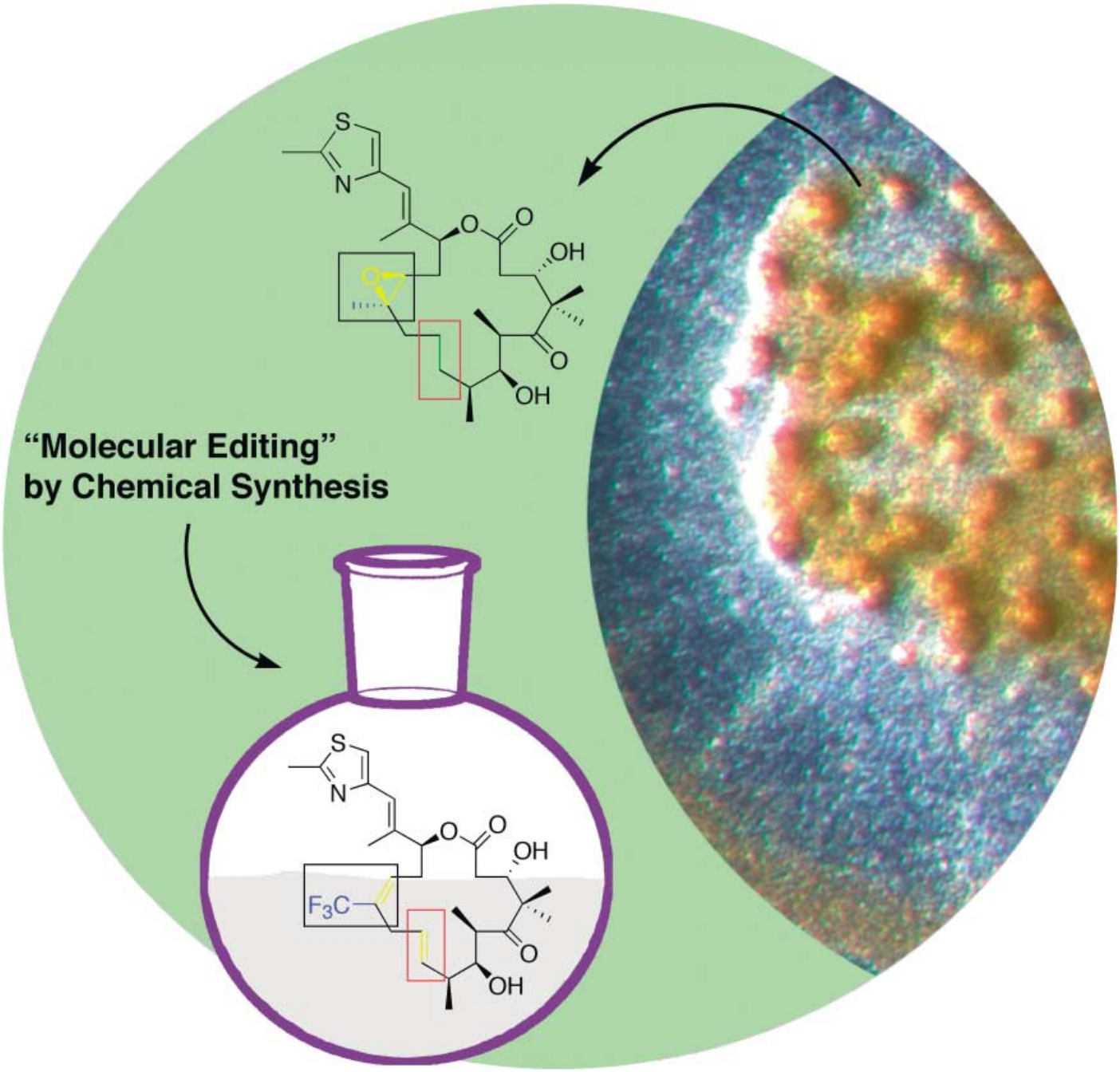
Communications



Molecular editing of epothilone B (isolated from a myxobacterium) led to the discovery of a 26-trifluoro analogue that is remarkably active in treating xenograft tumors in nude mice. These findings underscore the potential of directed multistep total synthesis in the quest for new drugs, as discussed by S. J. Danishefsky and co-workers on the following pages.

