

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

Palakodety Radha Krishna* and T. Jagannadha Rao

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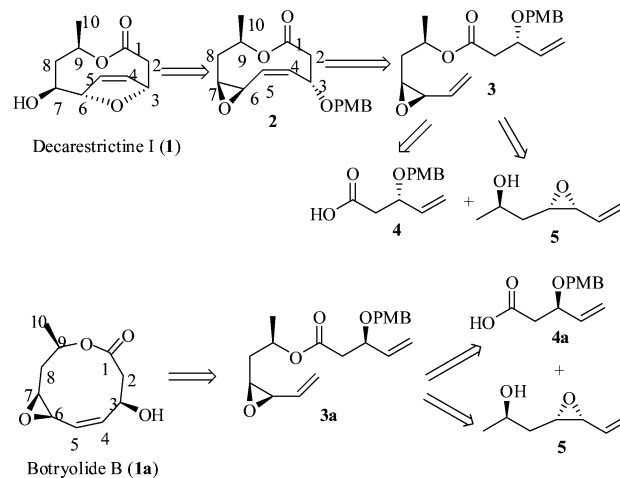
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A convergent stereoselective total synthesis of decarestrictine I (**1**) and botryolide B (**1a**) invoking a common synthetic strategy is reported. The key steps are: ring-closing metathesis of epoxy dienoic esters obtained through the Yamaguchi 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 reference⁴ 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.

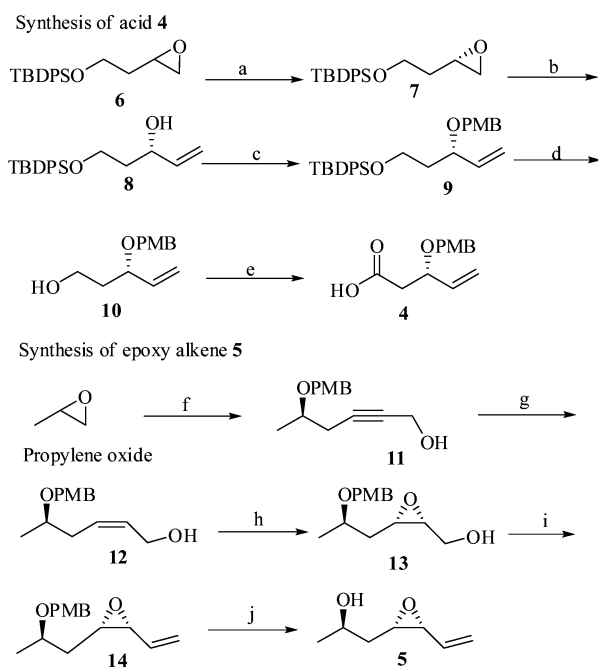
The RCM of substrates possessing diversely protected chiral centers adjacent to the reacting olefins is still a challenging proposition, herein substrates **3** and **3a** were chosen as RCM precursors. Most often than not, such dienes result in products as *Z*-isomers either predominantly or exclusively.⁷ 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 perchlorate oxidation (NaClO₂–NaH₂PO₄·2H₂O–*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)₂·4H₂O–NaBH₄ in ethanol¹⁰ under H₂ atmosphere. Allylic alcohol **12** on Sharpless asymmetric epoxidation [(–)-DIPT–Ti(O^{*i*}Pr)₄–cumenylhydroperoxide/–20 °C] afforded epoxy alcohol

D-211, Discovery Laboratory, Organic Chemistry Division-III, Indian Institute of Chemical Technology, Hyderabad 500 607, India. E-mail: prkgenius@iict.res.in; Fax: +91-40-27160387

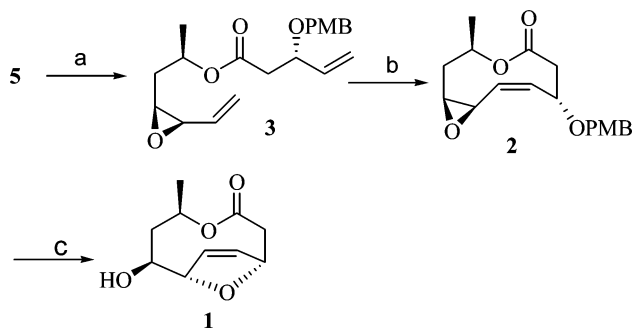
† Electronic supplementary information (ESI) available: Experimental procedures and spectral data. See DOI: 10.1039/c004556j



