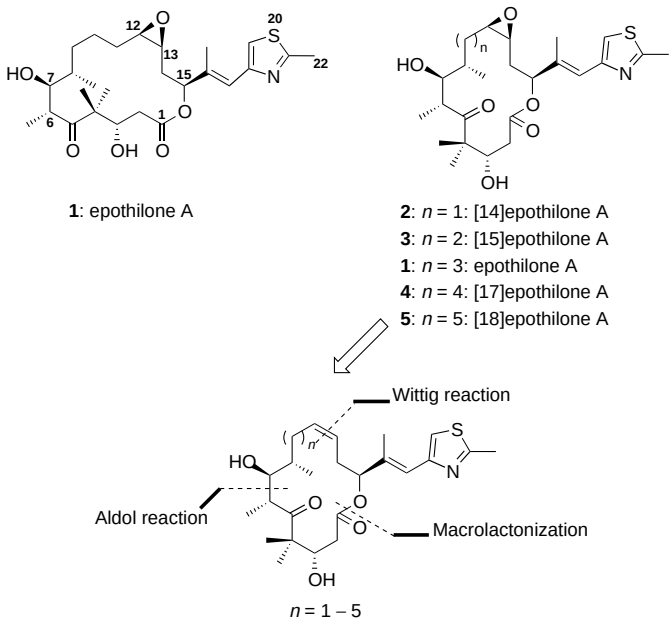
Probing the Ring Size of Epothilones: Total Synthesis of [14]-, [15]-, [17]-, and [18]Epothilones A**

K. C. Nicolaou,* Francisco Sarabia, Sacha Ninkovic, M. Ray V. Finlay, and Christopher N. C. Boddy

The discovery,[1] structural elucidation,[2] and biological activity[1–4] of the epothilones rapidly propelled them to the forefront of chemical[5] and biological research.[3, 4] Particularly exciting and stimulating was the recognition of their Taxol-like[6] mechanism of action[3] as antitumor agents and their ability to eradicate Taxol-resistant tumor cells.[4] Total syntheses of the 16-membered macrolactones epothilones A (**1**, Scheme 1),[7–11] B (**1** with a CH_3 group at C-12 instead of H),[10, 12, 13] and E (**1** with a CH_2OH group at C-21 instead of CH_3)[14] have been achieved, and many analogues[7–18] have already been synthesized and biologically investigated. From these studies, the epothilone pharmacophore has emerged as a well-defined and rather precise molecular structure tolerating only certain changes.[7–18] To probe the effect of the size of the macrocycle on its biological activity, we targeted the 14-, 15-, 17-, and 18-membered ring analogues of epothilone A (**1**), thus completing the [*n*]epothilone A series where $n = 1-5$ (Scheme 1). We report here on the successful total syntheses as well as the biological properties of these compounds (**2**–**5**).

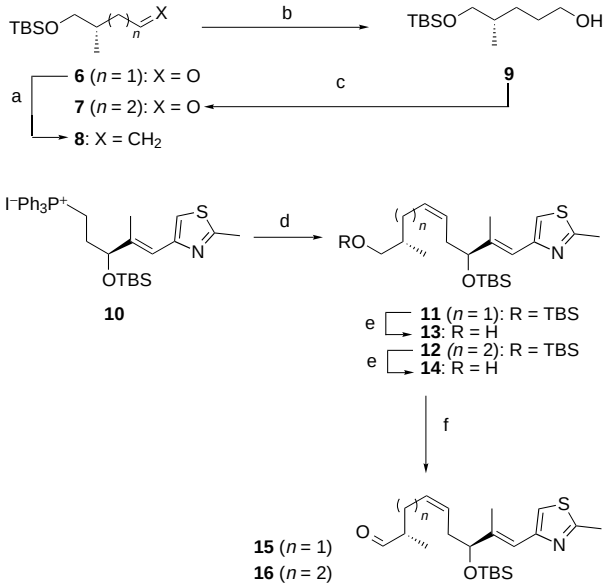
Molecular modeling and molecular dynamics of [14]-, [15]-, [17]-, and [18]epothilones A led to the minimized structures shown in Figure 1 (see p. 82). These models revealed considerable structural distortions for the 14-, 15-, and 17-membered ring epothilones. In contrast the overall shape of [18]epothilone A was very similar to that of natural epothilone A ([16]epothilone A), heightening expectations for biological activity of the latter compound, if not for the others.

