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The furan approach to oxacycles. Part 4: A synthesis of (+)-decarestrictine L

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Abstract—We describe an efficient new approach for the enantioselective synthesis of (+)-(2*R*,3*S*,6*R*)-decarestrictine L from commercially available starting material using our newly developed methodology based on the oxidation of a furan ring with singlet oxygen followed by an intramolecular hetero Michael addition.

Decarestrictine L is a minor component of the decarestrictine family and was first isolated in 1992[1] from a culture of *Penicillium simplicissimus*. While the major components of the decarestrictine family show a 10-membered lactone ring system, decarestrictine L is unique in possessing a tetrahydropyranyl nucleus (Fig. 1).

Decarestrictine L has been shown to inhibit HMG-CoA reductase, involved in the first step of the biosynthesis of cholesterol.[2] The interesting biological property of this molecule, coupled with the extreme scarcity of the natural material make it an appealing synthetic target. Some good total syntheses of decarestrictine L can be found in the literature.[3] We recently described a new methodology for the synthesis of oxacyclic compounds using either methoxyallene[4a,e] or furan[4b,d] as a starting material. The scope and limitations of this very powerful methodology are being determined and its application to the synthesis of cyclic as well as polycyclic natural products is currently under way in our laboratories. We report herein a synthesis of (+)-decarestrictine L using the furan approach.[4b,d] Furan **1** was chosen as a chiral starting material and was synthesized according to Scheme 1.

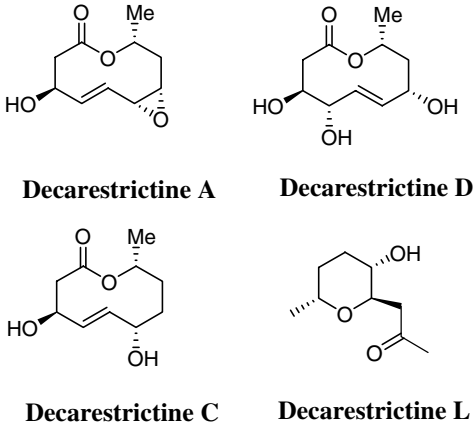

Figure 1.

Commercially available chiral hydroxyester **3** reacted with TBDPSCl to give **4**[5] in 99% yield. Hydrolysis of ester **4** with Dibal afforded 99% yield of alcohol **5**[5] which was easily converted into iodide **6**.[5,6] Lithiation of furan **7** and reaction with **6** afforded the targeted alkylated furan **1**.[7a] It was anticipated that oxidation of furan **1** with singlet oxygen followed by treatment with acetic anhydride in pyridine, would lead to butenolide **8**, direct precursor of decarestrictine L (Scheme 2).

Indeed oxidation of **1** with singlet oxygen followed by treatment with acetic anhydride in pyridine, afforded butenolide **8**[5] in excellent yield (99%). Removal of the TBDPS group of **8** with TBAF gave the bicyclic lactone **9**[5] through an intramolecular Michael addition (72% yield, mixture of two diastereoisomeric compounds). Lactone **9** was opened using $LiAlH_4$ in the presence of $BF_3{\cdot}OEt_2$ to afford a 95% yield of **10**[5] as a mixture of diastereoisomeric diols.[5,4c,d] Selective protection of the primary alcohol of **10** followed by oxidation with

