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Stereoselective total synthesis of (−)-decarestrictine D from L-malic acid☆

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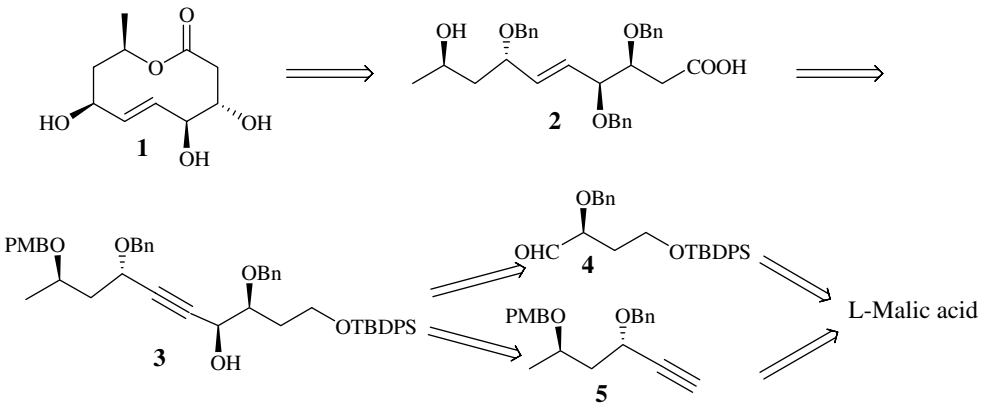
Abstract—A convergent stereoselective total synthesis of (−)-decarestrictine D from L-malic acid is reported.

1. Introduction

(−)-Decarestrictine D (**1**) was independently isolated from different strains of *Penicillium* (*P. corylophilum, P. simplicissimum*)[1] and *Polyporous tuberaster* along with various other 10-membered lactones (decarestrictines A_1/A_2, B, C_1/C_2) of this family. Among this class of compounds, (−)-decarestrictine D potentially inhibits liver cell cholesterol biosynthesis (HEP cells, IC_{50} of 100 nm)[1] and the structural difference between **1** and other inhibitors such as mevinolin and compactin suggests a different mode of action. Also, **1** is highly bio-selective with no significant antibacterial, antifungal, antiprotozoal or antiviral activity.[1] Considering its selective biological profile, compound **1** has been identified by many research groups worldwide as an attractive synthetic target towards developing new cholesterol-lowering drugs. Consequently, the synthesis of **1** and its seco acid have been reported by various research groups.[2–5]

As part of our interest in the synthesis of bioactive natural products,[6] herein, we report a stereoselective total synthesis of (−)-decarestrictine D by a convergent strategy wherein both the intermediates are derived from the common, inexpensive starting material, L-malic acid. Our strategy relies on Sharpless asymmetric epoxidation, acetylenic addition onto a chiral aldehyde, 1,2-*syn* selective reduction and Yamaguchi macrolactonization as the key steps. Retrosynthetic analysis reveals

Retrosynthetic analysis



Keywords: Decarestrictine D; L-Malic acid; 1,2-*syn* selective reduction; Sharpless asymmetric epoxidation; Yamaguchi macrolactonization.
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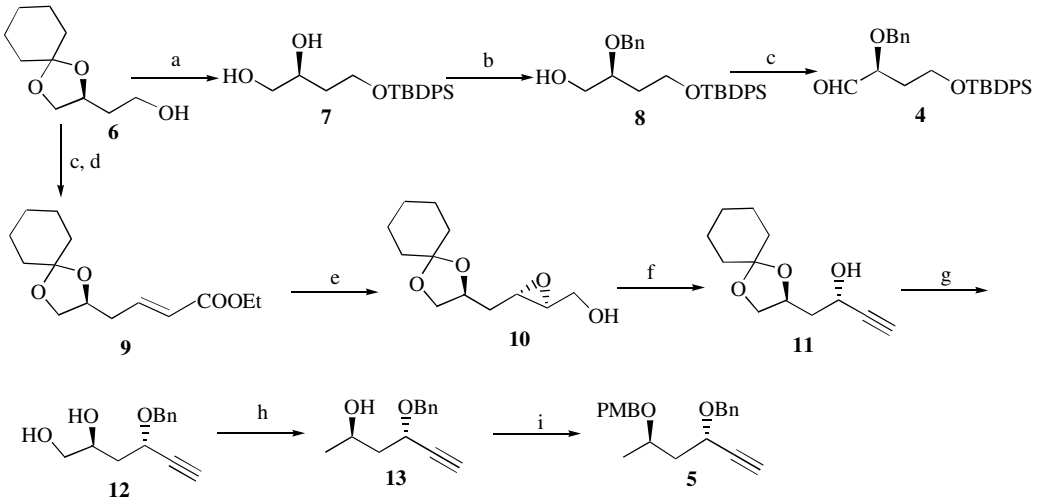


