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A Flexible Approach toward *trans*-Fused Polycyclic Tetrahydropyrans. A Synthesis of Prymnesin and Yessotoxin Units

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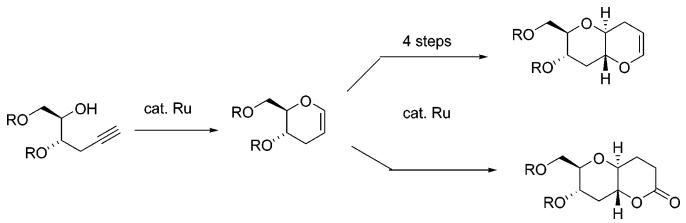
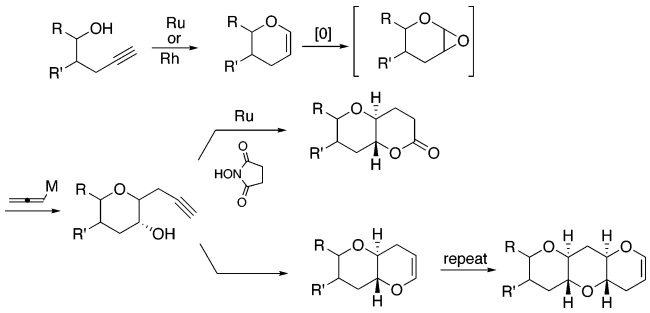
ABSTRACT



Ru-catalyzed cycloisomerization and oxidative cyclization of bis-homopropargylic alcohols provide a rapid iterative approach to structural units of the ladder toxins.

Cycloisomerization of bis-homopropargylic alcohols to dihydropyrans and their oxidative cyclization[1] to δ-valerolactones provide useful building blocks to the structurally fascinating marine ladder toxins.[2,3] An iterative approach[4] to the construction of fused polycyclic compounds can be envisioned as shown in Scheme 1. This strategy comple-

Scheme 1. An Iterative Approach to Fused Polycylic Tetrahydropyrans



ments an iterative approach based upon a stoichiometric tungsten-mediated process involving the intermediacy of 2-stannyldihyropyrans.[5] Considering the BCD ring fragment of yessotoxin (**1**)[6] and the AB ring fragment of prymnesin (**2**),[7] we chose to investigate this strategy using the readily available ynediol **3**, which derives from the diastereoselective Barbier addition of propargyl bromide using zinc to the acetonide of (*R*)-glyceraldehyde (dr 8:1).[8] Subjecting 3−7.5 mol % of the Ru complex **4** in DMF as shown in eq 1 gave the dihydropyran **5a** in 70% yield. None of the seven-membered ring product was observed even

(1) (a) For a Ru-catalyzed divergent approach to dihydropyrans and valerolactones, see: Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 2528. (b) For Rh-catalyzed cycloisomerization of bis-homopropargylic alcohols, see: Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2003**, *125*, 7482.

(2) For a review on the marine ladder toxins, see: Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897.

(3) (a) For other examples that utilize dihydropyrans as building blocks, see: Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123 and references therein. (b) For other examples that utilize valerolactones as building blocks, see: Kadota, I.; Takamura, H.; Sato, K.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 3494 and references theirein.

(4) For other examples of iterative approaches, see: Marmsater, F. P.; West, F. G. *Chem. Eur. J.* **2002**, *8*, 4347 and references theirein.

(5) Bowman, J. L.; McDonald, F. E. *J. Org. Chem.* **1998**, *63*, 3680.

(6) (a) Murata, M.; Kumagai, M.; Lee, J. S.; Yasumoto, T. *Tetrahedron Lett.* **1987**, *28*, 5869. (b) Naoki, H.; Murata, M.; Yasumoto, T. *Rapid Commun. Mass Spectrom.* **1993**, *7*, 179.

(7) Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, *17*, 293.

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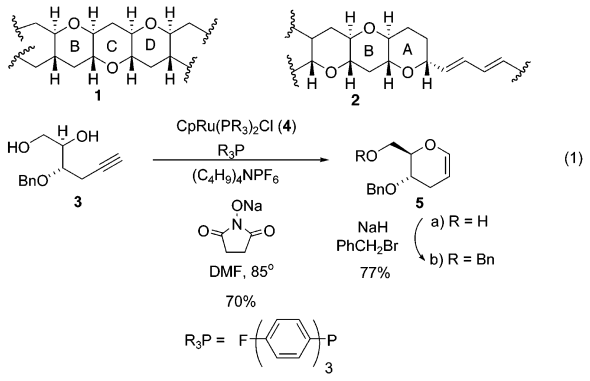
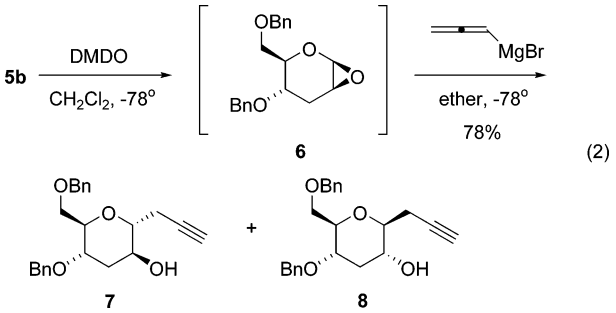
though that would have involved attack by the less hindered primary hydroxyl group.

