Tetrahedron Letters 51 (2010) 4017–4019

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

First stereoselective total synthesis of decarestrictine O via RCM protocol

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ARTICLE INFO

Article history:
Received 31 March 2010
Revised 12 May 2010
Accepted 17 May 2010
Available online 31 May 2010

Keywords:
Decarestrictine O
Propylene oxide
Jacobsen hydrolytic kinetic resolution
Sharpless asymmetric epoxidation
Yamaguchi esterification
Grubbs' II generation catalyst

ABSTRACT

A convergent first stereoselective total synthesis of decarestrictine O via RCM protocol starting from 1,3-propanediol and propylene oxide is reported.

Decarestrictines represent a family of novel 10-membered lactones produced by different strains of *Penicillium*.[1] So far, six components of the family of decarestrictines have been identified. The identical carbon skeleton that constitutes a 10-membered lactone ring varies in the oxygen patterns ranging from carbon 3–7 and the presence of one *E*-configured double bond located either at C-4 or at C-5. This seems to be a result of dehydration during biosynthesis. The decarestrictines show interesting activity in cell line tests with HEP-G2 liver cells[2,3] due to an inhibitory effect on cholesterol biosynthesis. Against this backdrop, we embarked on a program to synthesize some members of this class of compounds. Earlier, we accomplished the total synthesis of the most potent member of this family, decarestrictine D[4a] and other bio-active 10-membered macrolides as well.[4b,4c] Later we took up the synthesis of decarestrictine O for two reasons. The first one being, to the best of our knowledge, so far no synthesis has been reported for **1** and the other one is to accomplish a total synthesis involving RCM (of **2**, Scheme 1) as the key reaction. Though 10-membered macrolides were earlier synthesized via RCM,[5] their synthesis through RCM is still a challenging proposition because such a strategy is highly dependent on substrate as well as on its compatible protecting groups at allylic positions besides the low predictability of the olefin geometry. Herein we report the first stereoselective total synthesis of decarestrictine O **1** by a convergent strategy wherein both the advanced intermediates are derived from the inexpensive starting materials viz. 1,3-propanediol and propylene oxide.

Our strategy relies on Jacobsen kinetic resolution, Sharpless asymmetric epoxidation, Yamaguchi esterification, and ring-closing metathesis (RCM) as the key steps. Retrosynthetic analysis reveals that the target compound **1** (Scheme 1) can be obtained from RCM of diene **2** and subsequent deprotection of PMB-group, diene **2** in turn, could be obtained from Yamaguchi esterification of **4** and **3**. Acid **3** can be realized from epoxy alcohol **6** which in turn could be obtained starting from 1,3-propanediol by simple chemical transformations. And hydroxy alkene **4** can be realized from propylene oxide through simple chemical transformations.

Accordingly, the synthesis of **1** starts with known allylic alcohol **5**[6] (Scheme 2) from propanediol that was subjected Sharpless asymmetric epoxidation once with [(+)-DIPT/Ti(O^iPr)$_4$/cumenehydroperoxide/−20 °C] to afford epoxy alcohol **6**[7] (75%) which was converted to allylic alcohol **7** by a two step process; first by converting to chloro epoxy compound which on Na/ether mediated-elimination afforded the allylic alcohol **7** (75% yield over two steps). The hydroxyl group in **7** was protected as its PMB ether (PMB-Br/NaH/THF/0 °C to rt) to afford **8** (90%), and the TBDPS group in **8** was deprotected with TBAF in THF to afford primary alcohol **9** (91%) which were converted to acid **3** by a two-step process firstly; to an aldehyde by Swern oxidation and then by perchlorite oxidation ($NaClO_2$/$NaH_2PO_4{\cdot}2H_2O$/*t*-BuOH/2-methyl-2-butene) to afford acid **3**[5a] (80% over two steps).

