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Regio- and Stereocontrolled Dieckmann Approach to Treprostinil-Inspired, Polycyclic Scaffold For Building Macrocyclic Diversity

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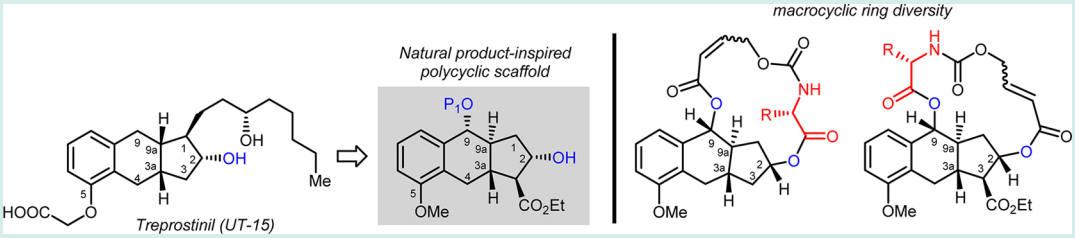
Supporting Information



ABSTRACT: We developed a regio- and stereocontrolled Dieckmann cyclization approach to the synthesis of a novel, natural-product-like scaffold that was inspired from treprostinil (UT-15). This was further utilized in a diversity-based, 15-membered macrocyclic synthesis of two different sets of hybrid compounds. The amino acid moiety embedded in the macrocyclic skeleton allow exploring various chiral side chain groups within the ring.

KEYWORDS: *treprostinil, Dieckmann cyclization, natural-product-inspired scaffolds, macrocycles*

Treprostinil (UT-15, Figure 1, **1**) is a synthetic drug with a proven track record for the treatment of pulmonary hypertension, a fatal lung disease.[1−3] The design and synthesis of this drug was achieved, initially by starting with prostacyclin (PGI_2, **2**), which is a key physiological prostanoid.[4,5] Prostacyclin (PGI_2) is one of the major metabolic products from arachidonic acid during the vasculature process and is normally produced in endothelium and smooth muscles.[6−12] PGI_2 is a highly potent endogenous vasodilator in both systemic and pulmonary circulation and is also known to inhibit the platelet aggregation and adhesion.[8,13−15] Because of the limitations associated with PGI_2 (i.e., short half-life etc.), the synthesis efforts for obtaining a better compound eventually led to reaching a successful drug, treprostinil!

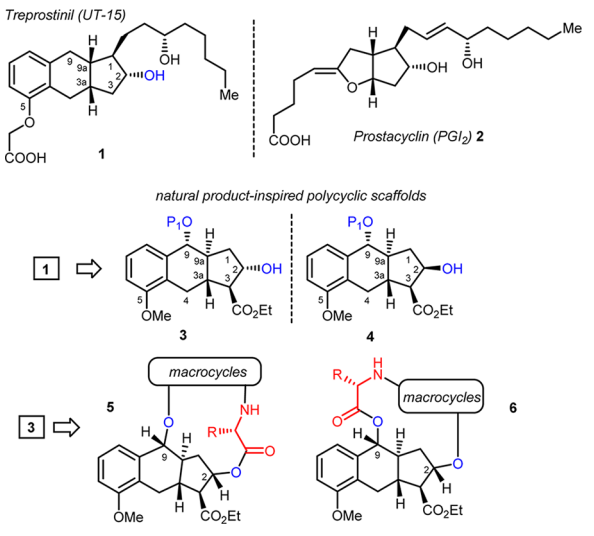


Figure 1. Treprostinil-inspired, polycyclic scaffolds for building a toolbox with different macrocycles.

With our growing interest[16−25] in selecting the critical fragments or scaffolds from natural products and other bioactive compounds, and, their utilization in diversity-based synthesis to obtain hybrid macrocycles, treprostinil caught our attention. The presence of a tricyclic moiety with the stereodefined functional groups was attractive to us, and, the tricyclic scaffold of this nature (i.e., either cis- or trans-fused at C-3a and C-9a) can be taken further for building a hybrid macrocyclic toolbox. With this objective, shown in Figure 1 are two tricyclic scaffolds **3** and **4** that we plan to synthesize and they offer several unique features, such as (i) the presence of a tricyclic moiety having a trans-fused six- and five-membered rings at C3a and C-9a; (ii) the −OH group at C-2 in a five membered ring can have a cis or trans relationship with the benzylic hydroxyl at C-9 of a six membered ring; and (iii) the carboxyl ester moiety at C-3 trans to hydroxyl at C-9. Using either of these tricyclic scaffolds (**3** and **4**), our plan is to explore building the macrocyclic diversity for producing a diverse set of hybrid macrocycles, (for example, **5** and **6** from **3**).

