# Synthesis of Epothilone Analogues by Antibody-Catalyzed Resolution of Thiazole Aldol Synthons on a Multigram Scale. Biological Consequences of C-13 Alkylation of Epothilones

Subhash C. Sinha,*[a] Jian Sun,[a] Markus Wartmann,[b] and Richard A. Lerner*[a]

*Three monoclonal aldolase antibodies (84G3, 85H6, and 93F3), generated against a β-diketone hapten (**II**) by the reactive immunization technique, catalyzed highly enantioselective retro-aldol reactions of the racemic thiazole aldols **13**–**20**. Antibody 84G3 (0.0004–0.005 mol%) was used to resolve (±)-**13**–(±)-**18** to afford compounds **13**–**18** in multigram quantities. Multiple 13-alkyl analogues of epothilone (**7**–**12**) and their* trans *isomers ((*E*)-**7**–(*E*)-**12**) were synthesized starting from thiazole aldols **13**–**18**. Construction of the trisubstituted olefin moiety in compounds **7**–**12** and (*E*)-**7**–(*E*)-**12** was catalyzed by Grubbs' catalyst (**X**). Initial biological testing with compounds **7**–**10** and their* trans *isomers showed that compounds **9**, **10**, and (*E*)-**10** have appreciable tubulin polymerization and antiproliferative activities that approached those of epothilone C. The most active compound, (*E*)-**9**, even displayed potencies comparable to those observed for epothilones A and D. Interestingly, all* trans *analogues were more potent than their corresponding* cis *isomers. While introduction of an alkyl group at C-13 in the* cis *series led to an overall reduction in biological activity (compared to epothilone C), appropriate modification of the thiazole moiety (replacement of the 2-methyl substituent by a 2-methylthio group) was able to compensate for this loss. These results are encouraging in view of the expectation that epoxidations of these compounds should further increase their cellular activities. Thus, compounds **9**, **10**, and (*E*)-**9** and (*E*)-**10** represent highly promising candidates for further studies.*

**KEYWORDS:**

aldol reaction · catalytic antibodies · chiral resolution · epothilones · thiazoles

## Introduction

Epothilones A–F (**1**–**6**) are sixteen-membered macrolides isolated from myxobacteria (*Sorangium cellulosum* strain 90).[1] Several total syntheses of epothilones A–D have been achieved, and their biological properties have been recorded.[2–4] Recently, total syntheses of epothilones E and F[5] have been reported by the groups of Nicolaou and Danishefsky.[6, 7] Our own work led to the catalytic antibody route for the syntheses of epothilones A–F.[8]

The search for new and more potent analogues of epothilones began as soon as the total synthesis of the naturally occurring epothilones was accomplished. Thus, many epothilone analogues have been synthesized, some of which possess biological activities comparable to those of the natural ones.[9] The structure–activity relationships derived from an examination of known analogues of the epothilones has revealed that alterations can only be tolerated in the thiazole ring and its vicinity; changes to other regions result in a significant loss of activity. Since thiazole aldols, namely **13** and its analogues (see Table 1), can be elaborated on to provide 13-alkylepothilones, we thought that the synthesis and biological evaluation of the latter, that is, compounds **7**–**12**, would be worth pursuing. Here we report the syntheses of several new 13-alkylepothilone analogues **7**–**12** and their *trans* isomers (*E*)-**7**–(*E*)-**12**, starting from thiazole aldols **13**–**18**.[10, 11] These thiazole aldols were obtained by resolution of their racemic mixtures on a multigram scale, catalyzed by aldolase antibodies 84G3, 85H6, and 93F3. We also present the results of preliminary biological evaluations of **7**–**10** and their *trans* isomers.

### Retrosynthetic analysis

We anticipated that like the synthesis of naturally occurring epothilones **1**–**6**, their 13-alkyl analogues **7**–**12** could also be synthesized by macrolactonization or the metathesis approach

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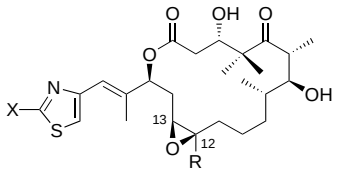
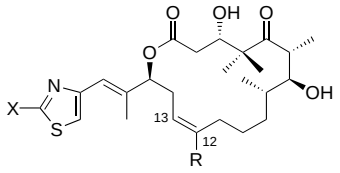
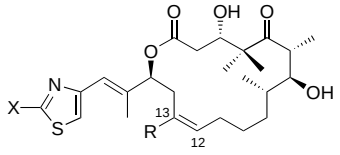


**1**: epothilone A; R = H, X = Me
**2**: epothilone B; R = X = Me
**5**: epothilone E; R = H, X = $CH_2OH$
**6**: epothilone F; R = Me, X = $CH_2OH$



**3**: epothilone C; R = H, X = Me
**4**: epothilone D; R = X = Me



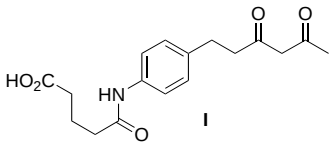
**7**: epothilone MM; R = X = Me
**8**: epothilone ME; R = Et, X = Me
**9**: epothilone SM; R = Me, X = SMe
**10**: epothilone SE; R = Et, X = SMe
**11**: epothilone HM; R = Me, X = $CH_2OH$
**12**: epothilone HE; R = Et, X = $CH_2OH$

as shown in Scheme 1. Thus, compounds **7** – **12** can be obtained from **III** in the macrolactonization approach and from **IV** in the metathesis process. Compound **III** can be synthesized by the aldol reaction between **V** and **29**, and the intermediate **V** can be obtained by the Wittig reaction between **VI** and **13** – **18**. For the metathesis route, diene **IV** can be prepared by esterification of acid **38** with alcohol **VII**. Once again, compound **VII** can be synthesized from **13** – **18** by a Wittig reaction with methylene-triphenylphosphorane. Considering the relevance of aldolase antibodies to the total syntheses of epothilones, we imagined that compounds **13** – **18** could be obtained by using the former.

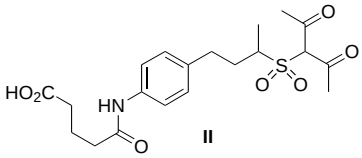
## Results and Discussion

### Enantioselective resolution of 13 – 20

Recently, two sets of aldolase monoclonal antibodies, 38C2 and 33F12, and 84G3, 85H6, and 93F3, were generated against $\beta$-diketone haptens **I** and **II**, respectively, by using the reactive



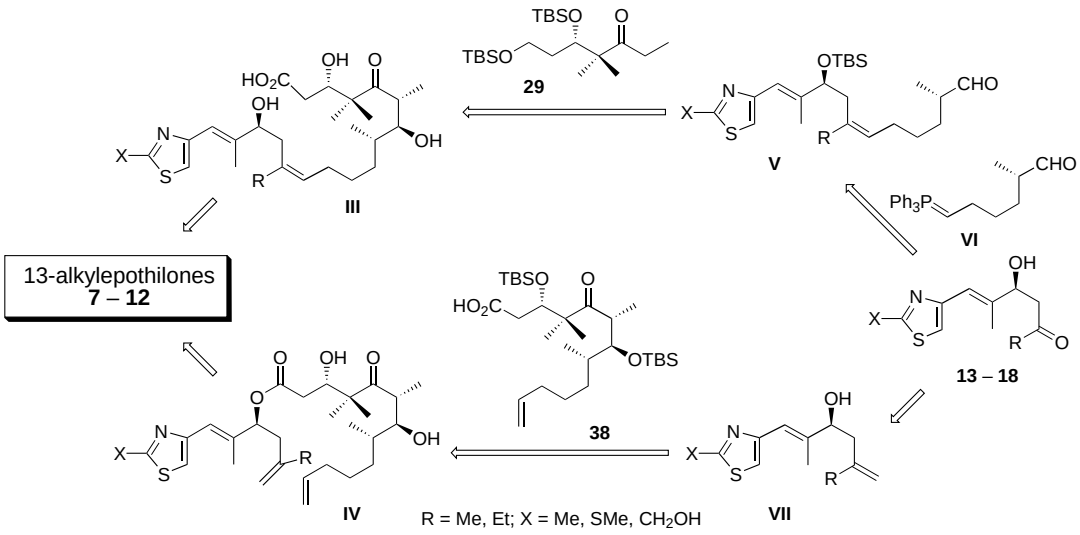
**I**



**II**

immunization technique.[12, 13] These antibody catalysts behave like natural aldolases and catalyze aldol and retro-aldol reactions by an enamine mechanism,[14] yet they accept a much broader range of substrates. Thus, both sets of antibodies have been found to be very useful for synthetic organic chemistry.[15] Aldolase antibodies 38C2 and 33F12 are complementary to 84G3, 85H6, and 93F3 by having antipodal reactivities and thus produce compounds with opposite facial selectivities. Two of the new catalysts, 84G3 and 93F3, operate with the highest catalytic proficiencies yet observed with antibodies, $(k_{cat}/K_m)/k_{uncat} > 10^{13}\,M^{-1}$.