The charted route projected epoxidation of the C12–C13 double bond of the macrocycle as the final step and a convergent assembly of the epothilone skeleton by means of a Wittig reaction, an aldol condensation, and a macrolactonization.[8b, 10, 13] This strategy required fragments **6**, **7**, and **10**[10, 13] for the construction of the key intermediates **15** and **16**, which were needed for the 14- and 15-membered rings, respectively (see Scheme 2). A slightly different strategy for the synthesis of key building blocks **33** and **35**, needed for the 17- and 18-membered rings, respectively, was adopted, which required fragments **19**, **21**, and **22**[13] (see Scheme 3).



Scheme 1. Structures and numbering of the epothilones A with $n = 1-5$.

Aldehyde **6** (Scheme 2) was prepared by a literature procedure[19] and served as a precursor for the second



Scheme 2. Synthesis of aldehydes **15** and **16**. a) 2.0 equiv $Ph_3P^+CH_3Br^-$, 1.98 equiv NaHMDS, THF, 0°C, 15 min; then 1.0 equiv **6** in THF, 0°C, 0.5 h, 95%; b) 1.5 equiv 9-BBN 0.5 M, THF, 25°C, 3 h; then 6 equiv 3 N NaOH and 6.0 equiv 30% H_2O_2, 0°C, 1 h, 85%; c) 2.0 equiv $(COCl)_2$, 4.0 equiv DMSO, 6.0 equiv Et_3N, CH_2Cl_2, $-78 \rightarrow 0$°C, 1.5 h, 98%; d) 1.2 equiv **10**, 1.2 equiv NaHMDS, THF, 0°C, 15 min; then 1.0 equiv **6** or **7**, 0°C, 15 min, 77% (*Z*:*E* ≈ 9:1) for **11** or 83% (*Z*:*E* ≈ 9:1) for **12**; e) 1.0 equiv CSA added portionwise over 1 h, CH_2Cl_2/MeOH (1/1), $0 \rightarrow 25$°C, 0.5 h, 81% for **13** and 61% for **14**; f) 2.0 equiv $SO_3 \cdot Py$, 10.0 equiv DMSO, 5.0 equiv Et_3N, CH_2Cl_2, 25°C, 0.5 h, 81% for **15** and 84% for **16**. NaHMDS = sodium bis(trimethylsilyl)amide; 9-BBN = 9-borabicyclo[3.3.1]nonane; DMSO = dimethylsulfoxide; CSA = 10-camphorsulfonic acid; TBS = *tert*-butyldimethylsilyl; Py = pyridine.

[*] Prof. Dr. K. C. Nicolaou, Dr. F. Sarabia, Dr. S. Ninkovic, Dr. M. R. V. Finlay, C. N. C. Boddy
Department of Chemistry and
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)
Fax: Int. code + (1) 619-784 2469

[**] We thank Dr. D. H. Huang and Dr. G. Siuzdak for assistance with recording NMR and mass spectra, respectively. This work was supported by Novartis, the National Institutes of Health (USA), The Skaggs Institute for Chemical Biology, and the CaP CURE Foundation. Fellowships from Fundación Ramón Areces (Spain) (F. S.) and the Fullbright Commission (M. R. V. F.), and grants from Merck, DuPont-Merck, Schering Plough, Hoffmann La Roche, and Amgen are acknowledged.