Scheme 1. Reagents and conditions: (a) (i) TBDPSCl, imidazole, CH_2Cl_2, 0 °C–rt, 4 h (90%); (ii) CSA, MeOH, rt, 0.5 h (85%); (b) (i) α,α-Dimethoxytoluene, PPTS, CH_2Cl_2, 0 °C–rt, 3 h (78%); (ii) DIBAL–H, CH_2Cl_2, 0 °C–rt, 3 h (75%); (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C (95%); (d) $Ph_3PCHCOOEt$, benzene, reflux, 2 h (70%); (e) $LiAlH_4/AlCl_3$, ether, 0 °C, 6 h (65%); (ii) (+)-DIPT, $Ti(O^iPr)_4$, cumene hydroperoxide, CH_2Cl_2, −20 °C, 12 h (85%); (f) CCl_4, Ph_3P, $NaHCO_3$, reflux, 1 h (90%); (ii) LDA, THF, −78 °C to −40 °C, 3 h (65%); (g) (i) BnBr, NaH, THF, 0 °C–rt, 6 h (80%); (ii) CSA, MeOH, rt, 0.5 h (85%); (h) (i) TsCl, Et_3N, CH_2Cl_2, 0 °C–rt, 12 h (75%); (ii) $LiAlH_4$, THF, 0 °C–rt, 2 h (90%); (i) PMBBr, NaH, THF, 0 °C–rt, 12 h (75%).

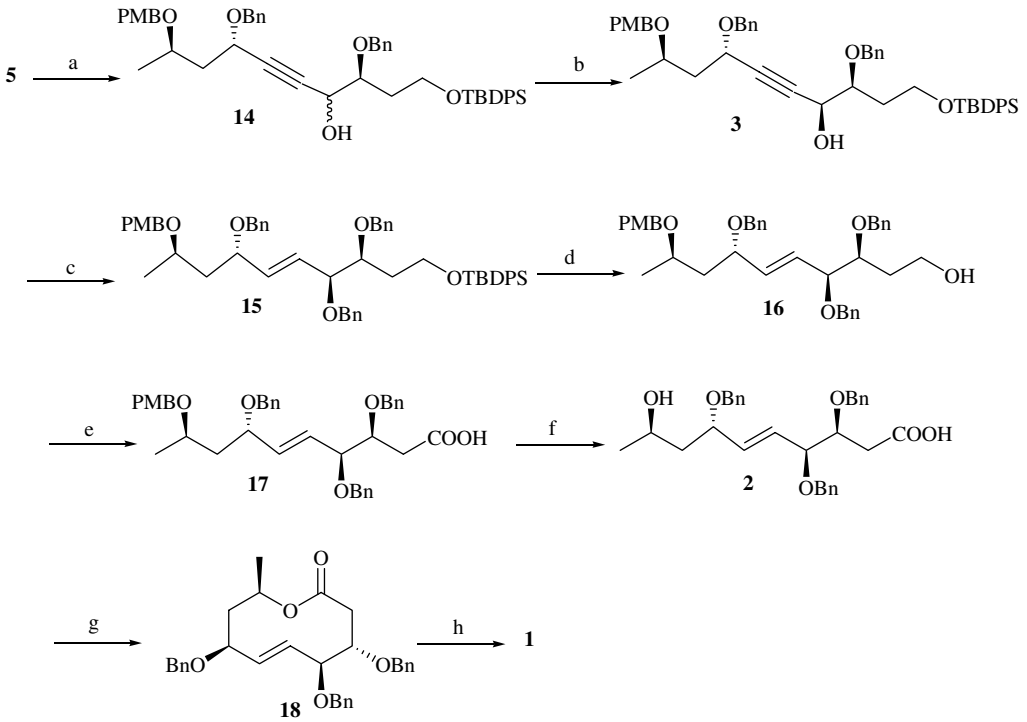
that target compound **1** can be obtained from seco acid **2** by Yamaguchi macrolactonization and subsequent deprotection of the benzyl groups. Seco acid **2**, in turn, could be obtained from chiral propargylic alcohol **3** and compound **3** itself by coupling fragments **4** and **5** followed by an oxidation–reduction protocol to generate the 1,2-*syn* diol system. Both fragments **4** and **5** can be realized independently from L-malic acid by simple chemical transformations.

