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Synthesis of epothilones B and D from D-glucose

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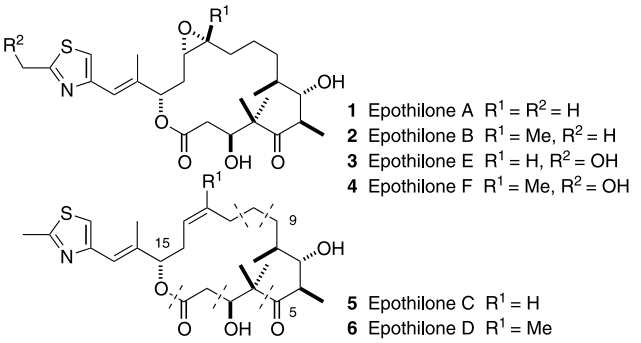
Abstract—An enantiospecific total synthesis of epothilones B and D from D-glucose is reported.

Ever since the discovery of taxol-like tubulin binding properties of epothilones,[1] some 30 research groups worldwide have embarked on the synthesis of this group of natural products (**1**–**6**) and hundreds of their synthetic analogs.[2] A large amount of total[3,4] or partial syntheses of the epothilones has established four different modes for installation of the C12–C13 epoxide, three distinct macrocyclization strategies, and the skeleton assembly along all but one (C7–C8) carbon–carbon bonds. Nevertheless, the continuous stream of publications proves that there is still enough room here for inspiration and practical improvements with regards to the yield, stereoselectivity or industrial application compliance. In this paper we wish to disclose some results culminating in the total synthesis of epothilones D and B.

Considering the common functionality pattern present, the epothilone molecules might be dissected for two large chiral fragments, C5–C9 and C11–C16, covering, respectively, the crucial polypropionate and *Z* homoallylic alcohol regions, as shown below. The stereochemistry present therein could be conveniently secured by stereospecific transformations on a carbohydrate template.

As applied to our synthesis of epothilones D and B, both the fragments were synthesized from a common key intermediate, the branched-chain carbohydrate derivative **7**,[5] easily available in three steps and 52–55% overall yield from methyl-α-D-glucopyranoside (Scheme 1). Thus, an improved procedure over the existing method[5] allowed preparation of the unsaturated pyranoside diacetate **8** in high yield. A borohydride deoxygenation of the allylic acetate function of **8** in the



presence of a number of palladium catalysts afforded the inseparable mixture of the tri-substituted alkene **9** and its di-substituted regiomer **10** in varying, sometimes for no apparent reason, ratio (3:2–7:1) and yield. A close investigation of the reaction mechanism and extensive screening and optimization for numerous reaction parameters brought about the conditions for highly regioselective transformation (**9**:**10** = 41:1); the residual trace amount of **10** was easily removed in the next step. The product **9**, bearing the crucial 15*S* and *Z* alkene functionality of epothilone D, was then forwarded to the methyl ketone **12**. It should be noted that an intermediate aldehyde is very volatile and unstable, and only the one–step Swern oxidation/Grignard addition procedure[6] afforded the alcohol **11** in high yield. The olefination of the methyl ketone **12** with the lithium reagents of the known phosphonate **14a**[7] or the corresponding phosphine oxide **14b**[9] afforded the diene **15** in disappointingly low yield and selectivity (40–45%; *Z*,*E*:*Z*,*Z* = 5–7:1), while some highly polar adduct persisted. Further studies revealed that of two diastereomeric primary adducts, β-hydroxyphosphonates, the major one, giving rise to the undesired *Z*,*Z* diene, requires more drastic conditions to eliminate. Considering the ability of β-hydroxyphosphonates to equilibrate, the olefination of **12** with the potassium phosphonate **14a** was attempted to give, in very mild

