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# Studies on Oxidopyrylium [5 + 2] Cycloadditions: Toward a General Synthetic Route to the C12-Hydroxy Daphnetoxins

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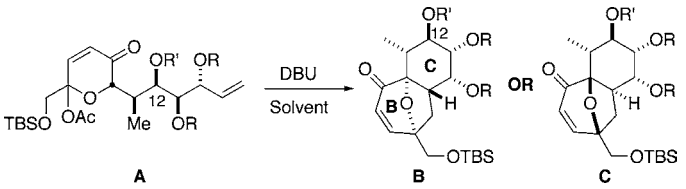
## ABSTRACT




**12-Hydroxydaphnetoxins, members of the structurally fascinating daphnane diterpene family, exhibit a wide range of significant biological activities. A general route to the BC-ring system of 12-hydroxy daphnetoxins is reported based on D-ribose. Depending on the choice of protecting groups and solvent, the oxidopyrylium–alkene [5 + 2] cycloaddition originating from A provides cycloadduct diastereomer B or C with good to excellent selectivity.**

The daphnane diterpenes represent a large family of structurally complex and densely functionalized natural products that collectively exhibit remarkably diverse biological activities, including neurotrophic, cytoprotective, antileukemic, antihyperglycemic, antitumor, inflammatory, piscicidal, insecticidal, nematocidal, and tumor-promoting.[1] Within the daphnane diterpene family are the C12-hydroxy daphnetoxins, which have additional oxygenation in the C-ring. The 12-hydroxy daphnetoxins gnididin, gniditrin, and gnidicin (Figure 1), all of which possess C12-acyl groups, have antileukemic activity, whereas the parent 12-hydroxydaphnetoxin is devoid of similar activity.[2] The additional oxygenation could have significant biological implications, as a variety of acyl groups are tolerated in this position.

To date, there is only one total synthesis of a daphnane (resiniferatoxin).[3] Relatively few synthetic approaches to such compounds have been described,[4] and no reports on synthetic routes to C12-hydroxydaphnetoxins have appeared. Several years ago, we started to investigate strategies for the synthesis of the C12-hydroxydaphnetoxins and describe herein our first report on this project in the form of a stereocontrolled synthesis of a potentially general 12-hydroxydaphnane

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(1) For reviews on daphnane diterpenes, see: (a) Kowalski, J. A. Ph.D. Thesis, Stanford University, Stanford, CA, 2005, pp 31−109. (b) He, W.; Cik, M.; Appendino, G.; Puyvelde, L. C.; Leysen, J. E.; De Kimpe, N. *Mini-Rev. Med. Chem.* **2002**, *2*, 185−200. (c) Borris, R. P.; Blasko, G.; Cordell, G. A. *J. Ethnopharmacol.* **1988**, *24*, 41−92. (d) Evans, F. J.; Soper, C. J. *Lloydia* **1978**, *41*, 193−233.

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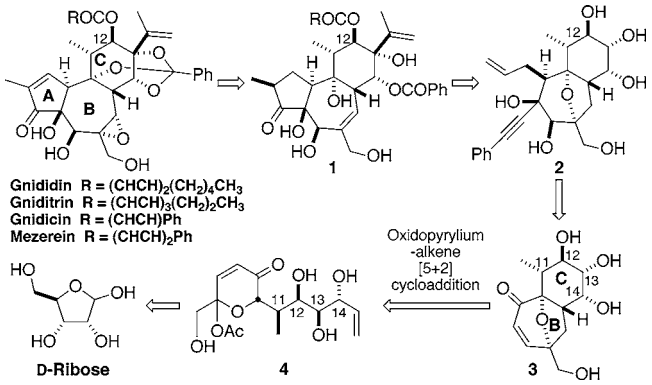


**Figure 1.** Retrosynthetic analysis.

precursor incorporating a highly elaborated and functionally differentiated BC bicyclic core.