2. Results and discussion

Accordingly, the synthesis of **1** starts with compound **6** (Scheme 1), which is readily obtained from L-malic acid.[7] Thus, **6** was silylated (TBDPSCl/imidazole/CH_2Cl_2/rt) and then on exposure to CSA in MeOH gave diol **7** (85%). Diol **7** was converted into a benzylidene derivative (α,α-dimethoxytoluene/PPTS/CH_2Cl_2), which on subsequent regioselective reductive ring-opening reaction with DIBAL–H in CH_2Cl_2 afforded the free primary alcohol **8** (75%), which was oxidized under Swern conditions to afford aldehyde **4** (95%).

To prepare alkyne **5**, alcohol **6** was subjected to Swern oxidation followed by a Wittig olefination reaction ($Ph_3PCHCOOEt$/benzene/reflux) to afford *trans* α,β-unsaturated ester **9** (70%). The reduction with $LiAlH_4$–$AlCl_3$ in diethyl ether and then exposure of the ensuing allylic alcohol to Sharpless epoxidation [(+)-DIPT/$Ti(O^iPr)_4$/cumene hydroperoxide/CH_2Cl_2/−20 °C] afforded epoxy alcohol **10** (85%). Epoxide **10** was chlorinated (CCl_4/Ph_3P/reflux) followed by a base induced double elimination (LDA/THF) to afford propargylic alcohol **11**. The hydroxyl group in **11** was protected as its benzyl ether (BnBr/NaH//THF/rt) and the cyclohexylidene group was cleaved (CSA/MeOH/rt) to afford the corresponding diol **12** (85%). The primary hydroxyl group in diol **12** was selectively monotosylated (TsCl/Et_3N/CH_2Cl_2/rt), which upon exhaustive reduction (excess $LiAlH_4$/THF) generated alkyne **13** with the terminal methyl group being installed. Finally, the secondary hydroxyl group was protected as its PMB ether (PMBBr/NaH/THF/rt) to furnish fragment **5**.

In order to prepare **3**, alkyne **5** (Scheme 2) was treated with *n*-BuLi in THF at −78 °C and the resulting acetylenic anion was quenched with **4** to yield **14** (70%) as a diastereomeric mixture (de 20%). In order to increase the diastereoslectivity, and to obtain the requisite stereocentre at the newly created site, hydroxy alkyne **14** was oxidized to its corresponding keto compound (Dess–Martin periodinane/CH_2Cl_2) and selectively reduced with K-Selectride[8] in THF at −78 °C to give **3** (80%) and its diastereomer (15%) (de 70%) as a separable mixture. The reaction of **3** with Red-Al, in diethyl ether gave the corresponding olefin, and the resulting allylic hydroxyl group was protected as its benzyl ether (BnBr/NaH/THF–DMF/rt) to afford **15** (75%). TBDPS deprotection (TBAF/THF/rt) afforded primary alcohol **16** (95%), which was oxidized to the corresponding acid by a two-step process; firstly to an aldehyde by Swern oxidation and then on perchlorite oxidation ($NaClO_2$/$NaH_2PO_4.2H_2O$/*t*-BuOH/2-methyl-2-butene) to the acid **17** (80% over two steps). Treatment with DDQ in CH_2Cl_2–H_2O afforded seco acid **2** as its tri benzyl ether derivative. Yamaguchi macrolactonization[9] yielded **18** (45%) and finally global debenzylation ($TiCl_4/CH_2Cl_2$/0 °C–rt) gave the target compound **1** (65%), $[\alpha]_D^{25}$ −60.3 (*c* 0.4, $CHCl_3$) {natural **1**; $[\alpha]_D^{25}$ −62.0 (*c* 1.0, $CHCl_3$)[1a] and synthetic **1**, $[\alpha]_D^{25}$ −67.0 (*c* 0.26, $CHCl_3$),[2] $[\alpha]_D^{25}$ −68 (*c* 0.066, $CHCl_3$)[5]}. The physical and spectroscopic data of our synthetic sample **1**[10] were identical to those of the reported natural and synthetic products.



