Crystallographic data for **3**: $C_{14}H_{36}N_3Si_3In_2$, $M_r = 560.37$, monoclinic, space group $P2_1/n$, $a = 11.365(2)$, $b = 17.046(2)$, $c = 12.484(2)$ Å, $\beta = 90.03(1)$, $V = 2418.5(6)$ Å^3, $Z = 4$, $\mu_{calcd} = 1.539\ \mathrm{Mg\,m^{-3}}$, $\lambda = 71.073$ pm, $T = 293(2)$ K, $(\mathrm{Mo}_{K\alpha}) = 2.056\ \mathrm{mm^{-1}}$, all data were collected from a crystal ($0.3 \times 0.3 \times 0.2$ mm) sealed in a capillary in the range of $4 \leq 2\theta \leq 52°$ on a Enraf-Nonius CAD4 instrument. Of the 5487 collected reflections, 2744 were unique. The structure was solved by direct methods [24a] and refined by full-matrix least-squares on F^2 [24b]. $R1 = (I > 2\sigma(I)) = 0.032$ and $wR2 = 0.093$ (all data) with $R1 = \sum||F_0| - |F_c||/|F_0|$ and $wR2 = (\sum w(F_o^2 - F_c^2)^2/\sum(F_o^2)^2)^{0.5}$; highest residual electron density peak: 0.43 e Å^{-3}; all data for all three structures were corrected for absorption. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-179-134. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: Int. code +(1223) 336-033; e-mail: deposit@chemcrys.cam.ac.uk).

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Laser Chemistry in Suspensions: New Products and Unique Reaction Conditions for the Carbon–Steam Reaction[**]

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Gerald J. Diebold*

Small particles can have sufficiently large optical absorption cross sections[1, 2] that on irradiation of a suspension by a laser pulse with a few hundred mJ of energy, extremely high temperatures are produced in spite of the strong influence of heat diffusion into the surrounding fluid. We describe here the chemical reactions that take place in suspensions of carbon black in water irradiated by the output of a *Q*-switched laser and the morphological changes that take place in the particles as they are consumed.

Perhaps the most striking feature of the laser-initiated reaction of carbon black with water is the transformation of the optical absorption of the suspension after several minutes of irradiation: a few mL of a suspension of carbon black in water that is originally completely opaque to the eye becomes almost completely transparent after irradiation with 6000 shots of 1.06 μm radiation from a *Q*-switched Nd:YAG laser. The suspensions are made by adding dry carbon particulate 25 nm in diameter[3] at a concentration of 200 $\mathrm{mg\,L^{-1}}$ to distilled water in a glass beaker, which is then placed in an ultrasonic bath for approximately 30 s to disperse the particles. A portion of the suspension, 7.5 mL, is drawn into a glass hypodermic syringe fitted at the end with a rubber septum. The laser produces 700 mJ in a pulse 16 ns in length and is fired at 10 Hz, irradiating a spot approximately 1 cm in diameter on the side of the syringe. After several laser shots, hundreds of extremely fine bubbles can be seen rising to the surface of the liquid.[4] After 10 min of irradiation the suspension appears almost completely transparent, with a slight tint of gray, and approximately 1 cm^3 of gas has collected at the top of the syringe. Over the course of several days, a precipitate slowly forms in the suspension.[5]

Dynamic light scattering experiments showed that before irradiation the particles (25 nm in diameter) are agglomerated in large groups[6] with a mean hydrodynamic diameter of 500 nm. Light scattering measurements showed a significant reduction in the agglomerated particle diameters as a result of the laser irradiation. Although some carbon in the solution is consumed, the predominant factor in changing the optical absorption of the suspension according to Mie theory[1, 2] is the reduction in size of the particulates by the action of the laser.

