Tetrahedron: *Asymmetry* 20 (2009) 2027–2032

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Stereoselective synthesis of the C1–C12 fragment of the thuggacins

Shoubin Tang [a], Zhengshuang Xu [a,b,*], Tao Ye [a,b,*]

[a] *Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Shenzhen Graduate School of Peking University, Shenzhen 518055, China*
[b] *Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Kowloon, Hong Kong, China*

ARTICLE INFO

Article history:
Received 6 July 2009
Accepted 17 August 2009
Available online 14 September 2009

ABSTRACT

A concise asymmetric synthesis of the C1–C12 fragment of the antibacterial natural product thuggacins has been achieved. The stereochemistry of this fragment was established efficiently via stereoselective reduction and Evans-aldol condensation. Hanztsch's method and a Horner–Wadsworth–Emmnons reaction were employed for thiazole formation and the construction of the *E*-α,β-unsaturated double bond.

1. Introduction

Nature has consistently provided mankind with structurally diverse and multi-bioactive pharmaceutical leads. The search for new antibacterial drugs for the treatment of serious infections in clinical practices is very important nowadays, as multi-drug resistant bacteria pose a large threat to human health. Using a bioactivity-guided protocol for new natural chemical entities, the natural products thuggacin A **1**, B **2**, and C **3** (Fig. 1)[1] were isolated from the myxobacterium Sorangium cellulosum by Jansen et al. The thuggacins show strong antibiotic activity against various organisms including mycobacterium tuberculosis. Thuggacin A has an IC_{50} value of 8 ng/mL and thuggacin B and C have IC_{50} values of around 20 ng/mL.[1] Further study indicated their biological mechanism of targeting the bacterial respiratory chain.[2]

All three thuggacins share the same structural features except for the size of the macrolactone ring. The gross structures and their stereochemistry were disclosed by two independent research groups, Jansen et al.[1] and Kirschning et al.[3] in 2007. The feature of the thuggacins comprises a 17–19 membered unsaturated macrolactone ring with eight stereogenic centers, five alkenes, a thiazole ring, and an *n*-hexyl side chain at C2. The complicated structures of the thuggacins and their excellent bioactivities have made them attractive synthetic targets for drug development purposes. In 2008, Kirschning et al. completed the first total synthesis of thuggacin B.[4] Their convergent synthesis involved 23 linear steps (longest linear sequence) with 0.6% overall yield.

The cross-metathesis strategy was applied to construct the C11–C12 double bond.[4] Since this cross-metathesis strategy requires the expensive second generation Grubbs catalyst, which makes it hard for scale-up preparations, a study on a new synthetic approach could be meaningful for further applications.

As part of our research program on the synthesis of bioactive natural products,[5] especially those with novel structural features, we herein report a concise approach toward the synthesis of the C1–C12 fragment of the thuggacins.

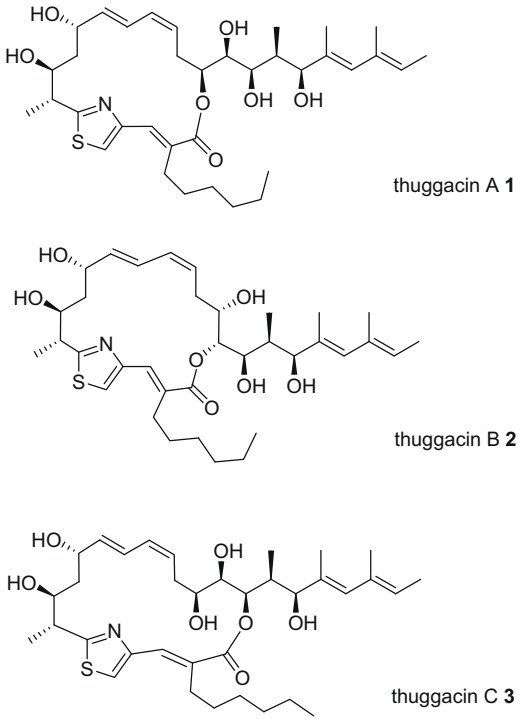


Figure 1. Thuggacin A **1**, B **2**, and C **3**.

* Corresponding authors. Tel.: +852 34008722; fax: +852 22641912 (T. Ye).
E-mail addresses: xuzs@szpku.edu.cn (Z. Xu), bctaoye@inet.polyu.edu.hk (T. Ye).

0957-4166/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2009.08.015

2. Results and discussion

Our retrosynthetic analysis (Scheme 1) of thuggacins A–C is based on a macrolactonization at the C1–C16 ester bond; a Sonogashira coupling reaction would be adopted to form the C12–13 bond linkage, thus the C1–C12 fragment **4** would serve as a key intermediate for the total synthesis of the thuggacins. Fragment **4** can be prepared by a Horner–Wardsworth–Emmnons reaction to form the C2–C3 *E*-double bond, which gives **5** and **6** as the key intermediates. Aldehyde **6** can be derived from iodination of the C11–C12 terminal alkyne, while the thiazole ring can be prepared via Hantzsch condensation of thioamide **7** with bromopyruvate. Thioamide **7** could be obtained from aldehyde **8** via a classical Evans asymmetric aldol reaction.[6] Aldehyde **8** is a known intermediate that can be prepared via different methods.[7–9]

