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Cyclotrimerization Strategy toward Analogues of Amaryllidaceae Constituents. Synthesis of Deoxygenated Pancratistatin Core

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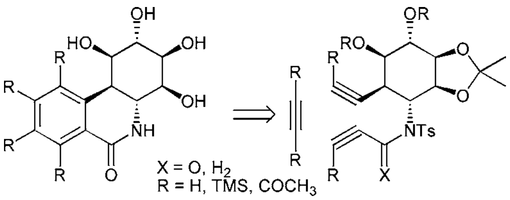
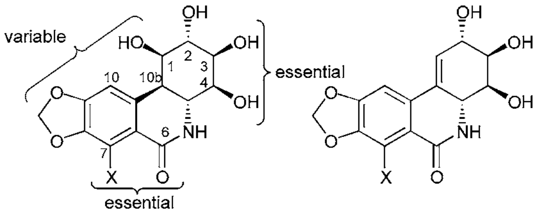
ABSTRACT



A derivative of pancratistatin having no oxygenation in the aromatic ring was synthesized by a new strategy based on the cobalt-catalyzed cyclotrimerization of acetylenes as a prelude to diversity-oriented synthesis of further analogues.

Activity in the total synthesis of Amaryllidaceae constituents[1] has been intense for over 20 years. The major targets in this group of natural products, pancratistatin (**1**), 7-deoxypancratistatin (**2**), narciclasine (**3**), and lycoricidine (**4**), have all been synthesized several times by diverse and creative strategies.[2] Driven by promising antitumor activities especially of the phenol-containing compounds **1** and **3**, major effort has been devoted to the preparation of many unnatural analogues in order to ameliorate the bioavailability of these poorly soluble agents.[3] The precise mode of action of the most potent constituent, pancratistatin, is unknown, and only limited information is available concerning the interactions of narcilasine with RNA.[4] The search for the minimum pharmacophore and the mode of action resulted in the syntheses and biological screening of many unnatural derivatives, yielding essential information about some of the functional groups required for activity. Those regions that are crucial to maintaining the activity of pancratistatin are indicated in Figure 1.



1 pancratistatin, X = OH
2 7-deoxypancratistatin, X = H
3 narciclasine, X = OH
4 lycoricidine, X = H

Figure 1. Amaryllidaceae constituents.

First, the presence of phenol and phenanthridone functionalities as a potential donor−acceptor pair is essential; the absence of phenolic hydroxyl, as in 7-deoxypancratistatin,

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(1) At the suggestion of Professor R. Pettit (Arizona State University) we no longer use the descriptor "alkaloids" when referring to the members of the amaryllidaceae family. With the exception of lycorine-type alkaloids none contain a basic nitrogen.

(2) For reviews of synthetic strategies, see: (a) Prabhakar, S.; Tavares, M. R. *Alkaloids Chem. Biol.* **2001**, *15*, 433. (b) Rinner, U.; Hudlicky, T. *Synlett* **2005**, 365. (c) Polt, R. *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI: Greenwich, CT, 1997; Vol. 3, p 109. (d) Martin, S. F. In *The Alkaloids*; Bross, A. R., Ed.; Academic: New York, 1987; Vol. 40, p 251. (e) Jin, Z. *Nat. Prod. Rep.* **2003** *20*, 606. (f) Jin, Z. *Nat. Prod. Rep.* **2005**, *22*, 111.

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leads to a 8- to 32-fold decrease in activity in those cell lines against which both pancratistatin and 7-deoxypancratistatin were tested.[4f,5] Up to now, it has been assumed that compounds lacking the amide carbonyl are inactive, as has recently been demonstrated with lactone analogues of lycoricidine and pancratistatin.[6]

Second, changes in the substitution patterns or functionalities elsewhere in the aromatic core lead to compounds with decreased activity, as has recently been shown with several analogues,[4f] including an indole-containing mimic of **1**.[4e,7] Third, the aminoinositol moiety must remain essentially intact, except for variations of substituents, functionalities, and configuration at C-1.[4a,4b] Finally the trans-ring junction is essential to activity; the cis-fused 7-deoxypancratistatin is inactive.[8] Thus the potential for variation in structure appears to be the greatest in the region between C-1 and C-8/C-9/C-10 portion of the aromatic core. Examination of all recent strategies reveals that no general method has yet been implemented that would permit access to a large variety of structures with systematic variations in the aromatic nucleus only. In this manuscript we report the successful synthesis of the deoxygenated aromatic core of pancratistatin by cyclotrimerization of acetylene derivatives with scaffolds that will allow also for the synthesis of heteroaromatic variants by incorporation of nitriles into the coupling sequence. Our strategy to access analogues of the title compounds such as **5** from fully oxygenated scaffold **7** is shown in Figure 2.

