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Tetrahedron
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Tetrahedron 62 (2006) 73–78

A concise enantioselective synthesis of the fungal metabolite (+)-decarestrictine L

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Received 5 August 2005; revised 15 September 2005; accepted 29 September 2005

Available online 28 October 2005

Abstract—A stereoselective 10-step synthesis of the fungal metabolite (+)-decarestrictine L from commercially available ethyl (*R*)-3-hydroxybutyrate is described in which tandem oxonium ylide formation and rearrangement is used to construct the tetrahydropyranyl core of the natural product.

1. Introduction

The decarestrictines are secondary metabolites that were isolated from various *Penicillium* strains and identified as bioactive compounds by chemical screening.[1] Several members of the decarestrictine family of natural products have been shown to inhibit the biosynthesis of cholesterol in both a HEP-G2 liver cell assay and in vivo.[1c,d] Of the 15 decarestrictines isolated to date, 13 possess a 10-membered lactone core,[1a,b] a structural feature that is common to other fungal metabolites (Fig. 1). Decarestrictines L and M differ substantially in structure from the other decarestrictines—decarestrictine L contains a tetrahydropyranyl system whilst decarestrictine M is an ether-bridged bicyclic lactone (Fig. 1).[1c]

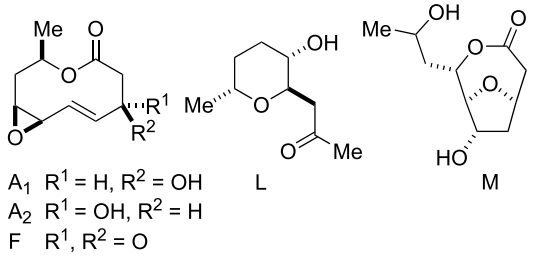
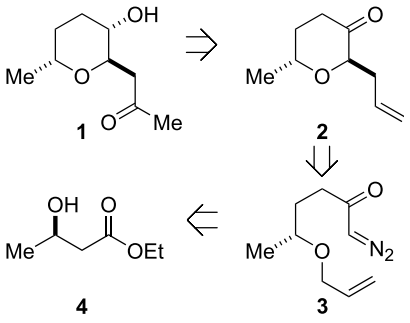


Figure 1. Representative members of the decarestrictine family of natural products.

Decarestrictine L was isolated as a minor component from a culture broth of *Penicillium simplicissimum* (strain FH-A 6090) by Thiericke and co-workers in 1992,[1c] and the relative configurations of the stereogenic centres were established using NMR spectroscopy. Although it is a relatively simple natural product, decarestrictine L has aroused considerable synthetic interest. The first synthesis of (+)-decarestrictine L was reported by Kobayashi and co-workers in 1993 and this established the absolute configuration of the natural product as (2*R*,3*S*,6*R*).[2] Subsequently, four other syntheses of the natural (+) enantiomer have been reported,[3–6] and in addition we have synthesised the compound as its racemate.[7] The syntheses of (+)-decarestrictine L published to date all suffer from one or more shortcomings with regard to following issues: the number of steps, overall chemical yield, stereoselectivity or the availability and expense of the starting materials.[2–6] We now wish to report a short (10-step) stereoselective synthesis of (+)-decarestrictine L that commences from the relatively inexpensive and readily available chiral pool material ethyl (*R*)-3-hydroxybutyrate.

2. Results and discussion

The synthesis of (+)-decarestrictine L was conceived following the retrosynthetic analysis outlined in Scheme 1.



Scheme 1. Retrosynthetic analysis of (+)-decarestrictine L (**1**).

Keywords: Decarestrictine; Stereoselective synthesis; Metal carbenoid; Oxonium ylide; Rearragement.
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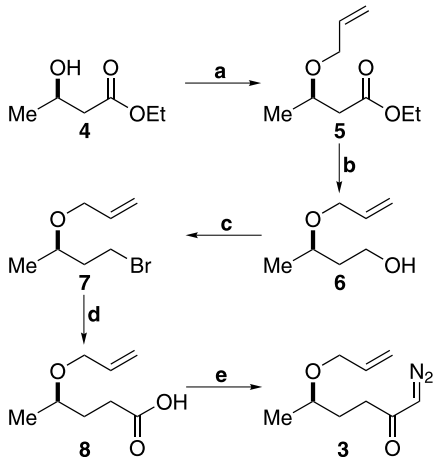
doi:10.1016/j.tet.2005.09.144

