Toward the total synthesis of Tubelactomicin A

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C500 report
4/22/05

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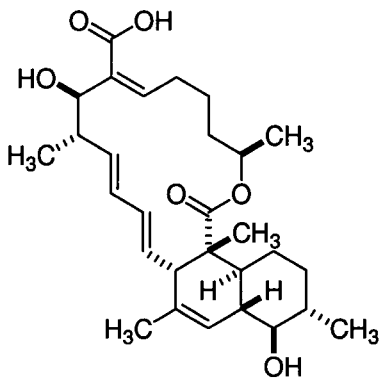
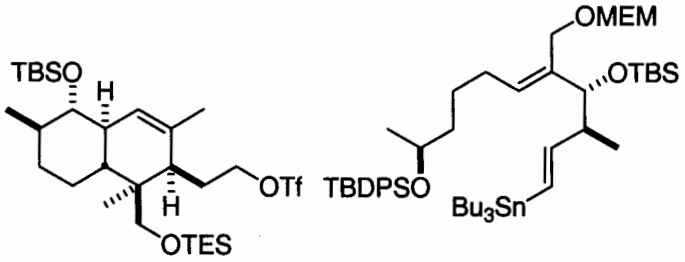


1 Tubelactomicin A

Tubelactomicin A(**1**) is a 16-membered lactone isolated from actinomycete strain, *Nocardia* sp. MK703-102F1. Tubelactomicin A(**1**) is a novel antibiotic which shows potent and specific antimicrobial activity against acid-fast bacteria, including those which show resistance toward known drugs. Due to the prevalence of HIV related tuberculosis, the search for new effective drugs to combat the disease is necessary. The number of antitubercular and anti atypical mycobacterial drugs is low. Therefore novel compounds with new structural motifs and modes of action are particularly interesting, both for their usefulness as drugs, but also for the study of the novel mode of antibacterial potency[1].

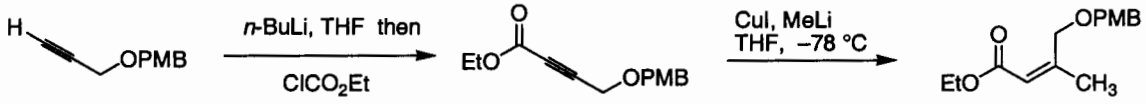
Macrolactone (**1**) is an interesting target for synthesis because of its nine stereogenic centers with multiple contiguous stereogenic centers and a quaternary carbon contained in its structure. Tubelactomicin A also contains a large 16 membered macrolactone ring. There have currently been no studies reported on the chemical synthesis of **1**, but work has been performed suggesting the possible roles of a Diels-Alderase enzyme in its biosynthesis[2].

The synthesis of **1** can be envisioned as the convergence of two halves of the molecule. The first half being the *trans*-decalin ring system **2**, and the second half being the carbon chain **3**.



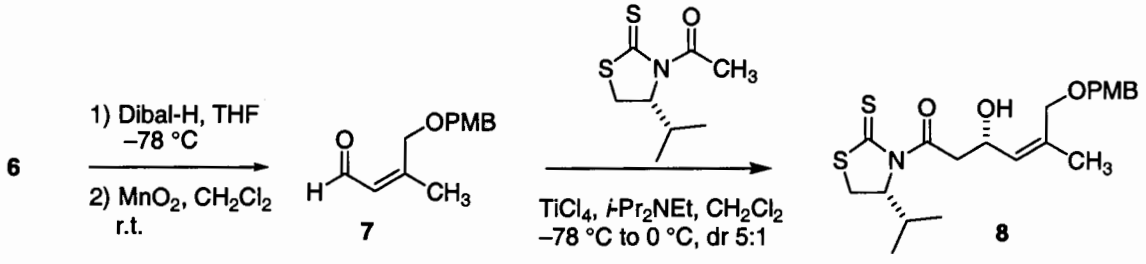
2 **3**

The goal of this project is the construction of the *trans*-decalin ring system. The synthesis will begin from alkyne **4**. Acylation of **4** with ethyl chloroformate provides **5**. Syn addition of methane to **5** gives allylic ester **6**.