The synthesis of fragment **4** started with ketone **9**, (Scheme 2) which was readily prepared according to reported methods.[10] Firstly, (1*S*)-alpine-9-BBN (93% ee, from Aldrich) mediated Midland reduction[11,12] converted ketone **9** into alcohol **10** in 72% yield with 82% ee (as determined by the Mosher ester method, its absolute stereochemistry was also confirmed by conversion of **10** into a known compound[13]). Silyl-protection of the secondary hydroxyl group, followed by oxidative removal of the PMB ether, produced the primary alcohol **11** (83% yield over two steps). Alcohol **11** was then oxidized to aldehyde **8** with Dess–Martin periodinane.[14] Aldehyde **8** was reacted with the boron enolate of (*R*)-4-benzyl-3-propionyloxazolidin-2-one **12**, in an Evans asymmetric aldol reaction resulting in a 77% yield of **13** in >92% de (by ^{1}H NMR). The resulting secondary alcohol was protected as a *tert*-butyldimethylsilyl (TBS) ether **14**, and the chiral auxiliary moiety was then removed under basic conditions to give acid **14** in 74% yield. It is noteworthy that the base-sensitive TMS-protecting group of **14** was stable under the conditions employed for the cleavage of the Evans chiral auxiliary. With the key intermediate **15** in hand, we were ready for the construction of the thiazole moiety via thioamide **7** as shown in Scheme 1. Thus, acid **15** was first converted into thioamide **7**, in two steps and 62% yield, by amide formation and the Lawesson reagent.[15,16] A modified Hantzsch's thiazole synthesis procedure[17] was employed for the preparation of chiral thiazole **17** to avoid epimerization. Thus the reaction of thioamide **7** with 4 equiv of ethyl bromopyruvate at room temperature, followed by treatment of the resulting thiozoline intermediate with trifluoroacetic anhydride and lutidine at −20 °C provided **17** in 68% yield. After removal of the TMS group in **17**, the palladium-catalyzed hydrostannation/iodination of the alkyne **18** afforded the *E*-vinyl iodide **19** in 87% yield (over two steps).[18] Treatment of **19** with DIBAl-H at −78 °C gave the corresponding aldehyde **6** in 84% yield. A straightforward Horner–Wardsworth–Emmnons olefination of **6** with ethyl 2-(diethoxyphosphinyl)-octanate **5** produced the desired product **4** in 74% yield. The geometry of the *E*-acrylate was ascertained by a sharp acrylic proton at 7.26 ppm, which was identical with the reported value.[4]

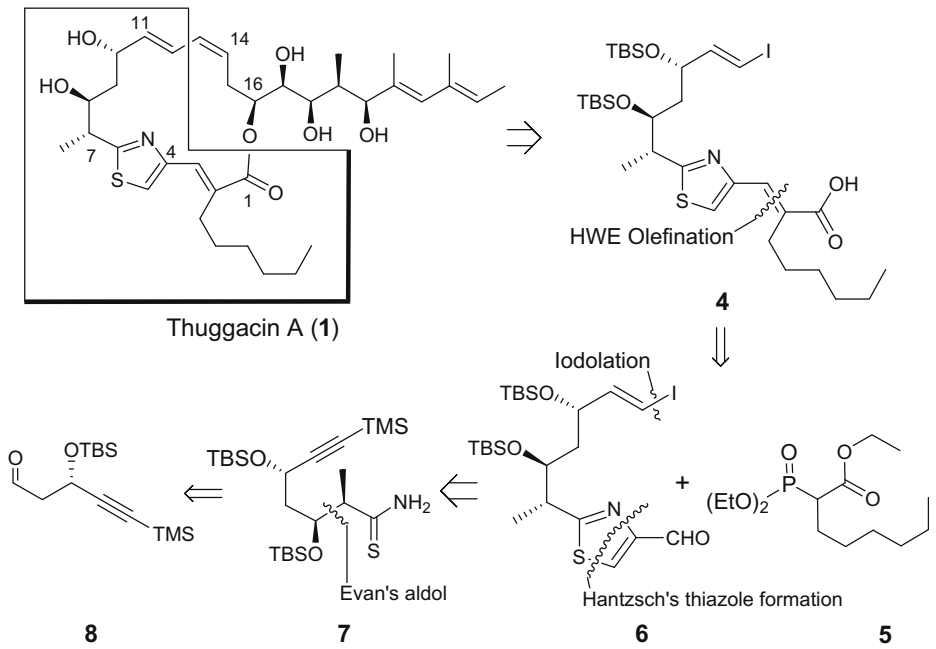
3. Conclusion

In conclusion, we have completed the synthesis of the C1–C12 fragment of thuggacins in 13 linear steps with 4.8% overall yield. The synthesis started with commercially available precursors and no expensive catalysts were applied. Further studies toward the total synthesis thuggacins will be reported in due course.

