Total synthesis of decarestrictine I and botryolide B *via* RCM protocol†

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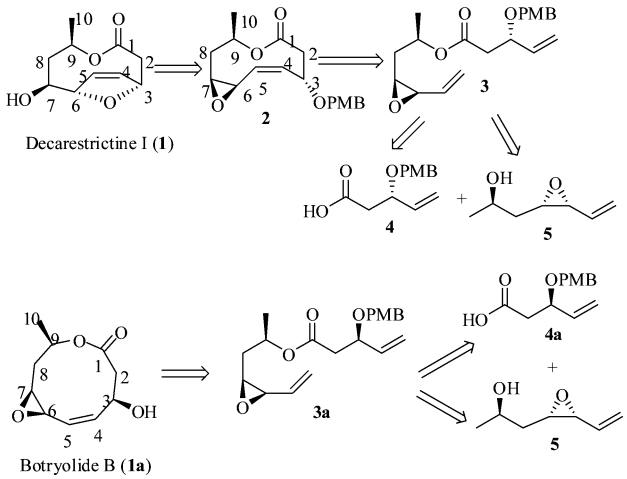
A convergent stereoselective total synthesis of decarestrictine I (1) and botryolide B (1a) invoking a common synthetic strategy is reported. The key steps are: ring-closing metathesis of epoxy dienoic esters obtained through the Yamaguchi esterification of their respective intermediates to furnish the respective *Z*-macrocycles (2 and 2a) which were further extrapolated to their respective targets.

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 forms a 10-membered lactone ring, which varies in the oxygen patterns ranging from carbon 3 to 7, and the presence of one *E*-configured double bond located either at C-4 or at C-5 are the salient structural features of this class of compounds. The decarestrictines show interesting activity in cell line tests with HEP-G2 liver cells[2,3] due to an inhibitory effect on cholesterol biosynthesis. Amongst this family, decarestrictine I (**1**) has the most unique structural features: a 10-membered lactone fused with a dihydrofuran framework and a *Z*-configured double bond to accommodate the bicyclic structure. Excepting a patent reference[4] no synthesis is reported so far. As a part of our ongoing program on the total synthesis of bioactive 10-membered macrolides,[5] we accomplished the total synthesis of decarestrictine D earlier.[5a]

In continuation, we became interested in the synthesis of **1** primarily due to its impressive structural features and report the same herein through a tandem RCM/intramolecular epoxide-ring opening reaction sequence to access the bicyclic framework en route to **1**. Alongside, a related stratagem involving Yamaguchi esterification followed by the RCM/deprotection set furnished yet another target **1a**. Interestingly, botryolides are biosynthetically related new decarestrictine analogs isolated from *Botryotrichum* sp. (NRRL).[6]

We envisioned a convergent strategy *via* the assembly of late-stage intermediates **4** and **5** (**4a** and **5**, Scheme 1) that are conveniently accessed from the inexpensive starting materials like 1,4-butanediol and propylene oxide. While the application of Jacobsen hydrolytic kinetic resolution and Sharpless asymmetric epoxidation helped us garner the stereogenic centers of the target molecules; Yamaguchi esterification, RCM and intramolecular epoxide ring-opening reaction are the other key steps adopted to accomplish the total synthesis of **1**. A similar strategy was planned for the first total synthesis of **1a**.



Scheme 1 Retrosynthesis for decarestrictine I and botryolide B.

The RCM of substrates possessing diversely protected chiral centers adjacent to the reacting olefins is still a challenging proposition, herein substrates **3** and **3a** were chosen as RCM precursors. Most often than not, such dienes result in products as *Z*-isomers either predominantly or exclusively.[7] Bearing this in mind, the synthesis was planned to derive the *Z*-macrocycles **2** and **2a** (Scheme 3 and 4). PMB-deprotection of **2** predictably led to the dihydrofuran ring (**1**) *via* the intramolecular epoxide ring-opening reaction. However, **2a** under the same reaction conditions afforded **1a**. A 6,7-β-epoxide was chosen since all the members of decarestrictine family followed a common biogenetic pathway and the C7 mostly bears a β-hydroxy stereogenic center.

Accordingly, the synthesis of **1** starts with the known silyl derivative of homoallyl alcohol. Thus, the olefin of homoallyl alcohol derivative was subjected to epoxidation with *m*-chloroperbenzoic acid. Then the racemic epoxide **6** (Scheme 2) was subjected to Jacobsen's hydrolytic kinetic resolution to afford the optically enriched epoxide **7**. Epoxide **7** on ring-opening reaction with n-butyl lithium and TMSI afforded allylic alcohol **8**[8] (70%). The hydroxyl group in **8** was protected as its PMB ether (PMBBr–NaH–THF/0 °C–rt) to afford **9** (84%), the TPS group in **9** was deprotected with TBAF in THF to afford primary alcohol **10** (91%) which was converted to acid **4** by a two step process; firstly to an aldehyde on Swern oxidation and then on perchlorite oxidation ($NaClO_2$–$NaH_2PO_4{\cdot}2H_2O$–*t*-BuOH–2-methyl-2-butene) to the acid **4** (80% over two steps).

