the formation of precipitates. Note that extraction of the particle diameters from the light scattering data presumes the existence of spherical particles only, which appears to make the agglomeration diameters somewhat larger than those determined by electron microscopy.

[17] Smaller, but somewhat similar structures have been reported in the laser irradiation of soot in flames. See R. L. Vander Wal, M. Y. Choe, K. O. Lee, *Combustion Flame* **1995**, *102*, 200–294.

[18] Absorbing solids also can undergo chemical reactions when driven to high temperatures with a laser. See S. Mohr, H. Muller-Bbuschbaum, *Angew. Chem.* **1995**, *107*, 671–677; *Angew. Chem. Int. Ed. Engl.* **1995** *34*, 634–640.

[19] K. S. Suslick, P. Boudjouk in *Ultrasound, Its Chemical, Physical and Biological Effects* (Ed.: K. S. Suslick), VCH, New York, **1988**.

[20] Preliminary experiments with lampblack in toluene give a number of products incuding C_2H_2 and C_2H_4, products not seen in the sonolysis on toluene [19].

Total Synthesis of Epothilone A: The Olefin Metathesis Approach**

Zhen Yang, Yun He, Dionisios Vourloumis, Hans Vallberg, and K. C. Nicolaou*

Dedicated to Professor Thomas J. Katz on the occassion of his 60th birthday

Epothilone A (**1**)[1,2] is an exciting new natural product, isolated from the myxobacteria *Sorangium cellulosum* strain 90, with novel molecular architecture, important biological properties, and an intriguing mechanism of action. Amongst its biological properties are potent antifungal and selective cytotoxic activities.[1–4] Its mechanism of action against tumor cells has been attributed to the binding and stabilization of microtubules,[4] and in that respect it resembles taxol.[5] Following our recent report[6] on a metathesis-based approach[7] towards this class of compounds, we now disclose the total synthesis of epothilone A (**1**) by this novel strategy.

Figure 1 shows the strategic bond disconnections that led to the convergent strategy utilized in this synthesis. The plan calls for the construction of the three key building blocks **5**, **6**, and **10** (Scheme 1), their union and elaboration to the 16-membered macrocycle, and final epoxidation. For the present approach, the olefin metathesis step and the selective epoxidation of the $\Delta^{12,13}$-double bond in the final step were considered, at the outset, both risky and crucial.

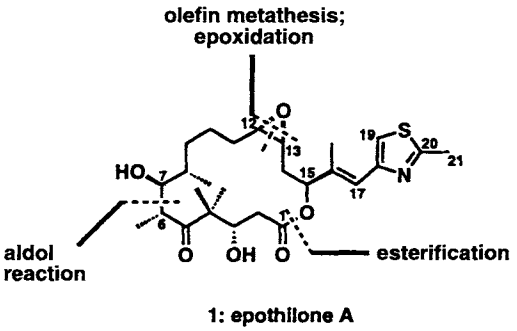
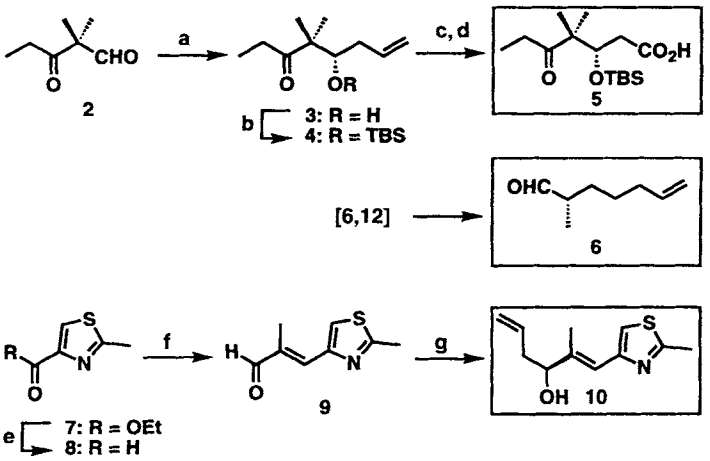


Figure 1. Structure and retrosynthetic analysis of epothilone A (**1**).