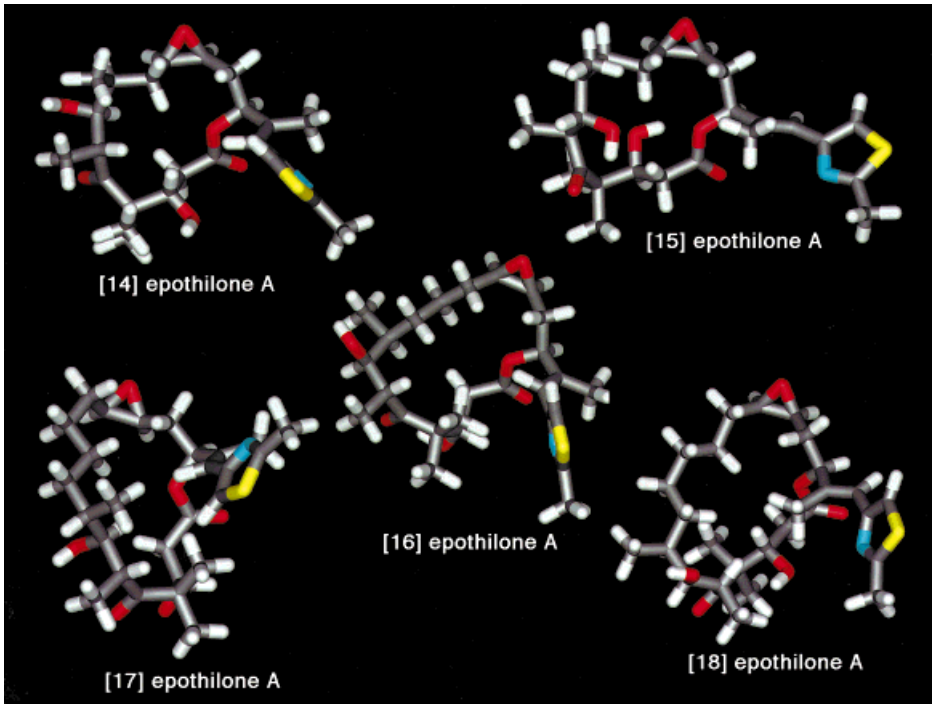
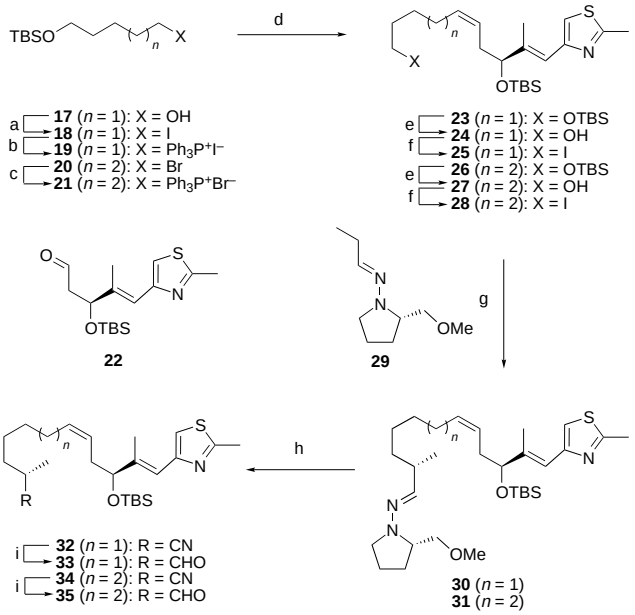


Figure 1. Computer-generated minimum-energy structures of [14]-, [15]-, [16]-, [17]-, and [18]epothilones A. Carbon = gray, hydrogen = white, oxygen = red, nitrogen = blue, sulfur = yellow. Molecular dynamics and minimization calculations (CV Force Field) were performed on a SGI Indigo-2 workstation using the program Insight II (Biosym Technologies Inc., San Diego, CA). Pictures were created with AVS software (AVS Inc., Waltham, MA) and locally developed modules running on a DEC Alpha 3000/500 with a Kubota Pacific Denali graphics card.

required aldehyde, **7**. Thus, olefination of **6**, hydroboration of the resulting olefin **8**, and oxidation of the formed primary alcohol **9** furnished the desired aldehyde **7** in excellent overall yield (Scheme 2). Each of these two aldehydes (**6** and **7**) was condensed separately with the ylide derived from phosphonium salt **10** (NaHMDS, THF) to afford the corresponding (*Z*) olefins (**11**, 77 % and **12**, 83 %) as the major geometrical isomer in each case (ca. 9:1 ratio). The silyl group was then selectively removed from the primary hydroxyl group by the action of CSA[20] leading to alcohols **13** (81 %) and **14** (61 %). Finally, oxidation of **13** and **14** with $SO_3 \cdot Py$ (DMSO/Et_3N) led to the targeted intermediates **15** and **16** in 81 and 84 % yield, respectively.