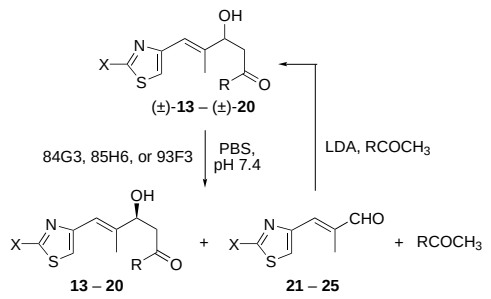
In our previous studies, we found that the kinetic resolution of the racemic mixtures of thiazole aldols **13** – **17**, using the




***Scheme 1.*** *Retrosynthetic analysis of 13-alkylepothilones. TBS* = tert-*butyldimethylsilyl.*

antibodies 84G3, 85H6, or 93F3, which were raised against hapten **II**, was an appropriate method for the production of enantiomerically pure thiazole aldols **13** – **17**. In continuation, we studied the resolution of additional analogues, **18** – **20**, using antibodies 84G3, 85H6, and 93F3 (Table 1). Once again, all three catalysts gave similar results, with antibodies 84G3 and 93F3 demonstrating a rate enhancement slightly greater than that with 85H6. The unreacted aldol compounds, from the reaction of (±)-**13** – (±)-**20** and antibodies, were found to be essentially in enantiomerically pure form at 50% conversion and identified as compounds **13** – **20** (see below).

***Table 1.*** *Resolution of compounds (±)-**13** – (±)-**20** by antibody-catalyzed enantioselective retro-aldol reactions.*




| Entry | Compound | Catalytic antibody 84G3, *ee* [%][a] | 85H6, *ee* [%][a] | 93F3, *ee* [%][a] | Aldehyde |
|---|---|---|---|---|---|
| 1 | **13**: R = X = Me | 98(50) | 94(50) | 98(50) | **21** |
| 2 | **14**: R = Et, X = Me | 99(51) | 99(50) | 99(50) | **21** |
| 3 | **15**: R = Me, X = SMe | 99(53) | 99(50) | 99(54) | **22** |
| 4 | **16**: R = Et, X = SMe | 99(50) | 99(50) | 99(52) | **22** |
| 5 | **17**: R = Me, X = $CH_2OH$ | 99(50) | 99(50) | 99(50) | **23** |
| 6 | **18**: R = Et, X = $CH_2OH$ | > 99(50) | n.t.[b] | n.t. | **23** |
| 7 | **19**: R = Me, X = $CH_2OMOM$ | 99(50) | 99(50) | > 99(51) | **24** |
| 8 | **20**: R = Me, X = $CH_2F$ | > 99(50) | n.t. | n.t. | **25** |

[a] Enantiomeric excess (*ee*) was recorded in percent. Numbers in parentheses represent the percent conversion. [b] n.t. = not tested. – LDA = lithium diisopropylamide.

Based on our previous and current studies, the following conclusions were made. The relative rates of the retro-aldol reactions increased from methyl ketones to ethyl ketones. Thus, compound **14** was resolved faster than **13** and as fast as the corresponding propyl ketone. Similarly, compounds **16** and **18** were resolved faster than **15** and **17**, respectively. The substituent on the thiazole ring also influenced the rate. Substituion of a methyl group on the aromatic ring with a hydroxymethyl group has little effect on the relative rate. Displacement of the same with a fluoromethyl group decreased the rate, while that with a methylthio group, as in **15** – **16**, dramatically increased the overall rate and efficiency of the reaction. Thus, compound **16** was found to be the fastest reacting substrate with all three antibodies, and could be resolved with more than 99% enantioselectivity in less than 10 min employing 0.5 mol% antibody 93F3. When the amount of catalyst was reduced to 0.01 mol%, the reaction was complete after overnight incubation. Furthermore, on a large-scale reaction, only 0.0003 mol% of antibody 84G3 was required to have satisfactory results (see below).

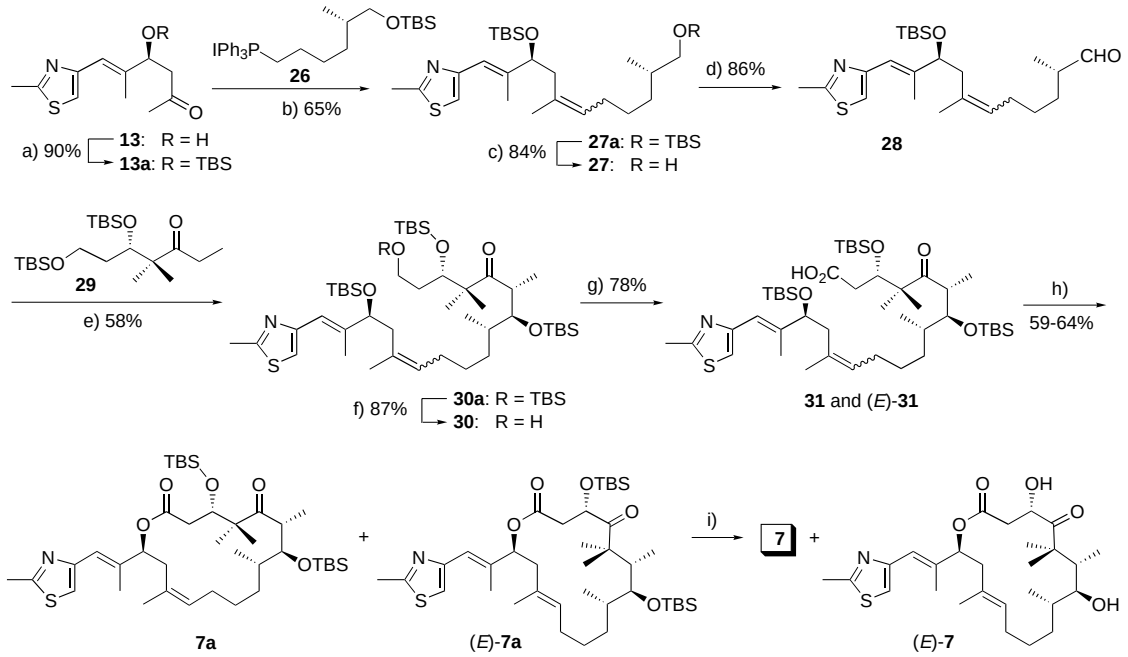
For our synthesis of **7** – **12**, we resolved compounds (±)-**13** – (±)-**18** on a synthetically useful scale using antibody 84G3. Compound (±)-**13** (16.8 g, 74.7 mmol) was resolved by incubation with 0.003 mol% of antibody 84G3 (340 mg, 0.00227 mmol) in PBS buffer (pH 7.4) at 37 °C. Progress of the reaction was followed by the disappearance of the peak for *ent*-**13** in the HPLC trace. In this way, the racemic mixture was resolved to afford **13** with more than 97% enantiomeric purity in 45%, and aldehyde **21** in 42% yield of isolated product. The thiazole aldehyde obtained from this reaction was reused to synthesize the starting aldol compound. Thus, even though the process is a kinetic resolution, the overall yield is good because the products can be recycled. Similarly, compounds (±)-**14** (6.43 g, 26.9 mmol), (±)-**15** (3.30 g, 12.8 mmol), (±)-**16** (8.40 g, 30.8 mmol), (±)-**17** (1.45 g, 6.0 mmol), and (±)-**18** (8.80 g, 34.5 mmol) were resolved using 0.0004 – 0.005 mol% of antibody 84G3.[12, 13b] The best substrate in this series, (±)-**16** (8.40 g, 30.8 mmol), was resolved with as little as 20 mg (0.000133 mmol, 0.0004 mol%) of the antibody 84G3 to afford **16** in 48% and the corresponding aldehyde **22** in 45% yield of isolated product.

### Determination of absolute configuration of 13 – 20

The absolute configuration of compound **13** obtained from the resolution of the corresponding racemic mixture was determined by comparison with a synthetic sample of **13**. The latter was prepared by the method of Paterson et al. using a chiral boron enolate of acetone.[16] Thus, compound **21** was reacted with prop-1-en-2-ol diisopinocampheylborinate, generated from (+)-$(Ipc)_2BOTf$ and acetone, to afford **13** in 70% enantiomeric purity. The identity of the two samples was verified by chiral-phase HPLC analysis.[8] The absolute configuration of the other analogues of **13**, that is, **14** – **20**, obtained from resolutions of their corresponding racemic mixtures catalyzed by antibodies 84G3, 85H6, and 93F3, were assigned by comparing their specific rotation and, in some cases, HPLC traces with those of **13**.

### Synthesis of 7 and (*E*)-7 by the macrolactonization approach

We began the synthesis of **7** starting from **13** (Scheme 2). Compound **13** was first silylated as its TBS ether to afford **13a**, which was then converted to olefin **27a** as a mixture of *E* and *Z* isomers in a ratio of 55:45 by a Wittig reaction with **26**.[3d] The mixture of Wittig product **27a** was taken to the next step without separation. The primary alcohol function in **27a** was deprotected to yield alcohol **27**, which was then oxidized to afford aldehyde **28**. An aldol reaction of the latter aldehyde with a known ketone, **29**,[17] was carried out by using LDA as a base to afford the corresponding aldol compounds. The major aldol product was purified from the minor isomer and the free hydroxy group in the former was then protected as its TBS ether affording compound **30a**. The primary alcohol function in **30a** was then selectively deprotected to provide alcohol **30**, which




***Scheme 2.*** *Total synthesis of 13-methylepothilone C (**7**) and its* trans *isomer (*E*)-**7** by the macrolactonization approach. a) TBSCl, imidazole, DMF, RT, 16 h; b) **26**,* n*BuLi, THF, RT, 1 h; c) TsOH, MeOH/$CH_2Cl_2$, 0 °C, 2 h; d) Dess – Martin reagent, $CH_2Cl_2$, RT, 2 h; e) 1. **29**, LDA, THF, −78 °C, 0.5 h, 2. TBSOTf, lutidine, $CH_2Cl_2$, −78 →0 °C, 4 h; f) TsOH, MeOH/$CH_2Cl_2$, 0 °C, 0.5 h; g) 1. Dess – Martin reagent, $CH_2Cl_2$, RT, 2 h, 2. $NaClO_2$, 2-methyl-2-butene, $NaH_2PO_4$,* tert*-BuOH/$H_2O$, RT, 20 min; h) 1. Separation by column chromatography, silica gel,* n*-hexane/EtOAc, 2. TBAF, THF, RT, 16 h, 3. 2,4,6-trichlorobenzoyl chloride, $Et_3N$, THF, 0 °C, 1 h, then slow addition to dilute solution of DMAP in toluene, 75 °C, 2 h; i) HF · pyridine, THF, 0 °C →RT, 2 h. DMAP = 4-(dimethylamino)pyridine, TBAF = tetrabutylammonium fluoride, Tf = trifluoromethanesulfonyl, Ts = toluene-4-sulfonyl.*

