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Total synthesis of epothilone D by sixfold ring cleavage of cyclopropanol intermediates

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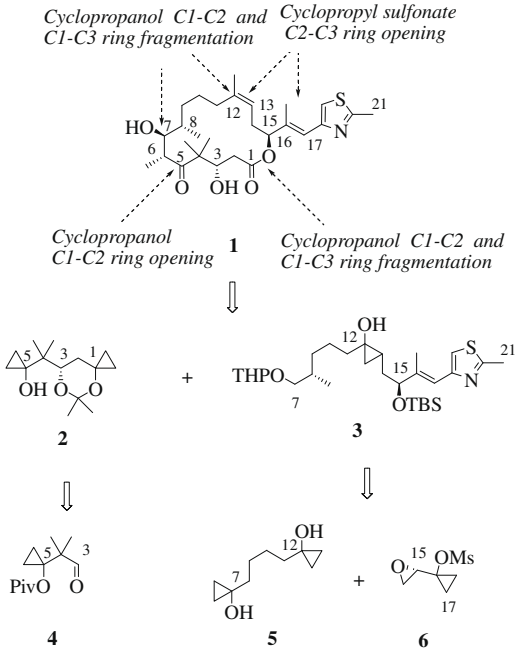
ABSTRACT

The ring-opening or ring fragmentation reactions of cyclopropanol intermediates are used in the total synthesis of epothilone D for the creation of trisubstituted double bonds, an ethyl ketone functionality, as well as for the protection of carboxylic and ester groups. Epothilone D is obtained in 1.6% overall yield (24 steps in the longest linear sequence) starting from (*R*)-methyl 2,3-*O*-isopropylideneglycerate. The key cyclopropanol intermediates are efficiently obtained by titanium(IV)-catalyzed reactions of readily available esters with Grignard reagents.

Ring-opening and ring fragmentation reactions have been widely used in organic synthesis.[1] For small-ring compounds having ion-stabilizing substituents, these reactions usually proceed under mild conditions with high regioselectivity. Such transformations are typical for cyclopropanols and their derivatives affording carbonyl compounds, esters, allyl alcohols, allyl halides, and other products.[2] After finding that the reaction of esters with Grignard reagents in the presence of titanium alkoxides leads to substituted cyclopropanols,[3] we started systematic studies on their use as synthetically useful intermediates.[4] In the present work we were interested to apply cyclopropanol synthetic methodologies to the total synthesis of the microtubule-stabilizing anticancer agent, epothilone D (**1**),[5] by sequential applications of cyclopropanation and cyclopropanol ring-opening reactions for the preparation of the appropriate synthetic intermediates. The choice of this target molecule allowed us to study the synthesis of complex polyfunctional compounds as well as to gauge the relative strength of the elaborated cyclopropanol approach to the synthesis of epothilone D in comparison with the many alternative routes described in the literature.[6]

In this work the frequently used macrolactonization strategy[7] was applied to the synthesis of epothilone D (**1**). Cyclopropanol ring fragmentation reactions were utilized to generate the corresponding functionalities at C1, C7, and C12, whereas ring-opening reactions were exploited for the generation of the carbonyl group at C5 as well as for the creation of the C12–C13 and C16–C17 double bonds (Scheme 1). Advanced cyclopropanol intermediates, compounds **2** and **3**, were, in turn, prepared via cyclopropanol precursors **4**–**6**.

The C1–C6 subunit **2** was synthesized starting from ester **7**,[8] which was smoothly converted into the substituted cyclopropanol **8** by treatment with ethylmagnesium bromide in the presence of titanium(IV) isopropoxide.[3] The reaction of the magnesium alcoholate of the product **8** with pivaloyl chloride gave the ester **9** and hydrolysis of the acetal group afforded aldehyde **4** (Scheme



Scheme 1.

