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Improved Synthesis of the Northern Hemisphere of Epothilone A by a Sharpless Asymmetric Dihydroxylation

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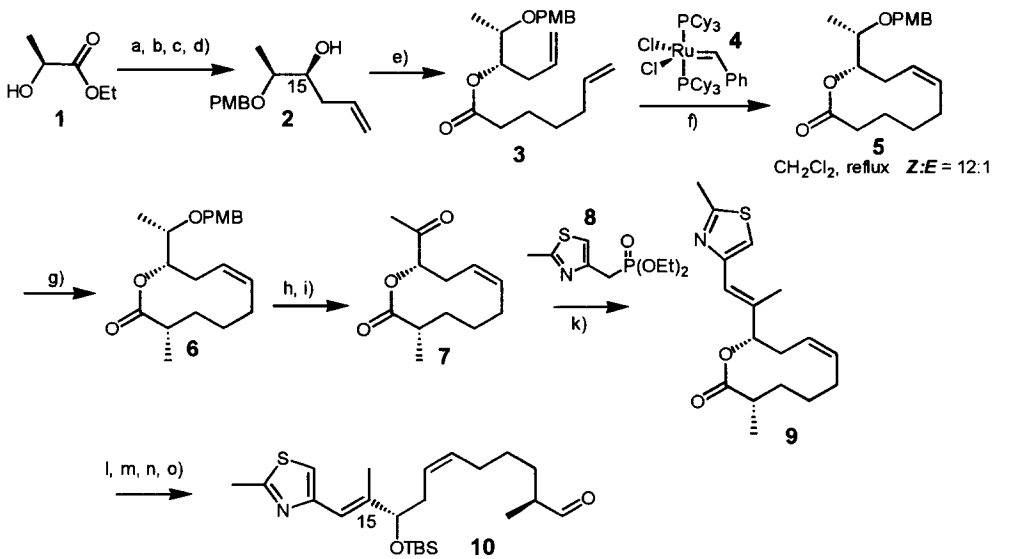
Abstract: An improved synthesis of the northern hemisphere of epothilone A is described. This approach utilizes the Sharpless asymmetric dihydroxylation of 5-hexen-2-one (allyl acetone) to generate the precursor for the Wittig reaction and the subsequent ring closing metathesis reaction (RCM). This strategy allows to generate precursor **13** as both enantiomers from ready available starting material in a very efficient manner.

Our strategy to circumvent the unsatisfactory *E/Z* ratios observed in ring closing metathesis reaction to generate the 16-membered epothilones[1] involved formation of a rigid 10-membered lactone (**5**).[2] This lactone was constructed from alcohol **2** and 6-heptenoic acid by a ring closing metathesis reaction with the Grubb's catalyst (**4**). Alcohol **2** on the other hand was derived from (*S*)-ethyl lactate (**1**) and the chirality at C15 was introduced *via* diastereoselective allylation of the corresponding aldehyde (Scheme 1).



Scheme 1: a) PMB trichloroacetimidate, CSA, CH_2Cl_2, 0 °C→r.t., 88%; b) $LiAlH_4$, Et_2O, 0 °C→r.t., 74%; c) Swern oxidation, 77%; d) allyltrimethylsilane, $SnCl_4$, CH_2Cl_2, -78 °C, 88%; e) 6-heptenoic acid, DCC, DMAP, CH_2Cl_2, r.t., 94%; f) ring closing metathesis, 0.22 eq **4**, high dilution, CH_2Cl_2, reflux, 3h, 63%, *Z:E* = 12:1; g) NaHMDS, THF, MeI, -78 °C, 82%; h) DDQ, CH_2Cl_2/H_2O 18:1, r.t., 1h, 98%; i) TPAP, NMO, 3 Å sieves, CH_2Cl_2, r.t., 1h, 83%; k) **8**, BuLi, -78 °C→r.t., 2h, 65%; l) $LiAlH_4$, Et_2O, 0 °C, 1h, 95%; m) TBDMS triflate, 2,6-lutidine, CH_2Cl_2, -78 °C, 91%; n) CSA, CH_2Cl_2/MeOH 1:1, 0 °C, 92%; o) Dess-Martin periodinane, CH_2Cl_2, 0 °C, 1h, 93%.