The gas above the suspension was sampled through the septum and analyzed by gas chromatography with flame ionization and thermal conductivity detection. The gases detected in the chromatographs followed by their volume per unit mass of carbon in the suspension were determined to be CO (630 $\mathrm{mL\,g^{-1}}$), H_2 (260 $\mathrm{mL\,g^{-1}}$), C_2H_2 (20 $\mathrm{mL\,g^{-1}}$), CH_4 (8.9 $\mathrm{mL\,g^{-1}}$), and C_2H_4 (2.8 $\mathrm{mL\,g^{-1}}$). Also found were O_2, N_2, and small amounts of CO_2 and C_2H_6. The production of CO, H_2, and

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CO_2 can be ascribed to the well-known carbon–steam and shift reactions (a) and (b), respectively, which are the primary reactions in coal gasification.[7] Small amounts of CH_4 are known to be produced in reactors containing carbon and steam at high pressures;[7] C_2H_2 and C_2H_4 are not normally reported as reaction products.[8]

$$C + H_2O \longrightarrow H_2 + CO \tag{a}$$

$$CO + H_2O \longrightarrow H_2 + CO_2 \tag{b}$$

Unfortunately, the purity of the carbon black used in the experiments was not sufficiently high to rule out the possibility that the hydrocarbons detected were simply desorbed from the interior of the particles as a result of the high temperatures produced by the absorption of laser radiation. That is, a standard chemical analysis[5] of the carbon black showed the original sample contains H (0.30 wt%), N (0.39 wt%), and O (2.20 wt%); the amount of H in the carbon black is thus at least enough to account for all of the hydrocarbons detected by gas chromatography. An experiment in which the carbon black was prepared in deuterated water and the gas products were analyzed by gas chromatography/mass spectrometry (GC-MS) was carried out to investigate the possibility of simple desorption of existing hydrocarbons from the carbon black. Although all of the acetylene detected in the mass spectrometer[9] appeared as C_2D_2, which strongly argues against simple desorption as the mechanism for producing acetylene in the gas bubble, this result could be explained as well by H/D scrambling following desorption at high temperatures.

Finally, a sample of graphite powder with particles 1 µm in diameter that was analyzed[10] to contain 0.0038 wt% H was prepared as a somewhat unstable suspension and irradiated as described above. Chromatographic analysis showed the H content of the hydrocarbons over the suspension to exceed that in the graphite powder by a factor of 200, confirming chemical reaction as the source of the hydrocarbons.

In the course of carrying out experiments with different size particles, it was found that the production of hydrocarbons varied with particle diameter. The data in Figures 1 and 2 show that the production of all gases when normalized to the mass of C in the suspension increases with increasing particle diameter.

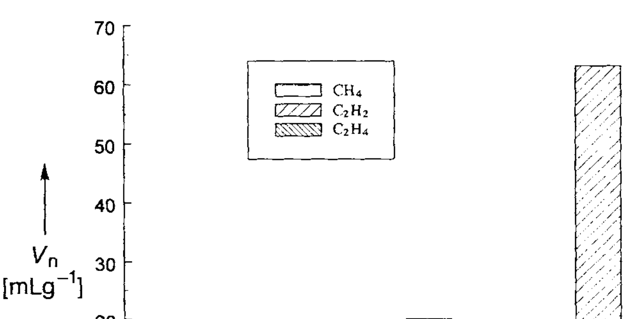

Figure 1. Composition of the hydrocarbons in the gas above the irradiated suspension (normalized volumes V_n in milliliters of gas per gram of carbon) versus particle diameter d. The suspensions were made with 200 mg of carbon per liter and were irradiated by a 700 mJ laser beam under identical conditions. The particle sizes refer to the unagglomerated particle diameters.

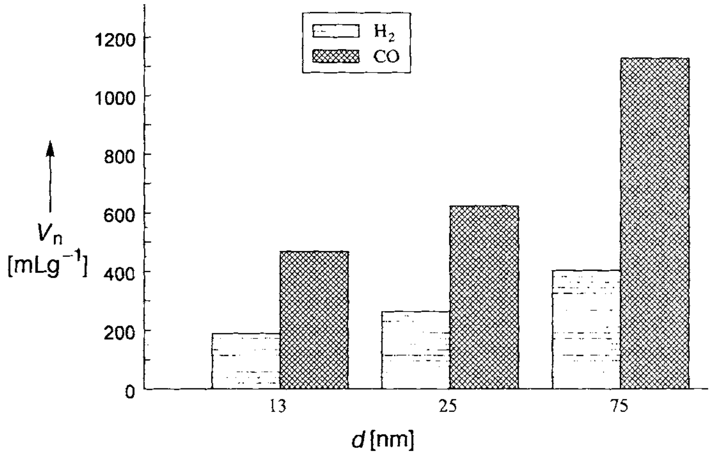

Figure 2. H_2 and CO content of the evolved gas in milliliters of gas per gram of carbon in the suspension versus particle diameter as in Figure 1.

