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Divergent Approach to Building a Latrunculin Family Derived Hybrid Macrocyclic Toolbox

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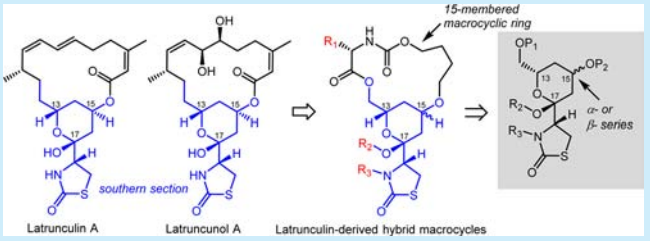
Supporting Information

ABSTRACT: A divergent approach to obtain a latrunculin family based hybrid macrocyclic toolbox is developed. A practical, stereoselective synthesis of a common substructure present in latrunculin A and latrunculol A was achieved. This was further utilized in the macrocyclic diversity synthesis. The amino acid moiety embedded in the 15-membered macrocyclic ring allows for the exploration of various chiral side chains as one of the diversity sites.



Isolated from Red Sea sponges *Negombata magnifica* and other unrelated species, the latrunculin natural products family is structurally unique and exhibits biological responses as highly potent inhibitors of actin polymerization and cytotoxicity against a wide variety of cancer cell lines.[1] One of the first compounds isolated in this series is a latrunculin A (**1**, Figure 1),[1a] and in 2008, another interesting member, latrunculol A

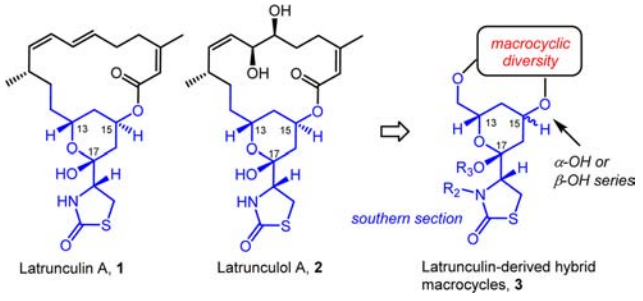


Figure 1. Latrunculin A (**1**), latrunculol A (**2**), and the proposed hybrid macrocyclic natural products **3**.

(**2**),[1d] was further reported. The structures of latrunculin A and B (note: the structure is shown only for latrunculin A) were assigned on the basis of extensive spectroscopic studies and the single-crystal X-ray of the methyl glycoside derivative of latrunculin A.[2] Several members of the latruculin family, such as latrunculin A, latrunculin B, and latrunculol A, bear a common southern substructure having a stereodefined tetrahydropyran ring coupled to a thiazolidinone moiety. In some cases, the northern macrocyclic substructures vary in the ring sizes (for example, 14- and 16-membered rings). There are also slight variations in the functional groups of the northern, macrocyclic region among several family members. Latrunculins are known to disrupt the microfilament organization by binding specifically to a cytoskeleton protein called actin through forming a 1:1 complex without affecting the microtubule dynamics.[1a,b] The X-ray crystal structure of the actin monomer binding to latrunculin A revealed that the interactions made by the pyran ring containing thiazolidinone substitution with actin are crucial for the biological activity.[3]

Because of the excellent biological properties that are shown by this family of natural products and the scarcity of accessing these compounds in sufficient amounts from the natural sources, several groups worked on the synthesis of latrunculins.[1c,4] In 2013, the Smith group reported the first total synthesis of epimeric latrunculol A.[5] As part of our continuous interest in developing modular approaches to building a toolbox having different types of natural product-inspired macrocyclic compounds,[6] we focused our attention on the common southern part of latrunculin A and latrunculol A and on utilizing this scaffold in obtaining a diverse set of hybrid macrocyclic natural product-based small molecules (**3**). Having a diverse set of chemical toolbox in hand, our interest is in exploring the value of these hybrid compounds to search for a new family of cytoskeleton modulators as well as in other selected pathways involved in cytoskeleton and cell migration biology.[7] Our long-term goal in this exercise is to identify novel sets of compounds as selective modulators of protein−protein interactions[8,9] and, in some of the signaling pathways.