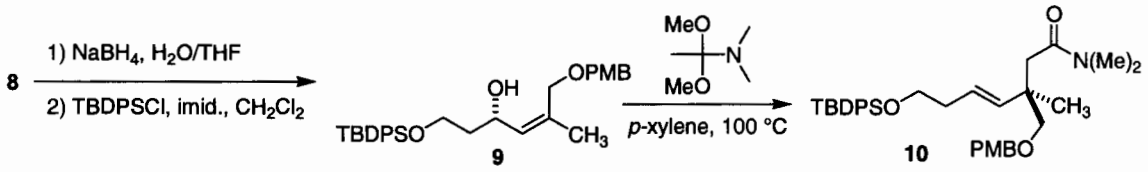
4 **5** **6**

Ester (**6**) is then reduced to the aldehyde (**7**) and is subjected to a modified Nagano acetate-aldol condensation to give **8** with a 5:1 diastereomeric ratio of products.

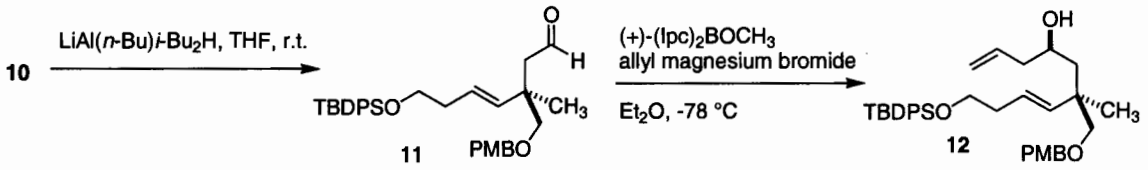


7 **8**

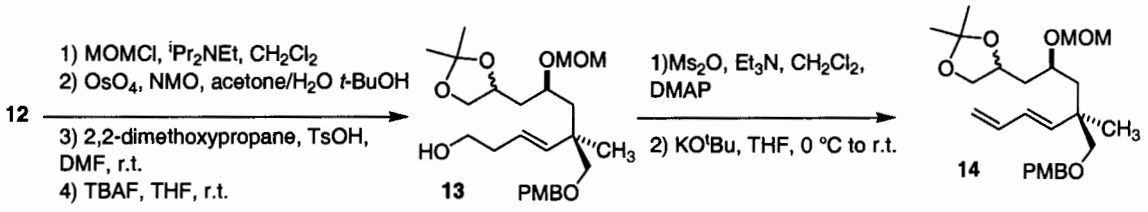
The thiazolidine thione (**8**) is cleaved, and the resulting alcohol is protected to give **9**[3].



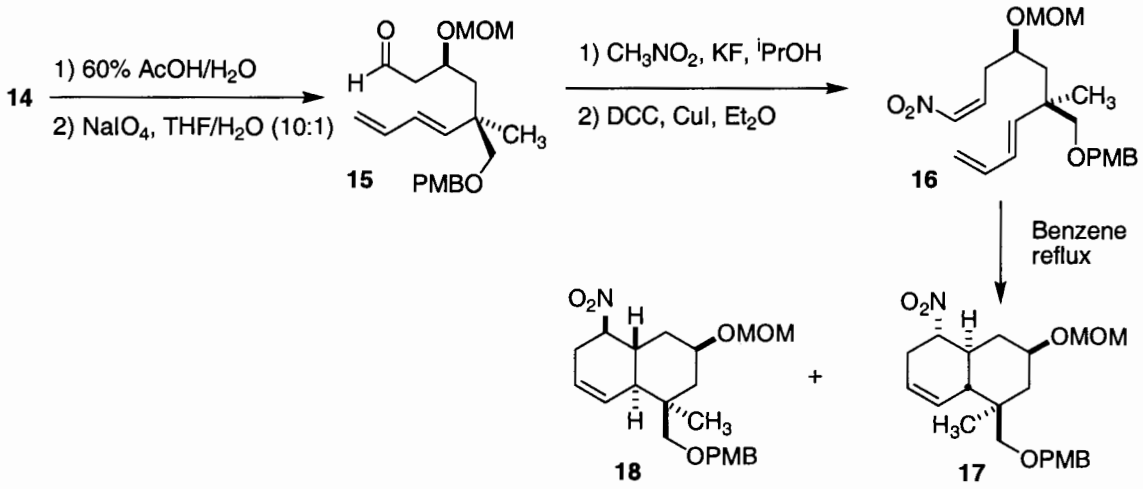
Compound **9** then is subjected to eschenmoser-claisen rearrangement to give **10**[4]. Acetamide (**10**) is then directly reduced to the aldehyde (**11**)[5]. The aldehyde (**11**) then undergoes brown allylation to give **12**.