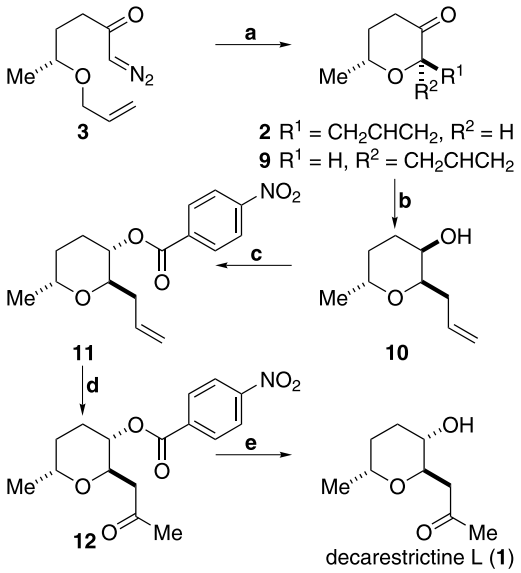
Functional group interconversion in the propyl side chain and on the ring led to the dihydro-2*H*-pyran-3(4*H*)-one **2** as the key intermediate. Recognition of the ketone **2** as the rearrangement product of allylic oxonium ylide then led to the diazo ketone **3** as an acyclic precursor,[7] and further disconnections revealed ethyl (*R*)-3-hydroxybutyrate (**4**) as an ideal chiral pool starting material.

Our synthesis commenced with the allylation of ethyl (*R*)-3-hydroxybutyrate (**4**) using the procedure of Bundle and co-workers that we have employed previously for the allylation of related alcohols (Scheme 2).[7,8] Treatment of the alcohol **4** with allyl 2,2,2-trichloroacetimidate and a sub-stoichiometric amount of triflic acid afforded the allyl ether **5** in good yield. The ester group of allyl ether **5** was then reduced using lithium aluminium hydride to give the alcohol **6** and this was converted into the bromide **7** by treatment with carbon tetrabromide and triphenylphosphine. The bromide was converted into the corresponding Grignard reagent by reaction with magnesium turnings, and subsequent treatment with solid carbon dioxide delivered the carboxylic acid **8** in excellent yield. The diazo ketone **3**, the key cyclisation precursor, was then obtained by conversion of the carboxylic acid **8** into the corresponding acid chloride and subsequent reaction with an ethereal solution of diazomethane.



Scheme 2. Reagents and conditions: (a) $CH_2CHCH_2OC(NH)CCl_3$, CF_3SO_3H, CH_2Cl_2–C_6H_{14}, rt (82%); (b) $LiAlH_4$, THF, 0 °C (89%); (c) CBr_4, PPh_3, CH_2Cl_2, 0 °C→rt (94%); (d) (i) Mg, THF, reflux, (ii) CO_2(s), −78 °C→rt (92%); (e) (i) $(COCl)_2$, DMF (cat.), CH_2Cl_2, (ii) CH_2N_2, Et_2O, 0 °C (72%).

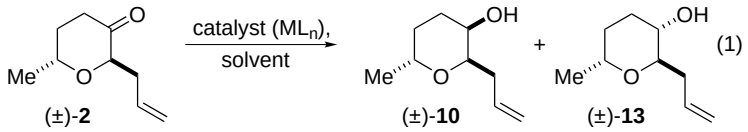
The key ring-forming reaction was effected by treatment of the diazo ketone **3** with copper(II) trifluoroacetylacetonate (2 mol%) in dichloromethane at reflux (Scheme 3).[7,9] Tandem catalytic carbenoid generation, ylide formation and rearrangement delivered a mixture of the isomeric pyranones **2** and **9** (91:9) in 60% yield with the required diastereoisomer (**2**) predominating. The use of copper(II) trifluoroacetylacetonate as catalyst provided the best combination of yield and diastereoselection from the cyclisation reaction, a result that is consistent with our previous work.[9]



Scheme 3. Reagents: (a) $Cu(tfacac)_2$, CH_2Cl_2, reflux (60% **2** and **9**, 91:9); (b) L-Selectride®, THF, −78 °C (95%); (c) *p*-$O_2NC_6H_4CO_2H$, DEAD, PPh_3, THF, rt (46%); (d) $PdCl_2$, CuCl, O_2, DMF aq, rt (89%); (e) K_2CO_3, MeOH aq, rt (96%).

Reduction of the ketone **2** to give the required diastereoisomer (**13**) proved to be problematic (Eq. 1, Table 1). The reduction reaction was effected using a variety of reducing agents, but in most cases the undesired diastereoisomer **10** was obtained as the major product (entries 1–3, Table 1).[10] In two cases (entries 4 and 5, Table 1) attempted reduction, using procedures developed for the stereoselective reduction of related cyclic ketones,[11,12] resulted in decomposition of the ketone **2** and neither the required alcohol **13** nor the diastereoisomeric compound **10** was obtained. At this stage we decided to perform the reaction at low temperature using L-Selectride® as the reducing agent

Table 1.