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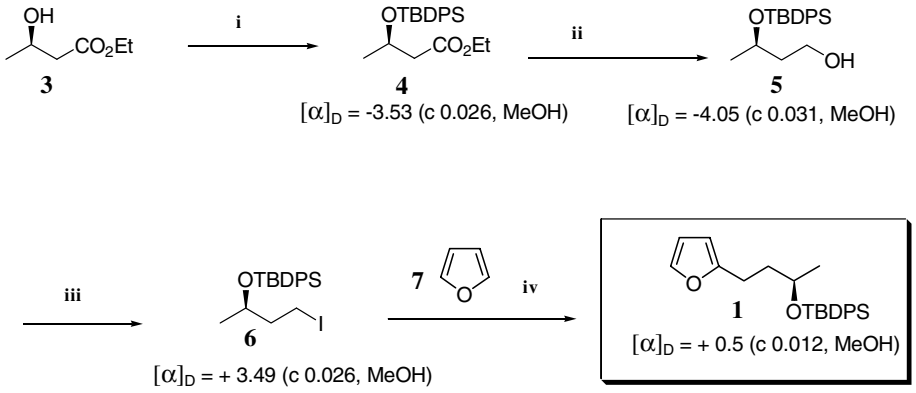
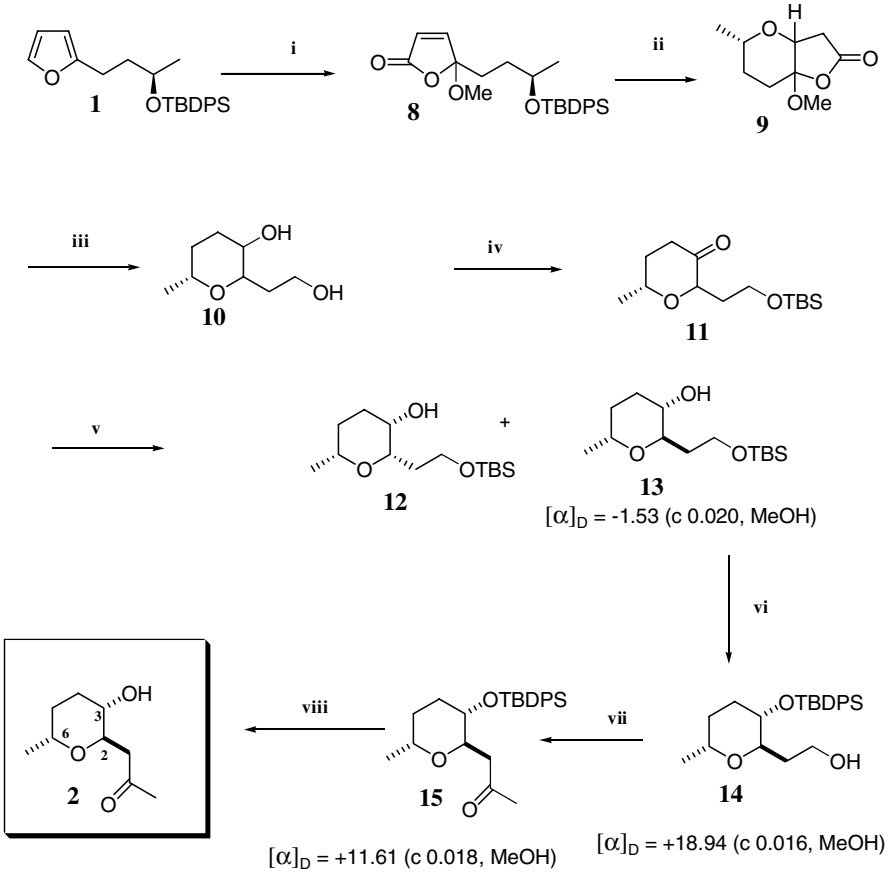


Scheme 1. Reagents and conditions: (i) TBDPSCl, Imid, DMF (99%); (ii) Dibal, CH_2Cl_2, −78 °C (99%); (iii) PPh_3, I_2, Imid, THF, 0 °C (93%); (iv) **7**, bipy, *n*BuLi, THF, 0 °C to rt (99%).



Scheme 2. Reagents and conditions: (i) (a) $^1O_2$, MeOH, rose bengal, *hv*; (b) Ac_2O, py, DMAP (96%, two steps); (ii) TBAF, THF, rt (72%); (iii) LAH, $BF_3{\cdot}OEt_2$ (95%); (iv) (a) TBSCl, Imid, THF (91%); (b) TPAP, NMO, CH_2Cl_2 (83%); (v) $NaBH_4$, MeOH–CH_2Cl_2, −78 °C (97% **12**/**13**: 4.5/5.5); (vi) (a) TBDPSCl, Imid, DMF (80%); (b) CSA, CH_2Cl_2/MeOH (1:1), 0 °C (90%); (vii) (a) TPAP, NMO, CH_2Cl_2 (90%); (b) MeLi, Et_2O, −78 °C (99%); (c) TPAP, NMO, CH_2Cl_2 (91%); (viii) TBAF, THF, rt (82%).

tetrapropylammonium perruthenate (TPAP) afforded a mixture of two diastereoisomeric ketones **11**,[5] which on reaction with sodium borohydride in MeOH–CH_2Cl_2 at −78 °C gave a mixture of two diastereoisomeric alcohols **12**[7b] [R_f: 0.49 (50% EtOAc/hexane)] and **13**.[7c] [R_f: 0.59 (50% EtOAc/hexane), total yield 97%, **12**/**13** = 4.5/5.5] easily separable by column chromatography using 10% EtOAc/hexane as eluent. The relative stereochemistry of **13** was established by NOE experiments (Fig. 2).