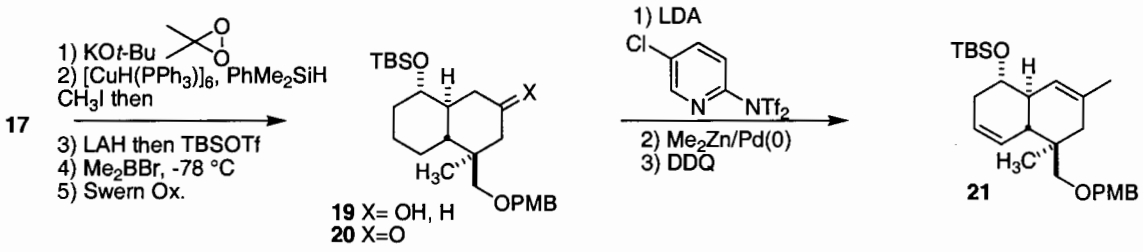
The alcohol is protected as the MOM ether, followed by oxidation of the terminal alkene to the diol which is then protected as the dioxolane, followed by cleavage of the TBDS ether to give the free alcohol **13**. The diene **14** is formed by mesylation then elimination of **13**.



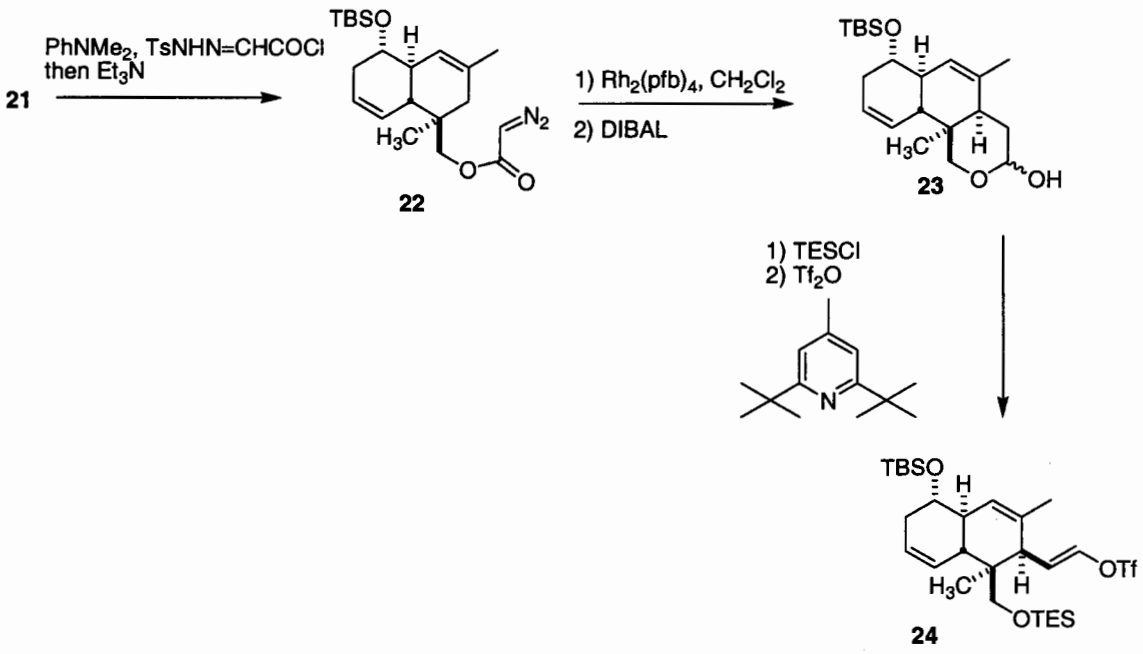
The diol is then deprotected, and oxidatively cleaved to the aldehyde **15**. The aldehyde **15** is then subjected to aldol condensation. The resulting nitro compound is then refluxed in benzene to give the desired diels-alder product **17** and diastereomer **18**[6].



The desired diastereomer **17** is then treated with a modified Nef reaction, conjugate reduction, and α-alkylation to give **19**[7].



Diazoacetate is installed via the Corey-Meyers procedure to give **22**[8], which is transformed to **24**, the functionalized *trans*-decalin portion of Tubelactomicin A.