Keeping in mind the importance of the southern region of latrunculin family, we planned our synthesis with the following objectives, and these are (i) to develop a novel and practical route to access sufficient amounts of the southern scaffold and (ii) to utilize this key scaffold in building a diverse set of macrocyclic architectures with an embedded amino acid moiety. The incorporation of an amino acid moiety in the macrocyclic ring would allow exploring the variation in the chiral side chain functionality as one of the diversity sites. Our approach to obtaining latrunculin-derived hybrid macrocycles is outlined in Scheme 1. The first objective is to develop a stereoselective synthesis for obtaining the southern scaffold

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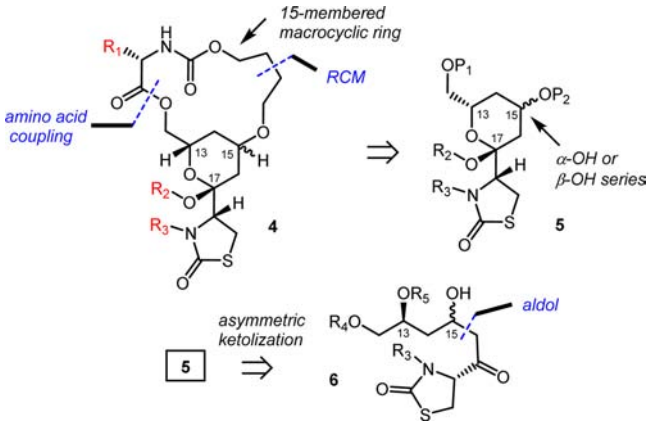
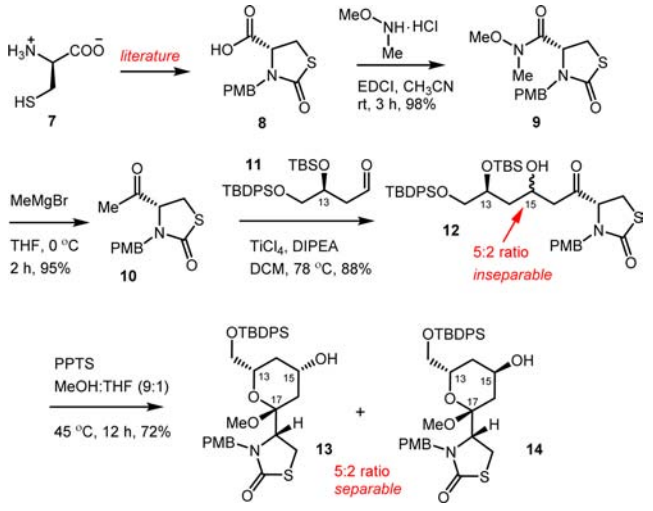
Scheme 1. Our Plan To Obtain Latrunculin-Derived Hybrid Macrocycles (4) from the Southern Scaffold 5 Which Can Be Obtained from 6 by Ketolization



(both series having α- and β-OH group at C-15) in large quantities having two orthogonally protected hydroxyl groups on the pyran moiety. The primary −OH group at C-13 can be acylated using an amino acid moiety, which after the coupling could be subjected to ring-closing metathesis as the stitching approach for obtaining a 15-membered ring. The scaffolds having α- and β-OH groups at C-15 would allow building macrocyclic rings utilizing *cis* and *trans* orientations of two functional groups at C-13 and C-15, respectively. In our plan, we aimed at accessing **5** from **6** by an asymmetric ketolization. The synthesis of **6** can be achieved by an aldol reaction (see the disconnection).

Synthesis of the southern scaffold as pyran fragments **13** and **14** is shown in Scheme 2. The thiazolidinone acid **8** was

Scheme 2. Synthesis of the Southern Scaffold of Latrunculins 13 and 14



obtained from L-cysteine (**7**) in two steps following the reported protocol (see the Supporting Information). The coupling of hydroxylamine hydrochloride with acid **8** using EDCI reagent gave Weinreb amide **9**, which was further treated with methylmagnesium bromide to obtain methyl ketone **10** in a good yield. Titanium tetrachloride mediated aldol reaction[10] between the aldehyde **11**, which was obtained from *S*-malic acid in four steps (see the Supporting Information), and methyl ketone **10** gave β-hydroxy ketone **12** as an inseparable 5:2 (from ^{1}H NMR) diastereomeric mixture in 88% yield. Desilylation of the secondary hydroxyl group protected as −OTBS at C-13 followed by an asymmetric ketolization of the aldol product **12** in the presence of pyridinium *p*-toluenesulfonate (PPTS) and methanol smoothly furnished the separable mixture of methylacetals **13** (50%) and **14** (20%).

