Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 2091–2095
Tetrahedron

Asymmetric aldol reactions using catalytic D(+)-proline: a new, economic and practical approach to a commonly employed C1–C6 keto-acid synthon of the epothilones

Yansong Zheng[a] and Mitchell A. Avery[a,b,c,*]

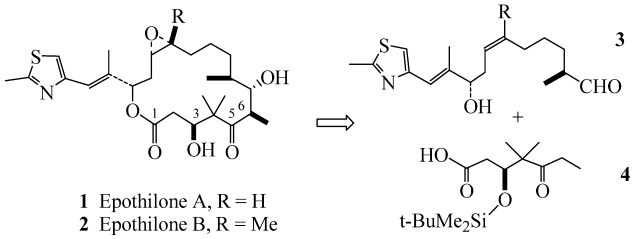
[a]*Department of Medicinal Chemistry, University of Mississippi, University, MS 38677, USA*
[b]*National Center for Natural Products Research, School of Pharmacy, University, MS 38677, USA*
[c]*Department of Chemistry & Biochemistry, University of Mississippi, University, MS 38677, USA*

Received 25 November 2003; revised 19 December 2003; accepted 19 December 2003

Abstract—A new approach to ketoacid **4**, a common C1–C6 fragment used in the total synthesis of epothilones was initiated by direct aldol reaction of acetone with a pivaldehyde-like substance **5**, catalyzed with D-proline, leading to a 2,6-diketoalcohol with better than 99% ee. Further intramolecular closure of the diketone **8** followed by oxidation of the silyl protected hydroxycyclohexenone **14** led to the desired product **4**. None of the steps have been optimized, yet the overall yield for the four-step process is 31%. The use of commercially available D-proline to construct the chiral center of **4** under very mild reaction conditions provided an economical and practical method for its construction.

1. Introduction

Since their discovery in 1993,[1] epothilones A–D have evoked a strong interest from the scientific community because of their taxotere-like anticancer activity.[2] One of the common strategies for total synthesis of epothilones includes construction of a C1–C6 fragment, for example, a ketoacid **4**, which undergoes aldol condensation with an aldehyde to set important stereochemical features of the epothilone architecture (Scheme 1).[3–8]

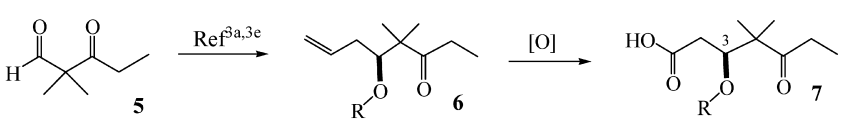


1 Epothilone A, R = H
2 Epothilone B, R = Me

Scheme 1.

The key for preparation of the C1–C6 fragment is to introduce a hydroxyl group at the C-3 position in an optically pure form. Nicolaou et al. has used Brown's allyl isopinocampheyl borane reagent [(+)-Ipc_2B(allyl)] to react with ketoaldehyde **5** to provide enantiomerically pure homoallyl alcohol (ee>98%), which was then oxidized to an alcohol derivative, ketoacid **7** (Scheme 2).[3a,e]

Wessjohann et al. obtained the alcohol **7** (92% de, R=*t*-$BuMe_2Si$) by a chromium-Reformatsky reaction of a chiral *N*-bromoacyloxazolidinone with the ketoaldehyde **5**, wherein the amide portion of the alcohol was hydrolyzed to ketoacid.[8] We found that the aldol reaction of chiral *N*-methylthioacetyloxazolidinones with the ketoaldehyde **5** can furnish the alcohol **7**, but the enantioselectivity is reversed if the boron reagents for forming the boron-enolate were different. With dibutylboron triflate the desired *S*-isomer was obtained in 54% de.[9] DeBrabander et al. reported that aldol reaction of acetylbornanesultam with the ketoaldehyde **5** can afford the alcohol **7** (R=*t*-$BuMe_2Si$) with 88% de.[10] Recently Altmann et al.[7] scaled up



Scheme 2.

