Communications

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

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.

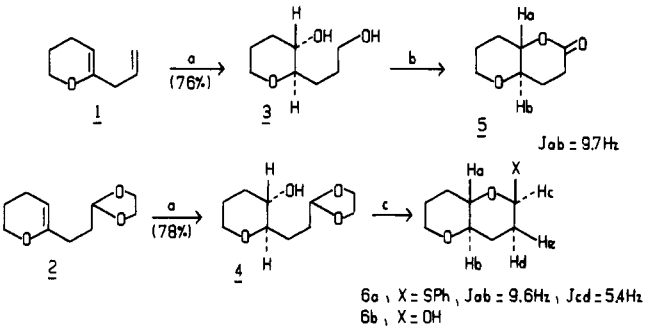
Sir: In examining the unique structure presented by the marine natural product brevetoxin B,[1] we were struck by the fact that one could perhaps assemble such a compound in the laboratory through a scheme involving repetitive pyrano (or larger oxygen ring) annulation reactions. Accordingly, we have 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 diacetoxypyran.

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 acetal[3] 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 hydroborated[4] 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 Celite[5] 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 ^{1}H 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-Selectride[7] reduction is carried out to deliver primarily the axial alcohol (^{1}H NMR ratio ≃ 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.

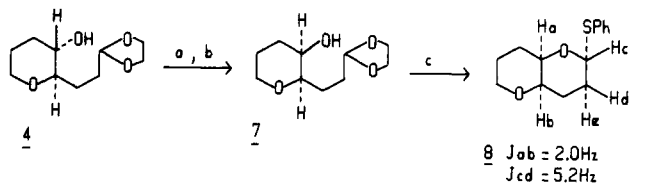
As an alternative to the metalation reaction, we have also studied the hydroxylation of dihydropyran, followed by acetate formation and "anomeric allylation". As shown, the vicinal diol of dihydropyran can be procured as a 60:40 mixture by employing either osmium tetraoxide or *m*-chloroperbenzoic acid as the oxidizing reagent.[8] After acetylation, treatment of the resulting diacetates with allyltrimethylsilane and BF_3·OEt_2 in acetonitrile provides

Scheme I[a]



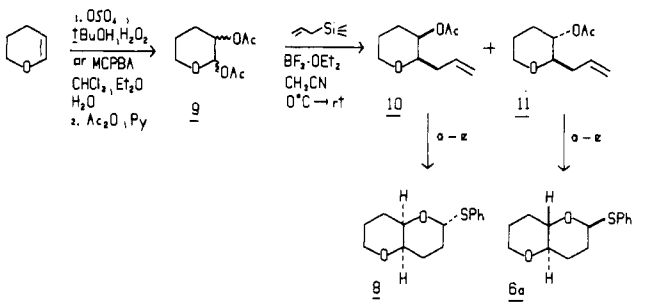
[a] (a) BH_3·THF/H_2O_2, OH^-; (b) Ag_2CO_3-Celite, C_6H_6 (↑↓) (89%); (c) C_6H_5SH, TsOH, CH_2Cl_2 or H_3O^+ (97%).

Scheme II[a]



[a] (a) CrO_3·py_2, Ac_2O (82%); (b) L-Selectride, THF, −78 °C (88%); (c) C_6H_5SH, 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) $(COCl)_2$, Me_2SO, Et_3N, −78 °C (82%); (e) C_6H_5SH, TsOH, CH_2Cl_2 (70%).

(1) Lin, Y.-Y.; Risk, M.; Ray, S. M.; Engen, D. V.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773.
(2) Boeckman, R. K.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997. Oakes, F. T.; Sebastian, J. F. *J. Org. Chem.* **1980**, *45*, 4959. Cohen, T.; Bhupathy, M. *Tetrahedron Lett.* **1983**, *24*, 4163. We have found *t*-BuLi in combination with TMEDA to be far superior to *t*-BuLi alone for these metalation/alkylation reactions.
(3) This iodide was prepared from the known bromide (ref 8) by sodium iodide/acetone treatment.
(4) Zweifel, G.; Plamondon, J. *J. Org. Chem.* **1970**, *35*, 898. Gore, J.; Guigues, F. *Bull. Soc. Chim. Fr.* **1970**, 3521.
(5) Fetizon, M.; Golfier, M.; Louis, J.-M. *Tetrahedron* **1975**, *31*, 171.
(6) Kirby, A. J. "The Anomeric Effect and Related Stereoelectronic Effects at Oxygen"; Springer-Verlag: Berlin, 1983.
(7) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.
(8) Hurd, C. D.; Kelso, C. D. *J. Am. Chem. Soc.* **1948**, *70*, 1484. Sweet, F.; Brown, R. K. *Can J. Chem.* **1967**, *45*, 1007.