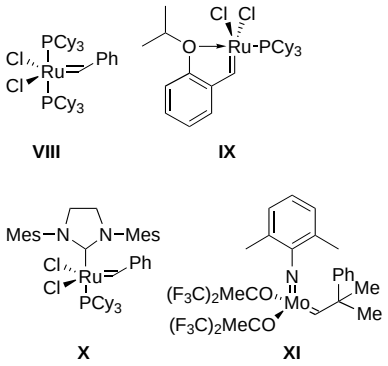
was subsequently oxidized in two steps via the aldehyde to the corresponding acid. The crude acid product was then separated by column chromatography affording **31** and (*E*)-**31**. Selective deprotection of the TBS ether at C-15 followed by lactonization under the Yamaguchi condition afforded the corresponding lactones **7a** and (*E*)-**7a**, which were then deprotected with HF · pyridine, affording **7** and its isomer (*E*)-**7**.

Although it was possible to complete the synthesis of **7** and (*E*)-**7** by the macrolactonization approach, this method caused problems for the synthesis of other 13-alkyl analogues, particularly **9**, **10**, and their *trans* isomers. In these cases, the Wittig reaction of **26** with ketones **15a** or **16a** was not successful. Instead, the elimination product of the corresponding ketone was obtained as a major product.

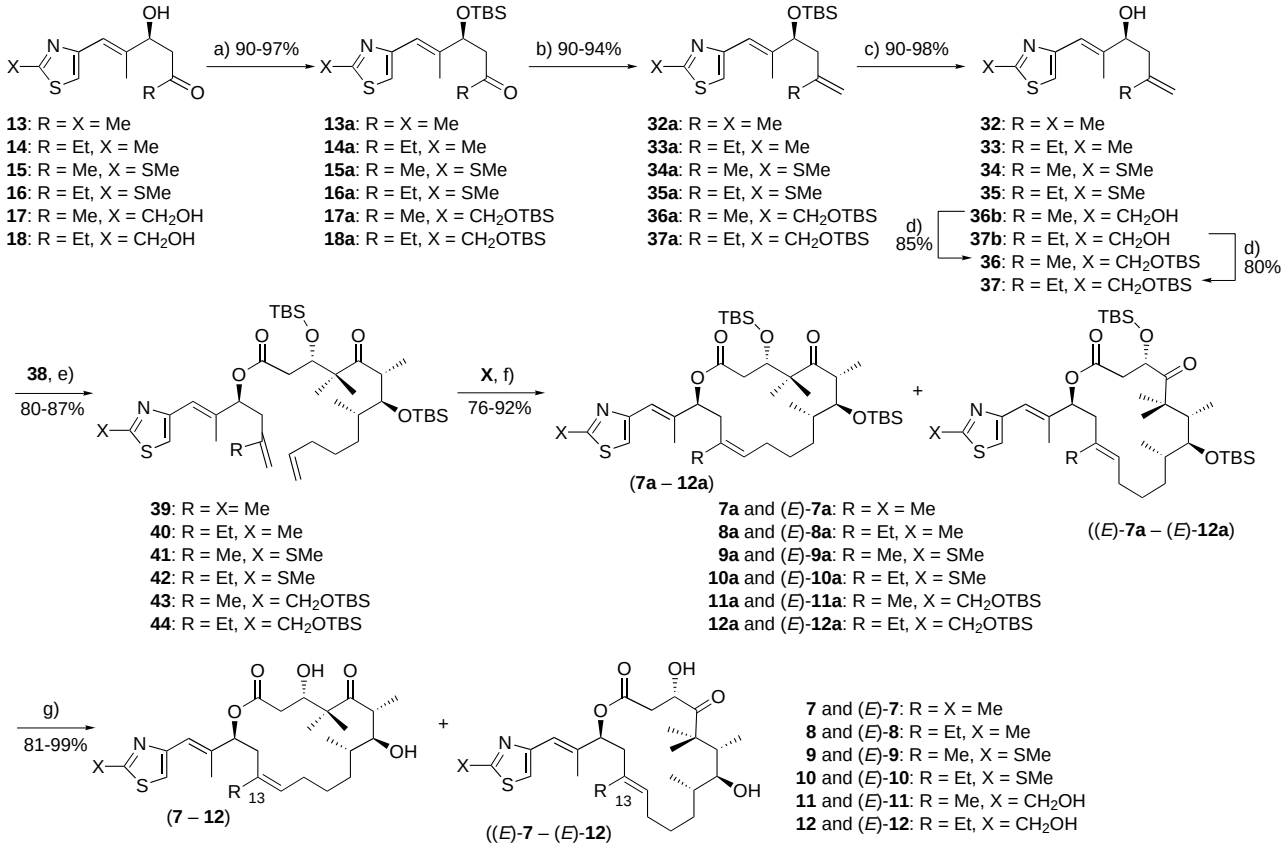
### Synthesis of 7 – 12 and (*E*)-7 – (*E*)-12 by the metathesis approach

Before we achieved the synthesis of **7** by the macrolactonization approach, we had anticipated that compounds **7** – **12** and (*E*)-**7** – **12** could also be obtained by the metathesis approach. The synthesis of **7** by the metathesis approach also began with **13** (Scheme 3). Thus, compound **13a** was synthesized from **13** and subsequently olefinated using the Wittig reaction with methylene-triphenylphosphorane to afford alkene **32a**. The alkene **32a** was then deprotected to afford allylic alcohol **32**. Compound **32** was esterified with acid **38**, affording compound **39**, which was now ready for the metathesis reaction.

Initially, we evaluated Grubbs' metathesis catalyst **VIII**[18], which has been used in the synthesis of most of the naturally occurring epothilones as well as their analogues. However, in this




case, the treatment of compound **39** with **VIII** did not result in any formation of the corresponding cyclized product, instead dimerization of **39** was observed.[19] We also tested Hoveyda's modified catalyst **IX**,[20] which gave a similar result. In the meantime, Grubbs reported a new catalyst, **X**, which possesses comparable activity with respect to Schrock's catalyst **XI**,[21] and described it as a powerful catalyst by using a wide variety of substrates.[22] Consistent with the report, we found that **X** was also a highly effective catalyst for the formation of epothilones B and F. To our delight, compound **39** also was cleanly converted, by reaction with 20% of **X** in $CH_2Cl_2$ under reflux, to the desired cyclized compounds **7a** and (*E*)-**7a** in a ratio of 3:2. The mixture




***Scheme 3.*** *Total synthesis of 13-alkylepothilones* ***7*** *–* ***12*** *and* (E)-***7*** *–* (E)-***12*** *by the metathesis approach. a) TBSCl, imidazole, DMF, RT, 6 – 24 h; b) $MePPh_3I$, nBuLi, THF, RT, 0.5 h; c) TBAF, THF, 0 °C, 1 h; d) TBSCl, $iPr_2EtN$, $CH_2Cl_2$, 0 °C → RT, 8 h; e) EDC, DMAP, $CH_2Cl_2$, 0 °C → RT, 16 h; f) $CH_2Cl_2$, reflux, 20 – 96 h; g) HF·pyridine, THF, RT, 2 – 6 h, or TFA, $CH_2Cl_2$, 0 °C, 1 – 4 h. EDC* = N′*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride.*

of cyclized olefins **7a** and (*E*)-**7a** thus obtained was deprotected by using HF in pyridine and then separated to afford **7** and (*E*)-**7** (Scheme 3).

Following the same reaction sequence, compounds **14** – **18** were first protected to afford compounds **14a** – **18a** and then olefinated to give alkenes **33a** – **37a**, respectively. No problems were encountered in the methylenation of ketones, including **15a** – **16a**, by a Wittig reaction using methylene-triphenylphosphorane. The TBS ether function in compounds **33a** – **35a** was deprotected by using TBAF to afford the required allylic alcohols **33** – **35**, respectively. Similar treatment with compounds **36a** and **37a** afforded the corresponding diols **36b** and **37b**, of which the primary hydroxy group was then selectively protected by using TBSCl and $iPr_2EtN$ to yield compounds **36** and **37**, respectively. Compounds **33** – **37** were esterified with acid **38** as before to afford esters **40** – **44** and then the latter products were metathesized by using **X** as the catalyst to afford the mixtures of **8a** – **12a** and their corresponding *trans* isomers. Interestingly, metathesis of **40**, **42**, and **44**, which possess an ethyl group instead of a methyl group as in compounds **39**, **41**, and **43**, afforded better selectivity for *Z* isomers with respect to the latter compounds, probably due to steric requirements. Final deprotection of compounds **8a** – **12a** and (*E*)-**8a** – (*E*)-**12a** gave the corresponding analogues **8** – **12** and (*E*)-**8** – **12**, respectively.