DOI: 10.1002/anie.200352361

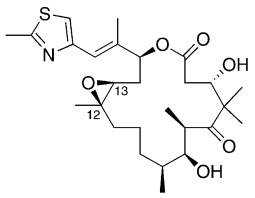
Epothilones: Synthesis and Activity

Design and Total Synthesis of a Superior Family of Epothilone Analogues, which Eliminate Xenograft Tumors to a Nonrelapsable State**

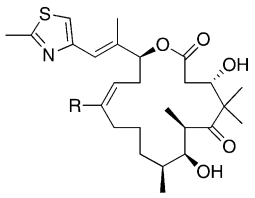
*Ting-Chao Chou, Huajin Dong, Alexey Rivkin, Fumihiko Yoshimura, Ana E. Gabarda, Young Shin Cho, William P. Tong, and Samuel J. Danishefsky**

The epothilone macrolides, first discovered by Höfle et al. in fermentation broths, have elicited a great deal of interest as potential agents in cancer chemotherapy.[1–8] A key paper of Bollag et al.[9] seeded the now multicenter epothilone initiative. This disclosure revealed the cellular target of the epothilones to be microtubule stabilization, which is the same mode of action as the established, clinically useful taxoids exhibit. Moreover, the epothilones were shown to manifest virtual imperviousness to the defenses of otherwise multidrug-resistant (MDR) cells.[10] As susceptibility to disablement by MDR cells is one of the main liabilities of the taxoid drugs, the robustness of the epothilones in this regard is of particular significance. Following extensive multidisciplinary research into the biology, chemistry, pharmacology, toxicology, and biosynthesis of the structurally new epothilones, three agents, including compound **2** (see below), have already been advanced to late phase I and phase II clinical trials, and additional structural variants are being made ready to be approved for investigation.[11]

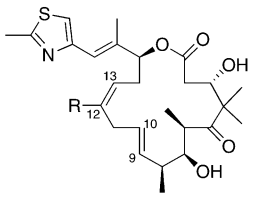
A governing concept in our laboratory had been the notion that the 12,13-oxido linkage of the epothilones is a site of non-tumor-selective toxicity.[12] Therefore, this linkage was "edited", initially through chemical synthesis, to provide 12,13-desoxyEpoB (dEpoB, **2**) and related desoxy congeners.[13,14] Although it is significantly less cytotoxic than epothilone B (EpoB, **1**) itself, in xenograft models dEpoB is roughly equipotent with paclitaxel (taxol)[15] and taxotere, the currently leading tubulin-directed anticancer drugs. dEpoB benefits from a much broader therapeutic index in xenograft models than taxoids or other epothilones, which contain epoxides. The major advantage of dEpoB over paclitaxel in these nude-mouse xenograft models is its particularly dramatic activity against resistant tumors. dEpoB has been entered into human clinical trials.[11]



1



2: R = Me
3: R = CF_3



4: R = Me
5: R = CF_3

In a second-generation 12,13-desoxyepothilone drug candidate, we hoped to recover some of the loss of potency that had been sustained by deletion of the oxido linkage from EpoB. For further development, we also required a second-generation epothilone to exhibit a clinically and readily exploitable therapeutic index, and in particular to lead to complete and nonreversible cures in xenograft models. This standard is seldom, if ever, set in the search for new anticancer drugs. We also hoped to produce an agent type of greater pharmacostability in humans than dEpoB, which has a potentially vulnerable macrolide (cyclic ester) linkage.

By a combination of chemical synthesis, molecular modeling, and spectroscopic analysis, we discovered that the introduction of an *E*-9,10 double bond (see compound **4**) leads to an approximately 10-fold enhancement of drug potency in xenograft experiments with drug-resistant MX-1 tumors.[16] It was apparent from the correlation of in vitro and in vivo experiments focused on MX-1 tumor types that **4** is inherently more cytotoxic than **1**. A second contributing factor is that the lactone functionality in the 9,10-dehydro series is significantly more stable in mouse and human plasma than that in the 9,10-saturated congeners. The sum of these two complementary effects was to render **4** capable of complete tumor suppression in a variety of xenografts at 3 mg kg^{-1}, in contrast to the 30 mg kg^{-1} dose required for **2**.

However, along with this much-enhanced antitumor activity in **4**, significant non-tumor-specific toxicity was observed, which sorely complicated the full eradication of its tumor targets. As with other potent chemotherapeutic

[*] Prof. S. J. Danishefsky, Dr. A. Rivkin, Dr. F. Yoshimura, Dr. A. E. Gabarda, Dr. Y. S. Cho
Laboratory for Bioorganic Chemistry
Sloan-Kettering Institute for Cancer Research
1275 York Avenue, New York, NY 10021 (USA)
Fax: (+1) 212-772-8691
E-mail: s-danishefsky@ski.mskcc.org
and
Department of Chemistry, Columbia University
Havemeyer Hall, 3000 Broadway, New York, NY 10027 (USA)
Dr. T.-C. Chou, Dr. H. Dong
Preclinical Pharmacology Core Facility
Sloan-Kettering Institute for Cancer Research
1275 York Avenue, New York, NY 10021 (USA)
Dr. W. P. Tong
Analytical Pharmacology Core Facility
Sloan-Kettering Institute for Cancer Research
1275 York Avenue, New York, NY 10021 (USA)

