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A [3 + 3] Annelation Approach to (+)-Rhopaloic Acid B

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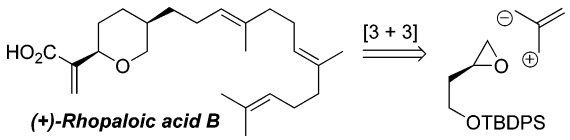
ABSTRACT



A general and enantiospecific [3 + 3] reaction toward functionalized pyrans is reported that has been employed in the first enantioselective synthesis of (+)-rhopaloic acid B.

The rhopaloic acids (Figure 1) are a class of novel norsesterterpenes that were first isolated from the marine sponge

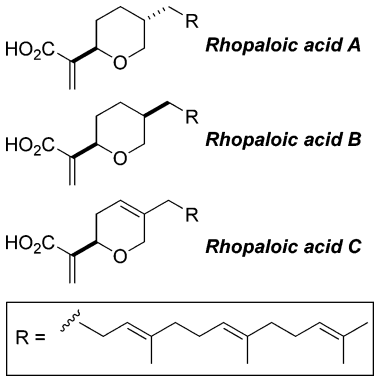


Figure 1. Rhopaloic acids.

Rhopaloeides sp. by Ohta and Ikegami,[1] and subsequently also from *Hippospongia* sp. by Andersen and co-workers.[2] These compounds exhibit potent inhibition of the gastrulation of starfish embryos, in vitro cytotoxicity toward human myeloid K-562 cells, human MOLT-4 leukemia cells, and murine L1210 cells, and RCE protease inhibitory activity. The interesting biological acitivty of these compounds coupled with the paucity of material available from their natural sources has inspired some significant synthetic effort toward these molecules. Specifically, Snider developed a short synthesis of racemic rhopaloic acid A that also provided minor quantities of rhopaloic acid B methyl ester.[3] Additionally, enantioselective syntheses of rhopaloic acid A have been reported by Ogasawara[4] and Ohkata.[5] The former required some 30 steps from an enantiomerically pure dioxabicyclo-[3.2.1]octane while the latter, shorter synthesis featured an inefficient pyran-forming cyclization (30−40% yield). We hoped to develop a new approach to the rhopaloic acids that would deliver short, enantioselective routes to this family of compounds.[6] We report herein an unusual [3 + 3] annelation approach to pyrans toward this end, and its application in the first enantioselective synthesis of (+)-rhopaloic acid B.

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(1) (a) Ohta, S.; Uno, M.; Yoshimura, M.; Hiraga, Y.; Ikegami, S. *Tetrahedron Lett.* **1996**, *37*, 2265. (b) Yanai, M.; Ohta, S.; Ohta, E.; Ikegami, S. *Tetrahedron* **1998**, *54*, 15607.
(2) Craig, K. S.; Williams, D. E.; Hollander, I.; Frommer, E.; Mallon, R.; Collins, K.; Wojciechowicz, D.; Tahir, A.; Van Soest, R.; Andersen, R. J. *Tetrahedron Lett.* **2002**, *43*, 4801.
(3) Snider, B. B.; He, F. *Tetrahedron Lett.* **1997**, *38*, 5453.
(4) Kadota, K.; Ogasawara, K. *Heterocycles* **2003**, *59*, 485.
(5) (a) Takagi, R.; Sasaoka, A.; Kojima, S.; Ohkata, K. *Chem. Commun.* **1997**, 1887. (b) Takagi, R.; Sasaoka, A.; Nishitani, H.; Kojima, S.; Hiraga, Y.; Ohkata, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 925.
(6) For a recent enantioselective synthesis of related hippospongic acid A and lead references see: Trost, B. M.; Machacek, M. R.; Tsui, H. C. *J. Am. Chem. Soc.* **2005**, *127*, 7014.

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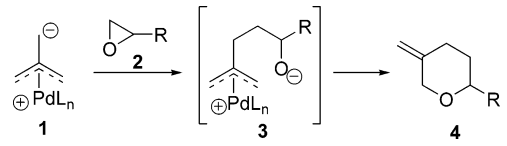
Recent studies in our laboratories have endeavored to develop a series of [3 + 3] annelation processes for the synthesis of piperidines by the addition of conjunctive reagents to aziridines.[7,8] Preliminary investigations highlighted that in situ generated Pd-trimethylenemethane [Pd−TMM][9] could be employed to good effect in this regard,[8a,b] and that the reaction was efficient for a range of 2-alkylaziridines. It occurred to us that a similar strategy could be employed to access functionalized pyrans.[10] Specifically, as outlined in Scheme 1, nucleophilic addition of Pd−TMM **1**