Our specific design and synthesis plans to building a 15-membered ring, macrocyclic toolbox are shown in Scheme 1. The first milestone is to develop the synthesis of two key tricyclic scaffolds having an α- and β-OH groups at C-2 (see **9**).

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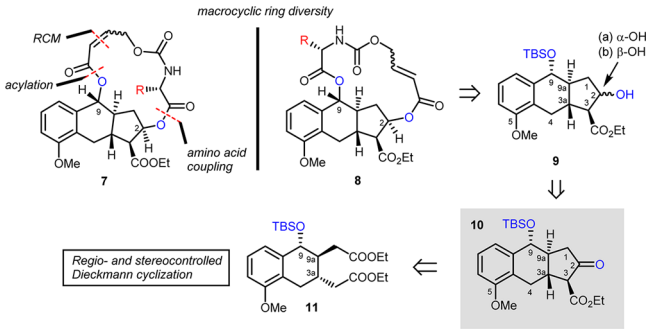
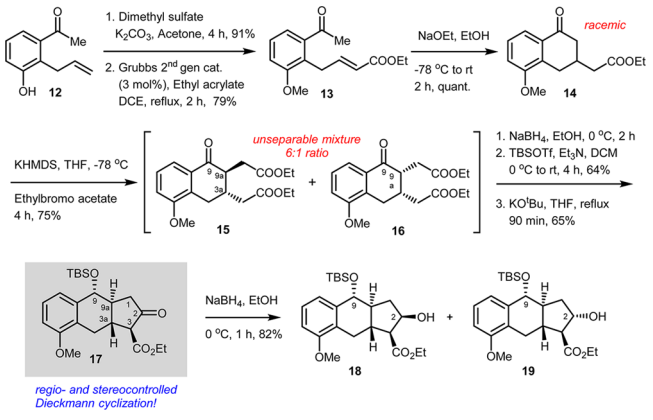
Scheme 1. Plan to Obtain 15-Membered Ring, Hybrid Macrocycles Using 9 (α- or β-OH Series) as the Key Starting Material



For example, using **9b** (with β-OH at C-2), the plan is to carry-out a stepwise acylation with the amino acid moiety at C-2 and then acryloylation of −OH group at C-9. This would lead to accessing a key precursor to test the ring closing metathesis as the stitching reaction for obtaining a 15-membered ring (**7**). Through the utilization of different amino acids in the acylation step, one can obtain various side chains on the macrocyclic ring as the diversity site. In a similar manner, using the −OH group at C-9 for an acylation with the amino acid moiety, it would be possible to obtain another type of a 15-membered macrocyclic ring (**8**). The choice of the scaffolds (**9** with α- or β-OH at C-2) would allow building the macrocyclic rings having either trans or cis relationships at C-2 and C-9. Finally, our plan to obtain **10** as a precursor to **9** was centered around the regio- and stereocontrolled Dieckmann cyclization utilizing **11** as the key starting material. There are several examples in the literature[26−30] where Dieckmann reaction is commonly utilized in the synthesis of bioactive natural products and related analogs.

The synthesis of **10** was started from the phenolic derivative **12**, which was synthesized by a Claisen rearrangement of 1-(3-(allyloxy)phenyl) ethanone (see Scheme 2).[31] Compound **12**

Scheme 2. Regio- and Stereocontrolled Dieckmann Cyclization Approach to Tricyclic Scaffold, 17