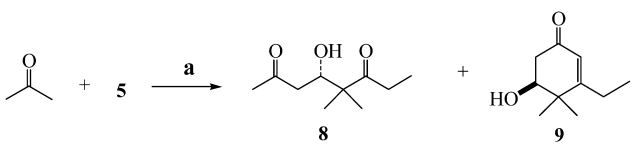
Keywords: Epothilone; C1–C6 Keto-acid synthon; Asymmetric aldol reaction; Proline.
* Corresponding author. Tel.: +1-662-915-5879; fax: +1-662-915-5863; e-mail address: mavery@olemiss.edu

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.048

DeBrabander's synthesis, and determined the sign of optical rotation for *S*-ketoacid **4** should be negative instead of positive as reported by Nicolaou and DeBrabander's group, which was also confirmed by Avery.[11] Besides the above asymmetric aldol reactions, Kalesse et al. has made use of Sharpless's asymmetric epoxidation to establish the chiral center at the hydroxyl carbon (C-3), and furnished the ketoacid **7** by at least 13 steps from a chiral epoxide.[3] In addition, optical resolution has been used to prepare the ketoacid **7**. Shioji et al. reported that the corresponding racemic ketoacid *tert*-butyl ester of **7** can be resolved to its optical pure *S*-isomer by lipase.[12] Liu et al. treated a racemic terminal epoxide of a vinyl ketone with Jacobson's hydrolytic kinetic resolution to afford its required enantiomer, which was transferred to ketoacid **7** by carbomethoxylation and hydrolysis.[6] Here we report that the key C-3 chiral center connected with **4** could be introduced by the direct aldol condensation of ketoaldehyde **5** with acetone catalyzed by D-proline. Processing of the terminal methylketone group to a carboxylic acid was achieved in an unexpected fashion as outlined below.

2. Results and discussion

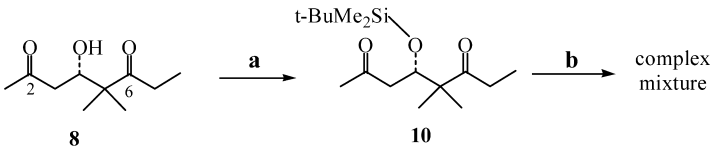
In 2000, List et al. found that the reaction of acetone with branched aldehydes such as isobuytraldehyde in the presence of L-proline can give very high yields and very high enantioselectivities of aldol products.[13] If List's conditions were used to construct the key C-3 chiral center such as **7**, it could provide an outstanding method for preparation of ketoacid **5**. We found that the 24 h reaction of D-proline (35 mol%) in DMSO/acetone with ketoaldehyde **5**[14] furnished aldol product **8** in 75% yield and with better than 99% ee (Mosher ester analysis). In addition, 1.9% of intramolecular cyclization product **9** was obtained from **8** (Scheme 3).



Scheme 3. (a) 0.35 equiv. D-proline, DMSO–acetone 4:1, rt, 24 h, 75% yield and >99% ee for **8**, 1.9% yield for **9**.

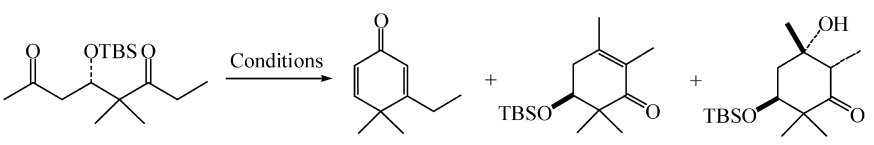
Silylation of **8** with *tert*-butyldimethylsilyl triflate (TBSOTf) afforded protected product **10** in 90% yield. Transformation of the methyl ketone group of **10** by selective bromoform reaction would be the most expedient synthetic route to ketoacid **4**. Unfortunately, attempted bromoform or iodoform reaction of **10** gave only complex mixtures when **10** was halogenated under basic conditions (Scheme 4). This is not surprising given the availability of 7 carbonyl α-protons in **10**, for which multiple reaction pathways can be envisioned for **10** under strongly basic conditions. Alternatively, low temperature kinetic enolization of the C1 methyl ketone of **7** or **9** providing an easily oxidizable silyl enol ether is an approach currently being investigated.