Scheme 1. Synthesis of building blocks **5**, **6**, and **10**. a) 1.1 equiv (+)-Ipc_2B(allyl), Et_2O/pentane, −100 °C, 0.5 h, 74%; b) 1.1 equiv TBSOTf, 1.2 equiv 2,6-lutidine, CH_2Cl_2, 25 °C, 1 h, 98%; c) O_3, CH_2Cl_2, −78 °C, 0.5 h, then excess Ph_3P, −78 → 25 °C, 1 h, 82%; d) 3 equiv $NaClO_2$, 4 equiv 2-methyl-2-butene, 1.5 equiv NaH_2PO_4, *t*BuOH:H_2O 5:1, 25 °C, 2 h, 93%; e) 1.1 equiv DIBAl-H, CH_2Cl_2, −78 °C, 0.5 h, 90%; f) 1.1 equiv Ph_3P=C(Me)CHO, benzene, 80 °C, 1 h, 90%; g) 1.1 equiv (+)-Ipc_2B(allyl), Et_2O/pentane, −100 °C, 0.5 h, 96%. TBS = *tert*-butyldimethylsilyl; Ipc_2B(allyl) = diisopinocampheylallylborane.

Scheme 1 summarizes the construction of the key building blocks **5**, **6**, and **10**. The synthesis of carboxylic acid **5** commenced with the known ketoaldehyde **2**,[8] which reacted selectively with Brown's allyl isopinocampheyl borane reagent [(+)-Ipc_2B(allyl)][9] in ether/pentane at −100 °C to afford alcohol **3**[10] in 74% yield. Protection of this alcohol with TBSOTf-2,6-lutidine afforded the silyl ether **4** in 98% yield. Ozonolytic cleavage of the double bond in **4** followed by $NaClO_2$ oxidation of the resulting aldehyde gave the targeted carboxylic acid **5** in 75% yield. The preparation of the heterocyclic component **10** was carried out from the known thiazole ester **7**[11] by a) reduction to the corresponding aldehyde (**8**) with Dibal-H (90% yield), b) Wittig reaction with Ph_3P=C(Me)CHO to afford the conjugated aldehyde **9** (90% yield), and c) condensation of **9** with (+)-Ipc_2B(allyl) in ether/pentane at −100 °C (96% yield).[10]

Having secured the requisite building blocks, we then turned our attention to their coupling and further elaboration. Scheme 2 depicts these final stages of the present total synthesis of epothilone A (**1**). Condensation of the dianion of **5** (2.2 equiv of LDA, THF, −78 to −40 °C) with aldehyde **6**[6,12] (1.2 equiv) at −78 to −40 °C resulted in the formation of the desired aldol product (**11**) as the major isomer, together with its 6*S*,7*R*-diastereomer in high yield and approximately a 2:1 ratio. Esterification of this mixture with the hydroxy component **10** (2.0 equiv) proceeded in the presence of DCC and 4-DMAP in toluene at 25 °C to afford compound **12** and its 6*S*,7*R*-diastereomer in 70% overall yield[13] from ketoacid **5**. The two isomers were chromatographically separated [silica gel, ethyl acetate:hexane (1:5), R_f = 0.29 (**12**, 45% overall yield from **5**), 0.24 (6*S*,7*R*-diastereomer of **12**, 25% yield from **5**)], and the major product (**12**) was taken forward in the synthesis as a pure

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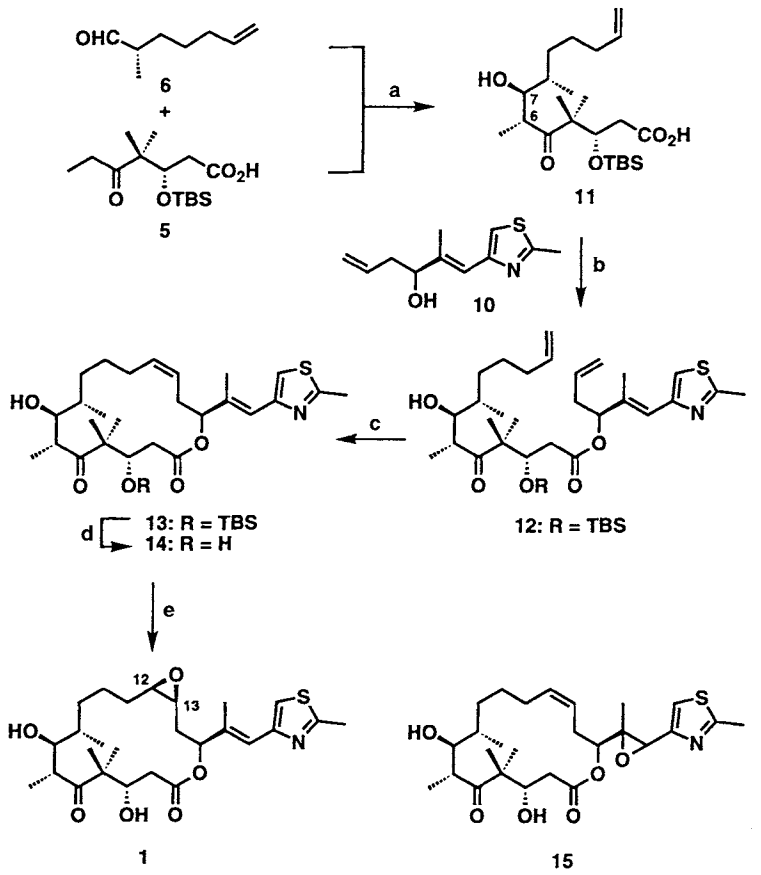