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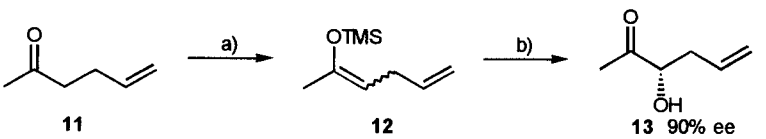
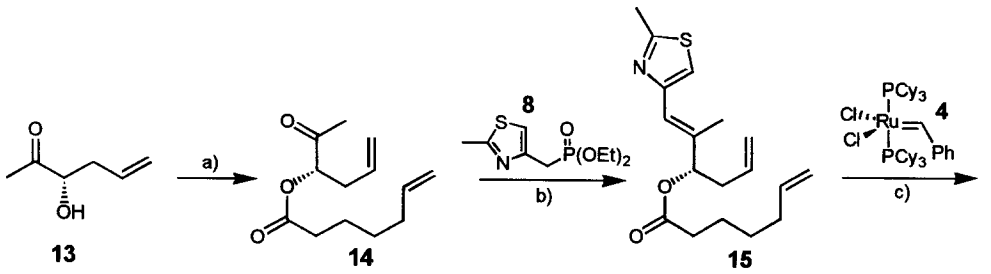
Despite the good yields and excellent diastereoselectivity observed in the transformation of (*S*)-ethyl lactate to lactone **5**, the lengthy access to alcohol **2** and the fact that the inherent chirality of the starting material was sacrificed in the oxidation step prior to the Horner-Emmons reaction, led us to develop a more stringent route for the appropriate metathesis precursor.

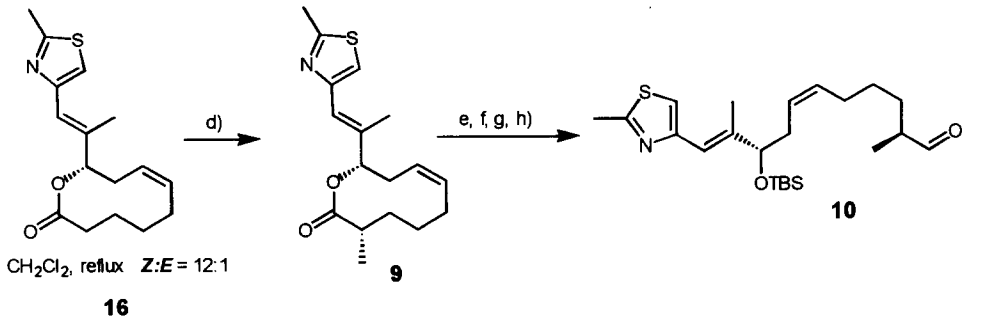
We envisioned that (*S*)-3-hydroxy-5-hexen-2-one (**13**) would be the suitable precursor for the construction of key intermediate **9**. It contains the hydroxyl functionality for attaching heptenoic acid, the double bond for the metathesis reaction as well as the carbonyl group necessary for introducing the thiazole fragment. Starting from 5-hexen-2-one (**11**) the hydroxyl group could be introduced selectively by means of the Sharpless asymmetric dihydroxylation (Scheme 2).[3] Transformation of the ketone with HMDS and TMSI[4] resulted in a mixture of the corresponding silyl enol ethers (**12**). Subsequent dihydroxylation with the AD-mix-α gave the desired (*S*)-3-hydroxy-5-hexen-2-one (**13**) in 87% yield and 90% ee.[5] The enantiomeric excess was determined by NMR shift experiments with europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate. The (R)-enantiomer was synthesized accordingly with the AD-mix-β.



Scheme 2: a) HMDS, TMSI, THF, 86%; b) α-AD-Mix, *t*-BuOH, 87%, 90% ee.

