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Methods for Pyranoannulation: An Approach to a New Class of Polyethers

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Summary:

Several methods have been developed for fusing a pyran ring to an existing pyran ring structure such that the ring oxygens assume a vicinal (ethylene glycol) relationship. The tricyclic structure **13**, a previously unknown substance, was prepared through a combination of these methods.

Registry No. **1**, 92056-26-3; **2**, 97102-43-7; **3**, 97102-44-8; **4**, 97102-45-9; 4-one, 97102-61-9; **5**, 60378-39-4; **5** (Grignard adduct), 97102-72-2; **6a**, 97102-46-0; **6b**, 97102-47-1; **7**, 97102-48-2; **8** (isomer 1), 97134-64-0; **8** (isomer 2), 97169-11-4; **9** (isomer 1), 2396-74-9; **9** (isomer 2), 3021-94-1; **10**, 97102-49-3; **10-ol**, 97102-64-2; **10-ol** (THP), 97102-66-4; **10-diol** (THP), 97102-68-6; **10-alol** (THP), 97102-70-0; **11**, 97102-50-6; **11-ol**, 97102-65-3; **11-ol** (THP), 97102-67-5; **11-diol** (THP), 97102-69-7; **11-al** (THP), 97102-71-1; **12**, 97102-51-7; **12-ol**, 97102-73-3; **13** (isomer 1), 97102-52-8; **13** (isomer 2), 97134-65-1; **14**, 82921-66-2; **14** (allyl deriv.), 82921-70-8; **15**, 97102-53-9; **15-ol**, 97134-66-2; **16**, 97102-54-0; **17** (isomer 1), 97112-50-0; **17** (isomer 2), 97102-55-1; **18**, 92619-83-5; **18** (benzyl ether), 97134-67-3; **19**, 97102-56-2; **20**, 97102-57-3; i, 97102-58-4; ii, 97112-51-1; iii, 97102-59-5; 6-(phenylthio)octahydro-2*H*-pyrano[3,2-*b*]oxepin, 97102-60-8; dihydropyran, 110-87-2; 3-iodopropionaldehyde ethylene acetal, 83665-55-8; *cis*-2,3-di-hydroxytetrahydropyran, 97102-62-0; *trans*-2,3-dihydroxytetra-hydropyran, 97102-63-1; 3-bromopropionaldehyde ethylene acetal, 18742-02-4; allyl bromide, 106-95-6; allyltrimethylsilane, 762-72-1.

Supplementary Material Available: Tables of the atomic positional and thermal parameters, bond distances, and bond angles for **13** and the physical and spectral data for **4**, **5**, **6a**, **8**, **13**, **17**, and **20** (11 pages). Ordering information is given on any current masthead page.

(a) *t*-BuLi, TMEDA; ; HMPA; (b) BH₃·THF/

H₂O₂, NaOH (67% overall); (c) C₆H₅SH, TsOH, CH₂Cl₂, room temperature (96%).

(prepared as in ref 14e)

(a) 9-BBN/H₂O₂, NaOH; (b) Swern oxidation (82% overall); (c) NH₂OH·HCl, py; NaOCl, Et₃N, CH₂Cl₂ (89%); (d) Raney Ni, *i*-PrOH, H₂O; (e) MCPBA, CH₂Cl₂ (88% overall from ii).

Sir:

In examining the unique structure presented by the marine natural product brevetoxin B,¹ we were struck by the fact that one could perhaps assemble such a compound in the laboratory through a scheme involving repetitive pyrano (or larger oxygen ring) annulation reactions. Accordingly, we have sought to develop methods for effecting the annulation of a pyran ring to an existing pyran ring structure. We disclose herein methods for accomplishing this which are based on (a) the ring metalation/alkylation of a dihydropyran, (b) Grignard addition to a δ -lactone, and (c) the anomeric allylation of a carbohydrate or di-acetoxypyran.

The type a process is illustrated by the following set of transformations starting from dihydropyran. Firstly, this heterocycle was metalated by using *t*-BuLi in combination with TMEDA,² and the resulting anion was trapped with both allyl bromide and 3-iodopropionaldehyde ethylene acetal³ to deliver the α -alkylated dihydropyrans **1** and **2**. From these intermediates, the pyranoannulation could be completed in several different ways. Both **1** and **2** were hydroborated⁴ and oxidized to the trans-disubstituted pyrans **3** and **4** (Scheme I). Because of the syn specificity of the hydroboration process, the newly introduced hydroxyl group of the pyran ring emerges trans to the carbon chain. From **3**, silver carbonate on Celite⁵ affords the pyrano- δ -lactone **5** in good yield. With intermediate **4**, simple acid treatment in the presence of thiophenol or water leads to pyranopyrans **6a** and **6b**, respectively. Because of the anomeric effect,⁶ the hydroxyl group and the phenylthio substituent assume predominantly an axial position in these pyranopyrans as revealed by the vicinal ¹H NMR coupling constant data.

A cis-fused pyranopyran ring system can be prepared from **4** as well. The equatorial hydroxyl group is oxidized to ketone, and then an L-Selectride⁷ reduction is carried out to deliver primarily the axial alcohol (¹H NMR ratio $\approx$ 12:1). Treatment of this new hydroxypyran **7** with thiophenol under acidic conditions (Scheme II) results in the formation of the pyranopyran **8** (anomeric mixture, ratio 4.5:1). For the major isomer, the stereochemistry of the sulfur-bearing center relative to that of the ring fusion is assumed to be as drawn based on thermodynamic considerations.