Scheme 2. Synthesis of epothilone A (**1**): a) 2.2 equiv LDA, THF, $-78 \rightarrow -40\,^{\circ}C$, 0.5 h, then 1.2 equiv **6** in THF, $-78 \rightarrow -40\,^{\circ}C$, 0.5 h, high yield of **11** and its (6*S*,7*R*)-diastereomer; b) 2.0 equiv **10**, 1.5 equiv DCC, 1.5 equiv 4-DMAP, toluene, 25 °C, 12 h, **12** (45% overall yield from **5**) and (6*S*,7*R*)-diastereomer of **12** (25% overall yield from **5**); c) **12** (0.006 M in CH_2Cl_2), 15 mol% $[RuCl_2(=CHPh)(PCy_3)_2]$ cat., 25 °C, 8 h, 50% plus $\Delta^{12,13}$-*trans*-isomer of **13** (35%); d) CF_3COOH (20 vol.%), CH_2Cl_2, 0 °C, 4 h, 98%; e) 1.1 equiv *m*CPBA, benzene, 0 °C, 20 h, **1** (55%) and 12α,13α-epoxide (20%) plus regioisomeric epoxide **15** (20%); LDA = lithium diisopropylamide, DCC = dicyclohexylcarbodiimide, 4-DMAP = 4-dimethylaminopyridine.

isomer. Its structure was eventually confirmed by conversion into epothilone A (**1**). The olefin metathesis reaction of **12** proceeded smoothly in the presence of $[RuCl_2(=CHPh)(PCy_3)_2]$ catalyst[14] in dilute CH_2Cl_2 solution at 25 °C to afford, in 50% yield, the *Z*-olefin **13**,[15] together with its *E*-isomer (35%).[15] After chromatographic purification [silical gel, benzene:ethyl acetate:hexane (2:1:2), $R_f = 0.21$ (*Z*-isomer), 0.45 (*E*-isomer)], the silyl group was removed from macrocycle **13** by exposure to CF_3COOH in CH_2Cl_2 at 0 °C to afford the dihydroxy lactone **14** in 98% yield. Finally, selective epoxidation of the $\Delta^{12,13}$-double bond of **14** was effected with *m*CPBA in CH_2Cl_2 at 0 °C to afford epothilone A (**1**) in 55% yield [silica gel, methanol: CH_2Cl_2 (1:20), $R_f = 0.23$], together with its 12α,13α-epoxide isomer [20% yield, silica gel, methanol:CH_2Cl_2 (1:20), $R_f = 0.16$] and its regioisomer **15** [20% yield, silica gel, methanol:CH_2Cl_2 (1:20), $R_f = 0.22$, stereochemistry unassigned]. Chromatographically purified synthetic epothilone A (**1**) exhibited identical properties (^1H and ^{13}C NMR, mass spectrum, $[\alpha]_D$, TLC and HPLC) to those of an authentic natural sample (Table 1).[16]

The reported total synthesis[17] demonstrates the power of the olefin metathesis reaction in complex molecule construction and renders epothilone A (**1**) readily accessible. Most importantly, its brevity, convergent nature, and flexibility should allow the generation of a diverse epothilone library for further biological investigations. In addition to the olefin metathesis approach reported herein, Figure 1 points to at least two more, distinctly different approaches[18] to epothilones: a) a macrolactonization approach and b) an approach in which an intramolecular aldol reaction may play the crucial role of constructing the macrocyclic skeleton. These and other strategies towards these compounds are currently under investigation in these laboratories.

