Tetrahedron Letters 53 (2012) 6048–6050

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

The first stereoselective total synthesis of the *Z*-isomer of cytospolide E

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ARTICLE INFO

Article history:
Received 6 July 2012
Revised 23 August 2012
Accepted 24 August 2012
Available online 1 September 2012

Keywords:
Cytotoxic
Macrolide
Evan's aldol
Ring closing metathesis

ABSTRACT

A convergent and highly stereoselective total synthesis of the *Z*-isomer of cytospolide E has been achieved via Evan's aldol reaction, Sharpless kinetic resolution and RCM cyclisation.

The genus *Cytospora* sp. is a rich source of biologically active secondary metabolites such as antibiotic grahamimycins,[1] antibacterial cytoskyrins[2] and cytotoxic cytosporinols.[3] Of these, cytospolides A–E (Fig. 1) are of immense interest because of their potent anticancer activity. These cytotoxic nonanolides were isolated from the endophytic fungus *Cytospora* sp.[4] The structure was established by spectroscopic, chemical and single-crystal X-ray analyses. The C-2 methyl group plays an important role in growth inhibition of tumour cell lines. Due to their fascinating biological profiles and structural features, cytospolides have become highly attractive synthetic targets. Of these, cytospolide E shows high cytotoxic activity, which encouraged us to take up its total synthesis. In continuation of our interest on the total synthesis of biologically active molecules,[5] herein, we report the synthesis of cytospolide E.

Our retrosynthetic analysis of cytospolide E, **1** reveals that it could be synthesised by means of RCM cyclisation of precursor **14**, which in turn could be prepared through the esterification of acid **6** with alcohol **13**. The intermediates **6** and **13** could easily be prepared from a commercially available acrolein **2** and *n*-hexanal **7** 'respectively' (Scheme 1).

Accordingly, we began the synthesis of cytospolide E by means of asymmetric aldol reaction between acrolein **2** and imide **3** to afford the Evans' *syn*-aldol product **4** in 88% yield (de >95:5).[6] Protection of the resulting alcohol **4** with MOMCl in the presence of Hunig's base afforded the MOM ether **5** in 92% yield. Hydrolysis

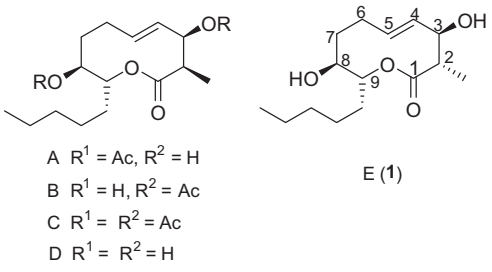
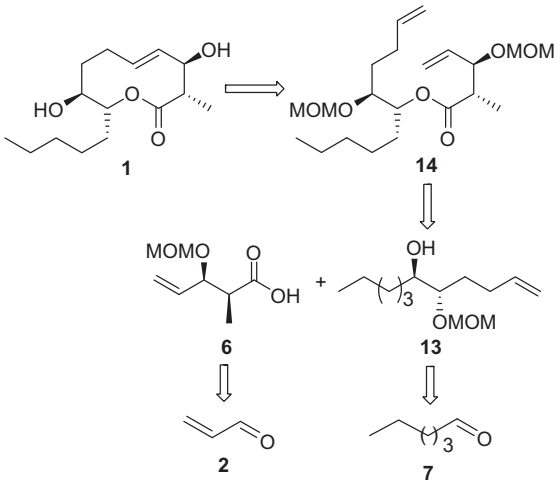


Figure 1. Structure of cytospolide A–E.



Scheme 1. Retrosynthetic analysis of cytospolide E.

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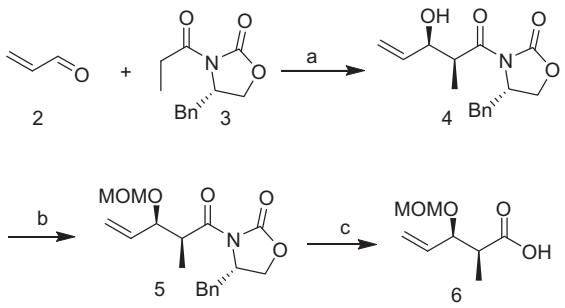
http://dx.doi.org/10.1016/j.tetlet.2012.08.108



Scheme 2. Synthesis of fragment **6** via Evan's aldol reaction. Reagents and conditions: (a) *n*-Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, −78–0 °C, 1 h, 88%; (b) DIPEA, MOMCl, CH_2Cl_2, 0 °C, 2 h, 92%; (c) LiOH, 35% aq H_2O_2, THF/H_2O (4:1) 0 °C, 5 h, 90%.

of the **5** with $LiOH/H_2O_2$[7] afforded the corresponding acid **6** in 90% yield (Scheme 2).