[**] This work was supported by the National Institutes of Health (CA-28824). F.Y. is a Uehara Memorial Foundation Fellow. A.R. is a NIH Cancer Pharmacology Fellow (T32-CA62948). A.E.G. is a MSKCC Experimental Therapeutics Center Fellow. We thank Sylvi Rusli (NMR Core Facility, CA-02848) and Anna Dudkina for mass-spectral analyses. We thank Dr. Klaus Gerth and Dr. Rolf Müller of GBF, Germany for the picture of *Sorangium cellulos* that is part of the frontispiece design.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  DOI: 10.1002/anie.200352361

agents, easily perceptible tumors reappeared in some fraction of the animals upon suspension of treatment. Accordingly, fully synthetic **4** does not, at least at present, qualify as having a highly favorable effective therapeutic index and causing elimination of tumors to a nonrelapsing state, as we had aimed for in a second-generation drug candidate.

These findings directed our attention to the consequences of substituting the three hydrogen atoms of the 26-methyl group of **4** with three fluorine atoms. We anticipated that incorporation of fluorine atoms at this position could lead to improved stability of the C12–C13 double bond toward oxidation.[17] Previous experience had pointed to some attenuation of cytotoxicity when polar groups were placed near the C12–C13 double bond.[16] Herein we report on the total synthesis and antitumor activity of 9,10-dehydro-26-trifluoroepothilones, with particular emphasis on the unique biological activity of the parent structure **5**.

The therapeutic efficacy of dEpoB (30 mg kg^{-1}), paclitaxel (20 mg kg^{-1}), and F_3-deH-dEpoB (**5**, 20 and 30 mg kg^{-1}) against human-mammary-carcinoma MX-1 xenografts was closely studied in terms of tumor disappearance and relapse (Table 1). Each dose group consisted of four or more nude mice. "Body weight" refers to total body weight minus tumor weight. Tumor disappearance was observed for all three compounds. On the 10th day after suspension of treatment, 5/10 (dEpoB), 2/7 (paclitaxel), and 0/4 (compound **5**) mice relapsed. Extended observation following suspension of treatment with 20 mg kg^{-1} dosages of **5** showed a long-term absence of tumors until day 27, at which point 2/4 mice relapsed. Remarkably, treatment with dosages of **5** of 30 mg kg^{-1} resulted in complete tumor disappearance and the absence of any relapse for over two months after suspension of treatment.

When the dose of agent **5** was lowered to 10 mg kg^{-1} (Q2Dx12 = administered every other day, 12 doses in total), nine doses were required for tumor disappearance to be observed (Figure 1a). As an added challenge, chemotherapeutic treatment was delayed until the size of the tumor reached 0.5 g (~2.3% of body weight). Treatment with dosages of 25 mg kg^{-1} (Q2Dx7 = administered every other day, 7 doses in total) of **5** then caused all four of the mouse tumors to disappear. By contrast, dosages of 30 mg kg^{-1} (Q2Dx8) of dEpoB were required to induce the disappearance of tumors in 3/4 mice. Furthermore, the apparent tumor disappearance that occurred following treatment with dEpoB was subject to relapse with time (Figure 1b).

The fact that agent **5** completely suppressed the growth of the human-mammary-carcinoma MX-1 xenografts, shrank the tumors, and eliminated the tumors for as long as 64 days is impressive. Moreover, following the cures by **5** (20 mg kg^{-1} or 30 mg kg^{-1} Q2Dx6, six-hour intravenous infusion, Table 2), body weight returned to pretreatment control level within 12–18 days after the suspension of treatment. This finding suggests a lack of vital-organ damage. Most remarkably, at a curative low dosage of 10 mg kg^{-1}, Q2Dx12 (Figure 1a), the maximal decrease in body weight was only 12%, with a gain in body weight of 6% during the last three doses. The body weight recovered to the pretreatment control level only three days after the cessation of treatment. Table 2 shows that the animals could survive body-weight losses of as much as 27%.

