



Pergamon

Tetrahedron Letters 41 (2000) 1863–1866

TETRAHEDRON
LETTERS

Enzymatic resolution of thiazole-containing vinyl carbinols. Synthesis of the C12–C21 fragment of the epothilones

Bin Zhu and James S. Panek *

*Department of Chemistry, Metcalf Center for Science and Engineering, Boston University, 590 Commonwealth Avenue,
Boston, MA 02215, USA*

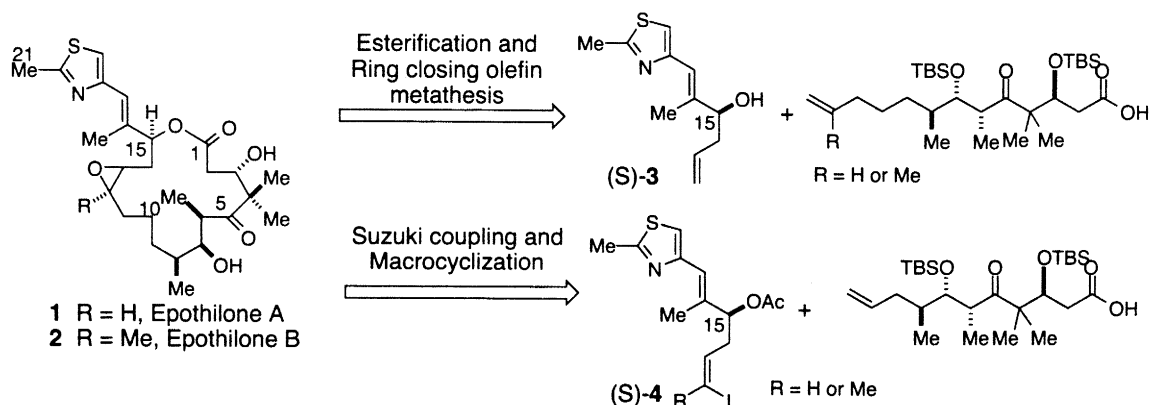
Received 21 December 1999; accepted 6 January 2000

Abstract

An operationally simple enzymatic kinetic resolution has been applied in an efficient synthesis of C12–C21 fragment of epothilones. The key step, a lipase resolution, has been employed on three different thiazole-containing vinyl carbinol substrates to give highly enantiomerically enriched alcohols bearing the key C15 stereocenter. © 2000 Elsevier Science Ltd. All rights reserved.

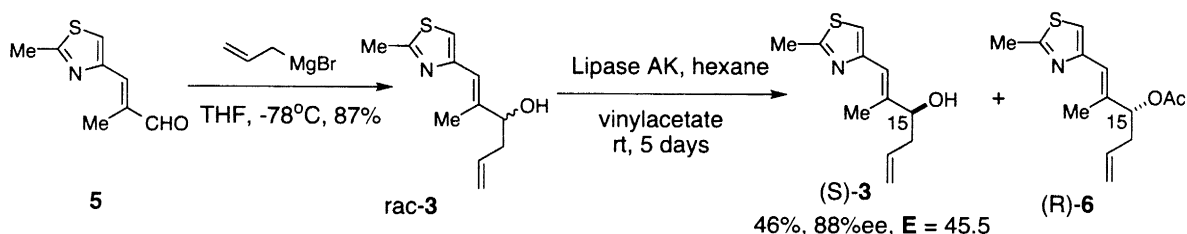
Epothilone A (**1**) and B (**2**) are cytotoxic macrolides isolated from myxobacterium *Sorangium cellulosum*. These compounds exhibit potent antitumor properties, and their mechanism of action is similar to that of TaxolTM (paclitaxel), which is through induction of tubulin polymerization and microtubule stabilization. Moreover, epothilones are effective against a number of paclitaxel-resistant tumor cell lines.¹ As a result, the epothilone-class of natural products hold considerable potential to be developed as powerful anticancer agents. In that regard, it comes as no surprise that a large number of publications concerning the synthesis of epothilones and their analogs have recently appeared.^{1,2} However, the development of convergent and practical routes toward these compounds would continue to constitute a useful contribution to this field. Among the many synthetic approaches en route to the epothilones, ring closing olefin metathesis^{1a,3} and Suzuki coupling/macrocyclization^{1,2a,3b} strategies have been successfully used in several approaches (Scheme 1). These two strategies required the construction of two advanced intermediates, a chiral secondary alcohol bearing a terminal olefin (*S*)-**3** or a vinyl iodide (*S*)-**4** respectively. We report herein our approach to the synthesis of these two fragments, which utilized a convenient lipase resolution to give highly enantiomerically enriched vinyl carbinols and establish the critical C15-hydroxyl stereocenter. In comparison to conventional chemical synthetic methods, enzymatic kinetic resolution with lipase generally uses mild reaction conditions and simple operational procedures.⁴ In addition, lipase resolution provides both stereoisomers with generally high enantiomeric excess, which may facilitate the preparation of analogs.

* Corresponding author.



Scheme 1.