Our synthetic plan (Figure 1) was designed to access various 12-hydroxydaphnetoxin derivatives through late-stage variation of the C12-ester and orthoester precursor groups in advanced intermediate **1**. This tricycle would arise from Pd-catalyzed cyclization of enyne **2**, which in turn would come from the BC-bicyclic system **3**. This intermediate represents a potentially general daphnane precursor, incorporating several target stereocenters and differentiated, conformationally biased functionality suitable for introduction of the A-ring and other groups. This bicycle would emerge from the D-ribose-derived pyranone **4** by an oxidopyrylium [5 + 2] cycloaddition.[5]

The oxidopyrylium−alkene [5 + 2] cycloaddition, a highly effective strategy level reaction,[6] has been successfully utilized by our group[7] as well as others[5,8] in synthesis. Asymmetric versions have also been reported in the literature.[9] Of relevance to the current study, we have previously shown that substitution at C11 and C12 of the tether in cycloaddition precursor **5** (Figure 2) allows for predictable

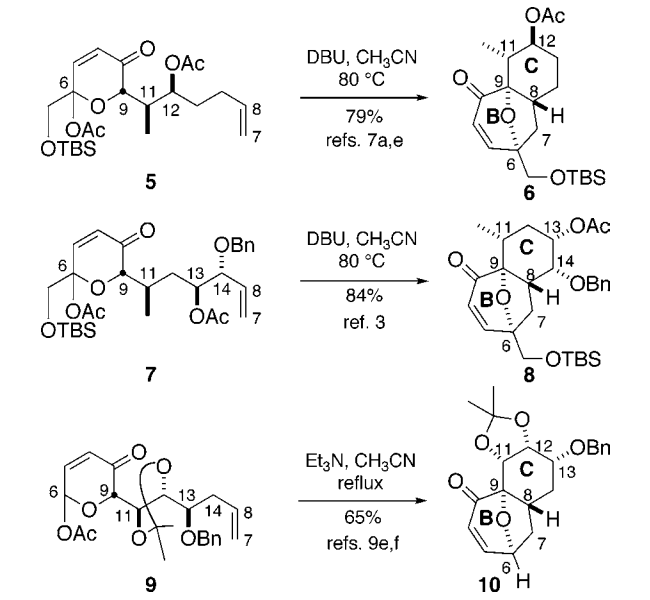


**Figure 2.** Previous examples of stereoselective intramolecular oxidopyrylium−alkene [5 + 2] cycloaddition.

control over the formation of the C6, C8, and C9 stereocenters in cycloadduct **6**, an intermediate in the synthesis of phorbol.[7a,e] This selectivity was also observed in the cycloaddition of **7** to give the C11-, C13-, and C14-substituted precursor **8** to resiniferatoxin.[3] More recently, Trivedi and co-workers reported an elegant enantiodivergent approach toward simpler systems (**10**) incorporating C11, C12, and C13 substituents derived from D-ribose.[9e,f] We herein report our progress on the first stereoselective intramolecular cycloaddition using *fully substituted* tethers, which provides access to the fully functionalized C-ring of 12-hydroxydaphnetoxins. The effect of protecting groups and solvent on the diastereoselectivity of the cycloaddition are also described.

Our synthesis starts with conversion of the commercially available chiral building block D-ribose to the known aldehyde **12** (Scheme 1).[10] Following the literature procedure, selective protection of D-ribose and primary iodide formation proceeded well (Scheme 1). However, subsequent zinc-mediated Vasella fragmentation[11] of **11** using the literature protocol with methanol as the solvent gave a large amount of the methyl hemiacetal side product as reported. We found that the use of a catalytic amount of acetic acid in THF/ethanol provides a more selective route to the desired aldehyde **12**. Treatment of **12** with EtMgBr followed by TPAP oxidation afforded ethyl ketone **13**. The C11 stereocenter was then set selectively by using a boron-mediated substrate-controlled aldol reaction[12] between ketone **13** and known furfuryl aldehyde **19**,[7e] providing hydroxy ketone **14**

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(8) For recent examples, see: (a) Magnus, P.; Shen, L. *Tetrahedron* **1999**, *55*, 3553−3560. (b) Magnus, P.; Waring, M. J.; Ollivier, C.; Lynch, V. *Tetrahedron Lett.* **2001**, *42*, 4947−4950. (c) Ohmori, N. *Chem. Commun.* **2001**, 1552−1553. (d) Lopez, F.; Castedo, L.; Mascareñas, J. L. *Chem. Eur. J.* **2002**, *8*, 884−899. (e) Baldwin, J. E.; Mayweg, A. V. W.; Pritchard, G. J.; Adlington, R. M. *Tetrahedron Lett.* **2003**, *44*, 4543−4545. (f) Snider, B. B.; Grabowski, J. F. *Tetrahedron Lett.* **2005**, *46*, 823−825.