was subjected to the phenolic hydroxyl protection followed by the cross metathesis reaction for obtaining an α, β-unsaturated carboxyl ester (**13**). It was then subjected to Michael addition using sodium ethoxide (NaOEt in ethanol at −78 °C and a dropwise addition of the starting material in THF) for producing the bicyclic compound **14**.[32] To access a starting material for testing the scope of the Dieckmann cyclization, **14** was further subjected to an enol ether alkylation conditions. The use of potassium hexamethyldisilazane (KHMDS) at −78 °C gave **15** and **16** as the unseparable diastereomeric mixture in 6:1 diastereomeric ratio. It was then directly treated with sodium borohydride to reduce the keto moiety at C-9. The crude mixture obtained from this reduction was subjected to −OTBS ether formation using triethyl amine as the base. At this stage, the major product obtained after the flash column chromatography was subjected to Dieckmann cyclization in the presence of potassium tertiary butoxide.[33] This reaction produced **17** as a single diastereomer and, the purity of this compound was confirmed by HPLC (>99%). As a test study, this was further subjected to the carbonyl reduction with $NaBH_4$ giving two separable diastereomeric −OH groups at C-2 (see **18** and **19**). Both of them were thoroughly subjected to extensive 1D and 2D NMR studies. The detailed structural assignments are provided in the Supporting Information. In one case, as shown in Figure 2, the X-ray crystal structure of **18**

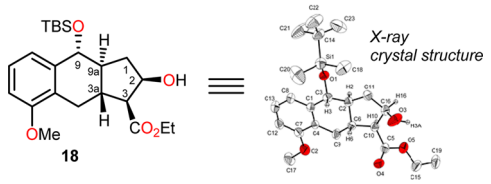


Figure 2. X-ray crystal structure of **18**.

further confirmed the structural assignments. The two stereodefined, natural product-like scaffolds, **18** and **19** can serve as the starting material for further developing the 15-membered macrocyclic diversity synthesis.

To our knowledge, the regio- and stereocontrolled Dieckmann cyclization approach to the synthesis of **17** from a mixture of **15** and **16** is novel and merits a plausible explanation (see Scheme 3). Assuming the carbonyl reduction at C-9 is stereoselective giving **20** as the major isomer, this can lead to several Dieckmann products as **17**, **22a**, **22b**, and **22c**. A plaussible explanation is that first, a regioselective enol ether is generated from the [b] site that is less sterically croweded compared with the [a] site (see **20** and **21**). Following an intramolecular alkylation cyclization, this can lead the −COOEt moiety in two orientations producing either **17** and/or **22a**. Once again, it appears that the trans (9a and 3a)-oriented scaffold favors the orientation of the −COOEt moiety as the β-position which is away from the core scaffold compared to an α-site.

Having an access to both tricyclic scaffolds **18** and **19** in sufficient amounts, we then decided to move forward with 15-membered macrocyclic diversity synthesis plans. As shown in Scheme 4, the hydroxyl group at C-2 was then acylated {1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide (EDC), 4-dimethylaminopyridine (DMAP)} with three amino acid derivatives giving **24** with R_1 as the diversity site. In two steps that included the TBS removal (under mild acidic conditions) and further subjection to acryloylation provided the key starting material **25** to test our crucial ring closing metathesis stitching reaction. This metathesis-based cyclization[34,35] worked-well in all the three cases and this further validates the scope of this type of macrocyclization giving a 15-membered ring on scaffold (**26**). Because of an overlapping of signals in NMR, it was not possible to assign the geometry across the double bond

