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Enantioselective synthesis of decarestrictine J

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ABSTRACT

An efficient total synthesis of decarestrictine J has been achieved using ring-closing metathesis and Yamaguchi esterification as key steps. The stereogenic centres were generated by means of iterative hydrolytic kinetic resolution (HKR) of racemic epoxides.

1. Introduction

Decanolides have attracted considerable attention over the last few years[1] of which an important class of compounds is the decarestrictine family. The decarestrictines are secondary metabolites that were isolated from various Penicillium strains and identified as bioactive compounds by chemical screening[2–4] (Fig. 1). Decarestrictine J,[4] a 10-membered lactone, has been isolated as a minor component of the decarestrictine family[2,3] from a culture broth of *Penicillium simplicissimum* and was shown to inhibit the biosynthesis of cholesterol. The absolute stereochemistry of decarestrictine J itself has not been reported. However, because it coexisted with decarestrictine B, whose absolute configuration had been determined by an X-ray analysis, Yamada et al.[5] suggested (7*R*,9*R*)-stereochemistry for natural (−)-decarestrictine J. Only one total synthesis of the proposed structure of (−)-decarestrictine J (**1a**) has been reported in the literature using a Sharpless asymmetric epoxidation and samarium(II) iodide-promoted Reformatsky reaction as the key steps.[5]

As a part of our research programme aimed at developing enantioselective synthesis of biologically active natural products based on hydrolytic kinetic resolution (HKR),[6] we became interested in devising a simple and concise route to decarestrictine J. Herein we report our successful endeavours towards the total synthesis of **1a** employing HKR,[7] Yamaguchi esterification[8] and ring-closing metathesis (RCM)[9] as the key steps.

The HKR method involves the readily accessible cobalt-based chiral salen complex as catalyst and water to resolve a racemic epoxide into an enantiomerically enriched epoxide and diol, which serve as useful precursor in the synthesis of various compounds of biological importance.[10]

Our retrosynthetic analysis for the synthesis of decarestrictine J is based on convergent approach as outlined in Scheme 1. We envisioned that the ring-closing could be effected by ring-closing metathesis of diene **17**. Diene **17** could be prepared by intermolecular Yamaguchi esterification of the alcohol **10** and acid **16**. Alcohol **10** could be obtained from *rac*-propylene oxide (**2**) via iterative HKR, while acid fragment **16** could be prepared from 1,3-propane diol (**11**).

2. Synthesis of alcohol fragment 10

As shown in Scheme 2, synthesis of alcohol fragment **10** started with a Jacobsen's hydrolytic kinetic resolution of *rac*-epoxide **2**

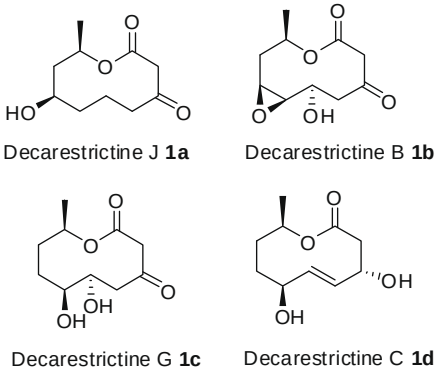

Figure 1. Examples of 10-membered lactones.

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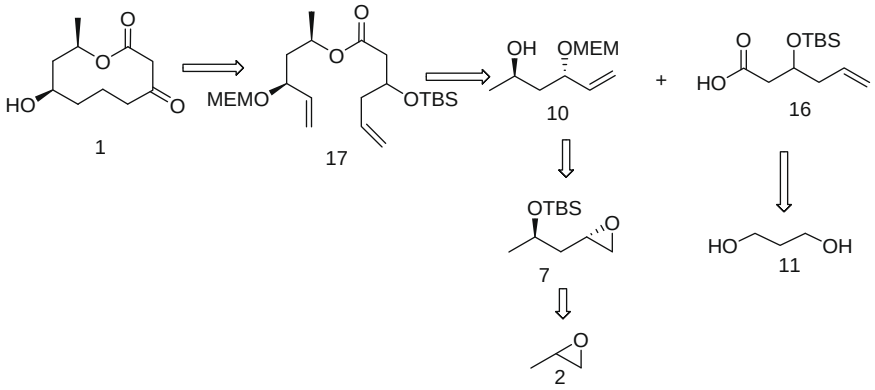
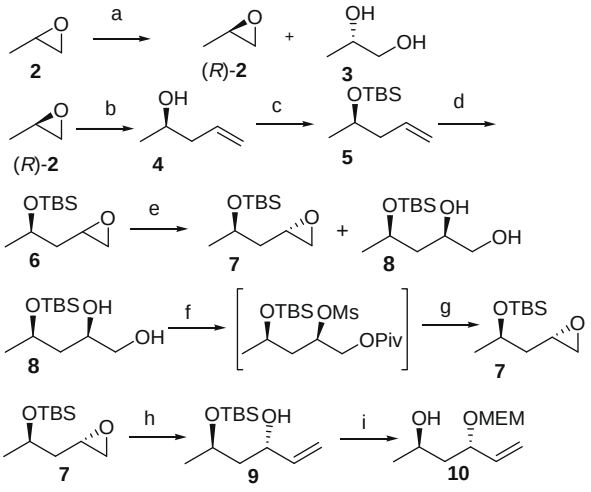


