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An Approach to Pancratistatins via Ring-Closing Metathesis: Efficient Synthesis of Novel 1-Aryl-1-deoxyconduritols F

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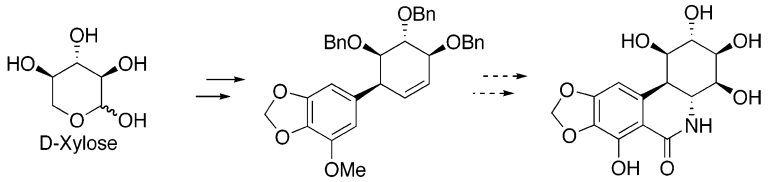
ABSTRACT



Structurally novel cyclitols, 1-aryl-1-deoxyconduritols F, were efficiently prepared from D-xylose, utilizing RCM as a key step. Various aromatic residues were incorporated in the cyclitol skeleton with total stereochemical control, utilizing a diastereoselective aryl cuprate addition to a γ-alkoxy enoate. The synthetic route establishes a firm foundation for a practical synthesis of the antitumor alkaloid pancratistatin and its aryl analogues.

Novel synthetic approaches to the naturally occurring cyclitols and their analogues are of considerable importance due to diverse biological properties associated with these compounds. For example, inositols and their phosphate derivatives mediate intracellular signal transduction pathways.[1] Conduritol epoxides and aminoconduritols act as glycosidase inhibitors.[2] Cyclophellitols are potent inhibitors of the human immunodeficiency virus.[3] Furthermore, the multifunctional nature and the stereochemical complexity of these compounds have made them convenient starting materials for the synthesis of more advanced structures. Recent notable examples include the synthesis of a C1−C14 model of Halichondrin B from (+)-conduritol E[4] and the synthesis of both enantiomers of cyclophellitol via a kinetic resolution of racemic conduritol B.[5] Although the published approaches to cyclitols are numerous, the growing demand for these compounds fuels further synthetic work aimed at improving the preparative efficiency and achieving high levels of stereo- and regiocontrol. In this context, the naturally occurring arylcyclitols pancratistatin (**1**) and narciclasine (**3**), as well as their 7-deoxy analogues (**2** and **4** in Figure 1), have presented the synthetic community with a tremendous challenge.[6]

Despite the promising antitumor and antiviral activities exhibited by pancratistatin, its preclinical development by the National Cancer Institute has been put on hold as a result of the extremely small quantity of the alkaloid available from isolation.[7] Although extensive synthetic work has led to a number of total syntheses of pancratistatin[8] and its conge-

(1) For a review, see: Berridge, M. J.; Irvine, R. F. *Nature* **1989**, *341*, 197.
(2) (a) Legler, G.; Herrchen, M. *FEBS Lett.* **1981**, *135*, 139. (b) Legler, G.; Bause, E. *Carbohydr. Res.* **1973**, *28*, 45.
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(4) Lambert, W. T.; Burke, S. D. *Org. Lett.* **2003**, *5*, 515.
(5) Trost, B. M.; Patterson, D. E.; Hembre, E. J. *Chem. Eur. J.* **2001**, *7*, 3768.
(6) For discussion of the synthetic problems posed by pancratistatin and its congeners, see: Polt, R. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1996; Vol. 3, p 109.
(7) Pettit, G. R.; Gaddamidi, V.; Cragg, G. M.; Herald, D. L.; Sagawa, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1693.

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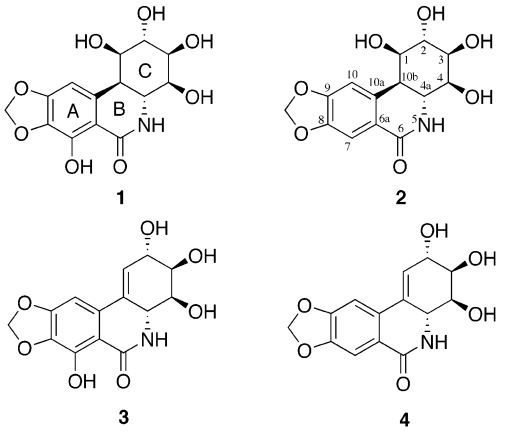
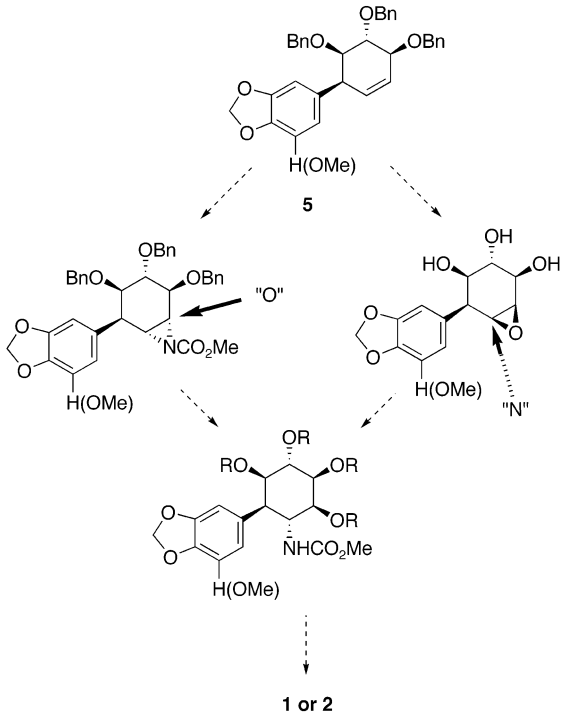