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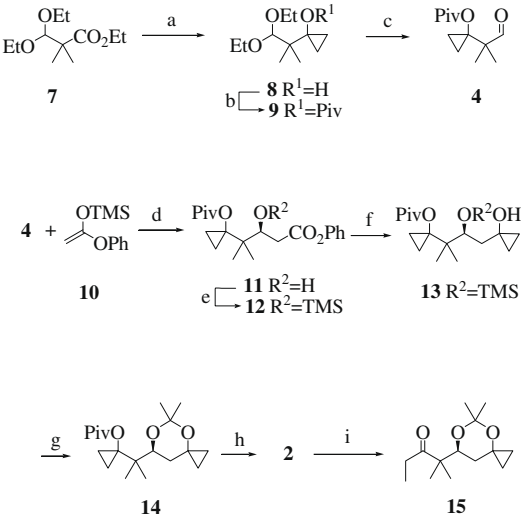
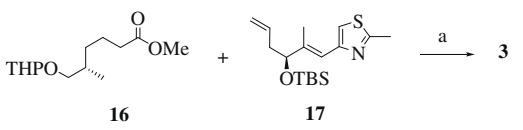
2). Condensation of the latter with trimethylsilyl ketene acetal **10** in the presence of *N*-tosyl-(*S*)-valine-derived oxazaborolidinone[9] led to hydroxy ester **11** with 96% *ee*.[10] The hydroxy group in compound **11** was silylated and the resulting product **12** was subjected to a titanium-catalyzed reaction with ethylmagnesium bromide in ether at −35 °C. Site-selective cyclopropanation of the less-hindered ester group was achieved under these conditions and the bis-cyclopropanol **13**[11] was further converted into acetonide **14**. The pivaloyl-protecting group was removed by treatment of compound **14** with lithium aluminum hydride and the resulting crude cyclopropanol **2** was heated under reflux in methanol in the presence of potassium hydroxide. Cleavage of the C1–C2 cyclopropane bond[12] of the unprotected cyclopropanol moiety was observed under these conditions affording ethyl ketone **15** bearing the oxycyclopropane fragment as a latent carboxylic group (see below).

The preparation of the cyclopropanol C7–C21 intermediate **3** was performed by cyclopropanation of ester **16** with the alkoxytitanacyclopropane reagent generated by ligand exchange[13] of TBS-protected homoallyl alcohol **17**[14] and the alkoxytitanacyclopropane precursor, generated from titanium(IV) isopropoxide and cyclopentylmagnesium chloride (Scheme 3).[15] Addition of the latter to the mixture of ester **16**, olefin **17**, and titanium(IV) isopropoxide in THF provided disubstituted (*E*)-cyclopropanol **3** in 66% yield based on ester **16** and 95% yield based on recovered alkene **17**. The reaction proceeded with high (*E*)-diastereoselectivity to afford compound **3** as the mixture of diastereomers (1.4:1) with undetermined relative configuration of the chiral centers.[16]

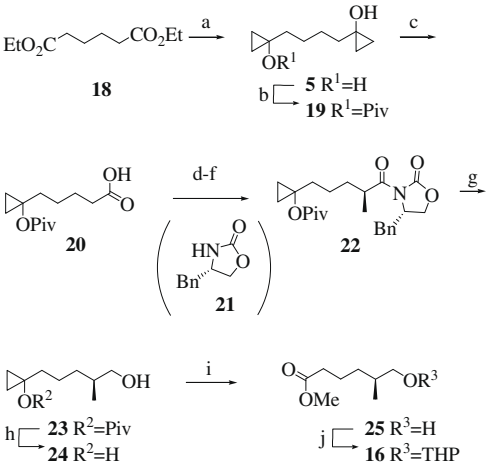
THP-protected hydroxy ester **16** was prepared from diethyl adipate (**18**) via bis-cyclopropanol **5** (Scheme 4).[17] Esterification of the latter with 1 equiv of pivaloyl chloride and subsequent Rubottom–



Scheme 2. Reagents and conditions: (a) EtMgBr (5 equiv), Ti(O*i*-Pr)$_4$ (0.5 equiv), THF, 82%; (b) EtMgBr, Et$_2$O, THF, then PivCl, 99%; (c) H$_2$O, TsOH, acetone, 90%; (d) **10** (2 equiv), *N*-Ts-(*S*)-valine (1.25 equiv), BH$_3$·THF (1.25 equiv), CH$_2$Cl$_2$, 58%; (e) TMSCl, Et$_3$N, THF, 88%; (f) EtMgBr (6 equiv), Ti(O*i*-Pr)$_4$ (2 equiv), Et$_2$O, −35 °C, 74%; (g) 2,2-dimethoxypropane, PPTS, acetone, 99%; (h) LiAlH$_4$, Et$_2$O; (i) KOH, MeOH, reflux, 78% over two steps.



