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A concise asymmetric route to the antibiotic macrolides patulolide A and pyrenophorin

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Abstract—In this letter, we describe an enantiospecific route to patulolide A and pyrenophorin through the synthesis of known protected seco acid precursors starting from commercially available (*S*)-ethyl lactate.

Molecules belonging to the medium and large size ring lactones have attracted considerable attention from synthetic chemists due to their interesting biological properties. Though many macrolides have complex structures with high substitution, simple macrolides also possess important properties which make them worth exploring.[1] Most of the physiologically active macrolactones often have a double bond at the α,β-position and a keto or hydroxy functional group at the γ-position (see, Fig. 1).[2]

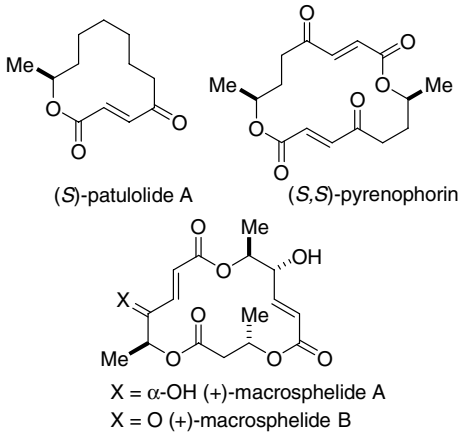
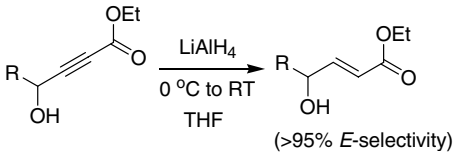


Figure 1. Selected antibiotic macrolides with γ-keto-α,β-unsaturated (*E*)-alkenoic acid moieties.

Recently, we disclosed an efficient and highly trans-selective conjugate hydride addition on γ-hydroxy-α,β-alkynoic esters using $LiAlH_4$ to produce γ-hydroxy-α,β-(*E*)-alkenoic esters (Scheme 1).[3] As a direct application of this method, we were interested in the synthesis of bioactive macrocycles possessing γ-hydroxy or γ-keto-α,β-(*E*)-alkenoic ester functionalities. In this letter, we report asymmetric routes to (*S*)-patulolide A and (*S*,*S*)-pyrenophorin via their seco acid precursors.

Patulolide A is a twelve-membered lactone isolated from the culture broth of *Penicillium urticae* mutant S11R59.[4] The interesting biological activity[5] (antifungal, antibacterial, and antiinflammatory) of this twelve-membered lactone and related molecules has attracted the attention of synthetic chemists and resulted in several syntheses.[6] In our synthesis, commercially available (*S*)-ethyl lactate **1** was converted into aldehyde **2** following the literature protocol.[7] Wittig olefination followed by reduction of the double bond gave saturated ester **3**. The aldehyde **4** obtained from **3** through DIBAL–H reduction, was coupled with ethyl propiolate in the presence of LDA



Scheme 1.