Entry	Reducing agent	Solvent	Temperature (°C)	Ratio (**10**:**13**)[a]	Yield (**10**+**13**)[b]
1	$NaBH_4$	EtOH	25	80:20	67%
2	MAD, *t*-BuMgCl	PhMe	−78	95:5	58%
3	L-Selectride	THF	−78	>99:1	88%
4	Na–NH_3	NH_3	−40	—	—
5	Et_3SiH, $(Ph_3P)_3RhCl$	C_6H_6	80	—	—

[a] Isomer ratio determined by ^1H NMR analysis.
[b] Yield of purified product.

in order to obtain a single diastereoisomeric product (**10**). Subsequent protection of the alcohol as the 4-nitrobenzoyl ester using Mitsunobu conditions delivered the ester **11** as the sole isolable product with clean inversion of configuration at the hydroxyl-bearing stereogenic centre, albeit in modest yield.[13] The side chain carbonyl group was then installed by palladium-catalysed Wacker oxidation of the terminal alkene.[14] Finally, treatment of the ketone **12** with potassium carbonate in methanol removed the 4-nitrobenzoyl ester group and furnished (+)-decarestrictine L in good yield. The spectroscopic and optical rotation data {$[\alpha]_D^{26}$ +22 (c=0.40, MeOH)} of synthetic (+)-decarestrictine L closely matched that reported for the natural product.[1c]

3. Conclusions

In summary, a stereoselective synthesis of the fungal metabolite (+)-decarestrictine L from commercially available ethyl (*R*)-3-hydroxybutyrate has been completed in 10-steps and in an overall yield of 9%. The important features of the synthesis are the use of tandem oxonium ylide formation and rearrangement from a catalytically generated copper carbenoid for diastereoselctive construction of the tetrahydropyranyl core, and conversion of the allyl side chain into the required methyl ketone using a Wacker oxidation reaction.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in deuterochloroform at ambient temperature using Bruker AM 400, AV 400 or DRX 500 instruments. Chemical shift values are quoted in parts per million (ppm) and J values are given in Hertz. ^{1}H NMR signals are described as singlets (s), doublets (d), triplets (t), quartets (q), multiplets (m), or broad (br) or a combination of these. Signals in ^{13}C NMR spectra are quoted in parts per million (ppm), with residual chloroform (δ=77.1 ppm) as the internal standard. Signals are given as (C), (CH), (CH_2), (CH_3) indicating the number of protons attached to each carbon atom as determined using DEPT sequences. IR spectra were recorded using a Perkin–Elmer 1600 series FT-IR spectrometer with internal calibration using solution cells unless otherwise stated. Mass spectra and accurate mass measurements were recorded using a Fisons VG Autospec, VG Micromass 70E or Micromass LCT instrument. Optical rotations were determined using a Jasco DIP-370 digital polarimeter. Reactions were monitored by TLC performed on Merck Kieselgel 60 F_{254} plates, and TLC plates were visualized by a combination of UV light and ethanolic anisaldehyde with heat. Flash column chromatography was performed using Fluka silica gel 60. Solvents and reagents were distilled using standard methods prior to use and air sensitive compounds were handled under either nitrogen or argon. All moisture-sensitive reactions were performed in flame-dried glassware under nitrogen or argon.

4.1.1. Ethyl (*R*)-3-(allyloxy)butanoate (5). Trifluoromethanesulfonic acid (300 μL, 3.39 mmol) was added dropwise to a solution of ethyl (*R*)-3-hydroxybutyrate (6.58 g, 50.0 mmol) and allyl 2,2,2-trichloroacetimidate (20.3 g, 100 mmol) in dry dichloromethane (50 mL) and hexane (100 mL). The mixture was stirred at room temperature for 16 h and then quenched by addition of excess triethylamine. The mixture was filtered through Celite and the filtrate was evaporated. The resulting liquid was purified by distillation to give the title compound as a colourless liquid (7.05 g, 82%): bp 31–33 °C at 0.23 mmHg; $[\alpha]_D^{27}$ −9.1 (c=0.86, $CHCl_3$); ν_{max} ($CHCl_3$) 2972, 2933, 2904, 2872, 1732, 1373, 1646, 994, 943, 913, 871 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddt, 1H, J=17.2, 10.4, 5.6 Hz, C*H*=CH_2), 5.26 (ddt, 1H, J=17.2, 1.7, 1.6 Hz, CH=C*H*$_2$ *trans*), 5.14 (ddt, 1H, J=10.4, 1.7, 1.3 Hz, CH=C*H*$_2$ *cis*), 4.13 (q, 2H, J=7.1 Hz, O*CH*$_2$CH$_3$), 4.03 (dddd, 1H, J=12.6, 5.6, 1.6, 1.3 Hz, O*CH*$_2$CH=CH_2), 3.95 (dddd, 1H, J=12.6, 5.6, 1.6, 1.3 Hz, O*CH*$_2$CH=CH_2), 3.96–3.87 (m, 1H, O*CH*CH$_3$), 2.58 (dd, 1H, J=15.0, 7.2 Hz, C*H*$_2$CO$_2$), 2.37 (dd, 1H, J=15.0, 5.9 Hz, C*H*$_2$CO$_2$), 1.25 (t, 3H, J=7.1 Hz, OCH$_2$C*H*$_3$), 1.21 (d, 3H, J=6.2 Hz, OCHC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.5 (C), 135.1 (CH), 116.7 (CH_2), 71.8 (CH), 69.8 (CH_2), 60.4 (CH_2), 42.1 (CH_2), 19.9 (CH_3), 14.2 (CH_3); LRMS (CI) *m/z* 173 (M^++H, 100); HRMS (CI) for $C_9H_{17}O_3$ [M^++H] calcd 173.1178, found 173.1175.