Protection of the secondary alcohol of **13** and selective removal of the TBS group afforded alcohol **14**. TPAP oxidation of alcohol **14** followed by reaction of the resulting aldehyde with MeLi afforded a secondary alcohol which was oxidized to ketone **15**.[7d] The stage was set

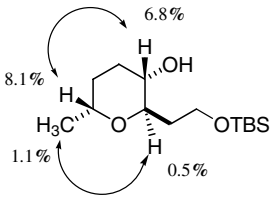


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Figure 2. NOE correlations for **13**.

for the final TBAF deprotection step which afforded (+)-decarestrictine L (**2**) which was spectroscopically identical to the natural product.[1,3f]

In conclusion, a new and efficient method for the enantioselective synthesis of (+)-decarestrictine L (**2**) from commercially available chiral hydroxyester **3** is described. This synthesis enlarges the scope of our newly developed methodology for the synthesis of oxacyclic systems. The use of this methodology for the synthesis of various natural products is now under way in our laboratories.

Acknowledgements

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7. (a) Compound **1**: $[\alpha]_D^{25}$ +0.5 (*c* 0.012, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.70 (4H, d, $J = 6.94$), 7.46–7.40 (6H, m), 7.39–7.33 (1H, m), 6.25 (1H, dd, $J = 2.04$, 2.84), 5.88 (1H, d, $J = 2.84$), 3.94 (1H, q, $J = 5.93$), 2.72–2.66 (2H, m), 1.87–1.77 (2H, m), 1.10 (3H, d, $J = 6.14$), 1.08 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 156.23 (C), 140.64 (CH), 135.86 (CH), 134.76 (C), 129.50 (CH), 127.50 (CH), 110.00 (CH), 104.44 (CH), 68.87 (CH), 37.46 (CH_2), 27.02 (CH_3-^{t}Bu), 23.81 (CH_3), 23.12 (CH_2), 19.29 (C-^{t}Bu); HRMS (FAB+) calcd for $C_{24}H_{29}O_2Si$ 377.1937, found 377.1951; (b) Compound **12**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.92 (1H, s), 3.85–3.80 (1H, m), 3.76–3.70 (1H, m), 3.39 (1H, m), 3.32–3.27 (1H, m), 3.16–3.11 (1H, m), 2.08–2.05 (1H, m), 1.89–1.83 (2H, m), 1.67 (1H, m), 1.47–1.18 (2H, m), 1.14 (3H, d, $J = 5.98$), 0.89 (9H, s), 0.07 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 81.15 (CH), 73.44 (CH), 70.21 (CH), 60.38 (CH_2), 37.59 (CH_2), 32.90 (CH_2), 32.09 (CH_2), 25.84 (CH_3-^{t}Bu), 21.46 (CH_3), 18.21 (C-^{t}Bu), −5.47 (CH_3Si), −5.55 (CH_3Si); HRMS (FAB+) calcd for $C_{14}H_{31}O_3Si$ 275.2042, found 275.2049; (c) Compound **13**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.91–3.85 (2H, m), 3.79–3.45 (3H, m), 2.80 (1H, s), 1.95–1.84 (2H, m), 1.83–1.76 (1H, m), 1.75–1.64 (1H, m), 1.60–1.53 (1H, m), 1.40–1.24 (1H, m), 1.17 (3H, d, $J = 6.52$), 0.89 (9H, s), 0.06 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 74.25 (CH), 67.19 (CH), 66.88 (CH), 60.19 (CH_2), 32.34 (CH_2), 27.88 (CH_2), 26.57 (CH_2), 26.26 (CH_3-^{t}Bu), 18.84 (CH_4), 18.24 (C-^{t}Bu), −5.46 (CH_3Si); HRMS (FAB+) calcd for $C_{14}H_{31}O_3Si$ 275.2042, found 275.2049; (d) Compound **15**: $[\alpha]_D^{25}$ +11.61 (*c* 0.018, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.66–7.62 (4H, m), 7.42–7.35 (6H, m), 4.25 (1H, m), 3.92 (1H, m), 3.64 (1H, m), 2.91 (1H, dd, $J = 4.05$, 15.13), 2.73 (1H, dd, $J = 10.42$, 15.09), 2.11 (3H, s), 1.60–1.58 (4H, m), 1.04 (9H, s), 0.99 (3H, d, $J = 6.13$); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 207.84 (CO), 135.71, 135.69, 133.97, 129.90, 129.77, 127.79, 127.62, 72.75 (CH), 69.06 (CH), 65.03 (CH), 40.71 (CH_2), 31.57 (CH_2), 29.70, 27.46.77 (CH_2), 26.95 (CH_3-^{t}Bu), 20.89 (C-^{t}Bu), 19.15 (CH_3).