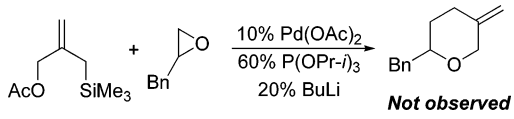
Scheme 1



to epoxide **2** would provide intermediate **3** that could cyclize to generate the desired pyran **4**. A point of concern at this stage was the potential incompatibility of the hard alkoxide nucleophile and the Pd π-allyl moiety.[11] However, we were encouraged by the elegant studies of Trost and co-workers that highlighted the successful use of Sn- and In-based Lewis acids in facilitating related cyclizations during [3 + 2] annelations onto aldehydes and ketones.[12]

Preliminary studies aimed at establishing this Pd-catalyzed [3 + 3] annelation were disappointing. Employment of standard conditions for the in situ generation of Pd−TMM failed to provide the corresponding pyran (Scheme 2).

Scheme 2

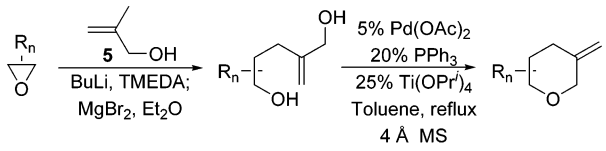


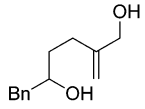
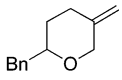
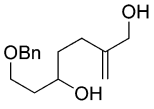
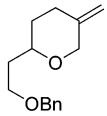
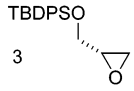
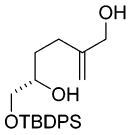
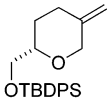
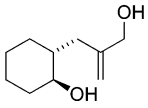
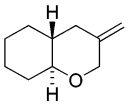
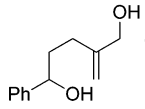
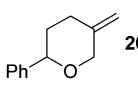
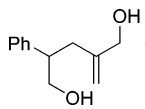
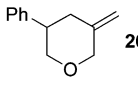
Moreover, the employment of Bu_3SnOAc or $In(acac)_3$ Lewis acid cocatalysts was unsuccessful in promoting the reaction and starting epoxide was returned in all cases.

Our failure to observe the addition of Pd−TMM to epoxides prompted us to consider an alternative strategy. In this context, we had shown that an analogous, but stepwise, [3 + 3] annelation process toward piperidines could be realized by the addition of the dianion of methallyl alcohol to aziridines followed by a Pd-catalyzed cyclization.[8e] We therefore decided to explore the scope of this approach with respect to pyran synthesis.[13]

As outlined in entry 1 of Table 1, double deprotonation of methallyl alcohol **5** followed by transmetallation provided an organomagnesium reagent that underwent addition to epoxide **6** in good yield. Moreover, subsequent treatment of adduct **7** with a Pd-catalyst in the presence of Ti(OPr-i)$_4$ facilitated ring closure to the desired pyran **8**.[14] Notably, the inclusion of the Ti Lewis acid significantly promotes this cyclization as longer reaction times (24 h as opposed to 1 h) and poorer conversions are observed in its absence. The enantiospecificity of the stepwise annelation was confirmed by the synthesis of pyran **14** (entry 3) while extension of the methodology to include bicyclic pyrans was also demonstrated by the synthesis of **17** (entry 4). Addition of the in situ generated organomagnesium reagent to styrene oxide **18** gave the expected mixture of regioisomers **19a**/**b** (entry 5);[15] however, both were readily separated and cyclized in good yield.

Table 1. [3 + 3] Annelation of Epoxides[a]



entry	epoxide	addition product		pyran	
1	 **6**		**7**; 76%		**8**; 82%
2	 **9**		**10**; 74%		**11**; 85%
3	 **12**		**13**; 82%		**14**; 83%
4	 **15**		**16**; 50%		**17**; 67%
5	 **18**		**19a**; 20%		**20a**; 66%
			**19b**; 61%		**20b**; 79%

[a] Organomagnesium reagent prepared by addition of TMEDA (2.1 equiv) and *n*BuLi (2.1 equiv) to **5** followed by $MgBr_2$ (2.1 equiv). 1.5 equiv of this reagent added to epoxide. Entry 5: 2.5 equiv of Grignard used in this case.