The synthesis of olefin (*S*)-**3** began with the known thiazole aldehyde **5**,¹ which was treated with allyl magnesium bromide at low temperature (-78°C) in THF to give the racemic secondary alcohol *rac*-**3**. This material was subjected to lipase resolution to give the corresponding acetate (*R*)-**6** and the enantiomerically enriched alcohol (*S*)-**3** with good yield and enantioselectivity (46% yield, 88% ee, $E=45.5$) (Scheme 2).⁵

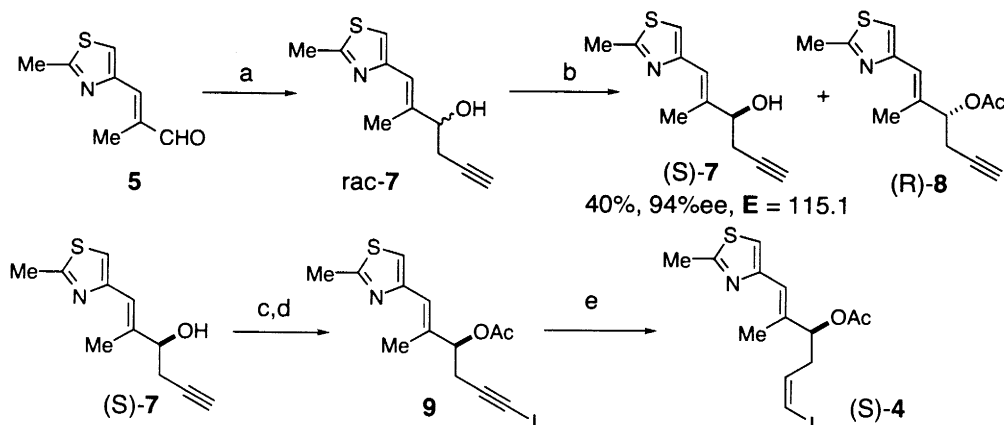


Scheme 2.

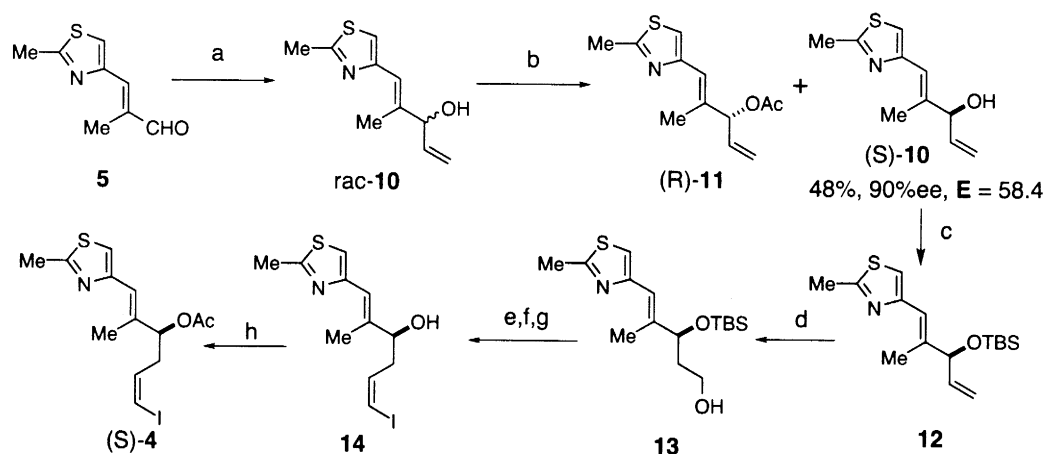
In the planned synthesis of (*S*)-**4**, aldehyde **5** was treated with zinc dust and 1-trimethylsilyl-3-bromopropyne in the presence of HgCl_2 in refluxing THF. The resulting material was deprotected (TBAF, THF) to give racemic alcohol *rac*-**7**. Lipase resolution of *rac*-**7** led to enantiomerically enriched alcohol (*S*)-**7** with 40% yield (50% conversion) and 94% ee ($E=115.1$),⁵ along with the opposite acetate (*R*)-**8**. The alcohol (*S*)-**7** was acetylated under standard conditions and further transformed to alkynyl iodide **9** ($n\text{-BuLi}$, I_2 , THF, -78°C), which was then reduced using Corey's protocol⁶ to give vinyl iodide (*S*)-**4** (Scheme 3).

While the lipase resolution of *rac*-**7** provided desired (*S*)-**7** with good yield and high ee, the length of resolution time (7 to 14 days) was a point of serious concern. We then turned our attention to the divinyl carbinol *rac*-**10**, which was easily obtained from the reaction of aldehyde **5** with vinyl magnesium bromide (THF, -78°C). Gratifyingly, the rate of the resolution of *rac*-**10** proved to be much faster than that of *rac*-**3** and *rac*-**7**, and the resulting enantiomerically enriched alcohol (*S*)-**10** was obtained in 48% yield (50% conversion) and 90% ee ($E=58.4$).^{5,7} This alcohol was then protected as its silyl ether **12** (TBSCl, imidazole, DMF). Selective hydroboration of the terminal olefin of **12** with dicyclohexylborane followed by oxidation led to alcohol **13**. Vinyl iodide **14** was obtained from **13** by a three-step sequence, including Dess–Martin oxidation, Wittig olefination and HF desilylation. Acetylation of **14** finished the synthesis of vinyl iodide (*S*)-**4** (Scheme 4).