Nonetheless, it was recognized that the intramolecular aldol product, hydroxycyclohexenone **9**, could be transformed to ketoacid **4** by oxidative cleavage after its protection with various groups. For this study, the *tert*-butyldimethylsilyl moiety was used affording **10**. Results of intramolecular aldol reaction of **10** are shown in Table 1. When NaOH was reacted with **10** in H_2O/ethanol (1:1), the major product **12** was produced in 50% yield from attack of the $\Delta^{6,7}$ enolate on the C-2 ketone followed by β-elimination. Also produced in 25% yield was the dienone **11**, resulting from attack of the $\Delta^{1,2}$ enolate on the C-6 ketone followed by two β-eliminations. Product distributions in the reaction of **10** with amine bases such as pyrrolidine or proline were dependent on solvent effects. For example, reaction of **10** with 1 equiv. of pyrrolidine in THF gave 56% of the aldol adduct **13** in addition to 23% of dienone **11**. The



Scheme 4. (a) TBSOTf, DIPEA, CH_2Cl_2, −78 °C to rt, 2.5 h, 90% yield; (b) Br_2, NaOH, dioxane, H_2O, 0 °C.

Table 1. Products for intramolecular aldol condensation of **10** under different conditions



Entry	Conditions	**11** (%)	**12** (%)	**13** (%)
1	4 equiv. NaOH/H_2O/ethanol, 0 °C, 1 h	25	50	0
2	1 equiv. Pyrrolidine/THF, rt, 72 h	23	0	56
3	1 equiv. Pyrrolidine/CH_3CN, rt, 72 h	68	9.1	0
4	0.5 equiv. DL-Proline/DMF, 65 °C, 2 h	53	32	0

configuration of **13** was determined by the 2D-NMR NOESY spectrum.

On the other hand, the same reaction conducted in acetonitrile led to 68% of dienone **11** and only 9.1% of enone **12**. The β-silyloxy group in cyclohexenones readily undergoes elimination as reported by Corey et al.[15] in the related cyclopentanones. Clearly, ethyl substituted products (3-ethyl) produced in basic equilibria are capable of dual β-eliminations because the *gem*-dimethyl moiety does not interfere with the second elimination. Those products (2,3-dimethyl) from the other mode of aldol reaction can only readily eliminate HOH, and not the silyloxy group. In acetonitrile, elimination is faster than in THF, as evidenced by the high yield of the aldol intermediate **13** in THF but not acetonitrile.

With racemic proline in DMF at 65 °C for 2 h (entry 4), dienone **11** was the major product produced in 53% yield, while the remaining isolable material was the 2,3-dimethyl enone **12** (23% yield). Certainly the elevated temperature, zwitterionic proline and polar solvent were effective in solvolyzing aldol adducts thus producing the thermodynamic endpoint, dienone **11**, over other more sensitive intermediates leading to **11**. From the other manifold, aldol adduct **12** could not undergo the second elimination due to the gem-dimethyl group.

We reasoned that because the hydroxyl group is a poorer leaving group than a silyloxy group, that intramolecular aldol reaction of hydroxydiketone **8** in the presence of pyrrolidine could provide enhanced selectivity for 5β-hydroxy-2-eneone **9**, and suppress formation of undesired **11**. Thus, upon treatment of the diketo-alcohol **8** with pyrrolidine in dichloromethane at ambient temperature, compound **9** was produced in 76% yield and 41% of **8** was recovered.[16] Now, protection of **9** as the TBDMS silyl ether could be readily achieved in 81% unoptimized yield using the Corey method[15] with TBSCl and imidazole. On the other hand, with TBSOTf as the silylating agent, a variety of amine bases lead to dual elimination product **11**: DIPEA, 2,6-lutidine or pyridine. Finally, the double bond of **14** could be smoothly cleaved to the desired ketoacid **4** in 67% yield by the Sharpless method[17] employing $NaIO_4$ and $RuCl_3$ in $CCl_4/CH_3CN/H_2O$ (1:1:1.6) (Scheme 5). The keto-acid thus obtained (**4**) had a negative sign of optical rotation ($[\alpha]_D^{25}=-15.8$ (*c* 4.7, $CHCl_3$); while **4** prepared by a literature method[7,10] showed $[\alpha]_D^{25}=-15$ (*c* 0.56, $CHCl_3$). Further, **4** had an identical ^1H and ^{13}C NMR spectra compared to literature values.[2e,7] This result confirmed that the absolute configuration at the chiral center of **8** was 3*S*.