Scheme 1. Retrosynthetic analysis of decarestrictine J.



Scheme 2. Reagents and conditions: (a) (*R*,*R*)-salen-Co-(OAc)(0.5 mol %), dist. H_2O (0.55 equiv), 0 °C, 14 h, (45% for (*R*)-2, 43% for 3); (b) vinylmagnesium bromide THF, CuI, −20 °C, 90%, 12 h; (c) TBDMSCl, imidazole, CH_2Cl_2, 4 h, 0 °C to rt, 95%; (d) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 93%, 2 h; (e) (*S*,*S*)-salen-Co-(OAc) (0.5 mol %), dist. H_2O (0.55 equiv), 0 °C, 20 h, (70% for **7**, 22% for **8**); (f) (i) PivCl, Et_3N, cat. DMAP, rt, 2 h; (ii) MsCl, Et_3N, DMAP, 0 °C to rt, 1 h; (g) K_2CO_3, MeOH, rt, overnight (61% for three steps); (h) $(CH_3)_3SI$, 2 h, *n*-BuLi, THF, 70%; (i) (i) DIPEA, MEMCl, CH_2Cl_2, 0 °C to rt, 8 h; (ii) TBAF, THF, 0 °C to rt, 5 h, 80% from two steps.

using (*R*,*R*)-salen-Co-(OAc) catalyst to give epoxide (*R*)**-2** as a single isomer which was easily isolated from diol **3** by distillation.[7b]

Epoxide (*R*)**-2** was treated with vinylmagnesium bromide in the presence of cuprous iodide to give homoallylic alcohol **4** in 90% yield.[6e] Protection of the hydroxy group of **4** as a TBDMS ether followed by epoxidation with *m*-CPBA afforded epoxide **6**. The epoxide thus obtained was found to be a mixture of two diastereomers (*anti*:*syn*/3:1). In order to improve the diastereoselectivity, we attempted the hydrolytic kinetic resolution (HKR) method as depicted in Scheme 2. Thus, the HKR was performed on epoxide **6** with (*S*,*S*)-salen-Co-(OAc) complex (0.5 mol %) and water (0.55 equiv) in THF (0.55 equiv) to afford the diastereomerically pure epoxide **7** in 70% yield (>95% ee) and diol **8** in 22% yield. As the HKR method provided the desired epoxide **7** along with unwanted diol **8**, we thought that it would be appropriate to convert diol **8** into the required epoxide **7** via internal nucleophilic substitution of a secondary mesylate.[11] Accordingly chemoselective pivalation of diol **8** with pivaloyl chloride followed by mesylation of the secondary hydroxyl and treatment of the crude mesylate with K_2CO_3 in methanol led to the deprotection of the pivalate ester. Concomitant ring closure via intramolecular S_N2 displacement of the mesylate furnished the epoxide **7** in 61% overall yield. Epoxide **7** on reaction with dimethylsulfonium methylide[12] afforded one-carbon homologated allylic alcohol **9** in 70% yield, which was protected as its MEM ether followed by TBDMS removal to furnish the alcohol fragment **10** in 80% yield (Scheme 2). It may be noted that the alcohol fragment **10** could be synthesised in eight steps employing iterative HKR method, while our previous method involving Sharpless asymmetric dihydroxylation required three additional steps to prepare the same alcohol fragment.[6h]