Next we attempted the synthesis of compound **13** from a commercially available *n*-hexanal. Initially, *n*-hexanal was converted into allylic alcohol **8** in 92% yield using vinyl magnesium bromide. The Sharpless kinetic resolution[8] of allylic alcohol **8** using $Ti(O^iPr)_4$, (−)-DIPT and TBHP in dichloromethane gave the enantiomerically pure epoxy alcohol **9** in 42% yield (ee 97%). Protection of secondary hydroxyl group with TBSCl in the presence of imidazole afforded the TBS ether **10** in 91% yield. The regioselective opening of epoxide **10** with allyl magnesium bromide in the presence of CuCN gave the secondary alcohol **11** in 95% yield. Protection of secondary alcohol with MOMCl in the presence of diisopropylethylamine gave the MOM ether **12** in 90% yield. Desilylation of compound **12** with TBAF gave the alcohol **13** in 92% yield (Scheme 3).

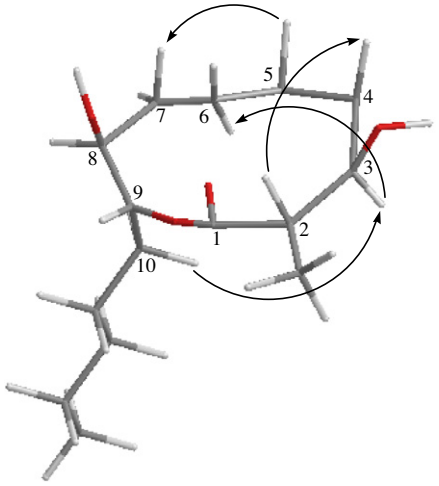
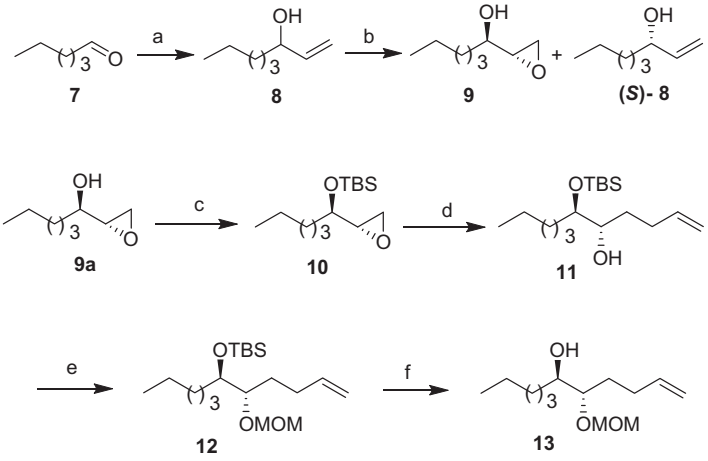
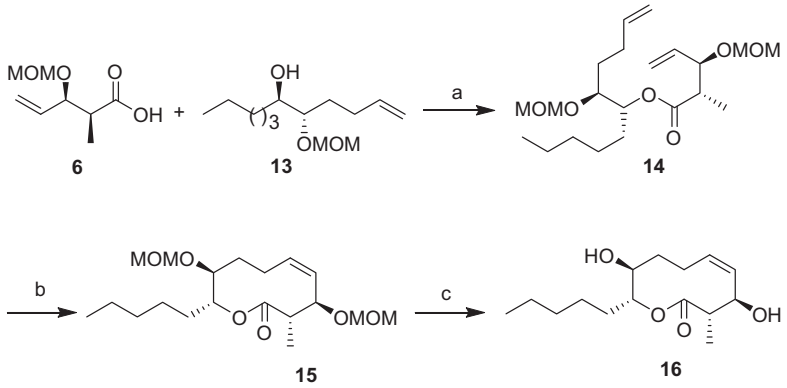


Figure 2. Characteristic nOe's of the *Z*-isomer of cytospolide E.