Table 1: Therapeutic effect of dEpoB (**2**), paclitaxel, and F_3-deH-dEpoB (**5**) against an MX-1 xenograft in nude mice.[a]

Drug	Dosage [mg kg^{-1}]	Change in body weight [%][b] day 4	day 8	Tumor-free after treatment period	Tumor reappearance[c]
2	30	−25.3 ± 2.1	−9.1 ± 4.1	10/10	5/10
paclitaxel	20	−23.9 ± 3.7	−8.7 ± 0.7	7/7	2/7
5	20	−22.4 ± 0.6	−7.3 ± 0.7	4/4	0/4[d]
5	30	−27.1 ± 2.7	−17.4 ± 5.5	4/4	0/4[e]

[a] Human-mammary-carcinoma MX-1 xenograft tissue (50 mg) was implanted subcutaneously on day 0. The treatment (Q2Dx6 6-h intravenous infusion) was started on day 8 and stopped on day 18. [b] Change in body weight on day 4 and day 8 of treatment, measured after administration of the drug. [c] Number of mice in sample in which tumor reappeared on the 10th day after the end of the treatment period. [d] Detectable tumor reappearance in 2/4 mice on the 27th day after treatment was stopped. No further tumor reappearance between the 28th and 64th days after treatment was stopped. [e] No tumor reappearance during 64 days after treatment was stopped, at which point the experiment was terminated.

Table 2: Profile of dEpoB derivatives.

Compound	IC_{50} [nM][a]	Maximal drop in body weight without death [%]	Stability half-life Mouse plasma [min]	Human-liver S9 fraction [h]	Solubility in water [μg mL^{-1}]	Lipophilicity octanol/water partition (POW)	Therapeutic dose regimen [mg kg^{-1}][b]	Relative therapeutic index at MTD[c]
1	0.53 ± 0.2	15	57	15.8	n.d.	n.d.	0.6–0.8	+++
2	5.6 ± 2.8	32	46 ± 7	1.0 ± 0.1	9.4	4.4	25–30	++++
4	0.90 ± 0.40	29	84 ± 6	4.9 ± 0.7	27	3.3	3–4	++++
3	9.3 ± 5.2	22	66 ± 7	1.6 ± 0.4	8	4.1	15–20	++
5	3.2 ± 0.3	33	212 ± 88	10.5 ± 2.3	20	3.3	10–30	+++++

[a] IC_{50} values are for CCRF-CEM leukemic cells. Values are the range of two experiments. All values are obtained from eight time points. n.d. = not determined. [b] Therapeutic dose regimen for Q2D 6-h intravenous infusion. [c] Graded relative therapeutic index (TI) at MTD (maximal tolerated dose): + Tumor growth suppressed by 25–50%. ++ Tumor growth suppressed by 50–100%. +++ Tumor shrinkage but no tumor disappearance. ++++ Tumor disappearance in some or all nude mice with slow body-weight recovery and/or with relapse in some mice within one week after treatment was stopped. +++++ Tumor disappearance in all nude mice with rapid body-weight recovery and/or without relapse. The therapeutic effects of epothilones against human xenografts in nude mice, such as MX-1, were studied in references [15] and [27].