4.1.2. (*R*)-3-(Allyloxy)butan-1-ol (6). A solution of $LiAlH_4$ (27 mL of 1 M solution in THF, 27 mmol) was added to a solution of ester **5** (4.40 g, 25.6 mmol) in THF (50 mL) at 0 °C. The mixture was stirred at room temperature for 16 h and excess $LiAlH_4$ was quenched by careful addition of 2 M NaOH at 0 °C. The biphasic mixture was stirred vigorously for 2 h and the aqueous layer extracted with diethyl ether. The combined organic extracts were dried ($MgSO_4$), filtered and the solvent was evaporated (caution, volatile product). The residue was purified by flash column chromatography on silica gel (*n*-pentane/diethyl ether, 1:1) to afford the alcohol **6** as a colourless liquid (2.96 g, 89%): $[\alpha]_D^{26}$ −59 (c=0.75, $CHCl_3$); ν_{max} ($CHCl_3$) 3497, 2972, 2932, 2868, 1646, 994, 965, 908 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92, (dddd, 1H, J=17.2, 10.4, 5.8, 5.4 Hz, C*H*=CH_2), 5.28 (dddd, 1H, J=17.2, 1.6, 1.5, 1.4 Hz, CH=C*H*$_2$ *trans*), 5.18 (dddd, 1H, J=10.4, 1.6, 1.5, 1.4 Hz, CH=C*H*$_2$ *cis*), 4.11 (ddt, 1H, J=12.6, 5.4, 1.5 Hz, C*H*$_2$CH=CH_2), 3.93 (ddt, 1H, J=12.6, 5.8, 1.4 Hz, C*H*$_2$CH=CH_2), 3.84–3.70 (m, 3H, CH$_3$C*H*, C*H*$_2$OH), 2.56 (br, 1H, O*H*), 1.81–1.70 (m, 2H, C*H*$_2$CH$_2$OH), 1.21 (d, 3H, J=6.2 Hz, C*H*$_3$CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 134.9 (CH), 116.8 (CH_2), 74.8 (CH), 69.4 (CH_2), 61.0 (CH_2), 38.7 (CH_2), 19.4 (CH_3); LRMS (ES) *m/z* 153 (M^++Na, 100); HRMS (ES) for $C_7H_{14}O_2Na$ [M^++Na] calcd 153.0891, found 153.0881.

4.1.3. (*R*)-3-(Allyloxy)-1-bromobutane (7). Carbon tetrabromide (8.95 g, 27.0 mmol) and triphenylphosphine (7.08 g, 27.0 mmol) were added sequentially to a solution of alcohol **6** (2.34 g, 18.0 mmol) in dichloromethane (60 mL) at 0 °C. The mixture was then stirred at 0 °C for 1 h and at room temperature for a further 2 h. Silica gel (~10 g) was added and the solvent was evaporated at 0 °C (caution, volatile product) and the solid residue was dry

loaded on a silica flash column. Elution (*n*-pentane/diethyl ether, 10:1) afforded the desired compound as a colourless liquid (3.27 g, 94%). The product was used in the next reaction without further purification: $[\alpha]_D^{29}$ −49.6 (c=2.65, $CHCl_3$); ν_{max} ($CHCl_3$) 2973, 2932, 2865, 1646, 994, 941, 915, 875 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.94 (ddt, 1H, J=17.2, 10.4, 5.6 Hz, C*H*=CH_2), 5.30 (dddd, 1H, J=17.2, 1.6, 1.5, 1.4 Hz, CH=CH_2 *trans*), 5.19 (dddd, 1H, J=10.4, 1.6, 1.5, 1.4 Hz, CH=CH_2 *cis*), 4.13–4.08 (m, 1H, CH_2CH=CH_2), 3.98–3.93 (m, 1H, CH_2CH=CH_2), 3.71–3.66 (m, 1H, CH_3C*H*), 3.60–3.47 (m, 2H, CH_2Br), 2.14–2.05 (m, 1H, CH_2CH_2Br), 1.99–1.90 (m, 1H, CH_2CH_2Br), 1.20 (d, 3H, J=6.1 Hz, CH_3CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 135.2 (CH), 116.7 (CH_2), 72.6 (CH), 69.7 (CH_2), 40.0 (CH_2), 30.4 (CH_2), 19.4 (CH_3).

