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A Concise and Modular Synthesis of Pyranicin

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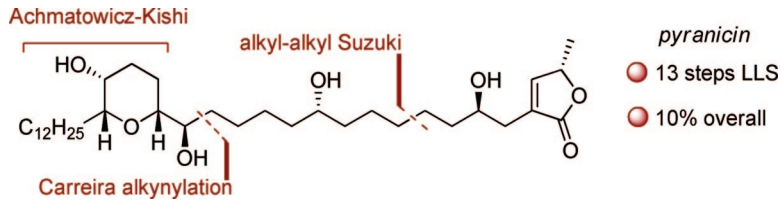
ABSTRACT



A modular, 13-step synthesis of the tetrahydropyran-containing annonaceous acetogenin pyranicin is reported. Key features are the use of an Achmatowicz oxidation−Kishi reduction sequence for the assembly of a pyranone from a furan and the application of Fu's alkyl−alkyl Suzuki coupling for subunit union.

The annonaceous acetogenins, a group of polyketides that are generally identified by the presence of one or two tetrahydrofuran rings, now number greater than 400 compounds.[1] A small subset of the acetogenins, including mucocin and jimenezin, contain both a tetrahydrofuran ring and a tetrahydropyran ring. As a class, these compounds have attracted substantial scientific attention due to their rich and varied biological activities which include anticancer, antiinfective, immunosuppressive, pesticidal, and antifeedant properties.

Pyranicin (**1**, Figure 1) was isolated from the stem bark of *Goniothalamus giganteus* and is the prototype of acetogenins that contain a single tetrahydropyran ring.[2] Despite what could be argued to be substantial structural simplification relative to more complex acetogenins, pyranicin retains impressive biological activity, with <1 μg/mL ED_{50} values against a number of cancer cell lines and particularly noteworthy effects against the PACA-2 (pancreatic cancer) cell line ($ED_{50} = 1.3$ ng/mL). As part of our ongoing interest in the synthesis of natural product inhibitors of electron transport,[3] we describe in this communication a total synthesis of **1**.[4]

From the outset, an overarching goal of our studies was to develop a concise and modular synthesis that would be amenable to the synthesis of a variety of compounds that could illuminate SAR for pyranicin. With this in mind, we settled on a strategy that called for the preparation of three key subunits: pyran **2**, alkynyl olefin **3**, and butenolide **4**. Pyran **2** would be prepared by our recently described Achamatowicz oxidation−Kishi

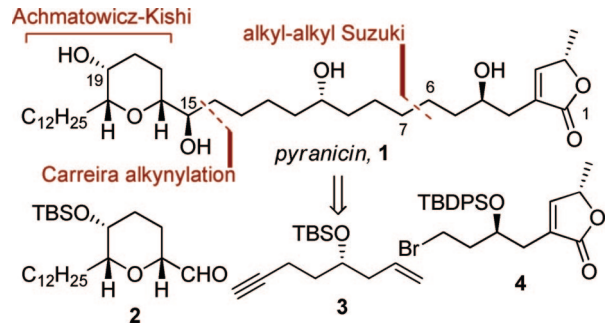


Figure 1. Pyranicin and overall synthesis strategy.

(1) For a review see: Bermejo, A; Figadere, B.; Zafra-Polo, M.-C.; Barrachina, I; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269, and references cited therein.

(2) Alali, F. Q.; Rogers, L.; Zhang, Y.; McLaughlin, J. L. *Tetrahedron* **1998**, *54*, 5833.

(3) Keaton, K. A.; Phillips, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 408.

(4) For other total syntheses see: (a) Strand, D.; Norrby, P.-O.; Rein, T. *J. Org. Chem.* **2006**, *71*, 1879. (b) Strand, D.; Rein, T. *Org. Lett.* **2005**, *7*, 199. (c) Takahashi, S.; Kubota, A.; Nakata, T. *Org. Lett.* **2003**, *5*, 1353. (d) Hattori, Y.; Furuhata, S.-i.; Okajima, M.; Konno, H.; Abe, M.; Miyoshi, H.; Goto, T.; Makabe, H. *Org. Lett.* **2008**, *10*, 717. (e) Furuhata, S.-i.; Hattori, Y.; Okajima, M.; Konno, H.; Abe, M.; Miyoshi, H.; Goto, T.; Makabe, H. *Tetrahedron* **2008**, *64*, 7695.

