Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 6979–6981
Tetrahedron Letters

A cyclopropanol approach to the synthesis of the C13–C21 fragment of epothilones from diethyl (*S*)-malate

Andrei V. Bekish, Vladimir E. Isakov and Oleg G. Kulinkovich*

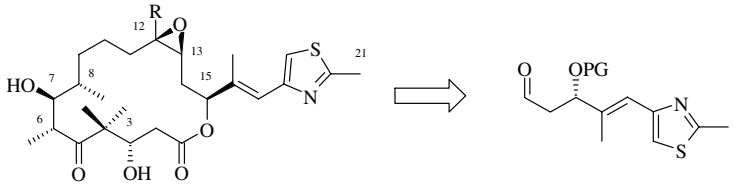
Department of Organic Chemistry, Belarusian State University, Fr. Skaryny Av. 4, 220050 Minsk, Belarus

Received 29 June 2005; revised 9 August 2005; accepted 17 August 2005

Abstract—A convenient new approach to the synthesis of the C13–C21 epothilone fragment using the cyclopropanation of the ethoxycarbonyl groups in *O*-THP protected diethyl (*S*)-malate with ethylmagnesium bromide in the presence of titanium(IV) isopropoxide followed by site-selective cyclopropane cleavage as the key steps has been performed.

Cyclopropanol derivatives are highly reactive compounds which, under mild conditions, may be involved in cyclopropane cleavage to form ketones, allyl halides, esters and some other classes of organic compounds.[1] There are several simple and effective methods for the preparation of cyclopropanols and these substances may serve as convenient intermediates in organic synthesis.[1,2] In the preceding article, we described effective routes for differentiation between the alkoxycarbonyl groups in *O*-THP protected diethyl malate by its conversion into the corresponding bis-cyclopropanol using titanium-catalyzed cyclopropanation with ethylmagnesium bromide and subsequent site-selective cyclopropane cleavage or expansion.[3] In the present work, we report the use of this approach to obtain the thiazole-containing C13–C21 fragment of epothilones **1** (Fig. 1), which are considered as promising anti-tumor agents with a taxol-like mechanism of action.[4]

Thiazole fragment **2a** was obtained for the first time by Nicolaou et al.[5] and was used by this and other research groups for selective formation of the C12–C13 double bond via Wittig[6] or Wittig–Horner reactions.[7] Most of the syntheses of the thiazole derivative **2a** were based on creation of the chiral centre at C15 by chemical[5,6c,8] or biochemical[9] asymmetric reactions with different enantioselectivities. Mulzer et al.[7b] also reported an effective synthesis of compound **2a** starting from naturally occurring (*S*)-malic acid, which was transformed into the corresponding α-oxymethyl ketone in moderate yield by the use of a site-selective reduction of one of the carboxylic groups in the corresponding acetonide with $BH_3{\cdot}SMe_2$. Reported below is an alternative and practical approach to the synthesis of *O*-THP protected compound **2b**, based on the transformation of carboxylic groups in (*S*)-malic acid into the required functionalities via the reductive cyclopropanation[10] of diester **3** (Scheme 1).



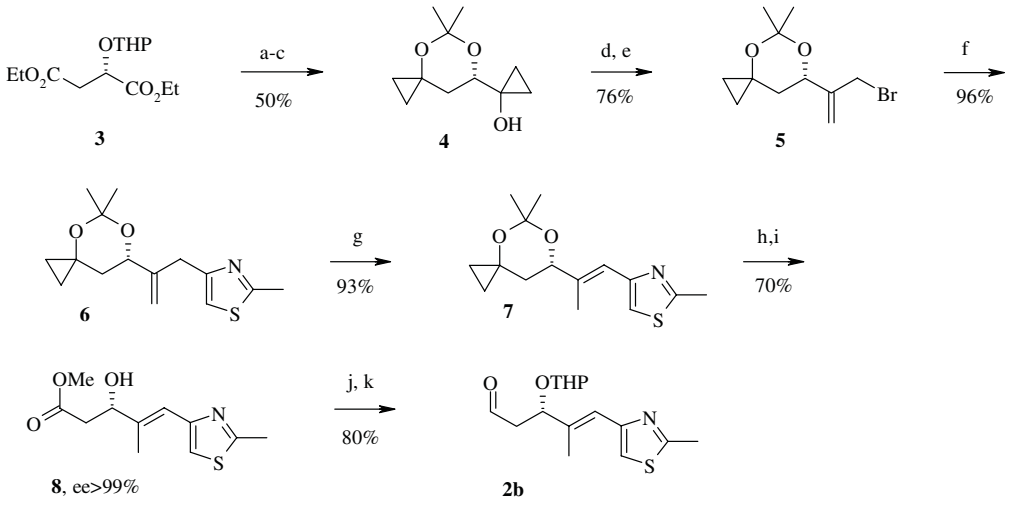
epothilone A (**1a**), R = H
epothilone B (**1b**), R = Me

2a, PG = TBDS
2b, PG = THP

Figure 1. The epothilones A and B and the C13–C21 precursors.