Scheme 3. Reagents and conditions: (a) cyclopentylmagnesium chloride (4 equiv), Ti(O*i*-Pr)$_4$ (1 equiv), THF, 66% yield based on **16** and 95% yield based on recovered **17**.

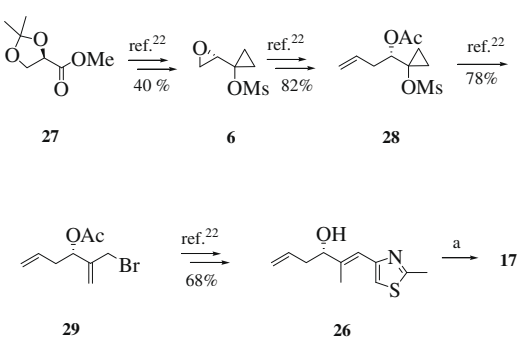


Scheme 4. Reagents and conditions: (a) EtMgBr (5 equiv), Ti(O*i*-Pr)$_4$ (0.2 equiv), THF, 90%; (b) PivCl, Py, DMAP, 63%; (c) PhI(OAc)$_2$, AcOH, H$_2$O, 93%; (d) SOCl$_2$, CHCl$_3$; (e) **21**, BuLi, THF, hexane, 89% over two steps; (f) NaHMDS, MeI, THF, 92%; (g) LiBH$_4$, MeOH, THF, 89%; (h) LiAlH$_4$, Et$_2$O, 90%; (i) PhI(OAc)$_2$, MeOH, 87%; (j) DHP, PPTS, CH$_2$Cl$_2$, 99%.

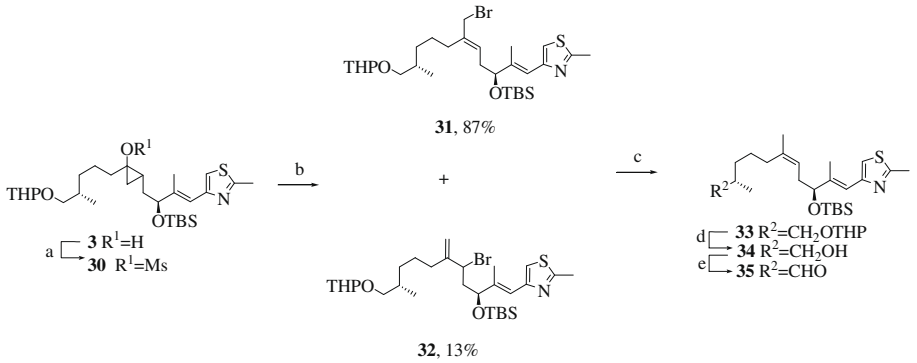
Kirihara oxidative fragmentation of the unprotected cyclopropanol moiety[18] by treatment of pivalate **19** with phenyliodine(III) diacetate in acetic acid led to acid **20** along with its anhydride and the mixed anhydride with acetic acid. Dilution of the reaction mixture with aqueous THF and a short reflux enabled hydrolysis of the anhydrides furnishing the acid **20** in 93% yield.[19] Conversion of the acid **20** into the acid chloride followed by coupling of the product with the Evans chiral auxiliary **21** and diastereoselective methylation led to imide **22** in 92% yield. The chiral auxiliary of **22** was removed by reduction with lithium borohydride, and the resulting alcohol **23** was treated with lithium aluminum hydride to yield cyclopropanol **24**. Oxidative fragmentation of the latter with phenyliodine(III) diacetate in methanol[18] led to regeneration of the ester group to form hydroxyester **25** with 88% ee.[20,21] Protection of the hydroxy group in **25** furnished compound **16**.

The olefin subunit **17** was obtained, in turn, by silylation of the homoallylic alcohol **26**,[14] whose preparation starting from the ester **27** via cyclopropanol derivatives **6**, **28**, and allyl bromide **29** was described in our previous Letter (Scheme 5).[22]

The trisubstituted C12–C13 double bond of the target molecule **1** was formed by the cationic cyclopropyl-allyl rearrangement of the cyclopropanol sulfonate **30** (Scheme 6).[23] The latter was treated with magnesium bromide (3 equiv) in ether at room temperature to give a mixture of regioisomeric allyl bromides **31** and **32** in an 87:13 ratio and with more than 99% stereoselectivity toward the (*E*)-trisubstituted double bond in the primary allyl bromide **31**. Reductive dehalogenation of the mixture of the compounds



