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Function-Oriented Synthesis: Studies Aimed at the Synthesis and Mode of Action of 1α-Alkyldaphnane Analogues

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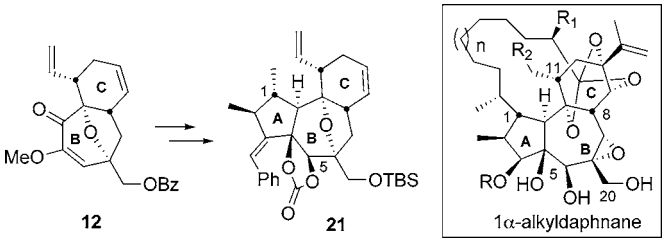
ABSTRACT



An efficient synthetic route to the ABC tricyclic core of 1α-alkyldaphnanes has been developed. The conformational bias imparted by the C6–C9 oxo-bridge of BC-ring system 12 was used to elaborate the ABC-ring system precursor including the introduction of the *β*-C5 hydroxyl group. A completely diastereoselective palladium-catalyzed enyne cyclization was then employed to establish the A-ring with a C1 appendage.

The daphnanes, tiglianes, and ingenanes represent a remarkable collection of synthetically challenging and biomedicinally important natural product leads.[1] These compounds incorporate a variety of ring sizes including, in the case of gnidimacrin (**1**), a macrocycle of 13 members as well as a highly varied array of functionalities punctuated by a rather uncommon chiral ortho ester. All but one of the 14 carbons that define the 5-7-6 core ring system of gnidimacrin are stereogenic centers. Little is known about the biogenesis of this natural product or its role in nature. However, it is interesting that it has been isolated from three different plants of three different continents,[2] suggesting a primitive origin to this compound class.

Of significance from a human health perspective, gnidimacrin and other 1α-alkyldaphnanes have been found to exhibit potent and diverse biological activities such as neurotrophic and antitumor activity.[1b−e] Gnidimacrin in particular is active against a variety of cancer cell lines (stomach, nonsmall cell lung, and leukemias) with IC_{50} values as low as 0.35 nM.[3] Significantly, however, it is not a general toxin as many cell lines are insensitive to gnidimacrin exposure.[3,4] Of special therapeutic relevance, gnidimacrin's anticancer activity has also been shown in animal cancer models in which significant life extensions and even cures

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(3) Yoshida, M.; Feng, W. J.; Saijo, N.; Ikekawa, T. *Int. J. Cancer* **1996**, *66*, 268−273.

(4) Gnidimacrin has been screened against the NCI-60 panel showing a difference of 2 to 3 orders of magnitude between some cell lines. These data are available from the National Cancer Institute at the URL: http://dtp.nci.nih.gov/dtpstandard/cancerscreeningdata/index.jsp.

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have been reported.[3] Yoshida et al. have provided compelling evidence implicating protein kinase C (PKC) βII in the activity of gnidimacrin, showing in one study that gnidimacrin-insensitive cells can be rendered sensitive by PKCβII transfection.[5a−c] Gnidimacrin is not alone in its fascinating structure and therapeutic promise. Kirkinine B (**2**) (Figure 1), another 1α-alkyldaphnane, isolated from *Synaptolepis*

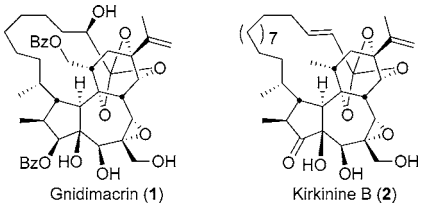


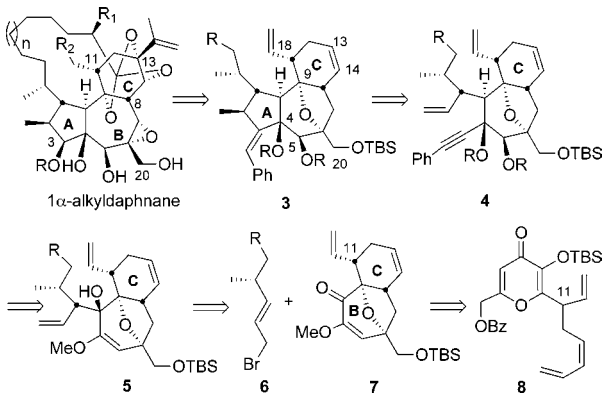
Figure 1. Some representative 1α-alkyldaphnanes.