The optical absorption of suspensions after irradiation was found to decrease with increasing particle diameter, indicating a higher total consumption of C in suspensions of the large-diameter particles. A rudimentary calculation of the temperature profile of a small, uniformly heated sphere in a heat conducting medium shows that the surface of a sphere is driven to higher temperatures, the larger its diameter.[11] Since C_2H_2 is more stable than other hydrocarbons at temperatures higher than 1350 °C,[8] the trend of increasing relative C_2H_2 production with an increase in particle diameter shown in Figure 1 provides some evidence for the hypothesis of surface temperatures that increase with increasing particle diameter. A process whereby reduction of the particle diameter through reaction to a point at which its thermal inertia is so small that its temperature rise is limited and no further reaction follows on subsequent absorption of radiation is consistent with the findings that for suspensions initially made of large particles the gas volume is greater than and the postirradiation optical density less than that of suspensions initially made of small particles.

The data in Figure 2 show, irrespective of particle size, that the $CO:H_2$ ratio in the reaction products is consistently higher than the 1:1 ratio dictated by reaction (a). An experiment was performed with carbon particles 25 nm in diameter in ^{18}O-enriched water to investigate the possibility that part of the CO arises from sources other than chemical reaction. The results of the GC-MS analysis showed significant dilution of the ^{18}O in the CO and CO_2; the O in the original carbon black sample is the likely source[12] of the ^{16}O.

Aside from chemical reaction, two salient features of the interaction of high-power laser radiation with carbon suspensions are the generation of an audible sound wave above suspensions open to the atmosphere,[13] and the production of diffuse white light along the path of the exciting laser beam.[14] Experiments with a photomultiplier positioned to view the irradiated region of a cell showed that the radiation was coincident with the 16 ns laser pulse to within the time resolution of the phototube.[15] Since reaction rates are typically a strong function of temperature, it is expected that the products are formed predominantly during the 16 ns period in which light is emitted from the suspension. Although there appears to be no calculations of the time profile of the pressure around laser-heated particles, the qualitative behavior of the "giant" photoacoustic effect[13] together with the empirically determined dependence of CH_4 production on pressure points to the generation of high pressures at the surfaces of the particles.

The question of the morphogenesis of the carbon particles under laser irradiation was investigated by examining the particles after various irradiation times using a transmission electron microscope.[16] Samples of a few µL of an irradiated suspension were placed on a standard graphite-coated electron microscope grid and left to dry. Figure 3 shows a micrograph of a sample of a suspension that had been irradiated for 15 shots. The figure shows agglomerates made up of particles 25 nm in diameter as they are typically seen in the initial suspension. As the irradiation proceeds, the large, nearly spherical structures[17] shown in Figure 3 appear as the number of agglomerates of small particles decreases. The uniform spatial profile of the original, 25 nm diameter spherical particles in the micrograph can be contrasted with the shell-like structure of the large particles. Large structures with diameters ranging up to 400 nm in which a dense shell surrounds a lower density core have been found by both transmission and scanning electron microscopy.

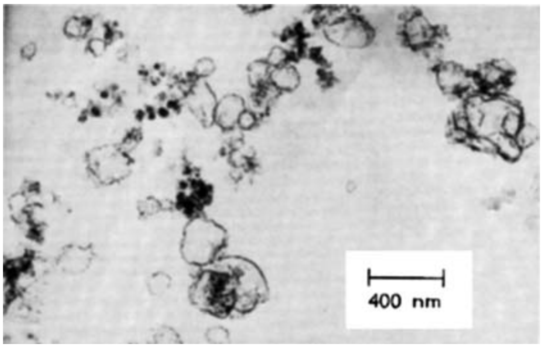

Figure 3. Electron micrograph of a sample after 15 laser shots showing the large-diameter structures generated by laser irradiation of a suspension of carbon black particles 25 nm in diameter. Several agglomerates consisting of particles 25 nm in diameter can be seen, as are typically found in micrographs taken before irradiation.

