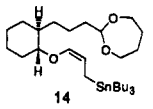
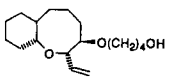
only 8% yield. The low yield was presumably due to the flexibility of the carbon chain.[7] Incorporation of a cyclohexane ring into the chain enhanced the chemical yield. Thus, **14** gave **15**, as a single isomer, in 36% yield. It is noteworthy that the relative stereochemistry at the α,α' and β carbons of **15** corresponds to that of brevetoxin and related compounds.



14



15

The most attractive aspect of the procedure is its potential for iterative ring construction (Scheme II). The triflate of optically active **16** (100% ee)[2b] was converted to **17** in 64% yield by copper-mediated coupling to a Grignard reagent.[8] Allylation of **17** gave **18** in 93% yield with 100% ee. Compound **18** was converted to the allyltin **19** in 80% yield. The cyclization of **19** gave a 11:1 mixture of α,β-*trans*-**20** and α,β-*cis*-**20** in 30% yield. Starting with 6-8 bicyclic **20** it should be possible to construct a 6-8-6 tricyclic system.[9] We are actively pursuing such a possibility.

Supplementary Material Available: Synthetic methods and spectra for **1–20** (18 pages). Ordering information is given on any current masthead page.

(7) Incorporation of a cis-double bond or a carbocycle into the carbon chain is required for an efficient synthesis of medium-sized ring systems.[2a]

(8) Kotsuki, H.; Kadota, I.; Ochi, M. *Tetrahedron Lett.* **1989**, *30*, 1281.

(9) Selective hydroboration of the exocyclic carbon-carbon double bond with 9-BBN, followed by oxidation, should give the corresponding hydroxyethyl derivative. Oxidation of the alcohol to an aldehyde and subsequent conversion to an acetal, followed by removal of the hydroxypropyl group, should produce the hydroxy acetal. Then, allylation, stannylation, and cyclization should give the 6-8-6 system.

(10) With certain Lewis acids, the cyclization gave high yields, and the result will be reported shortly.

Armed/Disarmed Effects[1] in Glycosyl Donors: Rationalization and Sidetracking[2]

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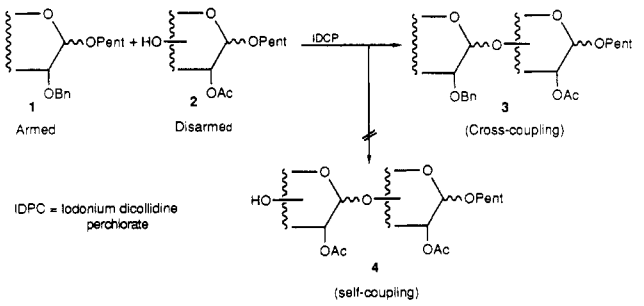
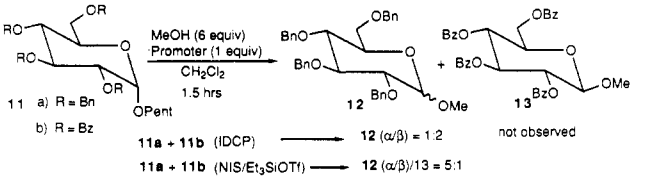
Summary: A general rationalization for armed/disarmed effects, first recognized in *n*-pentenyl glycosides but recently extended to a variety of other glycosyl donors, is postulated. Reaction of a glycosyl donor with an appropriate electrophile gives a positively charged intermediate which is less favorable when there is an adjacent electron-withdrawing group (for example OCOR, as in a disarmed donor) than when there is an adjacent alkoxy group (as in the armed counterpart). The latter therefore reacts faster and if, in the reaction medium, there is a disarmed species carrying a free hydroxyl group, a pathway based on Le Chatelier's principle can be envisaged that leads to products of cross-coupling with (virtually) none of the self-coupled analogue. In *n*-pentenyl glycosides activation of the anomeric center involves two preequilibrium steps, the second of which can be sidetracked to afford a vicinal dibromo derivative. The ability to prepare such derivatives in near quantitative yields allows the normal armed/disarmed protocol for saccharide assembly to be reversed.

In the course of investigating the chemistry of *n*-pentenyl glycosides (NPGs) we noted that the rate of oxidative hydrolysis was substantially affected by the nature of the C2 protecting group,[3] and this observation subsequentially led us to demonstrate that glycosyl donors could be "armed" or "disarmed" by a C2 ether or C2 ester group, **1** and **2**, respectively.[4] This observation was developed into a procedure for selective coupling to give **3** (Scheme I), and our report[4] was followed by accounts of similar effects with other glycosyl donors,[5-7] thereby suggesting that the armed/disarmed protocol of oligosaccharide assembly could have general applicability. We have therefore sought to obtain a fuller understanding of the phenomenon, and in this paper we disclose some recent results which show, inter alia, how the effect can be sidetracked in the case of NPGs.