kirkii, has been shown to have nanomolar activity against K562/C1000 human leukemia cells, as well as significant neurotrophic activity.[6]

Studies on the therapeutic potential of 1α-alkyldaphnanes have been hampered by low isolation yields and at least initially by the absence of validated cellular targets. Prompted by our interest in unaddressed synthetic problems and in new modes of therapeutic action, we initiated studies some time ago to access analogues of the 1α-alkyldaphnanes and to elucidate the structural determinants for their activity as needed to further investigate their mode of action and clinical potential. The synthetic challenges presented by this class of compounds are highlighted by the fact that no work on their synthesis has appeared and only one member of the daphnane family, resiniferatoxin (RTX), has been successfully synthesized.[7] This communication describes our initial studies directed at accessing 1α-alkyldaphnane analogues using a strategy that allows for introduction of variable functionalities at sites potentially critical for biological potency and selectivity.

As exemplified by our bryostatin analogue program,[8] our studies on the 1α-alkyldaphnanes are directed at achieving step-economical syntheses of structurally simplified analogues that exhibit functional activity comparable or superior to the natural product lead. Connectivity analysis[9] guided by analogue design considerations suggested that a preferred synthetic route to 1α-alkyldaphnanes and simplified derivatives would introduce the macrocycle at the end of the synthesis for maximum strategic flexibility. Because the role, if any, of the macrocycle in biological activity is not known, this approach was expected to allow access to both acyclic and macrocyclic analogues as needed for comparative evaluation. The ABC tricycle **3** was identified as a potentially flexible precursor scaffold, as it incorporates differentiated oxygen functionalities at C4, C5, C9, and C20 and latent oxygen functionality at C3, C18, C13, and C14 in the form of three selectively oxidizable alkenes (Scheme 1). Although

Scheme 1. Retrosynthetic Analysis of 1α-Alkyldaphnanes



the synthesis of a related 5-7-6 tricyclic core found in phorbol[10] and RTX has been reported, the introduction of a C1 alkyl group and oxidation at C5 and C18 pose entirely new and significant challenges. In principle, tricycle **3** would arise from a metal-catalyzed closure of enyne **4** which in turn would be generated from the conjunction of allylic bromide **6** and enone **7** followed by C5 oxygenation. Controlling stereogenesis at C10, C4, and C5 would be the bridged bicyclic subunit in **7** that conformationally fixes and sterically biases the hydropyranyl subunit. Bicycle **7** would emerge from the known oxidopyrylium−alkene [5+2] cycloaddition of pyrone **8**.[11]

Although ultimately our strategy incorporates a C1 side chain functionalized with an appropriate handle for late-stage modifications, it was decided to start with incorporation of a methyl group at C1 to validate our synthetic plan and provide a reference control for testing biological activity.

Our synthesis starts with the preparation of the substrate for the key oxidopyrylium [5+2] cycloaddition[12] that estab-

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(6) He, W.; Cik, M.; Van Puyvelde, L.; Van Dun, J.; Appendino, G.; Lesage, A.; Van der Lindin, I.; Leysen, J. E.; Wouters, W.; Mathenge, S. G.; Mudida, F. P.; De Kimpe, N. *Bioorg. Med. Chem.* **2002**, *10*, 3245−3255.

(7) Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976−12977.

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(9) (a) Wender, P. A.; Miller, B. *Org. Synth.: Theory Appl.* **1993**, *2*, 27. (b) Barone, R.; Chanon, M. *Tetrahedron* **2005**, *61*, 8916−8923.

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(11) Wender, P. A.; Mascarenas, J. L. *J. Org. Chem.* **1991**, *56*, 6267−6269.

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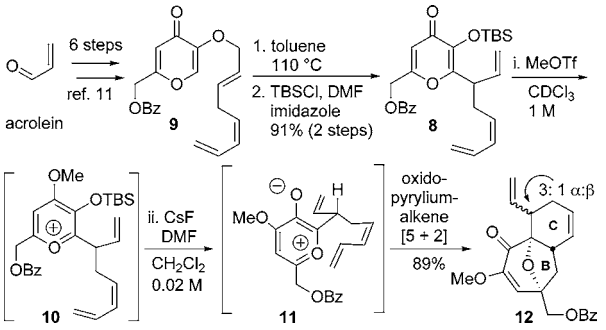
lishes the BC core. The conversion of **9** to **8** through a Claisen rearrangement sets the C11 stereocenter which in turn is intended to control all other stereocenters in our plan (Scheme 2). We have preliminarily investigated asymmetric

