Pergamon

Tetrahedron Letters 42 (2001) 8373–8377

TETRAHEDRON LETTERS

Total syntheses of epothilones B and D: applications of allylstannanes in organic synthesis

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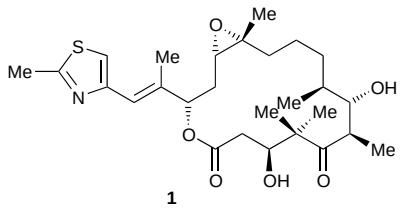
Received 15 June 2001; revised 1 September 2001; accepted 10 September 2001

Abstract—Following exploratory studies which culminated in syntheses of the alcohol **16**, a total synthesis of epothilones B and D is reported in which the trisubstituted 12,13-double-bond is introduced stereoselectively using the tin(IV) bromide-promoted reaction between the allylstannane **22** and the aldehyde **17**. A Barton deoxygenation then gave the C(7)–C(15) fragment **25**. After development of the thiazole containing side-chain, an aldol condensation with the ethyl ketone **36** gave the adduct **37** which was taken through to epothilone D **2** and then to epothilone B **1**.

The epothilones,[1] e.g. epothilones B **1** and D **2**, are of considerable interest at present because of their potent cytotoxic activity with modes of action closely related to that of taxol.[2] Several total syntheses of epothilones have been reported together with extensive studies of the synthesis of analogues for biological evaluation.[3] One well established strategy for epothilone synthesis involves an aldol condensation between an aldehyde **3** and an ethyl ketone, e.g. **4**, to form the C(6)–C(7) bond, followed by functional group manipulation and macrocyclisation.[4]



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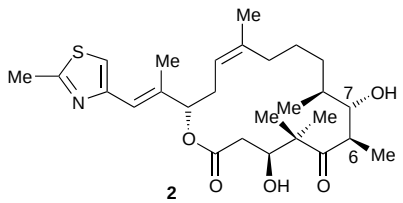

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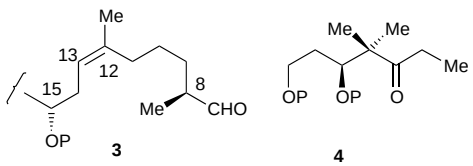

3 **4**

(P = protecting groups)

The aldehydes **3** contain two stereogenic centres and a trisubstituted double-bond. We now report two allylstannane[5] based approaches to this fragment evaluated by syntheses of the model alcohol **16**. In one sequence, the tin chemistry was coupled with an Ireland–Claisen rearrangement[6] so that the stereogenic centre at C(15) has controlled the introduction of that at C(8) providing an example of 1,8-stereocontrol, a strategy rarely used in the synthesis of aliphatic compounds.[7] In the second, more convergent, synthesis of **16** the allyltin chemistry was used to introduce the trisubstituted double-bond with excellent stereoselectivity. This second synthesis of **16** was then modified by the use of a differently protected stannane **22** to prepare the triol derivative **25** which was incorporated into a total synthesis of epothilones B and D.

The allylstannane **9** required for the model work was prepared as outlined in Scheme 1. Alkylation of 2-methylpropenyl phenyl sulfone[8] using the iodide **5**[9] gave the alkylated sulfone **6** as a mixture of diastereoisomers. These were not separated, but were hydrolysed to give the diol **7** which was monosilylated and the silyl ether converted into the 5-hydroxyhex-2-enylstannane **9** as a 50:50 mixture of (*E*)- and (*Z*)-isomers using tributyltin hydride.[10]

The first synthesis of the alcohol **16** is outlined in Scheme 2. Transmetallation of the stannane **9** using tin(IV) bromide generated an allyltin tribromide which reacted with (*E*)-crotonaldehyde with modest 1,6-stereocontrol[11] to give a mixture of the diol **10** and its epimer at C(7), ratio 80:20, in favour of the required isomer **10**. It may be that formation of the minor isomer is due to competing co-ordination of the *tert*-

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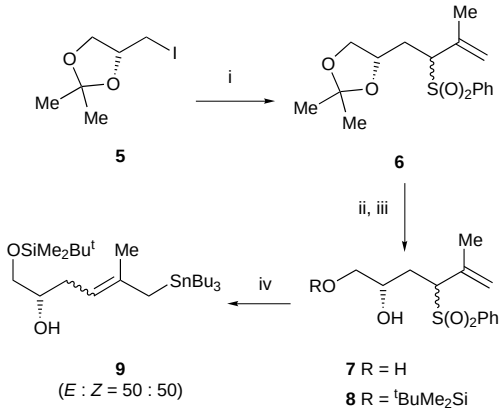