In conclusion, efficient syntheses of two C12–C21 fragments of epothilones have been achieved



Scheme 3. (a) (i) Zn, 1-trimethylsilyl-3-bromopropyne, HgCl_2 (cat.), THF, reflux, 16 h, 91%; (ii) TBAF, THF, rt, 30 min, 94%; (b) Lipase AK (100% wt), hexane/ether, vinyl acetate, 7 to 14 days; (c) Ac_2O , Et_3N , DMAP, CH_2Cl_2 , 95%; (d) $n\text{-BuLi}$, I_2 , THF, -78°C , 80%; (e) $\text{BH}_3 \cdot \text{Me}_2\text{S}$, cyclohexene, HOAc, Et_2O , 60%



Scheme 4. (a) Vinyl magnesium bromide, THF, -78°C , 90%; (b) Lipase AK (50% wt), vinyl acetate, hexane, rt, 48 to 72 h; (c) TBSCl, imidazole, DMF, 95%; (d) $\text{BH}_3 \cdot \text{THF}$, cyclohexene, THF, NaOH, H_2O_2 , >90%; (e) Dess–Martin reagent, CH_2Cl_2 ; (f) $\text{CH}_2\text{I} \cdot \text{PPh}_3$, NaHMDS, THF; (g) HF (48% aqueous), CH_3CN , 65% for three steps; (h) Ac_2O , Et_3N , DMAP, CH_2Cl_2 , 95%

utilizing a lipase catalyzed resolution to establish the C15-hydroxyl stereocenter. Three different thiazole-containing vinyl carbinols were successfully resolved under essentially similar reaction conditions. In all cases, the *S*-absolute configuration of the resolved alcohols is in complete agreement with literature precedents. Overall, the enzymatic resolution approach may offer an attractive choice for practical synthesis of epothilones and their analogs.

Acknowledgements

Financial support was obtained from the NIH (GM 55740).

References

1. (a) Nicolaou, K. C.; Roschangar, F.; Vourloumis, D. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2014–2045 and references cited therein. (b) Harris, C. R.; Danishefsky, S. J. *J. Org. Chem.* **1999**, *64*, 8434–8456 and references cited therein.
2. (a) Harris, C. R.; Kuduk, S. D.; Balog, A.; Savin, K.; Glunz, P. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 7050–7062. (b) Mulzer, J.; Mantoulidis, A.; Ohler, E. *Tetrahedron Lett.* **1998**, *39*, 8633–8636. (c) May, S. A.; Grieco, P. *Chem. Commun.* **1998**, 1597–1598. (d) White, J. D.; Carter, R. G.; Sundermann, K. F. *J. Org. Chem.* **1999**, *64*, 684–685. (e) White, J. D.; Sundermann, K. F.; Carter, R. G. *Organic Lett.* **1999**, *1*, 1431–1434.
3. (a) 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. (b) 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. (c) Schinzer, D.; Limberg, A.; Bauer, A.; Bohm, O. M.; Cordes, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 523–524. (d) Ref. 2c.
4. Synthesis of C12–C21 fragment utilizing aldolase: (a) Machajewski, T. D.; Wong, C. H. *Synthesis* **1999**, 1469–1472. (b) Sinha, S. C.; Sun, J.; Miller, G.; Barbas III, C. F.; Lerner, R. A. *Organic Lett.* **1999**, *1*, 1623–1626.
5. The ees were determined by ^1H NMR spectroscopic analysis of crude mandelate ester derived from the chiral alcohol and (*R*)-(*O*)-acetyl mandelic acid. The absolute stereochemistry was assigned by comparing the $[\alpha]_{\text{D}}$ of the obtained (*S*)-**3** and (*S*)-**4** with the reported data. The enzymatic stereoselectivity factor **E** was calculated according to the method of Kagan. See: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249–330.
6. Corey, E. J.; Cashman, J. R.; Eckrich, T. M.; Corey, D. R. *J. Am. Chem. Soc.* **1985**, *107*, 713–715.
7. Illustrative procedure for the lipase resolution: A stirred solution of racemic alcohol *rac*-**10** (3.60 g, 18.3 mmol) in hexane (170 mL) and vinyl acetate (17 mL) was treated with lipase AK powder (1.80 g, 50wt%, Amano Pharmaceutical Co., Inc.) at room temperature. The progress of the reaction was monitored by ^1H NMR, measuring the integration of the methine proton adjacent to the hydroxyl group and the methine proton adjacent to the acetate group. When the ratio of acetate and alcohol in the reaction mixture reached ca. 1:1 (72 h), the insoluble enzyme was removed by filtration, and washed with ether (200 mL). Concentration of the filtrate in vacuo and silica gel flash chromatography afforded the acetate (*R*)-**11** (15% ethyl acetate in hexane, 2.1 g, 48%, light yellow oil) and the unreacted alcohol (*S*)-**10** (35% acetate in hexane, 1.73 g, 48%, light yellow oil).