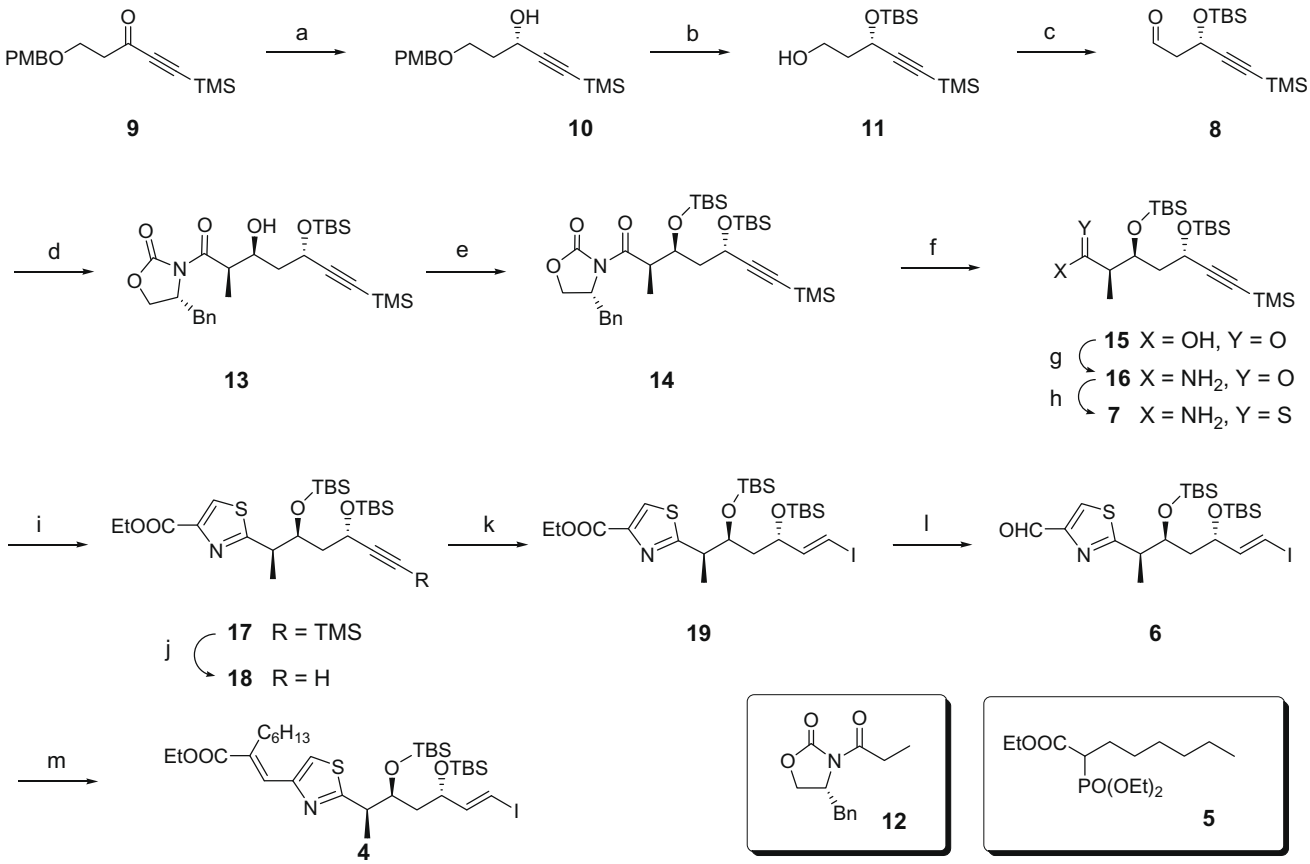
4. Experimental

4.1. General

All non-aqueous reactions were run under an inert atmosphere (nitrogen or argon) with rigid exclusion of moisture from reagents and all reaction vessels were oven-dried. Solvents were distilled prior to use: THF from Na/benzophenone, dichloromethane, DMF, triethylamine, and diisopropylethylamine from CaH_2. NMR spectra were recorded on Bruker Avance DPX 300 MHz or AV 500 MHz spectrometers. Chemical shifts are reported in parts per million (ppm), relative to either a tetramethylsilane internal standard or the signals due to the solvent. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and br = broad), and coupling constants. High-resolution ESI mass spectra were obtained using a JMS SX-102A



Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) (1*S*)-alpine-9BBN, THF, 72%; (b) (i) TBSCl, Imi. DMF, rt; (ii) DDQ, 0 °C, DCM, 83% (two-steps); (c) DMP, DCM, 0 °C, 90%; (d) **12**, Bu_2BOTf, TEA, −78 °C, 77%; (e) TBSOTf, 2,6-lutidine, −20 °C, 96%; (f) $LiOH/H_2O_2$, THF, 0 °C, 74%; (g) $ClCO_2Et$, TEA, THF, 0 °C, then −15 °C NH_3/MeOH, 86%; (h) DCM, Lawesson's reagent, rt, 72%; (i) ethyl bromopyruvate, THF, then −20 °C, TFAA, 2,6-lutidine, 68%; (j) K_2CO_3, EtOH, 95%; (k) $Pd(PPh_3)_2Cl_2$, Bu_3SnH, 0 °C, then −78 °C, I_2, 92%; (l) DIBAL-H, −78 °C 84%; (m) **22**, NaHMDS, −30 °C, 74%.

mass spectrometer. Specific optical rotations were recorded on a Perkin-Elmman 343 polarimeter. TLC was carried out using pre-coated sheets (Qingdao Silica Gel 60-F250, 0.2 mm) and compounds were visualized at 254 nm, and/or stained in *p*-anisole, ninhydrin, or phosphomolybdic acid solution followed by heating. Flash column chromatography was performed using the indicated solvents (with R_f 1.5–3.0 for the desired component) on Qingdao Silica Gel 60 (230–400 mesh ASTM).

4.2. 1-Trimethylsilyl-5-(4-methoxybenzyloxy)-1-pentyn-3-one 9

At −78 °C, to a solution of trimethylsilyl acetylene (2.5 mL, 17.4 mmol) and HMPA (5 mL, 26.0 mmol) in THF (45 mL) was added *n*-butyl lithium (10 mL, 21.0 mmol, 2.1 M in hexane) dropwise. The mixture was stirred for 30 min, then 3-(4-methoxybenzyloxy)-propionaldehyde (2.66 g, 13.6 mmol) in THF (10 mL) was added via a cannula. The solution was stirred at −78 °C for 1 h and allowed to warm to −40 °C within 1.5 h. Saturated aqueous ammonium chloride (40 mL) was added to quench the reaction and the mixture was extracted with ether (50 mL × 2). The combined organic layers were sequentially washed with saturated ammonium chloride (30 mL), water (30 mL), and brine (30 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo. The crude product was dissolved in CH_2Cl_2 (40 mL) and pre-activated MnO_2 powder (8.90 g, 69.5 mmol) was added to the solution in one portion. The reaction mixture was then stirred at room temperature overnight before it was filtered through a pad of Celite. The filtrate was dried over anhydrous magnesium sulfate and evaporated to afford a crude oil, which was purified by flash chromatography (5% ethyl acetate in *n*-hexane) to provide **9** (2.43 g, 62%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 (2H, d, J = 8.1 Hz), 6.78 (2H, d, J = 8.1 Hz), 4.37 (2H, s), 3.70 (2H, t, J = 7.8 Hz), 3.69 (3H, s), 2.73 (2H, t, J = 7.8 Hz), 0.1 (9H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.4, 159.3, 130.1, 129.3, 113.8, 101.9, 98.2, 72.9, 64.5, 55.2, 45.5, −0.8 ppm. HR-ESIMS for $C_{16}H_{23}O_3Si$ (M+H) (*m/z*): calcd 291.1416, observed 291.1394.