The stereochemical assignments of the major and minor products were made by NOE experiments (see Figure 2). The NOE between two protons at C-13 and C-15 and proton at C-13 and C-17 OMe in **13** was observed, whereas **14** did not show any NOE between two protons at C-13 and C-15.

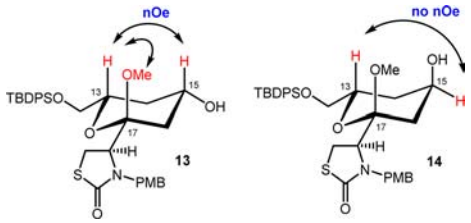
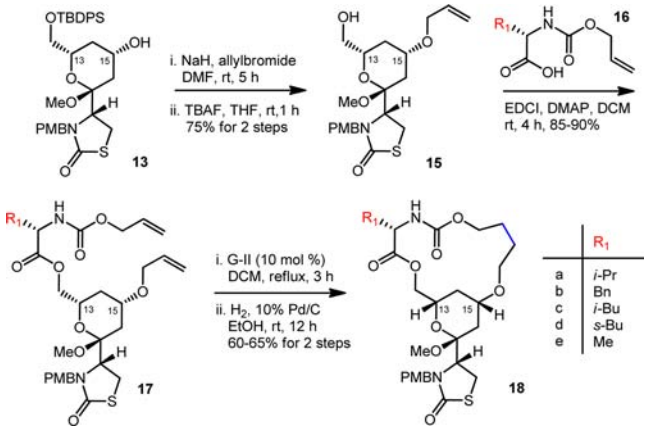


Figure 2. Stereochemical assignment through NOE studies.

Allylation of the secondary hydroxyl group at C-15 of the pyran fragment **13** with allyl bromide and NaH followed by a removal of the TBDPS group with tetrabutylammonium fluoride gave the primary alcohol **15** in 75% yields (Scheme 3). Coupling of *N*-alloc-amino acid **16** with primary alcohol **15**

Scheme 3. Synthesis of 15-Membered Macrocyclic Ring Using *Cis* Oriented Hydroxyls at C-15 and C-13



in the presence of EDCI and DMAP gave the bisallyl precursor **17** which was then subjected to ring-closing metathesis using Grubbs' II catalyst (10 mol %). This was then followed by hydrogenation of an olefin with 10% Pd−C in the presence of hydrogen gas to obtain the macrocycle **18** in a very good yield. To explore the generality of 15-membered ring formation using a ring-closing metathesis approach and to obtain several analogues with a variation in the chiral side chain, five amino acids were tried. In all cases, the large ring formation using the *cis* orientation of the stitching substituents at C-13 and C-15 (**17**), did occur without any problem. The synthesis details and a full structural characterization are provided in the experimental details in the Supporting Information. Although not shown here, compound **18** having a PMB group on the

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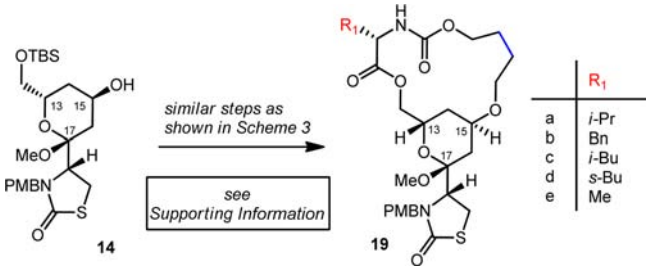
thiazolidinone moiety can further be utilized in building the second diversity site.

In a similar manner, we also succeeded in the synthesis of macrocycles **19** starting from the pyran fragment **14** having *trans* stitching functional groups at C-13 and C-15. In this series, we faced no problem, and the 15-membered macrocyclic ring formation appeared to be independent of the stereochemistry of the functional group at C-15. Again, in this series, five amino acids were used to validate the generality of this reaction and to explore one of the diversity sites on the macrocyclic ring skeleton. Although not attempted yet, the utilization of β-amino acid moieties in our macrocyclic synthesis planning in both series shown in Schemes 3 and 4 can lead to accessing 16-membered ring architectures.