Scheme 2. Reagents and conditions: (a) *n*-BuLi, **4**, THF, −78 °C, 3 h (70%); (b) (i) Dess–Martin periodinane, CH_2Cl_2, 0 °C–rt, 2 h (90%); (ii) K-Selectride, THF, −78 °C, 3 h (80%); (c) (i) Red-Al, ether, 0 °C–rt, 2 h (95%); (ii) BnBr, NaH, THF–DMF (9:1), 0 °C–rt, 4 h (75%); (d) TBAF, THF, 0 °C–rt, 12 h (95%); (e) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C 1 h; (ii) $NaClO_2$, $NaH_2PO_4 \cdot 2H_2O$, *t*-BuOH–2-methyl-2-butene (3:1), 0°C–rt, 12 h (80% for two steps); (f) DDQ, CH_2Cl_2–H_2O (19:1), rt, 1 h, (80%); (g) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 0 °C–rt, 4 h, then DMAP, toluene, reflux, 12 h (45%); (h) $TiCl_4$, CH_2Cl_2, 0 °C–rt, 1 h (65%).

The present synthesis of **1** differs from that published by Andrus et al.[2] in the sense that 1,2-*syn* selective reduction of the ketone of **14** derived from L-malic acid was invoked for accessing the vicinal *syn* diol system (**15**) in a more defined manner. This overcomes the ambiguity arising from isomeric products obtained during Sharpless dihydroxylation of a diene as in the earlier strategy. Likewise, one of the hydroxyl groups (C9–OH) of the 1,3-*anti* diol system was realized from the pre-existing chirality in L-malic acid and the other (C7–OH) through the Sharpless asymmetric epoxidation protocol.

3. Conclusion

In conclusion, a stereoselective synthesis of (−)-decarestrictine D **1** was accomplished by means of a versatile strategy, wherein L-malic acid was used as the common starting material for accessing both the advanced intermediates for use in a convergent total synthesis.

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10. The spectral data of selected compounds. Compound **3**: Thick syrup; $[\alpha]_D^{25}$ −108.46 (*c* 2.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.61 (d, 4H, $J = 7.2$ Hz), 7.37–7.30 (m, 6H), 7.26–7.23 (m, 10H), 7.08 (d, 2H, $J = 8.3$ Hz), 6.73 (d, 2H, $J = 8.3$ Hz), 4.73–4.67 (m, 2H), 4.60 (d, 1H, $J = 11.3$ Hz), 4.46–4.27 (m, 5H), 4.16 (d, 1H, $J = 11.1$ Hz), 3.78–3.75 (m, 3H), 3.72 (s, 3H), 2.06–1.80 (m, 4H), 1.16 (d, 3H, $J = 5.8$ Hz), 1.04 (s, 9H); ^{13}C NMR