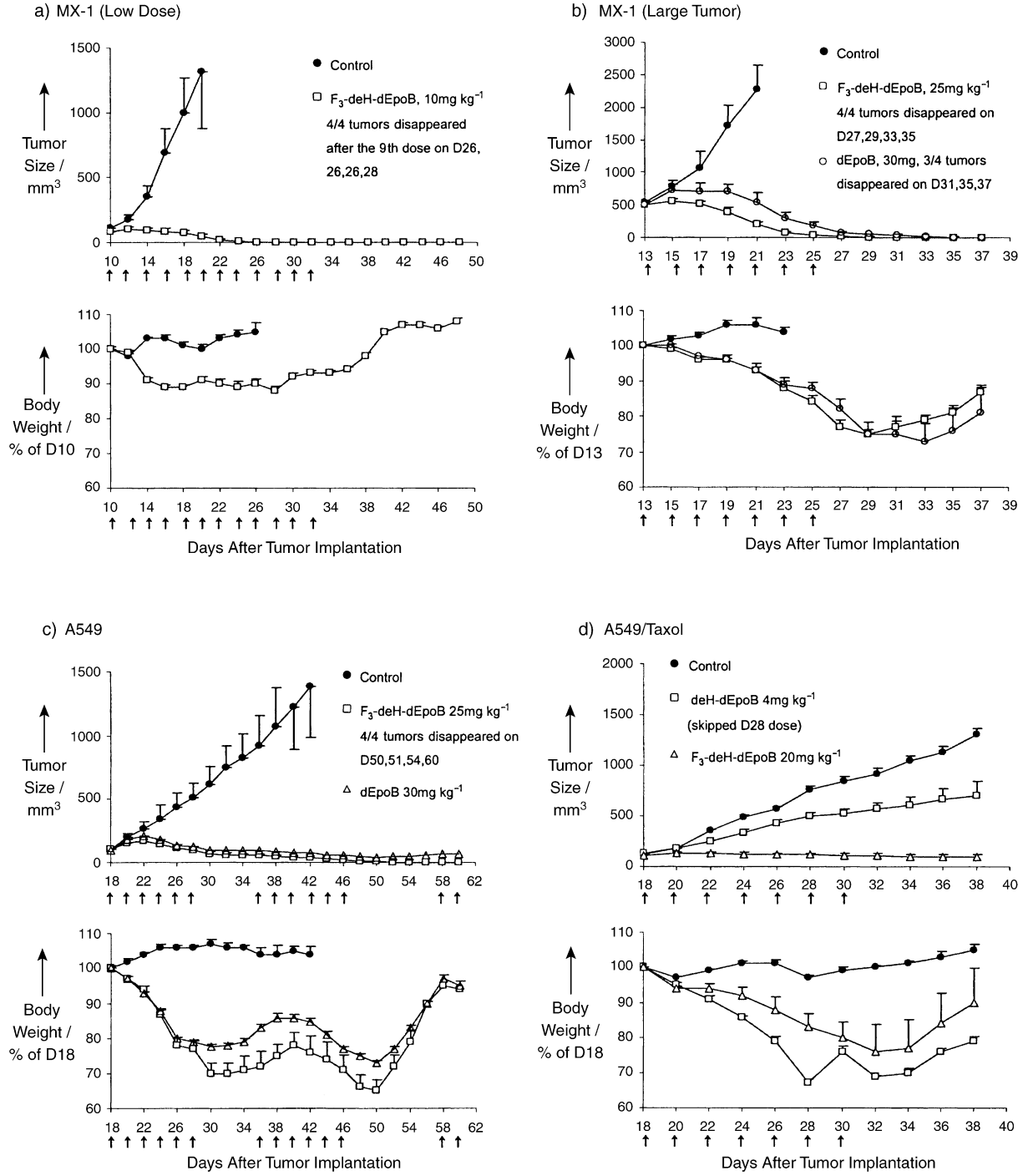


Figure 1. Chemotherapeutic effect against human tumor xenografts in nude mice. Tumor tissue (40–50 mg) was implanted subcutaneously on day 0. Treatment was started when tumor size reached about 100 mm^3 or larger, as indicated. All treatments, indicated by arrows, were carried out by six-hour intravenous infusion into the tail vein with a minicatheter and programmable pump as described previously.[7,14] Each dose group consisted of four or more mice. "Body weight" refers to the total body weight minus the tumor weight, with the assumption that 1 mm^3 of tumor tissue has a weight of 1 mg. a) Mammary-carcinoma MX-1 xenograft treated with a low dose of **5** (10 $mg\,kg^{-1}$) relative to the experiments in Table 1 (20 $mg\,kg^{-1}$ and 30 $mg\,kg^{-1}$). b) MX-1 large xenografts (500 mm^3) treated with **5** (25 $mg\,kg^{-1}$) and dEpoB (30 $mg\,kg^{-1}$). c) Slow-growing A549 lung-carcinoma xenograft treated with **5** (25 $mg\,kg^{-1}$) and dEpoB (30 $mg\,kg^{-1}$). d) A549/taxol (44-fold resistance to paclitaxel in vitro) xenograft treated with **5** (20 $mg\,kg^{-1}$) and **4** (4 $mg\,kg^{-1}$). The treatment with deH-dEpoB on day 28 was skipped as a result of marked and rapid decreases in body weight. D = day.

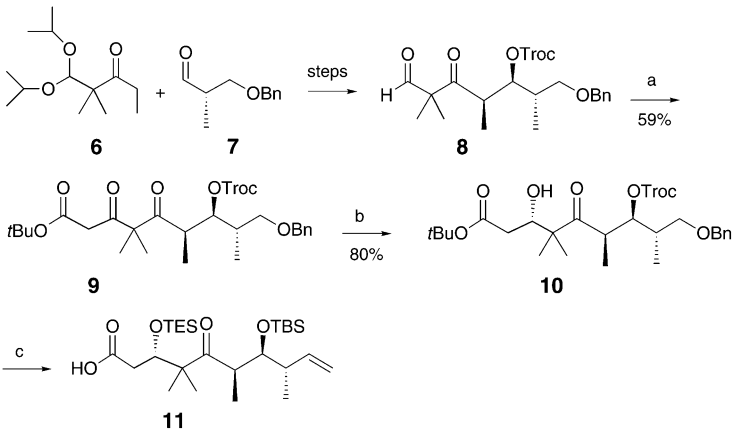
The therapeutic safety margin observed in this work is remarkably broad for a curative therapeutic agent against cancer. The therapeutic efficacy of **5** against human-lung-carcinoma xenograft (A549) and the paclitaxel-resistant human-lung-carcinoma A549/taxol xenografts was also evaluated (Figure 1c,d). The slow-growing lung-carcinoma xenografts A549 were treated with **5** (25 $mg\,kg^{-1}$, Q2Dx6, twice, eight days apart), which resulted in 99.5 % tumor suppression