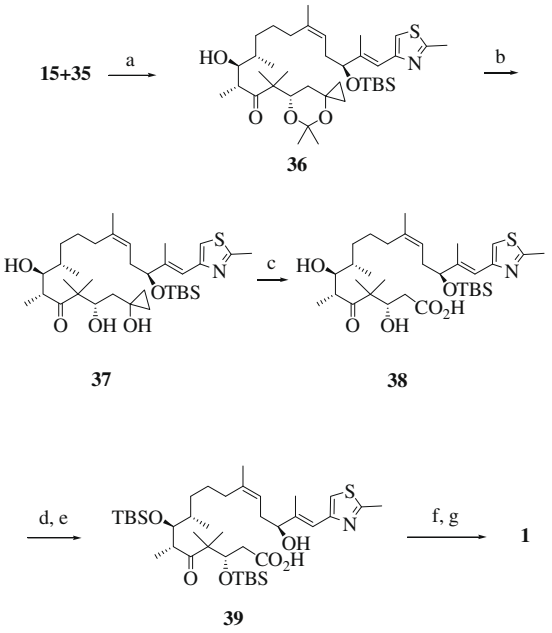
Scheme 5. Reagents and conditions: (a) TBSCl, imidazole, DMF, 92%.



Scheme 6. Reagents and conditions: (a) MsCl, Et_3N, Et_2O, 99%; (b) $MgBr_2$, Et_2O, 99%, 87:13 **31**/**32**; (c) $LiAlH_4$, Et_2O, then KOAc, TEBA, DMF, 60%; (d) PPTS, *i*-PrOH, 94%; (e) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, 92%.

31 and **32** with lithium aluminum hydride led to *Z*-alkene **33** together with unreacted bromide **32**. To facilitate chromatographic purification of product **33**, the secondary allyl halide **32** was converted into the corresponding acetate by reaction with potassium acetate in DMF in the presence of TEBA.[23b] The THP-protecting group was removed by treatment of compound **33** with isopropyl alcohol in the presence of PPTS to afford known alcohol **34**,[24] which was further oxidized using the Swern method to give aldehyde **35**[14] in 51% overall yield (five steps).

The formation of the carbon backbone of the target epothilone D (**1**) was accomplished in a similar way to earlier described procedures[14,24] by *syn*-selective addition of the lithium enolate of ethyl ketone **15** to aldehyde **35** to give product **36** in 80% yield (Scheme 7). The acetonide-protecting group was removed from compound **36** by treatment with a mixture of ether and 80% formic acid (1:1) at room temperature over 6 h. The cyclopropanol group of **37** was transformed into a carboxyl group, in excellent yield, by treatment with phenyliodine(III) diacetate in aqueous THF[18] and standard manipulation of the protecting groups of the resulting compound **38** was carried out to deliver hydroxy acid **39**. The latter



Scheme 7. Reagents and conditions: (a) LDA, THF, 80%; (b) 80% HCO_2H, Et_2O, 77%; (c) $PhI(OAc)_2$, THF, H_2O, 91%; (d) TBSOTf (4.5 equiv), 2,6-lutidine (7.5 equiv), CH_2Cl_2, then AcOH, H_2O, THF, 87%; (e) TBAF, THF, 69%; (f) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, toluene, 77%; (g) TFA, CH_2Cl_2, 80%.

was macrolactonized by Yamaguchi's method,[7,25] and after TBS deprotection, epothilone D (**1**)[26] was isolated in 34% overall yield based on the cyclopropanol derivative **37**.

In conclusion, the ring-opening reactions of the cyclopropanols were successfully used in the total synthesis of epothilone D **1**, for the formation of the (*Z*)-C12–C13 and (*E*)-C16–C17 trisubstituted double bonds in intermediates **17** and **33**, the ethyl ketone fragment in intermediate **15**, and for the protection of the carboxylic or ester groups in compounds **20**, **25**, and **38**. The overall yield in the longest linear sequence of 23 steps from diethyl adipate (**18**) and 24 steps from isopropylideneglycerate **27** was 2% and 1.6%, respectively. These values are close to the average number of steps (22) and average overall yield (2.3%) in the previously reported total syntheses of epothilone D (**1**).[6k,7b,c,14,27] At the same time, the cyclopropanol approach is substantially longer than the most efficient synthesis performed by Danishefsky (16 steps, 4.1% yield).[7b] It is evident that one-step introduction of the desired functionalities into a target molecule is more preferable in terms of the man-hours costs of a synthesis than the corresponding two or even multi-step sequences. Nevertheless, experimental simplicity and efficiency of cyclopropanol preparation, along with their ability to undergo smooth ring-opening or ring fragmentation reactions on treatment with inexpensive reagents or catalysts, could attach strategic importance to synthetic methods based on such transformations.[28]