Keywords: (*S*)-Malic acid; Cyclopropanols; Allyl halides; Epothilones.
* Corresponding author. Tel.: +375 17 2095459; fax: +375 17 2265609; e-mail: kulinkovich@bsu.by

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.08.075



Scheme 1. Reagents and conditions: (a) EtMgBr (6 equiv), Ti(O*i*-Pr)$_4$ (50 mol %), rt; (b) MeOH, PPTS (5 mol %), reflux, 15 min; (c) acetone, $CuSO_4$ (2 equiv), PPTS (5 mol %); (d) MsCl (1.5 equiv), Et_3N (3 equiv), Et_2O; (e) $MgBr_2$ (3 equiv), Et_2O–$CHCl_3$, reflux, 5 h; (f) 2-methylthiazol-4-ylmagnesium bromide (1.5 equiv), CuI (10 mol %), 0 °C to rt; (g) 0.25 M *t*-BuOK in *t*-BuOH, reflux, 1.5 h; (h) MeOH, PPTS (5 mol %), reflux; (i) PhI(OAc)$_2$ (1 equiv), MeOH, rt, 2 h; (j) DHP (3 equiv), PPTS (5 mol %), $CHCl_3$, reflux; (k) DIBAL-H (1.3 equiv), toluene, −78 °C, 1 h.

THP-protected diethyl (*S*)-malate **3** was transformed into bis-cyclopropanol **4** according to our previously reported procedure[3] (Scheme 1). Based on ^{1}H NMR spectra of the (+)- and (+/−)-MTPA-esters[11] of compound **4**[12], we found that the enantiomeric purity of alcohol **4** was more than 99%.[13] Cyclopropanol **4** was smoothly converted into 2-substituted allyl bromide **5**[14] by $MgBr_2$-induced cationic cyclopropyl–allyl rearrangement of the corresponding mesylate.[3] Compound **5** was then subjected to the CuI-catalyzed reaction with 2-methylthiazol-4-ylmagnesium bromide (prepared via the corresponding organolithium derivative[15]) to form disubstituted thiazole **6**.[16]

The trisubstituted C16–C17 double bond of the thiazole fragment was created by the base-catalyzed allylic shift of the disubstituted carbon–carbon double bond in compound **6** to the thermodynamically more stable conjugated position. The reaction was complete after 1.5 h at reflux with 0.25 M *t*-BuOK in *t*-BuOH to form exclusively the (*E*)-isomeric compound **7**.[17] Acid-catalyzed methanolysis of the acetonide **7** followed by oxidative fragmentation of the resulting cyclopropanol moiety under treatment with PhI(OAc)$_2$[18] led to ester **8** in good yield.[19,20] The enantiomeric purity of compound **8**, based on ^{1}H NMR spectra of its (+)- and (+/−)-MTPA-esters, was more than 99%.[21] Ester **8** was transformed into aldehyde **2b** by the tetrahydropyranylation of the hydroxy group, followed by reduction of the methoxycarbonyl moiety with DIBAL-H.[22]

In conclusion, the reductive cyclopropanation of *O*-THP protected diethyl (*S*)-malate and subsequent cyclopropane cleavage have transformed the alkoxycarbonyl groups into the requisite functionalities of the C13–C21 fragment **2** of epothilones **1** with commensurable or better overall yields as compared to those previously reported in the literature, using inexpensive starting materials and reagents.

Acknowledgements

This work was supported by the Ministry of Education and the Belarusian Fund for Scientific Research.