Scheme 2 Reagents and conditions: a) (*S,S*)-(salen) Co^{III}(OAc), 0.55 eq. H₂O, rt, 18 h; (b) *n*-BuLi, Me₃S⁺I⁻, THF, -20 °C-rt, 3 h, 70%; c) PMBBBr, NaH, THF, 0 °C-rt, 12 h (84%), d) TBAF, THF, 0 °C-rt, 2 h (91%); e) i) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C, 1 h, ii) NaClO₂, NaH₂PO₄·2H₂O, *t*-BuOH-2-methyl-2-butene (3 : 1), 0 °C-rt, 12 h (80% over two steps); f) ref. 9; g) Ni(OAc)₂·4H₂O, NaBH₄, H₂, EtOH, rt, 2 h (67%); h) (-)-DIPT, Ti(O^{*i*}Pr)₄, cumenehydroperoxide, CH₂Cl₂, -20 °C, 12 h (93%); i) i) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C, 1 h, ii) Ph₃PCH₃⁺I⁻, KO^{*t*}Bu, THF, 0 °C, 8 h (62%); j) DDQ, CH₂Cl₂-H₂O (19 : 1), rt, 1 h, (90%).

13¹¹ (93%), which on Swern oxidation followed by 1C Wittig olefination (Ph₃PCH₃⁺I⁻-KO^{*t*}Bu-THF) afforded epoxy alkene **14** (80% over two steps). The PMB group in **14** was deprotected with DDQ in CH₂Cl₂-H₂O to obtain alcohol intermediate **5** (90%).

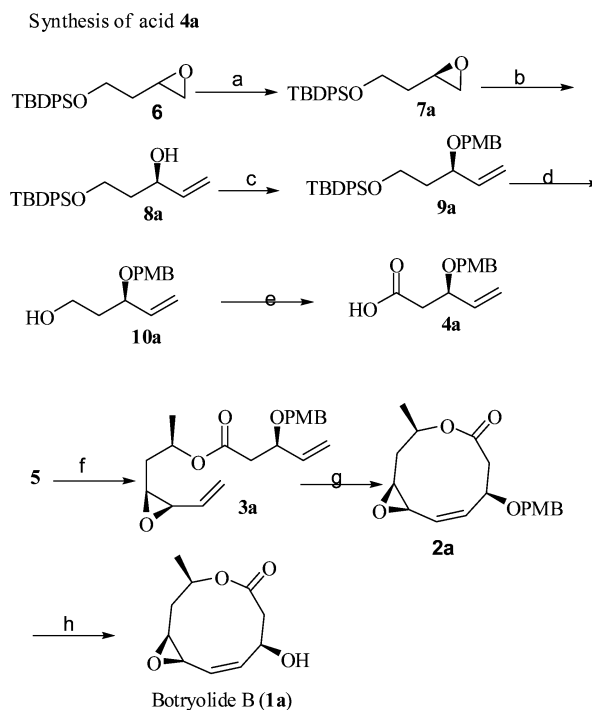
The acid **4** (Scheme 3) on coupling with **5** under Yamaguchi conditions (2,4,6-trichlorobenzoyl chloride-Et₃N-THF then DMAP-toluene) afforded the dienoic ester **3**¹² (82%). Compound **3** underwent RCM smoothly upon using 10 mol% of Grubbs' II generation catalyst at reflux in CH₂Cl₂ to provide the desired macrolactone (*Z*)-**2**⁷ (~63%) as the major product. Next, lactone **2** on treatment with DDQ in CH₂Cl₂ underwent PMB-deprotection and a spontaneous second ring-closure to afford the



Scheme 3 Reagents and conditions: a) 2,4,6-trichlorobenzoyl chloride, Et₃N, THF, 0 °C-rt, 4 h, then DMAP, **4**, toluene, 0 °C-rt, 12 h (82%); b) Grubbs' II generation catalyst, CH₂Cl₂, reflux, 12 h (63%); c) DDQ, CH₂Cl₂-H₂O, 0 °C-rt, 1 h, (69%).