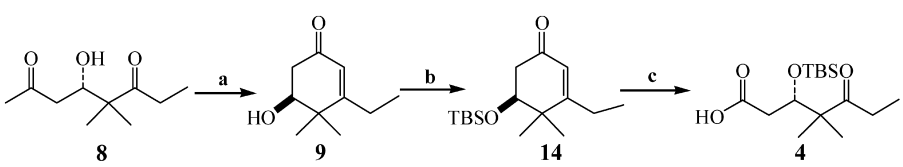
In summary, we have developed a new approach to ketoacid **4**, a common C1–C6 fragment for total synthesis of epothilones initiated by direct aldol reaction of acetone with a pivaldehyde-like substance **5**, catalyzed with D-proline, leading to a diketoalcohol with better than 99% ee. Further intramolecular closure of the diketone **8** followed by oxidation of the silyl protected hydroxycyclohexenone **14** led to the desired product. None of the steps have been optimized, yet the overall yield for the four-step process is 31%. The use of commercially available D-proline to construct the chiral center of **4** under very mild reaction conditions provided an economical and practical method for its construction.

3. Experimental

Reactions requiring anhydrous conditions were performed with the usual precautions for rigorous exclusion of air and moisture. Where necessary, chemicals were purified according to reported procedures.[18] For example, tetrahydrofuran was distilled from sodium benzophenone ketyl prior to use and could be stored over 4A molecular sieves to ensure the lowest levels of water. Thin layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates from EM reagents and visualized with a 254 nm UV light. Flash chromatography was carried out on silica gel 60 (E. M. Merck, particle size 0.040–0.063 mm, 230–400 mesh ASTM). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 at 400 and 100 MHz, respectively. The chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane, and *J*-values were in Hz. IR spectra were obtained on an ATI Mattson FT/IR spectrometer. Mass spectra were recorded on a Bruker BioApex FTMS system. Optical rotations were determined on a Rudolph Autopol IV polarimeter. All mps were uncorrected.

3.1. General

3.1.1. (−)-4*S*-4-Hydroxy-5,5-dimethyl-2,6-octanedione (8). A mixture of D-proline (2.0 g, 0.35 mmol) in anhydrous acetone (50 mL) and anhydrous DMSO (200 mL) was stirred at room temperature for 15 min. At this time, the aldehyde **5** was added and the mixture stirred at room temperature for 24 h. Saturated aqueous ammonium chloride (250 mL) was added and the reaction mixture was extracted with ethyl acetate (3×200 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and the solvent was evaporated. The residue was subjected to flash chromatography (silica gel, EtOAc–hexanes 1:1) providing **8** (7.0 g, 75%) and **9** (160 mg, 1.9%) as colorless oils; for **8**. R_f=0.53 (silica gel, 50% ethyl acetate in hexane); $[\alpha]_D^{25}=-48.8$ (*c*=1.2, $CHCl_3$); IR (thin film) ν_{max} 3493, 2975, 2940, 2857, 1704, 1701, 1469, 1366, 1099, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.02 (m,



Scheme 5. (a) 0.1 equiv. pyrrolidine, CH_2Cl_2, rt, 3 h, 76% yield; (b) TBSCl, imidazole, DMF, rt, 72 h, 81%; (c) 0.03 equiv. $RuCl_3$, 5.5 equiv. $NaIO_4$, CCl_4–CH_3CN–H_2O 1:1:1.6, 1 h, 67%.

1H, C*H*OH), 3.46 (s, 1H, O*H*), 2.35–2.28 (m, 4H, CHCH_2CO, CH_3CH_2CO), 1.95 (s, 3H, CH_3CO), 0.90, 0.87 (2s, 6H, C(CH_3)$_2$), 0.76 (t, J=6.8 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.9, 209.0, 71.7, 51.0, 45.1, 31.0, 30.4, 20.8, 19.5, 7.5; ESI$^+$ HRMS m/z 209.1108, M+Na$^+$ calcd for $C_{10}H_{18}O_3Na$ 209.1154.