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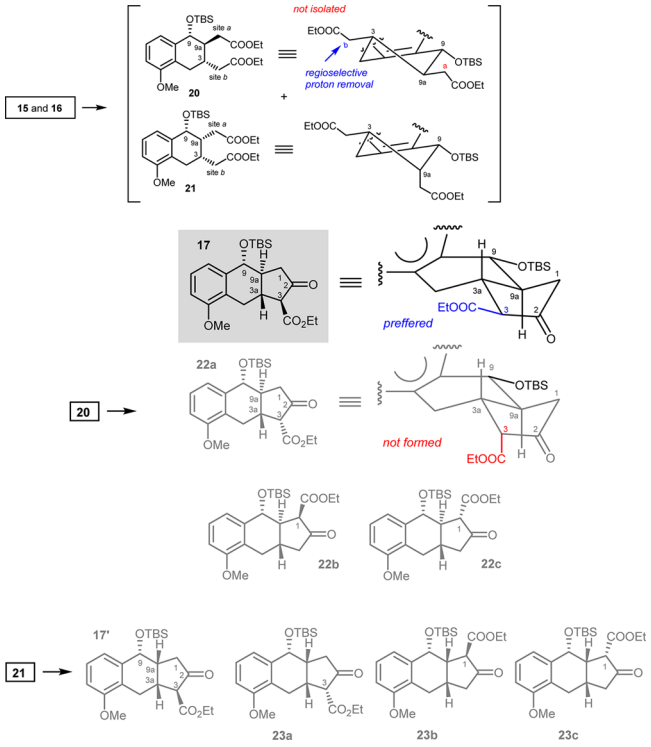
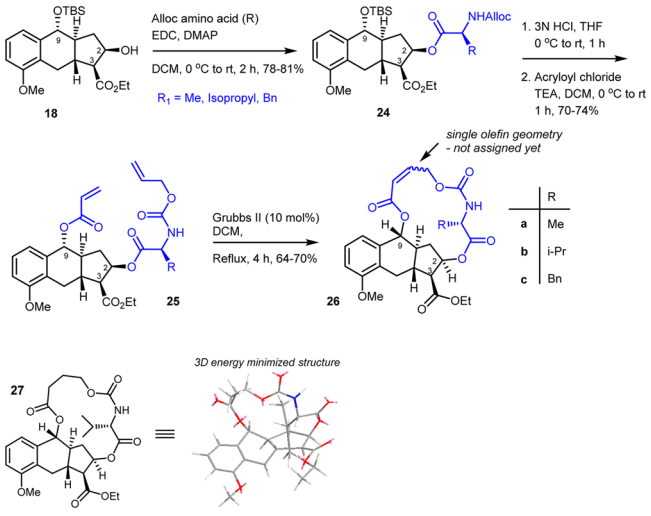
Scheme 3. Possible Formation of Several Products in Dieckmann Cyclization



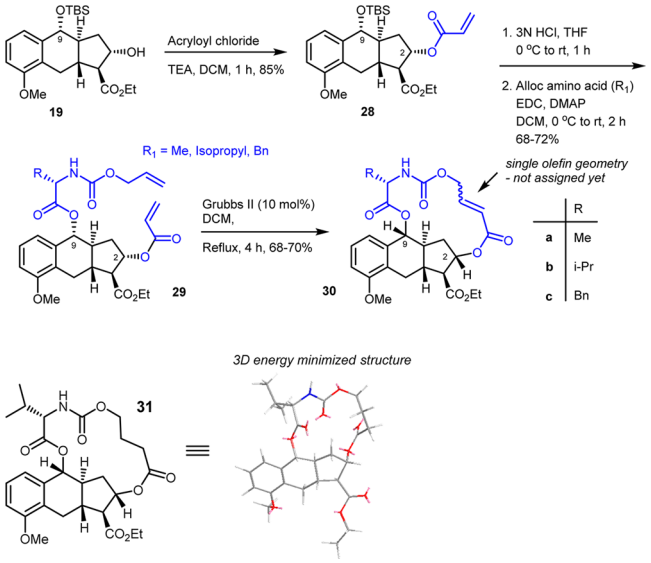
Scheme 4. Diversity Synthesis of Macrocycles, 26



although the ring closing metathesis gave a single isomeric product. The synthesis details and full structural assignments of all the compounds in this series are provided in the Supporting Information. In one case, the 3D energy minimized structure of a macrocyclic derivative with the reduced double bond is also shown (see **27**).

To explore the scope of other diastereoemeric tricyclic scaffold, **19** having a cis relationship between the two hydroxyl groups at C-2 and C-9, this was further utilized in the macrocyclic synthesis. The synthetic steps to reaching this objective are shown in Scheme 5. Compound **19** was subjected to acryloylation giving **28** in a high yield. Following the removal of the silyl group under mild acidic conditions, the free benzylic −OH group was then acylated using three different *N*-alloc

Scheme 5. Diversity Synthesis of Hybrid Macrocycles with a 15-Membered Ring (30) from 19



protected amino acids giving the key precursor (**29**) to study the 15-membered ring formation by a ring closing metathesis stitching approach. As in the previous study, this reaction also worked-well, and in all the three cases, macrocyclic ring was obtained (see **30**). The reaction appears to independent of the stereochemistry of -O-acryloyl group at C-2 and with the choice of different amino acid moieties utilized for acylation at C-9. The olefin was not assigned due to overlapping signals in NMR. To obtain some insight information about the nature of the 15-membered ring, in one case, the reduced derivative was also subjected to 3D energy minimization studies (see **31**). As before, the detailed synthesis and products characterization are provided in the Supporting Information.