References and notes

1. (a) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597–2632; (b) Gibson, D. H.; De Puy, C. H. *Chem. Rev.* **1974**, *74*, 605–623.
2. (a) Kulinkovich, O. G. *Izv. Akad. Nauk. Ser. Khim.* **2004**, 1022–1043; (b) Kulinkovich, O. G. *Eur. J. Org. Chem.* **2004**, *22*, 4517–4529; *Russ. Chem. Bull. (Engl. Transl.)* **2004**, *53*, 1065–1086; (c) Kulinkovich, O. G.; De Meijere, A. *Chem. Rev.* **2000**, *100*, 2789–2834; (d) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835–2886; (e) Kuwajima, I.; Nakamura, E. *Top. Curr. Chem.* **1990**, *133*, 3–40.
3. Bekish, A. V.; Kulinkovich, O. G. *Tetrahedron Lett.* **2005**, *46*, in this issue, see doi:10.1016/j.tetlet.2005.08.076.
4. (a) Nicolaou, K. C.; Roschangar, F.; Vourloumis, D. *Angew. Chem., Int. Ed.* **1998**, *37*, 2014–2045; (b) Harris, C. R.; Danishefsky, S. J. *J. Org. Chem.* **1999**, *64*, 8434–8456; (c) Wartmann, M.; Altmann, K.-H. *Curr. Med. Chem. Anti-Cancer Agents* **2002**, *2*, 123–148; (d) Altmann, K.-H. *Minirev. Med. Chem.* **2003**, *3*, 149–158; (e) Rivkin, A.; Cho, Y. S.; Gabarda, A. E.; Yoshimura, F.; Danishefsky, S. J. *J. Nat. Prod.* **2004**, *67*, 139–143; (f) Nicolaou, K. C.; Ritzen, A.; Namoto, K. *Chem. Commun.* **2001**, 1523–1535.
5. 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.
6. (a) Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073–10092; (b) Nicolaou, K. C.; Winssinger, N.; Pastor, J. A.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E. *Nature* **1997**, *387*, 268–272; (c) Taylor, R. E.; Chen, Y. *Org. Lett.* **2001**, *3*, 2221–2224.
7. (a) Mulzer, J.; Mantoulidis, A.; Ohler, E. *Tetrahedron Lett.* **1997**, *38*, 7725–7728; (b) Mulzer, J.; Mantoulidis, A.; Ohler, E. *J. Org. Chem.* **2000**, *65*, 7456–7467.