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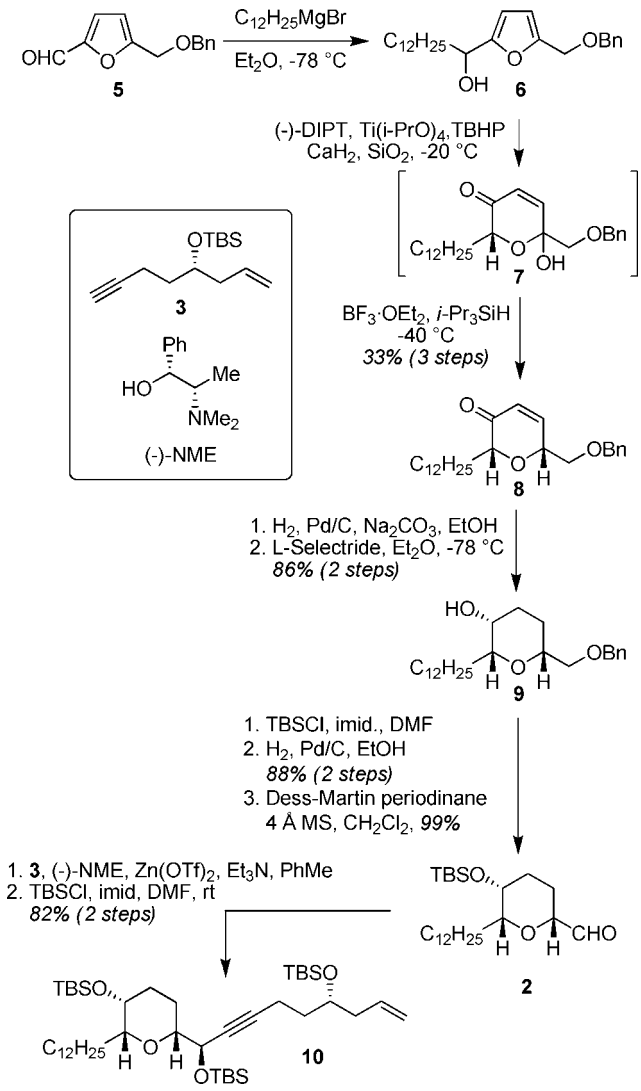
reduction sequence,[5] and our plans for subunit coupling involved the use of Carreira's asymmetric alkynylation[6] and Fu's recently described alkyl−alkyl Suzuki coupling.[7]

The synthesis of the tetahydropyran-containing domain commenced with commercially available furan **5**[8] (Scheme 1).

Scheme 1. Synthesis of the C7−C32 Pyran-Containing Domain



Addition of dodecylmagnesium bromide produced furfuryl alcohol **6**, which was subjected to the Sharpless asymmetric kinetic resolution reported by Sato[9,10] to yield the intermediate pyranone hemiacetal **7**. Immediate reduction with *i*-Pr_3SiH in the presence of BF_3•OEt_2 gave pyran **8** as a single diastereoisomer (>20:1 by ^1H NMR analysis). This three-step sequence conveniently provided the desired pyran in 33% overall yield. Hydrogenation of the enone, followed by reduction of the ketone with L-Selectride gave axial alcohol **9** in 86% yield (two steps). Protection of the secondary alcohol as the TBS ether, removal of the benzyl ether (88% yield, two steps), and oxidation with Dess−Martin periodinane led to aldehyde **2** (99% yield). Reaction with known alkyne **3**[11] under Carreira's asymmetric alkynylation conditions (Et_3N, $Zn(OTf)_2$, (−)-NME, PhMe) and subsequent protection of the secondary alcohol as the TBS ether gave **10** (82% yield over two steps).

The synthesis of butenolide **4** began with the alkylation of alkyne **11**[12] with epoxide **12**[13] in the presence of BF_3•OEt_2, followed by immediate protection of the homopropargyl alcohol with TBDSPCl to give **13** in 88% yield (Scheme 2). Careful removal of the TBS ether with ethanolic PPTS (95% yield) and hydroalumination−iodination of the alkyne following Denmark's procedure[14] produced vinyl iodide **14** in 90% yield. In accord with Stille's original report[15] and Hoye's application in the context of acetogenin synthesis,[16] when **14** was subjected to Pd(0) under 50 psi CO, carbonylative lactonization occurred to yield the desired butenolide **15** in 90% yield. Oxidative removal of the PMB ether with DDQ in wet CH_2Cl_2 (82% yield) unveiled primary alcohol **16**. Conversion of the alcohol to the bromide **4** was readily achieved by Hannesian's NBS-Ph_3P protocol[17] in 87% yield.