dihydrofuran ring containing decastrictine I¹³ (**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-CH₂Cl₂-H₂O/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. H₂O, rt, 18 h; (b) *n*-BuLi, Me₃S⁺I⁻, THF, -20 °C-rt, 3 h, 85%; c) PMBBBr, NaH, THF, 0 °C-rt, 12 h (70%), d) TBAF, THF, 0 °C-rt, 2 h (80%); e) i) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C, 1 h, ii) NaClO₂, NaH₂PO₄·2H₂O, *t*-BuOH-2-methyl-2-butene (3 : 1), 0 °C-rt, 12 h (80% over two steps); f) 2,4,6-trichlorobenzoyl chloride, Et₃N, THF, 0 °C-rt, 4 h, then DMAP, **4**, toluene, 0 °C-rt, 12 h (85%); g) Grubbs' II generation catalyst, CH₂Cl₂, reflux, 12 h (75%); h) DDQ, CH₂Cl₂-H₂O, 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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Notes and references

- (a) S. Grabley, E. Granzer, K. Hütter, D. Ludwig, M. Mayer, R. Thiericke, G. Till, J. Wink, S. Philipps and A. Zeeck, *J. Antibiot.*, 1992, **45**, 56–65; (b) A. Göhr, A. Zeeck, K. Hütter, R. Kirsch, H. Kluge and R. Thiericke, *J. Antibiot.*, 1992, **45**, 66–73; (c) A. W. Ayer, M. Sun, L. M. Browne, L. S. Brinen and J. Clardy, *J. Nat. Prod.*, 1992, **55**, 649–653.
- N. B. Javitt and K. Budai, *Biochem. J.*, 1989, **262**, 989–992.
- M. Mayer, R. Thiericke and A. G. Hoechst, *J. Antibiot.*, 1993, **46**, 1372–1380.
- S. Philipps, M. Mayer, A. Göhr, E. Granzer, P. Hammann, R. Kirsch and R. Thiericke, EP, 0497300A12, 1992.
- (a) P. Radha Krishna and P. V. Narasimha Reddy, *Tetrahedron Lett.*, 2006, **47**, 7473–7476; (b) P. Radha Krishna and M. Narsingam, *Synthesis*, 2007, 3627–3634; (c) P. Radha Krishna and A. Sreeshailam, *Synlett*, 2008, 2795–2798.
- A. A. Sy, D. C. Swenson, J. B. Gloer and D. T. Wicklow, *J. Nat. Prod.*, 2008, **71**, 415–419.
- (a) D. K. Mohapatra, D. K. Ramesh, M. A. Giardello, M. S. Chorghade, M. K. Gurjar and R. H. Grubbs, *Tetrahedron Lett.*, 2007, **48**, 2621–2625; (b) C. V. Ramana, T. P. Khaladkar, S. Chatterjee and M. K. Gurjar, *J. Org. Chem.*, 2008, **73**, 3817–3822; (c) D. K. Mohapatra, D. Uttam, P. Ramesh Naidu and J. S. Yadav, *Synlett*, 2009, 2129–2132; (d) R. H. Grubbs, S. J. Miller and G. C. Fu, *Acc. Chem. Res.*, 1995, **28**, 446–452; (e) A. Deiters and S. F. Martin, *Chem. Rev.*, 2004, **104**, 2199–2238.
- P. Radha Krishna and R. Srinivas, *Tetrahedron Lett.*, 2007, **48**, 2013–2015.
- G. V. M. Sharma and K. V. Babu, *Tetrahedron: Asymmetry*, 2007, **18**, 2175–2184.
- (a) D. Sandrine, P. Jean-Luc and S. Maurice, *Synthesis*, 1998, 1015–1018; (b) C. A. Brown and V. K. Ahuja, *J. Org. Chem.*, 1973, **38**, 2226–2230.
- K. B. Sharpless, H. C. Kolb and M. S. VanNieuwenhze, *Chem. Rev.*, 1994, **94**, 2483–2547.
- J. Inanaga, K. Hirata, H. Saeki, T. Katsuki and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1989–1993.
- J. M. Peter and L. H. Ronald, *J. Am. Chem. Soc.*, 2003, **125**, 1712–1713.
- For experimental procedures and spectral data, see *Supplementary Information*.
- (a) J. S. Yadav, K. A. Lakshmi, N. M. Reddy, A. R. Prasad and B. V. Subba Reddy, *Tetrahedron*, 2010, **66**, 334–338; (b) P. S. Chowdhury, P. Gupta and P. Kumar, *Tetrahedron Lett.*, 2009, **50**, 7188–7190; (c) P. Gupta and P. Kumar, *Eur. J. Org. Chem.*, 2008, 1195–1202; (d) D. K. Mohapatra, G. Sahoo, D. K. Ramesh, J. S. Rao and G. N. Sastry, *Tetrahedron Lett.*, 2009, **50**, 5636–5639.