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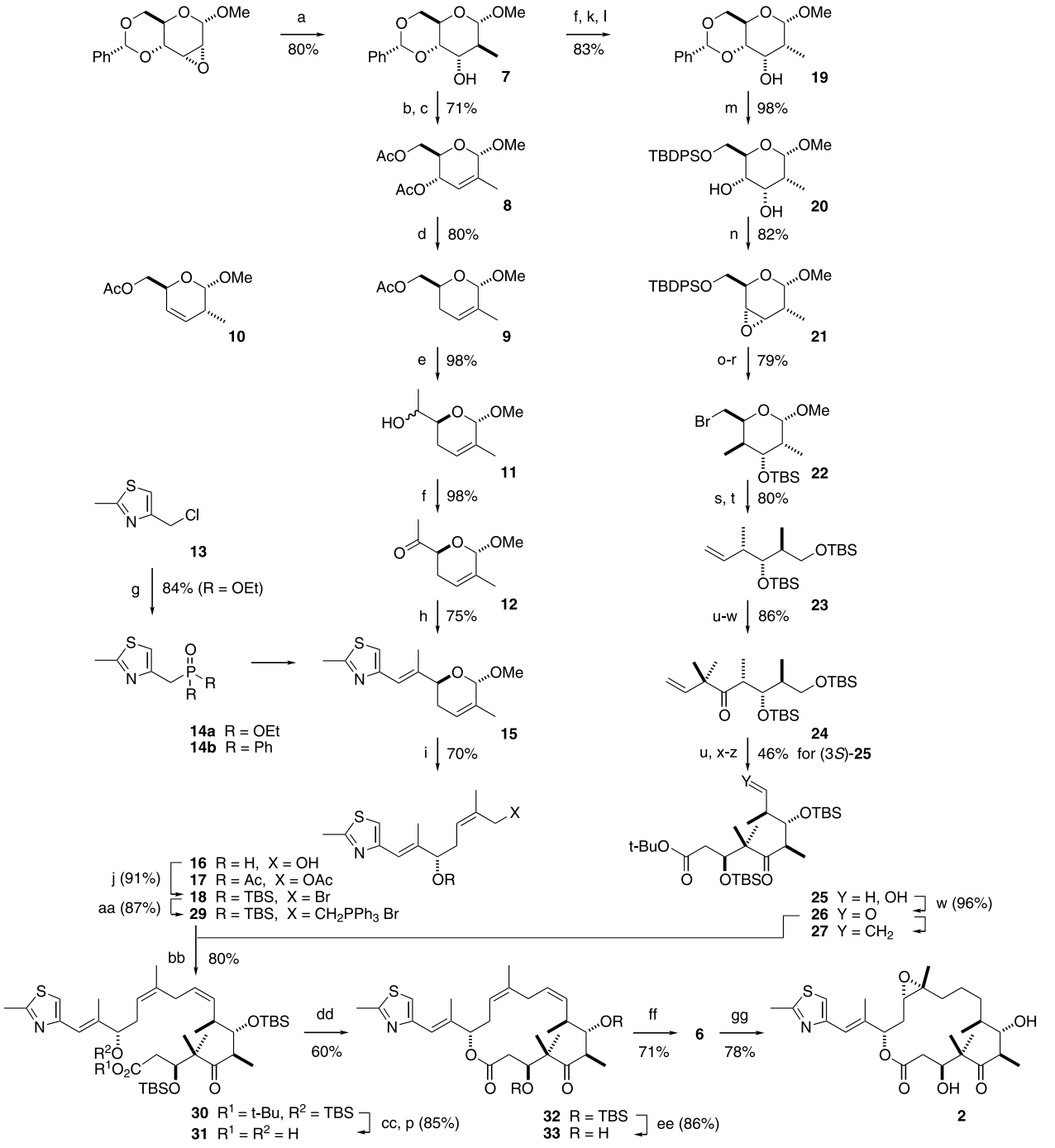