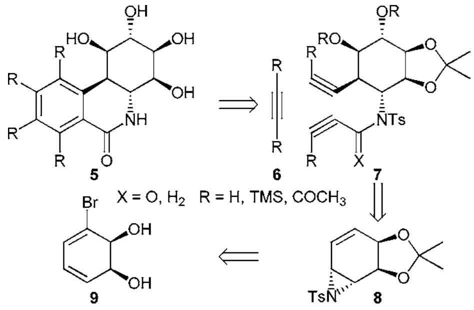

Figure 2. Retrosynthetic view of analogue synthesis by cyclotrimerization.

Cyclotrimerization of acetylenes, discovered by Berthelot in 1866,[9] has been used extensively in the syntheses of carbo- and heterocyclic compounds[10] and occasionally applied to natural product synthesis. Vollhardt's estrone preparation is perhaps the best known application.[11] The proposed strategy for the synthesis of Amaryllidaceae analogues depends on the cyclotrimerization of scaffold **7** with acetylene derivatives equipped with substituents capable of yielding oxygen or other functionalities through further manipulations. A review of literature suggests that cyclotrimerizations are, in general, not high yielding (an exception being the above-mentioned estrone synthesis), and the choice of catalysts and precise reaction engineering require substantial research effort. Despite such limitations we viewed the cyclotrimerization approach as a viable route to a large number of compounds with extensive variations in the aromatic core, attainable from a simple scaffold such as **7**. Because functional and configurational changes at C-1 of the natural products do not greatly diminish biological activity, we chose to pursue the synthesis of both the natural series as well as the series epimeric at C-1 in order to provide possibilities of further functionalization in that region of the targets. The synthesis required a medium-to-large scale optimization for the preparation of tosylaziridine **8**,[12] which is available by a three-step protocol (49% over three steps) from the optically pure diol **9**,[13] Scheme 1.

Exposure of **8** to the aluminum complex derived from lithium trimethylsilylacetylene provided tosylamide **10** in 69% yield after reprotection of the *cis*-diol. The cyclic sulfate **12** was prepared from diol **11** (OsO_4/NMO; 44%, 76% by conversion) by treatment with SO_2Cl_2 and NEt_3 in 82% yield.[14] Reaction of **12** with ammonium benzoate provided a mixture of **13** and enyne **14** (1:2), the latter compound possessing the features of narciclasine or lycoricidine in the aminoconduritol ring. A study of this reaction revealed that **14** is not derived from a syn elimination of the cyclic sulfate from C-1 (pancratistatin numbering) but rather by trans elimination of the intermediate sulfate anion derived from **13**. The sulfate anion is situated syn to the proton at C-10b and facilites the elimination of the benzoate group intramolecularly. The cyclic sulfate **12** and the alcohol **13** are stable to reaction conditions that exclude ammonium benzoate. It will eventually be desirable to optimize this reaction in order

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(10) For reviews, see: (a) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539. (b) Bönnemann, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 248. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 46. (d) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081. (e) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (f) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787.

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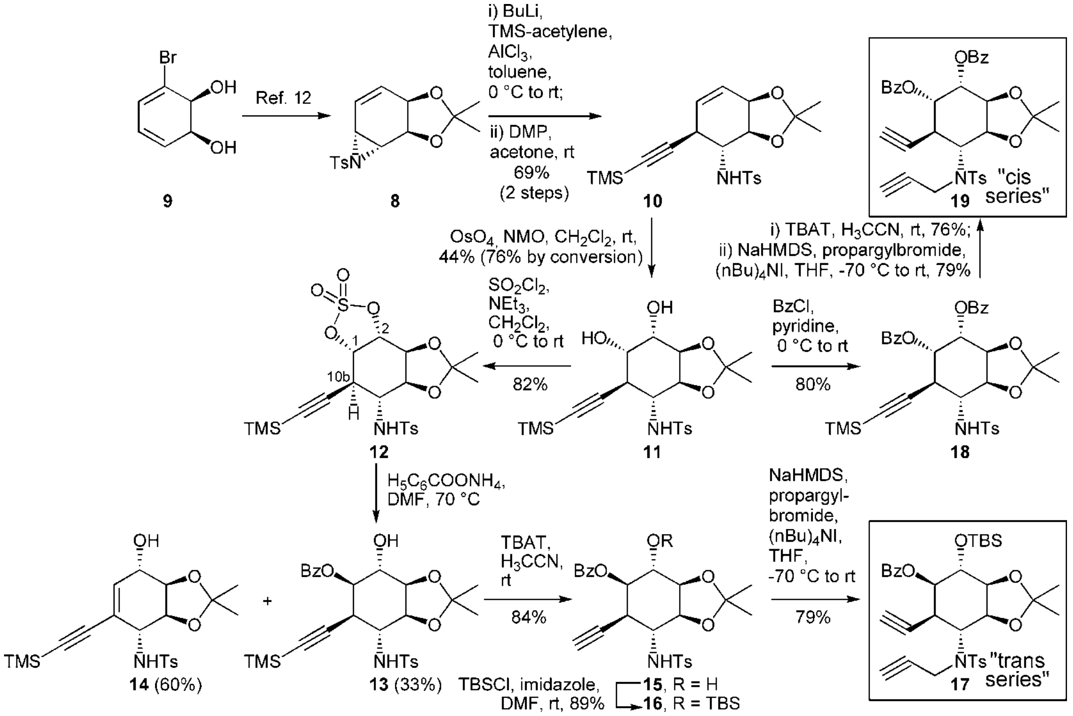
Scheme 1