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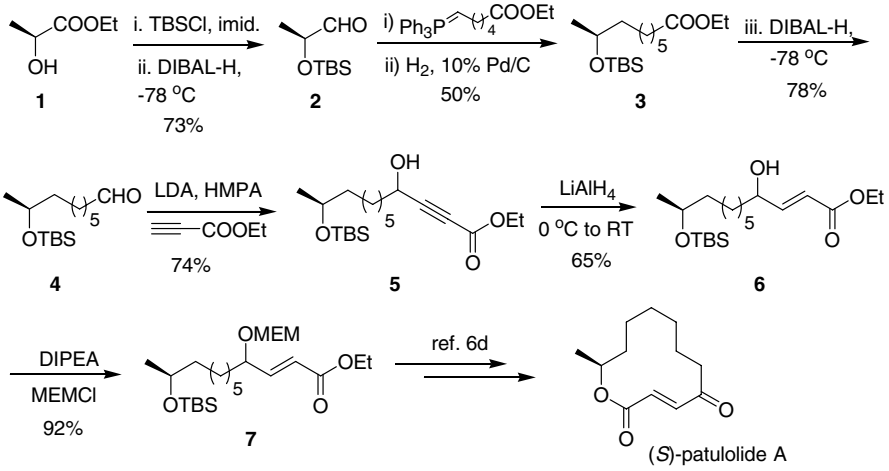
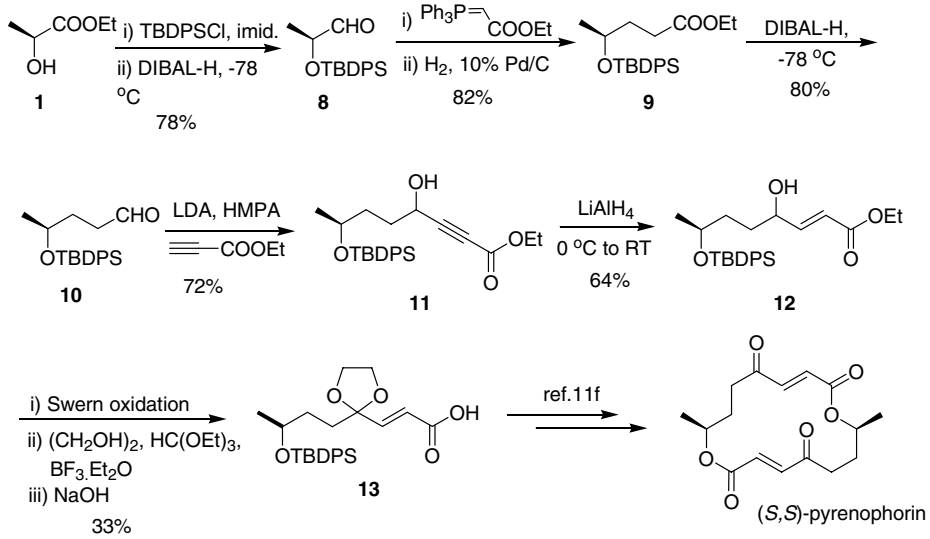


Scheme 2.

to give compound **5** as diastereomeric mixture.[8] The stereochemistry of the newly formed center is not important as this center represents a carbonyl group in the natural product. As expected, conjugate reduction of **5** using $LiAlH_4$ resulted in the desired (*E*)-alkenoic ester **6** in 65% isolated yield (Scheme 2). The hydroxy functional group was protected as its 2-methoxyethoxymethyl ether to furnish known seco acid precursor **7**, which has previously been used to prepare the natural product (*S*)-patulolide A.[6d] The spectral data of compound **7** were compared with literature data and found to be identical.[9]

Pyrenophorin, a sixteen-membered diolide isolated from *Pyrenophora avenae*, is a powerful antifungal agent. This C_2-symmetric dilactone is derived by head-to-tail dimerization of two identical C8 units.[10] This compound has been a target for many groups due to its interesting structural features combined with its biological activity.[11] In our route to pyrenophorin, aldehyde **8**[12] was converted to the ester **9** via two-carbon homologation followed by hydrogenation. The homologated ester **9** was transformed into the γ-hydroxy-α,β-(*E*)-alkenoic ester **12** via intermediates **10** and **11** using a similar procedure to that described for patulolide A. Finally, the known protected seco acid precursor **13**[11f] of (*S*,*S*)-pyrenophorin was synthesized from compound **12** through oxidation of the hydroxyl group and protection of the resulting ketone with ethylene glycol, followed by hydrolysis (Scheme 3). The spectral data for compound **13** were compared with the reported data of the same compound and found to be identical.[9]

In summary, we have prepared known seco acid precursors **7** and **13** starting from commercially available (*S*)-ethyl lactate. We have demonstrated the utility of the recently developed trans-selective conjugate reduction of γ-hydroxy-α,β-alkynoic esters to γ-hydroxy-α,β-(*E*)-alkenoic esters in macrocyclic natural product synthesis. Application of this methodology for the synthesis of other bioactive natural products will be the subject of future publications.



Scheme 3.