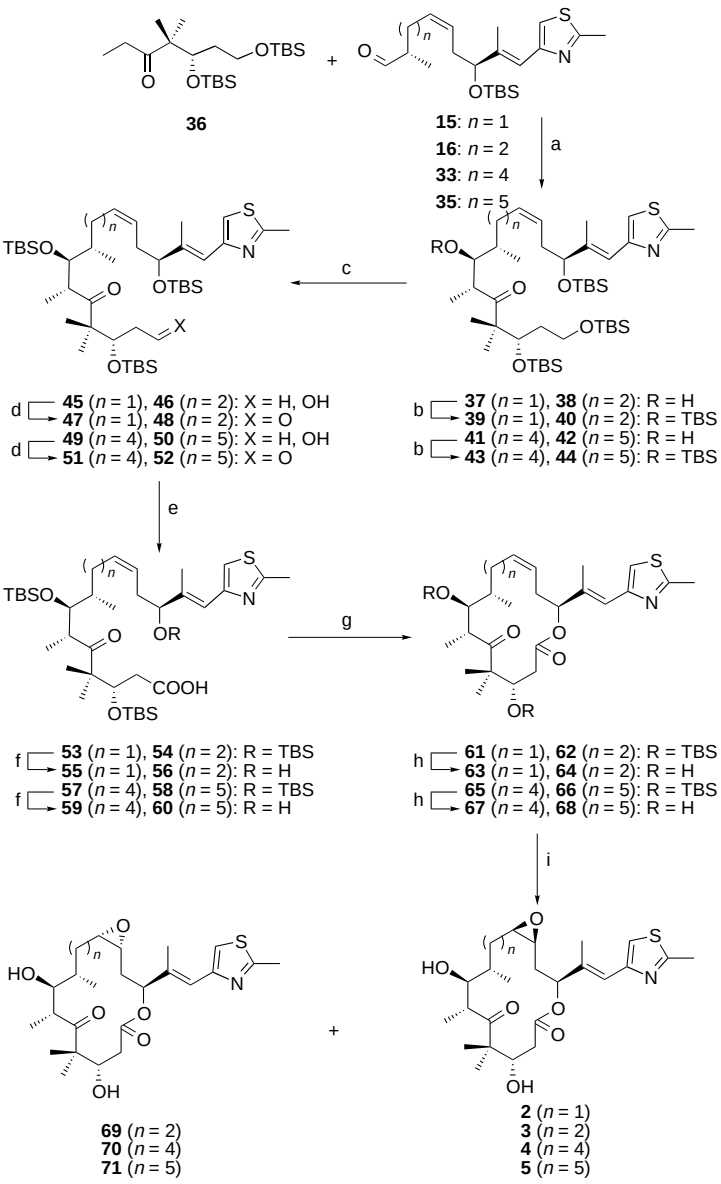
The reverse ylide – aldehyde condensation approach shown in Scheme 3 was utilized for the construction of advanced intermediates **33** and **35**. Thus, alcohol **17** was converted into iodide **18** by treatment with Ph_3P/I_2/imidazole (95 %) and thence to phosphonium salt **19** by heating with Ph_3P (neat, 100 °C, 97 %). A similar sequence was used to prepare phosphonium salt **21** from the bromide **20** as the intermediate. The ylides derived from **19** and **21** (NaHMDS, THF) were treated with aldehyde **22** to produce (*Z*) olefins **23** and **26** in 85 and 79 % yields, respectively, as the major isomers ($Z{:}E \approx$ 9:1). Each product, **23** and **26**, was selectively desilylated at the primary position with CSA, furnishing alcohols **24** (99 %) and **27** (95 %), respectively, and then converted into the corresponding iodides **25** (84 %) and **28** (98 %) by exposure to Ph_3P/I_2/imidazole. The iodides **25** and **28** were used to alkylate SAMP hydrazone **29** according to the method of Enders,[21] furnishing compounds **30** and **31** in 60 and 82 % yield, respectively. Each hydrazone (**30** and **31**) was converted into the corresponding nitrile[22] (**32**, 99 % and **34**, 96 %) by reaction with MMPP, and then into the desired aldehydes **33** (90 %) and **35** (81 %) by DIBAL reduction.