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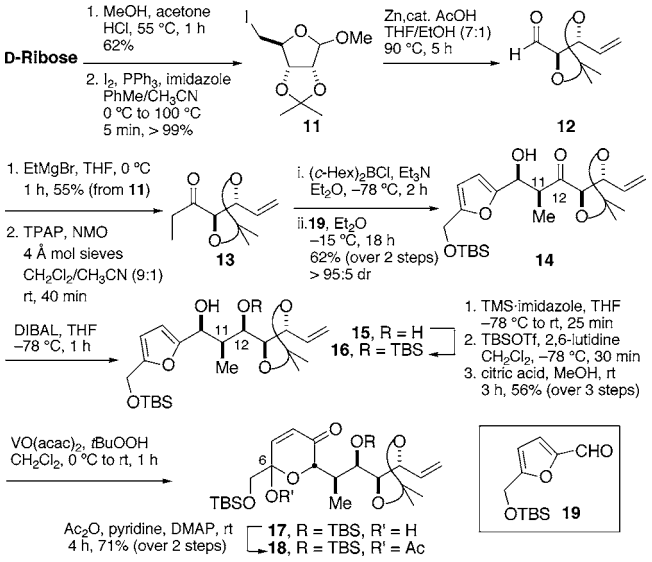
(11) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990−2016.

**Scheme 1.** Synthesis of Acetonide-Protected Pyranone **18**




in a >95:5 diastereomeric ratio. Chelation-controlled reduction of ketone **14** with DIBAL[13] and selective protection[14] of the C12 alcohol gave alcohol **16**. Oxidative ring expansion using $VO(acac)_2$/*t*-BuOOH[15] followed by acetylation provided the cycloaddition precursor **18** as an inconsequential mixture of C6 epimers.

The key intramolecular oxidopyrylium−alkene [5 + 2] cycloaddition was conducted by treating **18** with DBU (2.0 equiv) in acetonitrile at 80 °C. This resulted in the exclusive formation of the undesired cycloadduct **20** in 84% yield. The structure of **20** was initially assigned through 1D NOE NMR experiments and subsequently confirmed by a single-crystal X-ray analysis (Figure 3).

The stereochemical outcome of this cycloaddition differs from prior work and is potentially a consequence of the acetonide protecting group preventing the tether from adopting the necessary chairlike transition state that would lead to the desired cycloadduct (Figure 4).[7e] We anticipated that replacing the acetonide with more flexible protecting groups would allow access to the chairlike transition structure and thus reverse the diastereoselectivity.

Dibenzyl ether **26a** was prepared to test this hypothesis (Scheme 2). Methanolysis and tritylation of D-ribose, followed by protection of the remaining diol as benzyl ethers, yielded **21**. The trityl group was removed and the resulting alcohol converted to primary iodide **22**. In contrast to the heterogeneous Vasella fragmentation conditions, we found conditions to effect a tandem zinc-mediated reductive fragmentation−diethylzinc addition.[16] This new procedure not only saved one step but also improved the reproducibility