Esterification[6] with heptenoic acid gave ester **14** which was subjected to a Horner-Emmons reaction with thiazole **8**. The ring closing metathesis reaction of **15** was performed under standard conditions[7] with Grubbs' catalyst[8] and gave the desired *Z*-isomer[9] as the major compound (*Z*/*E* = 12:1) as observed for compound **5**. The important methylation of lactone **16** could be achieved diastereoselectively with NaHMDS and MeI at -78 °C.[10] Reductive ring opening followed by TBS-protection/deprotection and Swern oxidation as described earlier[2b] established the northern hemisphere (C7-C15) of epothilone A (Scheme 3).





Scheme 3: a) 6-heptenoic acid, DCC, DMAP, CH_2Cl_2, r.t., 79%; b) **8**, BuLi, -78 °C→r.t. 2h, 60%; c) ring closing metathesis, 0.22 eq **4**, high dilution, CH_2Cl_2, reflux, 3h, 53%, *Z:E* = 12:1; d) NaHMDS, THF, -78 °C, MeI, 66%; e) $LiAlH_4$, Et_2O, 0 °C, 76%; f) TBDMS triflate, lutidine,CH_2Cl_2, -78 °C, 91%; g) CSA, CH_2Cl_2/MeOH 1:1, 0 °C, 92%; h) Dess-Martin periodinane, CH_2Cl_2, 0 °C, 1h, 93%.

We described an efficient route to the northern hemisphere of epothilone A. The rapid access of hydroxy ketone **13** by means of the Sharpless asymmetric dihydroxylation, together with the ring closing metathesis reaction of compound **15** are the key steps in this approach. In particular hydroxyl ketone **13** as a highly functionalized intermediate can also be used in the synthesis of various natural products and demonstrates how efficiently the Sharpless dihydroxylation can be applied in synthesizing key intermediates.

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5. Alcohol **13**: AD-mix-α (1.4 g) was dissolved in a mixture of *t*-BuOH and water (10 ml, 1:1). The solution was cooled to 0 °C and silyl enol ether **12** (170 mg, 1 mmol) was added. The reaction was stirred for 2h and Na_2SO_3 was added at 0 °C. After stirring for 1 h at room temp. the mixture was extracted twice with CH_2Cl_2 (20 ml) dried over Na_2SO_4 and concentrated. Flash chromatography with pentanes/ether (5:1) gave alcohol **13** (107 mg, 87 %) $[\alpha]^{20}_D$ +24.2° (c = 1.0 in $CHCl_3$); FTIR ($CHCl_3$) 3607, 2999, 2875, 1602, 1468, 1370, 1146 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.74-5.88 (m, 1H), 5.13-5.23 (m, 2H), 4.27 (t, *J* = 6 Hz, 1H), 3.49 (s, 1H), 2.60-2.69 (m, 1H), 2.35-2.44 (m, 1H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.72, 131.09, 117.23, 75.04, 36.66, 25.6.
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9. Lactone **16**: To a refluxing solution of $RuCl_2(PCy_3)_2CHC_6H_5$ (60 mg, 0.072 mmol, 20 mol%) in CH_2Cl_2 (120 mL) was added dropwise a solution of diene **15** (115 mg, 0.0.361 mmol) in CH_2Cl_2 (15 mL) over a period of 1 h. After refluxing for 3 h the mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (PE/EtOAc 30:1) to provide a colorless oil (70 mg, 0.24 mmol, 66 %): $[\alpha]^{20}_D$ –88.0° (c = 0.6 in $CHCl_3$); FTIR ($CHCl_3$) 2924, 2856, 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.59 (d, *J* = 0.5 Hz, 1H), 5.40-5.55 (m, 2H), 5.37 (t, *J* = 4.2 Hz, 1H), 2.73 (s, 3H), 2.33-2.43 (m, 1H), 2.20-2.33 (m, 2H), 2.11 (s, 3H), 1.96-2.08 (m, 2H), 1.55-1.80 (m, 4H), 1.22 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.30, 164.64, 152.74, 136.77, 135.03, 123.24, 119.00, 115.80, 77.20, 42.45, 32.06, 31.91, 29.68, 27.55, 19.34, 19.22, 16.47; HRMS m/e calcd for $C_{17}H_{23}N_1O_2S_1$ 305.1449, found 305.1449.
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