with the eventual complete eradication of all four tumors after two more doses (Figure 1c). Interestingly, the body weight of the mice decreased as much as 35% without any lethality, and suspension of the treatment led to rapid body-weight recovery to near the pretreatment control level (Figure 1c). In contrast, a parallel study with dEpoB (30 mg kg^{-1}, Q2Dx6) resulted in 97.6% tumor suppression but led to no tumor eradication. In an additional study of **5** (dosage: 20 mg kg^{-1}) against A549/taxol-resistant xenografts (Figure 1d), tumor growth was totally suppressed, and the tumor was eventually reduced by 24.4% of the pretreatment control. During this study, the maximal body weight decreased by 24%. However, upon suspension of drug treatment the body weight returned to 90% of the pretreatment control. In a comparison study with (*E*)-9,10-dehydro-dEpoB (**4**, 4 mg kg^{-1}), tumor growth was suppressed by 41.6%.

We wanted to assess the factors responsible for the remarkable therapeutic index of compound **5**. The pertinent data for this analysis in conjunction with corresponding data for closely related congeners are provided in Table 2. A whole order of magnitude is lost in moving from EpoB(**1**) to dEpoB (**2**) in terms of inherent cytotoxicity. About 60% of this loss is restored in the case of 9,10-dehydro-dEpoB (**4**). Some of this inherent cytotoxicity is forfeited by the inclusion of the CF_3 group in **5**, which is ~1.8 times as cytotoxic as the benchmark compound **2**, at least in the cell.

Among the 12,13-dehydroepothilones, **5** exhibited by far the highest stability in mouse plasma and was also the most stable in human liver S9 plasma. We also observed that in the two sets of 12,13-dehydro isomers, the 26-trifluoromethyl substituent gives rise to decreased lypophilicity and somewhat increased water solubility. It would appear that the excellent therapeutic activity of **5** arises from improvements in serum stability and bioavailability.

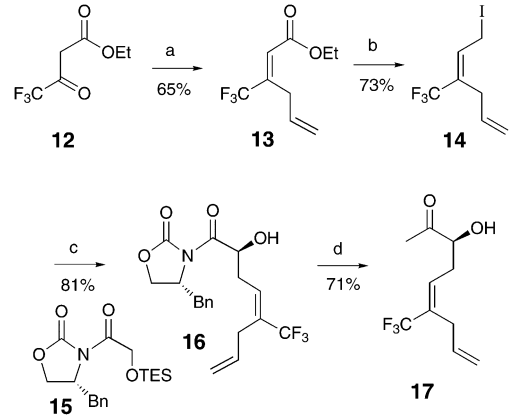
All of the agents **2**–**5** were initially discovered through total synthesis. A practical synthesis of **2** has been described previously.[13,14] First-generation discovery-level routes to **4** and **5** have also been described.[16,18–20] Selective reduction of the C9–C10 double bond of **5** afforded **3**. The remarkable results obtained from the xenograft studies described above for **5**, which is currently the most promising compound, clearly called for its advancement to detailed toxicology and pharmacokinetic studies in higher animals, and from there, if appropriate, to human clinical trials. Such prospects completely altered the nature of the synthetic challenge from the preparation of probe samples to the preparation of multigram quantities of these new epothilone derivatives. We carried out a major revamp of our previous routes, which were initially conceived and demonstrated in a discovery setting. In particular, our new protocols allowed major simplifications in the stereospecific elaboration of the C3 and C26 centers. Aldehyde **8** was prepared as described previously (Scheme 1).[16] In the new synthesis, the stereocenters C6, C7, and C8 are derived from the readily available ketone **6** and aldehyde **7**. Condensation of the aldehyde **8** with *tert*-butyl acetate, as shown, afforded an aldol-like product. As the condensation is not diastereomerically controlled, it was followed by oxidation of the resulting 1:1 mixture of C3



Scheme 1. Synthesis of the acyl sector **11**. Reagents and conditions: a) 1. LDA, *tert*-butyl acetate, THF, 80%; 2. Dess–Martin periodinane, 74%; b) Noyori catalyst (10 mol%), MeOH/HCl, H_2, 1200 psi, 80%; c) 1. TESCl, imidazole, 77%; 2. Zn, AcOH, THF, 99%; 3. TBSOTf, 2,6-lutidine, 82%; for remaining steps, see reference [16]. Troc = trichloroethoxycarbonyl, LDA = lithium diisopropylamide, TES = triethylsilyl, TBS = *tert*-butyldimethylsilyl.

epimers to the ketone **9**, which was then subjected to a highly successful Noyori reduction[21] under the conditions shown. The C3 alcohol product **10** was converted into the acid **11** in a few additional simple steps, as shown.