**Biological activity of the 13-alkylepothilones 7 – 10 and (*E*)-7 – (*E*)-10**

To study the biological effect of some of our analogues, tubulin polymerization studies were carried out comparing compounds **7** – **10** and (*E*)-**7** – (*E*)-**10** to epothilones A – D (**1** – **4**). Compounds **7** – **10** showed tubulin polymerization activities between 2% and 54%, with **7** being the least and **10** being the most potent compound (Table 2). While (*E*)-**7** – (*E*)-**10** displayed tubulin polymerization activities with a similar potency ranking, each *trans* analogue was more potent than its corresponding *cis* isomer (tubulin polymerization activities 19 – 78%). Under the same conditions, epothilones A (**1**) and B (**2**) caused 67 and 84% tubulin polymerization, respectively, while the corresponding deoxy analogues gave values of 50% (epothilone C (**3**)) and 93% (epothilone D (**4**)). All *trans* isomers of 13-alkylepothilones **7** – **10** also proved to be more potent than their *cis* counterparts with respect to growth inhibition of KB-31 epidermoid carcinoma cells, with $IC_{50}$ values ranging from 4 to 245 nM (Table 2). The biochemical potency ranking of the compounds was well reiterated at the cellular level. As seen in the tubulin poymerization assay, compounds **7**, **8**, and (*E*)-**7** – (*E*)-**8** were significantly less active than epothilone C (**3**), suggesting that the introduction of an alkyl group (either ethyl or methyl) at the C-13 position reduces the overall biological activity. However, compounds **9**

**Table 2.** *Biological activity of 13-alkylepothilones.*

| Compound | Tubulin polymerization [%][a] | KB-31 Cell growth inhibition ($IC_{50}$) [nM][b] |
|---|---|---|
| **7** | 2 | 245 |
| (*E*)-**7** | 19 | 61.6 |
| **8** | 11 | 150 |
| (*E*)-**8** | 33 | 78.9 |
| **9** | 39 | 24.8 |
| (*E*)-**9** | 78 | 4.03 |
| **10** | 54 | 47.9 |
| (*E*)-**10** | 64 | 17.5 |
| **1** | 67 | 2.28 |
| **2** | 84 | 0.19 |
| **3** | 50 | 24.8 |
| **4** | 93 | 2.70 |

[a] Induction of polymerization of porcine brain-derived microtubule protein by 2 μM compound (**1**–**4**, **7**–**10**, and (*E*)-**7**–(*E*)-**10**) was quantified relative to the effect of 25 μM epothilone B (**2**) (which was defined as 100%) basically as described.[25] [b] Drug concentration required for half-maximal inhibition of KB-31 human epidermoid cancer cell growth was assessed after a 72-h drug exposure by quantification of cell mass using a protein dye method.[26]

and (*E*)-**9**, bearing a methylthio group at the 2-position of the thiazole ring, displayed activities similar to those observed for epothilones C (**3**) and D (**4**) (or A (**1**)), respectively. This demonstrates that appropriate heterocycle modifications can counteract the activity loss resulting from the introduction of an alkyl group at C-13. In summary, while none of the compounds reached the cellular potency of epothilone B (**2**), these results are encouraging in view of the expectation that epoxidation of compounds **7**–**10** and (*E*)-**7**–(*E*)-**10** should further increase their cellular activities, as exemplified by epothilone C (**3**) versus A (**1**) and epothilone D (**4**) versus B (**2**) (Table 2). Similar observations have been reported for most other epothilone analogues.[2]

## Conclusions

The synthesis of epothilone analogues **7**–**12** and their *trans* isomers has been achieved starting from thiazole aldols **13**–**18**. Thiazole aldols were obtained by resolution of their racemic mixtures catalyzed by the antibody 84G3, in multigram quantities and excellent enantiomeric excess at 50% conversion. All three aldolase antibody catalysts (8463, 85H6, and 93F3) possess very high catalytic activity needed for synthetic organic chemistry. The newly reported Grubbs' catalyst **X** is extremely useful for the synthesis of substituted olefins as in 13-alkylepothilones. Preliminary biological studies suggest that compounds **9**–**10** and (*E*)-**9**–(*E*)-**10** are highly promising candidates for further studies.

## Experimental Section

**General:** $^1$H and $^{13}$C NMR spectra were measured in $CDCl_3$. Positive-ion mass spectra, using the fast ion bombardment (FIB) technique, were obtained on a VG ZAB-VSE double-focusing, high-resolution mass spectrometer equipped with either a cesium or sodium ion gun. Optical rotations were measured at 23 °C in a one-decimeter (1.3 mL) cell using an Autopol III automatic polarimeter. TLC was performed on glass sheets precoated with silica gel (Merck, Kieselgel 60, $F_{254}$, Art. 5715). Column chromatographic separations were performed on silica gel (Mallinckrodt, 230–400 mesh, #V150) under pressure. THF was dried and distilled over sodium benzophenone ketyl. All antibody reaction solutions were degassed by passing a slow stream of argon gas into the reaction mixture and carried out under an argon atmosphere.

**Large-scale resolutions of thiazole aldols 13–18**

**General method:** Antibody 84G3 (0.0004–0.005 mol%) was added to a sterilized solution of the racemic thiazole aldol (**13**–**18**) in degassed $CH_3CN$ (10–20 mL g$^{-1}$ aldol) and a degassed buffer (phosphate-buffered saline (PBS), pH 7.4, 200 mL g$^{-1}$ aldol) in a plastic bottle and the mixture was incubated at 37 °C for 3–7 days. At more than 98% consumption of the *ent* enantiomer as judged by HPLC analysis, the mixture was dialyzed by using Amicon membranes to recover the antibody. The filtrate was passed through a reverse-phase column ($C_{18}$) to elute first water and then the organic compounds using methanol as eluant. Solvents were removed under vacuum and the residue was purified by column chromotography (CC) to afford the optically pure aldol compounds **13**–**18**[25] and the corresponding aldehydes **21**–**25**.

**14:** (±)-**14** (6.43 g, 26.9 mmol) was resolved by 84G3 (65 mg, 0.000434 mmol) in 5 days to afford **14** (3.00 g, 47% yield, 99% *ee*), CC conditions: silica gel, hexanes/EtOAc (3:1). $[\alpha]_D = -33.1°$ ($c = 1.28$, $CHCl_3$); $^1$H NMR (400 MHz): $\delta = 6.89$ (s, 1H), 6.55 (s, 1H), 4.58 (d, $J =$ 8.6 Hz, 1H), 3.57 (br s, 1H), 2.70 (dd, $J = 16.7$, 9.4 Hz, 1H), 2.66 (s, 3H), 2.64 (dd, $J = 16.7$, 3.0 Hz, 1H), 2.47 (q, $J = 7.3$ Hz, 2H), 2.00 (s, 3H), 1.04 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (100.6 MHz): $\delta = 211.7$, 164.7, 152.6, 140.5, 118.6, 115.7, 72.8, 47.4, 37.0, 19.1, 14.7, 7.5; MS: *m/z*: 240 [$M + H^+$], 262 [$M + Na^+$].

**15:** (±)-**15** (3.3 g, 12.8 mmol) was resolved by 84G3 (20 mg, 0.000133 mmol) in 7 days to afford **15** (1.58 g, 48% yield, 96% *ee*), CC conditions: silica gel, hexanes/EtOAc (4:1). $[\alpha]_D = -35.2$ ($c = 2.05$, $CHCl_3$); $^1$H NMR (400 MHz): $\delta = 6.93$ (s, 1H), 6.50 (s, 1H), 4.58 (m, 1H), 3.14 (d, $J = 3.0$ Hz, 1H), 2.70 (d, $J = 6.1$ Hz, 2H), 2.67 (s, 3H), 2.20 (s, 3H), 2.06 (d, $J = 1.2$ Hz, 3H); $^{13}$C NMR (100.6 MHz): $\delta = 209.2$, 165.1, 153.3, 140.3, 118.1, 115.8, 72.8, 48.6, 30.9, 16.6, 14.8; MS: *m/z*: 258 [$M + H^+$], 280 [$M + Na^+$].

**16:** (±)-**16** (8.4 g, 30.8 mmol) was resolved by 84G3 (20 mg, 0.000133 mmol) in 10 days to afford **16** (4.1 g, 49% yield, 99% *ee*), CC conditions: silica gel, hexanes/EtOAc (4:1). $[\alpha]_D = -35.6$ ($c = 0.92$, $CHCl_3$); $^1$H NMR (400 MHz): $\delta = 6.94$ (s, 1H), 6.57 (s, 1H), 4.60 (t, $J =$ 6.2 Hz, 1H), 3.32 (br s, 1H), 2.68 (s, 3H), 2.68 (m, 2H), 2.48 (q, $J =$ 7.3 Hz, 2H), 2.07 (s, 3H), 1.07 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (100.6 MHz): $\delta = 212.0$, 165.1, 153.3, 140.4, 118.1, 115.8, 72.9, 47.3, 37.0, 16.6, 14.8, 7.5; MS: *m/z*: 272 [$M + H^+$], 294 [$M + Na^+$].

**18:** (±)-**18** (8.80 g, 34.5 mmol) was resolved by 84G3 (250 mg, 0.00167 mmol) in 5 days to afford **18** (4.2 g, 48% yield, >99% *ee*), CC conditions: silica gel, hexanes/EtOAc (1:2). $[\alpha]_D = -23.4$ ($c = 1.08$, $CHCl_3$); $^1$H NMR (500 MHz): $\delta = 6.94$(s, 1H), 6.44 (s, 1H), 5.21 (br s, 1H), 4.76 (s, 2H), 4.50 (d, $J = 9.3$ Hz, 1H), 3.32 (br, 1H), 2.64 (dd, $J = 16.3$, 6.8 Hz, 1H), 2.51 (dd, $J = 16.3$, 3.02 Hz, 1H), 2.42 (q, $J = 7.3$ Hz, 2H), 1.86 (s, 3H), 0.96 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (125.75 MHz): $\delta = 211.4$, 171.5, 152.3, 141.4, 118.2, 115.9, 72.5, 61.3, 47.3, 36.9, 14.5, 7.3; MS: *m/z*: 278 [$M + Na^+$].