Scheme 4. Similar Approach to Obtain Latrunculin-Based Hybrid Macrocycles (19) Epimeric at C-15 of the Pyran Moiety



The utilization of *cis* and *trans* orientations of two stitching moieties to forming a 15-membered ring allowed two different sets of macrocyclic shapes **18** and **19**. An example of 3D-minimized structures of two types of macrocyclic compounds is shown in Figure 3.

In conclusion, we developed a novel and efficient methodology to synthesize a key pyran fragment (**13** and **14**) of latrunculin A and latrunculol A in gram quantities (note: the synthesis was achieved on a 10.0 g scale for both diastereomers). The amino acid moiety incorporated through the C-13 hydroxyl group allowed us to access a unique set of latrunculin-derived hybrid macrocyclic architectures. Further, biological investigations using these compounds are ongoing, and these studies will be made available when complete.

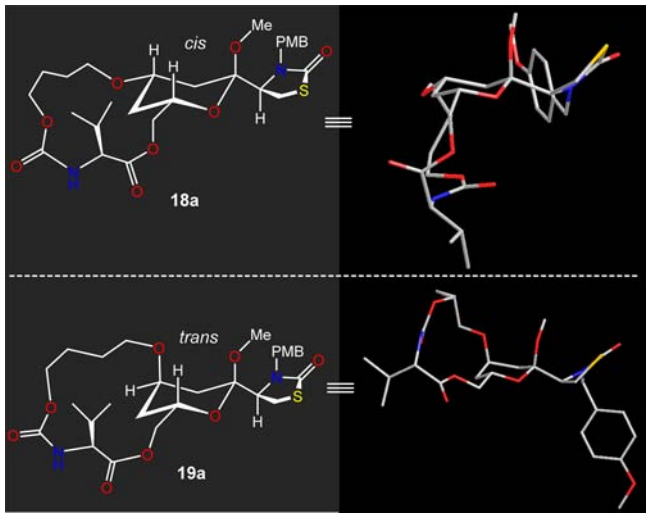


Figure 3. 3D structures with the energy minimization of hybrid macrocycles **18a** and **19a** having *cis*- and *trans*-substituted pyran rings at C-13 and C-15.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental section and spectral data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Spector, I.; Shochet, N. R.; Kashman, Y.; Groweiss, A. *Science* **1983**, *219*, 493. (b) Spector, I.; Shochet, N. R.; Blasberger, D.; Kashman, Y. *Cell. Motil. Cytoskeleton* **1989**, *13*, 127. (c) El Sayed, K. A.; Youssef, D. T.; Marchetti, D. *J. Nat. Prod.* **2006**, *69*, 219. (d) Amagata, T.; Johnson, T. A.; Cichewicz, R. H.; Tenney, K.; Mooberry, S. L.; Media, J.; Edelstein, M.; Valeriote, F. A.; Crews, P. *J. Med. Chem.* **2008**, *51*, 7234.

(2) Kashman, Y.; Groweiss, A.; Shmueli, U. *Tetrahedron Lett.* **1980**, *21*, 3629.

(3) Morton, W. M.; Ayscough, K. R.; McLaughlin, P. J. *Nat. Cell Biol.* **2000**, *2*, 376.

(4) (a) Zibuck, R.; Liverton, N. J.; Smith, A. B. *J. Am. Chem. Soc.* **1986**, *108*, 2451. (b) Fürstner, A.; Kirk, D.; Fenster, M. D.; Aissa, C.; De Souza, D.; Muller, O. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 8103. (c) Fürstner, A.; Kirk, D.; Fenster, M. D. B.; Aïssa, C.; De Souza, D.; Müller, O. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 8103. (d) Fürstner, A.; Turet, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 3462. (e) Fürstner, A.; De Souza, D.; Turet, L.; Fenster, M. D.; Parra-Rapado, L.; Wirtz, C.; Mynott, R.; Lehmann, C. W. *Chemistry* **2007**, *13*, 115. (f) Fürstner, A.; Kirk, D.; Fenster, M. D.; Aissa, C.; De Souza, D.; Nevado, C.; Tuttle, T.; Thiel, W.; Muller, O. *Chemistry* **2007**, *13*, 135. (g) Furstner, A.; Nagano, T.; Muller, C.; Seidel, G.; Muller, O. *Chemistry* **2007**, *13*, 1452. (h) Kudrimoti, S.; Ahmed, S. A.; Daga, P. R.; Wahba, A. E.; Khalifa, S. I.; Doerksen, R. J.; Hamann, M. T. *Bioorg. Med. Chem.* **2009**, *17*, 7517.