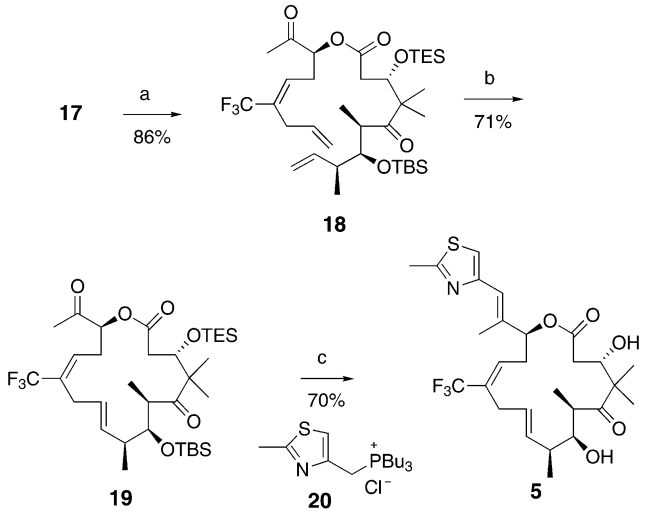
A new, straightforward synthesis, which can be scaled up readily, has also been developed for **17** (Scheme 2). The synthesis starts with the reaction of the commerically available trifluorinated β-ketoester **12** with allyl indium bromide. The key step in the synthesis is the regio- and stereospecific dehydration of the resulting tertiary alcohol to produce **13** in 65% yield from **12**. We surmise that the stereoselectivity observed in this reaction arises from a "dipolar effect", whereby a *trans* orientation of the strongly electron-withdrawing CF_3 and CO_2Et groups is favored, with respect to the double bond that is forming. The required iodide **14** was obtained in two steps from **13**. Alkylation of the



Scheme 2. Synthesis of the alkyl sector **17**. Reagents and conditions: a) 1. Allyl bromide, In, THF/H_2O (3:1), 48 °C, 85%; 2. $SOCl_2$, pyridine, 55 °C, 77%; b) 1. DIBAL-H, CH_2Cl_2, −78 °C→RT, 99%; 2. I_2, PPh_3, imidazole, CH_2Cl_2, 74%; c) 1. LiHMDS, THF, −78 °C→RT; 2. HOAc/THF/H_2O (3:1:1), 81% for two steps; d) 1. $AlMe_3$, MeONHMe, THF, 0 °C→RT, 97%; 2. MeMgBr, THF, 0 °C, 53% (73% based on recovered starting material). DIBAL-H = diisobutylaluminium hydride, HMDS = hexamethyldisilazide.

previously reported lithium enolate of **15** with iodide **14** in THF, followed by removal of the silyl protecting group, afforded **16** in 81% yield and with high diastereoselectivity (d.r. > 25:1). Compound **16** was advanced in two steps to **17** as shown.

With **11** and **17** in hand, the route to **5** was clear based on chemistry first developed in our discovery phase.[16] The key ring-closing metathesis reaction of **18** was carried out in toluene in the presence of the second-generation Grubbs catalyst (Scheme 3).[22–26] The reaction afforded the *trans*



Scheme 3. Final steps of the synthesis of **5**. Reagents and conditions: a) EDCI, DMAP, CH_2Cl_2, **11**, 0 °C→RT, 86% based on **11**; b) second-generation Grubbs catalyst, toluene, 110 °C, 20 min, 71%; c) 1. KHMDS, **20**, THF, −78 °C→−20 °C, 70%; 2. HF·pyridine, THF, 98%. EDCI = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, DMAP = 4-(dimethylamino)pyridine.

isomer **19** exclusively in 71% yield. Installation of the thiazole moiety, as shown in Scheme 3, was followed by removal of the two silyl protecting groups with HF·pyridine to give **5**. Compound **5** was converted into **3** in high yield by reduction of the C9–C10 double bond. Gram quantities of these structurally novel epothilones have been prepared by total synthesis in our laboratory.

At the moment there are no grounds on which to argue that the strikingly superior performance of **5** arises from factors other than the significantly improved pharmacokinetic and bioavailability features that were designed into the molecule through the medium of chemical synthesis. However, the possibility that the results reflect new (or enhanced) drug–target interactions is the object of continuing study. New areas of analogue synthesis are accessible through permutations of the late-stage olefination (e.g. **19** + **20**) by the use of other phosphonates. In this way, new design features that result in enhanced pharmaceutical properties are being explored further.

It is important to keep in mind that the ultimate purpose of the chemotherapeutic arm of cancer research is to provide clinically valuable treatment for patients with neoplastic diseases. Only progression to clinical trials can establish the value of any of the new epothilone agents with regard to this central goal.

