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Stereoselective synthesis of the C_7–C_{21} segment of epothilone A via asymmetric alkoxyallyl- and crotylboration☆

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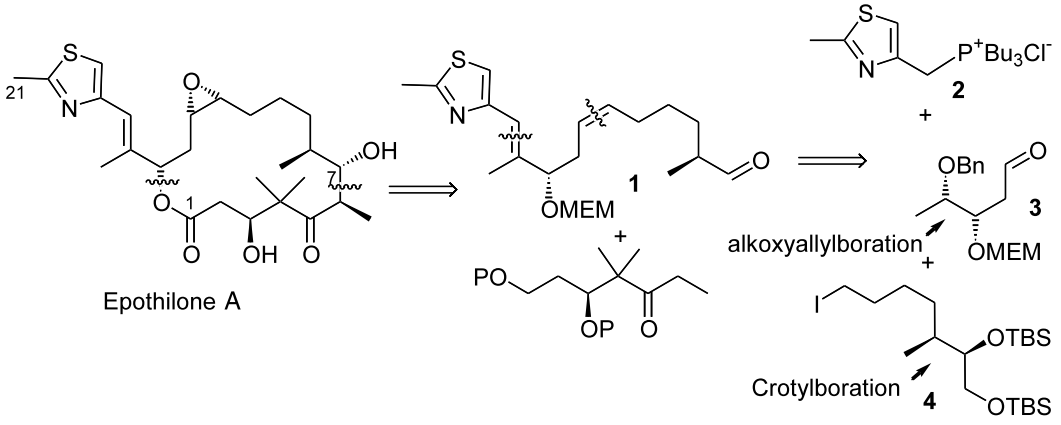
Abstract—The synthesis of the C_7–C_{21} fragment of epothilone A involving asymmetric alkoxyallyl- and crotylboration using α-pinene-derived reagents is described.

As part of our program on the applications of pinane-based versatile reagents[1] for organic syntheses, we have recently described the synthesis of several biologically active molecules via asymmetric allylboration–ring-closing metathesis pathway.[2] Herein we describe our approach towards the C_7–C_{21} synthon (**1**) of potent anti-cancer agent epothilone A[3,4] via α-pinene-derived asymmetric alkoxyallyl- and crotylboration. Our retrosynthetic analysis of **1** is shown in Scheme 1.

We envisaged the synthesis of **1** by the convergence of **2**, **3**, and **4**. 4-Chloromethyl-2-methylthiazole was prepared from 1,3-dichloroacetone and thioacetamide using a literature procedure[5] and converted to the Wittig salt **2**. We chose to prepare **3** starting with an alkoxyallylboration of acetaldehyde using *B*-(*Z*)-γ-(2-methoxyethoxy)-methoxyallyldiisopinocampheylborane.[6] Protection of **5** with benzyl bromide, followed by a hydroboration–oxidation provided the corresponding alcohol, which was oxidized using Dess–Martin periodinane (DMP)[7] to the required aldehyde **3** (Scheme 2). Although one of the chiral centers derived from alkoxyallylboration will be converted to the ketone **13**, the protocol does not necessitate any additional steps to create this chiral center.



Scheme 1.

Keywords: epothilone; alkoxyallylboration; crotylboration; α-pinene; Wittig reaction.

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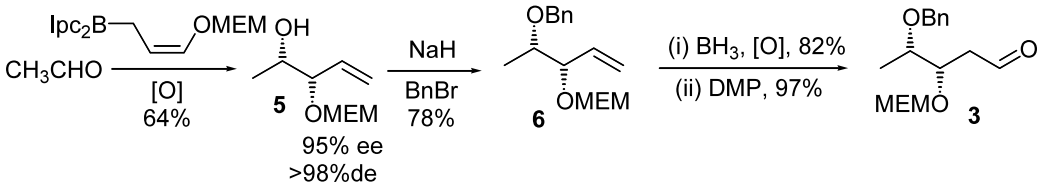


Scheme 2.