Scheme 3. Synthesis of fragment **13**. Reagents and conditions: (a) vinyl magnesium bromide, THF, 0 °C, 92%; (b) $Ti(O^iPr)_4$, (−)-DIPT, TBHP, CH_2Cl_2, 4 A MS, −20 °C 8 h, 42%; (c) TBSCl, imidazole, DCM, 1 h, 91%; (d) Mg, allyl chloride, CuCN, THF, 0 °C, 95%; (e) DIPEA, MOMCl, CH_2Cl_2, 0 °C, 2 h, 90%; (f) TBAF, THF, 0 °C, 92%.



Scheme 4. Synthesis of the *Z*-isomer of cytospolide E. Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, 0 °C to rt, 6 h, 85%; (b) Grubb's catalyst-II, CH_2Cl_2, reflux, 3 h, 70%; (c) $CeCl_3{\cdot}7H_2O$, CH_3CN, reflux, 3 h, 88%.

Finally, we attempted the coupling of **6** with **13** so as to construct a 10-membered ring via the RCM reaction. Accordingly, the coupling of acid **6** with alcohol **13** under Steglich conditions gave the ester **14** in 85% yield.[9] Upon treatment of **14** with the Grubbs' second generation catalyst[10] in CH_2Cl_2 at reflux temperature for 3 h gave the *Z*-isomer of cytospolide E **15** in 70% yield. The structure of **15** was ascertained by its NMR spectrum. The geometry of the olefin in **15** was determined as '*Z*' from its coupling constants, while one of the olefinic proton signals appears at δ 5.71 ppm as a dt (J = 3.0, 12.0 Hz) and another signal for the olefinic proton appears at δ 5.14 ppm as a triplet (J = 9.8 Hz) which clearly reveals the *Z* geometry of the olefin. Deprotection of MOM ethers of **15** using $CeCl_3{\cdot}7H_2O$[11] in refluxing CH_3CN gave the *Z*-isomer of cytospolide E **16** in 88% yield (Scheme 4).

The relative stereochemistry of **16** was deduced from the ^1H–^1H coupling constants and NOESY data. The geometry of the Δ^4 double bond was assigned as *Z* based on the proton coupling constant ($^3J_{H4,H5}$ = 11.1 Hz) and nOe studies. The presence of nOe between H-2 and H-4, H-5 and H-7β, indicates the β-orientation of these protons. The nOe between H-3 and H-10, H-3 and H-6α indicates the α-orientation of H-3, H6α and H10 (Fig. 2). The above observation reveals the *Z* stereochemistry of the cytospolide E.[12]

In summary, we have developed an efficient synthetic route for the stereoselective total synthesis of the *Z*-isomer of cytospolide E starting from a readily available acrolein and *n*-hexanal. The synthetic strategy involves asymmetric Aldol reaction, Sharpless kinetic resolution and RCM cyclisation as key steps. The total synthesis of **16** was accomplished in 12 steps, with 15% overall yield.

Acknowledgements

T.P., A.S., P.A.R., and A.R. are thankful to the UGC, CSIR, New Delhi, for the award of fellowships.