**Synthesis of epothilones 7–12 and (*E*)-7–(*E*)-12 by the metathesis approach**

**General method for the protection of thiazole aldols 13–18:**[25] TBSCl (1.5 equiv; 3.0 equiv for **17** and **18**) was added to a solution of the thiazole aldol (**13**–**18**, 1.0 equiv) and imidazole (3.0 equiv;

6.0 equiv for **17** and **18**) in DMF (2 M solution). The reaction mixture was stirred at RT for 6 – 24 h and was worked up with diethyl ether and water. The organic layer was separated and the water phase was extracted with diethyl ether. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. Solvents were evaporated and the residue was purified by column chromatography to afford the pure silyl ether (**13a** – **18a**).[26]

**14a:** Protection of **14** (3.0 g, 12.6 mmol) afforded pure silyl ether **14a** (4.13 g, 93%); CC conditions: silica gel, hexanes/EtOAc (10:1). $[\alpha]_D = -44.4$ ($c = 0.98$, $CHCl_3$); MS: *m/z*: 354 $[M+H^+]$.

**15a:** Protection of **15** (1.58 g, 6.1 mmol) afforded pure silyl ether **15a** (2.16 g, 95%); CC conditions: silica gel, hexanes/EtOAc (10:1). $[\alpha]_D = -47.1$ ($c = 0.95$, $CHCl_3$); MS: *m/z*: 372 $[M+H^+]$.

**16a:** Protection of **16** (2.36 g, 8.7 mmol) afforded pure silyl ether **16a** (3.02 g, 90%); CC conditions: silica gel, hexanes/EtOAc (12:1). $[\alpha]_D = -54.0$ ($c = 1.97$, $CHCl_3$); MS: *m/z*: 408 $[M+Na^+]$.

**18a:** Protection of **18** (3.2 g, 12.5 mmol) afforded pure silyl ether **18a** (5.46 g, 90%); CC conditions: silica gel, hexanes/EtOAc (20:1). $[\alpha]_D = -32.1$ ($c = 1.21$, $CHCl_3$); MS: *m/z*: 484 $[M+H^+]$, 506 $[M+Na^+]$.

**General method for the methylenation of 13a – 18a:** *n*BuLi (1.1 equiv) was added to a heterogeneous mixture of $MePPh_3I$ (1.2 equiv) in dry THF (0.5 M solution) at 0 °C. After the mixture was stirred for 0.5 h at room temperature, a solution of ketone (**13a** – **18a**, 1.0 equiv) in THF (2 M solution) was added. The reaction mixture was stirred for an additional 0.5 h and then quenched with a saturated aqueous solution of $NH_4Cl$ and extracted with diethyl ether. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. Solvents were removed under vacuum and the resultant residue was purified by column chromatography to afford the pure methylenated product (**32a** – **37a**).[26]

**32a: 13a** (500 mg, 1.48 mmol) was used to afford **32a** (411 mg, 92% yield, based on consumed **13a**) and recovered **13a** (51 mg, 0.15 mmol), CC conditions: silica gel, hexanes/EtOAc (20:1). $[\alpha]_D = +1.0$ ($c = 0.50$, $CHCl_3$); MS: *m/z*: 338 $[M+H^+]$.

**33a: 14a** (570 mg, 1.61 mmol) was used to afford **33a** (342 mg, 93% yield, based on consumed **14a**) and recovered **14a** (200 mg, 0.57 mmol), CC conditions: silica gel, hexanes/EtOAc (20:1). $[\alpha]_D = +4.6$ ($c = 1.00$, $CHCl_3$); MS: *m/z*: 352 $[M+H^+]$.

**34a: 15a** (620 mg, 1.67 mmol) was used to afford **34a** (528 mg, 93% yield, based on consumed **15a**) and recovered **15a** (50 mg, 0.14 mmol), CC conditions: silica gel, hexanes/EtOAc (22:1). $[\alpha]_D = -9.7$ ($c = 0.90$, $CHCl_3$); MS: *m/z*: 370 $[M+H^+]$.

**35a: 16a** (250 mg, 0.65 mmol) was used to afford **35a** (120 mg, 90% yield, based on consumed **16a**) and recovered **16a** (116 mg, 0.30 mmol), CC conditions: silica gel, hexanes/EtOAc (20:1). $[\alpha]_D = +0.1$ ($c = 1.55$, $CHCl_3$); MS: *m/z*: 384 $[M+H^+]$.

**36a: 17a** (715 mg, 1.52 mmol) was used to afford **36a** (622 mg, 94% yield, based on consumed **17a**) and recovered **17a** (50 mg, 0.11 mmol), CC conditions: silica gel, hexanes/EtOAc (40:1). $[\alpha]_D = -1.3$ ($c = 1.33$, $CHCl_3$); MS: *m/z*: 468 $[M+H^+]$, 490 $[M+Na^+]$.

**37a: 18a** (547 mg, 1.13 mmol) was used to afford **37a** (311 mg, 90% yield, based on consumed **18a**) and recovered **18a** (200 mg, 0.41 mmol), CC conditions: silica gel, hexanes/EtOAc (40:1). $[\alpha]_D = +1.5$ ($c = 2.53$, $CHCl_3$); MS: *m/z*: 482 $[M+H^+]$, 504 $[M+Na^+]$.

**General method for the deprotection of compounds 32a – 37a:** TBAF (1.2 equiv, 2.4 equiv for **36a** and **37a**) was added to a solution of the TBS ether (**32a** – **37a**, 1 equiv) in dry THF (0.3 M solution) at 0 °C. After stirring for 1 h at this temperature, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and solvents were removed. The residue was purified by column chromatography to afford the pure deprotected product (**32** – **35** and **36b** – **37b**).[26]

**32: 32a** (400 mg, 1.19 mmol) was deprotected to afford **32** (260 mg, 98% yield), CC conditions: silica gel, hexanes/EtOAc (4:1). $[\alpha]_D = -28.8$ ($c = 1.87$, $CHCl_3$); MS: *m/z*: 224 $[M+H^+]$.

**33: 33a** (292 mg, 0.83 mmol) was deprotected to afford **33** (193 mg, 98% yield), CC conditions: silica gel, hexanes/EtOAc (4:1). $[\alpha]_D = -24.0$ ($c = 0.73$, $CHCl_3$); MS: *m/z*: 238 $[M+H^+]$, 260 $[M+Na^+]$.

**34: 34a** (498 mg, 1.35 mmol) was deprotected to afford **34** (320 mg, 93% yield), CC conditions: silica gel, hexanes/EtOAc (5:1). $[\alpha]_D = -44.8$ ($c = 1.23$, $CHCl_3$); MS: *m/z*: 256 $[M+H^+]$.

**35: 35a** (120 mg, 0.31 mmol) was deprotected to afford **35** (81 mg, 96% yield), CC conditions: silica gel, hexanes/EtOAc (5:1). $[\alpha]_D = -30.5$ ($c = 1.13$, $CHCl_3$); MS: *m/z*: 270 $[M+H^+]$.

**36b: 36a** (492 mg, 1.05 mmol) was deprotected to afford **36b** (242 mg, 96% yield), CC conditions: silica gel, hexanes/EtOAc (1:2). $[\alpha]_D = -35.0$ ($c = 0.48$, $CHCl_3$); MS: *m/z*: 240 $[M+H^+]$, 262 $[M+Na^+]$.

**37b: 37a** (180 mg, 0.37 mmol) was deprotected to afford **37b** (85 mg, 90% yield), CC conditions: silica gel, hexanes/EtOAc (1:2). $[\alpha]_D = -23.3$ ($c = 1.33$, $CHCl_3$); MS: *m/z*: 254 $[M+H^+]$, 276 $[M+Na^+]$.

**Selective protection of compounds 36b and 37b**

**36:** TBSCl (140 mg, 0.93 mmol) was added to a solution of **36b** (180 mg, 0.75 mmol) and *i*$Pr_2$NEt (0.26 mL, 1.50 mmol) in dry $CH_2Cl_2$ (5 mL) at 0 °C and the mixture was stirred at 0 °C to room temperature for 8 h. The reaction mixture was worked up with water and $CH_2Cl_2$. The combined organic layer was washed with water and dried over anhydrous $MgSO_4$. Solvents were evaporated and the residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3:1) to afford **36b**[26] (226 mg, 85%). $[\alpha]_D = -26.3$ ($c = 1.54$, $CHCl_3$); MS: *m/z*: 354 $[M+H^+]$.

**37:** In a similar manner as described above, **37b** (80 mg, 0.32 mmol) was allowed to react with TBSCl (60 mg, 0.38 mmol) and *i*$Pr_2$NEt (0.11 mL, 0.64 mmol) in dry $CH_2Cl_2$ (3 mL) at 0 °C to afford **37**[26] (93 mg, 80%), CC conditions: silica gel, hexanes/EtOAc (3:1). $[\alpha]_D = -23.2$ ($c = 0.50$, $CHCl_3$); MS: *m/z*: 390 $[M+Na^+]$.