Scheme 2. Synthesis of the BC-Ring System

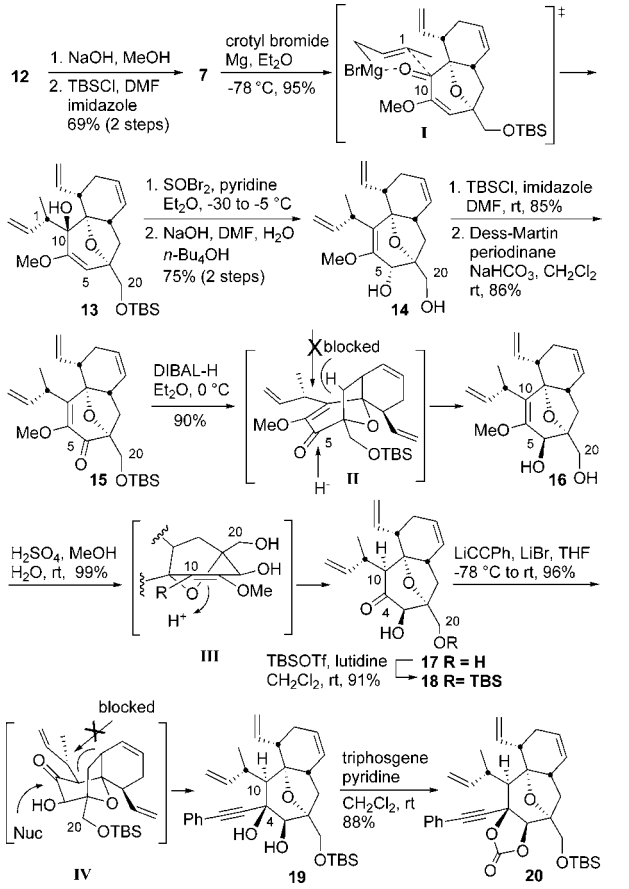


catalysis of this transformation using different Lewis acids in combination with Box,[13] Pybox,[14] and Arbox[15] ligands. The combination of Pybox and $Zn(OTf)_2$ gave enantiomeric excesses of up to 48%,[16] an encouraging result given the relative paucity of studies in this area.[17] However, given the immediate importance of addressing downstream strategic issues, further studies in this series were conducted with racemic compounds.

The original conditions employed in the [5+2] oxidopyrylium cycloaddition for the synthesis of **12** required optimization for scale-up purposes. Previously, it was reported that this reaction proceeds in 84% yield on a small scale using 2.0 equiv of methyl triflate. However, on larger scales, removing the excess methyl triflate became troublesome, increasing the possibility of overalkylation of oxidopyrylium **11**. It was found that complete conversion of **8** to **12** can be achieved using 1.0 equiv of MeOTf, provided that the concentration of **8** was increased to 1.0 M. $CDCl_3$ is used in the pyrone alkylation to allow NMR monitoring. Additional modifications to the established procedure included a slow addition of the pyrylium species **10** to a solution of CsF in DMF and CH_2Cl_2 under further dilution (0.02 M) to favor the intramolecular [5+2] cycloaddition over intermolecular processes. Ultimately, these conditions allowed for room-temperature oxidopyrylium generation and [5+2] cycloaddition of **8** in 20−30 g batches and conversion to cycloadduct **12** in 89% yield.

After debenzoylation of **12**, the primary alcohol was reprotected as TBS ether **7** (Scheme 3). Barbier-type cro-

Scheme 3. Synthesis of the Cyclization Precursor



tylation of cycloadduct **7** afforded the desired alcohol **13** in 95% yield. In this step, the desired stereochemistry at C1 is set with complete control of diastereoselectivity, presumably through a Zimmerman−Traxler six-membered transition state.[18]

Efforts to directly transpose the C10 alcohol in **13** to the C5 position encountered complications. Thus, this alcohol was first converted with complete stereoselectivity to the β-C5 bromide which was cleanly inverted to the α-C5 alcohol. During this step, the C20 TBS ether was partially cleaved, and upon workup, the crude mixture was treated with acidic conditions to complete the cleavage of the C20 TBS group which was reprotected in a subsequent step. Initial attempts to invert C5 either under Mitsunobu conditions or by acid-catalyzed epimerization were unsuccessful. This inversion was achieved, however, through a two-step sequence in which the C5 alcohol was first oxidized to the corresponding enone **15** which was then reduced with DIBAL-H from the less-encumbered α-face to provide the desired β-C5 alcohol **16**.