Table 1. Selected physical properties of compounds **1**, **12**, and **13**.

12: $R_f = 0.29$ (silica gel, ethyl acetate:hexane 1:5); $[\alpha]_D = -53.4$ ($c = 1.0$, MeOH); IR (film): 3508 (br., OH), 1736 (C(O)O), 1690 (COC), 1650 cm^{-1} (CH=CHCO); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.93$ (s, 1H, −C=CHS−), 6.47 (s, 1H, −C=CH−C=), 5.81–5.72 (m, 1H, $CH=CH_2$), 5.73–5.65 (m, 1H, $-CHCH_2-$), 5.27 (dd, 1H, $J_1 = 7.0$, $J_2 = 6.5$ Hz, −OCH−), 5.06 (dd, 2H, $J_1 = 17.5$, $J_2 = 10.0$ Hz, $CH=CH_2$), 4.92 (dd, 2H, $J_1 = 17.0$, $J_2 = 10.5$ Hz, $CH=CH_2$), 4.39 (dd, 1H, $J_1 = 4.0$, $J_2 = 6.0$ Hz, $-(CH_3)_2CCH-$), 3.42 (bs, 1H, OH), 3.28 (q, 1H, $J = 7.0$ Hz, $-CH(CH_3)C(O)-$), 3.24 (d, 1H, $J = 9.5$ Hz, CH(OH)), 2.67 (s, 3H, $-SC(CH_3)=N-$), 2.54 2.43 (m, 2H), 2.43 (dd, 1H, $J_1 = 4.0$, $J_2 = 10.0$ Hz, $-CH_2COO-$), 2.31 (dd, 1H, $J_1 = 6.0$, $J_2 = 10.0$ Hz, $-CH_2COO-$), 2.04 (s, 3H, $-C(CH_3)=C-$), 1.95 (m, 2H, $-CH_2CH=CH_2$), 1.75–1.65 (m, 1H), 1.48–1.43 (m, 1H), 1.43–1.36 (m, 1H), 1.22–1.10 (m, 2H), 1.17 (s, 3H, $-C(CH_3)_2-$), 1.09 (s, 3H, $-C(CH_3)_2-$), 1.01 (d, 3H, $J = 6.5$ Hz, $C(O)CH(CH_3)-$), 0.86 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.81 (d, 3H, $J = 7.0$ Hz, $-C(OH)CH(CH_3)-$), 0.09 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.04 (s, 3H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 221.8$, 170.9, 164.6, 152.4, 139.0, 136.6, 133.2, 121.0, 117.8, 116.4, 114.1, 78.8, 74.5, 73.4, 53.9, 41.2, 40.1, 37.4, 35.4, 34.1, 32.3, 26.0, 25.9, 21.9, 19.9, 19.2, 18.1, 15.2, 14.6, 9.7, −4.3, −4.9; HRMS calcd for $C_{34}H_{57}NO_5SSi$ ($[M + Cs]^+$): 752.2781, found: 752.2760.

13: $R_f = 0.21$ (silica gel, ethyl acetate:benzene:hexane 1:2:2); $[\alpha]_D = -97$ ($c = 0.2$, MeOH); IR (film): 3456 (br., OH), 1739 (C(O)O), 1692 (COC); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.94$ (s, 1H, −C=CHS−), 6.56 (s, 1H, −C=CHC=), 5.45 (dd, 1H, $J_1 = 10.5$, $J_2 = 3.0$ Hz, $-CH=CHCH_2-$), 5.35 (m, 1H, $-CH=CHCH_2-$), 5.02 (d, 1H, $J = 10.0$ Hz, −OCH−), 4.06 (dd, 1H, $J_1 = 7.0$, $J_2 = 5.5$ Hz, $-C(CH_3)_2CH-$), 3.94 (bt, 1H, $-CH(OH)-$), 3.05 (dq, 1H, $J_1 = 3.0$, $J_2 = 6.5$ Hz, $-C(O)CH(CH_3)-$), 3.00 (bs, 1H, OH), 2.82–2.78 (m, 2H), 2.78–2.69 (m, 1H), 2.71 (s, 3H, $-SC(CH_3)=N-$), 2.40–2.30 (m, 1H), 2.10 (s, 3H, $C(CH_3)=CHC=$), 2.10–2.00 (m, 1H), 1.99–1.90 (m, 1H), 1.75–1.65 (m, 1H), 1.70–1.50 (m, 2H), 1.45–1.35 (m, 1H), 1.21 (m, 1H, $-CH(CH_3)CH_2CH_2-$), 1.17 (s, 6H, $-C(CH_3)_2-$), 1.14 (d, 3H, $J = 5.0$ Hz, $-C(O)CH(CH_3)-$), 1.02 (d, 3H, $J = 5.0$ Hz, $-CH(CH_3)-$), 0.82 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.12 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.05 (s, 3H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 218.1$, 170.9, 164.7, 138.2, 134.7, 124.0, 119.6, 119.4, 116.0, 79.0, 76.3, 73.2, 53.5, 43.0, 39.1, 38.8, 33.6, 31.9, 28.4, 27.8, 26.1, 24.8, 22.9, 19.2, 18.6, 16.5, 15.3, 14.1, −3.6, −5.5; HRMS calcd for $C_{32}H_{53}NO_5SSi$ ($M + Cs^+$): 724.2468, found: 724.2479.