**General method for the esterification of acid 38 with alcohols 32 – 37:** EDC (3.0 equiv) and DMAP (0.1 equiv) were added to a solution of acid **38** (1.2 equiv) and the thiazole alcohol (**32** – **37**, 1.0 equiv) in dry $CH_2Cl_2$ (0.2 M solution) at 0 °C. After the reaction mixture was stirred for 16 h at 0 °C to room temperature, the solvent was evaporated under vacuum and the residue was purified by column chromatography to afford the corresponding pure ester (**39** – **44**).[26]

**39: 32** (35 mg, 0.16 mmol) was used to afford **39** (97 mg, 82% yield), CC conditions: silica gel, hexanes/EtOAc (10:1). $[\alpha]_D = -34.7$ ($c = 1.95$, $CHCl_3$); MS: *m/z*: 770 $[M+Na^+]$.

**40: 33** (43 mg, 0.18 mmol) was used to yield **40** (120 mg, 86% yield), CC conditions: silica gel, hexanes/EtOAc (10:1). $[\alpha]_D = -43.0$ ($c = 1.43$, $CHCl_3$); MS: *m/z*: 784 $[M+Na^+]$.

**41: 34** (46 mg, 0.18 mmol) was used to afford **41** (122 mg, 87% yield), CC conditions: silica gel, hexanes/EtOAc (12:1). $[\alpha]_D = -44.4$ ($c = 1.62$, $CHCl_3$); MS: *m/z*: 802 $[M+Na^+]$.

**42**: **35** (81 mg, 0.3 mmol) was used to afford **42** (204 mg, 85% yield), CC conditions: silica gel, hexanes/EtOAc (12:1). $[\alpha]_D = -39.2$ ($c = 1.10$, $CHCl_3$); MS: *m/z*: 794 $[M+H^+]$, 828 $[M+Cl^-]$.

**43**: **36** (65 mg, 0.18 mmol) was used to afford **43** (132 mg, 82% yield), CC conditions: silica gel, hexanes/EtOAc (15:1). $[\alpha]_D = -38.2$ ($c = 1.03$, $CHCl_3$); MS: *m/z*: 878 $[M+H^+]$.

**44**: **37** (46 mg, 0.13 mmol) was used to afford **44** (90 mg, 80% yield), CC conditions: silica gel, hexanes/EtOAc (15:1). $[\alpha]_D = -35.4$ ($c =$ 1.00, $CHCl_3$); MS: *m/z*: 892 $[M+H^+]$.

**General method for the metathesis of dienes 39–44:** Grubbs' catalyst **X** (0.2 equiv) was added to a solution of the diene (**39**–**44**, 1.0 equiv) in dry $CH_2Cl_2$ (0.002 M solution) and the solution was stirred under reflux for 20–96 h. After the reaction was completed, as judged by $^1$H NMR spectroscopic analysis, solvents were removed under vacuum and the residue was purified by column chromatography to afford a mixture of the metathesized products (**7a**–**12a** and (*E*)-**7a**–(*E*)-**12a**), which was used in the next step without separation.

**7a and (*E*)-7a:** Diene **39** (94 mg, 0.13 mmol) was metathesized to afford a mixture of **7a** and (*E*)-**7a** (ca 1.2:1, 70 mg, 77%); CC conditions: silica gel, hexanes/EtOAc (12:1). MS: *m/z*: 720 $[M+H^+]$.

**8a and (*E*)-8a:** Diene **40** (116 mg, 0.15 mmol) was metathesized to afford a mixture of **8a** and (*E*)-**8a** (ca. 2.8:1, 85 mg, 76%); CC conditions: silica gel, hexanes/EtOAc (12:1). MS: *m/z*: 734 $[M+H^+]$.

**9a and (*E*)-9a:** Diene **41** (104 mg, 0.13 mmol) was metathesized to afford a mixture of **9a** and (*E*)-**9a** (ca. 1.5:1, 80 mg, 80%); CC conditions: silica gel, hexanes/EtOAc (14:1). MS: *m/z*: 752 $[M+H^+]$.

**10a and (*E*)-10a:** Diene **42** (110 mg, 0.14 mmol) was metathesized to afford a mixture of **10a** and (*E*)-**10a** (ca. 2.4:1, 90 mg, 85%); CC conditions: silica gel, hexanes/EtOAc (14:1). MS: *m/z*: 766 $[M+H^+]$.

**11a and (*E*)-11a:** Diene **43** (125 mg, 0.14 mmol) was metathesized to afford a mixture of **11a** and (*E*)-**11a** (ca. 1.5:1, 111 mg, 92%); CC conditions: silica gel, hexanes/EtOAc (20:1). MS: *m/z*: 850 $[M+H^+]$.

**12a and (*E*)-12a:** Diene **44** (90 mg, 0.1 mmol) was metathesized to afford a mixture of **12a** and (*E*)-**12a** (ca. 2.3:1, 73 mg, 85%); CC conditions: silica gel, hexanes/EtOAc (20:1). MS: *m/z*: 864 $[M+H^+]$.

**Deprotection of compounds 7a and (*E*)-7a–12a and (*E*)-12a**

**General method A:** Trifluoroacetic acid (TFA; 4 equiv) was added dropwise to a solution of the cyclized compound in dry $CH_2Cl_2$ (0.1 M solution) at 0 °C and the mixture was stirred at the same temperature for 1–4 h and then concentrated under vacuum. The residue was dissolved in EtOAc, washed with brine and dried over anhydrous $MgSO_4$. Solvents were evaporated and the resulting residue was purified by preparative TLC (PTLC) to afford the pure epothilone analogue.

**General method B:** HF·pyridine (0.5 mL) was added to a solution of the cyclized compound in dry THF (0.05 M solution) at room temperature. The solution was stirred at the same temperature for 2–6 h. Completion of the reaction was judged by TLC. The reaction mixture was slowly poured into a cold aqueous solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. Solvents were evaporated under reduced pressure. The residue was purified by PTLC to yield the pure epothilone analogue.

**Epothilones MM (7) and (*E*)-7:** The mixture of **7a** and (*E*)-**7a** (1.2:1, 70 mg, 0.097 mmol) was deprotected by method B to afford pure **7** (26 mg, 54%) and (*E*)-**7** (21 mg, 45%); PTLC conditions: silica gel, hexanes/EtOAC (2:1).

**7:** $[\alpha]_D = -71.6$ ($c = 0.50$, $CHCl_3$); $^1$H NMR (600 MHz): $\delta = 6.95$ (s, 1H), 6.60 (s, 1H), 5.38 (d, $J = 11.1$ Hz, 1H), 5.20 (d, $J = 7.0$ Hz, 1H), 4.17 (d, $J = 10.9$ Hz, 1H), 3.76 (br s, 1H), 3.47 (m, 1H), 3.11 (m, 1H), 2.96 (br s, 1H), 2.89 (dd, $J = 14.3$, 11.5 Hz, 1H), 2.68 (s, 3H), 2.48 (dd, $J = 15.0$, 11.4 Hz, 1H), 2.37 (dd, $J = 15.0$, 2.3 Hz, 1H), 2.17 (m, 1H), 2.08 (s, 3H), 1.97–1.86 (m, 4H), 1.74 (m, 1H), 1.72 (s, 3H), 1.57 (m, 1H), 1.35–1.20 (m, 3H), 1.33 (s, 3H), 1.17 (d, $J = 6.9$ Hz, 3H), 1.09 (s, 3H), 0.99 (d, $J =$ 7.1 Hz, 3H); $^{13}$C NMR (150.9 MHz): $\delta = 220.3$, 170.6, 165.0, 152.0, 139.4, 129.9, 129.3, 119.3, 115.8, 76.7, 73.7, 72.5, 53.3, 42.0, 39.1, 38.1, 36.3, 32.5, 28.6, 28.1, 23.0, 22.8, 19.08, 19.04, 16.2, 15.7, 14.2, 13.5; HR-MS: calcd for $C_{27}H_{42}NO_5S$: 492.2784, found: 492.2760 $[M+H^+]$; calcd for $C_{27}H_{41}NO_5SNa$: 514.2603, found: 514.2589 $[M+Na^+]$.

**(*E*)-7:** $[\alpha]_D = -30.2$ ($c = 0.5$, $CHCl_3$); $^1$H NMR (600 MHz): $\delta = 6.96$ (s, 1H), 6.56 (s, 1H), 5.49 (dd, $J = 10.8$, 1.1 Hz, 1H), 5.29 (m, 1H), 4.01 (dt, $J = 10.7$, 2.5 Hz, 1H), 3.75 (br s, 1H), 3.19 (quintet, $J = 6.1$ Hz, 1H), 3.13 (d, $J = 3.2$ Hz, 1H), 2.69 (s, 3H), 2.53 (dd, $J = 14.9$, 10.7 Hz, 1H), 2.45 (dd, $J = 14.7$, 2.4 Hz, 1H), 2.44 (t, $J = 11.0$ Hz, 1H), 2.32 (m, 2H), 2.20 (m, 1H), 2.08 (d, $J = 0.9$ Hz, 3H), 1.87 (m, 1H), 1.82 (br s, 1H), 1.63 (m, 1H), 1.62 (s, 3H), 1.55 (m, 1H), 1.47 (m, 1H), 1.28 (s, 3H), 1.22 (m, 1H), 1.17 (d, $J = 6.8$ Hz, 3H), 1.10 (m, 1H), 1.05 (s, 3H), 0.96 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (150.9 MHz): $\delta = 219.7$, 170.6, 164.9, 152.2, 137.7, 131.4, 128.8, 119.9, 116.3, 76.6, 76.3, 73.2, 52.1, 44.3, 44.1, 38.4, 36.4, 28.4, 26.9, 22.0, 20.1, 19.2, 16.6, 15.8, 15.3, 13.9; HR-MS: calcd for $C_{27}H_{42}NO_5S$: 492.2784, found: 492.2798 $[M+H^+]$; calcd for $C_{27}H_{41}NO_5SNa$: 514.2603, found: 514.2640 $[M+Na^+]$.