3.1.2. (−)-5*S*-3-Ethyl-4,4-dimethyl-5-hydroxycyclohex-2-enone (9). To the solution of **8** (2.90 g, 15.6 mmol) in dichloromethane (10 mL) at room temperature was added pyrrolidine (0.11 g, 1.56 mmol). The solution was stirred at room temperature for 3 h and then concentrated on the rotary evaporator at room temperature. The residue was purified by flash chromatography (silica gel, 40% ethyl acetate in hexanes) to give the product **9** as a colorless oil (1.16 g, 76% based on converted **8**) along with recovered **8** (1.20 g or 41%). R_f=0.32 (silica gel, 50% ethyl acetate in hexane); $[\alpha]_D^{25}$=−17.8 (c=0.70, $CHCl_3$); IR (thin film) ν_{max} 3430, 2971, 2938, 2881, 1666, 1647, 1610, 1468, 1417, 1362, 1283, 1047, 863 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 (s, 1H, C*H*=C), 4.16 (s, 1H, O*H*), 3.70–3.60 (m, 1H, C*H*OH), 2.47–2.29 (m, 2H, HOCHCH_2), 2.10 (q, 2H, J=6.8 Hz, CH_2CH_3), 1.01, 0.96 (2s, 6H, C(CH_3)$_2$), 0.89 (t, J=6.8 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 173.5, 122.8, 73.7, 42.4, 41.1, 24.7, 23.9, 20.3, 11.3; ESI$^+$ HRMS m/z 151.1104, M−H_2O+H$^+$ calcd for $C_{10}H_{15}O$ 151.1123.

3.1.3. (−)-5*S*-3-Ethyl-4,4-dimethyl-5-(*tert*-butyldimethylsilyl)oxycyclohex-2-enone (14). To a solution of *tert*-butyldimethylsilylchloride (0.247 g, 1.65 mmol) at 0 °C was added a solution of **9** (0.180 g, 1.07 mmol) and imidazole (0.146 g, 2.14 mmol) in DMF (0.8 mL). The ice bath was removed and the solution was stirred at room temperature for 72 h until all of the starting material had disappeared by TLC. The mixture was directly subjected to flash chromatography to give **14** as a colorless oil (0.255 mg, 81%). R_f=0.88 (silica gel, 50% ethyl acetate in hexane); $[\alpha]_D^{25}$=−7.7 (c=0.58, $CHCl_3$); IR (thin film) ν_{max} 2957, 2931, 2884, 2857, 1673, 1614, 1471, 1256, 110, 1079, 837, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (s, 1H, C*H*=C), 3.65 (dd, 1H, J=9.6, 4.4 Hz, 1H, C*H*OH), 2.39 (dd, J=16.4, 4.4 Hz, 1H, HOCHCH_2), 2.08 (dd, J=16.4, 9.6 Hz, 1H, HOCHCH_2), 2.10 (q, 2H, J=6.0 Hz, CH_2CH_3), 0.98, 0.0.93 (2s, 6H, C(CH_3)$_2$), 0.89 (t, J=6.0 Hz, 3H, CH_2CH_3), 0.70 (s, 9H, SiC(CH_3)$_3$), −0.11, −0.12 (2s, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 172.2, 123.2, 74.7, 43.2, 41.7, 25.5, 24.8, 23.7, 20.5, 17.7, 11.6, −3.7, −4.4; ESI$^+$ HRMS m/z, 283.2106, M+H$^+$ calcd for $C_{16}H_{31}O_2Si$ 283.2093.