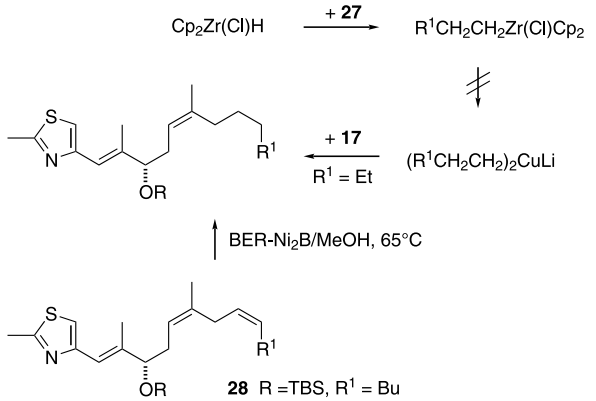
Scheme 1. *Reagents and conditions*: (a) $Me_2CuLi{\cdot}LiCN/Et_2O$–THF, rt, 1 h (cf. Ref. 4); (b) NaH, ImH (cat.), CS_2, MeI/THF; then Ph–Ph, 240°C, 1 h; then TsOH, 0.01 M in CH_2Cl_2–MeOH (3:1); (c) Ac_2O, Et_3N, DMAP (cat.)/CH_2Cl_2; (d) **8**, $Pd(OAc)_2$ (0.1 equiv.), DPPP (0.2 equiv.), Bu_4NOAc (0.1 equiv.), rt, 1 h; then $NaBH_4$ (portion-wise, 0.05 equiv. every 0.5 h; 1 equiv. total); (e) MeONa (cat.)/MeOH; then $(COCl)_2$, DMSO, Et_3N/THF; then MeMgCl/THF; −78°C to rt; (f) $(COCl)_2$, DMSO, Et_3N/CH_2Cl_2; (g) $P(OEt)_3$ (2 equiv.), 165°C, 2 h; (h) **14a**, *t*-BuOK/THF, then add **12**, −30°C to rt for 4 h; (i) AcOH–H_2O–THF (3:1:6) rt, 24 h; then $NaBH_4$/MeOH; (j) CBr_4, Ph_3P/CH_3CN, 0°C; then TBSOTf, 2,6-di-tert-butyl-4-methylpyridine, −40°C (one-pot); (k) Et_3N/CH_2Cl_2–MeOH (3:1), rt; (l) $NaBH_4$/MeOH–DMF (1:1); (m) H_2, Pd/C/AcOEt; then TBDPSCl, Py; (n) $CH_3C(OMe)_3$, TsOH (cat.); then Et_3N; AcBr/CH_2Cl_2; then MeONa/MeOH; (o) Me_2Mg/Et_2O; (p) Bu_4NF/THF; (q) CBr_4, Ph_3P/Py; (r) TBSCl, ImH/DMF; (s) Zn, *i*-PrOH–H_2O (19:1), Δ; then $NaBH_4$; (t) TBSCl/Py; (u) NMO, OsO_4 (0.02 equiv.)/*t*-BuOH–H_2O (9:1); then H_5IO_6; (v) $Me_2C{=}CHCH_2MgCl$/THF; (w) NMO, TPAP (0.05 equiv.), MS 4 Å/CH_3CN; (x) $LiCH_2CO_2Bu$-*t*/THF, −78°C, 0.5 h; (y) TBSOTf, *i*-Pr_2NEt/CH_2Cl_2, −78°C; (z) PPTS/EtOH, rt; (aa) $Ph_3P{=}CH_2$ (3 equiv.)/THF, −78°C; (bb) **28**+LiHMDS/THF, −78°C; then add **26**; (cc) TMSOTf, collidine/CH_2Cl_2, 0°C, 1 h; (dd) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, rt, 1 h; then slow addition to DMAP/$PhCH_3$, 80°C; (ee) TFA/CH_2Cl_2, 0°C; (ff) $TrisNHNH_2$, Et_3N/Et_2O, 39°C; (gg) dimethyldioxirane/CH_2Cl_2, −50°C.

conditions, the required *Z*,*E* diene **15** as a sole isomer and in good yield. Mild acid hydrolysis of the acetal function of **15** followed by borohydride reduction furnished the enantiomerically pure diol **16** from which two projected C11–C16 fragments of epothilone D, the diacetate **17** and the bromide **18**, were prepared.

On the other hand, the thermodynamically driven isomerization of **7** into **19**[10] followed by hydrogenolysis and selective silylation afforded the diol **20** which was converted into the epoxide **21** by an *ortho*ester method.[11] Oxirane ring opening of **21** with Me_2Mg[12] proceeded regio- and stereospecifically in high yield (91%). The following usual functional group manipulation afforded the bromide **22** which was subjected to a reductive fragmentation[13] to give, after borohydride reduction of a resulting aldehyde and silylation, the crucial polypropionate C5–C9 fragment of epothilones **23**. The double bond in **23** was split, and the resulting aldehyde was converted into the C3–C9 alkene **24** via a Grignard reagent addition. The procedure of alkene cleavage was repeated, and the C3–C9 aldehyde obtained was treated with α-lithio *tert*-butyl acetate to give a mixture of β-hydroxyesters (3*S*:3*R* ca. 7:3) from which the required isomer was easily isolated as the hydroxyester **25**. Its further transformations provided the C1–C9 aldehyde **26** and C1–C10 alkene **27**.