**Epothilones ME (8) and (*E*)-8:** The 2.8:1 mixture (70 mg, 0.096 mmol) of **8a** and (*E*)-**8a** was deprotected by method A to afford pure compounds **8** (29 mg, 60%) and (*E*)-**8** (11 mg, 21%); PTLC conditions: silica gel, hexanes/EtOAc (2:1).

**8:** $[\alpha]_D = -69.5$ ($c = 0.23$, $CHCl_3$); $^1$H NMR (600 MHz): $\delta = 6.95$ (s, 1H), 6.59 (s, 1H), 5.33 (d, $J = 10.5$ Hz, 1H), 5.20 (d, $J = 7.0$ Hz, 1H), 4.15 (d, $J = 10.9$ Hz, 1H), 3.77 (s, 1H), 3.39 (d, $J = 4.9$ Hz, 1H), 3.11 (qd, $J = 7.0$, 2.6 Hz, 1H), 2.90 (br s, 1H), 2.84 (dd, $J = 14.5$, 11.0 Hz, 1H), 2.69 (s, 3H), 2.47 (dd, $J = 14.9$, 11.0 Hz, 1H), 2.38 (dd, $J = 15.4$, 2.6 Hz, 1H), 2.21 (m, 1H), 2.08 (s, 3H), 2.03 (m, 3H), 1.93 (m, 1H), 1.75 (m, 1H), 1.73 (s, 3H), 1.59 (m, 1H), 1.39–1.24 (m, 3H), 1.33 (s, 3H), 1.17 (d, $J = 6.6$ Hz, 3H), 1.10 (s, 3H), 1.00 (d, $J = 7.4$ Hz, 3H), 0.99 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (150.9 MHz): $\delta = 220.1$, 170.7, 165.0, 152.0, 139.4, 135.4, 127.5, 119.4, 115.8, 76.5, 73.7, 72.7, 53.2, 42.2, 39.1, 37.9, 34.4, 32.5, 28.9, 28.6, 28.3, 22.7, 19.5, 19.1, 16.4, 15.6, 13.6, 12.8; HR-MS: calcd for $C_{28}H_{43}NO_5SNa$: 528.2754, found: 528.2735 $[M+Na^+]$.

**(*E*)-8:** $[\alpha]_D = -22.0$ ($c = 0.10$, $CHCl_3$); $^1$H NMR (600 MHz): $\delta = 6.96$ (s, 1H), 6.56 (s, 1H), 5.46 (d, $J = 11.0$ Hz, 1H), 5.25 (t, $J = 7.0$ Hz, 1H), 4.01 (d, $J = 10.6$ Hz, 1H), 3.76 (m, 1H), 3.21 (quintet, $J = 6.6$ Hz, 1H), 3.10 (d, $J = 2.6$ Hz, 1H), 2.70 (s, 3H), 2.54 (dd, $J = 15.4$, 11.0 Hz, 1H), 2.45 (m, 2H), 2.36 (dd, $J = 14.9$, 11.0 Hz, 1H), 2.19 (m, 1H), 2.13 (m, 1H), 1.96 (m, 1H), 1.89 (m, 1H), 1.66 (m, 1H), 1.60 (s, 3H), 1.57 (m, 1H), 1.49 (m, 1H), 1.29 (s, 3H), 1.28–1.20 (m, 2H), 1.18 (d, $J = 6.5$ Hz, 3H), 1.06 (s, 3H), 0.96 (d, $J = 7.0$ Hz, 3H), 0.94 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (150.9 MHz): $\delta = 219.7$, 170.6, 164.9, 152.2, 137.7, 137.2, 128.3, 119.9, 116.3, 76.8, 76.2, 73.1, 52.1, 44.2, 40.9, 38.4, 36.6, 29.7, 29.4, 27.2, 26.6, 22.7, 21.9, 20.0, 19.2, 16.6, 15.3, 12.9; HR-MS: calcd for $C_{28}H_{44}NO_5S$: 506.2935, found: 506.2926 $[M+H^+]$.

**Epothilones SM (9) and (*E*)-9:** The 1.5:1 mixture (77 mg, 0.10 mmol) of **9a** and (*E*)-**9a** was deprotected by method A to give pure compounds **9** (27 mg, 50%) and (*E*)-**9** (18 mg, 34%); PTLC conditions: silica gel, hexanes/EtOAc (2:1).

**9:** $[\alpha]_D = -80.6$ ($c = 0.50$, $CHCl_3$); $^1$H NMR (500 MHz): $\delta = 6.98$ (s, 1H), 6.52 (s, 1H), 5.39 (d, $J = 10.3$ Hz, 1H), 5.21 (d, $J = 8.5$ Hz, 1H), 4.11 (m, 1H), 3.77 (br s, 1H), 3.11 (qd, $J = 6.6$, 3.0 Hz, 1H), 2.95 (d, $J = 5.5$ Hz, 1H), 2.91 (dd, $J = 14.7$, 11.4, 1H), 2.86 (br s, 1H), 2.69 (s, 3H), 2.49 (dd, $J = 15.4$, 11.0 Hz, 1H), 2.40 (dd, $J = 15.4$, 3.0 Hz, 1H), 2.21–2.16 (m, 1H), 2.13 (d, $J = 1.5$ Hz, 3H), 1.95 (br s, 1H), 1.92 (br s, 1H), 1.78–1.74 (m, 1H), 1.72 (s, 3H), 1.62–1.55 (m, 1H), 1.39–1.24 (m, 3H), 1.32 (s, 3H), 1.17 (d, $J = 7.0$ Hz, 3H), 1.10 (s, 3H), 1.00 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (150.9 MHz): $\delta = 220.1$, 170.6, 165.7, 152.7, 139.3, 129.9, 129.4, 119.1, 115.9, 77.1, 73.7, 72.8, 53.1, 42.2, 39.1, 38.1, 36.2, 32.5, 28.7,

28.2, 23.1, 22.7, 19.6, 16.7, 16.2, 15.4, 13.6; HR-MS: calcd for $C_{27}H_{42}NO_5S_2$: 524.2499, found: 524.2522 [$M+H^+$].

**(*E*)-9:** $[\alpha]_D = -33.3$ ($c = 0.12$, $CHCl_3$); $^1$H NMR (500 MHz): $\delta = 6.98$ (s, 1H), 6.49 (s, 1H), 5.50 (d, $J = 9.6$ Hz, 1H), 5.31 (m, 1H), 4.00 (d, $J = 10.7$ Hz, 1H), 3.76 (m, 1H), 3.20 (quintet, $J = 6.3$ Hz, 1H), 3.02 (m, 1H), 2.69 (s, 3H), 2.56 – 2.40 (m, 3H), 2.18 (m, 1H), 2.14 (s, 3H), 1.98 – 1.84 (m, 2H), 1.66 (m, 1H), 1.64 (s, 3H), 1.48 (m, 1H), 1.33 (s, 3H), 1.24 (m, 3H), 1.17 (d, $J = 7.0$ Hz, 3H), 1.06 (s, 3H), 0.97 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (150.9 MHz): $\delta = 219.6$, 170.6, 165.4, 152.8, 137.9, 131.5, 128.8, 119.6, 116.3, 76.9, 76.3, 73.4, 52.0, 44.3, 44.2, 38.3, 36.4, 30.9, 29.2, 27.0, 26.9, 22.1, 19.9, 16.6, 15.8, 15.3, 15.1; HR-MS: calcd for $C_{27}H_{42}NO_5S_2$: 524.2499, found: 524.2515 [$M+H^+$].

**Epothilones SE (10) and (*E*)-10:** The 2.4:1 mixture (60 mg, 0.078 mmol) of **10a** and (*E*)-**10a** was deprotected by method A to yield pure compounds **10** (25 mg, 59%) and (*E*)-**10** (10 mg, 24%); PTLC conditions: silica gel, hexanes/EtOAc (3:1).

**10:** $[\alpha]_D = -64.9$ ($c = 1.46$, $CHCl_3$); $^1$H NMR (500 MHz): $\delta = 6.98$ (s, 1H), 6.51 (s, 1H), 5.34 (d, $J = 10.3$ Hz, 1H), 5.20 (dd, $J = 10.7$, 3.0 Hz, 1H), 4.10 (m, 1H), 3.78 (m, 1H), 3.11 (qd, $J = 7.0$, 3.3 Hz, 1H), 2.86 (m, 2H), 2.79 (br s, 1H), 2.69 (s, 3H), 2.48 (dd, $J = 15.4$, 11.0 Hz, 1H), 2.42 (dd, $J = 15.4$, 3.0 Hz, 1H), 2.21 (m, 1H), 2.14 (s, 3H), 2.04 (m, 3H), 1.93 (m, 1H), 1.74 (m, 1H), 1.38 – 1.25 (m, 3H), 1.33 (s, 3H), 1.18 (d, $J = 6.6$ Hz, 3H), 1.11 (s, 3H), 1.00 (d, $J = 7.0$ Hz, 3H), 0.99 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (150.9 MHz): $\delta = 219.9$, 170.6, 165.6, 152.7, 139.3, 135.3, 127.5, 119.0, 115.9, 77.5, 73.8, 72.9, 52.9, 42.4, 39.0, 37.9, 34.3, 32.4, 28.9, 28.6, 28.3, 22.7, 19.9, 16.6, 16.4, 15.3, 13.7, 12.8; HR-MS: calcd for $C_{28}H_{44}NO_5S_2$: 538.2655, found: 538.2646 [$M+H^+$].