3.1.4. (−)-4*S*-4-(*tert*-Butyldimethylsilyl)oxy-5,5-dimethyl-2,6-octanedione (10). To the solution of **8** (5.58 g, 30 mmol) and *N*,*N*-diisopropylethylamine (6.19 g, 48 mmol) in dichloromethane (200 mL) at −78 °C was slowly added *tert*-butyldimethylsilyl trifluoromethanesulfonate (11.9 g, 45 mmol). The solution was slowly warmed to room temperature and stirred for about 2 h until the starting material disappeared. The reaction was quenched with aqueous ammonium chloride and extracted with ethyl acetate. The organic solution was dried over anhydrous sodium sulfate and evaporated. The residue was purified by flash chromatography (silica gel, 10% ethyl acetate in hexanes) to give **10** as a colorless oil (8.1 g, 90%). R_f=0.79 (silica gel, 25% ethyl acetate in hexane); $[\alpha]_D^{25}$=−47.5 (c 1.67, $CHCl_3$); IR (thin film) ν_{max} 2956, 2934, 2886, 2857, 1716, 1471, 1362, 1254, 1091, 1024, 837, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32–4.45 (m, 1H, SiOC*H*CH_2), 2.52–2.25 (m, 4H, SiOCHCH_2, CH_2CH_3), 1.99 (s, 3H, COCH_3), 0.94, 0.95 (2s, 6H, C(CH_3)$_2$), 0.84 (t, 3H, J=7.2 Hz, CH_2CH_3), 0.70 (s, 9H, SiC(CH_3)$_3$), −0.05, −0.18 (2s, 6H, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.1, 206.2, 71.9, 52.4, 48.2, 31.8, 30.7, 25.9, 21.4, 20.4, 18.0, 7.6, −3.6, −4.4; ESI$^+$ HRMS m/z 323.2017, M+Na$^+$ calcd for $C_{16}H_{32}O_3NaSi$ 323.2018.

3.1.5. 3-Ethyl-4,4-dimethylcyclohex-2,5-dienone (11) and (+)-3*S*,5*S*,6*S*-3-(*tert*-butyldimethylsilyl)oxy-5-hydroxy-2,2,5,6-tetramethylcyclohexanone (13). To the solution of **10** (0.30 g, 1 mmol) in THF (1 mL) at room temperature was added pyrrolidine (0.071 g, 1 mmol). The solution was stirred at room temperature for 72 h. Saturated aqueous ammonium chloride was added and extracted with ethyl acetate. The organic phase was dried, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel, 20% ethyl acetate in hexanes) to give **13** (0.084 g, 56%) as a white solid and **11** (0.065 g, 23%) as colorless oil; **11**. R_f=0.52 (silica gel, 25% ethyl acetate in hexane); IR (thin film) ν_{max} 2971, 2936, 2879, 1666, 1625, 1603, 1486, 1294, 1138, 891 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85, 6.12 (2d, J=8 Hz, 2H, C*H*=C*H*), 6.08 (s, 1H, C*H*=C), 2.28 (q, J=6.2 Hz, 2H, CH_2CH_3), 1.18 (s, 6H, C(CH_3)$_2$), 1.15 (t, J=6.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.0, 170.5, 158.4, 126.5, 124.3, 40.6, 26.1, 24.2, 12.1; ESI$^+$ HRMS m/z 151.1122, M+H$^+$ calcd for $C_{10}H_{15}O$ 151.1123. **13**. R_f=0.53 (silica gel, 25% ethyl acetate in hexane); mp 93.2 °C; $[\alpha]_D^{25}$=+132 (c 0.41, $CHCl_3$); IR (thin film) ν_{max} 3499, 2933, 2887, 2857, 1703, 1463, 1378, 1255, 1093, 1061, 1030, 982, 867, 837, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (dd, J=9.6, 6.4 Hz, 1H, SiOC*H*CH_2), 2.68 (q, J=6.4 Hz, 1H, C*H*CH_3), 1.92–1.99 (m, 2H, SiOCHCH_2), 1.65 (s, 1H, O*H*), 1.31, 1.08, 1.06 (3s, 9H, CCH_3, C(CH_3)$_2$), 1.02 (d, J=6.4 Hz, 3H, CHCH_3), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.070, 0.041 (2s, 6H, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.0, 73.0, 72.5, 51.0, 48.2, 44.7, 28.9, 25.8, 21.8, 19.3, 18.0, 7.4, −4.1, −5.0; ESI$^+$ HRMS m/z 323.2020, M+Na$^+$ calcd for $C_{16}H_{32}O_3NaSi$ 323.2018.