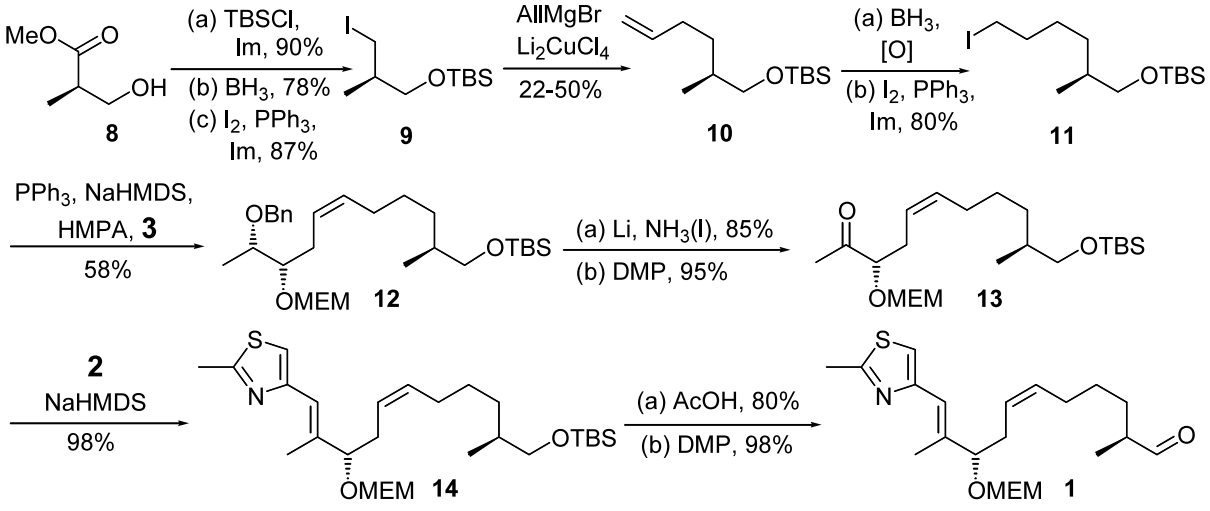
The preparation of **1** was initially attempted as shown in Scheme 3. TBS-protection of commercially available methyl (*R*)-3-hydroxy-2-methylpropionate **8**, followed by reduction of the methyl ester and iodination provided **9**. Nucleophilic substitution of the iodide with allyl magnesium bromide in the presence of catalytic amounts of lithium tetrachlorocuprate[8] or stoichiometric cuprous iodide afforded variable yields (22–50%) of **10**, which when subjected to hydroboration–oxidation, followed by iodination furnished the 1°-iodide **11**. Wittig coupling of aldehyde **3** with **11** gave 58% of the olefin **12**. Debenzylation under Birch reduction conditions, followed by DMP-oxidation provided the ketone **13**. The coupling[9] of Wittig salt **2** and **13** yielded **14**. Silyl deprotection, followed by a DMP-oxidation furnished the required synthon **1** for epothilone A (Scheme 3).

The unreliable yields during the allyl-substitution of the 1°-iodide **9** compelled us to modify the synthetic scheme. We designed a protocol utilizing pinane-based crotylboration.[10] A bonus from this procedure is the replacement of the relatively expensive chiral ester **8**.

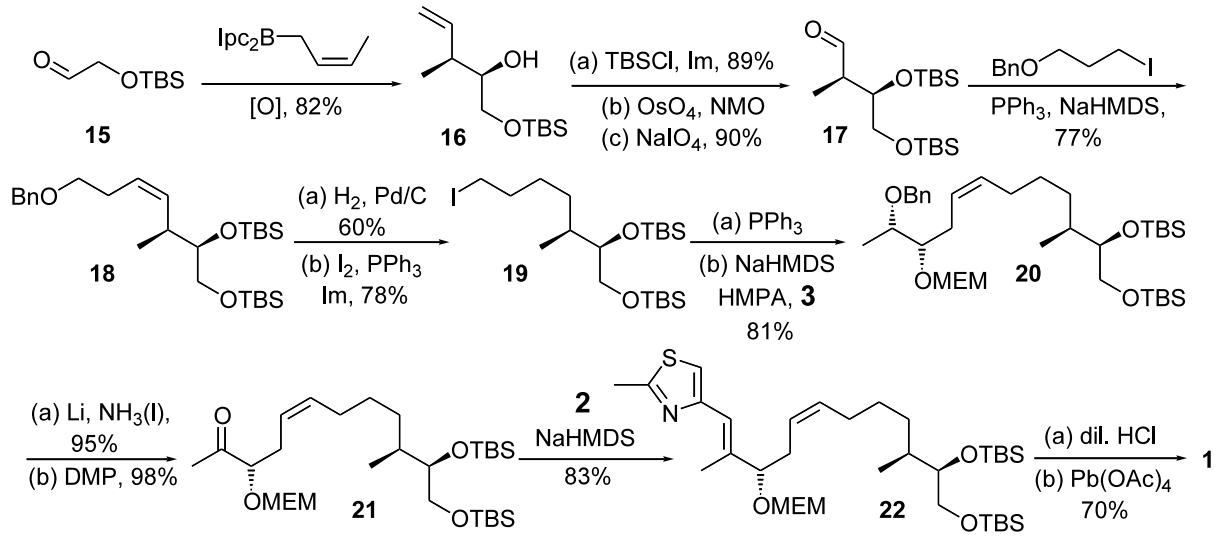
We began our synthesis with the *Z*-crotylboration of *tert*-butyldimethylsiloxyacetaldehyde **15** to provide the homoallylic alcohol **16**. Silyl protection of the hydroxyl group, followed by oxidative cleavage of the olefin furnished the aldehyde **17**. Wittig coupling with 3-benzyloxypropyl iodide provided the olefin **18**. A simultaneous debenzylation and reduction of the double bond was achieved by Pd-catalyzed hydrogenation. The alcohol was converted to the corresponding iodide **19**, which was utilized for a Wittig reaction with the aldehyde **3** to provide **20**. It is noteworthy that the *Z*-olefin was formed selectively and in high yields from the substrate that is prone to β-elimination. Debenzylation using lithium in liquid ammonia achieved the formation of the 2°-alcohol without affecting the double bond. The alcohol was oxidized using DMP to the ketone **21**, which was coupled[9] with **2** to provide **22** in good yields. Selective deprotection of the two silyl groups using dilute HCl, followed by $Pb(OAc)_4$ cleavage provided the target synthon **1** (Scheme 4).