With routes to **10** and **4** secured we were positioned to examine the proposed Fu-type Suzuki coupling for subunit union (Scheme 2).[18] To this end, when **10** was treated with 1.1 equiv of freshly prepared 9-BBN in THF at room temperature, hydroboration was selective for the terminal alkene over the internal alkyne[19] to yield intermediate borane **17**. When this borane was exposed to bromide **4**, $Pd(PCy_3)_2$ and K_3PO_4•H_2O smooth cross-coupling ensued to yield the desired compound **18** in 60% yield. In our hands, this coupling was robust with 20 mol % $Pd(PCy_3)_2$ catalyst loading and 1.2 equiv of bromide **4**. In the current example, deviation from these conditions resulted in decreased and variable yields of the desired compound. The synthesis was then completed in a straightforward fashion by removal of the silyl protecting groups with aqueous HF in acetonitrile (92% yield), and reduction of the alkyne to the hydrocarbon using Wilkinson's catalyst in benzene−ethanol to produce pyranicin **1** in 89% yield. The

(5) (a) Henderson, J. A.; Jackson, K. L.; Phillips, A. J. *Org. Lett.* **2007**, *9*, 5299. (b) Um, J. M.; Houk, K. N.; Phillips, A. J. *Org. Lett.* **2008**, *10*, 3769. (c) See also: Nicolaou, K. C.; Frederick, M. O.; Burtoloso, A. C. B.; Denton, R. M.; Rivas, F.; Cole, K. P.; Aversa, R. J.; Gibe, R.; Umezawa, T.; Suzuki, T. J. *Am. Chem. Soc.* **2008**, *130*, 7466.

(6) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687.

(7) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099.

(8) This furan is also readily prepared by benzylation of (hydroxymethyl) furfural. See: Cottier, L.; Descotes, G.; Eymard, L.; Rapp, K. *Synthesis* **1995**, 303.

(9) Kobayashi, Y.; Kusakabe, M.; Kitano, Y.; Sato, F. *J. Org. Chem.* **1988**, *53*, 1586.

(10) For the CaH_2/SiO_2 modified conditions employed here see: (a) Yang, Z. C.; Zhou, W. S. *Tetrahedron Lett.* **1995**, *36*, 5617. (b) Zhou, W. S.; Lu, Z.; Wang, Z. *Tetrahedron Lett.* **1991**, *32*, 1467. (c) Wang, Z.; Zhou, W.; Lin, G. *Tetrahedron Lett.* **1985**, *26*, 6221.

(11) Garcia-Fandino, R.; Aldegunde, M. J.; Codesido, E. M.; Castedo, L.; Granja, J. R. *J. Org. Chem.* **2005**, *70*, 8281.

(12) Brimble, M. A.; Bryant, C. J. *Org. Biomol. Chem.* **2007**, *5*, 2858.

(13) Marshall, J. A.; Schaaf, G.; Nolting, A. *Org. Lett.* **2005**, *7*, 5331.

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(15) Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193.