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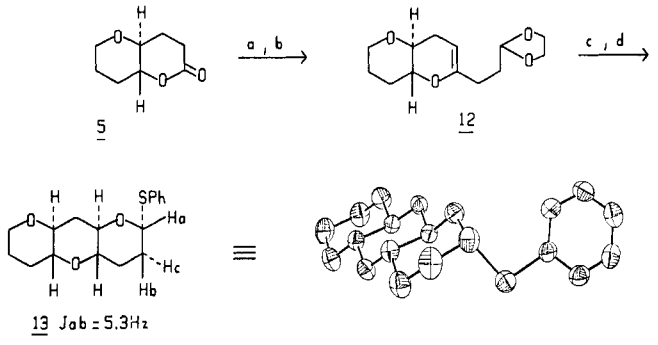
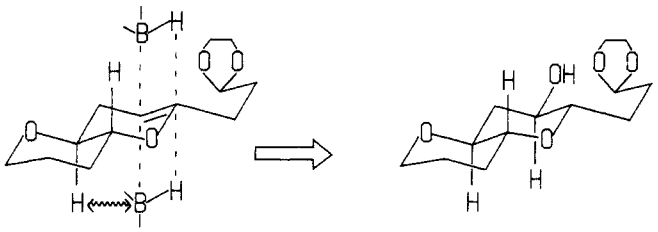
Scheme IV[a]



[a] (a) $BrMgCH_2CH_2CH$(O)(O), THF, −20 °C (71%); (b) MsCl, Et_3N (↑↓); (c) BH_3·THF/H_2O_2, OH^- (61% overall); (d) C_6H_5SH, TsOH (93%).

Scheme V

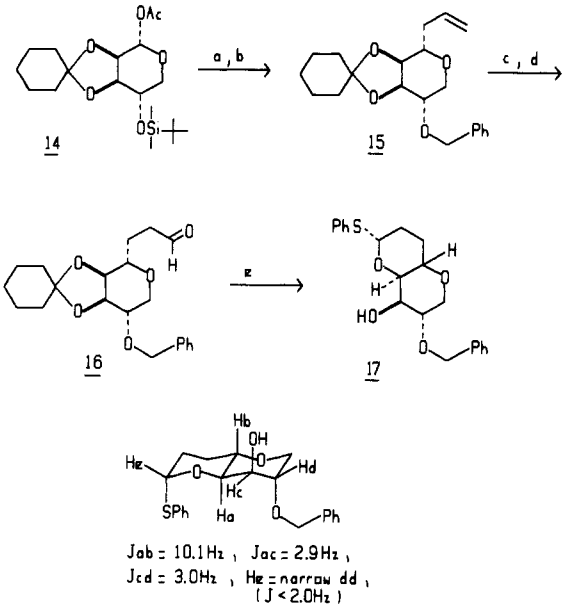


a 2.4:1 mixture of the acetoxypyrans **10** and **11**. The identity of these materials was confirmed by converting them to the corresponding phenylthio-substituted pyranopyrans as detailed in Scheme III.

To append a third ring to **6b** (X = OH), the lactol was oxidized to lactone, and this intermediate was reacted with the Grignard reagent[9] 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 stereochemical 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.

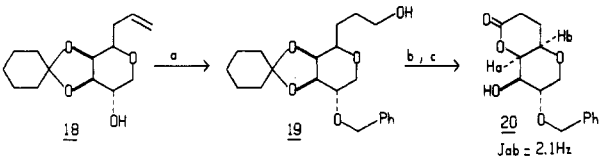
Since carbohydrates are imbued with readily manipulatable functionality,[12] we have also developed a method for their conversion to pyranopyrans. Using the *l*-lyxose derivative **14**[13] (Scheme VI) as the test substrate, this compound was first converted to its *C*-allyl derivative through use of our previously described method for the

Scheme VI[a]



[a] (a) CH_2=$CHCH_2SiMe_3$, BF_3·OEt_2, CH_3CN (88%); (b) NaH, $PhCH_2Br$, n-$Bu_4N^+I^-$, THF (91%); (c) BH_3·THF/H_2O_2, OH^- (79%); (d) $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2 (87%); (e) C_6H_5SH, TsOH, CH_2Cl_2 (93%).