The structures of all of the intermediates were confirmed by ^{13}C and ^{1}H NMR spectroscopy and mass spectrometry.

Thus, we have achieved a large-scale preparation of the C_7–C_{21} synthon **1**[11] of epothilone A using Wittig reaction and pinane-based alkoxyallyl- and crotylboration as key steps. Studies towards completing the preparation of epothilone A and the synthesis of other epothilones, particularly certain fluorinated analogs are under way.



Scheme 3.



Scheme 4.

Acknowledgements

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11. *Characterization of* ***1***: ^{1}H NMR: δ (ppm) ($CDCl_3$): 9.58 (d, $J=1.95$ Hz, 1H), 6.94 (s, 1H), 6.47 (s, 1H), 5.39–5.43 (m, 2H), 4.71 (d, $J=6.84$ Hz, 1H), 4.63 (d, $J=6.87$ Hz, 1H), 4.12 (t, $J=6.75$ Hz, 1H), 3.78–3.85 (m, 1H), 3.51–3.63 (m, 3H), 3.37 (s, 3H), 2.69 (s, 3H), 2.27–2.42 (m, 3H), 1.97–2.07 (m, 5H), 1.33–1.41 (m, 4H), 1.06 (d, $J=6.99$ Hz, 3H); ^{13}C NMR δ (ppm) ($CDCl_3$): 205.14, 164.58, 152.76, 138.28, 131.11, 125.98, 121.54, 115.98, 92.78, 81.56, 71.82, 67.06, 59.06, 46.24, 31.97, 30.08, 27.38, 26.88, 19.27, 13.84, 13.34; EI-MS: m/z 256, 89 [$(CH_3OCH_2CH_2OCH_2)^+$, 100%]; CI-MS: m/z 396 (M+H)$^+$, 290 [(M+H)–($HOCH_2OCH_2CH_2OCH_3$), 100%], 256, 168, 89; HRMS-CI: (M+H) 396.2205 (observed), 396.2209 (calcd).
Characterization of ***20***: ^{1}H NMR δ (ppm) ($CDCl_3$): 7.22–7.43 (m, 5H), 5.36–5.51 (m, 2H), 4.79 (s, 2H), 4.62 (d,

$J=11.88$ Hz, 1H), 4.51 (d, $J=11.82$ Hz, 1H), 3.55–3.73 (m, 5H), 3.46–3.53 (m, 4H), 3.38 (s, 3H), 2.24–2.45 (m, 2H), 1.97–2.08 (m, 2H), 1.61–1.64 (m, 1H), 1.26–1.42 (m, 3H), 1.19 (d, $J=5.49$ Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.82 (d, $J=6.57$ Hz, 3H), 0.05 (m, 12H); ^{13}C NMR δ (ppm) ($CDCl_3$): 138.85, 131.95, 128.30, 127.65, 127.45, 125.69, 95.48, 79.88, 75.87, 71.78, 71.29, 67.04, 65.36, 59.03, 35.31, 33.46, 28.13, 27.73, 26.04, 25.97, 18.39, 18.23, 15.32, 13.37, −3.93, −4.77, −5.24, −5.33; ESI: m/z 675 (Na adduct); HRMS-ESI: 675.4460 (actual), 675.4452 (calcd).

Characterization of ***22***: ^{1}H NMR δ (ppm) ($CDCl_3$): 6.92 (s, 1H), 6.48 (s, 1H), 5.32–5.48 (m, 2H), 4.71 (d, $J=6.87$ Hz, 1H), 4.63 (d, $J=6.87$ Hz, 1H), 4.12 (t, $J=6.86$ Hz, 1H), 3.79–3.86 (m, 1H), 3.44–3.63 (m, 6H), 3.37 (s, 3H), 2.69 (s, 3H), 2.31–2.45 (m, 2H), 1.99–2.10 (m, 5H), 1.59–1.64 (m, 1H), 1.07–1.44 (m, 4H), 0.87 (s, 9H), 0.86 (s, 9H), 0.79 (d, $J=6.87$ Hz, 3H), 0.02 (m, 12H); ^{13}C NMR δ (ppm) ($CDCl_3$): 164.48, 152.83, 138.41, 131.95, 125.23, 121.48, 115.88, 92.75, 81.67, 75.85, 71.83, 67.00, 65.34, 59.02, 35.24, 33.45, 31.91, 27.76, 27.69, 26.02, 25.95, 19.24, 18.36, 18.21, 13.79, 13.35, −3.95, −4.79, −5.26, −5.35; ESI: m/z 656, 678 (Na adduct); HRMS-ESI: 656.4202 (actual), 656.4200 (calcd).