Completed work

Synthetic work began with the *para*-methoxybenzyl protection of propargyl alcohol via the *para*-methoxybenzyl acetimidate with triflic acid catalyst to give starting material **4**. The protected alcohol was then acylated to give the ynoate ester **5** which was then subjected to syn addition with the cuprate to give **6**. The ester was then reduced to the allylic alcohol with DIBAL, which was then oxidized to the aldehyde **7** with manganese dioxide.

Concurrently with the above synthesis the Nagao thiazolidine thione acetate was synthesized starting from D-valine. The D-valine was reduced to the alcohol with iodine and sodium borohydride in THF. Yield in this reaction was only 46% with a large amount of n-butanol as a side product. Nevertheless, the D-valinol was reacted with carbon disulfide to give the thiazolidine thione. The thiazolidine thione was then acetylated with *n*-Butyllithium and acetyl chloride. The thiazolidine thione was

reacted with **7** from above in a modified nagao acetate aldol reaction. At this juncture despite storage at -20°C, the double bond in aldehyde **7** was observed to have isomerized giving a mixture of *E* and *Z* isomers.

At this point in the synthesis advanced intermediate **9** was made available by J. Cullen Klein. This material was treated with dimethyl acetamide dimethyl acetal and underwent an eschenmoser claisen rearrangement to give amide **10.** The amide was then reduced to the aldehyde with lithium aluminum diisobutyl *n*-butyl hydride to give aldehyde **11. 11** was then treated with (S)-Ipc allyl borane. The borane reagent was made from allyl magnesium bromide and (S)-IPC methoxy borane. The reaction gave no products and only returned starting material aldehyde. On further examination the allyl magnesium bromide solution used to make the borane reagent was no longer active, and fresh grignard agent will need to be made.

Future Work

The synthesis so far has proceeded according to the retrosynthetic analysis provided above. Future work will continue along the above retrosynthetic scheme toward the completion of the trans fused decalin system portion of Tubelactomicin A. Near term goals are to explore the chemistry of the intramolecular Diels-alder reaction.

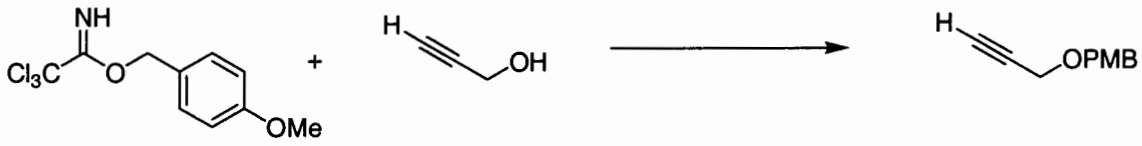
Experimental Procedures

General

Nuclear magnetic resonance spectra were all obtained on Varian GEM-300, Varian I-400 or Varian VXR-400 spectrometer. Samples were dissolved in $CDCl_3$ with residual $CHCl_3$ (δ7.26) as the internal standard. Precoated glass backed silica gel plates were used for thin layer chromatography. Short wave UV light was used for visualization. Flash chromatography was performed using Kieselgel-60 (230-400 mesh) silica gel. All solvents were freshly distilled prior to use, and all glassware was flame dried prior to use unless otherwise stated. All reactions were performed under argon atmosphere unless otherwise stated.

4-methoxybenzyl 2,2,2-trichloroacetimidate

To a stirred suspension of sodium hydride (0.12g, 5mmol) in diethyl ether (40 mL) was added dropwise a solution of *para*-methoxybenzyl alcohol(6.91g, 50mmol) in diethyl ether (10 mL). The resulting mixture was stirred for 1h at room temperature, then cooled to 0°C, and trichloroacetonitrile was added to the mixture. The mixture was allowed to warm to room temperature and stirred at room temperature for 2h. The reaction mixture was then evaporated to give a dark orange oil. The resulting oil was diluted with 50mL pentanes. The resulting suspension was filtered through celite with pentanes wash 50mL. The filtrate was evaporated to give 13.06g of a yellow oil, used without further purification.