Considerable effort was devoted to the problem of the epothilone *seco*-acid skeleton assembly that required one-carbon homologation to one of the fragments synthesized. Thus, our early modeling studies have shown that the diacetate **17** undergoes clear S_N2 substitution at the allylic position with retention of configuration of the double bond under treatment with alkyl cuprates (Scheme 2).

Consequently, the hydrozirconation of the derived olefin fragment **27** followed by transmetallation to copper was attempted.[14] Under numerous conditions tried the coupling of the alkene **27** and the diacetate **17** fragments failed, apparently due to lack of the Zr-to-Cu transmetallation. Also, it was demonstrated that the hydrogenation of the model triene **28** on the borohydride exchange resin–nickel boride (BER–Ni_2B)[15] proceeded selectively at the di-substituted double bond.



Scheme 2.

Guided by this observation, an one-pot, three-component coupling between Ph_3PCH_3Br, the C11–C16 bromide **18** and the C1–C9 aldehyde **26** was attempted to give the desired *seco*-acid (**30**) in only low yield (16%).† Several one-carbon homologations to C11–C16 fragment with ICH_2ZnI[16] (as an entry to a Wittig reagent) or $MeSO_2PT$[17] (for a Julia olefination) were made but finally ceased in favor of a simple two-step Wittig approach.[4g] The C10–C16 phosphonium bromide **29**, prepared in a separate step, was coupled with the C1–C9 aldehyde **26** to give the protected *seco*-acid of 9,10(*Z*)-dehydroepothilone D **30** which, however, resisted the hydrogenation on the BER–Ni_2B catalyst, apparently due to steric hindrance from both 8-CH_3 and 7-OTBS groups. In expectation of more favorable steric situation later on, the *tert*-butyl ester and 15-O-TBS groups were clearly removed, and the *seco*-acid **31** thus obtained was macrolactonized to give **32**. Unfortunately, both the protected (**32**) and the deprotected (**33**) 9,10-dehydroepothilone D resisted the hydrogenation in the above-mentioned conditions as well. Eventually, the hydrogenation of **33** into epothilone D **6** was achieved in acceptable yield by diimide generated from 2,4,6-triisopropylbenzenesulfonyl hydrazide ($TrisNHNH_2$)[18] in ether, though large excess of the reagent was required for full conversion of the starting product. Note, the functionality of **33** tolerated the reaction conditions. Finally, epoxidation of epothilone D **6** with dimethyl dioxirane[19] led to epothilone B **2**.[20]

In conclusion, we have completed an enantiospecific total synthesis of epothilones D and B from D-glucose. Further efforts directed to circumvent the bottle-neck partial hydrogenation step, as well as an adaptation of the strategy to the synthesis of the other members of the epothilone family, are considered.

References

1. (a) Höfle, G.; Bedorf, N.; Gerth, K.; Reichenbach, H. (GBF) DE-4138042, 1993; *Chem. Abstr*. **1993**, *120*, 52841; (b) Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 156; (c) Gerth, K.; Bedorf, N.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot*. **1996**, *49*, 560; (d) Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res*. **1995**, *55*, 2325.
2. For reviews, see: (a) Nicolaou, K. C.; Roschangar, F.; Vourloumis, D. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 2014; (b) Harris, C. R.; Danishefsky, S. J. *J. Org. Chem*. **1999**, *64*, 8434; (c) Mulzer, J. *Monatch. Chem*. **2000**, *131*, 205; (c) Altmann, K.-H.; Bold, G.; Caravatti, G.; End, N.; Flörsheimer, A.; Guagnano, V.; O'Reilly, T.; Wartmann, M. *Chimia* **2000**, *54*, 612; (d) Nicolaou, K. C.; Ritzén, A.; Namoto, K. *Chem. Commun*. **2001**, 1523. For

† This result was obtained using the *stoichiometrical* amounts of the components in a *sub-millimole* scale experiment. Subsequent publications from Professor J. D. White's laboratory[4g,h] suggested that both conditions are unfavorable for this reaction sequence.

recent list of natural epothilones, see: Hardt, I. H.; Steinmetz, H.; Gerth, K.; Sasse, F.; Reichenbach, H.; Höfle, G. *J. Nat. Prod.* **2001**, *64*, 847.