4.3. (3*S*)-1-Trimethylsilyl-5-(4-methoxybenzyloxy)-1-pentyn-3-ol 10

To a solution of **9** (1.90 g, 6.5 mmol) in THF (25 mL) under an argon atmosphere was added (*S*)-alpine-9-BBN (17 mL, 8.5 mmol, 0.5 M, 93% ee from Aldrich). The reaction mixture was stirred at 40 °C for 16 h before it was evaporated to dryness in vacuo. The crude residue was re-dissolved in ether (30 mL) and cooled to 0 °C. After ethanolamine (2 mL, 33.1 mmol) was added, the reaction mixture was stirred at 0 °C for 1 h, then it was filtered through a pad of Celite; the filter cake was further washed with ether (50 mL). The combined filtrate was dried over anhydrous magnesium sulfate and concentrated in vacuo to afford a crude oil, which was purified by flash chromatography (8% ethyl acetate in *n*-hexane) to provide **10** (1.40 g, 72%, 82% ee[13]) as a colorless oil. $[\alpha]_D^{20} = -13.7$ (*c* 2.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (2H, d, J = 8.0 Hz), 6.78 (2H, d, J = 8.0 Hz), 4.50 (1H, m), 4.41–4.36 (2H, m), 3.75 (1H, m), 3.73 (3H, s), 3.58 (1H, m), 2.98 (1H, br s), 2.00–1.98 (1H, m), 1.87–1.84 (1H, m), 0.09 (9H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 129.9, 129.4, 113.7, 106.5, 89.0, 72.8,

67.1, 61.2, 55.1, 36.8, −0.1 ppm. HR-ESIMS for $C_{16}H_{25}O_3Si$ (M+H) (*m/z*): calcd 293.1494, observed 293.1504.

4.4. (3*S*)-1-Trimethylsily-3-(*tert*-butyldimethylsilanyl-oxy)-1-pentyne-5-ol 11

To a solution of **10** (1.1 g, 3.8 mmol) in DMF (20 mL) were added *tert*-butyldimethylsilyl chloride (0.68 g, 4.5 mmol) and imidazole (0.61 g, 9.0 mmol) at room temperature. The reaction mixture was then stirred for 16 h before it was quenched by saturated sodium bicarbonate (20 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with water (50 mL) and brine (50 mL), evaporated in vacuo to afford a crude oil. The crude product, without further purification, was dissolved in CH_2Cl_2 (50 mL), after which DDQ (890 mg, 3.9 mmol) was added to the above solution at 0 °C. One hour later, the reaction was diluted with CH_2Cl_2 (100 mL) and washed with saturated aqueous sodium thiosulfate solution (50 mL × 2), followed with water (50 mL) and brine (50 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography (15% ethyl acetate in *n*-hexane) to give compound **11** (0.91 g, 83%) as a yellow syrup. $[\alpha]_D^{20} = -9.8$ (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.61 (1H, t, *J* = 5.6 Hz), 3.93–3.89 (1H, m), 3.81–3.75 (1H, m), 2.33 (1H, br s), 1.95–1.89 (2H, m), 0.90 (9H, s), 0.16 (3H, s), 0.15 (9H, s), 0.13 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 106.8, 90.0, 62.8, 60.3, 40.2, 25.9, 18.3, −0.13, −4.35, −4.95 ppm. HR-ESIMS for $C_{14}H_{31}O_2Si_2$ (M+H) (*m/z*): calcd 287.1862, observed 287.1869.

4.5. (3*S*)-5-Trimethylsily-3-(*tert*-butyldimethylsilanyl-oxy)-4-pentynaldehyde 8

To a solution of **11** (0.91 g, 3.2 mmol) in CH_2Cl_2 (20 mL) was added Dess–Martin periodate (5.30 g, 126.0 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h before it was diluted with ether (80 mL) and filtered through a pad of Celite. The filtrate was washed with saturated sodium bicarbonate (30 mL), water (30 mL), and brine (30 mL), and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the residue was purified by flash chromatography (5% ethyl acetate in *n*-hexane) to furnish compound **8** (0.80 g, 90%) as a yellow syrup. $[\alpha]_D^{20} = -13.2$ (*c* 2.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.79 (1H, t, *J* = 2.1 Hz), 4.84 (1H, dd, *J* = 7.2, 4.8 Hz), 2.75 (1H, ddd, *J* = 16.2, 7.2, 2.1 Hz), 2.63 (1H, ddd, *J* = 16.2, 4.8, 2.1 Hz), 0.87 (9H, s), 0.146 (12H, s, overlapped), 0.11 (3H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.2, 105.6, 90.6, 58.8, 51.4, 25.8, 18.2, −0.24, −4.42, −5.00 ppm. HR-ESIMS for $C_{14}H_{29}O_2Si_2$ (M+H) (*m/z*): calcd 285.1706, observed 285.1694.

4.6. (*R*)-4-Benzyl-3-[(*S*)-(5-*tert*-butyldimethylsilanyloxy)-(*S*)-3-hydroxy-(*R*)-2-methyl-7-trimethylsilyl-hept-6-ynoyl]-oxazolidin-2-one 13

At −20 °C, to a solution of (*R*)-4-benzyl-3-propionyl-oxazolidin-2-one **12** (0.65 g, 2.8 mmol) in CH_2Cl_2 (25 mL) was added *n*-Bu_2BOTf (0.8 mL, 3.6 mmol) dropwise, followed by triethylamine (0.3 mL, 3.9 mmol). The mixture was allowed to warm to 0 °C within 1 h and stirred at 0 °C for 15 min. The mixture was then cooled to −78 °C, and aldehyde **8** (0.8 g, 2.8 mmol) in CH_2Cl_2 (8 mL) was added. After being stirred at −78 °C for 3 h, the reaction was warmed to 0 °C and quenched by the addition of phosphate buffer (pH 7.0, 15 mL) and a pre-mixed solution of methanol—hydrogen peroxide (30% solution) (2:1, 8 mL). The mixture was further stirred at 0 °C for 1 h. Volatiles were removed in vacuo, the aqueous layer was extracted with ether (50 mL × 3). The combined organic phase was sequentially washed with saturated sodium bicarbonate (30 mL) and brine (30 mL), and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (15% ethyl acetate in *n*-hexane) to furnish the product **13** (1.13 g, 77%) as a colorless oil. $[\alpha]_D^{20} = -44.3$ (*c* 1.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26–7.23 (2H, m), 7.20–7.18 (1H, m), 7.14–7.11 (2H, m), 4.64–4.62 (1H, m), 4.59 (1H, dd, *J* = 7.8, 3.4 Hz), 4.23–4.20 (1H, m), 4.12 (1H, t, *J* = 9.0 Hz), 4.08 (1H, dd, *J* = 9.0, 2.8 Hz), 3.76–3.74 (1H, m), 3.18 (1H, dd, *J* = 13.0, 3.2 Hz), 2.70 (1H, dd, *J* = 13.0, 9.5 Hz), 1.80 (1H, ddd, *J* = 14.0, 10.0, 3.5 Hz), 1.68 (1H, ddd, *J* = 14.0, 8.0, 1.9 Hz), 1.18 (3H, d, *J* = 7.0 Hz), 0.87 (9H, s), 0.09, (9H, s), 0.08 (3H, s), 0.06 (3H, s) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 176.5, 153.1, 135.3, 129.5, 129.0, 127.4, 106.9, 89.5, 68.5, 66.2, 61.2, 55.3, 42.5, 41.6, 37.8, 25.9, 18.2, 11.3, −0.18, −4.5, −5.0 ppm. HR-ESIMS for $C_{27}H_{44}NO_5Si_2$ (M+H) (*m/z*): calcd 518.2758, observed 518.2775.