1-methoxy-4-((prop-2-ynyloxy)methyl)benzene

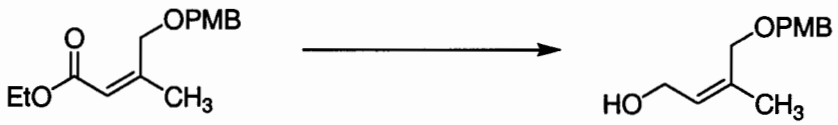
Para-methoxybenylalcohol acetimidate (13.06g, 74.1mmol) and propargyl alcohol (3.46g, 61.2mmol) were placed into a round bottom charged with 80mL diethyl ether. To the stirred mixture was added freshly distilled triflic acid (0.028g, 1.9mmol). Reaction mixture stirred at room temperature for 2h. 100mL saturated bicarbonate solution was then added to the mixture, which was then stirred at room temperature for 20min. The layers were separated and the aqueous layer was extracted twice with 100mL diethyl ether. The organic layers were combined, washed with 100mL brine and dried over magnesium sulfate, then filtered and evaporated to give an oily yellow solid. The solid was taken into 50mL pentanes and filtered. The resulting white solid was washed with 20mL pentanes. The combined filtrates were evaporated to give a yellowish oil which was then distilled under vacuum to give 6.91g of product as a pale yellow oil in 88% yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 2H), 6.89 (m, 2H), 4.55 (s, 2H), 4.14 (d, J =2.2 Hz, 2H), 3.81 (s, 3H), 2.46 (t, J =2.2, 1H).

Ethyl 4-(4-methoxybenzyloxy)but-2-ynoate

PMB (6.91g, 54.1mmol) protected alcohol dissolved in 140mL THF. Solution cooled to -78°C. Butyllithium 2.5M solution in hexanes (18.6mL, 46.4mmol) was added dropwise. Mixture was allowed to stir for 30min before ethyl chloroformate (5.87g, 54.1mmol) was added dropwise. The mixture was then stirred for 2h and then warmed to room temperature. The mixture was then evaporated and the residue was partitioned between 100mL diethyl ether and 100mL water. Aqueous layer was extracted twice with 100mL diethyl ether. Combined organic layers were washed with 100mL saturated ammonium chloride solution, dried over magnesium sulfate, filtered and concentrated to give 10.09g of a yellow oil. Crude product purified by flash chromatography eluting with 4:1 Ethyl acetate:Hexanes to give 7.03g of above named compound in 54% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29-7.23 (m, 2H), 6.90-6.84 (m, 2H), 4.54(s, 2H), 4.26-4.23 (m, 4H), 3.79(s, 3H), 1.31 (t, J =7.2Hz, 3H), 1.24 (t, J =7.2Hz, 3H).

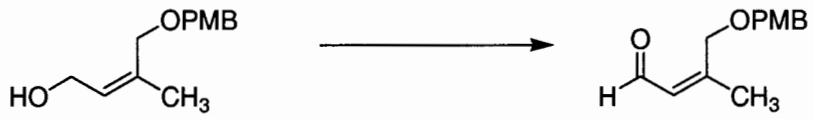
(Z)-ethyl 4-(4-methoxybenzyloxy)-3-methylbut-2-enoate

Copper iodide (7.03g, 28.3mmol) was suspended in 125mL THF. The suspension was cooled to -50°C, and methyllithium (1.6M solution in diethyl ether) was added dropwise then stirred for 30min. Mixture was then cooled to -78°C and ynoate ester (7.03g, 28.3mmol) solution in THF (25mL) was added dropwise to mixture and mixture stirred for 2h. Following the addition of 5mL ethanol the mixture was allowed to warm to room temperature. The mixture was then evaporated, and the resulting residue was partitioned between diethyl ether, 120mL and water 120mL. Layers were separated and the aqueous layer was extracted twice with 100mL diethyl ether. Organic layers were combined and washed with saturated ammonium chloride solution 100mL, dried over magnesium sulfate, and evaporated. Crude product purified by flash chromatography with silica gel eluting with 4:1 hexanes:ethyl acetate to give 3.48g of the title compound in 50% yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.25-7.23 (m, 2H), 6.85-6.83 (m, 2H), 5.72(d, J =1.2 Hz, 2H), 4.60(s, 2H), 4.09 (q, J =7.0 Hz, 2H), 3.75(s, 3H), 1.96 (d, J =0.8Hz, 3H), 1.23 (t, J =7.2Hz, 3H).