Scheme 3. Synthesis of aldehydes **33** and **35**. a) 1.5 equiv I_2, 3.0 equiv imidazole, 1.5 equiv Ph_3P, Et_2O/MeCN (3/1), 0 °C, 0.5 h, 95 %; b) 1.1 equiv Ph_3P, neat, 100 °C, 2 h, 97 %; c) 1.5 equiv Ph_3P, neat, 100 °C, 7 h, 99 %; d) 1.2 equiv **19** or **21**, 1.2 equiv NaHMDS, THF, 0 °C, 15 min; then 1.0 equiv **22**, 0 °C, 15 min, 85 % ($Z{:}E \approx$ 9:1) for **23**, 79 % ($Z{:}E \approx$ 9:1) for **26**; e) 1.0 equiv CSA added portionwise over 1 h, CH_2Cl_2/MeOH (1/1), 0 → 25 °C, 3 h, 99 % for **24**, 95 % for **27**; f) 1.5 equiv I_2, 3.0 equiv imidazole, 1.5 equiv Ph_3P, Et_2O/MeCN (3/1), 0 °C, 0.5 h, 84 % for **25**, 98 % for **28**; g) 1.5 equiv **29**, 1.5 equiv LDA, THF, 0 °C, 16 h; then 1.0 equiv **25** or **28** in THF, −100 → −20 °C, 10 h, 60 % for **30**, or 82 % for **31**; h) 2.5 equiv magnesium monoperoxyphthalate (MMPP), MeOH/phosphate buffer pH 7 (1/1), 0 °C, 1 h, 99 % for **32**, 96 % for **34**; i) 2.0 equiv DIBAL, toluene, −78 °C, 1 h, 90 % for **33**, 81 % for **35**. LDA = lithium diisopropylamide; DIBAL = diisobutylaluminum hydride.

Scheme 4 shows the coupling of the C1–C6 segment **36**[11] with fragments **15**, **16**, **33**, and **35**, and the elaboration of the products to the targeted epothilones. Thus, the (*Z*) enolate

  1433-7851/98/3701-0082 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **1998**, *37*, No. 1/2



Scheme 4. Synthesis of epothilone A analogues **2**–**5**. a) 1.2 equiv LDA, THF, 0°C, 15 min; then 1.2 equiv **36** in THF, −78°C, 1 h; then 1.0 equiv aldehyde (**15**, **16**, **33**, or **35**) in THF at −78°C, 71% for **37** (single diastereoisomer), 72% for **38** and its (6*S*,7*R*) diastereoisomer (ca. 4:1 ratio), 77% for **41** and its (6*S*,7*R*) diastereoisomer (ca. 6:1 ratio), 60% for **42** and its (6*S*,7*R*) diastereoisomer (ca. 5:1 ratio); b) 1.5 equiv TBSOTf, 2.0 equiv 2,6-lutidine, CH_2Cl_2, 0°C, 1 h, 94% for **39**, 93% for **40**, 85% for **43**, 95% for **44**; c) 1.0 equiv CSA added portionwise over 1 h, CH_2Cl_2/MeOH (1/1), 0°C, 3 h, 77% for **45**, 82% for **46**, 91% for **49**, 83% for **50**; d) 2.0 equiv $(COCl)_2$, 4.0 equiv DMSO, 6.0 equiv Et_3N, CH_2Cl_2, −78 →0°C, 1.5 h, 93% for **47**, 85% for **48**, 99% for **51**, 95% for **52**; e) 5.0 equiv $NaClO_2$, 10.0 equiv 2-methyl-2-butene, 2.5 equiv NaH_2PO_4, *t*BuOH/H_2O (5/1), 0°C, 1 h, 99% for **53**, 95% for **54**, 99% for **57**, 98% for **58**; f) 6.0 equiv TBAF, THF, 25°C, 10 h, 92% for **55**, 77% for **56**, 85% for **59**, 85% for **60**; g) 2.5 equiv 2,4,6-trichlorobenzoyl chloride, 5.0 equiv Et_3N, THF, 0 →25°C, 1 h; then slow addition (1 mL h^{-1}) to a solution of 2.0 equiv 4-DMAP in toluene (0.005 M based on hydroxy acid), 70°C, 0.5–8 h, 70% for **61**, 82% for **62**, 73% for **65**, 75% for **66**; h) 20% HF · Py (by volume) in THF, 25°C, 24 h, 82% for **63**, 91% for **64**, 86% for **67**, 71% for **68**; i) methyl(trifluoromethyl)dioxirane, MeCN, 0°C, 54% for **2** (single diastereoisomer), 35% **3** and 35% **69** (ca. 1:1 ratio of diastereoisomers), 97% for **4** and **70** (ca. 6:1 ratio of diastereoisomers), 53% of **5** and 26% of **71** (ca. 2:1 ratio of diastereoisomers). Tf = triflate; TBAF = tetra-*n*-butylammonium fluoride; 4-DMAP = 4-dimethylaminopyridine.