1: $R_f = 0.23$ (silica gel, MeOH:CH_2Cl_2 1:2); HPLC (Watman EOC, C-18, 4 m, 108 × 4.6 mm column, solvent: gradient: 0 → 20 min, 30 → 80% MeOH in H_2O, $R_t = 14.8$ min; $[\alpha]_D = -45.0$ ($c = 0.02$, MeOH); ^1H NMR (500 MHz, C_6D_6): $\delta = 6.78$ (s, 1H, −C=CHS), 6.52 (s, 1H, −C=CHC=), 5.52 (dd, 1H, $J_1 = 6.0$, $J_2 = 2.0$ Hz, OCH), 4.24 (d, 1H, $J = 10.0$ Hz, CH(OH)), 3.86 (m, 1H, $CH(OH)$), 3.81 (bs, 1H, OH), 3.10 (m, 1H, CH_2CHO), 2.84 (m, 1H, C(O)CH), 2.67 (m, 1H, CH_2CHO), 2.49 (dd, 1H, $J_1 = 11.0$, $J_2 = 14.5$ Hz, $-OOCCH_2$), 2.27 (s, 3H, $-SC(CH_3)=N$), 2.24 (dd, 1H, $J_1 = 14.5$, $J_2 = 3.5$ Hz, $OOCCH_2$), 2.11 (s, 3H, $-C(CH_3)=$), 1.92 (m, 1H, CH_2CHO), 1.84 (m, 1H, CH_2CHO), 1.74 (m, 1H), 1.57 (m, 1H), 1.27–1.42 (m, 5H), 1.11 (d, 3H, $J = 7.0$ Hz, $C(O)CH(CH_3)$), 1.09 (s, 3H, $C(CH_3)_2$), 1.03 (s, 3H, $C(CH_3)_2$), 1.01 (s, 3H, $CH(CH_3)$); ^{13}C NMR (125 MHz, C_6D_6): $\delta = 218.7$, 169.9, 164.1, 152.6, 137.2, 119.5, 119.3, 76.3, 74.8, 73.1, 56.9, 53.9, 52.6, 43.4, 38.8, 36.0, 31.4, 30.0, 27.0, 23.6, 20.8, 20.2, 18.4, 17.0, 15.4, 14.3; HRMS calcd for $C_{26}H_{39}NO_6S$ ($M + Cs^+$): 626.1552, found: 626.1551.