4.1.4. (*R*)-4-(Allyloxy)pentanoic acid (8). A crystal of iodine was added to a suspension of magnesium turnings (392 mg, 16.3 mmol) in dry THF under gentle heating (water bath). The bromide **7** (3.00 g, 15.5 mmol) was then added dropwise to the suspension causing an exotherm. After addition was complete, the mixture was heated at 50 °C for 30 min, before being cooled to −78 °C. Solid carbon dioxide (2 g, 3 equiv) was then added in one portion to the solution and the mixture was allowed to warm to room temperature. The resulting white suspension was stirred for 1 h and 1 M aqueous HCl was added until the pH of the aqueous layer was acidic. The aqueous layer was extracted with ethyl acetate and combined organic extracts were dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash column chromatography on silica gel (petrol 40–60/ethyl acetate, 1:1) to afford the carboxylic acid **8** as a colourless liquid (2.25 g, 92%): $[\alpha]_D^{25}$ −31 (c=0.45, $CHCl_3$); ν_{max} ($CHCl_3$) 3174, 2972, 2931, 2864, 1745, 1710, 995, 943, 914 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (dddd, 1H, J=17.2, 10.4, 5.7, 5.5 Hz, C*H*=CH_2), 5.27 (ddt, 1H, J=17.2, 1.6, 1.4 Hz, CH=CH_2 *trans*), 5.16 (ddt, 1H, J=10.4, 1.6, 1.4 Hz, CH=CH_2 *cis*), 4.06 (ddt, 1H, J=12.6, 5.5, 1.4 Hz, CH_2CH=CH_2), 3.92 (ddt, 1H, J=12.6, 5.7, 1.4 Hz, CH_2CH=CH_2), 3.58–3.48 (m, 1H, CH_3C*H*), 2.51–2.45 (m, 2H, CH_2C=O), 1.85–1.79 (m, 2H, CH_2CH_2C=O), 1.18 (d, 3H, J=6.2 Hz, CH_3CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 179.7 (C), 135.1 (CH), 116.7 (CH_2), 73.8 (CH), 69.5 (CH_2), 31.3 (CH_2), 30.2 (CH_2), 19.4 (CH_3); LRMS (ES) m/z 181 (M^++Na, 100); HRMS (ES) for $C_8H_{14}O_3Na$ [M^++Na] calcd 181.0841, found 181.0842.

4.1.5. (*R*)-5-(Allyloxy)-1-diazohexan-2-one (3). Oxalyl chloride (0.29 mL, 3.3 mmol) was added to a solution of the carboxylic acid **8** (0.40 g, 2.5 mmol) in dichloromethane (5 mL), followed by two drops of dry DMF. The mixture was stirred at room temperature for 6 h and transferred to an ethereal solution of diazomethane at 0 °C. The mixture was stirred at room temperature for 3 h and excess diazomethane was quenched by careful addition of acetic acid (2 mL). The ether solution was washed with saturated aqueous $NaHCO_3$ (20 mL) and the aqueous layer was back-extracted with diethyl ether (20 mL). The combined organic layers and extracts were dried ($MgSO_4$), filtered and evaporated to give a yellow oil. Purification by flash column chromatography (hexane/diethyl ether, 2:1) afforded the diazo ketone **3** as a bright yellow liquid (0.33 g, 72%): $[\alpha]_D^{25}$ −28 (c=0.43, $CHCl_3$); ν_{max} ($CHCl_3$) 3117, 2973, 2930, 2863, 2109, 1639, 995, 914 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddt, 1H, J=17.2, 10.4, 5.6 Hz, C*H*=CH_2), 5.29–5.23 (br, 1H, C*H*N_2), 5.28 (ddt, 1H, J=17.2, 1.6, 1.5 Hz, CH=CH_2 *trans*), 5.17 (ddt, 1H, J=10.4, 1.6, 1.4 Hz, CH=CH_2 *cis*), 4.06 (dddd, 1H, J=12.7, 5.6, 1.5, 1.4 Hz, CH_2CH=CH_2), 3.90 (dddd, 1H, J=12.7, 5.6, 1.5, 1.4 Hz, CH_2CH=CH_2), 3.56–3.47 (m, 1H, CH_3C*H*), 2.51–2.38 (m, 2H, CH_2C=O), 1.92–1.73 (m, 2H, CH_2CH_2C=O), 1.18 (d, 3H, J=6.1 Hz, CH_3CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 195.0 (C), 135.2 (CH), 116.5 (CH_2), 73.8 (CH), 69.4 (CH_2), 54.2 (CH), 36.7 (CH_2), 31.6 (CH_2), 19.5 (CH_3); LRMS (ES) m/z 205 (M^++Na, 100), 183 [(M^++H, 10)]; HRMS (ES) for $C_9H_{14}N_2O_2Na$ [M^++Na] calcd 205.0953, found 205.0946.