Hydroxy alkene **4** (Scheme 3) was synthesized from the known chiral propyleneoxide[8] and its ring-opening reaction with THP-protected propargyl alcohol followed by protection–deprotection-LAH reduction gave the allylic alcohol **10** in good yields. Allylic alcohol **10** on benzoylation under conventional conditions followed by Sharpless dihydroxylation (AD-mix-α) and protection

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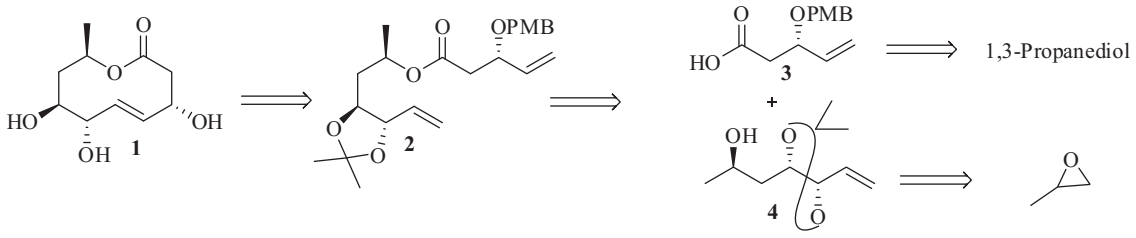
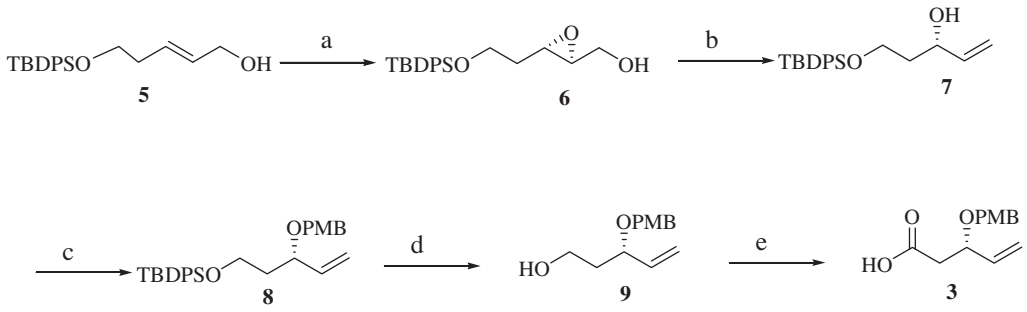
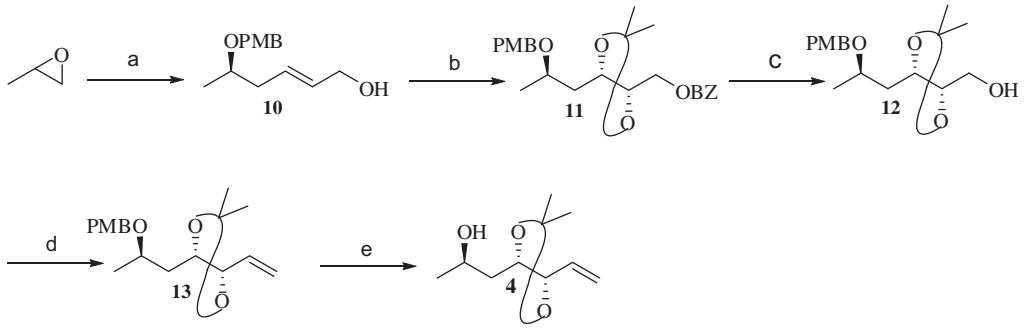
doi:10.1016/j.tetlet.2010.05.064



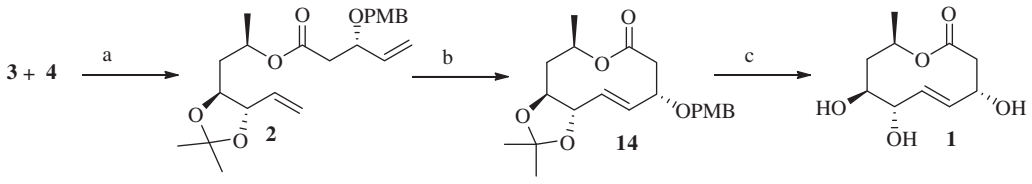
Scheme 1. Retrosynthetic analysis.



Scheme 2. Synthesis of acid **3**. Reagents and conditions: (a) (+)-DIPT, $Ti(O^iPr)_4$, cumenehydroperoxide, CH_2Cl_2, −20 °C, 12 h, 75%; (b) (i) CCl_4, Ph_3P, $NaHCO_3$, reflux, 1 h, (ii) Na/ether, ether, 0 °C to rt, 3 h (75% over two steps); (c) PMB-Br, NaH, THF, 0 °C to rt, 12 h, 90%; (d) TBAF, THF, 0 °C to rt, 2 h, 91%; (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 to rt, 12 h, 80% for two steps).