4.7. (*R*)-4-Benzyl-3-[(*S*)-3-(*R*)-5-bis-(*tert*-butyl-dimethyl-silanyloxy)-(*R*)-2-methyl-7-trimethylsilyl-hept-6-ynoyl]-oxazolidin-2-one 14

To a solution of **13** (1.10 g, 2.2 mmol) in CH_2Cl_2 (15 mL) were sequentially added 2,6-lutidine (0.5 mL, 4.4 mmol) and TBSOTf (1.0 mL, 4.2 mmol) dropwise at −20 °C. The reaction was allowed to warm to 0 °C within 4 h, and then quenched by the addition of phosphate buffer (pH 7.0, 25 mL). The mixture was extracted with ethyl acetate (50 mL × 3). The combined organic phase was washed with brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed in vacuo, after which the residue was purified by flash chromatography (5% ethyl acetate in *n*-hexane) to produce the title compound **14** (1.32 g, 96%) as a colorless oil. $[\alpha]_D^{20} = -38.4$ (*c* 2.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32–7.30 (2H, m), 7.27–7.25 (1H, m), 7.21–7.19 (2H, m), 4.61–4.58 (1H, m), 4.44 (1H, dd, *J* = 8.5, 4.8 Hz), 4.09–4.01 (3H, m), 3.98–3.96 (1H, m), 3.28 (1H, dd, *J* = 13.5, 2.8 Hz), 2.78 (1H, dd, *J* = 13.5, 4.5 Hz), 2.04–1.95 (2H, m), 1.21 (3H, d, *J* = 7.0 Hz), 0.90 (9H, s), 0.87 (9H, s), 0.19 (3H, s), 0.17 (3H, s), 0.16 (9H, s), 0.08 (3H, s), 0.01 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.0, 153.1, 135.6, 129.6, 129.1, 127.5, 107.8, 89.5, 70.5, 66.0, 60.2, 55.9, 44.7, 43.2, 37.8, 26.1, 26.0, 18.4, 18.2, 11.8, −0.1, −3.5, −4.05, −4.17, −4.72 ppm. HR-ESIMS for $C_{33}H_{58}NO_5Si_3$ (M+H) (*m/z*): calcd 632.3622, observed 632.3596.

4.8. (2*R*,3*S*,5*S*)-3,5-Di-(*tert*-butyldimethylsilyloxy)-2-methyl-7-trimethylsilyl-6-heptynoic-acid 15

To a solution of **14** (1.25 g, 2.0 mmol) in THF (25 mL) were sequentially added H_2O_2 (0.36 g, 3.2 mmol, 30% solution) and LiOH (12 mL, 12.0 mmol, 1.0 M in water) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h, then allowed to warm to room temperature, and stirred for 16 h. The reaction was quenched by saturated aqueous sodium thiosulfate solution (30 mL). THF was removed under reduced pressure and the aqueous layer was extracted with ether (50 mL × 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography (8% ethyl acetate in *n*-hexane) to give **15** as a colorless oil (0.68 g, 74%). $[\alpha]_D^{20} = -28.8$ (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.35 (1H, dd, *J* = 8.4, 4.8 Hz), 4.22–4.20 (1H, m), 2.63–2.61 (1H, m), 1.85–1.80 (1H, m), 1.77–1.73 (1H, m), 1.06 (3H, d, *J* = 7.0 Hz), 0.82 (9H, s), 0.81 (9H, s), 0.10 (3H, s), 0.09 (9H, s), 0.08 (3H, s), 0.04 (3H, s), 0.01 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.3, 107.0, 89.8, 70.1, 60.3, 44.7, 43.5, 26.0, 25.9, 18.3, 18.1, 10.0, −0.17, −3.78, −4.12, −4.43, −4.70 ppm. HR-ESIMS for $C_{23}H_{49}O_4Si_3$ (M+H) (*m/z*): calcd 473.2938, observed 473.2915.

4.9. (2*R*,3*S*,5*S*)-3,5-Di-(*tert*-butyldimethylsilyloxy)-2-methyl-7-trimethylsilyl-6-heptynamide 16

To a 0 °C solution of acid **15** (0.53 g, 1.1 mmol) in THF (15 mL) were added ethyl chloroformate (0.14 mL, 1.5 mmol) and triethylamine (0.22 mL, 1.6 mmol). The reaction mixture was stirred at 0 °C for 0.5 h, then cooled to −15 °C before methanolic solution of ammonia (2.5 mL, 10 mmol, 4.0 M) was added. Then the reaction mixture was stirred at −15 °C for another 1.5 h and diluted with ethyl acetate (100 mL). The organic phase was washed with water (100 mL × 3) and brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the residue was purified by flash chromatography (5% ethyl acetate in *n*-hexane) to furnish the desired compound **16** (0.46 g, 86%) as a yellow oil. $[\alpha]_D^{20} = -34.5$ (*c* 3.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.47 (1H, br s), 6.30 (1H, br s), 4.31 (1H, dd, *J* = 8.8, 4.5 Hz), 3.89–3.86 (1H, m), 2.45–2.40 (1H, m), 1.74–1.65 (2H, m), 0.92 (3H, d, *J* = 7.0 Hz), 0.75 (9H, s), 0.72 (9H, s), 0.02 (3H, s), −0.02 (9H, s), −0.03 (3H, s), −0.04 (3H, s) ppm, −0.08 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.2, 107.4, 90.0, 71.2, 59.9, 45.4, 42.2, 26.0, 18.2, 18.0, 12.5, −0.20, −3.34, −4.11, −4.47, −4.54 ppm. HR-ESIMS for $C_{23}H_{50}NO_3Si_3$ (M+H) (*m/z*): calcd 472.3098, observed 472.3101.