3.1.6. (+)-5*S*-2,3,6,6-Tetramethyl-5-(*tert*-butyldimethylsilyl)oxy-cyclohex-2-enone (12). To the solution of **4** (0.30 g, 1 mmol) in ethanol (20 mL) and H_2O (18 mL) NaOH (0.16 g, 4 mmol in 2 mL of water) was added at 0 °C. The reaction mixture was stirred at above temperature for 2 h and extracted with ethyl acetate. The organic phase was dried, filtered and evaporated in reduced pressure. The residue was purified by flash chromatography to give **12** (0.141 mg, 50%) and **11** (0.038 g, 25%) as colorless oil. R_f=0.61 (silica gel, 25% ethyl acetate in hexane); $[\alpha]_D^{25}$=+57.8 (c 0.64, $CHCl_3$); IR (thin film) ν_{max} 2955, 2930, 2892, 2857, 1667, 1641, 1471, 1379, 1255, 1102, 1069, 873, 837, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70–3.60 (m, 1H, SiOC*H*CH_2), 2.30–2.40 (m, 2H, SiOCHCH_2), 1.83, 1.67, 1.05, 1.03 (4s, 12H, CH_3C=CCH_3, C(CH_3)$_2$), 0.82 (s, 9H, SiC(CH_3)$_3$), 0.0029–0.020 (m, 6H,

$Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 148.8, 129.4, 73.8, 47.2, 39.2, 25.9, 22.1, 21.4, 18.4, 18.1, 11.5, −4.1, −4.8; ESI^+ HRMS *m/z* 151.1122, M−TBSOH+H^+ calcd for $C_{10}H_{15}O$ 151.1123.

3.1.7. (−)-3*S*-3-(*tert*-Butyldimethylsilyl)oxy-4,4-dimethyl-5-oxo-heptanoic acid (4). Sodium periodate (1.18 g, 5.5 mmol) was added into the solution of enone **14** (282 mg, 1.0 mmol) in CCl_4 (1.8 mL) and CH_3CN (1.8 mL). Under vigorous magnetic stirring, $RuCl_3$ (2.9 mL, 9.28 mM in distilled H_2O, 0.027 mmol) was added and stirring was continued for about 1 h until the starting material had disappeared by TLC. Water was gradually added until the separated $NaIO_3$ dissolved and the mixture was then extracted with ethyl acetate (3×5 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and the solvent was then rotary evaporated. The residue was subjected to flash chromatography (silica gel, 50% ethyl acetate in hexanes) to give **4** (0.202 g, 67%) as a colorless oil. $[\alpha]_D^{25}=-15.8$ (*c* 4.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H, COO*H*), 4.45 (dd, 1H, *J*=6.8, 3.6 Hz, SiOC*H*), 2.62–2.42 (m, 3H, CH_2CH_{-3}, CH_2COOH), 2.34, 2.30 (dd, *J*=6.8, 16 Hz, $SiOCHCH_2$), 1.12, 1.06 (2s, 6H, $2CH_3$), 0.98 (t, 3H, *J*=7.2 Hz, CH_2CH_{-3}), 0.83 (s, 9H, $SiC(CH_3)_3$), 0.036, 0.017 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.4, 178.5, 73.7, 52.7, 39.5, 31.9, 26.1, 21.1, 20.7, 18.3, 7.9, −4.2, −4.7.

3.2. Synthesis of Mosher ester

Into a flask **8** (37.2 mmg, 0.2 mmol), *R*-(+)-α-methoxy-α-trifluromethylphenylacetic acid (MPTA, 56.2 mg, 0.24 mmol), DCC (53.6 mg, 0.26 mmol), DMAP (6.1 mg, 0.05 mmol) and dichloromethane (5 mL) were added in order. The mixture was stirred at room temperature for 24 h and directly subjected to flash chromatography (silica gel, 40% ethyl acetate in hexanes) to give the Mosher ester (22 mg, 30% for **8** and 45 mg, 56% for racemic **8**).

Acknowledgements

We wish to thank NaPro Biotherapeutics, Inc. for financial support of this research.