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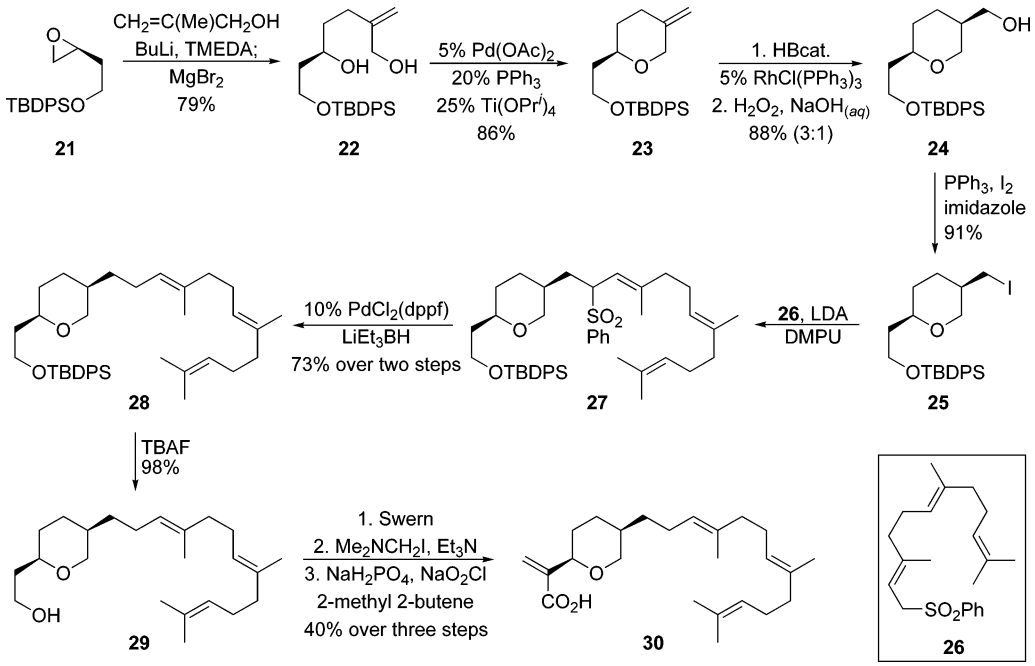
Scheme 3



Having established the validity of the [3 + 3] annelation strategy for the synthesis of functionalized pyrans, we turned our attention to its application in the enantioselective synthesis of (+)-rhopaloic acid B. Accordingly, the required enantiopure epoxide **21** for the synthesis of the pyran core was prepared by using Jacobsen's kinetic resolution protocol (Scheme 3).[16] Addition of the Grignard reagent and subsequent cyclization proceeded without incident to provide pyran **23** in good overall yield. Diastereoselective functionalization of the exomethylene group in **23** would set the stage for elaboration of this intermediate to each specific member of the rhopaloic acids. In the event, we decided to employ hydroboration and found that Rh-catalyzed methodology[17] provided the desired *cis*-**24** in high yield, albeit with modest diastereoselectivity.

Installation of the farnesyl chain was carried out after conversion of **24** to the corresponding iodide **25** and alkylation with sulfone **26**. Product sulfone **27** was found to be contaminated by some unreacted **26** and so the crude material was subjected to Pd-catalyzed reduction[6,18] to provide **28** in 73% yield over two steps. Finally, conversion of the protected 2-hydroxyethyl chain to the required α,β-unsaturated acid was carried out by cleavage of the silyl ether with TBAF followed by Swern oxidation, Mannich methylenation, and Pinnick oxidation.

In conclusion, we have developed a stepwise [3 + 3] annelation approach to functionalized pyrans and demonstrated its employment in the enantioselective synthesis of rhopaloic acid B. The employment of this strategy in the synthesis of other members of the rhopaloic acids is underway and will be reported in due course.

Acknowledgment. We thank the University of Sheffield and GSK for financial support.

Supporting Information Available: Full experimental details for the syntheses reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For [3 + 3] approaches to pyrans see: (a) Hua, D. H.; Chen, Y.; Sin, H.-S.; Maroto, M. J.; Robinson, P. D.; Newell, S. W.; Perchellet, E. M.; Ladesich, J. B.; Freeman, J. A.; Perchellet, J.-P.; Chiang, P. K. *J. Org. Chem.* **1997**, *62*, 6888. (b) Hsung, R. P.; Shen, H. C.; Douglas, C. J.; Morgan, C. D.; Degen, S. J.; Yao, L. J. *J. Org. Chem.* **1999**, *64*, 690. (c) Shen, H. C.; Wang, J.; Cole, K. P.; McLaughlin, M. J.; Morgan, C. D.; Douglas, C. J.; Hsung, R. P.; Coverdale, H. A.; Gerasyuto, A. I.; Hahn, J. M.; Liu, J.; Wei, L.-L.; Sklenicka, H. M.; Zehnder, L. R.; Zificsak, C. A. *J. Org. Chem.* **2003**, *68*, 1729. (d) Epstein, O. L.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 16480.

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(13) Addition of a related Grignard reagent to epoxides has been shown to produce pyrans. However, this reagent is prepared in two steps in modest yield. Moreover, the Grignard formation was found to be highly prone to Wurtz coupling in our hands. van der Louw, J.; van der Baan, J. L.; Out, G. J. J.; de Kanter, F. J. J.; Bickelhaupt, F.; Klumpp, G. W. *Tetrahedron* **1992**, *48*, 9901.

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