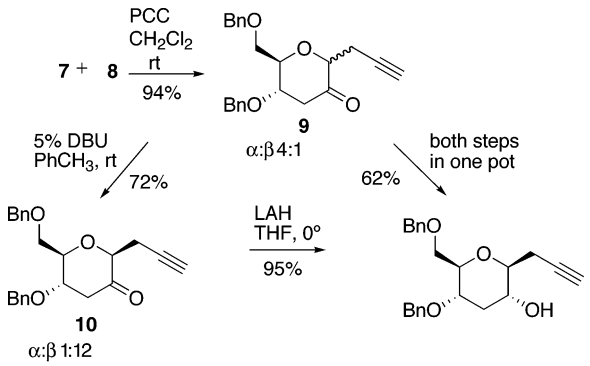


Epoxidation of dihydropyran **5b** proceeded diastereoselectively (4:1) to give **6** as the major diastereomer. Its lability led to its in situ reaction with allenylmagnesium bromide to give the *trans* hydroxy alkynes **7** and **8** in a 4:1 ratio in a 78% overall yield (eq 2).[9] Stereoelectronic effects account



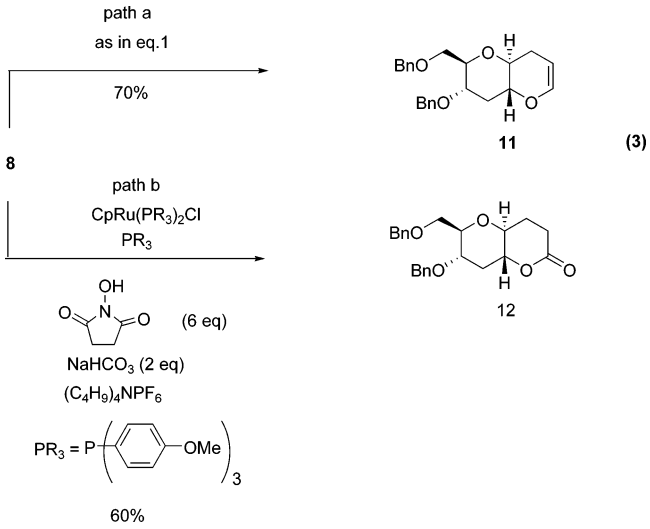
for the diastereoselectivity. Thus, this route provides good access to diastereomer **7**. For synthetic purposes, good access to diastereomer **8** was also desirable. Direct epoxidation methods to favor the opposite (i.e., α) epoxide diastereomer proved fruitless. On the other hand, a very simple solution evolved as shown in Scheme 2. The ketone **9** undergoes

Scheme 2. Diastereoselective Synthesis of **8**



facile base equilibration that strongly favors epimer **10** (dr 12:1). Simple LAH reduction then provides diastereomer **8** of excellent diastereoselectivity (dr 9:1). Thus, both diastereomers **7** and **8** are available in high diastereoselectivity. Because the base equilibration and diastereoselective ketone can be performed in one pot, any mixture of **7** and **8** can now be transformed into diastereomer **8** of high selectivity, requiring just four steps from starting alkyne **3**.

As depicted in Scheme 1, diastereomer **8** conceptually can diverge to the cycloisomer **11** (eq 3, path a) or the oxidatively cyclized lactone **12** (eq 3, path b) by simple manipulation



of the ligands on the Ru catalyst.[1] Thus, subjecting terminal alkyne **8** to the conditions of eq 1 provides the dihydropyran **11** in 70% yield with 6% of lactone **12**[3b] as a minor side product. On the other hand, increasing the amount of the *N*-hydroxysuccinimide and using a more electron-rich phosphine, *p*-anisylphosphine, provides the lactone **12** as the major product in 60% yield with only 8% of the dihydropyran **11**.

The dihydropyran **11** corresponds to the B and C rings of the ladder toxin yessotoxin (**1**). As previously, stereoelectronic considerations predict that epoxidation of **11** would give the *β*-epoxide[10] predominantly, which indicates that an iterative approach would necessitate a sequence as shown in Scheme 2. This sequence has the advantage that neither the stereochemistry of the epoxidation nor of the epoxide ring opening is relevant because all stereoisomers funnel to the same requisite diastereomer. Scheme 3 illustrates that next iterative cycle. Epoxidation followed directly by addition of allenylmagnesium bromide gave a mixture of diastereomers that were not characterized.[11] Subjecting the mixture to PCC oxidation gave a good yield of ketone **14** predominantly as one diastereomer (dr 11:1). Base equilibration followed by reduction either in two separate operations or