to produce **13** and **14** selectively, as the latter compounds will be used in intramolecular variants of the cyclotrimerization to access directly the narciclasine and lycoricidine analogues. The synthesis of scaffold **17** was completed by desilylation of the acetylene moiety, protection of C-2 alcohol (pancratistatin numbering), and alkylation of the tosylamide with propargyl bromide providing the key intermediate for the "natural" or "trans series" in seven operations (eight steps) from aziridine **8**. The *cis*-diol **11** was protected as a dibenzoate and converted to **19** in two steps to serve as a scaffold for the unnatural, or "cis series" of analogues epimeric at C-1.

The literature reports on cyclotrimerization involving bis-trimethylsilylacetylene (BTMSA) mention moderate yields as well as desilylation problems and incorporation of CO ligands into reaction products.[15] The optimum conditions for the formation of tetracycle **20** (83% yield) were found by slow addition (syringe pump, 36 h) of a mixture of **17**, CpCo(CO)$_2$, and BTMSA to a heated solution of BTMSA in xylene, Scheme 2. After distillation and recovery of BTMSA, the product was isolated by chromatography on silica. Similary, the "cis" scaffold **19** was converted to the core of pancratistatin in 87% yield.[16]

Oxidation of**20** to imide **24** was accomplished in 10−15% yield with NaIO$_4$/RuCl$_3$.[17] An exchange of the TBS group for a benzoate group led to compound **26**, whose oxidation under the same conditions gives the imide **27** in 9−10% yield. Buffering this acidic reaction with Na$_2$CO$_3$ to a neutral suspension increases the yield to 33%. Oxidation of the aromatic product obtained from cyclotrimerization of scaffold **19** ("cis series") with benzyltriethylammonium permanganate yielded the corresponding imide in 53% yield, whereas the oxidation of the C-1 epimeric scaffold **26** ("trans series") with this oxidizing agent produced the imide **27** in only 12−14% yield.

To examine the most effective approach to either **24** or **27** we tested the cyclotrimerization of a propargylimide, prepared in two steps from the "cis" scaffold **18** by desilylation and acylation with propargylic anhydride. Under identical conditions used in cyclotrimerizations leading to **20**, the imide provided the aromatic product in only 5% yield, perhaps because of unfavorable rotamer population derived from the propargyl imide or possible imide resonance forms (*E*/*Z* forms). For these reasons the sequence involving the cyclotrimerization of propargylamines followed by benzylic oxidation proved vastly superior. Following the reductive removal of the tosyl group, methanolysis, and deprotection, the core of pancratistatin containing the trimethylsilyl groups was attained.

Some of the intermediates and the two fully hydroxylated analogues, **23** and **28**, were subjected to biological evaluation in order to determine what effect the lack of aromatic oxygenation and the lipophilic silyl groups have on the potency of these analogues. The biological evaluation of this series proved interesting. Of the compounds tested against the cancer cell lines the only inactive one was the fully