4.10. (2*R*,3*S*,5*S*)-3,5-Di-(*tert*-butyldimethylsilyloxy)-2-methyl-7-trimethylsilyl-6-heptyne-thioamide 7

To a solution of **16** (0.40 g, 0.85 mmol) in CH_2Cl_2 (10 mL) was added Lawesson's reagent (0.69 g, 1.7 mmol) at room temperature. The reaction mixture was stirred for 16 h before it was concentrated in vacuo. The residue was dissolved in ether (100 mL) and washed with saturated solution of sodium bicarbonate (50 mL) and brine (50 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure, the residue was purified by flash chromatography (5% ethyl acetate in *n*-hexane) and gave **7** (0.29 g, 72%) as a yellow liquid. $[\alpha]_D^{20} = -26.8$ (*c* 0.85, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (1H, br s), 7.80 (1H, br s), 4.35 (1H, dd, *J* = 8.5, 4.8 Hz), 4.05–4.01 (1H, m), 2.84–2.79 (1H, m), 1.82–1.78 (1H, m), 1.73–1.68 (1H, m), 1.21 (3H, d, *J* = 7.5 Hz), 0.85 (9H, s), 0.83 (9H, s), 0.02 (3H, s), 0.01 (9H, s), −0.01 (3H, s), −0.02 (3H, s), −0.03 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 212.1, 107.4, 90.2, 72.8, 60.0, 51.2, 42.1, 26.0, 25.9, 18.2, 18.0, 15.7, −0.20, −3.56, −4.27, −4.31, −4.54 ppm. HR-ESIMS for $C_{23}H_{50}NO_2Si_3S$ (M+H) (*m/z*): calcd 488.2870, observed 488.2880.

4.11. 2-[(1′*R*,2′*S*,4′*S*)-2′,4′-Di(*tert*-butyldimethyl-silyloxy)-1′-methyl-6′-trimethylsilyl-5′-hexynyl]-4-thiazolecarboxy-lic acid, ethyl ester 17

To a solution of **7** (0.15 g, 0.3 mmol) in THF (15 mL) was added ethyl bromopyruvate (0.19 mL, 1.5 mmol), and the reaction mixture was stirred at room temperature for 1 h. Then the reaction mixture was cooled to −20 °C, a pre-mixed solution of trifluoroacetic anhydride (0.11 mL, 0.8 mmol) and 2,6-lutidine (0.18 mL, 1.5 mmol) in THF (5 mL) was added dropwise via a cannula over 30 min. The reaction mixture was stirred at −20 °C for 1.5 h and warmed to 0 °C within 1 h. Phosphate buffer (pH 7.0, 15 mL) was used to quench the reaction. Volatiles were removed in vacuo, and the aqueous phase was extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with water (30 mL) and brine (30 mL), and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (1% ethyl acetate in *n*-hexane) to produce the desired compound **17** (0.12 g, 68%) as a yellow oil. $[\alpha]_D^{20} = -18.4$ (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (1H, s), 4.42–4.37 (3H, m), 4.26–4.22 (1H, m), 3.41–3.39 (1H, m), 1.92 (1H, ddd, *J* = 14.0, 8.5, 2.8 Hz), 1.67 (1H, ddd, *J* = 14.0, 6.5, 2.0 Hz), 1.41 (3H, d, *J* = 7.0 Hz), 1.38 (3H, t, *J* = 7.0 Hz), 0.89 (9H, s), 0.86 (9H, s), 0.15 (3H, s), 0.14 (3H, s), 0.13 (9H, s), 0.06 (3H, s), −0.13 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.1, 161.9, 146.5, 127.2, 107.4, 90.0, 72.4, 61.2, 60.4, 44.2, 43.5, 26.1, 26.0, 18.4, 18.2, 14.5, −0.12, −3.66, −4.14, −4.35 ppm. HR-ESIMS for $C_{28}H_{54}NO_4Si_3S$ (M+H) (*m/z*): calcd 584.3081, observed 584.3088.

4.12. 2-[(1′*R*,2′*S*,4′*S*)-2′,4′-Di(*tert*-butyldimethyl-silyloxy)-1′-methyl-5′-hexynyl]-4-thiazole carboxylic acid, ethyl ester 18

To a solution of **17** (0.12 g, 0.2 mmol) in absolute ethanol (10 mL) was added K_2CO_3 (0.30 g, 2.17 mmol), the mixture was stirred at room temperature for 2 h before it was poured into a saturated aqueous ammonia chloride solution (20 mL) and extracted with ethyl acetate (25 mL × 3). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by flash chromatography (3% ethyl acetate in *n*-hexane) to give compound **18** (0.098 g, 95%) as a yellow oil. $[\alpha]_D^{20} = -21.4$ (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (1H, s), 4.42–4.38 (3H, m), 4.24–4.22 (1H, m), 3.40 (1H, dd, *J* = 7.0, 3.5 Hz), 2.40 (1H, d, *J* = 2.0 Hz), 1.93 (1H, ddd, *J* = 14.5, 8.5, 2.8 Hz), 1.70 (1H, ddd, *J* = 14.5, 6.5, 2.0 Hz), 1.42 (3H, d, *J* = 7.0 Hz), 1.38 (3H, t, *J* = 7.0 Hz) 0.89 (9H, s), 0.86 (9H, s), 0.15 (3H, s), 0.13 (3H, s), 0.06 (3H, s), −0.12 (3H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.9, 161.8, 146.5, 127.2, 85.4, 73.4, 72.4, 61.2, 59.8, 44.3, 43.7, 26.1, 26.0, 18.3, 18.2, 14.7, 14.5, −3.79, −4.18, −4.19, −4.45 ppm. HR-ESIMS for $C_{25}H_{46}NO_4Si_2S$ (M+H) (*m/z*): calcd 512.2686, observed 512.2688.