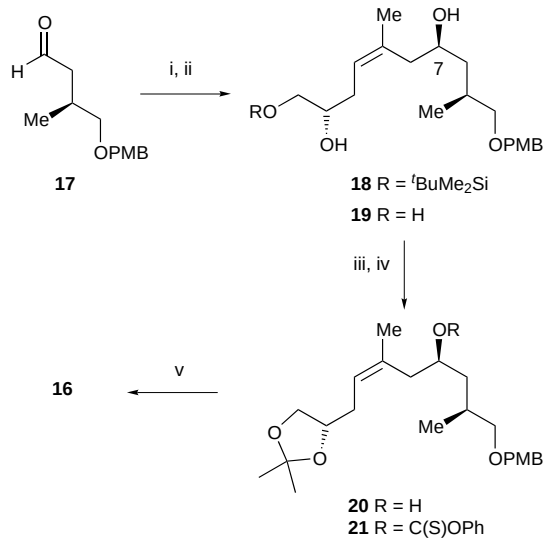
Scheme 1. *Reagents and conditions*: i, DMPU, ^{n}BuLi, $PhS(O)_2CH_2C(CH_3)=CH_2$ (86%); ii, Amberlyst 15; iii, $^{t}BuMe_2SiCl$, imid. (86% from **6**); iv, Bu_3SnH (62%).

butyldimethylsilyloxy substituent with the tin bromide[5,11] but this was not investigated any further. Instead, deprotection gave the triol **11** together with its epimer which were separated by recrystallisation to give the diastereomerically pure triol **11**. After protection of the vicinal diol unit as an acetonide, the remaining secondary alcohol was esterified to give the (*p*-methoxybenzyloxy)acetate **12**. This was subjected to an Ireland–Claisen rearrangement to give the methyl ester **13** after a hydrolytic work-up and treatment with trimethylsilyldiazomethane.

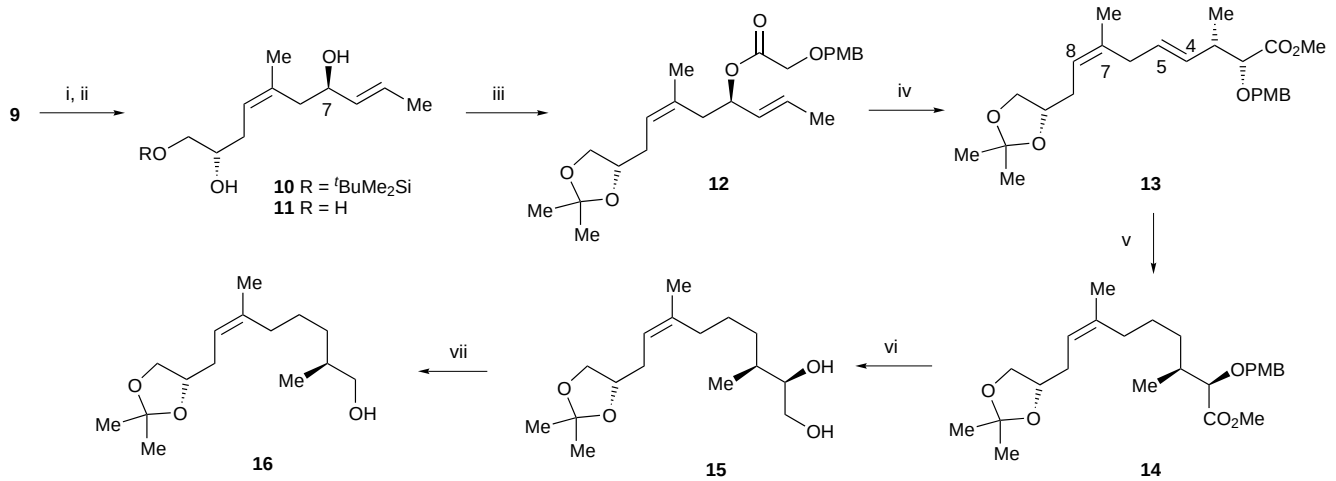
The structure of the rearrangement product **13** was assigned on the basis that the (*Z*)-ketene acetal had been formed from ester **12** via the co-ordinated lithium enolate,[7,12] and that this ketene acetal had rearranged via a chair-like transition state.[6] This assignment was confirmed by the second synthesis of the C(8)–C(15) alcohol **16**, vide infra.