Acknowledgements

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9. All products were characterized on the basis of spectral data (IR, ^{1}H NMR, ^{13}C NMR, and MS). Compound **6**: To a suspension of lithium aluminium hydride (20 mg, 0.54 mmol) in 10 ml of dry THF was added compound **5** (0.2 g, 0.54 mmol) in 5 ml of THF dropwise at 0 °C and the reaction allowed to stir at room temperature. After the starting material had disappeared (tlc), the reaction was quenched with saturated ammonium chloride solution, diluted with ether, filtered over celite, and the organic layer dried over Na_2SO_4. The residue obtained after removal of the solvent was purified by column chromatography (eluent: 0–3% ethyl acetate: petroleum ether) to furnish the desired compound (130 mg) as a colorless liquid. Yield = 65%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.96 (dd, $J_1 = 5.1$ Hz, $J_2 = 15.85$ Hz, 1H), 6.04 (dd, $J_1 = 1.6$ Hz, $J_2 = 15.85$ Hz, 1H), 4.31 (t, $J = 4.8$ Hz, 1H), 4.23 (q, $J = 7.0$ Hz, 2H), 3.78 (q, $J = 5.9$ Hz, 1H), 1.64–1.25 (m, 16H), 1.11 (d, $J = 6.2$ Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): −4.7, −4.4, 14.2, 18.1, 23.8, 25.1, 25.7, 25.9, 29.4, 29.5, 36.7, 39.7, 60.4, 68.6, 71.2, 120.2, 150.0; MS (CI) 373 (M+1, 30%); HRMS calcd. for $C_{20}H_{41}O_4Si$ (M+1): 373.2774, found. 373.2780. Compound **7**: A mixture of compound **6** (51 mg, 0.137 mmol), DIPEA (0.07 ml, 0.41 mmol) in 3 ml of dichloroethane was stirred for 30 min at room temperature. The mixture was cooled to 0 °C and MEMCl (37 mg, 0.3 mmol) was added dropwise and the mixture heated to reflux for 60 h. The reaction mixture was cooled to room temperature, diluted with DCM, washed with $NaHCO_3$ solution, and brine, the organic phase dried over Na_2SO_4, and concentrated. The crude product was purified over silica gel (eluent: 0–3% ethyl acetate: petroleum ether) to give the required compound **7** (58 mg) as a colorless liquid. Yield = 92%; IR (neat): 2931, 2858, 1724 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.82 (dd, $J_1 = 6.4$ Hz, $J_2 = 15.86$ Hz, 1H), 5.97 (dd, $J_1 = 1.35$ Hz, $J_2 = 15.85$ Hz, 1H), 4.69 (s, 2H), 4.21–4.16 (m, 3H), 3.78–3.73 (m, 2H), 3.66–3.61 (m, 1H), 3.54 (t, $J = 4.84$ Hz, 2H), 3.37 (s, 3H), 1.34–1.31 (m, 12H), 1.30 (t, $J = 6.98$ Hz, 3H), 1.10 (d, $J = 6.2$ Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): −4.72, −4.42, 14.2, 23.7, 25.0, 25.8 (3C), 29.5, 34.7, 39.6, 58.9, 60.4, 67.1, 68.5, 71.6, 75.3, 76.3, 77.0, 77.6, 93.6, 121.8, 147.8, 166.2; MS (CI) 461 (M+1, 50%). Compound **13**: A solution of oxalyl chloride (0.79 g, 6.27 mmol) in 30 ml of DCM was cooled to −78 °C and DMSO (0.98 g, 12.5 mmol) in 10 ml of DCM was added dropwise. After stirring for 30 min, alcohol **12** (2.3 g, 5.2 mmol) in 10 ml of DCM was added dropwise. After 1 h, triethylamine (3.6 ml) was added, the mixture again stirred for 1 h at −78 °C and at room temperature for 30 min. Ammonium chloride solution was added to the reaction mixture which was extracted with DCM. The organic layer was washed with water, brine and dried over Na_2SO_4. The residue obtained after removal of the solvent was purified using flash column chromotography to give the corresponding keto ester (1.37 g) as a colorless liquid. Yield = 60%; IR (neat): 2932, 2858, 1727, 1702, 1472, 1427 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67–7.64 (m, 4H), 7.44–7.34 (m, 6H), 6.98 (d, $J = 15.85$ Hz, 1H), 6.58 (d, $J = 16.1$ Hz, 1H), 4.29 (q, $J = 7.25$ Hz, 2H), 3.95 (pent, $J = 6.18$ Hz, 1H), 2.68–2.60 (m, 2H), 1.80–1.71 (m, 2H), 1.35 (t, $J = 6.98$ Hz, 3H), 1.08 (d, $J = 6.17$ Hz, 3H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz): 10.5, 15.4, 19.5, 23.2, 28.9, 33.3, 57.6, 64.6, 123.7, 123.8, 125.8, 125.9, 126.7, 130.2, 130.5, 131.9, 132.0, 135.5, 161.6, 195.6; MS (CI) 439 (M+1, 10%), 381 (10%), 361 (20%), 183 (100%); HRMS calcd. for $C_{26}H_{35}O_4Si$ (M+1): 439.2304, found. 439.2298. To a solution of the above keto ester (1.3 g, 2.9 mmol) in 20 ml of benzene were added ethanediol (0.39 g, 6.2 mmol), ethyl orthoformate (0.82 g, 5.5 mmol), 4–5 drops of $BF_3{\cdot}(OEt)_2$ and the resulting mixture was refluxed for 24 h. The reaction mixture was cooled to room temperature, diluted with dichloromethane, washed with $NaHCO_3$ solution, and brine and the organic phase dried over Na_2SO_4, and concentrated. The crude product was purified over silica gel (eluent: 0–3% ethyl acetate: petroleum ether) to give the required compound (1.14 g) as a viscous liquid. Yield = 80%; IR (neat): 2962, 2858, 1723, 1472, 1428 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.69–7.65 (m, 4H), 7.42–7.33 (m, 6H), 6.70 (d, $J = 15.58$ Hz, 1H), 6.04 (d, $J = 15.58$ Hz, 1H), 4.23 (q, $J = 6.99$ Hz, 2H), 3.91–3.80 (m, 5H), 1.81–1.68 (m, 2H), 1.56–1.50 (m, 2H), 1.32 (t, $J = 7.26$ Hz, 3H), 1.04 (d, $J = 2.96$ Hz, 3H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz): 14.2, 19.2, 23.1, 27.0 (3C), 29.4, 32.5, 33.1,60.5, 64.83, 64.85, 69.1, 108.3, 119.4, 121.6, 127.4 (2C), 127.5 (2C), 129.3, 129.4, 134.3, 134.7, 135.8,