(Z)-4-(4-methoxybenzyloxy)-3-methylbut-2-en-1-ol

Allylic ester (3.48g, 13.9mmol) dissolved in 125mL diethyl ether. Solution was cooled to -78°C and DIBAL-H 1M solution in hexanes (36mL, 36mmol) was added dropwise and mixture was stirred for 2h. Reaction mixture was then allowed to warm to room temperature over 2h and stirred at room temperature for 1h before being cooled to -50°C. Dilute solution of sodium potassium tartrate was added slowly to mixture, and the mixture was then stirred at room temperature for 10h. Layers were separated and the aqueous layer was extracted twice with diethyl ether 100mL. Combined organic layers were then dried over sodium sulfate, filtered and evaporated to give 2.96g of alcohol, used without further purification, 96% yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.27-7.24 (m, 2H), 6.90-6.86 (m, 2H), 5.63 (d, *J* =6.8, 1H), 4.41 (s, 2H), 4.08 (d *J* =6.8Hz, 2H), 3.98 (s, 2H), 3.79 (s, 3H), 2.17 (br, 1H), 1.81 (s, 3H).



(*Z*)-4-(4-methoxybenzyloxy)-3-methylbut-2-enal

Allylic alcohol (2.96g, 13.3 mmol) was dissolved in 200mL methylene chloride. Manganese dioxide (6.50g, 66.6mmol) was added in one portion, and the resulting suspension was stirred at room temperature for 5h. A second portion of Manganese dioxide (6.5g, 66.6mmol) was added and the mixture was stirred at room temperature for another hour. Mixture was then filtered through a pad of celite, and the filtrate was evaporated to give 2.20g of the aldehyde. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.01 (d, *J* =8.0 Hz, 1H), 7.27-7.25(m, 2h), 6.90-6.88 (m, 2H), 5.96 (dd, *J* =7.6, 1.2Hz, 1H), 4.49 (s, 2H), 4.40 (s, 2H), 3.81 (s, 3H), 2.02 (d, *J* =1.2 Hz, 3H).

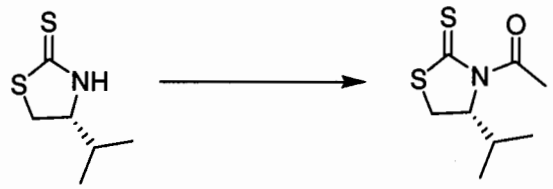
(*R*)-2-amino-3-methylbutan-1-ol

D-Valine (20g, 0.171 mol) was suspended in 240mL THF, and sodium borohydride (15.5g, 0.41mol) was added in one portion before being cooled to 0°C. Iodine(43.3g, 0.171 mol) in 120mL THF, was added dropwise over 30min. Mixture was then heated until evolution of bubbles ceased. The mixture was then refluxed 16h. The mixture was then cooled to room temperature before 5mL methanol was added, and stirred until bubbles ceased to evolve. Mixture was then evaporated to a white semisolid. The residue was taken into 204mL 10% KOH aqueous solution and stirred for 16h. The solution was then extracted 3 times with 200mL methylene chloride. Combined organic layers were dried over magnesium sulfate, filtered and

concentrated to a yellow oil, which was then purified via bulb to bulb distillation to give a white crystalline solid 8.28g in 47% yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.60 (dd, *J* =10.8, 3.9 Hz, 1H), 3.27 (dd, *J* = 10.8, 8.7 Hz, 1H), 2.58-2.48 (m, 1H), 2.26-1.91 (br, 3H), 1.64-1.46 (m, 1H), 0.88 (q, *J* =3.3 Hz, 6H).

(*R*)-4-isopropylthiazolidine-2-thione

Amino alcohol (8.28g, 80.3mmol) dissolved in 401mL potassium hydroxide 1M in methanol solution. Mixture stirred at reflux for 18h before being cooled to room temperature. Mixture was then extracted twice with 400mL methylene chloride. Combined organic layers were dried over sodium sulfate filtered and concentrated to give 10.01g of the thione product in 77% yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.83 (br, 1H), 4.09-4.00 (m, 1H), 3.50 (dd, *J* =11.1, 8.1 Hz, 1H), 3.31 (dd, *J* = 11.1, 8.3 Hz, 1H), 1.97 (s, 1H), 1.03 (d, *J* =6.9 Hz, 3H), 0.99 (d, *J* =6.9 Hz, 3H).