The disubstituted double-bond in the ester **13** was reduced selectively by a three-step sequence involving protection of the 7,8-double-bond as its epoxide, catalytic hydrogenation of the 4,5-double-bond, and stereospecific regeneration of the (*Z*)-7,8-double-bond using potassium selenocyanate[13] to give the alkene **14**. Oxidative deprotection followed by reduction then gave the diol **15** which was taken through to the alcohol **16** by cleavage using sodium periodate followed by reduction with sodium borohydride. The alcohol **16**, a possible precursor of aldehydes **3**, corresponds to the C(7)–C(16) fragment of epothilone D.

The second synthesis of the alcohol **16** is outlined in Scheme 3. Reaction of the chiral aldehyde **17**[14] with the



Scheme 3. *Reagents and conditions*: i, **9**·$SnBr_4$, −78°C (72%; 80:20); ii, $^{n}Bu_4NF$; iii, $Me_2C(OMe)_2$ (79% from **18**); iv, PhOCS·Cl, py (84%); v, (a) Bu_3SnH, AIBN (90%), (b) DDQ (79%).



Scheme 2. *Reagents and conditions*: i, $SnBr_4$, −78°C, (*E*)-MeCH=CH·CHO [73%, 80:20 at C(7)]; ii, $^{n}Bu_4NF$ (98%) then separate diastereoisomers (ca. 60% of **11**); iii, (a) 2,2-dimethoxypropane (81%), (b) $PMBOCH_2CO_2H$, DIC, DMAP (82%); iv, $LiN(SiMe_3)_2$, −78°C, Me_3SiCl, 30 min, then rt 4 h followed by Me_3SiCHN_2 (78%); v, (a) MCPBA (88%), (b) H_2, PtO_2 (98%), (c) KSeCN (79%); vi, (a) DDQ (80%), (b) $LiAlH_4$ (78%); vii, $NaIO_4$ then $NaBH_4$ (74%).

stannane **9** gave a mixture of the diol **18** and its epimer at C(7), ratio 80:20 in favour of the diol **18**. Desilylation gave the triol **19**, which was converted into the acetonide **20**. A Barton deoxygenation followed by oxidative cleavage of the *p*-methoxybenzyl ether then gave the alcohol **16** identical to a sample prepared by the first route (Mosher's derivatives).

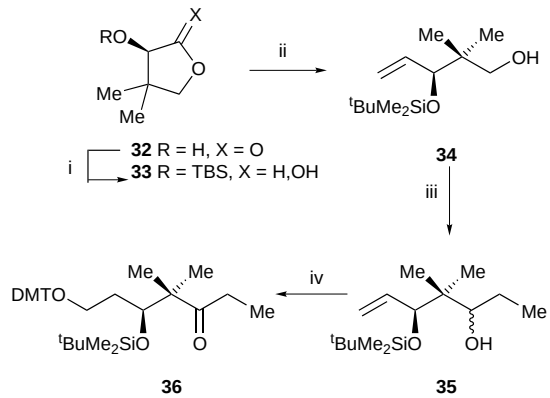
These two syntheses of alcohol **16** use allyltin chemistry for the stereoselective and regiospecific introduction of the C(12)–C(13) double-bond. The first synthesis also incorporates a procedure for 1,8-stereocontrol. However, the second approach is more convergent and efficient.[15]

At this point it was decided to attempt to complete a total synthesis of epothilones using the approach used in the second, more convergent, synthesis of alcohol **16**. However, it was decided to modify this approach by using a different allylstannane so that protecting group interconversions would be reduced.