3. **Epothilones A/C/E**: (a) Balog, A.; Meng, D.; Kamenecka, T.; Bertinato, P.; Su, D.-S.; Sorensen, E. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2801; (b) Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 166; (c) Nicolaou, K. C.; Sarabia, F.; Ninkovic, S.; Yang, Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 525; (d) Schinzer, D.; Limberg, A.; Bauer, A.; Böhm, O. M.; Cordes, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 523; (e) 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; (f) 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; (g) Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073; (h) 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**, *557*, 268; (i) Sinha, S. C.; Barbas, C. F., III; Lemer, R. A. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 14603; (j) Nicolaou, K. C.; He, Y.; Roschangar, F.; King, N. P.; Vourloumis, D.; Li, T. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 84; (k) Schinzer, D.; Bauer, A.; Böhm, O. M.; Limherg, A.; Cordes, M. *Chem. Eur. J.* **1999**, *5*, 2483; (l) Nicolaou, K. C.; King, N. P.; Finlay, M. R. V.; He, Y.; Roschangar, F.; Vourloumis, D.; Vallberg, H.; Sarabia, F.; Ninkovic, S.; Hepworth, D. *Bioorg. Med. Chem.* **1999**, *7*, 665; (m) Sawada, D.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 209; (n) Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 10521; (o) Zhu, B.; Panek, J. S. *Org. Lett.* **2000**, *2*, 2575; (p) Fürstner, A.; Mathes, C.; Grela, K. *Chem. Commun.* **2001**, 1057; (q) Bode, J. W.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 3611; (r) Hindupur, R. M.; Panicker, B.; Valluri, M.; Avery, M. A. *Tetrahedron Lett.* **2001**, *42*, 7341; (s) Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410.
4. **Epothilones B/D/F**: (a) Su, D.-S.; Meng, D.; Bertinato, P.; Balog, A.; Sorensen, E. J.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 757; (b) Balog, A.; Harris, C.; Savin, K.; Zhang, X.-G.; Chou, T.-C.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1998**; *37*, 2675; (c) May, S. A.; Grieco, P. A. *Chem. Commun.* **1998**, 1597; (d) Mulzer, J.; Mantoulidis, A.; Öhler, E. *Tetrahedron Lett.* **1998**, *39*, 8633; (e) Schinzer, D.; Bauer, A.; Schieber, J. *Chem. Eur. J.* **1999**, *5*, 2492; (f) Harris, C. R.; Kuduk, S. D.; Balog, A.; Savin, K.; Glunz, P. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 7050; (g) White, J. D.; Carter, R. G.; Sundermann, K. F. *J. Org. Chem.* **1999**, *64*, 684; (h) White, J. D.; Sundermann, K. F.; Carter, R. G. *Org. Lett.* **1999**, *1*, 1431; (i) Martin, H. J.; Drescher, M.; Mulzer, J. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 581; (j) Mulzer, J.; Karig, G.; Pojarliev, P. *Tetrahedron Lett.* **2000**, *41*, 7635; (k) Mulzer, J.; Mantoulidis, A.; Öhler, E. *J. Org. Chem.* **2000**, *65*, 7456; (l) Nicolaou, K. C.; Hepworth, D.; King, N. P.; Finlay, M. R.; Scarpelli, R.; Pereira, M. M.; Bollbuck, B.; Bigot, A.; Werschkun, B.; Winssinger, N. *Chem. Eur. J.* **2000**, *6*, 2783; (m) Martin, H. J.; Pojarliev, P.; Kahlig, H.; Mulzer, J. *Chem. Eur. J.* **2001**, *7*, 2261; (n) White, J. D.; Carter, R. G.; Sundermann, K. F.; Wartmann, M. *J. Am. Chem. Soc.* **2001**, *123*, 5407; (o) Valluri, M.; Hindupur, R. M.; Bijoy, P.; Labadie, G.; Jung, J. C.; Avery, M. A. *Org. Lett.* **2001**, *3*, 3607; (p) Martin, N.; Thomas, E. J. *Tetrahedron Lett.* **2001**, *42*, 8373; (q) Lee, C. B.; Wu, Z.; Zhang, F.; Chappell, M. D.; Stachel, S. J.; Chou, T.-C.; Guan, Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 5249. See also Ref. 3f,g,n,s.