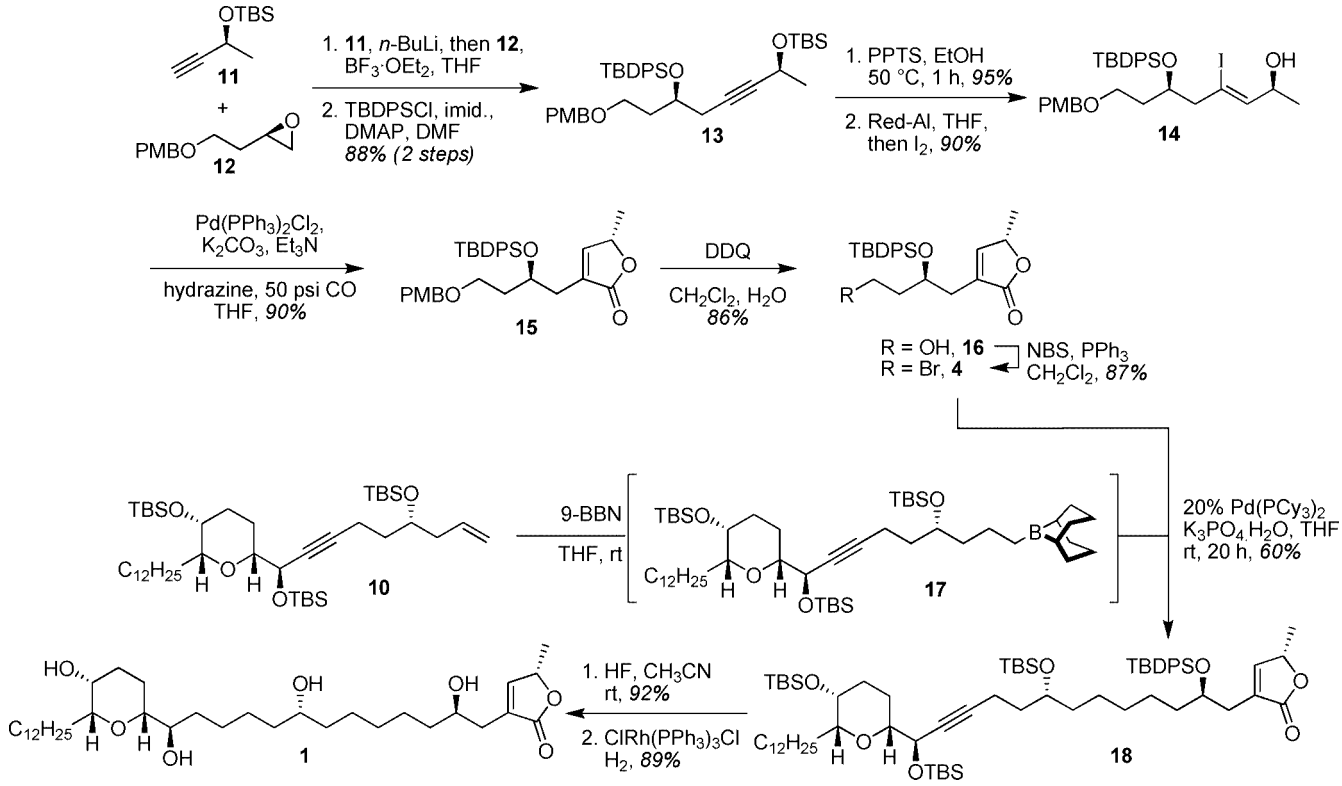
(16) Hoye, T. R.; Humpal, P. E.; Jimenez, J. I.; Mayer, M. J.; Tan, L.; Ye, Z. *Tetrahedron Lett.* **1994**, *35*, 7517.

(17) Ponpipom, M. M.; Hanessian, S. *Carbohydr. Res.* **1971**, *18*, 342.

(18) For other examples of the use of this reaction in total synthesis see: (a) Das, S.; Abraham, S.; Sinha, S. C. *Org. Lett.* **2007**, *9*, 2273. (b) Keaton, K. A.; Phillips, A. J. *Org. Lett.* **2007**, *9*, 2717.

(19) Brown, C. A.; Coleman, R. A. *J. Org. Chem.* **1979**, *44*, 2328.

Scheme 2. Synthesis of the Butenolide Domain and Completion of the Synthesis



physical characteristics of synthetic material (^{1}H and ^{13}C NMR, HRMS) matched those reported by McLaughlin.[2] Optical rotation data was in accord with that reported by Rein and Takahashi.[20,21]

(20) As described and discussed by Rein and Takahashi in references 4a, 4b, and 4c, there is a discrepancy between the optical rotations for synthetic and natural pyranicin: natural pyranicin $[\alpha]_D$ −9.7 (*c* 0.008, $CHCl_3$); synthetic pyranicin (Takahashi): $[\alpha]_D$ +19.5 (*c* 0.55, $CHCl_3$); synthetic pyranicin (Rein): $[\alpha]_D$ +21.1 (*c* 0.24, $CHCl_3$). Our material had optical rotation of $[\alpha]_D$ +24.8 (*c* 0.20, $CHCl_3$).

(21) The possibility of the discrepancy in optical rotations being due to aggregation effects seemed unlikely as the rotation in chloroform for our synthetic material does not vary significantly with changing concentration:

concentration (*c*)	α	$[\alpha]_D$
0.200	+0.049	+24.8
0.125	+0.022	+17.8
0.063	+0.016	+26.3
0.031	+0.007	+22.7
0.015	+0.003	+21.3

In conclusion, we have described a concise (13 steps longest linear sequence) and efficient (10% overall yield) synthesis of pyranicin. Beyond these metrics, the synthesis is modular and will prove amenable to the synthesis of a variety of analogues. This work also highlights the utility of the Achmatowicz oxidation−Kishi reduction sequence for the assembly of pyrans and the strategic potential of alkyl−alkyl Suzuki couplings in a complex setting.

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Supporting Information Available: Procedures for the synthesis of new compounds, along with characterization data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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