Figure 1.

ners,[9] the problem of supply has not been solved. The limited availability has also plagued structure−activity studies, and although some SAR data are available for the pancratistatin analogues with the modified cyclitol ring C,[10] the structural and electronic requirements of the aromatic ring A have not been studied to the best of our knowledge. One of us has previously coauthored a report describing utilization of the ring-closing metathesis process in the rapid construction of the cyclitol rings of conduritols B and F as well as L-*chiro*- and *myo*-inositols starting from readily available monosaccharides such as D-xylose.[11,12] We intend to apply this powerful strategy to the more challenging cyclitol structures of the pancratistatin alkaloids. The key intermediates in our synthetic design are 1-aryl-1-deoxy analogues (**5**) of conduritol F, incorporating most of the structural and stereochemical complexity of the target alkaloids (Scheme 1). We

Scheme 1



envision that these compounds will be converted to *trans*-4,4a-oxycarbamates either via α-selective aziridination and subsequent *trans*-diaxial ring opening with an oxygen-based nucleophile or via allylic alcohol-directed *β*-selective epoxidation, followed by epoxide ring opening with a nitrogen-based nucleophile. A regioselective Bischler−Napieralski-type cyclization could potentially complete the synthesis of each target alkaloid.

Herein, we report an efficient multigram synthesis of various 1-aryl-1-deoxyconduritols F, which establishes a firm foundation for achieving a practical synthesis of not only pancratistatin alkaloids themselves but also their aryl analogues, paving the way for more systematic SAR studies of these promising anticancer agents.

A brief retrosynthetic analysis of the target conduritols **5** reveals that application of an RCM process for construction of the cyclitol ring would require an efficient pathway to 3,4,5-trialkoxy-6-aryloctadienes **8** (Scheme 2).

Although we envisioned that the three alkoxy stereocenters of dienes with general structure **8** could originate from readily

(8) Eight total syntheses of pancratistatin have been reported to date: (a) Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829. (b) Hudlicky, T.; Tian, X.; Königsberger, K.; Maurya, R.; Rouden, J.; Fan, B. *J. Am. Chem. Soc*. **1996**, *118*, 10752. (c) Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143. (d) Magnus, P.; Sebhat, I. K. *J. Am. Chem. Soc.* **1998**, *120*, 5341. (e) Rigby, J. H.; Maharoof, U. S. M.; Mateo, M. E. *J. Am. Chem. Soc.* **2000**, *122*, 6624. (f) Doyle, T. J.; Hendrix, M.; VanDerveer, D.; Javanmard, S.; Haseltine, J. *Tetrahedron* **1997**, *53*, 11153. (g) Pettit, G. R.; Melody, N.; Herald, D. L. *J. Org. Chem.* **2001**, *66*, 2583. (h) Kim, S.; Ko, H.; Kim, E.; Kim, D. *Org. Lett.* **2002**, *4*, 1343.