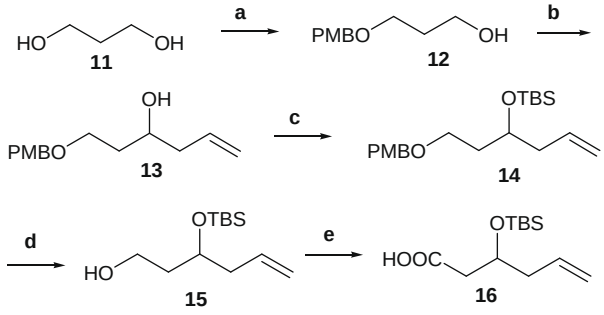
3. Synthesis of acid fragment

As shown in Scheme 3, synthesis of acid fragment **16** started from 1,3-propanediol (**11**). Selective monoprotection of hydroxy group with *p*-methoxybenzyl bromide (PMBBr) in the presence of NaH afforded compound **12** in 89% yield, which was subjected to Swern oxidation[13] followed by the reaction of the resulting aldehyde with allylmagnesium bromide to furnish the homoallyllic alcohol **13** in 80% yield.

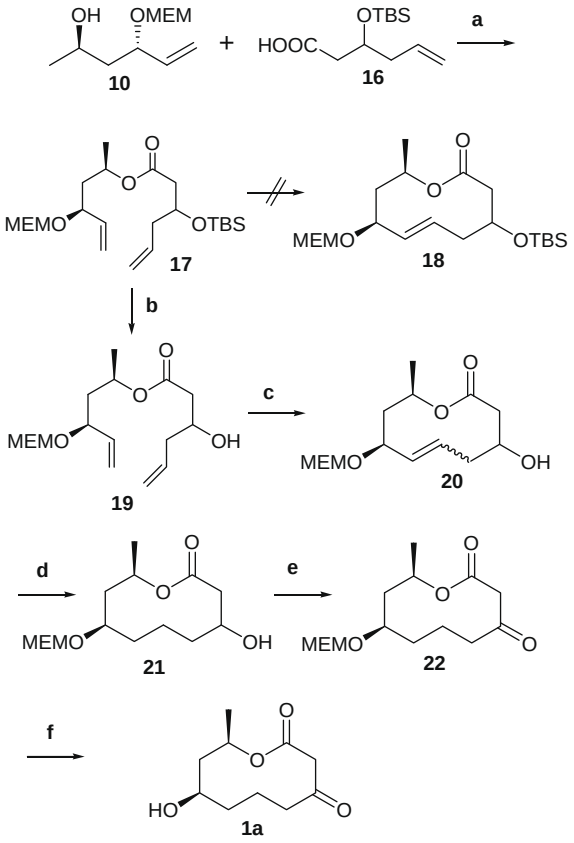
Protection of the hydroxy group of **13** as its TBDMS ether followed by removal of the PMB group[14] by DDQ resulted in the primary alcohol **15** with 94% yield. The alcohol **15** was oxidised to the aldehyde using 2-iodoxybenzoic acid (IBX) followed by subsequent oxidation using $NaClO_2$ to give the required acid fragment **16**[15] in 80% yield.

4. Coupling of acid and alcohol fragments

With substantial amount of both the fragments in hand the coupling of alcohol **10** and acid **16** was achieved by using the



Scheme 3. Reagents and conditions: (a) PMBBr, NaH, THF, 0 °C to rt, 5 h, 89%; (b) (i) $(COCl)_2$, DMSO, −78 °C to −60 °C, Et_3N, CH_2Cl_2; (ii) allylmagnesium bromide, THF, 80%; (c) TBDMSCl, imidazole, CH_2Cl_2, 0 °C to rt, 90%; (d) DDQ, CH_2Cl_2/H_2O (1:1), rt, 1 h, 94%; (e) (i) IBX, EtOAc, reflux; (ii) $NaClO_2$, NaH_2PO_4, DMSO, overnight, 80% from two steps.



Scheme 4. Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, THF, 0 °C–rt, 20 h, 89%; (b) TBAF, THF, 6 h, 75%; (c) $(PCy_3)_2$ $Ru(Cl)_2$ = CH–Ph (20 mol %), CH_2Cl_2, reflux, 14 h, 82%; (d) 10% Pd/C, H_2 (balloon), ethanol, rt, 90%, 2 h; (e) DMP, CH_2Cl_2, rt, 80%, 1 h; (f) $TiCl_4$, CH_2Cl_2, 0 °C–rt, 30 min, 78%.