Scheme 3. Synthesis of alcohol **4**. Reagents and conditions: (a) Ref. 8; (b) (i) Bz–Cl, Et_3N, 0 °C to rt, (ii) AD-mix-ß, 75%, (iii) 2,2-DMP, CH_2Cl_2, PTSA; (c) K_2CO_3, MeOH, 2 h (75% over three steps); (d) (i)$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h, (ii) $Ph_3PCH_3{}^+I^-$, KO^t-Bu, THF, 0 °C, 8 h, 78% (over two steps); (e) DDQ, CH_2Cl_2/H_2O (19:1), rt, 1 h, 93%.



Scheme 4. Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 0 °C to rt, 4 h, then DMAP, **4**, toluene, 0 °C to rt, 12 h, 88%; (b) Grubbs' II generation catalyst (10 mol %), CH_2Cl_2, reflux, 12 h, 75%; (c) TFA, CH_2Cl_2, rt, 1 h, 68%.

of the ensuing diol as acetonide afforded compound **11** (75% over three steps). Compound **11** on debenzoylation, Swern oxidation followed by 1C Wittig olefination ($Ph_3PCH_3{}^+I^-$/KO^t-Bu/THF) afforded epoxy alkene **13** (78% over two steps). The PMB-group in **13** was deprotected with DDQ in CH_2Cl_2/H_2O to obtain intermediate **4** (93%).

With two building blocks **3** and **4** in hand, the next task was to couple them as ester (Scheme 4) under Yamaguchi esterification protocol[9] (2,4,6-trichloro benzoyl chloride/Et_3N/THF then DMAP/toluene) to afford the diene **2** (88%). The diene **2** underwent RCM smoothly using Grubb's II generation catalyst to yield lactone[10] **14** (75%) as a chromatographically separable mixture in 80:20 ratio in favor of *E*-isomer. The compound was characterized by its spectral data.[11] The geometry of the olefin was established as '*E*' from its coupling constants, while one of the olefinic proton appeared at δ 5.75 ppm as a double doublet (J = 8.3, 15.6 Hz) and the other one showed at δ 5.57 ppm as a double doublet (J = 9.3, 15.6 Hz). Finally lactone **14** on global deprotection of PMB ether and acetonide

(TFA/CH_2Cl_2/rt/1 h) afforded the final product decarestrictine O (**1**, 68%). The spectral data of the synthetic compound matched with the literature values.[3,11]

In summary, we accomplished the first total synthesis of decarestrictine O via the RCM protocol.

Acknowledgment

One of the authors (T.J.R.) thanks CSIR, New Delhi, for the financial support in the form of a fellowship.

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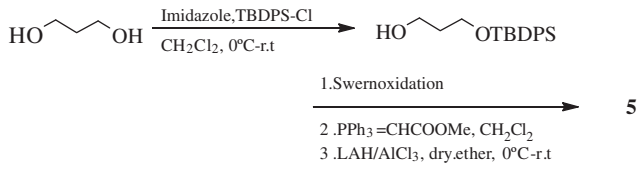
6. Allylic alcohol **5** was prepared by the synthetic route as shown below:



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11. *Spectral data for selected compounds. Compound* **12**: yellow liquid; $[\alpha]_D^{25}$ −54.7 (*c* 0.20, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, *J* = 8.3 Hz, 2H, Ar-H), 6.82 (d, *J* = 8.3 Hz, 2H, Ar-H), 4.46 (d, *J* = 11.3 Hz, 2H, $-OCH_2Ph$), 3.99–3.91 (m, 1H, –OCH), 3.78 (s, 3H, OCH_3), 3.74–3.67 (m, 1H, –OCH), 3.67 (d, *J* = 4.5 Hz, 1H, –OCH), 3.56–3.53 (m, 1H, –OCH), 1.96–1.87 (m, 1H, CH_2), 1.71–1.63 (m, 1H, CH_2), 1.36 (d, *J* = 3.7 Hz, 6H, CH_3), 1.25 (d, *J* = 6.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 135.5, 135.3, 135.1, 129.3, 129.1, 118.8, 114.2, 113.6, 108.4, 82.9, 77.4, 71.9, 69.0, 55.1, 38.3, 27.2, 26.8, 19.6; ESI-MS: *m*/*z* 333 $[M+Na]^+$. Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.80; H, 8.50. *Compound* **13**: yellow liquid; $[\alpha]_D^{25}$ −4.4 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.79 (d, *J* = 8.3 Hz, 2H, Ar-H), 5.79–5.68 (m, 1H, olefinic), 5.35–5.28 (m, 1H, olefinic), 5.17 (d, *J* = 10.5 Hz, 1H, olefinic), 4.45 (d, *J* = 11.3 Hz, 1H, $-OCH_2Ph$), 4.35 (d, *J* = 11.3 Hz, 1H, $-OCH_2Ph$), 3.98 (t, *J* = 7.5 Hz, 1H, –OCH), 3.78 (s, 3H, $-OCH_3$), 3.74–3.66 (m, 2H, –OCH), 1.93–1.84 (m, 1H, $-CH_2$), 1.66–1.58 (m, 1H, $-CH_2$), 1.36 (d, *J* = 3.7 Hz, 6H, $-CH_3$), 1.19 (d, *J* = 6.1 Hz, 3H, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): 159.1, 135.2, 129.2, 119.1, 113.5, 108.5, 82.9, 77.4, 71.7, 69.7, 55.1, 38.5, 27.3, 19.9; IR (neat); 3049, 2932, 1614, 1512, 1454, 1375, 1090, 824 cm^{-1}; ESI-MS: *m*/*z* 329 $[M+Na]^+$. Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.60; H, 8.52. *Compound* **4**: yellow syrup oil; $[\alpha]_D^{25}$ −15.5 (*c* 0.3, $CHCl_3$): ^1H NMR (500 MHz, $CDCl_3$): δ 5.78–5.71 (m, 1H), 5.35 (d, *J* = 10.7 Hz, 1H), 3.97–3.93 (m, 2H, –OCH), 3.73 (td, *J* = 2.9, 10.7 Hz, 1H, –OCH), 2.83 (br s, 1H, –OH), 1.65 (d, *J* = 14.6 Hz, 1H), 1.59–1.52 (m, 1H, CH_2), 1.40 (s, 6H, CH_3), 1.16 (d, *J* = 5.8 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.9, 119.4, 83.1, 80.9, 67.2, 40.1, 27.1, 26.9, 23.2; ESI-MS: *m*/*z* 209 $[M+Na]^+$. *Compound* **3**: colorless liquid; $[\alpha]_D^{25}$ −36.3 (*c* 0.50, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.16 (d, 2H, *J* = 8.3 Hz, Ar-H), 6.78 (d, 2H, *J* = 8.3 Hz, Ar-H), 5.82–5.71 (m, 1H, olefinic), 5.34–5.23 (m, 2H, olefinic), 4.49 (d, 1H, *J* = 11.3 Hz, $-OCH_2C_6H_4$), 4.28 (d, 1H, *J* = 11.3 Hz, $-OCH_2C_6H_4$), 4.25–4.16 (m, 2H, $-OCH_2$), 3.78 (s, 3H, $-OCH_3$), 2.64 (dd, 1H, *J* = 8.3, 15.8 Hz, $-CH_2$), 2.51 (dd, 1H, *J* = 8.3, 15.8 Hz, 1H, $-CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 138.4, 129.3, 117.0, 113.6, 72.8, 70.7, 66.5, 55.5, 