**(*E*)-10:** $[\alpha]_D = -8.6$ ($c = 0.40$, $CHCl_3$); $^1$H NMR (600 MHz): $\delta = 6.98$ (s, 1H), 6.49 (s, 1H), 5.46 (d, $J = 10.5$ Hz, 1H), 5.26 (t, $J = 7.0$ Hz, 1H), 3.99 (d, $J = 10.5$ Hz, 1H), 3.75 (m, 1H), 3.20 (quintet, $J = 6.6$ Hz, 1H), 3.04 (d, $J = 2.6$ Hz, 1H), 2.70 (s, 3H), 2.53 (dd, $J = 14.9$, 7.5 Hz, 1H), 2.46 (dd, $J = 15.4$, 2.3 Hz, 1H), 2.42 (br s, 1H), 2.37 (dd, $J = 14.8$, 10.9 Hz, 1H), 2.21 (m, 1H), 2.14 (d, $J = 0.8$ Hz, 3H), 2.12 (m, 2H), 1.95 (dd, $J = 14.0$, 7.4 Hz, 1H), 1.89 (m, 1H), 1.65 (m, 1H), 1.52 – 1.45 (m, 1H), 1.29 (s, 3H), 1.27 – 1.21 (m, 3H), 1.18 (d, $J = 7.0$ Hz, 3H), 1.06 (s, 3H), 0.96 (d, $J = 7.0$ Hz, 3H), 0.95 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (150.9 MHz): $\delta = 219.7$, 170.6, 165.4, 152.8, 137.9, 137.2, 128.2, 119.5, 116.4, 77.1, 76.1, 73.2, 52.0, 44.1, 40.9, 38.4, 36.5, 29.4, 27.2, 26.5, 22.6, 22.0, 19.9, 16.61, 16.56, 15.2, 15.1, 12.9; HR-MS: calcd for $C_{28}H_{44}NO_5S_2$: 538.2655, found: 538.2651 [$M+H^+$].

**Epothilones HM (11) and (*E*)-11:** The 1.5:1 mixture (100 mg, 0.12 mmol) of **11a** and (*E*)-**11a** was deprotected by method B to give pure compounds **11** (32 mg, 55%) and (*E*)-**11** (22 mg, 36%); PTLC conditions: silica gel, hexanes/EtOAc (1:2).

**11:** $[\alpha]_D = -70.0$ ($c = 0.29$, $CHCl_3$); $^1$H NMR (600 MHz): $\delta = 7.10$ (s, 1H), 6.60 (s, 1H), 5.39 (d, $J = 10.7$ Hz, 1H), 5.21 (d, $J = 9.0$ Hz, 1H), 4.91 (s, 2H), 4.16 (d, $J = 9.8$ Hz, 1H), 3.75 (m, 1H), 3.37 (br s, 1H), 3.11 (qd, $J = 6.9$, 2.7 Hz, 1H), 2.93 (br s, 1H), 2.89 (dd, $J = 14.6$, 11.3 Hz, 1H), 2.62 (s, 1H), 2.48 (dd, $J = 15.3$, 11.4 Hz, 1H), 2.37 (dd, $J = 15.1$, 2.6 Hz, 1H), 2.16 (d, $J = 3.1$ Hz, 3H), 1.94 (m, 2H), 1.77 – 1.73 (m, 1H), 1.72 (s, 3H), 1.58 (m, 1H), 1.34 (s, 3H), 1.24 (br s, 4H), 1.17 (d, $J = 6.9$ Hz, 3H), 1.09 (s, 3H), 0.97 (d, $J =$ Hz, 3H); $^{13}$C NMR (150.9 MHz): $\delta = 220.2$, 170.5, 170.0, 152.3, 139.7, 129.9, 129.4, 118.9, 116.5, 73.7, 72.5, 69.5, 61.9, 53.7, 53.2, 42.0, 39.1, 38.0, 36.2, 32.5, 29.7, 29.2, 28.6, 28.1, 23.0, 22.8, 19.1, 16.2, 15.7, 13.6; HR-MS: calcd for $C_{27}H_{41}NO_6SNa$: 530.2547, found: 530.2544 [$M+Na^+$].

**(*E*)-11:** $[\alpha]_D = -36.6$ ($c = 0.24$, $CHCl_3$); $^1$H NMR (600 MHz): $\delta = 7.11$ (s, 1H), 6.59 (s, 1H), 5.49 (d, $J = 10.5$ Hz, 1H), 5.29 (t, $J = 6.8$ Hz, 1H), 4.92 (s, 2H), 4.06 (d, $J = 10.6$ Hz, 1H), 3.78 (br s, 1H), 3.75 (m, 1H), 3.20 (quintet, $J = 6.6$ Hz, 1H), 3.08 (br s, 1H), 2.62 (s, 1H), 2.54 (dd, $J = 15.0$, 10.7 Hz, 1H), 2.47 (m, 2H), 2.35 (m, 2H), 2.20 (m, 1H), 2.16 (s, 3H), 1.89 (m, 1H), 1.62 (s, 3H), 1.60 – 1.44 (m, 2H), 1.28 (s, 3H), 1.24 (br s, 4H), 1.18 (d, $J = 6.8$ Hz, 3H), 1.05 (s, 3H), 0.97 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (150.9 MHz): $\delta = 219.6$, 170.6, 169.8, 152.5, 138.2, 131.3, 129.0, 119.6, 116.7, 76.5, 73.1, 69.5, 62.1, 53.7, 52.1, 44.4, 43.9, 38.5, 36.4, 31.7, 29.2, 27.1, 21.8, 20.3, 16.7, 16.0, 15.5, 15.4; HR-MS: calcd for $C_{27}H_{42}NO_6S$: 508.2727, found: 508.2730 [$M+H^+$].

**Epothilones HE (12) and (*E*)-12:** The 2.3:1 mixture (70 mg, 0.08 mmol) of **12a** and (*E*)-**12a** was deprotected by method B to afford pure compound **12** (26 mg, 63%) and (*E*)-**12** (12 mg, 27%); PTLC conditions: silica gel, hexanes/EtOAc (1:2).

**12:** $[\alpha]_D = -46.1$ ($c = 0.30$, $CHCl_3$); $^1$H NMR (600 MHz): $\delta = 7.10$ (s, 1H), 6.60 (s, 1H), 5.35 (d, $J = 10.9$ Hz, 1H), 5.20 (d, $J = 7.4$ Hz, 1H), 4.91 (s, 2H), 4.13 (d, $J = 10.9$ Hz, 1H), 3.77 (t, $J = 3.3$ Hz, 1H), 3.28 (br m, 1H), 3.11 (qd, $J = 6.8$, 3.0 Hz, 1H), 2.85 (dd, $J = 14.5$, 11.2 Hz, 1H), 2.62 (s, 3H), 2.48 (dd, $J = 15.2$, 11.2 Hz, 1H), 2.39 (dd, $J = 15.3$, 2.7 Hz, 1H), 2.20 (m, 1H), 2.09 (s, 3H), 2.07 – 2.00 (m, 3H), 1.94 (m, 1H), 1.75 (m, 1H), 1.58 (m, 1H), 1.35 (s, 3H), 1.30 – 1.22 (m, 3H), 1.17 (d, $J = 6.8$ Hz, 3H), 1.09 (s, 3H), 1.00 (d, $J = 7.2$ Hz, 3H), 0.99 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (150.9 MHz): $\delta = 220.1$, 170.6, 169.9, 152.4, 139.7, 135.3, 127.6, 119.0, 116.6, 73.8, 72.7, 62.0, 53.7, 53.1, 42.3, 39.1, 37.9, 34.3, 32.4, 29.7, 29.2, 28.9, 28.6, 28.3, 22.7, 19.5, 16.4, 15.6, 13.7, 12.8; HR-MS: calcd for $C_{28}H_{44}NO_6S$: 522.2884, found: 522.2889 [$M+H^+$].

**(*E*)-12:** $[\alpha]_D = -18.1$ ($c = 0.16$, $CHCl_3$); $^1$H NMR (600 MHz): $\delta = 7.11$ (s, 1H), 6.58 (s, 1H), 5.45 (d, $J = 10.2$ Hz, 1H), 5.24 (t, $J = 6.6$ Hz, 1H), 4.93 (s, 2H), 4.05 (d, $J = 10.4$ Hz, 1H), 3.77 (s, 1H), 3.75 (d, $J = 4.8$ Hz, 1H), 3.20 (quintet, $J = 6.9$ Hz, 1H), 3.05 (br s, 1H), 2.60 (br s, 1H), 2.54 (dd, $J = 15.0$, 10.6 Hz, 1H), 2.46 (m, 2H), 2.37 (dd, $J = 14.4$, 10.5 Hz, 1H), 2.25 – 2.18 (m, 1H), 2.10 (s, 3H), 2.10 – 2.04 (m, 1H), 1.97 (m, 1H), 1.90 (m, 1H), 1.50 (m, 1H), 1.28 (s, 3H), 1.28 – 1.20 (m, 4H), 1.18 (d, $J = 6.7$ Hz, 3H), 1.05 (s, 3H), 0.98 (d, $J = 7.0$ Hz, 3H), 0.95 (t, $J = 6.5$ Hz, 3H); $^{13}$C NMR (150.9 MHz): $\delta = 219.6$, 170.6, 169.6, 152.5, 138.2, 137.0, 128.5, 119.6, 116.8, 76.4, 73.0, 62.1, 53.7, 52.1, 44.3, 40.7, 38.5, 36.6, 31.7, 29.2, 27.2, 26.6, 22.8, 21.8, 20.3, 16.7, 15.40, 15.36, 12.9; HR-MS: calcd for $C_{28}H_{44}NO_6S$: 522.2884, found: 522.2888 [$M+H^+$].

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[26] For $^{1}H$ and $^{13}C$ NMR spectral data of these compounds, see the Supporting Information.

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