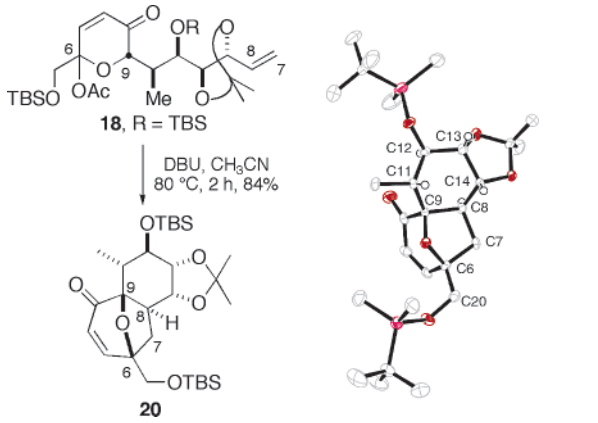



**Figure 3.** Oxidopyrylium−alkene [5 + 2] cycloaddition of acetonide **18** and ORTEP diagram of cycloadduct **20**.

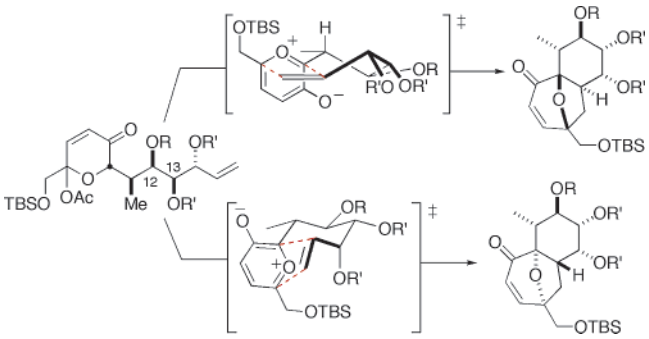


**Figure 4.** Proposed transition states in the oxidopyrylium−alkene [5 + 2] cycloaddition.

of the reaction. Subsequent TPAP oxidation gave ethyl ketone **23**. Following the sequence used for acetonide **13**, ketone **23** was converted to acetoxy pyranone **26a** (Scheme 2).

Treatment of acetoxypyranone **26a** with DBU in acetonitrile produced cycloadducts **27a** and **28a** in 84% yield as a 3.5:1 mixture, favoring **27a** (Scheme 2). This is a reversal of the diastereoselectivity observed for the cycloaddition of acetonide **18**. The stereochemical assignments of both diastereomers were made by chemical correlation with cycloadduct **20** (Scheme 3). Both cycloadducts **27a** and **28a** were subjected to hydrogenation, hydrogenolysis, and acetonide protection procedures to afford **29** and **30**, respectively. When cycloadduct **20** was hydrogenated, the product was **30**, indicating that the minor diastereomer **28a** arising from the cycloaddition of **26a** has the same stereochemistry as that of cycloadduct **20** produced from **18**.[17]

(12) (a) Paterson, I.; Wallace, D J.; Velázquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083−9086. (b) Carda, M.; Falomir, E.; Murga, J.; Castillo, E.; González, F.; Marco, J. A. *Tetrahedron Lett.* **1999**, *40*, 6845−6848.

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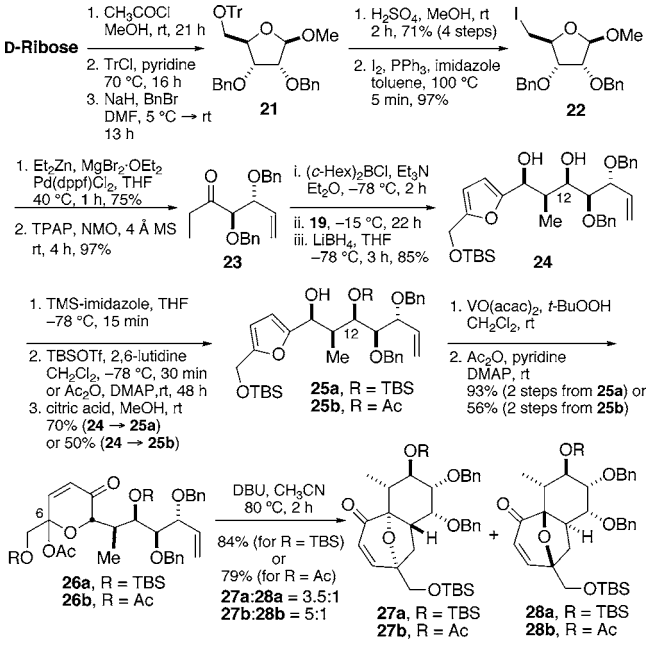
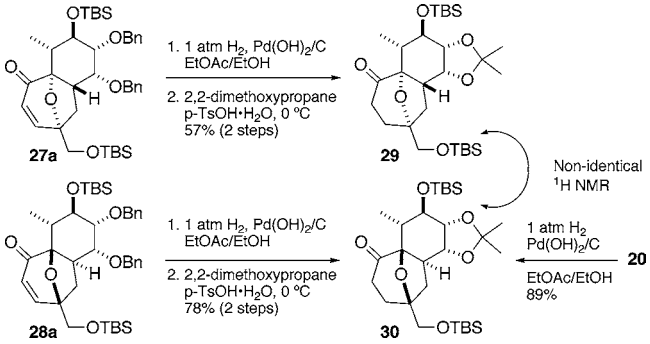
(17) Chemical derivatization followed of **27a** followed by NOE analysis confirmed its stereochemistry as indicated. See the Supporting Information for details.