The conditions produced by the laser irradiation of carbon particles[18] can be likened to those found in intense sound beams where short bursts of high temperature and pressure likewise initiate chemical reactions.[19] While the laser method is somewhat more restricted than the sonochemical one in that it requires an optical absorber, it should be applicable to any suspension[20] for which an absorption of the particles can be matched to the wavelength of a laser. Since the power of the laser together with the rate of heat conduction from the particle surface by the surrounding fluid determines the amount of reaction and governs the rise and fall of the state variables near the particles, manipulation of the laser power and pulselength provides a somewhat unconventional, but straightforward means of controlling the conditions under which the reactions take place. The facile production of hydrocarbons, in particular, acetylene and ethylene, in aqueous carbon suspensions points to unique reaction conditions at the carbon–water interface characterized by high temperatures and pressures of extremely short duration and a chemical environment rich in carbon.

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[3] The carbon particles, kindly donated by Cabot Inc. ("Black Pearls" 1300, 470, and 130) have individual particle diameters specified as 13, 25, and 75 nm, and agglomerate diameters of 36, 94, and 236 nm, respectively.

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[5] Standard oxidative elemental analysis of the C, H, N, and O content of the carbon black was performed by National Chemical Consulting, Tenafly, NJ (USA). The precipitate was found to contain C (71.59 wt%), H (3.01 wt%), N (1.62 wt%), and O (21.23 wt%).

[6] Transmission electron microscopy confirmed the agglomeration of the 25 nm particles into large groups in aqueous solution (see ref. [16]). The suspensions of carbon in water were stable for several hours. Surfactants can be used to stabilize the suspensions in water to form India inks, which qualitatively act the same as the carbon black suspensions when irradiated; however, inks were not used in these experiments in order to limit extraneous sources of H or O.

[7] C. G. von Fredersdorff, M. A. Elliott in *Chemistry of Coal Utilization, Supplementary Volume*, Wiley, New York, **1963**. The actual species involved in the reactions may include reactive clusters of carbon, for example, C_2–C_{200}. See S. H. Yang, C. L. Pettiette, J. Conceicao, O. Cheshnovsky, R. E. Smalley, *Chem. Phys. Lett.* **1987**, *139*, 223–238; E. A. Rohlfing, D. M. Cox, A. Kaldor, *J. Chem. Phys.* **1984**, *81*, 3322–3330; D. W. Arnold, S. E. Bradforth, T. N. Kitsopoulos, D. M. Neumark, *J. Chem. Phys.* **1991**, *95*, 8753–8764.

[8] C_2H_2 is found in the quenched, high-temperature plasma pyrolysis of coal; unlike the carbon used here, coal is rich in a variety of hydrocarbons. See N. Berkowitz, *An Introduction to Coal Technology*, Academic Press, New York, **1994**, Section 6.7.

[9] No undeuterated acetylene could be detected in the mass spectra within the detection limits (estimated to be less than 1% of the peak amplitude of the deuterated acetylene). Signals for C_2D_4 and C_2D_6 were found, with additional small peaks near the characteristic peaks for these species; however, the spectra were not consistent with either the purely or singly hydrogenated analogues of these species.

[10] The ultrasensitive analysis of the graphite for hydrogen (by chromatographic methods) was carried out by LECO Inc., Midland, MI (USA). Although the aqueous suspension of graphite powder produced gases on irradiation by the laser, the quality of the suspension was so poor that comparison of composition of the gas with that of the suspensions of carbon black, as shown in Figures 1 and 2, was judged to be inappropriate. In addition, these particles are a bit too large (1 µm diameter) to be considered within the Rayleigh limit discussed in ref. [11].

[11] Particles whose radii are small compared with the wavelength of the exciting radiation (the Rayleigh limit), in the absence of any cooling mechanism, reach the same final temperature irrespective of particle diameter. The calculation of the temperature with heat diffusion is based on Equation 10.2.6 in H. S. Carslaw, J. C. Jaeger, *Conduction of Heat in Solids*, 2nd ed. Oxford University Press, New York, **1956**, for a sphere with the same diffusivity as the surrounding material. In addition to heat conduction, several other heat loss mechanisms can be operative, including phase changes, chemical reaction, and radiation. However, for any loss mechanism dependent on surface area, the increase in the thermal inertia of a sphere with increasing radius (but still within the Rayleigh limit) argues for a higher average surface temperature for large particles, as well.

[12] Temperature-programmed desorption of dry carbon black with particles 25 nm in diameter from 30 to 1250 °C showed that gas with a charge-to-mass ratio of 28 was evolved. This finding is consistent with the observed dilution of the ^{18}O signal in the CO.

[13] See H. X. Chen, G. J. Diebold, *Science* **1995**, *270*, 963–966. The sound waves can be strong enough to fracture the glass wall of the syringe at the concentrations and power levels used here.