4.13. 2-[(1′*R*,2′*S*,4′*S*)-2′,4′-Di-(*tert*-butyldimethyl-silyloxy)-6′-iodo-1′-methyl-(*E*)-5′–hexenyl]-4-thiazole carboxylic acid, ethyl ester 19

To a solution of **18** (0.094 g, 0.2 mmol) in THF (7 mL) was added $Pd(PPh_3)_2Cl_2$ (5 mg, 3% mmol catalyst) under an argon atmosphere. The solution was cooled to 0 °C, and tri-*n*-butylstannane (0.14 mL, 0.5 mmol) was added via a cannula. The reaction mixture was then stirred at 0 °C for 2 h, and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 mL) and titrated with a solution of iodine in CH_2Cl_2 (0.02 g/mL) at −78 °C until a purple-brown color persisted. The reaction was then added to a saturated aqueous sodium thiosulfate solution (30 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with saturated aqueous sodium thiosulfate solution (30 mL), water (30 mL), and brine (30 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was further purified by flash chromatography (3% ethyl acetate in *n*-hexane) to give compound **19** (0.10 g, 92%) as a yellow oil. $[\alpha]_D^{20} = -27.2$ (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (1H, s), 6.48 (1H, dd, *J* = 14.5, 7.5 Hz), 6.25 (1H, d, *J* = 14.5 Hz), 4.40 (2H, q, *J* = 7.0 Hz), 4.15–4.10 (2H, m), 3.34 (1H, dd, *J* = 7.0, 3.5 Hz), 1.76 (1H, ddd, *J* = 14.0, 8.5, 4.5 Hz), 1.41 (3H, d, *J* = 7.0 Hz), 1.39 (3H, t, *J* = 7.0 Hz), 1.32–1.29 (1H, m), 0.87 (9H, s), 0.86 (9H, s), 0.06 (3H, s), 0.05 (3H, s), 0.02 (3H, s), 0.01 (3H, s) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8, 161.8, 149.3, 146.6, 127.2, 77.3, 73.2, 72.6, 61.3, 44.6, 42.9, 26.1, 26.0, 18.3, 18.2, 14.8, 14.5, −3.7, −4.1, −4.2, −4.4 ppm. HR-ESIMS for $C_{25}H_{47}INO_4Si_2S$ (M+H) (*m/z*): calcd 640.1809, observed 640.1832.

4.14. 2-[(1′*R*,2′*S*,4′*S*)-2′,4′-Di-(*tert*-butyldimethyl-silyloxy)-6′-iodo-1′-methyl-(*E*)-5′–hexenyl]-4-formylthiazole 6

To a solution of **19** (0.09 g, 0.14 mmol) in THF (10 mL) at −78 °C, DIBAL-H (0.18 mL, 0.3 mmol, 1.7 M in hexane) was added under an argon atmosphere. The reaction mixture was stirred for 2 h, and

quenched by careful addition of methanol (3 mL) before it was poured into aqueous sodium potassium tartate (10 mL, 1 M). Volatiles were removed in vacuo, and the aqueous phase was extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by flash chromatography (3% ethyl acetate in *n*-hexane) to produce compound **6** (0.07 g, 84%) as a colorless oil. $[\alpha]_D^{20} = -14.3$ (*c* 1.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 10.0 (1H, s), 8.07 (1H, s), 6.47 (1H, dd, *J* = 14.5, 7.5 Hz), 6.25 (1H, d, *J* = 14.5 Hz), 4.19–4.13 (2H, m), 3.34 (1H, ddd, *J* = 7.0, 3.5 Hz), 1.76 (1H, ddd, *J* = 14.0, 8.5, 4.5 Hz), 1.43 (3H, d, *J* = 7.0 Hz), 1.37 (1H, ddd, *J* = 14.0, 8.5, 3.5 Hz), 0.87 (9H, s), 0.86 (9H, s), 0.07 (3H, s), 0.06 (3H, s), 0.04 (3H, s), −0.09 (3H, s) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 185.2, 174.5, 154.4, 149.2, 127.0, 77.3, 73.3, 72.7, 44.6, 42.6, 26.1, 26.0, 18.3, 18.2, 14.5, 1.15, −3.58, −4.16, −4.31 ppm. HR-ESIMS for $C_{23}H_{43}INO_3Si_2S$ (M+H) (*m*/*z*): calcd 596.1546, observed 596.1534.

4.15. Ester 4

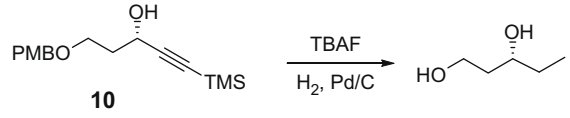
To a solution of ethyl 2-(diethoxyphosphinyl)-octanoate **5** (0.05 g, 0.2 mmol) in THF (5 mL) at −30 °C, NaHMDS (0.24 mL, 0.12 mmol, 0.5 M in THF) was added dropwise. After being stirred for 20 min, a solution of **6** (0.035 g, 0.06 mmol) in THF (3 mL) was added via a cannula. The reaction mixture was then stirred at −30 °C for 30 min and allowed to warm to 0 °C within 1 h, before it was poured into a saturated aqueous ammonium chloride solution (20 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by flash chromatography (5% ethyl acetate in *n*-hexane) to produce compound **4** (*E* isomer, 0.34 g, 74%) as a colorless oil. $[\alpha]_D^{20} = -36.3$ (*c* 1.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.51 (1H, s), 7.26 (1H, s), 6.48 (1H, dd, *J* = 15.5, 7.5 Hz), 6.24 (1H, d, *J* = 15.5 Hz), 4.25 (2H, q, *J* = 7.0 Hz), 4.15–4.12 (2H, m), 3.30 (1H, dd, *J* = 7.0, 3.5 Hz), 2.93–2.90 (2H, m), 1.77 (1H, ddd, *J* = 14.0, 8.5, 4.5 Hz), 1.40 (3H, d, *J* = 7.0 Hz), 1.37 (3H, t, *J* = 7.0 Hz), 1.33–1.24 (9H, m), 0.88 (9H, s), 0.87 (9H, s), 0.06 (3H, s), 0.05 (3H, s), 0.03 (3H, s), −0.09 (3H, s) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3, 169.0, 151.6, 149.4, 133.9, 130.2, 121.5, 77.3, 73.3, 73.0, 60.8, 44.6, 42.7, 32.0, 29.8, 29.4, 28.0, 26.1, 26.0, 22.8, 18.3, 18.2, 14.7, 14.5, 14.2, −3.6, −4.2, −4.3, −4.4 ppm. HR-ESIMS for $C_{33}H_{61}INO_4Si_2S$ (M+H) (*m*/*z*): calcd 750.2904, observed 750.2880.