With the β-C5 alcohol installed, the C4 ketone was revealed through hydrolysis of the C4 methyl enol ether. The

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(14) For a review on Box and Pybox catalysts, see: (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335. (b) Evans, D. A.; Rovis, T.; Johnson, J. S. *Pure Appl. Chem.* **1999**, *71*, 1407−1415.

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(16) In this case, the asymmetric induction was opposite to the desired configuration; however, this can be easily reversed by changing the chiral ligand.

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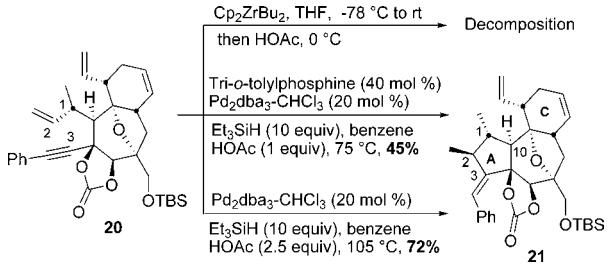
C10 stereochemistry was set during the process, consistent with a stereoelectronically controlled axial protonation. Subsequently, the C20 alcohol was reprotected as a TBS ether.

Addition of lithium phenyl acetylide to ketone **18** provided the desired C4, C5 diol in excellent yield. This stereoselectivity results from attack of the nucleophile from the less-encumbered α-face. The relative stereochemistry at C4, C5, and C10 was assigned on the basis of NOE experiments. Subsequent protection of diol **19** as a cyclic carbonate completed the synthesis of cyclization precursor **20**.

Different conditions were screened for the key enyne cyclization of **20** (Scheme 4). Initial attempts using di-*n*-butyl-zirconocene[19] resulted in decomposition of **20**. This was attributed to instability of the carbonate moiety under the reaction conditions.

Scheme 4. Enyne Cyclization Studies



Alternative conditions using palladium catalysis[20] gave better results. Treatment of carbonate **20** with 20 mol % of Pd_2dba_3·$CHCl_3$, 40 mol % of tri-*o*-tolylphosphine, 1 equiv of acetic acid, and 10 equiv of triethylsilane afforded a 45% yield of **21**. To improve the yield and reliability of this reaction, different ligands were explored, and it was discovered that the "ligandless" palladium conditions worked best. Thus, treatment of carbonate **20** with 20 mol % of Pd_2dba_3·$CHCl_3$ in the presence of 2.5 equiv of acetic acid and 10 equiv of triethylsilane provided the desired product with complete diastereoselectivity in 72% yield.

The relative stereochemistry of the ABC tricyclic core was assigned through 1D NOE NMR experiments (Figure 2).

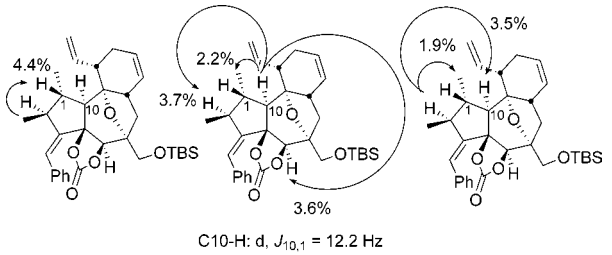


Figure 2. NOE data for the ABC-ring system **21**.

Also the C1, C10 coupling constant of 12.2 Hz indicated a *trans*-diaxial relationship between these two protons.

The completion of this ABC tricyclic daphnane core represents the first example of a synthetic incorporation of a C1 substituent into the A ring and a C5 hydroxyl group into the B ring of a daphnane precursor/analogue compound. This synthetic strategy allows step-economical access to the complete daphnane core tricycle in only 22 steps and is expected to allow access to the 1α-alkyldaphnanes and more immediately to analogues incorporating the highly oxygenated AB-ring functionality that putatively contacts the receptor surface. Further studies incorporating a C1 side chain with an appropriate functionalization handle and the rest of the required functionality of the 1α-alkyldaphnanes are under investigation in our laboratory.

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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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