Another intermediate, epoxy alkene **5** (Scheme 2) was synthesized from the known propargylic alcohol **11**.[9] Compound **11** was converted to *cis*-allylic alcohol **12** (67%) *via* partial reduction with $Ni(OAc)_2{\cdot}4H_2O$–$NaBH_4$ in ethanol[10] under H_2 atmosphere. Allylic alcohol **12** on Sharpless asymmetric epoxidation [(–)-DIPT–$Ti(O^iPr)_4$–cumenehydroperoxide/–20 °C] afforded epoxy alcohol

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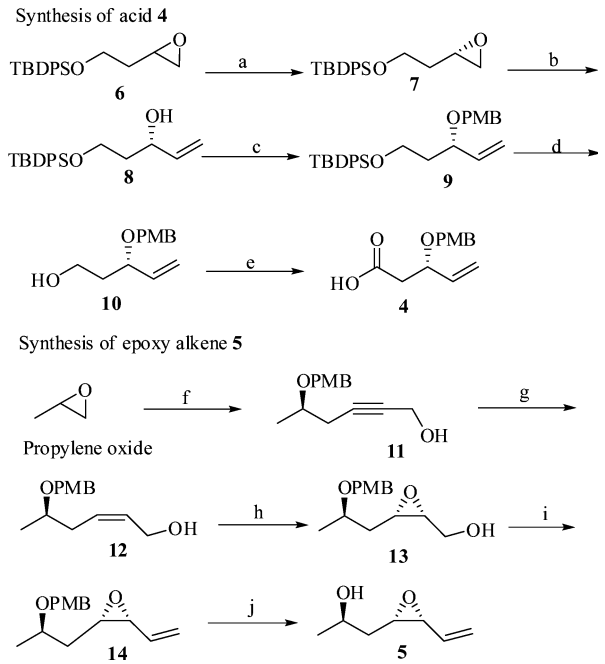
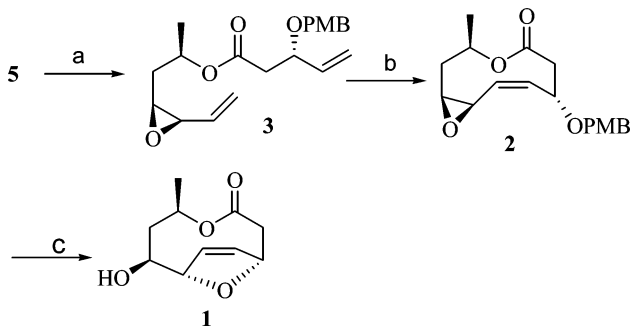


Scheme 2 *Reagents and conditions*: a) (*S*,*S*)-(salen) Co^{III}(OAC), 0.55 eq. H_2O, rt, 18 h; (b) *n*-BuLi, $Me_3S^+I^-$, THF, –20 °C–rt, 3 h, 70%; c) PMBBr, NaH, THF, 0 °C–rt, 12 h (84%), d) TBAF, THF, 0 °C–rt, 2 h (91%); e) i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 1 h, ii) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, *t*-BuOH–2-methyl-2-butene (3 : 1), 0 °C–rt, 12 h (80% over two steps); f) ref. 9; g) $Ni(OAc)_2{\cdot}4H_2O$, $NaBH_4$, H_2, EtOH, rt, 2 h (67%); h) (–)-DIPT, $Ti(O^iPr)_4$, cumenehydroperoxide, CH_2Cl_2, –20 °C, 12 h (93%); i) i) $(COCl_2)$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 1 h, ii) $Ph_3PCH_3^+I^-$, KO^tBu, THF, 0 °C, 8 h (62%); j) DDQ, CH_2Cl_2–H_2O (19 : 1), rt, 1 h, (90%).

13[11] (93%), which on Swern oxidation followed by 1C Wittig olefination ($Ph_3PCH_3^+I^-$–KO^tBu–THF) afforded epoxy alkene **14** (80% over two steps). The PMB group in **14** was deprotected with DDQ in CH_2Cl_2–H_2O to obtain alcohol intermediate **5** (90%).