References and notes

1. (a) Höfle, G.; Bedorf, N.; Gerth, K.; Reichenbach, H. (GBF) DE-4138042, 1993; *Chem. Abstr.* **1993**, *120*, 52841. (b) Gerth, K.; Bedorf, N.; Höfle, G.; Irschik, K.; Reichenbach, H. *J. Antibiot.* **1996**, *49*, 560–563. (c) Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1567–1569.
2. (a) Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 166–168. (b) Nicolaou, K. C.; Sarabia, F.; Ninkovic, S.; Yang, Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 525–527. (c) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T. *Nature* **1997**, *387*, 268–272. (d) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I. *J. Am. Chem. Soc.* **1997**, *119*, 7960–7973. (e) Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Vallberg, H.; Finlay, M. R. V.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 7974–7991. (f) Nicolaou, K. C.; Vourloumis, D.; Li, T.; Pastor, J.; Winssinger, N.; He, Y.; Ninkovic, S.; Sarabia, F.; Vallberg, H.; Roschangar, F.; King, N. P.; Finlay, M. R. V.; Giannakakou, P.; Verdier-Pinard, P.; Hamel, E. *Angew. Chem., Int. Engl.* **1997**, *36*, 2097–2103. (g) Nicolaou, K. C.; Vallberg, H.; King, N. P.; Roschangar, F.; He, Y.; Vourloumis, D.; Nicolaou, C. G. *Chem. Eur. J.* **1997**, *3*, 1957–1970.
3. Kalesse, M.; Quitschalle, M.; Claus, E.; Gerlach, K.; Pahl, A.; Meyer, H. *Eur. J. Org. Chem.* **1999**, 2817–2823.
4. Borzilleri, R. M.; Zheng, X.; Schmidt, R. J.; Johnson, J. A.; Kim, S.-H.; DiMarco, J. D.; Fairchild, C. R.; Gougoutas, J. Z.; Lee, F. Y. F.; Long, B. H.; Vite, G. D. *J. Am. Chem. Soc.* **2000**, *122*, 8890–8897.
5. (a) Hindupur, R. M.; Panicker, B.; Valluri, M.; Avery, M. A. *Tetrahedron Lett.* **2001**, *42*, 7341–7344. (b) Valluri, M.; Hindupur, R. M.; Bijoy, P.; Labadie, G.; Jung, J.-C.; Avery, M. A. *Org. Lett.* **2001**, *3*, 3607–3609.
6. Liu, Z.-Y.; Chen, Z.-C.; Yu, C.-Z.; Wang, R.-F.; Zhang, R.-Z.; Huang, C.-S.; Yan, Z.; Cao, D.-R.; Sun, J.-B.; Li, G. *Chem. Eur. J.* **2002**, *8*, 3747–3756.
7. Altmann, K.-H.; Bold, G.; Caravatti, G.; Denni, D.; Florsheimer, A.; Schmidt, A.; Rihs, G.; Wartmann, M. *Helv. Chim. Acta* **2002**, *85*, 4086–4110.
8. Gabriel, T.; Wessjohann, L. *Tetrahedron Lett.* **1997**, *38*, 1363–1366.
9. Panicker, B.; Karle, J. M.; Avery, M. A. *Tetrahedron* **2000**, *56*, 7859–7868.
10. De Brabander, J.; Rosset, S.; Bernardinelli, G. *Synlett* **1997**, 824–826.
11. Avery, M. A. WO 02/030356 A2, Synthesis of Epothilones and Related Analogs, 18 April 2002.
12. Shioji, K.; Kawaoka, H.; Miura, A.; Okuma, K. *Synth. Commun.* **2001**, *31*, 3569–3575.
13. List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
14. Inukai, T.; Yoshizawa, R. *J. Org. Chem.* **1967**, *32*, 404–407.
15. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.
16. See Section 3.1.2: '…was purified by flash chromatography (silica gel, 40% ethyl acetate in hexanes) to give the product **9** as a colorless oil (1.16 g, 76% based on converted **8**) along with recovered **8** (1.20 g or 41%)'.
17. (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938. (b) Webster, F. X.; Rivas-Enterrios, J.; Silverstein, R. M. *J. Org. Chem.* **1987**, *52*, 689–691.
18. Perrin, D. D.; Armarego, L. F.; Perrin, D. R. *Purification of laboratory chemicals*; 2nd ed. Pergamon: New York, 1980.