(5) Williams, B. D.; Smith, A. B. *Org. Lett.* **2013**, *15*, 4584.

(6) (a) Jimmidi, R.; Shroff, G. K.; Satyanarayana, M.; Reddy, B. R.; Reddy, J.; Sawant, M. A.; Sitaswad, S. L.; Arya, P.; Mitra, P. *Eur. J. Org. Chem.* **2014**, *20*, 1151. (b) Jogula, S.; Bhanudas Dasari, B.; Khatravath, M.; Chandrasekar, G.; Kitambi, S. S.; Arya, P. *Eur. J. Org. Chem.* **2013**, *19*, 5036. (c) Guduru, S. K. R.; Chamakuri, S.; Chandrasekar, G.; Kitambi, S. S.; Arya, P. *ACS Med. Chem. Lett.* **2013**, *4*, 666. (d) Dasari, B.; Jogula, S.; Borhade, R.; Balasubramanian, S.; Chandrasekar, G.; Kitambi, S. S.; Arya, P. *Org. Lett.* **2013**, *15*, 432. (e) Chamakuri, S.; Guduru, S. K. R.; Pamu, S.; Chandrasekar, G.; Kitambi, S. S.; Arya, P. *Eur. J. Org. Chem.* **2013**, *19*, 3959. (f) Aeluri, M.; Pramanik, C.; Chetia, L.; Mallurwar, N. K.; Balasubramanian, S.; Chandrasekar, G.; Kitambi, S. S.; Arya, P. *Org. Lett.* **2013**, *15*, 436. (g) Aeluri, M.; Gaddam, J.; Davarakonda, V. K. S. T.; Chandrasekar, G.; Kitambi, S. S.; Arya, P. *Eur. J. Org. Chem.* **2013**, *19*, 3955.

DOI: 10.1021/ol503465p
Org. Lett. 2015, 17, 472−475

(7) (a) Rennebaum, S.; Caflisch, A. *Proteins* **2012**, *80*, 1998. (b) Sumiya, E.; Shimogawa, H.; Sasaki, H.; Tsutsumi, M.; Yoshita, K.; Ojika, M.; Suenaga, K.; Uesugi, M. *ACS Chem. Biol.* **2011**, *6*, 425. (c) Miao, B.; Skidan, I.; Yang, J.; You, Z.; Fu, X.; Famulok, M.; Schaffhausen, B.; Torchilin, V.; Yuan, J.; Degterev, A. *Oncogene* **2011**. (d) Cipres, A.; O'Malley, D. P.; Li, K.; Finlay, D.; Baran, P. S.; Vuori, K. *ACS Chem. Biol.* **2010**, *5*, 195. (e) Saito, S. Y. *Prog. Mol. Subcell. Biol.* **2009**, *46*, 187. (f) Ng, D. C.; Gebski, B. L.; Grounds, M. D.; Bogoyevitch, M. A. *Cell Motil. Cytoskeleton* **2008**, *65*, 40.

(8) (a) Wells, J. A.; McClendon, C. L. *Nature* **2007**, *450*, 1001. (b) Arkin, M. R.; Wells, J. A. *Nat. Rev. Drug Discovery* **2004**, *3*, 301. (c) Wells, J.; Arkin, M.; Braisted, A.; DeLano, W.; McDowell, B.; Oslob, J.; Raimundo, B.; Randal, M. *Ernst Schering Res. Found. Workshop* **2003**, 19.

(9) Aeluri, M.; Chamakuri, S.; Dasari, B.; Guduru, S. K.; Jimmidi, R.; Jogula, S.; Arya, P. *Chem. Rev.* **2014**, *114*, 4640.

(10) (a) Fürstner, A.; De Souza, D.; Parra-Rapado, L.; Jensen, J. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 5358. (b) Fürstner, A.; Turet, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 3462.

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Org. Lett. 2015, 17, 472−475