Scheme VII[a]



[a] (a) NaH, $PhCH_2Br$, n-$Bu_4N^+I^-$, THF; BH_3·THF/H_2O_2, OH^- (83%); (b) chromatography on silica gel; (c) Ag_2CO_3-Celite, C_6H_6 (↑↓) (69% overall).

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 pyrano-δ-lactone is also possible. Accordingly, the C-4 hydroxy group of **18**, available from *l*-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

(9) Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122. While **6b** could be dehydrated to the fused dihydropyran, attempts to metalate this material have not been successful.

(10) Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. L. *J. Am. Chem. Soc.* **1980**, *102*, 6577.

(11) Pasto, D. J.; Klein, F. M. *J. Org. Chem.* **1968**, *33*, 1468.

(12) Hanessian, S. "Total Synthesis of Natural Products: The 'Chiron' Approach"; Pergamon Press: Oxford, 1983.

(13) Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1984**, *25*, 2085.

(14) The use of allylsilanes in the anomeric functionalization of carbohydrates has been studied by a number of investigators. See: (a) Kozikowski, A. P.; Sorgi, K. L.; Wang, B. C.; Xu, Z.-b. *Tetrahedron Lett.* **1983**, *24*, 1563. (b) Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383. (c) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. (d) Williams, R. M.; Stewart, A. O. *Tetrahedron Lett.* **1983**, *24*, 2715. (e) Rawe, R. D.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1981**, 1180. (f) Cupps, T. L.; Wise, D. S.; Townsend, L. B. *J. Org. Chem.* **1982**, *47*, 5115. (g) Danishefsky, S.; Kerwin, J. F. *Ibid.* **1982**, *47*, 3803. (h) Sakurai, H.; Sasaki, K.; Hayashi, J.; Hosomi, A. *J. Org. Chem.* **1984**, *49*, 2808.

diverse and evergrowing structure class. Further applications of this methodology to the construction of rigid "ball-shaped" polyethers is in progress.[15,16]

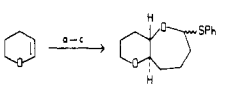
Acknowledgment. We are indebted to the National Institutes of Health for their support of these investigations. We thank Dr. J. Abola and Mr. J. Mandel for the X-ray structure determination which was carried out on the NIH supported (Grant 1 S1O RR02381-01) X-ray facility of the University of Pittsburgh Chemistry Department.

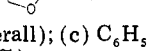
Registry No. **1**, 92056-26-3; **2**, 97102-43-7; **3**, 97102-44-8; **4**, 97102-45-9; **4**-one, 97102-61-9; **5**, 60378-39-4; **5** (Grignard adduct), 97102-72-2; **6a**, 97102-46-0; **6b**, 97102-47-1; **7**, 97102-48-2; **8** (isomer 1), 97134-64-0; **8** (isomer 2), 97169-11-4; **9** (isomer 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-dihydroxytetrahydropyran, 97102-62-0; *trans*-2,3-dihydroxytetrahydropyran, 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.

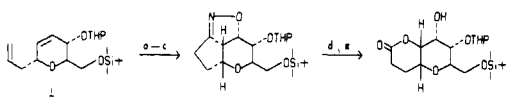
(15) For some other recent approaches to pyranopyrans, see: Nicoll-Griffith, D.; Weiler, L. *J. Chem. Soc., Chem. Commun.* **1984**, *659*. Martin, O. R.; Szarek, W. A. *Carbohydr. Res.* **1984**, *130*, 195. Ichikawa, Y.; Isobe, M.; Goto, T. *Tetrahedron Lett.* **1984**, *25*, 5049.

(16) We have also assembled the pyran system below containing a fused seven-membered ring using the type a methodology.



(a) *t*-BuLi, TMEDA;  ; HMPA; (b) BH_3·THF/H_2O_2, NaOH (67% overall); (c) C_6H_5SH, TsOH, CH_2Cl_2, room temperature (96%).

(17) The INOC reaction can also serve as a device for the construction of cis-fused pyranolactones as illustrated below.