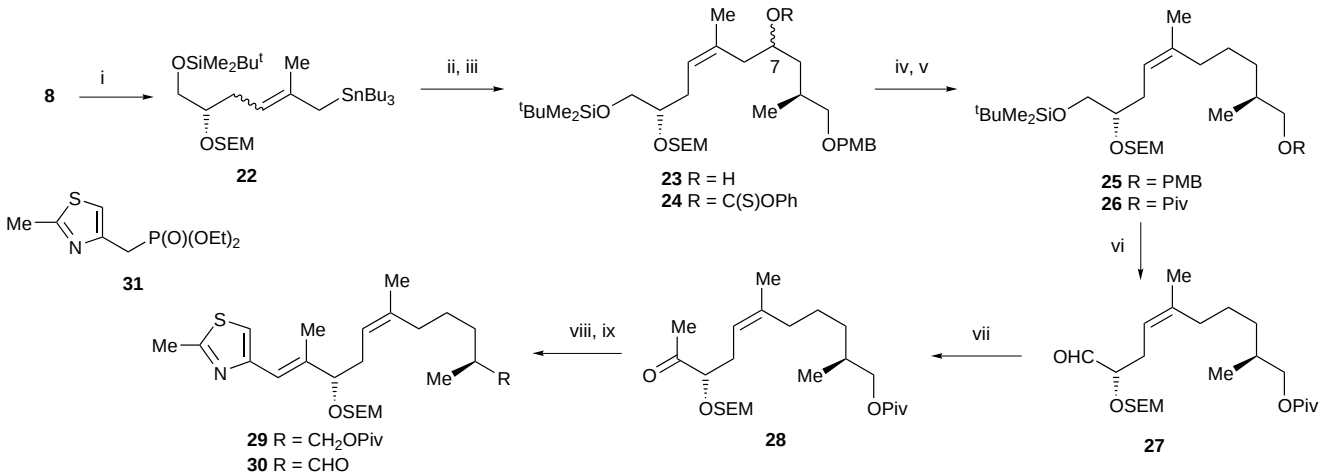
A synthesis of the intact C(7)–C(17) fragment of the epothilones using the convergent allylstannane strategy is outlined in Scheme 4. In this synthesis a bis-protected dihydroxyalkeneylstannane **22** was used. This stannane, prepared from the allylic sulfone **8**, was transmetallated using tin(IV) bromide to generate an allyltin tribromide which reacted with the aldehyde **17** to give the alcohols **23**. As expected for a (5-alkoxyhexenyl)stannane,[5,11] a 50:50 mixture of the C(7)-epimers was obtained but the control of the geometry of the trisubstituted double-bond was excellent, less than 2% of any isomeric (*E*)-alkene being obtained.

The 7-hydroxyl group was removed by reduction of the thionocarbonate **24** using tributyltin hydride to give the differentially protected triol **25**. It was necessary at this point to replace the *p*-methoxybenzyl group by a different protecting group since literature precedent suggested that difficulties would be encountered in removing it later in the synthesis.[16] Oxidative cleavage gave the corresponding alcohol which was reprotected as its pivalate ester **26**. Selective removal of the *tert*-butyldimethylsilyl group followed by Dess–Martin oxidation led to the aldehyde **27** which was taken through to the ketone **28** by addition of methyl magnesium bromide followed by further oxidation. Condensation of this ketone with the phosphonate **31**[17] gave the diene **29** together with ca. 10% of its (*Z*)-isomer. Reductive removal of the pivalate ester followed by a Dess–Martin oxidation provided the aldehyde **30**.

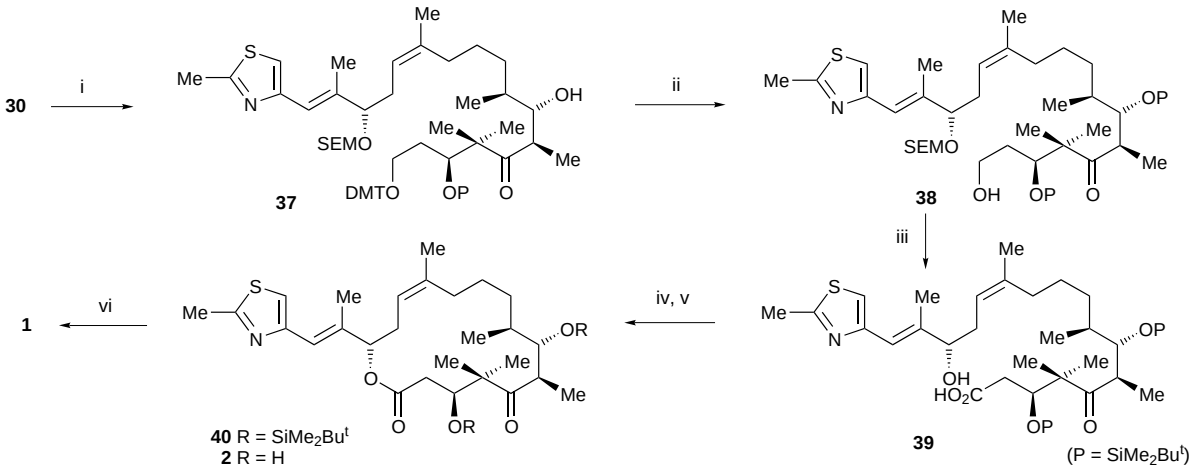
The C(1)–C(6) fragment, the ethyl ketone **36** was prepared from (*R*)-pantolactone **32** (Scheme 5). Thus protection of pantolactone as its *tert*-butyldimethylsilyl ether followed by reduction gave the lactols **33** which were converted into the alkenol **34** using an excess of the Tebbe reagent.[18] Dess–Martin oxidation and addition of ethylmagnesium bromide gave the alcohol **35** as



Scheme 5. *Reagents and conditions*: i, (a) $^{t}BuMe_2SiCl$, imid., (b) DIBAL-H (75% from **32**); ii, Tebbe reagent (88%); iii, (a) Dess–Martin, (b) EtMgBr, $CeCl_3$ (76% from **34**); iv, (a) BH_3·THF then H_2O_2, (b) DMTCl, $EtN^{i}Pr_2$, DMAP (52% from **35**), (c) Dess–Martin (89%).