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12. *Spectral data for (S)-4-Benzyl-3-((2S,3R)-3-hydroxy-2-methylpent-4-enoyl) oxazolidin-2-one* (**4**): $[\alpha]_D^{20}$ 53.7 (c = 0.7, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.31 (m, 2H), 7.31–7.25 (m, 1H), 7.21 (d, J = 6.9 Hz, 2H), 5.86 (ddd, J = 17.3, 10.4, 5.7 Hz, 1H), 5.36 (d, J = 17.3 Hz, 1H), 5.23 (d, J = 10.4 Hz, 1H), 4.75–4.68 (m, 1H), 4.53–4.49 (m, 1H), 4.26–4.17 (m, 2H), 3.92–3.85 (m, 1H), 3.26 (dd, J = 13.8, 3.4 Hz, 1H), 2.80 (dd, J = 12.7, 9.2 Hz, 1H), 1.26 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 176.4, 153.0, 137.2, 134.9, 129.3, 128.9, 127.3, 116.2, 72.5, 66.1, 55.0, 42.4, 37.7, 10.9; IR (neat): υ_{max} 3489, 2926, 2851, 1778, 1697, 1605, 1454, 1386, 1213, 1108, 977, 702 cm^{-1}. MS (ESI): m/z 312 $[M+Na]^+$. *(S)-4-Benzyl-3-((2S,3R)-3-(methoxymethoxy)-2-methylpent-4-enoyl) oxazolidin-2-one* (**5**): $[\alpha]_D^{20}$ 23.7 (c = 2.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.37–7.19 (m, 5H), 5.87–5.74 (ddd, J = 17.3, 10.5, 7.5 Hz, 1H), 5.29 (d, J = 7.5 Hz, 1H), 5.25 (s, 1H), 4.68–4.58 (m, 2H), 4.55–4.50 (m, 1H), 4.26 (t, J = 6.7 Hz, 1H), 4.19–4.16 (m, 2H), 4.12 (t, J = 6.7 Hz, 1H), 3.35 (s, 3H), 3.29 (dd, J = 13.5, 3.7 Hz, 1H), 2.77 (dd, J = 13.5, 9.8 Hz, 1H), 1.28 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.8, 152.7, 135.1, 134.8, 128.9, 128.4, 126.8, 118.4, 93.5, 76.5, 65.5, 55.2, 55.1, 41.6, 37.3, 12.3; IR (neat): υ_{max} 3065, 2981, 2934, 2849, 1781, 1700, 1604, 1454, 1385, 1216, 1097, 1029, 703 cm^{-1}. MS (ESI): m/z 356 $[M+Na]^+$. *(2S,3R)-3-(Methoxymethoxy)-2-methylpent-4-enoic acid* (**6**): $[\alpha]_D^{20}$ −67.5 (c = 2.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 5.82–5.68 (ddd, J = 17.5, 10.0, 8.1 Hz, 1H), 5.33 (d, J = 2.2 Hz, 1H), 5.29 (d, J = 1.7 Hz, 1H), 4.64 (q, J = 6.8 Hz, 2H), 4.31 (t, J = 6.2 Hz, 1H), 3.37(s, 3H), 2.71 (t, J = 6.0 Hz, 1H), 1.23 (d, J = 6.9 Hz, 3H); ^{13}C NMR $CDCl_3$, 75 MHz): δ 179.2, 135.0, 119.4, 93.8, 77.9, 55.6, 44.5, 11.8; IR (neat)): υ_{max} 3084, 2984, 2940, 1736, 1713, 1458, 1383, 1219, 1153, 1032, 772 cm^{-1}; MS (ESI): m/z 197 $[M+Na]^+$. *(5S,6R)-6-(tert-Butyldimethylsilyloxy)undec-1-en-5-ol* (**11**): $[\alpha]_D^{20}$ −12.6 (c = 2.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.88–5.78 (m, 1H), 5.04 (d, J = 16.8 Hz, 1H), 4.97 (d, J = 9.8 Hz, 1H), 3.64–3.56 (m, 2H), 2.30–2.20 (m, 1H), 2.15–2.04 (m, 1H), 1.65 (brs, 1H), 1.56–1.17 (m, 10H), 0.91–0.85 (m, 12H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.5, 114.7, 75.3, 73.9, 32.0, 30.9, 30.7, 30.3, 25.8, 25.3, 22.5, 18.0, 14.0, −4.4; IR (neat): υ_{max} 3480, 3078, 2931, 2858, 1641, 1465, 1362, 1255, 1081, 836, 775 cm^{-1}. MS (ESI): m/z 323 $[M+Na]^+$. *(5S,6R)-5-(But-3-enyl)-8,8,9,9-tetramethyl-6-pentyl-2,4,7-trioxa-8-siladecane* (**12**): $[\alpha]_D^{20}[\alpha]_D^{20}$ −33.6 (c = 2.