To summarize, we report a regio- and stereocontrolled Dieckmann cyclization approach for obtaining natural product-like scaffolds, **18** and **19** that were further utilized in a diversity synthesis to build a different set of macrocyclic compounds. To our knowledge, the Dieckmann approach reported here is novel for obtaining this type of stereodefined scaffold, and, this can also lead to the synthesis of enantiomerically pure version of the racemic tricyclic scaffolds, **18** and **19**. Work is in progress in this direction! In addition, the biological studies with the use of our chemical toolbox reported herein are ongoing to search for novel small molecule modulators of protein−protein interactions[36−39] and selected signaling pathways,[40−45] and will be reported when available.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedure and a full characterization all compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.5b00076.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Chu, D. H.; Jambusaria, A.; Hanna, B.; Treat, J. R. Cutaneous reaction to inhaled treprostinil. *J. Am. Acad. Dermatol.* **2011**, *65*, e123−4.

(2) Ferrantino, M.; White, R. J. Inhaled treprostinil sodium for the treatment of pulmonary arterial hypertension. *Expert Opin. Pharmacother.* **2011**, *12*, 2583−93.

(3) Ghonem, N.; Yoshida, J.; Stolz, D. B.; Humar, A.; Starzl, T. E.; Murase, N.; Venkataramanan, R. Treprostinil, a prostacyclin analog, ameliorates ischemia- reperfusion injury in rat orthotopic liver transplantation. *Am. J. Transplant.* **2011**, *11*, 2508−16.

(4) Moriarty, R. M.; Rani, N.; Enache, L. A.; Rao, M. S.; Batra, H.; Guo, L.; Penmasta, R. A.; Staszewski, J. P.; Tuladhar, S. M.; Prakash, O.; Crich, D.; Hirtopeanu, A.; Gilardi, R. The intramolecular asymmetric Pauson-Khand cyclization as a novel and general stereoselective route to benzindene prostacyclins: synthesis of UT-15 (treprostinil). *J. Org. Chem.* **2004**, *69*, 1890−902.

(5) Finney, P.; Tran, Q.; Tinker, A.; Clapp, L. UT-15, a novel prostacyclin analogue displays potent antiproliferative acitivity in human pulmonary artery smooth muscle cells. *Eur. Respir. J.* **2000**, *16*, 1029.

(6) Johnson, R. A.; Morton, D. R.; Kinner, J. H.; Gorman, R. R.; McGuire, J. C.; Sun, F. F.; Whittaker, N.; Bunting, S.; Salmon, J.; Moncada, S. The chemical structure of prostaglandin X (prostacyclin). *Prostaglandins* **1976**, *12*, 915−928.

(7) Collins, P. W.; Djuric, S. W. Synthesis of therapeutically useful prostaglandin and prostacyclin analogs. *Chem. Rev.* **1993**, *93*, 1533−1564.

(8) Galie, N.; Manes, A.; Branzi, A. Medical therapy of pulmonary hypertension. The prostacyclins. *Clinics in chest medicine* **2001**, *22*, 529−37.

(9) Olschewski, H.; Rose, F.; Schermuly, R.; Ghofrani, H. A.; Enke, B.; Olschewski, A.; Seeger, W. Prostacyclin and its analogues in the treatment of pulmonary hypertension. *Pharmacol. Ther.* **2004**, *102*, 139−53.

(10) Gomberg-Maitland, M.; Olschewski, H. Prostacyclin therapies for the treatment of pulmonary arterial hypertension. *Eur. Respir. J.* **2008**, *31*, 891−901.

(11) Gryglewski, R. J. Prostacyclin among prostanoids. *Pharmacological reports: PR* **2008**, *60*, 3−11.

(12) Sridharan, M.; Bowles, E. A.; Richards, J. P.; Krantic, M.; Davis, K. L.; Dietrich, K. A.; Stephenson, A. H.; Ellsworth, M. L.; Sprague, R. S. Prostacyclin receptor- mediated ATP release from erythrocytes requires the voltage-dependent anion channel. *American journal of physiology. Heart and circulatory physiology* **2012**, *302*, H553−9.

(13) Galie, N.; Manes, A.; Branzi, A. Emerging medical therapies for pulmonary arterial hypertension. *Prog. Cardiovasc. Dis.* **2002**, *45*, 213−24.

(14) Gildea, T. R.; Arroliga, A. C.; Minai, O. A. Treatments and strategies to optimize the comprehensive management of patients with pulmonary arterial hypertension. *Cleveland Clin. J. Med.* **2003**, *70* (Suppl 1), S18−27.