generated from ketone **36** (LDA, THF, −78°C) reacted smoothly with aldehydes **15**, **16**, **33**, and **35** to afford compounds **37** (71%), **38** (72%), **41** (77%), and **42** (60%), respectively, together with their (6*S*,7*R*) diastereoisomers (see Scheme 4 for individual yields), which were removed by silica gel chromatography. These compounds were then silylated (TBSOTf/2,6-lutidine) leading to tetrasilyl ethers **39**, **40**, **43**, and **44** in 85–95% yield. Selective removal of the silyl group from the primary position with CSA led to alcohols **45**, **46**, **49**, and **50**, which were oxidized under Swern conditions [$(COCl)_2$/DMSO/Et_3N] to give the corresponding aldehydes (**47**, **48**, **51**, and **52**) in 85–99% yield. Further oxidation to the desired carboxylic acids (**53**, **54**, **57**, and **58**) was achieved by reaction with $NaClO_2$ (95–98% yield). The carboxylic acids were then selectively desilylated at C-15 by the action of TBAF[8b] producing hydroxy acids **55**, **56**, **59**, and **60** in 77–92% yield. Cyclization of **55**, **56**, **59**, and **60** was accomplished by the Yamaguchi method[23] as previously described for epothilones A and B[8b, 10, 13, 16] to furnish macrocyclic lactones **61**, **62**, **65**, and **66**, respectively, in yields ranging from 70 to 82% (Scheme 4). The silyl ethers were removed from **61**, **62**, **65**, and **66** by exposure to HF · Py in THF, leading to [14]-, [15]-, [17]- and [18]desoxyepothilones **63**, **64**, **67** and **68**, respectively (71–91% yield).

Epoxidation of [14]desoxyepothilone A (**63**) with methyl (trifluoromethyl)dioxirane[24] gave [14]epothilone A (**2**) essentially as a single product (52% yield), whereas epoxidation of the [15]desoxyepothilone A (**64**) under the same conditions led to a mixture of [15]epothilone A (**3**) and its diastereomeric epoxide **69** (70% yield, ca. 1:1 ratio). The [17]-membered macrolactone **67** furnished diastereomeric epoxides in a 6:1 ratio (97% combined yield) and the [18]-membered analogue provided products in a 2:1 ratio (79% total yield). In all cases the isomeric epoxides were separated by chromatography but their configurations have not yet been assigned.

Preliminary biological investigations with these compounds revealed significant tubulin polymerization activity for [18]desoxyepothilone A (**68**) (40% as compared to 72% for epothilone A and 53% for Taxol), but relatively weak activity for the two epimeric [18]epothilones A (**5** and **71**) and for all [14]-, [15]-, and [17]epothilones A (**63**, **64**, **67**, **2**–**4**, **69**, and **70**) in the filtration–colorimetric tubulin assay.[3] These results provide further support for the limited tolerance of the epothilone pharmacophore and its highly specific binding to the tubulin receptor. Further biological studies with **68** and related compounds are in progress.

Received: August 7, 1997 [Z10787IE]
German version: *Angew. Chem.* **1998**, *110*, 85–89

Keywords: epothilones · natural products · total synthesis · tubulin polymerization

[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] 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.

  1433-7851/98/3701-0083 $ 17.50+.50/0

[4] R. J. Kowalski, P. Giannakakou, E. Hamel, *J. Biol. Chem.* **1997**, *272*, 2534 – 2541.

[5] a) 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; b) D. Meng, E. J. Sorensen, P. Bertinato, S. J. Danishefsky, *J. Org. Chem*. **1996**, *61*, 7998 – 7999; c) P. Bertinato, E. J. Sorensen, D. Meng, S. J. Danishefsky, *ibid.* **1996**, *61*, 8000 – 8001; d) D. Schinzer, A. Limberg, O. M. Böhm, *Chem. Eur. J.* **1996**, *2*, 1477 – 1482; e) J. Mulzer, A. Mantoulidis, *Tetrahedron Lett*. **1996**, *37*, 9179 – 9182; f) E. Claus, A. Pahl, P. G. Jones, H. M. Meyer, M. Kalesse, *ibid*. **1997**, *38*, 1359 – 1362; g) T. Gabriel, L. Wessjohann, *ibid.* **1997**, *38*, 1363 – 1366; R. E. Taylor, J. D. Haley, *ibid*. **1997**, *38*, 2061 – 2064.