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[1] a) G. Höfle, N. Bedorf, K. Gerth, H. Reichenbach (GBF), DE-4138042, **1993** (*Chem. Abstr.* **1993**, *120*, 52841); b) K. Gerth, N. Bedorf, G Höfle, H. Irschik, H. Reichenbach, *J. Antibiot.*, **1996**, *49*, 560 - 563.
[2] G. Höfle, N. Bedorf, H. Steinmetz, D. Schomburg, K. Gerth, H. Reichenbach, *Angew. Chem.* **1996**, *108*, 1671–1673; *Angew Chem. Int. Ed. Engl.* **1996**, *35*, 1567–1569.
[3] M. R. Grever, S. A. Schepartz, B. A. Chabner, *Semin. Oncol.* **1992**, *19*, 622 638.
[4] D. M. Bollag, P. A. McQueney, J. Zhu, O. Hensens, L. Koupal, J. Liesch, M. Goetz, E. Lazarides, C. M. Woods, *Cancer Res.* **1995**, *55*, 2325 2333.
[5] K. C. Nicolaou, W.-M. Dai, R. K. Guy, *Angew. Chem.* **1994**, *106*, 38 67; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15 - 44.
[6] K. C. Nicolaou, Y. He, D. Vourloumis, H. Vallberg, Z. Yang, *Angew. Chem.* **1996**, *108*, 2554 - 2556; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2399 2401. For other studies in the epothilone field, see a) D. Meng, E. J. Sorensen, P. Bertinato, S. J. Danishefsky, *J. Org. Chem.* **1996**, *61*, 7998 - 7999; b) P. Bertinato, E. J. Sorensen, D. Meng, S. J. Danishefsky, *J. Org. Chem.* **1996**, *61*, 8000 8001; c) D. Shinzer, A. Limberg, O. M. Böhm, *Chem. Eur. J.* **1996**, *2*, 1477 1482. For the first total synthesis of epothilone A, see A. Balog, D. Meng, T. Kamenecka, P. Bertinato, D.-S. Su, E. J. Sorensen, S. J. Danishefsky, *Angew. Chem.* **1996**, *108*, 2976 2978, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2801–2803.
[7] For the development of olefin metathesis as a ring forming reaction, see a) W. J. Zuercher, M. Hashimoto, R. H. Grubbs, *J. Am. Chem. Soc.* **1996**, *118*, 6634–6640; b) P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100 110; c) R. H. Grubbs, S. J. Miller, G. C. Fu, *Acc. Chem. Res.* **1995**, *28*, 446 -452 and references therein. For some earlier pioneering studies on this reaction, see a) T. J. Katz, S. J. Lee, N. Acton, *Tetrahedron Lett.* **1976**, 4247 4250; b) T. J. Katz, N. Acton, *Tetrahedron Lett.* **1976**, 4251 4254; c) T. J. Katz, J. McGinnis, C. Altus, *J. Am. Chem. Soc.* **1976**, *98*, 606 608; d) T. J. Katz, *Advances in Organomet. Chem.* **1977**, *16*, 283–317.
[8] Ketoaldehyde **11** was prepared from propionyl chloride according to a published procedure: T. Inukai, R. Yoshizawa, *J. Org. Chem.* **1967**, *32*, 404–407.
[9] U. S. Racherla, H. C. Brown, *J. Org. Chem.* **1991**, *56*, 401–404
[10] Mosher ester analysis (^{1}H NMR) revealed greater than 97% enantiomeric purity for compounds **3** and **10**.
[11] M. W. Bredenkamp, C. W. Holzapfel, W. J. van Zyl, *Synthetic Commun.* **1990**, *20*, 2235 2249.
[12] A. Fürstner, K. Langemann, *J. Org. Chem.* **1996**, *61*, 3942–3943.
[13] In this reaction (unoptimized) the eight-membered lactone corresponding to **11** was also observed (10 15%).
[14] P. Schwab, M. B. France, J. W. Ziller, R. H. Grubbs, *Angew. Chem.* **1995**, *107*, 2179 2181; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039 2041.
[15] Decoupling experiments (^{1}H NMR, 500 MHz, $CDCl_3$) revealed coupling constants (J) for H_{12}/H_{13} of 11.0 Hz for the *Z*-isomer (**13**) and 15.0 Hz for the *E*-isomer.
[16] We thank Dr. G. Höfle for kindly providing us with a natural sample of epothilone A (**1**).
[17] All new compounds exhibited satisfactory spectral and analytical and/or exact mass data.
[18] K. C. Nicolaou, F. Sarabia, S. Ninkovic, Z. Yang, *Angew. Chem.* **1997**, in press.

EVENTS

The eighth international symposium on inorganic ring systems will be held in Loughborough in August 1997. Invited speakers include: H. Nöth, M. F. Hawthorne, K. Wade, P. Power, D. Tilley, F. Feher, R. C. Haushalter, D. Fenske, A. Haas.

Contributed lectures and posters will be accepted on any aspect of inorganic rings, cages, including the interface with solid state chemistry.

Reduced registrations will be offered to students. Bursaries are available for younger participants.

Requests for further details should be sent to:

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See also: http://www-staff.lboro.ac.uk/~huadb/guide/home.htm