135.87, 146.3, 166.2; MS (CI) 483 (M+1, 40%). The ester (200 mg, 0.41 mmol) and NaOH (33 mg, 0.82 mmol) in a mixture of MeOH:THF:water (3:1:1) were stirred at room temperature for 4 days after which the mixture was acidified with 2 N HCl (~5 ml) and extracted with $CHCl_3$. The combined organic layer was washed with brine, and dried over Na_2SO_4. The residue obtained after the removal of the solvent was purified by flash column chromotography (eluent. 0–2% MeOH:$CHCl_3$) to give the seco acid **13** (130 mg) as a colorless liquid. Yield = 69%; IR (neat): 3382, 1703 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.67–7.65 (m, 4H), 7.42–7.33 (m, 6H), 6.80 (d, $J = 15.58$ Hz, 1H), 6.05 (d, $J = 15.58$ Hz, 1H), 3.92–3.82 (m, 5H), 1.82–1.68 (m, 2H), 1.55–1.48 (m, 2H), 1.05 (d, $J = 2.90$ Hz, 3H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz): 14.1, 19.2, 23.1, 27.0 (3C), 32.5, 60.4, 64.9, 69.1, 108.1, 120.7, 127.4 (2C), 127.49 (2C), 127.5 (2C), 129.4, 129.5, 134.3, 134.7, 135.8, 135.87, 149.0, 170.9; MS (CI) 472 (M+NH_4, 80%), 455 (M+H^{+1}, 90%), 199 (100%).

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12. Protection of the hydroxy group with TBDPS resulted in clean reactions and better yields compared to the TBDMS group.