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.87–5.76 (m, 1H), 5.02 (d, J = 15.0 Hz, 1H), 4.96 (d, J = 10.3 Hz, 1H), 4.69 (q, J = 6.9 Hz, 2H), 3.69–3.63 (m, 1H), 3.54–3.48 (m, 1H), 3.38 (s, 3H), 2.28–2.13 (m, 1H), 2.12–2.02 (m, 1H), 1.67–1.17 (m, 10H), 0.91–0.84 (m, 12H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$,75 MHz): δ 138.6, 114.5, 96.0, 79.9, 74.5, 55.7, 32.9, 32.0, 30.2, 29.8, 25.9, 25.5, 22.5, 18.1, 14.0, −4.2, −4.6; IR (neat): υ_{max} 3078, 2951, 2859, 1641, 1465, 1382, 1253, 1147, 1096, 1038, 915, 835, 775 cm^{-1}; MS (ESI): m/z 367 $[M+Na]^+$. *(5S,6R)-5-(Methoxymethoxy)undec-1-en-6-ol* (**13**): $[\alpha]_D^{20}$ 8.3 (c = 2.7, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 5.89–5.74 (m, 1H), 5.09–4.95 (m, 2H), 4.70 (q, J = 6.8 Hz, 2H), 3.65–3.50 (m, 2H), 3.43 (s, 3H), 2.30–2.16 (m, 1H), 2.15–2.00 (m, 1H), 1.74–1.17 (m, 10H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$,75 MHz): δ 138.2, 114.9, 97.2, 83.4, 73.0, 55.8, 31.9, 31.5, 29.3, 25.8, 25.6, 22.6, 14.0; IR (neat): υ_{max} 3456, 3077, 2931, 2858, 1736, 1642, 1455, 1378, 1150, 1098, 1036, 914 cm^{-1}; MS (ESI): m/z 253 $[M+Na]^+$. *(2S,3R)-((5S,6R)-5-(Methoxymethoxy) undec-1-en-6-yl) 3-(methoxymethoxy)-2-methylpent-4-enoate* (**14**): $[\alpha]_D^{20}$ −54.2 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 5.88–5.67 (m, 2H), 5.31–5.20 (m, 2H), 5.08–4.94 (m, 3H), 4.70 (dd, J = 9.0, 6.8 Hz, 2H), 4.55 (dd, J = 12.8, 6.8 Hz, 2H), 4.18 (t, J = 7.5 Hz, 1H), 3.66–3.59 (m, 1H), 3.38 (s, 3H), 3.36 (s, 3H), 2.64 (t, J = 6.8 Hz, 1H), 2.31–2.00 (m, 2H), 1.70–1.46 (m,3H), 1.38–1.16 (m, 10H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.7, 138.1, 135.7, 119.1, 115.0, 95.9, 93.9, 78.4, 77.2, 74.9, 55.7, 55.6, 45.2, 31.6, 29.8, 29.6, 29.2, 25.3, 22.5, 13.9, 13.1; IR (neat): υ_{max} 3079, 2930, 2857, 1733, 1641, 1458, 1377, 1153, 1034, 920, 768 cm^{-1}; MS (ESI): m/z 409 $[M+Na]^+$. *(3S,4R,9S,10R,Z)-4,9-Bis(methoxymethoxy)-3-methyl-10-pentyl-3,4,7,8,9,10-hexahydrooxecin-2-one* (**15**): $[\alpha]_D^{20}$ −37.5 (c = 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.73 (dt, J = 12.0, 3.0 Hz, 1H), 5.17 (t, J = 9.8 Hz, 1H), 5.08–5.00 (m, 1H), 4.73 (d, J = 6.8 Hz, 1H), 4.62 (q, J = 6.8 Hz, 2H), 4.51 (t, J = 6.8 Hz, 2H), 3.62 (t, J = 5.2 Hz, 1H), 3.42 (s, 3H), 3.38 (s, 3H), 2.67–2.51 (m, 2H), 2.19-2.00 (m, 2H), 1.70-1.46 (m, 3H), 1.43-1.22 (m, 10H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.7, 135.8, 127.0, 94.5, 93.9, 77.2, 74.9, 72.5, 55.7, 47.5, 31.5, 31.3, 30.3, 29.7, 24.9, 24.7, 22.5, 15.4, 13.9; IR (neat): υ_{max} 2931, 2857, 1740, 1456, 1370, 1252, 1152, 1099, 1035, 920, 745 cm^{-1}; MS (ESI): m/z 381 $[M+Na]^+$. *(3S,4R,9S,10R,Z)-4,9-Dihydroxy-3-methyl-10-pentyl-3,4,7,8,9,10-hexahydrooxecin-2-one* (**16**): White solid, mp 136–140 °C; $[\alpha]_D^{20}$ 26.6 (c = 0.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.75 (ddd, J = 11.1, 4.5, 1.1 Hz, 1H), 5.37 (dt, J = 9.9, 2.2 Hz, 1H), 5.12 (dt, J = 9.5, 3.7 Hz,1H), 4.64 (t, J = 9.9 Hz, 1H), 3.81 (dt, J = 4.6, 3.7 Hz, 1H), 2.73 (dq, J = 12.9, 3.9 Hz, 1H), 2.51 (qd, J = 9.9, 6.9 Hz, 1H), 2.13–1.90 (m, 2H), 1.67–1.49 (m, 2H), 1.44–1.20 (m, 10H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.6, 133.8, 129.9, 77.6, 74.3, 69.5, 49.1, 31.3, 30.8, 29.6, 25.2, 25.1, 22.4, 14.8, 13.8; IR (KBr): υ_{max} 3236, 2923, 2855, 1729, 1449, 1253, 1039, 766 cm^{-1}; MS (ESI): m/z 293 $[M+Na]^+$.