(9) Deoxypancratistatin: (a) Paulsen, H.; Stubbe, M. *Liebigs Ann. Chem.* **1983**, 535. (b) Tian, X.; Maurya, R.; Königsberger, K.; Hudlicky, T. *Synlett* **1995**, 1125. (c) Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Am. Chem. Soc*. **1995**, *117*, 7289. (d) Chida, N.; Jitsuoka, M.; Yamamoto, Y.; Ohtsuka, M.; Ogawa, S. *Heterocycles* **1996**, *43*, 1385. (e) Reference 8b. (f) Keck, G. E.; Wager, T. T.; McHardy, S. F. *J. Org. Chem.* **1998**, *63*, 9164. (g) Aceña, J. L.; Arjona, O.; León, M. L.; Plumet, J. *Org. Lett.* **2000**, *2*, 3683. Narciclasine: (h) Reference 8e. (i) Keck, G. E.; Wager, T. T.; Rodriquez, J. F. D. *J. Am. Chem. Soc.* **1999**, *121*, 5176. (j) Elango, S.; Yan, T.-H. *J. Org. Chem.* **2002**, *67*, 6954. (k) Hudlicky, T.; Rinner, U.; Gonzalez, D.; Akgun, H.; Schilling, S.; Siengalewicz, P.; Martinot, T. A.; Pettit, G. R. *J. Org. Chem.* **2002**, *67*, 8726. 7-Deoxynarciclasine: (l) Ohta, S.; Kimoto, S. *Chem. Pharm. Bull.* **1976**, *24*, 2977. (m) Reference 9a. (n) Martin, S. F.; Tso, H.-H. *Heterocycles* **1993**, *35*, 85. (o) Chida, N.; Ohtsuka, M.; Ogawa, S. *J. Org. Chem.* **1993**, *58*, 4441. (p) Hudlicky, T.; Olivo, H. F.; McKibben, B. *J. Am. Chem. Soc*. **1994**, *116*, 5108. (q) Keck, G. E.; Wager, T. T.; Rodriquez, J. F. D. *J. Am. Chem. Soc.* **1999**, *121*, 5176. (r) Elango, S.; Yan, T.-H. *Tetrahedron* **2002**, *58*, 7335.

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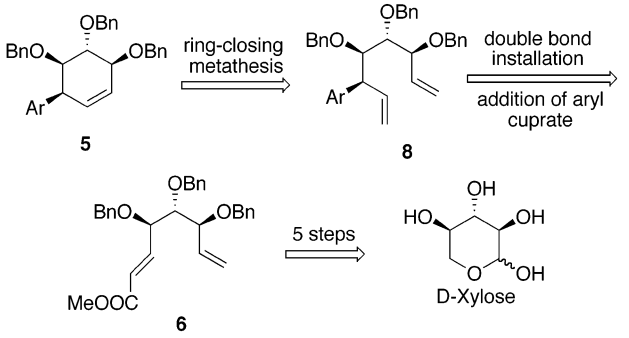
(11) (a) Kornienko, A.; d'Alarcao, M. *Tetrahedron: Asymmetry* **1999**, *10*, 827.

(12) For other cyclitol syntheses from carbohydrates utilizing RCM, see: (a) Seepersaud, M.; Al-Abed, Y. *Org. Lett*. **1999**, *1*, 1463. (b) Sellier, O.; Van de Weghe, P.; Eustache, J. *Tetrahedron Lett.* **1999**, *40*, 5859. (c) Ackermann, L.; El Tom, D.; Fürstner, A. *Tetrahedron* **2000**, *56*, 2195. (d) Marco-Contelles, J.; de Opazo, E. *Tetrahedron Lett*. **2000**, *41*, 2439. (e) Hanna, I.; Ricard, L. *Org. Lett*. **2000**, *2*, 2651. (f) Marco-Contelles, J.; de Opazo, E. *J. Org. Chem*. **2000**, *65*, 5416. (g) Boyer, F.-D.; Hanna, I.; Nolan, S. P. *J. Org. Chem*. **2001**, *66*, 4094. (h) Jorgensen, M.; Iversen, E. H.; Paulsen, A. L.; Madsen, R. *J. Org. Chem*. **2001**, *66*, 4630. (i) Nishikawa, A.; Saito, S.; Hashimoto, Y.; Koga, K.; Shirai, R. *Tetrahedron Lett*. **2001**, *42*, 9195. (j) Conrad, R. M.; Grogan, M. J.; Bertozzi, C. R. *Org. Lett*. **2002**, *4*, 1359. (k) Blériot, Y.; Giroult, A.; Mallet, J.-M.; Rodriguez, E.; Vogel, P.; Sinay, P. *Tetrahedron: Asymmetry* **2002**, *13*, 2553. (l) Heo, J.-N.; Holson, E. B.; Roush, W. R. *Org. Lett*. **2003**, *5*, 1697.