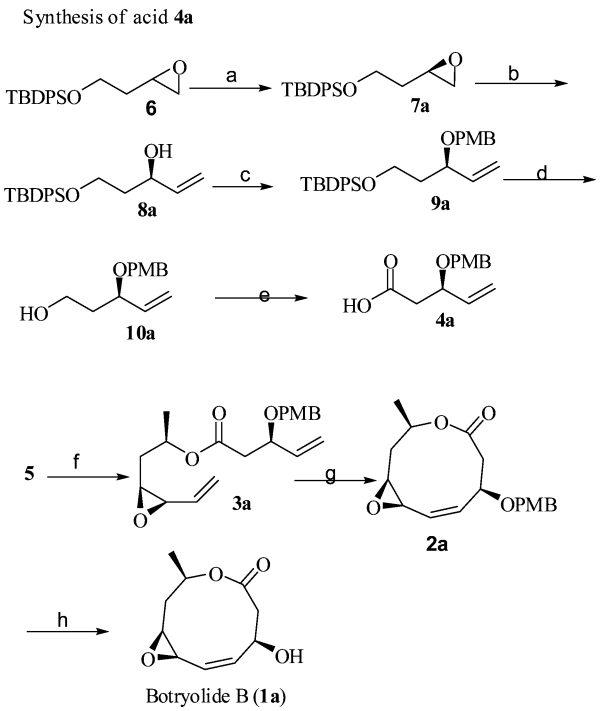
The acid **4** (Scheme 3) on coupling with **5** under Yamaguchi conditions (2,4,6-trichlorobenzoyl chloride–Et_3N–THF then DMAP–toluene) afforded the dienoic ester **3**[12] (82%). Compound **3** underwent RCM smoothly upon using 10 mol% of Grubbs' II generation catalyst at reflux in CH_2Cl_2 to provide the desired macrolactone (*Z*)-**2**[7] (~63%) as the major product. Next, lactone **2** on treatment with DDQ in CH_2Cl_2 underwent PMB-deprotection and a spontaneous second ring-closure to afford the



Scheme 3 *Reagents and conditions*: a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 0 °C–rt, 4 h, then DMAP, **4**, toluene, 0 °C–rt, 12 h (82%); b) Grubbs' II generation catalyst, CH_2Cl_2, reflux, 12 h (63%); c) DDQ, CH_2Cl_2–H_2O, 0 °C–rt, 1 h, (69%).

dihydrofuran ring containing decarestrictine I[13] (**1**, 69%), evidently through the intramolecular epoxide ring-opening reaction. The spectral data of synthetic **1** was matched with the reported data and found in agreement.[4]

To check whether only *anti*-configured 6,7-epoxide and 3-OPMB functional groups are conveniently positioned to undergo the dihydrofuran formation during the deprotection step and not otherwise, an independent study was undertaken. Accordingly, enantiomeric acid **4a** was synthesized using a related strategy (Scheme 4). Acid **4a** on Yamaguchi esterification with epoxy alcohol **5** gave ester **3a** in comparable yields. Later **3a** on RCM under similar reaction conditions furnished **2a** in comparable yields. Subsequently, following an analogous PMB-deprotection **2a** (DDQ–CH_2Cl_2–H_2O/rt) however did not result in the bicyclic system but rather furnished botryolide B (**1a**). Thus, the logic that spatial proximity plays an important role in facilitating an intramolecular epoxide ring-opening reaction holds good for **2** and a simple PMB-deprotection occurred in the case of lactone **2a** to afford botryolide B (**1a**, 75%) as the lone product. Compound **2a** was identified from its spectral analysis.[14]



Scheme 4 *Reagents and conditions*: a) (*R*,*R*)-(salen) Co^{III}(OAc), 0.55 eq. H_2O, rt, 18 h; (b) *n*-BuLi, $Me_3S^+I^-$, THF, –20 °C–rt, 3 h, 85%; c) PMBBr, NaH, THF, 0 °C–rt, 12 h (70%), d) TBAF, THF, 0 °C–rt, 2 h (80%); 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% over two steps); f) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 0 °C–rt, 4 h, then DMAP, **4**, toluene, 0 °C–rt, 12 h (85%); g) Grubbs' II generation catalyst, CH_2Cl_2, reflux, 12 h (75%); h) DDQ, CH_2Cl_2–H_2O, 0 °C-rt, 1 h, (72%).

Both the products (**1** and **1a**) were characterized by their spectral data. For instance, the *Z*-geometry of the double bond(s) was assigned based on the coupling constants of the olefinic protons ($J = 1.8, 8.3, 11.7$, and 1.5, 7.8, 10.9 Hz). Further, the structures of **1** and **1a** and their absolute stereochemistry were unambiguously established by comparing the spectral analysis.[14]

Incidentally, some of the other decarestrictines synthesized involving RCM are listed,[15] though the strategy to access the respective intermediates differ.

Conclusions

In conclusion, we described the stereoselective total synthesis of decarestrictine I (**1**) and botryolide B (**1a**) *via* an RCM of the respective dienoic esters possessing sensitive chiral functional groups on either side of the bisolefins. While macrolide **2** endowed with harmoniously positioned epoxide and –OPMB groups underwent a facile second cyclization to furnish **1** during the deprotection step *via* an intramolecular ring-opening reaction; the *syn*-diastereomer **2a** afforded **1a** under similar reaction conditions. The syntheses reported herein established the relative and absolute stereochemistry of both the targets.

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