(15) Truchetet, M. E.; Allanore, Y.; Montanari, E.; Chizzolini, C.; Brembilla, N. C. Prostaglandin I(2) analogues enhance already exuberant Th17 cell responses in systemic sclerosis. *Ann. Rheum. Dis.* **2012**, *71*, 2044−50.

(16) Jimmidi, R.; Shroff, G. K.; Satyanarayana, M.; Reddy, B. R.; Reddy, J.; Sawant, M. A.; Sitaswad, S. L.; Arya, P.; Mitra, P. The Prevention of Mitochondrial Membrane Permeabilization and Pancreatic β-Cell Death by an Enantioenriched, Macrocyclic Small Molecule. *Eur. J. Org. . Chem.* **2014**, *20*, 1151−1156.

(17) Jogula, S.; Dasari, B.; Khatravath, M.; Chandrasekar, G.; Kitambi, S. S.; Arya, P. Building a Macrocyclic Toolbox from C-Linked Carbohydrates Identifies Novel Anti angiogenesis Agents from Zebrafish Assay. *Eur. J. Org. Chem.* **2013**, *19*, 5036−5040.

(18) Reddy Guduru, S. K.; Chamakuri, S.; Chandrasekar, G.; Kitambi, S. S.; Arya, P. Tetrahydroquinoline-derived Macrocyclic Toolbox Identifies Novel Anti- angiogenesis Agents and Inhibitors of an Early Embryo Development in Zebrafish Assays. *ACS Med. Chem. Lett.* **2013**, *4*, 666−670.

(19) Dasari, B.; Jogula, S.; Borhade, R.; Balasubramanian, S.; Chandrasekar, G.; Kitambi, S. S.; Arya, P. Macrocyclic glycohybrid toolbox identifies novel antiangiogenesis agents from zebrafish assay. *Org. Lett.* **2013**, *15*, 432−5.

(20) Chamakuri, S.; Guduru, S. K. R.; Pamu, S.; Chandrasekar, G.; Kitambi, S. S.; Arya, P. A Modular Approach to Build the Macrocyclic Diversity on Aminoindoline Scaffold Identifies Novel Anti-angiogenesis Agents from Zebrafish Assay. *Eur. J. Org. Chem.* **2013**, *19*, 3959−3964.

(21) Aeluri, M.; Pramanik, C.; Chetia, L.; Mallurwar, N. K.; Balasubramanian, S.; Chandrasekar, G.; Kitambi, S. S.; Arya, P. 14-Membered Macrocyclic Ring-Derived Toolbox: The Identification of Small Molecule Inhibitors of Angiogenesis and Early Embryo Development in Zebrafish Assay. *Org. Lett.* **2013**, *15*, 436−439.

(22) Aeluri, M.; Gaddam, J.; Davarakonda, V. K. S. T.; Chandrasekar, G.; Kitambi, S. S.; Arya, P. An Intramolecular Heck Approach to Obtain 17-Membered Macrocyclic Diversity and the Identification of Anti-angiogenesis Agent from Zebrafish Study. *Eur. J. Org. Chem.* **2013**, *19*, 3955−58.

(23) Jimmidi, R.; Guduru, S. K. R.; Arya, P. Practical Stereoselective Synthesis of Eribulin Fragment toward Building a Hybrid Macrocyclic Toolbox. *Org. Lett.* **2015**, *17*, 468−471.

(24) Guduru, S. K. R.; Jimmidi, R.; Deora, G. S.; Arya, P. Stereoselective Synthesis of Rapamycin Fragment To Build a Macrocyclic Toolbox. *Org. Lett.* **2015**, *17*, 480−483.

(25) Aeluri, M.; Dasari, B.; Arya, P. Divergent Approach to Building a Latrunculin Family Derived Hybrid Macrocyclic Toolbox. *Org. Lett.* **2015**, *17*, 472−475.

(26) Hou, S.-H.; Tu, Y.-Q.; Liu, L.; Zhang, F.-M.; Wang, S.-H.; Zhang, X.-M. Divergent and Efficient Syntheses of the Lycopodium Alkaloids (−)-Lycojaponicumin C, (−)-8- Deoxyserratinine, (+)-Fawcettimine, and (+)-Fawcettidine. *Angew. Chem., Int. Ed.* **2013**, *52*, 11373−11376.