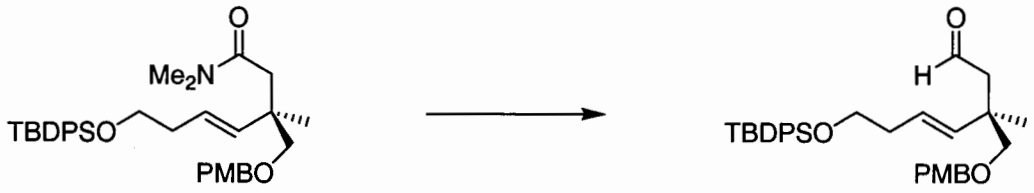


(*R*)-1-(4-isopropyl-2-thioxothiazolidin-3-yl)ethanone

Thione (10.01g, 62.1mmol) dissolved in 100mL THF before being cooled to -78°C. Butyllithium 2.5M solution in diethyl ether (27.3m, 68.3mmol) was added dropwise and the mixture stirred for 1h. Acetyl chloride (5.36g, 68.3mmol) was added dropwise to the solution and the mixture was stirred for 2h. 100mL saturated ammonium chloride solution was then added to the mixture, and stirred for 10min. Layers were separated and the aqueous layer was extracted twice with 100mL diethyl ether. Combined organic layers dried over magnesium sulfate, filtered and concentrated to give 9.0g of the product as a yellow oil in 66% yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.17-5.21 (m, 1H), 4.90 (dd, *J* =11.2, 8.0 Hz, 1H), 3.00 (d, *J* =11.2 Hz, 1H), 2.74 (s, 3H), 2.27-2.43 (m, 1H), 1.04 (d, *J* =6.9 Hz, 3H), 0.95 (d, *J* =6.9 Hz, 3H).

(*R,E*)-7-(tert-butyldiphenylsilyloxy)-3-((4-methoxybenzyloxy)methyl)-*N,N*,3-trimethylhept-4-enamide

Alcohol (0.425g, .84mmol), was dissolved in 9 mL xylenes. Dimethyl acetamide dimethyl acetal (0.38g, 3.3mmol) was added, and a short path distilling head was attached to the reaction vessel. Mixture was stirred at 110°C for 12h. Mixture was then evaporated and purified by silica gel flash chromatography eluting with 2:1 hexanes:ethyl acetate to give 0.37g of product as a pale yellow oil in 76% yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.69-7.62 (m, 4H), 7.44-7.32 (m, 6H), 7.25-7.18 (m, 2H), 6.88-6.80 (m, 2H), 5.67 (d, *J* =16.5 Hz, 1H), 5.40-5.50 (m, 1H), 4.38-4.47 (m, 2H), 3.79 (s, 3H), 3.66 (t, *J* =6.8 Hz, 2H), 3.40 (d, *J* =6.8 Hz, 1H), 3.32 (d, *J* =6.8 Hz 1H), 2.91 (s, 3H), 2.86 (s, 3H), 2.35-2.48 (m, 2H), 2.33-2.24 (m, 2H), 1.60 (s, 1H), 3.32 (s, 3H), 1.04 (s, 9H).



(*R,E*)-7-(tert-butyldiphenylsilyloxy)-3-((4-methoxybenzyloxy)methyl)-3-methylhept-4-enal

Amide (0.37g, 0.64mmol) was dissolved in 10mL THF and the resulting solution was stirred at 0°C. To the solution was added dropwise 0.5M solution of lithium aluminum diisobutyl isobutyl hydride (3.0mL, 1.5mmol). Reaction mixture was stirred at 0°C for 15 minutes before 10mL dilute solution of sodium potassium tartrate in water was added. Mixture was allowed to warm to room temperature and stirred for 10h. Layers were separated and aqueous layer was extracted twice with 20mL diethyl ether. Combined organic layers were dried over magnesium sulfate

filtered and concentrated. Crude product purified by silica gel chromatography eluting with 2:1 hexanes:ethyl acetate to give 0.21g of the product as a slightly cloudy colorless oil in 62% yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.71 (t, J =2.9 Hz, 1H), 7.69-7.62 (m, 4H), 7.45-7.33 (m, 6H), 7.23-7.17 (m, 2H), 6.89-6.83 (m, 2H), 5.59-5.46 (m, 2H), 4.41 (s, 2H), 3.80 (s, 3H), 3.70-3.64 (m, 2H), 3.28 (d, J =8.8 Hz, 1H), 3.20 (d, J =8.8 Hz 1H), 2.91 (d, J =2.4 Hz, 2H), 2.28 (q, J =6.3 Hz, 2H), 1.54 (s, 1H), 1.26 (s, 3H), 1.14 (s, 6H), 1.04 (s, 9H).