[6] S. B. Horwitz, S. Fant, P. B. Schiff, *Nature* **1979**, *277*, 665 – 667.

[7] a) 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; b) D. Meng, D.-S. Su, A. Balog, P. Bertinato, E. J. Sorensen, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He, S. B. Horwitz, *J. Am. Chem. Soc.* **1997**, *119*, 2733 – 2734.

[8] a) Z. Yang, Y. He, D. Vourloumis, H. Vallberg, K. C. Nicolaou, *Angew. Chem.* **1997**, *109,* 170 – 172; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 166 – 168; b) K. C. Nicolaou, F. Sarabia, S. Ninkovic, Z. Yang, *ibid*. **1997**, *109*, 539 – 540 and **1997**, *36*, 525 – 527.

[9] D. Schinzer, A. Limberg, A. Bauer, O. M. Böhm, M. Cordes, *Angew. Chem.* **1997**, *109,* 543 – 544; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 523 – 524.

[10] K. C. Nicolaou, N. Winssinger, J. A. Pastor, S. Ninkovic, F. Sarabia, Y. He, D. Vourloumis, Z. Yang, T. Li, P. Giannakakou, E. Hamel, *Nature* **1997**, *387*, 268 – 272.

[11] K. C. Nicolaou, Y. He, D. Vourloumis, H. Vallberg, F. Roschangar, F. Sarabia, S. Ninkovic, Z. Yang, J. I. Trujillo, *J. Am. Chem. Soc.* **1997**, *119*, 7960 – 7973.

[12] D.-S. Su, D. Meng, P. Bertinato, A. Balog, E. J. Sorensen, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He, S. B. Horwitz, *Angew. Chem.* **1997**, *109*, 775 – 777; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 757 – 759.

[13] K. C. Nicolaou, S. Ninkovic, F. Sarabia, D. Vourloumis, Y. He, H. Vallberg, M. R. V. Finlay, Z. Yang, *J. Am. Chem. Soc.* **1997**, *119*, 7974 – 7991.

[14] Isolation and structure elucidation: G. Höfle, personal communication. Total synthesis: K. C. Nicolaou, Y. He, F. Roschangar, N. P. King, D. Vourloumis, T. Li, *Angew. Chem.* **1998**, *110*, 89 – 92; *Angew. Chem. Int. Ed.* **1998**, *37*, 84 – 87.

[15] K. C. Nicolaou, H. Vallberg, N. P. King, F. Roschangar, Y. He, D. Vourloumis, C. G. Nicolaou, *Chem. Eur. J.* **1997**, *3*, 1957 – 1970.

[16] K. C. Nicolaou, F. Sarabia, M. R. V. Finlay, S. Ninkovic, N. P. King, D. Vourloumis, Y. He, *Chem. Eur. J.* **1997**, *3*, 1971 – 1986.

[17] A. Balog, P. Bertinato, D.-S. Su, D. Meng, E. J. Sorensen, S. J. Danishefsky, Y.-H. Zheng, T-C. Chou, L. He, S. B. Horwitz, *Tetrahedron Lett*. **1997**, *38*, 4529 – 4532.

[18] K. C. Nicolaou, D. Vourloumis, T. Li, J. Pastor, N. Winssinger, Y. He, S. Ninkovic, F. Sarabia, H. Vallberg, F. Roschangar, N. P. King, M. R. V. Finlay, P. Giannakakou, P. Verdier-Pinard, E. Hamel, *Angew. Chem.* **1997**, *109*, 2181 – 2187; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2097 – 2103.

[19] T. Eguchi, T. Terachi, K. Kakinuma, *J. Chem. Soc. Chem. Commun.* **1994**, 137 – 138.

[20] T. D. Nelson, R. D. Crouch, *Synthesis* **1996**, 1031 – 1069.

[21] a) D. Enders, *Asymmetric Synthesis Vol. 3*, Academic Press, **1984**, pp.275 – 339; b) D. Enders, M. Klatt, *Synthesis* **1996**, 1403 – 1418; c) D. Enders, H. Eichenauer, *Chem. Ber*. **1979**, *112*, 2933 – 2960; d) D. Enders, J. Tiebes, N. De Kimpe, M. Keppens, C. Stevens, G. Smagghe, O. Betz, *J. Org. Chem*. **1993**, *58*, 4881 – 4884; e) D. Enders, A. Plant, D. Backhaus, U. Reinhold, *Tetrahedron* **1995**, *51*, 10699 – 10714. We thank Prof. Enders for a generous gift of SAMP.