(27) Krabbe, S. W.; Johnson, J. S. Asymmetric Total Syntheses of Megacerotonic Acid and Shimobashiric Acid A. *Org. Lett.* **2015**, *17*, 1188−1191.

(28) Yin, J.; Kong, L.; Wang, C.; Shi, Y.; Cai, S.; Gao, S. Biomimetic Synthesis of Equisetin and (+)-Fusarisetin A. *Chem. - Eur. J.* **2013**, *19*, 13040−13046.

(29) Gui, C.; Li, Q.; Mo, X.; Qin, X.; Ma, J.; Ju, J. Discovery of a New Family of Dieckmann Cyclases Essential to Tetramic Acid and Pyridone-Based Natural Products Biosynthesis. *Org. Lett.* **2015**, *17*, 628−631.

(30) Mydock-McGrane, L.; Rath, N. P.; Covey, D. F. Synthesis of a Smoothened Cholesterol: 18,19-Di-nor-cholesterol. *J. Org. Chem.* **2014**, *79*, 5636−5643.

(31) Bruce, J. M.; Roshan-Ali, Y. Claisen rearrangement of meta-substituted allyl phenyl ethers. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2677−2679.

(32) Uno, H.; Naruta, Y.; Maruyama, K. Syntheses of (±)-aklavinones: Application of the stereocontrolled "zipper" bicyclo cyclization reaction. *Tetrahedron* **1984**, *40*, 4725−4741.

(33) Jeong, Y.-C.; Anwar, M.; Nguyen, T. M.; Tan, B. S. W.; Chai, C. L. L.; Moloney, M. G. Control of chemoselectivity in Dieckmann ring closures leading to tetramic acids. *Org. Biomol. Chem.* **2011**, *9*, 6663−6669.

(34) Grubbs, R. H. Olefin-metathesis catalysts for the preparation of molecules and materials (Nobel Lecture). *Angew. Chem., Int. Ed.* **2006**, *45*, 3760−3765.

DOI: 10.1021/acscombsci.5b00076
ACS Comb. Sci. 2015, 17, 437−441

(35) Lee, C. W.; Grubbs, R. H. Formation of Macrocycles via Ring-Closing Olefin methatesis. *J. Org. Chem.* **2001**, *66* (21), 7155−7158.
(36) Wells, J. A.; McClendon, C. L. Reaching for high-hanging fruit in drug discovery at protein-protein interfaces. *Nature* **2007**, *450*, 1001−9.
(37) Arkin, M. R.; Wells, J. A. Small-Molecule Inhibitors of Protein-Protein Interactions: Progressing Towards the Dream. *Nat. Rev. Drug Discovery* **2004**, *3*, 301−317.
(38) Wells, J.; Arkin, M.; Braisted, A.; DeLano, W.; McDowell, B.; Oslob, J.; Raimundo, B.; Randal, M. Drug discovery at signaling interfaces. *Ernst Schering Res. Found. Workshop* **2003**, 19−27.
(39) Aeluri, M.; Chamakuri, S.; Dasari, B.; Guduru, S. K.; Jimmidi, R.; Jogula, S.; Arya, P. Small molecule modulators of protein-protein interactions: selected case studies. *Chem. Rev.* **2014**, *114*, 4640−4694.
(40) Pawson, T.; Nash, P. Protein-protein interactions define specificity in signal transduction. *Genes Dev.* **2000**, *14*, 1027−1047.
(41) Scott, J. D.; Pawson, T. Cell communication: the inside story. *Sci. Am.* **2000**, *282*, 72−79.
(42) Pawson, T.; Scott, J. D. Protein phosphorylation in signaling - 50 years and counting. *Trends Biochem. Sci.* **2005**, *30*, 286−290.
(43) Pawson, T.; Linding, R. Network medicine. *FEBS Lett.* **2008**, *582*, 1266−1270.
(44) Scott, J. D.; Pawson, T. Cell signaling in space and time: where proteins come together and when they're apart. *Science* **2009**, *326*, 1220−1224.
(45) Pawson, C. T.; Scott, J. D. Signal integration through blending, bolstering and bifurcating of intracellular information. *Nat. Struct. Mol. Biol.* **2010**, *17*, 653−658.

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ACS Comb. Sci. 2015, 17, 437−441