Acknowledgment

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10. The ee value was determined by Mosher's method[30] from the integral intensities of the signals of the protons at $\delta = 5.83$ and 5.85 ppm (CHOMTPA) in the ^{1}H NMR spectra of the (*S*)-MTPA esters.
11. To a solution of ester **12** (1.52 g, 3.62 mmol) and Ti(O*i*-Pr)$_4$ (2.2 ml, 7.40 mmol) in Et$_2$O (36 ml) at −35 °C was added a solution of EtMgBr (2 M in Et$_2$O, 11 ml, 22 mmol) over 2 h. The reaction was quenched with H_2O (2.6 ml), the reaction mixture was filtered, and the filter cake was washed thoroughly with EtOAc. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel (petroleum ether/EtOAc) to give unreacted ester **12** (0.23 g, 15%) and cyclopropanol **13** (0.81 g, 63%, 74% based on recovered starting material). $[\alpha]_D^{20}$ −18 (*c* 2.0, $CHCl_3$). IR (CCl_4) ν_{max}: 3542, 1723 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.15 (s, 9H), 0.29–0.34 (m, 1H), 0.50–0.67 (m, 3H), 0.58 (s, 3H), 0.70–1.06 (m, 4H), 1.10 (s, 3H), 1.12 (s, 9H), 1.45 (dd, *J* = 14.3, 10.2 Hz, 1H), 2.44 (dd, *J* = 14.3, 1.5 Hz, 1H), 2.90 (s, 1H), 3.96 (dd, *J* = 10.2, 1.5 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ 1.2 (3 × C), 8.5, 11.7, 12.2, 14.1, 16.5, 25.6, 27.0 (3 × C), 39.0, 40.1, 42.1, 53.8, 65.0, 75.7, 178.5. Anal. Calcd for $C_{19}H_{36}O_4Si$: C, 64.00; H, 10.18. Found: C, 63.94; H, 10.35.
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16. A solution of cyclopentylmagnesium chloride (2 M in Et$_2$O, 4.1 ml, 8.22 mmol) was added over 40 min to a solution of ester **16** (0.50 g, 2.05 mmol), alkene **17** (1 g, 3.10 mmol), and Ti(O*i*-Pr)$_4$ (0.61 ml, 2.05 mmol) in THF (40 ml). The reaction mixture was stirred for 10 min, the reaction was quenched with H_2O (1.1 ml), the reaction mixture was filtered, and the filter cake was washed thoroughly with EtOAc. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel (petroleum ether/EtOAc) to give unreacted alkene **17** (0.54 g, 1.67 mmol) and cyclopropanol **3** (0.73 g, 66% based on ester **16**, 95% based on alkene **17**). IR (CCl_4) ν_{max}: 3609, 3468 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.00 (s, 3H), 0.06 (s, 3H), 0.06–0.11 (m, 1H), 0.78–0.89 (m, 3.5H), 0.88 (s, 9H), 0.92 (d, *J* = 7.7 Hz, 1.5H), 1.07–1.83 (m, 15H), 1.94 (s, 3H), 2.52 (br s, 1H), 2.68 (s, 3H), 3.14 (dd, *J* = 9.2, 6.5 Hz, 0.5H), 3.22 (dd, *J* = 9.2, 5.9 Hz, 0.5H), 3.45–3.53 (m, 1.5H), 3.58 (dd, *J* = 9.2, 6.5 Hz, 0.5H), 3.80–3.85 (m, 1H), 4.12–4.18 (m, 1H), 4.52–4.56 (m, 1H), 6.46 (s, 1H), 6.90 (s, 1H). Anal. Calcd for $C_{29}H_{51}O_4NSSi$: C, 64.76; H, 9.56. Found: C, 64.60; H, 9.45.