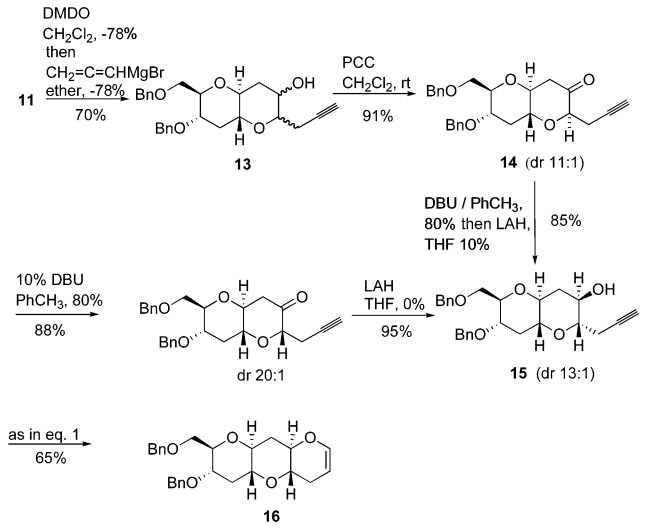
(8) Peng, Z.-H.; Li, Y.-L.; Wu, W.-L.; Liu, C.-X.; Wu, Y.-L. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1057.

(9) (a) The structure of **7** and **8** was confirmed by conversion into the corresponding acetates, which were easily separated by flash chromatography. For detailed experimental procedure, see Supporting Information. (b) The complete *trans* stereoselectivity in the propargylation step has been established; see ref 1a.

(10) A similar facial selectivity in the epoxidation of *trans*-fused bicyclic dihydropyrans has been reported; see: Rainier, J. D.; Allwein, S. P. *Tetrahedron Lett.* **1998**, *39*, 9601.

(11) The desired diastereomer **15** was formed as a minor diastereomer.

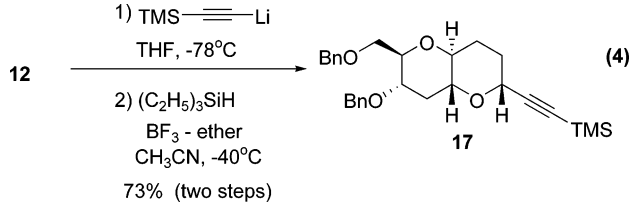
Scheme 3. An Iterative Cycle for Preparation of the Yessotoxin Fragment



a) DMDO, CH_2Cl_2, -78° then add CH_2=C=CHMgBr, ether, -78°. b) PCC, CH_2Cl_2, rt. c) 10% DBU, $PhCH_3$, 80°. d) LAH, THF, 0°. e) 10% DBU, $PhCH_3$, 80° then add LAH, THF, 0°. f) as in eq.1.

in one pot gave comparable results to form hydroxy alkyne **15** in similar yield (dr 13:1).[12] Ru-catalyzed cycloisomerization completes the cycle. Thus, each iterative cycle requires four steps. Starting from acyclic precursor **3** using the Ru-catalyzed cycloisomerization three times, the tricycle fragment corresponding to rings BC and D of yessotoxin is available in nine steps and 11% overall yield.

The lactone **12** illustrates a different dimension of this Ru-catalyzed methodology, the diastereoselective attachment of a side chain as in ring A of prymnesin. Because the diene side chain might be attached by a cross-coupling reaction of a vinylmetal, which in turn would derive by hydrometalation of an alkyne,[13] diastereoselective introduction of an alkyne onto lactone **12** is required. This transformation proved straightforward as shown in eq 4. Acetylide addition followed by a Lewis acid promoted reductive dehydroxylation with triethylsilane[14] gave bicycle **17** in 73% yield (over two steps) as a single diastereomer.



In summary, we developed a highly flexible approach toward *trans*-fused polycyclic tetrahydropyrans, structural motifs commonly present in the ladder toxins and related natural products. The ability of the Ru-catalyzed process to provide either cycloisomerization to dihydropyrans or oxidative cyclization to δ-valerolactones by minor modifications of the catalyst imparts great flexibility in accessing the different substitution patterns found on the pyrans. The ability to create fused polycyclic in an iterative approach requiring only four steps for each iteration should facilitate the partial and total synthesis of this structurally and biologically interesting class of of natural products.

Acknowledgment. We thank the National Institutes of Health General Medicine Sciences (GM 13598) and the National Science Foundation for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California-San Francisco supported by the NIH Division of Research Resources.

Supporting Information Available: Experimental procedures for the preparation of new compounds and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) This epimerization−reduction protocol has previously been used in other syntheses of *trans*-fused polycyclic tetrahydropyrans. (a) Marmsater, F. P.; West, F. G. *J. Am. Chem. Soc.* **2001**, *123*, 5144. (b) Evans, P. A.; Roseman, J. D.; Garber, L. T. *J. Org. Chem.* **1996**, *61*, 4880.

(13) (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998. (b) *Cross-Coupling Reactions. A Practical Guide*; Miyaura, N., Ed.; Topics in Current Chemistry; Springer: Berlin, 2002; Vol. 219.

(14) Grewal, G.; Kalia, N.; Franck, R. W. *J. Org. Chem.* **1992**, *57*, 2084.