Scheme 4. *Reagents and conditions*: i, (a) SEMCl, $EtN^{i}Pr_2$ (78%), (b) Bu_3SnH, AIBN (59%); ii, $SnBr_4$, −78°C, **17** (62%); iii, PhOCS·Cl, py. (80%); iv, Bu_3SnH, AIBN (59%); v, (a) DDQ (91%), (b) PivCl (96%); vi, (a) Bu_4NF (97%), (b) Dess–Martin; vii, (a) MeMgBr (85% over the two steps), (b) Dess–Martin (99%); viii, **31**, $^{n}BuLi$ (74%); ix, (a) DIBAL-H, (b) Dess–Martin (89% from **29**).



Scheme 6. *Reagents and conditions*: i, **36**·LiN^{i}Pr$_2$, −78°C (67%); ii, (a) ^{t}BuMe$_2$SiOTf (99%), (b) Cl$_2$CHCO$_2$H (79%); iii, (a) Dess–Martin, (b) NaClO$_2$, (c) MgBr$_2$, ^{n}BuSH, K$_2$CO$_3$ (62% from **38**); iv, 2,4,6-trichlorobenzoyl chloride, then DMAP (62%); v, F$_3$CCO$_2$H, DCM (91%); vi, DMDO, −50°C (82%, facial selectivity 4.2:1 in favour of epothilone B **1**).

a mixture of diastereoisomers which were not separated. Instead regioselective hydroboration–oxidation followed by selective protection of the primary alcohol as its dimethoxytrityl ether and Dess–Martin oxidation of the secondary alcohol provided the required ethyl ketone **36**.

The aldol condensation between the aldehyde **30** and the ethyl ketone **36** using lithium diisopropylamide as base gave the required product **37** with excellent stereoselectivity (Scheme 6). The configuration assigned to the aldol product was based initially on literature precedent[4] and was confirmed by the completion of a synthesis of the natural products **1** and **2**.

The 7-hydroxyl group was protected as its *tert*-butyldimethylsilyl ether and selective removal of the dimethoxytrityl group gave the primary alcohol **38**. This was oxidised to the corresponding carboxylic acid and the 15-hydroxyl group deprotected to give the hydroxy-acid **39**. Cyclisation using the modified Yamaguchi procedure followed by desilylation gave epothilone D **2** which had spectroscopic data (NMR, MS, IR) identical to those reported for the natural product. Regio- and stereoselective oxidation of the 12,13-double-bond using dimethyl dioxirane following the literature procedure[3] then gave epothilone B **1**, again with spectroscopic data identical to those published.

This work includes the completion of a total synthesis of epothilones B and D. Of interest is the use of allyltin chemistry for the convergent and stereoselective formation of the trisubstituted C(12)–C(13) double-bond. The exploratory work also exemplified a procedure for 1,8-stereocontrol.

Acknowledgements

We thank the EPSRC and Pfizer Global Research for a studentship (to N.M.) under the CASE scheme, and Dr. D. Rawson of Pfizer for many helpful discussions.

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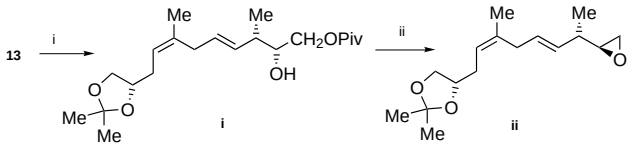
15. The Claisen product **13** was also converted into the epoxide **ii** via the alcohol **i**. This epoxide has the correct configuration at each of its three stereogenic centres and the requisite trisubstituted double-bond for incorporation into an alternative approach to the epothilones.



i, (a) $LiBHEt_3$ (97%) (b) $(CH_3)_3CCO.Cl$, py. (85%) (c) DDQ (80%). ii, (a) $MeSO_2Cl$, TEA (b) KO^tBu, MeOH (90% from **i**).

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