Scheme 2

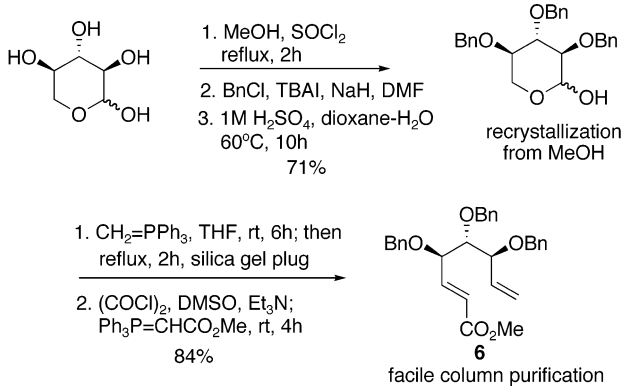


available carbohydrates, we anticipated that installation of the aryl residues with the required stereochemistry would be challenging. The required carbon−carbon bond-forming reaction would have to be (a) highly diastereoselective to avoid potentially troublesome chromatographic separations of epimers and (b) general for a variety of structurally diverse aromatic residues. We decided to explore a γ-benzyloxy-directed conjugate addition of arylcuprates to enoate **6**. Although moderate to high *anti*-diastereoselectivities have been observed for such additions, the majority of reported examples involve alkyl and vinyl cuprate reagents.[13] Literature searches reveal only one report of an *anti*-selective phenyl cuprate addition to highly chelating γ-benzyloxymethoxy(BOM)-α,β-enoates.[14]

Enoate **6** had been utilized previously in a total synthesis of (+)-cyclophellitol and is available from D-xylose via a synthetic sequence involving eight steps and six chromatographic purifications.[15] We sought a more practical route, which could be readily scaled-up. Thus, the mixture of α- and β-methyl xylosides, prepared by refluxing D-xylose and $SOCl_2$ in methanol, was directly benzylated with inexpensive BnCl/Bu_4NI and NaH. Hydrolysis of the crude benzylated anomeric mixture yielded tri-*O*-benzyl-D-xylose, which was purified by recrystallization from methanol in good overall yield (Scheme 3). This procedure has a significant advantage over the previously reported methods,[16] as it requires neither the separation of the intermediate xylose anomers nor purification of the synthetic intermediates.

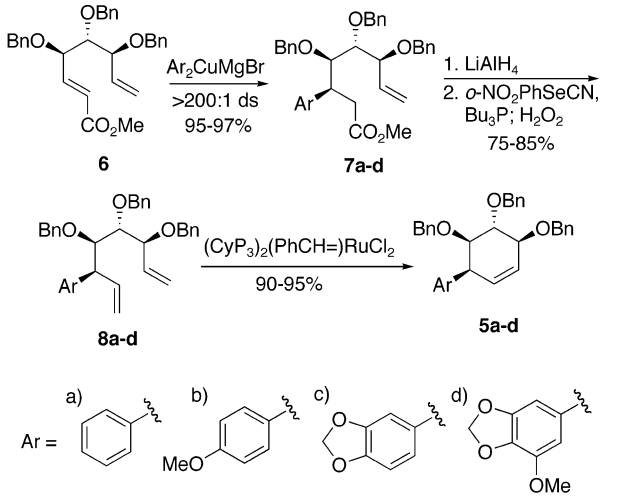
The sequence of Wittig methylenation at the free anomeric carbon, one-pot Swern oxidation, and olefination with the commercial $Ph_3P{=}CHCO_2Me$ reagent was pieced together from the existing literature procedures with only minor modifications for facile scale-up.[17] This high throughput five-step synthesis involves only one chromatographic purification and has allowed us to prepare ~100 g of **6**.

Scheme 3



Next, various "PhCu" reagents, derived from PhLi, PhMgBr, and PhZnCl, were tested in the conjugate addition reaction to enoate **6** under a variety of experimental conditions (Scheme 4). Although PhLi- and PhZnCl-derived

Scheme 4



arylcuprates did not provide useful levels of diastereoselectivity or gave low conversions, the reaction of $Ph_2CuMgBr$ in the presence of TMSCl afforded the desired addition product with complete *anti*-diastereoselectivity and in virtually quantitative yield. Performing the same reaction with a series of $Ar_2CuMgBr$ reagents revealed that the substitution pattern on the aromatic ring did not affect either the diastereoselectivity or the yield of the addition process. The origin of the high diastereoselectivities and the possible involvement of the δ- and ϵ-benzyloxy groups in directing the formation of the *anti*-addition products are currently being studied in our laboratory through the preparation of the truncated and epimeric at δ- and ϵ-positions enoates.

