Yadav, J. S.; Krishnam Raju, A.; Sunitha, V. *Tetrahedron Lett.* **2006**, *47*, 5269.