intermolecular Yamaguchi esterification protocol to afford the diene ester **17**[15] in 89% yield. Ring-closing metathesis of **17** under various conditions using Grubbs' 1st and 2nd generation catalysts failed to provide the required 10-membered lactone **18**. In order to circumvent the problem, we thought that it would be appropriate to first remove the TBDMS group and then use the ring-closing metathesis for macrocyclisation. Thus the TBDMS group of diene **17** was removed to give the alcohol **19** which on ring-closing metathesis by using Grubbs 1st generation catalyst furnished the cyclised product **20** as a mixture of *E/Z* isomers in 82% yield. Compound **20** was subjected to hydrogenation using 10% Pd/C to give **21**[15] in 90% yield, which was oxidised using Dess–Martin periodinane (DMP) to afford compound **22** in 80% yield. Finally removal of the MEM group using $TiCl_4$ afforded the target compound **1a** in 78% yield. $[\alpha]_D^{25} = -152.4$ (*c* 0.1, MeOH) [Ref. 5 $[\alpha]_D^{23} = -154.0$ (*c* 0.1, MeOH)]. The physical and spectroscopic data of **1a** were in full agreement with the literature data (Scheme 4).[5]

In conclusion, a convergent and efficient total synthesis of decarestrictine J with high enantioselectivities has been accomplished in which the stereocentres were generated by means of iterative Jacobsen's hydrolytic kinetic resolution, and cyclisation was achieved by ring-closing metathesis. This approach could be used for the synthesis of other members of decarestrictine family for structure–activity relationship. Currently work is in progress in this direction.

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15. *Spectral data of* **16**: IR ($CHCl_3$): *ν* 3310, 3078, 2856, 1714, 1642, 1515, 1361, 1091, 939, 837, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): *δ* 5.82–5.73 (m, 1H), 5.09–5.06 (m, 2H), 4.20–4.16 (m, 1H), 2.53–2.43 (m, 2H), 2.30–2.28 (m, 2H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): *δ* 177.2, 133.7, 118.1, 68.9, 41.9, 41.7, 25.7, 17.9, - 4.5, -4.9; Anal. Calcd for $C_{12}H_{24}O_3Si$ (244.403): C, 58.97; H, 9.90. Found: C, 58.82; H, 10.08. Spectral data of **17**: $[\alpha]_D^{25} = -36.17$ (*c* 3.19, $CHCl_3$), IR ($CHCl_3$): *ν* 2926, 2855, 1735, 1647, 1463, 1258, 1096, 837, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): *δ* 5.89–5.55 (m, 2H), 5.28–5.05 (m, 4H), 5.02–4.91 (m, 1H), 4.80–4.71 (m, 1H), 4.63–4.56 (m, 1H), 4.24- 4.00 (m, 2H), 3.83–3.67 (m, 1H), 3.65–3.58 (m, 1H), 3.55- 3.46 (m, 2H), 3.35 (s, 3H), 2.48–2.38 (m, 2H), 2.02–1.83 (m, 2H), 1.79–1.69 (m, 2H), 1.18 (d, *J* = 6.32 Hz, 3H), 0.84 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): *δ* 173.4, 137.6, 134.2, 127.9, 117.6, 92.7, 74.2, 71.7, 68.7, 67.8, 58.9, 42.1, 41.9, 41.8, 25.7, 20.6, 17.9, -4.6, -4.8; Anal. Calcd for $C_{22}H_{42}O_6Si$ (430.651): C, 61.36; H, 9.83. Found: C, 61.19; H, 9.97; Spectral data of **21**: $[\alpha]_D^{25} = -32.92$ (*c* 0.40, $CHCl_3$), IR ($CHCl_3$): *ν* 3459, 3015, 2932, 1729, 1462, 1378, 1253, 1179, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): *δ* 5.11–5.02 (m, 1H), 4.75–4.63 (m, 2H), 4.08–3.89 (m, 1H), 3.76–3.66 (m, 2H), 3.63–3.56 (m, 1H), 3.53–3.49 (m, 2H), 3.36 (s, 3H), 2.44–2.35 (m, 2H), 1.88–1.63 (m, 2H), 1.61–1.34 (m, 6H), 1.24 (d, *J* = 6.19 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): *δ* 172.7, 94.7, 71.7, 68.4, 67.9, 67.3, 59.0, 42.1, 40.4, 36.4, 27.1, 20.6, 9.06; Anal. Calcd for $C_{14}H_{26}O_6$ (290.353): C, 57.91; H, 9.03. Found: C, 57.95; H, 9.19.