37.3, 25.9, 19.0; IR (neat): 3410, 2923, 2362, 1713, 1612, 1513 cm^{-1}; MS (ESI): 259 $(M+Na)^+$ HRMS ($C_{13}H_{16}O_4Na$) found: 259.0949 calcd: 259.0940. *Compound* **2**: yellow syrup; $[\alpha]_D^{25}$ −12.8 (*c* 0.35, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.16 (d, *J* = 8.3 Hz, 2H), 6.78 (d, *J* = 8.3 Hz, 2H), 5.78–5.68 (m, 2H, olefinic), 5.33–5.17 (m, 4H, olefinic), 5.05 (q, *J* = 6.2 Hz, 1H, –OCH), 4.46 (d, *J* = 11.4 Hz, 1H, $-OCH_2Ph$), 4.30 (d, *J* = 11.4 Hz,1H, $-OCH_2Ph$), 4.19 (q, *J* = 7.2 Hz, 1H, –OCH), 3.92 (t, *J* = 7.2 Hz, 1H, –OCH), 3.77 (s, 3H, CH_3), 3.65 (hex, *J* = 4.1 Hz,1H, –OCH), 2.56 (dd, *J* = 8.3, 14.5 Hz, 1H, CH_2), 2.41 (dd, *J* = 6.2, 15.6 Hz, 1H, CH_2), 1.85 (quin, *J* = 6.2 Hz, 1H, CH_2), 1.72–1.65 (m, 1H, CH_2), 1.34 (d, *J* = 15.6 Hz, 6H, CH_3), 1.22 (d, *J* = 6.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 137.3, 135.1, 134.7, 129.5, 129.3, 119.4, 118.1, 117.8, 113.8, 82.6, 77.4, 76.3, 70.6, 68.5, 54.8, 41.3, 37.8, 27.3, 20.0, 19.6; HRMS *m*/*z* $[M+Na]^+$ found 427.2091 calcd 427.2096 for $C_{23}H_{32}O_6Na$. *Compound* **14**: thick syrup: $[\alpha]_D^{25}$ −52.2 (*c* 0.20, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.2 (d, *J* = 8.3 Hz, 2H, Ar-H), 6.82 (d, *J* = 8.3 Hz, 2H, Ar-H), 5.75 (dd, *J* = 8.3, 15.6 Hz, 1H, olefinic), 5.57 (dd, *J* = 9.3, 15.6 Hz, 1H, olefinic), 5.10 (m, 1H, –OCH), 4.53 (d, *J* = 12.4 Hz, 1H, OCH_2Ph), 4.33–4.23 (m, 2H, –OCH), 3.93–3.83 (m, 4H, –OCH), 3.79 (s, 3H, CH_3) 3.72 (t, *J* = 8.3 Hz, 1H, –OCH), 2.82 (dd, *J* = 9.3, 12.4 Hz, 1H, CH_2), 2.51 (dd, *J* = 3.1, 13.5 Hz, 1H, CH_2), 2.33–2.25 (m, 1H, CH_2), 1.75 (d, *J* = 15.6 Hz, 1H, CH_2), 1.4 (d, *J* = 9.3 Hz, 6H, CH_3), 1.28 (d, *J* = 6.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 134.3, 133.6, 131.3, 130.9, 129.1, 114.0, 113.6, 109.2, 84.1, 74.5, 70.6,68.4, 55.4, 43.2, 33.2, 29.6, 27.1, 18.7; HRMS *m*/*z* $[M+Na]^+$ found 399.1772 calculated 399.1783 for $C_{21}H_{28}O_7Na$. *Compound* **1**: thick syrup; $[\alpha]_D^{25}$ −18.5 (*c* 0.20, CH_3OH); ^1H NMR (500 MHz, acetone-d_6): δ 5.55 (dd, *J* = 7.1, 16.3 Hz, 1H, olefinic), 5.39 (dd, *J* = 8.1, 16.1 Hz, 1H, olefinic), 5.01 (m, 1H, -OCH), 4.57 (br s, 1H, –OH), 4.45 (m, 1H, –OCH), 4.26 (m, 1H, –OCH), 4.03 (br s, 1H, –OH), 3.45–3.40 (m, 1H, –OCH), 2.89 (dd, *J* = 7.9, 13.3 Hz, 1H, $-CH_2$), 2.31–2.25 (m, *J* = 4.5, 13.5 Hz, 1H, $-CH_2$), 1.36 (dd, *J* = 3.2, 15.6 Hz, 1H, $-CH_2$), 1.31 (m, 1H, $-CH_2$), 1.28 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, acetone-d_6): δ 170.7, 135.7, 131.0, 76.9, 74.0, 73.2, 71.5, 45.2, 39.7, 21.2; IR (neat): 3399, 2924, 1717, 1459 cm^{-1} HRMS *m*/*z* $[M+Na]^+$ found 239.0889; calcd 239.0895 for $C_{10}H_{16}O_5Na$.