**Scheme 2.** Synthesis and Cycloaddition of Dibenzyl Ether **26**




**Scheme 3.** Chemical Correlation of the Cycloadducts




The reversal in the diastereoselectivity of cycloadditions for **18** and **26a** is consistent with our hypothesis that the more flexible dibenzyl ethers enable the tether to adopt a chairlike transition state during the cycloaddition. Models suggest that this selectivity could be further improved by minimizing the unfavorable gauche interaction between the substituents at C12 and C13 when the tether adopts a chair conformation. To address this point, we replaced the C12-silyl ether with a smaller acetate group. The required substrate **26b** featuring a C12-acetate was prepared from diol **24** in a similar manner to the previous substrates. When pyranone **26b** was treated with DBU in acetonitrile at 80 °C, cycloadducts **27b** and **28b** were formed in 79% yield now in an improved 5:1 ratio favoring **27b**.

Given that the cycloaddition proceeds through a polar (zwitterionic) intermediate, the effects of solvent on the [5 + 2] cycloaddition of acetoxy pyranone **26a** were investigated. The rate and diastereoselectivity of the cycloaddition were solvent dependent (Table 1). The diastereomeric ratios varied from 3:1 to 8:1 in favor of the desired cycloadduct

**Table 1.** Solvent Effects on Cycloaddition Diastereoselectivity




| solvent ($\epsilon$)[a] | $T$ (°C) | time (h) | yield (%) | dr (**27a/28a**) |
|---|---|---|---|---|
| $PhCH_3$ (2) | rt | 100 | 60 | 8:1 |
| $CH_2Cl_2$ (9) | rt | 66 | 79 | 7:1 |
| acetone (21) | rt | 95 | 87 | 4.5:1 |
| DMF (37) | rt | 27 | 61 | 3:1 |
| $CH_3CN$ (38) | rt | 24 | 80 | 4:1 |
| $PhCH_3$ (2) | 98 °C | 24 | 66 | 5:1 |
| $CH_2Cl_2$ (9) | 38 °C | 48 | 63 | 5.5:1 |
| **$CH_2Cl_2$ (9)[b]** | **rt** | **18** | **83** | **7:1** |

[a] Reactions were run at 0.1 M. [b] Reaction was run at 0.4 M.

**27a**. The less polar the solvent, the better the selectivity and the longer the reaction time. Reaction times for complete conversion varied from 24 h (acetonitrile) to 100 h (toluene). A similar trend was observed by Mascareñas and co-workers in their sulfinyl-directed [5 + 2] cycloadditions.[9c] Heating the reaction further increased the rate but decreased the diastereoselectivity. We found, however, that the rate can be improved while maintaining high selectivity by running the cycloaddition at higher concentration.

In summary, we describe the first stereoselective intramolecular oxidopyrylium−alkene [5 + 2] cycloaddition using *fully substituted* tethers. Through variation in protecting groups and solvent, the diastereoselectivity of this process can be varied to favor either cycloadduct isomer. The resulting BC-ring system incorporates five of the daphnane target stereocenters. In addition, it incorporates differentiated and conformationally biased functionality needed for elaboration of these targets and, significantly, analogs. This versatile BC-bicyclic building block—a central element in our synthetic strategy—is available in homochiral form in 14 steps from ribose. The process is readily conducted on a preparative scale (>15 g). Further studies to advance the cycloaddition products toward such natural products and analogues are in progress.

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**Supporting Information Available:** Spectroscopic data and experimental procedures for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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