[14] In studies of optical limiting in carbon black suspensions, light emission is observed. See, for instance, K. Mansour, M. J. Soileau, E. W. Van Stryland, *J Opt. Soc. Am.* **1992**, *9*, 1100–1109; with regards to light emission and ionization, see also W. Robers, H. Schroder, K. L. Kompa, R. Niessner, *Z. Physikalische Chem.* **1988**, *159*, 129–148.

[15] The width of the white light pulse was found to be identical to that of the laser to within the time resolution of the apparatus. A 1P28 photomultiplier with a risetime of 2.2 ns and an oscilloscope with a 350 MHz bandwidth were used here.

[16] The results from transmission electron microscopy are somewhat at odds with those of light scattering. After 10 min of irradiation, no particulate matter could be found by the former technique, while the latter showed particles with a hydrodynamic diameter of 100 nm. We attribute this disparity to the drying that is required to prepare a sample for electron microscopy, which may cause

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].

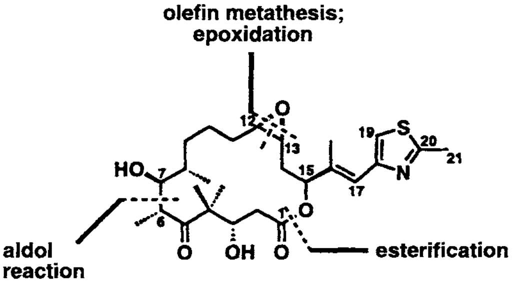
Total Synthesis of Epothilone A: The Olefin Metathesis Approach**

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

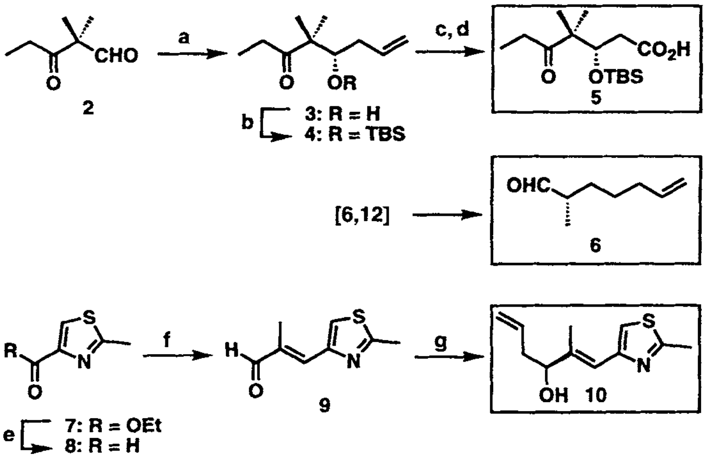
Epothilone A (1)[1,2] is an exciting new natural product, isolated from the myxobacteria *Sorangium cellulosum* strain 90, with novel molecular architecture, important biological properties, and an intriguing mechanism of action. Amongst its biological properties are potent antifungal and selective cytotoxic 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.



1: epothilone A

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$_2$B(allyl), Et$_2$O/pentane, −100 °C, 0.5 h, 74 %; b) 1.1 equiv TBSOTf, 1.2 equiv 2,6-lutidine, CH$_2$Cl$_2$, 25 °C, 1 h, 98 %; c) O$_3$, CH$_2$Cl$_2$, −78 °C, 0.5 h, then excess Ph$_3$P, −78 → 25 °C, 1 h, 82 %; d) 3 equiv NaClO$_2$, 4 equiv 2-methyl-2-butene, 1.5 equiv NaH$_2$PO$_4$, *t*BuOH:H$_2$O 5:1, 25 °C, 2 h, 93 %; e) 1.1 equiv DIBAl-H, CH$_2$Cl$_2$, −78 °C, 0.5 h, 90 %; f) 1.1 equiv Ph$_3$P=C(Me)CHO, benzene, 80 °C, 1 h, 90 %; g) 1.1 equiv (+)-Ipc$_2$B(allyl), Et$_2$O/pentane, −100 °C, 0.5 h, 96 %. TBS = *tert*-butyldimethylsilyl; Ipc$_2$B(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$_2$B(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$_3$P=C(Me)CHO to afford the conjugated aldehyde **9** (90 % yield), and c) condensation of **9** with (+)-Ipc$_2$B(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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