This study serves to underscore the potential applicability of directed total synthesis, even in a multistep setting, in the quest for new substances of material clinical benefit. The current research environment tends to favor recourse to massive numbers of compounds for screening, in preference to smaller numbers of more carefully crafted, hypothesis-driven candidate structures. However, there is much to be learnt from natural products, and these warrant close and continuing study.

Received: July 11, 2003 [Z52361]
Published Online: September 11, 2003
Please note: Minor changes have been made to this manuscript since its publication in *Angewandte* Early View. The Editor.

Keywords: antitumor agents · conformation analysis · epothilones · natural products · structure–activity relationships

[1] G. Höfle, N. Bedorf, K. Gerth, H. Reichenbach (GBF), DE-B 4138042, **1993**.
[2] G. Höfle, N. Bedorf, H. Steinmetz, D. Schumburg, K. Gerth, H. Reichenbach, *Angew. Chem.* **1996**, *108*, 1671; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1567.
[3] K. Gerth, N. Bedorf, G. Höfle, H. Irschik, H. Reichenbach, *J. Antibiot.* **1996**, *49*, 560.
[4] K. C. Nicolaou, A. Ritzén, K. Namoto, *Chem. Commun.* **2001**, *17*, 1523.
[5] K. H. Altmann, M. Wartmann, T. O'Reilly, *Biochim. Biophys. Acta* **2000**, *1470*, M79.
[6] C. R. Harris, S. J. Danishefsky, *J. Org. Chem.* **1999**, *64*, 8434.
[7] K. C. Nicolaou, F. Roschangar, D. Vourloumis, *Angew. Chem.* **1998**, *110*, 2120; *Angew. Chem. Int. Ed.* **1998**, *37*, 2014.
[8] G. A. Orr, S. B. Horwitz, *Drug Discovery Today* **2001**, *6*, 1153.
[9] 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.
[10] T.-C. Chou, X. G. Zhang, C. R. Harris, S. D. Kuduk, A. Balog, K. A. Savin, J. R. Bertino, S. J. Danishefsky, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 9642.
[11] For more information about clinical trials of dEpoB, visit: www.kosan.com.
[12] D.-S. Su, A. Balog, D. Meng, P. Bertinato, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He, S. B. Horwitz, *Angew. Chem.* **1997**, *109*, 2178; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2093.
[13] C. R. Harris, S. D. Kuduk, A. Balog, K. Savin, P. W. Glunz, S. J. Danishefsky, *J. Am. Chem. Soc.* **1999**, *121*, 7050.
[14] D. Meng, P. Bertinato, A. Balog, D.-S. Su, T. Kamenecka, E. J. Sorensen, *J. Am. Chem. Soc.* **1997**, *119*, 10073.
[15] T.-C. Chou, X. G. Zhang, C. R. Harris, S. D. Kuduk, A. Balog, K. A. Savin, J. R. Bertino, S. J. Danishefsky, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 15798.
[16] A. Rivkin, F. Yoshimura, A. E. Gabarda, T.-C. Chou, H. Dong, W. P. Tong, S. J. Danishefsky, *J. Am. Chem. Soc.* **2003**, *125*, 2899.
[17] B. E. Smart, *J. Fluorine Chem.* **2001**, *109*, 3.
[18] J. D. White, R. G. Carter, K. F. Sundermann, M. Wartmann, *J. Am. Chem. Soc.* **2001**, *123*, 5407.
[19] F. Yoshimura, A. Rivkin, A. E. Gabarda, T.-C. Chou, H. Dong, G. Sukenick, F. F. Morel, R. E. Taylor, S. J. Danishefsky, *Angew. Chem.* **2003**, *115*, 2622; Angew . *Chem. Int. Ed.* **2003**, *42*, 2518.
[20] A. Rivkin, J. T. Njardarson, K. Biswas, T.-C. Chou, S. J. Danishefsky, *J. Org. Chem.* **2002**, *67*, 7737.
[21] R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, S. Akutagawa, *J. Am. Chem. Soc.* **1987**, *109*, 5856.

[22] R. H. Grubbs, S. J. Miller, G. C. Fu, *Acc. Chem. Res.* **1995**, *28*, 446.
[23] T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18.
[24] *Alkene Metathesis in Organic Chemistry* (Ed.: A. Fürstner), Springer, Berlin, **1998**.
[25] A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012.
[26] R. R. Schrock, *Top. Organomet. Chem.* **1998**, *1*, 1.
[27] T.-C. Chou, O. A. O'Connor, W. P. Tong, Y. Guan, Z.-G. Zhang, S. J. Stachel, C. Lee, S. J. Danishefsky, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 8113 – 8118.