As an alternative to the metalation reaction, we have also studied the hydroxylation of dihydropyran, followed by acetate formation and "anomeric allylation". As shown, the vicinal diol of dihydropyran can be procured as a 60:40 mixture by employing either osmium tetroxide or *m*-chloroperbenzoic acid as the oxidizing reagent.⁸ After acetylation, treatment of the resulting diacetates with allyltrimethylsilane and BF₃•OEt₂ in acetonitrile provides a 2.4:1 mixture of the acetoxypyran **10** and **11**. The identity of these materials was confirmed by converting them to the corresponding phenylthio-substituted pyranopyrans as detailed in Scheme III.

To append a third ring to **6b** (X = OH), the lactol was oxidized to lactone, and this intermediate was reacted with the Grignard reagent⁹ prepared from 3-bromopropionaldehyde ethylene acetal (method b). The new lactol was dehydrated through its mesylate,¹⁰ and the resulting dihydropyran **12** was hydroborated and oxidized to afford an alcohol as nearly a single stereoisomer (Scheme IV). On treatment with thiophenol and

acid, the tricyclic material **13** was obtained (anomeric mixture, ratio 6:1). To rationalize the outcome of the hydroboration event, we assume that the developing 1,3-diaxial-like interaction between boron and the ring fusion hydrogen retards attack on the α -face (Scheme V).¹¹ β -Face hydroboration thus leads to the emergence of the equatorial alcohol, and thus to the trans-fused, all-chair conformation of **13**, a stereo-chemical feature of some relevance to the procurement of brevetoxin B through a total synthesis effort. The stereochemistry of **13** has been confirmed independently by a single-crystal X-ray analysis.

Since carbohydrates are imbued with readily manipulatable functionality,¹² we have also developed a method for their conversion to pyranopyrans. Using the *I*-lyxose derivative **14**¹³ (Scheme VI) as the test substrate, this compound was first converted to its *C*-allyl derivative through use of our previously described method for the anomeric allylation of carbohydrates.¹⁴ After reprotection of the C-4 alcohol as its benzyl ether, the double bond of **15** was hydrated, the intermediate alcohol was oxidized to aldehyde, and **16** was stirred with thiophenol and acid to furnish the desired trans-fused pyranopyran **17** (anomeric mixture, ratio 4.5:1).

Since the allylsilane reaction can be made to proceed in a fashion which appears to take on the character of an S_N2 reaction, access to a cis-fused pyranopyran or pyra-no- δ -lactone is also possible. Accordingly, the C-4 hydroxy group of **18**, available from *I*-lyxose as described previously,¹⁴ was benzylated and the allyl group hydrated in the standard way. Silica gel chromatography served to remove the cyclohexylidene ketal and subsequent silver carbonate treatment gave rise to the cis-fused pyrano- δ -lactone **20** (Scheme VII).

In summary, the methods disclosed herein should facilitate the synthetic chemist's access to the pyranopyran class of natural products, a now small yet remarkably diverse and evergrowing structure class. Further applications of this methodology to the construction of rigid "ball-shaped" polyethers is in progress.^{15,16}

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- (16). We have also assembled the pyran system below containing a fused seven-membered ring using the type a methodology.
- (17). The INOC reaction can also serve as a device for the construction of cis-fused pyranolactones as illustrated below.

Scheme 1^a

^a (a) BH_3 ; THF/ H_2O_2 OH^- ; (b) Ag_2CO_3 -Celite, C_6H_6 ($\uparrow\downarrow$) (89%); (c) $\text{C}_6\text{H}_5\text{SH}$, TsOH, CH_2Cl_2 or H_3O^+ (97%).

Scheme II^a

^a (a) $\text{CrO}_3 \cdot \text{py}_2$, Ac_2O (82%); (b) L-Selectride, THF, -78°C (88%); (c) $\text{C}_6\text{H}_5\text{SH}$, TsOH , CH_2Cl_2 (96%).

Scheme III^a

^a(a) 15% NaOH; (b) DHP, PPTS, CH_2Cl_2 (92% overall); (c) BH_3 -THF/ H_2O_2 , OH^- (71%); (d) $(\text{COCl})_2$, Me_2SO , Et_3N , -78°C (82%); (e) $\text{C}_6\text{H}_5\text{SH}$, TsOH , CH_2Cl_2 (70%).

Scheme IV^a^a (a)

, THF, -20°C (71%); (b) MsCl , Et_3N ($\uparrow\downarrow$); (c) $\text{BH}_3\cdot\text{THF}/\text{H}_2\text{O}_2$ OH^- (61% overall); (d) $\text{C}_6\text{H}_5\text{SH}$, TsOH (93%).

Scheme V.

Scheme VI^a

^a (a) $\text{CH}_2=\text{CHCH}_2\text{SiMe}_3$, $\text{BF}_3 \cdot \text{OEt}_2$, CH_3CN (88%); (b) NaH , PhCH_2Br , $n\text{-Bu}_4\text{N}^+\text{I}^-$, THF (91%); (c) $\text{BH}_3 \cdot \text{THF}/\text{H}_2\text{O}_2$ OH^- (79%); (d) $(\text{COCl})_2$, Me_2SO , Et_3N , CH_2Cl_2 (87%); (e) $\text{C}_6\text{H}_5\text{SH}$, TsOH , CH_2Cl_2 (93%).

Scheme VII^a

^a (a) NaH, PhCH₂Br, *n* Bu₄N⁺I⁻, THF; BH₂; THF/H₂O₂, OH⁻ (83%); (b) chromatography on silica gel; (c) Ag₂CO₃-Celite, C₆H₆ (↑↓) (69% overall).