4.1.6. (2*R*,6*R*)-2-Allyl-6-methyldihydro-2*H*-pyran-3(4*H*)-one (2) and (2*S*,6*R*)-2-allyl-6-methyldihydro-2*H*-pyran-3(4*H*)-one (9). A solution of diazo ketone **3** (0.30 g, 1.6 mmol) in dichloromethane (5 mL) was added dropwise to a solution of $Cu(tfacac)_2$ (25 mg, 5 mol%) in dichloromethane (10 mL) at reflux. The mixture was stirred under reflux for 20 min and the solvent was evaporated. Flash column chromatography (petrol 40–60/diethyl ether, 10:1) of the residue afforded a mixture of the ketones **2** and **9** (91:9) as a colourless liquid (0.15 g, 60%). *Ketone* **2**. $[\alpha]_D^{23}$ +157 (c=0.65, $CHCl_3$); ν_{max} ($CHCl_3$) 2976, 2936, 2873, 1722, 1642, 997, 915 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddt, 1H, J=17.1, 10.2, 6.9 Hz, C*H*=CH_2), 5.15 (dq, 1H, J=17.1, 1.5 Hz, CH=CH_2) 5.19–5.10 (m, 1H, CH=CH_2), 4.21–4.12 (m, 1H, CH_3C*H*), 4.10 (dd, 1H, J=8.3, 5.6 Hz, OC*H*C=O), 2.59–2.46 (m, 4H, CH_2C=O, CH_2CH=CH_2), 2.18–2.09 (m, 1H, CH_2CH_2C=O), 1.88–1.76 (m, 1H, CH_2CH_2C=O), 1.29 (d, 3H, J=6.2 Hz, CH_3CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 210.6 (C), 133.6 (CH), 117.6 (CH_2), 78.9 (CH), 66.6 (CH), 35.6 (CH_2), 34.4 (CH_2), 31.1 (CH_2), 20.5 (CH_3); HRMS (EI) for $C_9H_{14}O_2$ [M^+] calcd 154.0994, found 154.0978. *Ketone* **9**. $[\alpha]_D^{23}$ −67 (c=0.60, $CHCl_3$); ν_{max} ($CHCl_3$) 2977, 2927, 2855, 1722, 1642, 996, 908 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.83 (dddd, 1H, J=17.1, 10.2, 6.9, 6.8 Hz, C*H*=CH_2), 5.13 (dddd, 1H, J=10.2, 1.6, 1.4, 1.3 Hz, CH=CH_2) 5.07 (dddd, 1H, J=17.1, 1.6, 1.4, 1.3 Hz, CH=CH_2), 3.91–3.86 (m, 2H, CH_3C*H*, OC*H*C=O), 2.59 (dddt, 1H, J=14.6, 6.9, 4.5, 1.3 Hz, CH_2CH=CH_2), 2.55 (ddd, 1H, J=16.0, 6.3, 3.5 Hz, CH_2C=O), 2.45 (dddd, 1H, J=16.0, 11.3, 7.0, 0.8 Hz, CH_2C=O), 2.34 (dddt, 1H, J=14.6, 8.0, 6.8, 1.4 Hz, CH_2CH=CH_2), 2.08 (dddd, 1H, J=13.6, 7.0, 3.5, 3.0 Hz, CH_2CH_2C=O), 1.88 (dddd, 1H, J=13.6, 11.3, 10.5, 6.3, Hz, CH_2CH_2C=O), 1.30 (d, 3H, J=6.2 Hz, CH_3CH); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 208.7 (C), 134.4 (CH), 117.2 (CH_2), 82.4 (CH), 72.6 (CH), 37.7 (CH_2), 34.1 (CH_2), 33.5 (CH_2), 21.4 (CH_3); HRMS (EI) for $C_9H_{14}O_2$ [M^+] calcd 154.0994, found 154.1000.