Reduction of esters **7a**−**d** with $LiAlH_4$ in ether gave the corresponding primary alcohols, which were used without purification. All attempts to install a terminal double bond by the elimination reaction of primary tosylates, mesylates,

(13) For some leading references, see: (a) Yamamoto, Y.; Chounan, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. *J. Am. Chem. Soc*. **1992**, *114*, 7652. (b) Hanessian, S.; Gai, Y. H.; Wang, W. G. *Tetrahedron Lett.* **1996**, *37*, 7473. (c) Hanessian, S.; Sumi, K. *Synthesis* **1991**, 1083. (d) Reference 14.

(14) Hanessian, S.; Ma, J.; Wang, W. *Tetrahedron Lett.* **1999**, *40*, 4627.

(15) Ziegler, F. E.; Wang, Y. *J. Org. Chem.* **1998**, *63*, 7920.

(16) (a) Tejima, S.; Ness, R. K.; Kaufman, R. L.; Fletcher, H. G., Jr. *Carbohydr. Res.* **1968**, *7*, 485. (b) Tsuda, Y.; Nunozawa, T.; Yoshimoto, K. *Chem. Pharm. Bull*. **1980**, *28*, 3223.

(17) (a) Kornienko, A.; d'Alarcao, M. *Tetrahedron Lett*. **1997**, *38*, 6497. (b) Reference 15.

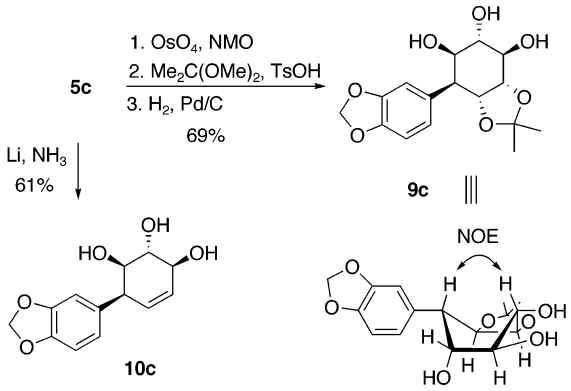
(18) Ahn, Y. M.; Yang, K.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1411.

triflates, and halides with various bases failed. Conducting these reactions at elevated temperatures resulted in mixtures of unidentifiable products, possibly resulting from the formation of the terminal double bond and its subsequent migration under the reaction conditions into conjugation with the adjacent aryl residue. The problem was solved by the conversion of the primary alcohols to arylselenides and subsequent selenoxide elimination. Dienes **8a**−**d** were obtained in good overall yields for the three-step sequence. Finally, ring-closing metathesis, performed with Grubbs' catalyst, cleanly afforded conduritols **5a**−**d** in excellent yields. Column purification of the target compounds was made facile by preliminary oxidation of the ruthenium catalyst with DMSO.[18] Three to five grams of each of conduritols **5a**−**d** were conveniently prepared utilizing this approach.

Although ^{1}H NMR analyses of the cyclized products supported our original stereochemistry assignment in aryl-cuprate conjugate addition reactions, we searched for unambiguous proof of stereochemistry through NOE experiments. To this end conduritol analogue **5c** was converted to the corresponding inositol **9c** by selectively dihydroxylating the α-face of the double bond, isopropylidenating the newly introduced *cis*-diol, and thereafter O-debenzylating (Scheme 5). The *cis*-ring fusion forced the inositol ring into a boat conformation; the proximity of H_1 and H_4 could clearly be detected by NOE difference experiments. In addition, to demonstrate the feasibility of accessing the deprotected 1-aryl-1-deoxyconduritols F, compound **5c** was treated with Li in liquid NH_3. The deprotected target conduritol analogue **10c** was obtained in an unoptimized 61% yield.

In summary, an efficient synthetic route to novel 1-aryl-1-deoxyconduritols F has been developed. The multistep sequence has been optimized for the production of gram quantities of these compounds, so that a firm foundation is now available for completion of a practical synthesis of natural pancratistatins and their aryl analogues. In addition, our synthesis allows access to simple aromatic conduritols and inositols. Their unprecedented structures make these compounds promising candidates for uncovering new biological targets. Finally, the highly diastereoselective aryl cuprate conjugate additions observed in this study warrant further investigation of this method as a general strategy for the incorporation of aromatic residues into advanced structures with high stereocontrol.

Scheme 5



Acknowledgment. We thank William Collins for the preparation of compound **7d** and the National Institutes of Health (CA99957) for financial support.

Supporting Information Available: Experimental procedures; characterization and copies of ^{1}H and ^{13}C NMR spectra for compounds **5a**−**d**, **7a**−**d**, **8a**−**d**, **9c** and **10c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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