(75 MHz, $CDCl_3$): 136.48, 129.63, 129.28, 128.35, 128.00, 127.65, 127.56, 113.66, 85.09, 84.51, 79.39, 73.37, 70.72, 70.46, 70.19, 65.34, 64.70, 60.22, 55.15, 43.84, 34.03, 29.64, 26.79, 19.66; IR (thin film) 3449, 2926, 1637, 1107 cm^{-1}; ESIMS; 779 $(M+Na)^+$. Anal. Calcd for $C_{48}H_{56}O_6Si$: C, 76.15; H, 7.46; Si, 3.71. Found: C, 76.19; H, 7.41; Si, 3.67%. Compound **2**: Thick syrup; $[\alpha]_D^{25}$ −57.52 (*c* 0.6, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.25–7.22 (m, 15H), 5.69–5.67 (m, 2H), 4.62 (br s, 2H), 4.56 (d, 1H, $J = 3.4$ Hz), 4.50 (d, 1H, $J = 3.0$ Hz), 4.40–4.27 (m, 2H), 4.07–3.99 (m, 4H), 2.67 (dd, 1H, $J = 3.8$, 15.9 Hz), 2.47 (dd, 1H, $J = 7.6$, 15.9 Hz), 1.69–1.63 (m, 2H), 1.15 (d, 3H, $J = 6.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 176.04, 138.12, 138.04, 134.95, 129.02, 128.61, 128.52, 128.44, 128.00, 127.83, 80.03, 79.65, 77.61, 77.53, 73.39, 71.04, 70.72, 64.93, 43.95, 36.22, 29.81, 23.47; IR (thin film) 3448, 2923, 2855, 1714, 1096 cm^{-1}; ESIMS; 505 $(M+H)^+$, 527 $(M+Na)^+$. Anal. Calcd for $C_{31}H_{36}O_6$: C, 73.79; H, 7.19. Found: C, 73.71; H, 7.22%. Compound **18**: Thick syrup; $[\alpha]_D^{25}$ −6.1 (*c* 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.17 (m, 15H), 5.84 (dd, 1H, $J = 9.6$, 16.2 Hz), 5.68 (dd, 1H, $J = 2.7$, 15.9 Hz), 5.13–5.08 (m, 1H), 4.82 (d, 1H, $J = 11.6$ Hz), 4.62 (d, 1H, $J = 12.0$ Hz), 4.53 (d, 1H, $J = 5.0$ Hz), 4.50 (d, 1H, $J = 5.4$ Hz), 4.41 (d, 1H, $J = 12.0$ Hz), 4.30 (d, 1H, $J = 12.0$ Hz), 4.06 (t, 1H, $J = 3.1$ Hz), 3.90–3.81 (m, 2H), 2.55 (dd, 1H, $J = 2.1$, 13.9 Hz), 2.46 (dd, 1H, $J = 6.9$, 13.9 Hz), 1.91–1.82 (m, 2H), 1.21 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 171.25, 138.02,137.56, 134.45, 129.00, 127.91, 126.00, 79.52, 78.02, 73.39, 71.04, 70.26, 42.83, 36.92, 29.23, 20.03; IR (thin film) 2923, 2855, 1727, 1096, 1068 cm^{-1}; ESIMS; 487 $(M+H)^+$, 509 $(M+Na)^+$. Anal. Calcd for $C_{31}H_{34}O_5$: C, 76.52; H, 7.04. Found: C, 76.58; H, 7.01%. Compound **1**: Yellowish solid; mp = 115–118 °C; $[\alpha]_D^{25}$ −60.3 (*c* 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.90 (dd, 1H, $J = 8.1$, 11.6 Hz), 5.87 (dd, 1H, $J = 2.1$, 15.8 Hz), 5.24 (ddq, 1H, $J = 1.7$, 6.4, 12.5 Hz), 4.41 (dd, 1H, $J = 1.4$, 3.7 Hz), 4.19 (ddd, 1H, $J = 3.9$, 8.4, 11.7 Hz), 4.09–4.00 (br s, 1H), 2.61 (dd, 1H, $J = 1.7$, 14.3 Hz), 2.39 (dd, 1H, $J = 6.4$, 14.3 Hz), 1.90–1.76 (m, 2H), 1.25 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 174.81, 133.86, 129.69, 73.98, 72.49, 72.11, 68.28, 43.04, 33.33, 21.23; IR (KBr) 3414, 2925, 2855, 1708, 1042 cm^{-1}; HRMS: Calcd *m/z* 239.0895 ($C_{10}H_{16}O_5Na$). Found *m/z* 239.0906, ppm error 4.4186. Literature data[2] of compound **1**: $[\alpha]_D$ −67.0 (*c* 0.26, $CHCl_3$) [lit.[1b] $[\alpha]_D$ −62.0 (*c* 0.4, $CHCl_3$)]; mp = 118–120 °C (lit.[1b] mp) 114–115 °C; ^1H NMR: δ 5.91 (dd, 1H, $J = 15.8$, 8.3 Hz), 5.85 (dd, 1H, $J = 15.8$, 2.4 Hz), 5.25 (ddq, 1H, $J = 14.0$, 6.4, 1.9 Hz), 4.54–4.78 (br s, 1H), 4.43 (dd, 1H, J= 3.7, 1.6 Hz), 4.20 (ddd, 1H, $J = 11.0$, 8.3, 4.0 Hz), 3.94–4.13 (br s, 1H), 2.61 (d, 1H, $J = 14.4$, 1.9 Hz), 2.40 (d, 1H, $J = 14.4$, 6.2 Hz), 1.92 (ddd, 1H, $J = 14.0$,4.0, 1.9 Hz), 1.81 (d, 1H, J= 14.0, 11.0 Hz), 1.52–1.72 (br s, 2 × OH), 1.25 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR: δ 174.9, 133.7, 129.9, 73.9, 72.5, 72.2, 68.2, 43.0, 33.2, 21.3 (lit.[1b] (CD_3OD) 174.7, 135.9, 129.4, 75.4, 73.6, 73.1, 69.4, 44.2, 35.6, 21.6).