4.1.7. (2*R*,3*R*,6*R*)-2-Allyl-6-methyltetrahydro-2*H*-pyran-3-ol (10). A solution of L-Selectride® (4.7 mL of a 1 M solution in THF, 4.7 mmol) was added dropwise to a solution of ketone **2** (0.24 g, 1.6 mmol) in THF (20 mL) at −78 °C. The mixture was stirred at −78 °C for 3 h and H_2O_2 (4 mL of a 30% aqueous solution) was added, followed by 2 M NaOH until pH ~10. The biphasic mixture was stirred vigorously at room temperature for 1 h and the layers separated. The aqueous layer was extracted

with diethyl ether (3×20 mL) and the combined extracts were dried, filtered and evaporated. The residue was purified by flash column chromatography (petrol 40–60/diethyl ether, 1:1) to afford the alcohol **10** as a colourless oil (0.23 g, 95%): $[\alpha]_D^{23}$ +51 (c=0.65, $CHCl_3$); ν_{max} ($CHCl_3$) 3611, 2975, 2938, 1642, 997, 970, 910, 864 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (ddt, 1H, J=17.1, 10.2, 6.9 Hz, C*H*=CH_2), 5.15 (dddd, 1H, J=17.1, 1.7, 1.6, 1.5 Hz, CH=C*H*$_2$ *trans*), 5.09 (ddd, 1H, J=10.2, 1.6, 1.5, 1.3 Hz, CH=C*H*$_2$ *cis*), 4.04–3.94 (m, 1H, CH_3C*H*), 3.83–3.73 (m, 2H, OC*H*C*H*OH), 2.45–2.37 (m, 1H, C*H*$_2$CH=CH_2), 2.35–2.26 (m, 1H, C*H*$_2$CH=CH_2), 2.00–1.91 (m, 1H, CH_3CHC*H*$_2$), 1.90–1.82 (m, 2H, C*H*HCHO*H*), 1.79–1.70 (m, 1H, C*H*$_2$CHOH), 1.34–1.25 (m, 1H, CH_3CHC*H*$_2$), 1.21 (d, 3H, J=6.6 Hz, C*H*$_3$CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 135.0 (CH), 116.8 (CH_2), 72.7 (CH), 67.1 (CH), 67.0 (CH), 33.3 (CH_2), 27.0 (CH_2), 26.5 (CH_2), 18.3 (CH_3); LRMS (EI) m/z 156 (M^+, 1), 141 (1), 115 (100), 97 (15), 79 (10), 71 (35), 57 (36); HRMS (EI) for $C_9H_{16}O_2$ [M^+] calcd 156.1150, found 156.1149.

4.1.8. (2*R*,3*S*,6*R*)-2-Allyl-6-methyltetrahydro-2*H*-pyran-3-yl 4-nitrobenzoate (11). To a solution of the alcohol **10** (60 mg, 0.38 mmol) in dry THF (10 mL) was added triphenylphosphine (0.20 g, 0.77 mmol), 4-nitrobenzoic acid (0.13 g, 0.77 mmol), followed by DEAD (120 μl, 0.77 mmol), and the reaction was stirred at room temperature for 16 h. The solvent was then evaporated, and the residue was purified by flash column chromatography on silica gel (hexane/diethyl ether, 10:1) to give the ester **11** (54 mg, 46%) as a colourless oil: $[\alpha]_D^{26}$ +27.4 (c=1.75, $CHCl_3$); ν_{max} ($CHCl_3$) 3112, 2947, 2872, 1721, 1642, 1609, 970, 908, 873, 859 cm^{-1}; ^1H NMR (400 MHz) δ 8.30 (d, 2H, J=9.0 Hz, Ar-*H*), 8.24 (d, 2H, J=9.0 Hz, Ar-*H*), 5.84 (ddt, 1H, J=17.1, 10.2, 6.9 Hz, CH_2C*H*C=CH_2), 5.16–5.09 (m, 2H, CH_2CH=C*H*$_2$), 4.97 (dt, 1H, J=5.0, 3.5 Hz, C*H*O_2CAr), 4.05–3.99 (m, 1H, C*H*OCH_2CH=CH_2), 3.95–3.89 (m, 1H, CH_3C*H*O), 2.58–2.48 (m, 1H, CHOC*H*$_2$CH=CH_2), 2.44–2.36 (m, 1H, CHOC*H*$_2$CH=CH_2), 2.12–2.02 (m, 1H, C*H*$_2$CHO_2CAr), 2.01–1.92 (m, 1H, C*H*$_2$CHO_2CAr), 1.71–1.63 (m, 2H, CH_3CHOC*H*$_2$), 1.24 (d, 3H, J=6.3 Hz, C*H*$_3$CHO); ^{13}C NMR (100.6 MHz) δ 164.1 (C), 150.6 (C), 135.9 (C), 133.9 (CH), 130.8 (CH), 123.5 (CH), 117.4 (CH_2), 73.9 (CH), 71.4 (CH), 66.0 (CH), 34.8 (CH_2), 28.1 (CH_2), 23.8 (CH_2), 20.6 (CH_3); HRMS (EI) for $C_{13}H_{14}NO_5$ [$M^+-C_3H_5$] calcd 264.0872, found 264.0885.