8. Reiff, E. A.; Nair, S. K.; Reddy, B. S. N.; Inagaki, J.; Henri, J. T.; Greiner, J. F.; Georg, G. I. *Tetrahedron Lett.* **2004**, *45*, 5845–5847.
9. (a) Sinha, S. C.; Sun, J.; Miller, G.; Barbas, C. F., III; Lerner, R. A. *Org. Lett.* **1999**, *1*, 1623–1626; (b) Zhu, B.; Panek, J. S. *Org. Lett.* **2000**, *2*, 2575–2578; (c) Zhu, B.; Panek, J. S. *Tetrahedron Lett.* **2000**, *41*, 1863–1866.
10. (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevski, D. A.; Prityts kaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244–2245; . *J. Org. Chem. USSR (Engl. Transl.)* **1989**, *25*, 2027–2028; (b) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevski, D. A. *Synthesis* **1991**, 234.
11. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.
12. $[\alpha]_D$ +30.6 (*c* 4.12, Et_2O).
13. The signals of the protons of the methoxy groups at $\delta = 3.52$ and 3.56 ppm were used to determine the enantiomeric purity.
14. $[\alpha]_D$ +29.2 (*c* 2.33, Et_2O).
15. The use of the corresponding organolithium derivative for alkylation of allyl bromide **5** led to a decrease in the yield of compound **6** due to homocoupling of the starting halogenide.
16. Compound **6**. $[\alpha]_D$ +30.5 (*c* 2.33, CH_2Cl_2); IR (CCl_4) 3095, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.37 (ddd, $J = 10.2$, 6.5, 5.4 Hz, 1H), 0.56 (ddd, $J = 10.2$, 6.5, 4.7 Hz, 1H), 0.72 (ddd, $J = 10.8$, 6.5, 5.4 Hz, 1H), 0.81 (dddd, $J = 10.8$, 6.5, 4.7, 1.8 Hz, 1H), 1.05 (dd, $J = 13.0$, 2.6 Hz, 1H), 1.39 (s, 3H), 1.48 (s, 3H), 2.20 (ddd, $J = 13.0$, 11.6, 1.8 Hz, 1H), 2.67 (s, 3H), 3.48–3.61 (m, 2H), 4.46–4.52 (m, 1H), 4.87–4.90 (m, 1H), 5.16–5.19 (m, 1H), 6.77–6.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.9, 14.4, 19.1, 21.1, 29.9, 34.6, 36.4, 53.7, 70.2, 100.3, 112.5, 114.1, 146.8, 154.1, 165.4. Anal. Calcd for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58. Found: C, 64.71; H, 7.52.
17. Preparation of **7**. Compound **6** (0.99 g, 3.5 mmol) was added to 0.25 M *t*-BuOK in *t*-BuOH (20 mL) and the reaction mixture was refluxed for 1.5 h under an argon atmosphere. The solvent was removed under reduced pressure and the residue was diluted with diethyl ether and washed with brine. The organic layer was separated and the aqueous layer was extracted with diethyl ether (5×5 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Compound **7** (0.92 g, 93%) was isolated by column chromatography on silica gel (eluent: petroleum ether–ethyl acetate). $[\alpha]_D$ +34.0 (*c* 2.33, CH_2Cl_2); IR (CCl_4) 3085, 1640 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.40 (ddd, $J = 10.2$, 6.5, 5.5 Hz, 1H), 0.64 (ddd, $J = 10.2$, 6.5, 4.8 Hz, 1H), 0.76 (ddd, $J = 10.8$, 6.5, 5.5 Hz, 1H), 0.87 (dddd, $J = 10.8$, 6.5, 4.8, 1.8 Hz, 1H), 1.08 (dd, $J = 13.1$, 2.6 Hz, 1H), 1.43 (s, 3H), 1.58 (s, 3H), 2.04 (d, $J = 1.3$ Hz, 3H), 2.25 (ddd, $J = 13.1$, 11.7, 1.8 Hz, 1H), 2.69 (s, 3H), 4.52–4.58 (m, 1H), 6.61–6.64 (m, 1H), 6.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.0, 14.6, 14.9, 19.2, 21.3, 29.9, 36.5, 53.7, 73.5, 100.3, 115.5, 119.0, 139.5, 152.9, 164.3. Anal. Calcd for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58. Found: C, 64.63; H, 7.54.
18. (a) Kirihara, M.; Yokoyama, S.; Kakuda, H.; Momose, T. *Tetrahedron Lett.* **1995**, *36*, 6907–6910; (b) Kirihara, M.; Yokoyama, S.; Kakuda, H.; Momose, T. *Tetrahedron* **1998**, *54*, 13943–13954; (c) Momose, T.; Nishio, T.; Kirihara, M. *Tetrahedron Lett.* **1996**, *37*, 4987–4990.
19. Compound **8**. $[\alpha]_D$ −4.6 (*c* 1.74, Et_2O); IR (CCl_4) 3615, 3535, 1720, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.06 (d, $J = 1.3$ Hz, 3H), 2.61–2.66 (m, 2H), 2.70 (s, 3H), 3.32 (br s, 1H), 3.73 (s, 3H), 4.57–4.64 (m, 1H), 6.59–6.64 (m, 1H), 6.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 19.1, 40.1, 51.9, 73.3, 115.9, 119.1, 140.0, 152.6, 164.7, 172.8. Anal. Calcd for $C_{11}H_{15}NO_3S$: C, 54.75; H, 6.27. Found: C, 54.92; H, 6.18.
20. The (*E*)-configuration of the acyclic carbon–carbon double bond in compound **8** was verified on the basis of NOE experiments. Irradiation of the olefinic proton of this double bond produced a strong enhancement (15%) of the methine proton signal at δ 4.57–4.64 ppm.
21. The signals of the protons of the methoxy groups at $\delta = 3.60$ and 3.68 ppm were used to determine the enantiomeric purity.
22. The yield of aldehyde **2b** was determined on the basis of ^1H NMR spectroscopy of the reaction mixture. ^1H NMR (400 MHz, $CDCl_3$): δ 1.43–1.88 (m, 6H), 2.02 (d, $J = 1.3$ Hz, 1.5H), 2.09 (d, $J = 1.3$ Hz, 1.5H), 2.51–2.63 (m, 1H), 2.69 (s, 1.5H), 2.70 (s, 1.5H), 2.76–2.90 (m, 1H), 3.38–3.56 (m, 1H), 3.74–3.88 (m, 1H), 4.54–4.65 (m, 1H), 4.74–4.83 (m, 1H), 6.54–6.57 (m, 0.5H), 6.59–6.62 (m, 0.5H), 6.95 (s, 0.5H), 6.96 (s, 0.5H), 9.76–9.79 (m, 0.5H), 9.82–9.85 (m, 0.5H).