(prepared as in ref 14e)

(a) 9-BBN/H_2O_2, NaOH; (b) Swern oxidation (82% overall); (c) NH_2OH·HCl, py; NaOCl, Et_3N, CH_2Cl_2 (89%); (d) Raney Ni, *i*-PrOH, H_2O; (e) MCPBA, CH_2Cl_2 (88% overall from ii).

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Stereoselection in the Michael Addition Reaction. 2. Stereochemistry of the Kinetic Michael Reaction of Amide Enolates with Enones[1]

Summary: An extensive study of structure–stereoselectivity relationships in the kinetic Michael addition of preformed lithium enolates to enones has uncovered some reactions of sufficiently high diastereoselectivity as to be synthetically attractive and has allowed the formulation of a coherent transition state hypothesis that incorporates the lithium enolate cluster as a dominant stereocontrol element.

Sir: The conjugate addition of enolates to unsaturated carbonyl compounds (Michael processes,[17] we one of the most widely used carbon–carbon bond-forming reactions.[3] However, in spite of its scope, the Michael reaction is not without limitations, which revolve mainly about the problems of regioselective enolate generation, the tendency for many enones to undergo polymerization under strongly basic conditions, and the availability of an attractive alternative reaction path in many cases (1,2 addition).[4,5] A number of methods for achieving stoichiometric enolate Michael additions have been devised.[6-16]

Because of our interest in the stereochemistry of carbon–carbon bond-forming processes,[17] we have initiated an investigation of the diastereoselectivity of the Michael addition reaction. In a previous communication[1] we reported results of a study of the acid-catalyzed process (Mukaiyama–Michael reaction); in this communication, we report preliminary results of a study of the stereochemistry of addition of amide enolates to enones. The results to date have revealed some kinetic Michael additions of sufficiently high diastereoselectivity as to be synthetically attractive. More importantly, the structure–stereoselectivity trends that have emerged from the study have allowed us to formulate for this important reaction a coherent transition state hypothesis, involving the lithium enolate cluster as a dominant stereocontrol element.

(1) Part 30 in the series "Acyclic Stereoselection". For part 29, see: Heathcock, C. H.; Norman, M. H.; Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797.

(2) (a) Michael, A. *J. Prakt. Chem.* **1887**, *35*, 349. (b) Michael, A.; Schulthess, O. *Ibid.* **1892**, *45*, 55. (c) Michael, A. *Ibid.* **1894**, *49*, 20. (d) Michael, A. *Am. Chem. J.* **1887**, *9*, 112. (e) Michael, A. *Chem. Ber.* **1894**, *27*, 2126. (f) Michael, A. *Ibid.* **1900**, *33*, 3731.

(3) Bergman, E. D.; Ginsburg, D.; Pappo, R. *Org. React. (N.Y.)* **1959**, *10*, 179.

(4) House, H. O. In "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin, Inc.: Menlo Park, 1972; 595–615.

(5) (a) House, H. O.; Lusch, M. J. *J. Org. Chem.* **1977**, *42*, 183. (b) See also: Bertrand, J.; Cabrol, N.; Gorrichon-Guigon, L.; Maroni-Barnard, Y. *Tetrahedron Lett.* **1973**, 4683.

(6) (a) Stork, G. A.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 6152. (b) Stork, G. A.; Ganem, B. *Ibid.* **1974**, *96*, 6181.

(7) (a) Boeckman, R. K. *J. Am. Chem. Soc.* **1973**, *95*, 6867. (b) Boeckman, R. K. *Ibid.* **1974**, *96*, 6179.

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(13) Mulzer, J.; Hartz, G.; Kühl, U.; Brüntrup, G. *Tetrahedron Lett.* **1978**, 2949.

(14) Viteva, L. Z.; Stefanovsky, Y. N. *Monatsh. Chem.* **1982**, *113*, 181 and previous papers in this series.

(15) (a) Bertrand, J.; Gorrichon, L.; Maroni, P. *Tetrahedron* **1984**, *40*, 4127. (b) Bertrand, J.; Gorrichon, L.; Maroni, P., Meyer, R. *Bull. Soc. Chim. (Fr.)*, submitted for publication.

(16) Häner, R.; Laube, T.; Seebach, D. *Chimia* **1984**, *38*, 255.

(17) Heathcock, C. H. *Science (Washington, D.C.)* **1981**, *214*, 395.

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