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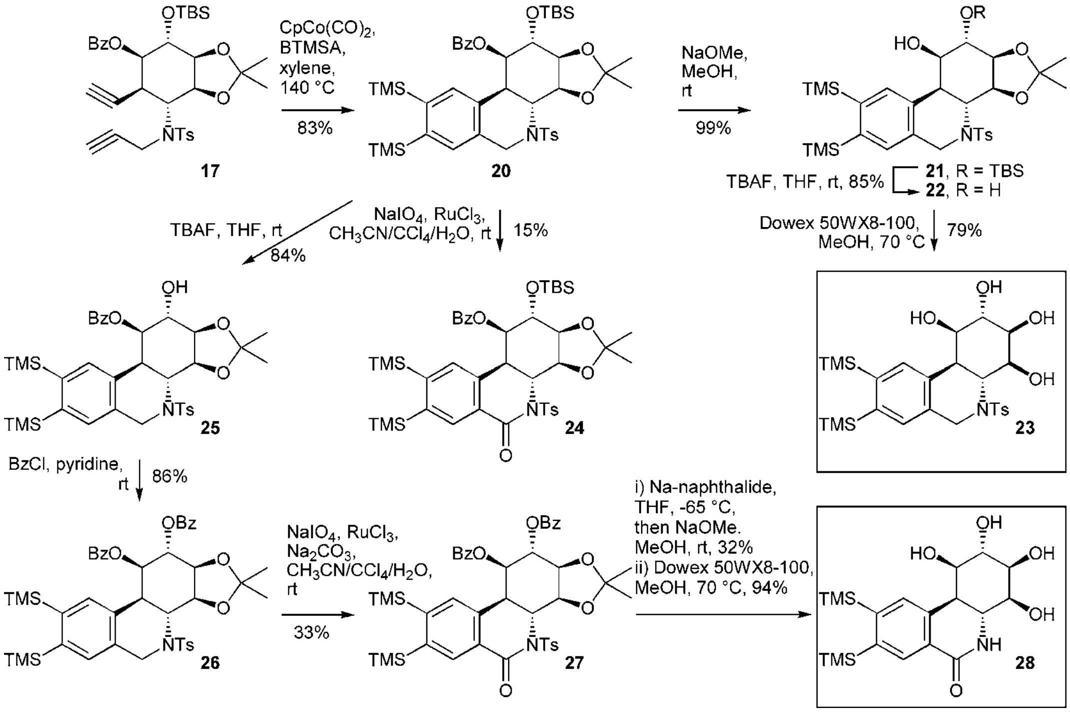
[15] (a) Rainier, J. D.; Imbriglio, J. E. *Org. Lett.* **1999**, *1*, 2037. (b) Rinner, U.; Hudlicky, T. Unpublished results.

[16] The details of the reaction sequence in the "cis series" (i.e., **19** → **28**) will be reported in an upcoming full paper in due course. The overall yield of fully hydroxylated derivative **23** via the "cis series" was 2.5-fold more efficient because the problems of elimination to **14** were not encountered in this series.

[17] Elango, S.; Yan, T. H. *Tetrahedron* **2002**, *58*, 7335.

Scheme 2



protected tosylamide **20**. As the free alcohol content increased (i.e., **21** and **22**) so did the activity against cell lines, with **22** and **23** having similar activity and being only 10-fold less active than 7-deoxypancratistatin.[18] This finding is both surprising and exciting since none of the compounds have the amide carbonyl thought to be essential to activity. Tosylamide **23** is the first active compound that lacks all oxygenation in the phenanthridone moiety, and this result, if supported by further testing of similar compounds, may lead to revision of the proposed mode of action.

The pancratistatin core, lacking aromatic oxygenation, has been synthesized by a high-yielding cyclotrimerization strategy in 11 steps from tosylaziridine **8** in both the natural and the C-1 epimeric series in an overall yield of 5% and 12%, respectively. The sequences proceeded in reasonable yields and the preparation of the key scaffolds, **17** and **19**, was successfully carried out on medium scale (2.5 g). The "cis" isomer was also converted to the natural stereoisomer **25** by late-stage opening of the cyclic sulfate after cyclotrimerization of scaffold **19**.[16] What remains to be established is the identification of the best precursors for the eventual installation of catechol/phenol functionalities onto the aromatic ring. The oxidative transformation of the silyl groups will be compared with Baeyer−Villiger oxidations of acetyl groups in similar tetracycles derived by using 2,5-dihydroxyhex-3-yne, 1,4-dihydroxybut-2-yne, or hex-3-yne-2,5-dione. Once the best combination of cyclotrimerization partners is established, the diversity-oriented synthesis of carbo- and heterocyclic analogues will be initiated. We will report the results of these endeavors in due course.

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Supporting Information Available: Experimental procedures and spectral data for key compounds **10**−**23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Details of the testing results will be reported in a full paper for all compounds. We thank Professor George R. Pettit (Arizona State University) for the biological evaluation of our natural product derivatives.