5. Hicks, D. R.; Fraser-Reid, B. *Can. J. Chem.* **1975**, *53*, 2017.
6. Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198.
7. Prepared in high yield from easily available 4-chloromethyl-2-methylthiazole **13**[8] by a modified procedure: Arbuzov, B. A.; Lugovkin, B. P. *Zh. Obshch. Khim.* **1951**, *21*, 1869; *Chem. Abstr.* **1952**, *46*, 6122e.
8. Marzoni, G. *J. Heterocycl. Chem.* **1986**, *23*, 577; **13** HCl is also commercially available from Lancaster.
9. Meng, D.; Sorensen, E. J.; Bertinato, P.; Danishefsky, S. J. *J. Org. Chem.* **1996**, *61*, 7998.
10. Hanessian, S.; Rancourt, G. *Can. J. Chem.* **1977**, *55*, 1111.
11. Kolb, H. C.; Sharpless, B. *Tetrahedron* **1992**, *48*, 10515.
12. Prepared by precipitation of $MgCl_2$·dioxane from MeMgCl in ether; the resulting slurry was used as obtained.
13. Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990.
14. For review, see: Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853.
15. Choi, J.; Yoon, N. M. *Synthesis* **1996**, 597.
16. Knochel, P.; Chou, T.-S.; Chen, H. G.; Yeh, M. C. P.; Rozema, M. J. *J. Org. Chem.* **1989**, *54*, 5202.
17. Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.
18. Cusack, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B. *Tetrahedron* **1976**, *32*, 2157.
19. Stachel, S. J.; Danishefsky, S. J. *Tetrahedron Lett.* **2001**, *42*, 6785.
20. Epothilone D **6**: $[\alpha]_D^{25}$ −89.1 (*c* 0.17, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.95 (s, 1H), 6.58 (s, 1H), 5.21 (dd, $J=9.7$, 1.6 Hz, 1H), 5.14 (dd, $J=10.1$, 4.8 Hz, 1H), 4.29 (dd, $J=10.9$, 2.4 Hz, 1H), 3.73 (dd, $J=4.2$, 2.2 Hz, 1H), 3.41 (br s, 1H), 3.16 (dq, $J=6.9$, 2.5 Hz, 1H), 3.02 (br s, 1H), 2.68 (s, 3H), 2.63 (dt, $J=15.1$, 10.1 Hz, 1H), 2.45 (dd, $J=15.0$, 11.0 Hz, 1H), 2.38–2.30 (m, 1H), 2.2 (dd, $J=14.7$, 2.7 Hz, 1H), 2.2 (br.d, $J=15.7$ Hz, 1H), 2.06 (d, $J=0.9$ Hz, 3H), 1.93–1.82 (m, 1H), 1.8–1.7 (m, 2H), 1.66 (s, 3H), 1.34 (s, 3H), 1.32–1.22 (m, 4H), 1.20 (d, $J=6.8$ Hz, 3H), 1.08 (s, 3H), 1.02 (d, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.6, 170.4, 165.6, 152.0, 139.2, 138.5, 120.9, 119.4, 115.6, 79.0, 74.2, 72.4, 53.5, 41.7, 39.7, 38.5, 32.6, 31.9, 31.8, 31.6, 25.4, 22.9, 19.1, 18.2, 15.9, 15.8, 13.4. Epothilone B **2**: $[\alpha]_D^{25}$ −36.0 (*c* 0.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.98 (s, 1H), 6.60 (s, 1H), 5.41 (dd, $J=7.9$, 2.4 Hz, 1H), 4.23 (br, 2H), 3.77 (t, $J=4.1$ Hz, 1H), 3.41 (br s, 1H), 3.31 (dq, $J=6.8$, 4.0 Hz, 1H), 2.80 (dd, $J=7.6$, 4.4, 1H), 2.70 (s, 3H), 2.63 (br.s, 1H), 2.55 (dd, $J=14.0$, 10.4 Hz, 1H), 2.35 (dd, $J=14.3$, 1.8 Hz, 1H), 2.16–2.07 (m, 1H), 2.09 (s, 3H), 1.90 (dt, $J=15.2$, 8.1, 1H), 1.8–1.7 (m, 2H), 1.60–1.45 (m, 2H), 1.45–1.34 (m, 3H), 1.39 (s, 3H), 1.28 (s, 3H), 1.17 (d, $J=7.0$ Hz, 3H), 1.08 (s, 3H), 1.00 (d, $J=7.0$ Hz, 3H).