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19. PhI(OAc)$_2$ (12.68 g, 39.4 mmol) was added portionwise over 20 min to a water cooled solution of compound **19** (10.00 g, 39.4 mmol) in AcOH (50 ml). The reaction mixture was stirred for 10 min, diluted with H_2O (50 ml) and THF (100 ml), and heated under reflux for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with H_2O (50 ml) and extracted with Et$_2$O. The organic layers were dried over $MgSO_4$, concentrated under reduced pressure, and the residue was chromatographed on silica gel (petroleum ether/EtOAc) to give acid **20** (8.96 g, 93%). IR (CCl_4) ν_{max}: 1739, 1712 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.61–0.64 (m, 2H), 0.75–0.78 (m, 2H), 1.13 (s, 9H), 1.40–1.48 (m, 2H), 1.61–1.69 (m, 2H), 1.73–1.77 (m, 2H), 2.34 (t, *J* = 7.4 Hz, 2H), 10.13 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7 (2 × C), 24.3, 25.3, 26.9 (3 × C), 33.8, 34.0, 38.6, 59.1, 178.4, 179.7. Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.39; H, 9.11.
20. *Compound* **25**: $[\alpha]_D^{20}$ −11 (*c* 2.2, $CHCl_3$). IR (CCl_4) ν_{max}: 3640, 3534, 1742 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (dd, *J* = 6.7, 0.8 Hz, 3H), 1.09–1.19 (m, 1H), 1.38–1.47 (m, 1H), 1.54–1.75 (m, 3H), 2.31 (t, *J* = 7.3 Hz, 2H), 2.31 (br s, 1H), 3.44 (ddd, *J* = 10.8, 6.4, 1.0 Hz, 1H), 3.49 (ddd, *J* = 10.8, 6.1, 1.0 Hz, 1H), 3.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 22.2, 32.5, 34.2, 35.4, 51.5, 67.9, 174.2. Anal. Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 59.85; H, 10.09.
21. The ee value was determined by Mosher's method[30] from the integral intensities of the signals of the protons at $\delta = 4.12$ and 4.06 ppm (*CH*$_2$OMTPA) in the ^{1}H NMR spectra of the (*S*)-MTPA esters of compound **23**.
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26. *The NMR spectra of the obtained epothilone D (**1**) are in full agreement with those reported earlier for this compound:*[14,6k] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, *J* = 6.9 Hz, 3H), 1.07 (s, 3H), 1.19 (d, *J* = 6.7 Hz, 3H), 1.24–1.32 (m, 3H), 1.34 (s, 3H), 1.66 (s, 3H), 1.69–1.77 (m, 2H), 1.85–1.91 (m, 1H), 2.06 (s, 3H), 2.24–2.35 (m, 3H), 2.46 (dd, *J* = 14.3, 11.3 Hz, 1H), 2.63 (dt, *J* = 14.8, 10.8 Hz, 1H), 2.69 (s, 3H), 3.08 (br s, 1H), 3.15 (q, *J* = 6.7 Hz, 1H), 3.64 (br s, 1H), 3.71–3.74 (m, 1H), 4.31 (d, *J* = 10.2 Hz, 1H), 5.14 (dd, *J* = 9.7, 4.6 Hz, 1H), 5.21 (d, *J* = 9.7 Hz, 1H), 6.59 (s, 1H), 6.96 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 15.7, 15.8, 17.9, 18.9, 22.8, 22.9, 25.3, 31.5, 31.6, 32.4, 38.3, 39.6, 41.6, 53.5, 72.1, 74.1, 78.8, 115.5, 119.0, 120.8, 138.3, 139.1, 151.9, 165.0, 170.3, 220.6.
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28. To support the validity of this statement, we roughly calculated the price[29] of the molar amounts of the chemicals used for the total syntheses of epothilone D.[6k,7b,c,14,27] The average value of this sum (37×10^3 Euro·mol^{-1}) is substantially higher than the corresponding sum calculated for the synthesis of epothilone D (**1**) by the cyclopropanol approach (11×10^3 Euro·mol^{-1}). The latter value is almost twofold lower than the value for the leading approach[7b] (21×10^3 Euro·mol^{-1}) and only slightly inferior to this one in obtaining the same amount of the target molecule (**1**).
29. http://www.sigmaaldrich.com/european-export.html.
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