[22] D. Enders, D. Backhaus, J. Runsink, *Tetrahedron* **1996**, *52*, 1503 – 1528.

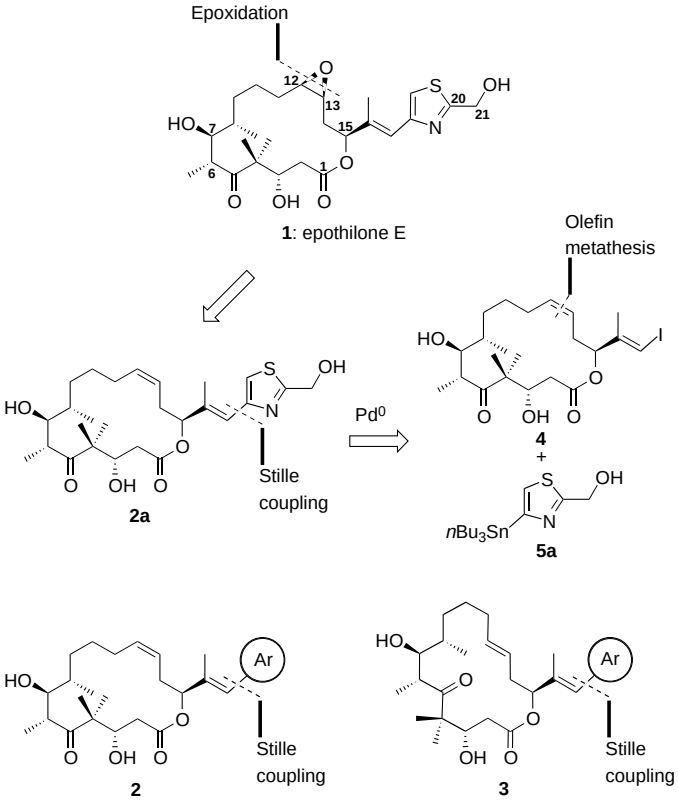
[23] a) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn*. **1979**, *52*, 1989; b) J. Mulzer, P. A. Mareski, J. Buschmann, P. Luger, *Synthesis* **1992**, 215 – 228; c) K. C. Nicolaou, A. P. Patron, K. Ajito, P. K. Richter, H. Khatuya, P. Bertinato, R. A. Miller, M. J. Tomaszewski, *Chem. Eur. J.* **1996**, *2*, 847 – 868.

[24] D. Yang, M.-K. Wong, Y.-C. Yip, *J. Org. Chem.* **1995**, *60*, 3887 – 3889.

Total Synthesis of Epothilone E and Analogues with Modified Side Chains through the Stille Coupling Reaction**

K. C. Nicolaou,* Yun He, Frank Roschangar, N. Paul King, Dionisios Vourloumis, and Tianhu Li

The epothilones are a growing class of naturally occurring antitumor agents[1–3] whose importance is clearly reflected in the increasing number of publications reporting on their total synthesis,[4–11] analogue construction,[4–16] and biological activity.[1, 3, 4, 5b, 8, 9, 12, 15–17] Here we report the first total synthesis of the naturally occurring epothilone E (**1**, Scheme 1)[16] in



Scheme 1. Retrosynthetic analysis and strategy for the total synthesis of epothilone E (**1**) and analogues with modified side chains. (Ar) = aromatic moiety.

[*] Prof. Dr. K. C. Nicolaou, Y. He, Dr. F. Roschangar, Dr. N. P. King, Dr. D. Vourloumis, Dr. T. Li
Department of Chemistry and The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)
Fax: Int. code + (1) 619-784 2469

[**] We thank Dr. D. H. Huang and Dr. G. Siuzdak for assistance with recording NMR and mass spectra, respectively. This work was supported by Novartis, the National Institutes of Health USA, The Skaggs Institute for Chemical Biology and the CaP CURE Foundation. Fellowships from the George E. Hewitt Foundation (N. P. K.), the Deutsche Forschungsgemeinschaft (F. R.), and Novartis (D. V.), and grants from Merck, DuPont-Merck, Schering Plough, Hoffmann La Roche, and Amgen are acknowledged.

  1433-7851/98/3701-0084 $ 17.50+.50/0