Acknowledgments

We acknowledge financial support from the Shenzhen Bureau of Science, Technology, and Information (Shenzhen Key Laboratory Advancement Scheme and Basic Research Scheme, 08systs-01). Z.S.X. would like to thank the support from Shenzhen foundation for R&D of Sciences and Technologies (SZKJ-2007011, SY200806300179A), Nanshan Branch of Shenzhen Science & Technology (NANKEYUAN2007019), and Natural Science Foundation of GuangDong Province (8451805704000656).

References

1. Steinmetz, H.; Irschik, H.; Kunze, B.; Reichenbach, H.; Hofle, G.; Jansen, R. *Chem. Eur. J.* **2007**, *13*, 5822–5832.
2. Irschik, H.; Reichenbach, H.; Hofle, G.; Jansen, R. *J. Antibiot.* **2007**, *60*, 733–738.
3. Bock, M.; Miller, R.; Buntin, K.; Kirschning, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2308–2311.
4. Bock, M.; Dehn, R.; Kirschning, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9134–9137.
5. (a) Li, S.; Liang, S.; Tan, W. F.; Xu, Z. S.; Ye, T. *Tetrahedron* **2009**, *65*, 2695–2702; (b) Ren, Q.; Dai, L.; Zhang, H.; Tan, W.; Xu, Z. S.; Ye, T. *Synlett* **2008**, 2379–2383; (c) Li, S.; Liang, S.; Xu, Z. S.; Ye, T. *Synlett* **2008**, 569–574; (d) Chen, Z.; Ye, T. *New J. Chem.* **2006**, *30*, 518–520; (e) Pang, H. W.; Xu, Z. S.; Chen, Z. Y.; Ye, T. *Lett. Org. Chem.* **2005**, *2*, 699–702; (f) Pang, H. W.; Xu, Z. S.; Ye, T. *Lett. Org. Chem.* **2005**, *2*, 703–706; (g) Xu, Z. S.; Ye, T. *Tetrahedron: Asymmetry* **2005**, *16*, 1905–1912; (h) Chen, H. L.; Xu, Z. S.; Ye, T. *Tetrahedron* **2005**, 11132–11140; (i) Chen, Z. Y.; Ye, T. *Synlett* **2005**, 2781–2785; (j) Xu, Z. S.; Chen, Z. Y.; Ye, T. *Tetrahedron: Asymmetry* **2004**, *15*, 355–363; (k) Peng, Y. G.; Pang, H. W.; Ye, T. *Org. Lett.* **2004**, *6*, 3781–3784; (l) Chen, Z. Y.; Deng, J. G.; Ye, T. *ARKIVOC* **2003**, *Part VII*, 268–285; (m) Xu, Z. S.; Peng, Y. G.; Ye, T. *Org. Lett.* **2003**, *5*, 2821–2824.
6. Evans, D. A.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
7. Reddy, Y. K.; Falck, J. R. *Org. Lett.* **2002**, *4*, 969–971.
8. Paquette, L. A.; Duan, M.; Konetzki, I.; Kempmann, C. *J. Am. Chem. Soc.* **2002**, *124*, 4257–4270.
9. Smith, A. B.; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935–3948.
10. Marshall, J. A.; Eidam, P.; Eidam, H. S. *J. Org. Chem.* **2006**, *71*, 4840–4844.
11. Midland, M. M.; Macdowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867–869.
12. Midland, M. M.; Tramontano, A. *J. Org. Chem.* **1978**, *43*, 1470–1471.
13. Esterification of alcohol **10** with (*S*)-MTPA chloride was carried out according to Mosher's method (Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2173–2176). ^1H NMR spectrum showed a clear split of the MTPA's methoxy signal of two isomers (δ_R = 3.86, δ_S = 3.79, Int_S:Int_R = 10:1), as well as the TMS methyl signal of two isomers (δ_S = 0.15, δ_R = 0.06, Int_S:Int_R = 10:1), thus ee% value was determined as around 82%. The (3*S*)-configuration of alcohol **10** was confirmed by removal of the TMS group and a subsequent hydrogenation to produce the known (3*R*)-1,3-pentanediol and the specific rotation data for this product were $[\alpha]_D^{20} = -17.4$ (*c* 1.88, EtOH), which were comparable to those reported in the literature. The reported specific rotation data for (3*R*)-1,3-pentanediol were $[\alpha]_D^{20} = -22.5$ (*c* 1.06, EtOH) (Bertelsen, S.; Diner, P.; Johansen, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 1536–1537); and the specific rotation data for (3*S*)-1,3-pentanediol were reported as $[\alpha]_D^{20} = +16.6$ (*c* 1.04, EtOH) (Yang, D.; Zhang, Y. H.; Zhang, D. W. *J. Org. Chem.* **2004**, *69*, 7577–7581).



10

14. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
15. Allali, H.; Tabti, B.; Alexandre, C.; Huet, F. *Tetrahedron: Asymmetry* **2004**, *15*, 1331–1333.
16. Rega, M.; Candal, P.; Jimenez, C.; Rodriguez, J. *Eur. J. Org. Chem.* **2007**, *6*, 934–942.
17. (a) Bredenkamp, M. W.; Holzapfel, C. W.; Van Zyl, W. J. *Synth. Commun.* **1990**, *20*, 2235–2238; (b) Dondoni, A.; Merino, P.. In *Comprehensive Heterocyclic Chemistry II*; Pergamon, 1996; Vol. 3. pp 432–434.
18. Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857–1867.