4.1.9. (2*R*,3*S*,6*R*)-6-Methyl-2-(2-oxopropyl)tetrahydro-2*H*-pyran-3-yl 4-nitrobenzoate (12). $PdCl_2$ (5.8 mg, 20 mol%) and CuCl (16 mg, 0.16 mmol) were added to a solution of the ester **11** (50 mg, 0.16 mmol) in DMF (2.5 mL) and water (0.25 mL) under an atmosphere of oxygen and the reaction was stirred vigorously at room temperature until consumption of the starting material was complete (~1.5 h). A saturated aqueous solution of sodium chloride was added and the mixture was then extracted with dichloromethane (4×20 mL). The combined organic extracts were washed with brine (25 mL) and the organic layer was dried (Na_2SO_4). The solvent was evaporated and the residue was purified by flash chromatography on silica gel (hexane/diethyl ether, 1:1) to give the ketone **12** (47 mg, 89%) as a colourless oil: $[\alpha]_D^{26}$ +12 (c=0.60, $CHCl_3$); ν_{max} ($CHCl_3$) 2953, 2872, 1721, 1609, 971, 908, 873 cm^{-1}; ^1H NMR (400 MHz) δ 8 31 (d, 2H, J=9.0 Hz, Ar-*H*), 8.23 (d, 2H, J=9.0 Hz, Ar-*H*), 4.92–4.87 (m, 1H, C*H*O_2CAr), 4.46 (ddd, 1H, J=8.8, 5.0, 4.9 Hz, C*H*OCH_2C=O); 4.01–3.92 (m, 1H, CH_3C*H*O), 2.86 (dd, 1H, J=15.5, 8.8 Hz, C*H*$_2$C=O), 2.64 (dd, 1H, J=15.5, 4.9 Hz, C*H*$_2$C=O), 2.21 (s, 3H, C*H*$_3$C=O), 2.10–1.93 (m, 2H, C*H*$_2$CHO_2CAr), 1.82–1.74 (m, 1H, CH_3CHOC*H*$_2$$CH_2$), 1.70–1.61 (m, 1H, CH_3CHOC*H*$_2$$CH_2$), 1.28 (d, 3H, J=6.4 Hz, C*H*$_3$CHO); ^{13}C NMR (100.6 MHz) δ 205.8 (C), 164.0 (C), 150.7 (C), 135.5 (C), 130.8 (CH), 123.6 (CH), 72.0 (CH), 70.0 (CH), 67.0 (CH), 45.2 (CH_2), 30.5 (CH_3), 28.1 (CH_2), 24.0 (CH_2), 19.5 (CH_3); HRMS (EI) for $C_{13}H_{14}NO_5$ [$M^+-C_3H_5O$] calcd 264.0872, found 264.0848.

4.1.10. 1-[(2*R*,3*S*,6*R*)-3-Hydroxy-6-methyltetrahydro-2*H*-pyran-2-yl]-acetone [(+)-decarestrictine L] (1). To a solution of the ketone **12** (39 mg, 12 mmol) in a mixture of methanol (5 mL) and water (0.1 mL) was added K_2CO_3 (17 mg, 12 mmol), and the reaction was stirred at room temperature for 45 min. The solvent was evaporated, and the residual material was purified by flash column chromatography on silica gel (diethyl ether) to give decarestrictine L (**1**) (20 mg, 96%) as a colourless oil: $[\alpha]_D^{26}$ +22 (c=0.40, MeOH) {lit. $[\alpha]_D^{20}$ +21.8 (c=0.5, MeOH)}; ν_{max} ($CHCl_3$) 3627, 3477, 2943, 2838, 1712, l602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.04–3.98 (m, 1H, C*H*OCHOH), 3.97–3.92 (m, 1H, CH_3C*H*O), 3.43–3.37 (m, 1H, C*H*OH), 2.75 (dd, 1H, J=15.6, 5.6 Hz, C*H*$_2$C=O), 2.70 (dd, 1H, J=15.6, 7.4 Hz, C*H*$_2$C=O), 2.20 (s, 3H, C*H*$_3$C=O), 2.17 (br, 1H, O*H*), 1.92–1.82 (1H, m, C*H*$_2$CHOH), 1.77–1.65 (m, 2H, C*H*$_2$C*H*$_2$), 1.61–1.52 (m, 1H, CH_3CHOC*H*$_2$), 1.22 (d, 3H, J=6.6 Hz, C*H*$_3$CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8 (C), 72.1 (CH), 69.4 (CH), 67.5 (CH), 46.3 (CH_2), 30.5 (CH_3), 28.3 (CH_2), 27.1 (CH_2), 18.4 (CH_3); HRMS (EI) for $C_9H_{14}O_2$ [M^+-H_2O] calcd 154.0994, found 154.0995.

Acknowledgements

We thank The University of Nottingham for financial support.

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