Scheme I



Scheme II



(1) The terms "armed" and "disarmed" are used[3] instead of activated and deactivated since a disarmed donor can, in fact, be readily activated.[11]

(2) This work was supported grants from the National Science Foundation (CHE 8920033), the National Institutes of Health (GM 41071), and Glycomed, Hayward, CA.

(3) Mootoo, D. R.; Date, V.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 2662.

(4) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583.

(5) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656.

(6) Mereyala, H. N.; Reddy, G. V. *17th IUPAC International Symposium on the Chemistry of Natural Products*, New Delhi, India, February 4–9, 1990.

(7) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331. Veeneman, G. H.; Van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 275.

0022-3263/90/1955-6068$02.50/0

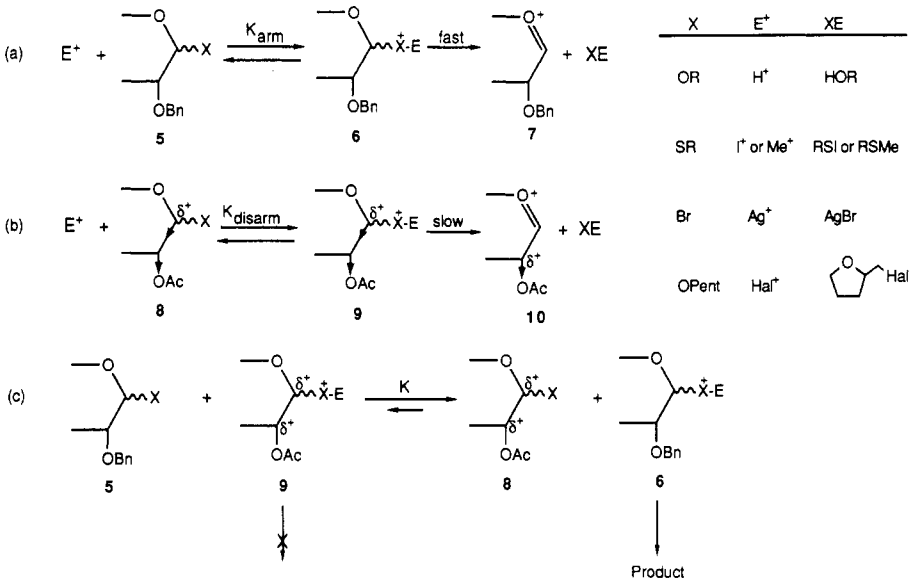
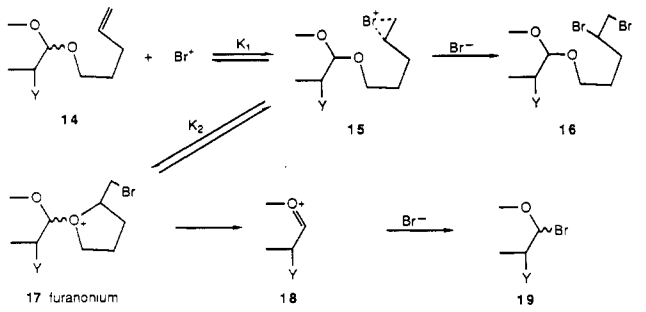


Figure 1. A rationale for armed/disarmed effects in glycosyl donors.

Scheme III



The fact that glycosides with a C2 electron-withdrawing group (e.g., OCOR, OSO_2R, halogen) are sluggish toward acid hydrolysis[8] was the launching point for the rationalization presented in Figure 1. Thus activation of any glycosyl donor, **5** or **8**, with the appropriate electrophile leads to the activated complex **6** or **9**.[9] The latter is disfavored because of the contiguous full and partial positive charges, a situation which will worsen with progress to the oxocarbenium **10**. Since intermediate **6** is not electrostatically destabilized, progress to **7** occurs more readily.

However if the approximately 6-fold difference in hydrolysis rates of the C2 benzyloxy and C2 acetoxy NPGs[3] in Figure 1, parts a and b, were the controlling factor, the product of self-coupling (**4**, Scheme I) should have been present in at least 10%. In fact, in our test case[4] self-coupling products such as **4** have not been detected in the mass spectrum of the crude reaction product. Its absence can be rationalized by postulating a third equilibrium K, in Figure 1c, which, in effect, transfers the electrophile from the bad to the good intermediate, thereby pumping the reaction along the favorable pathway toward **7** in accordance with Le Chatelier's principle.[10]

We have sought to obtain evidence in support of the above rationalization. The crucial requirement for cross-coupling emerges as the equilibrium represented in Figure 1c; however, its effectiveness depends on the position of the equilibria in Figure 1, parts a and b, and these should be altered by changing the electrophile.

This proposition was tested by the acetal exchange reactions shown in Scheme II in which 1 equiv of each of the armed and disarmed substrates, **11a** and **11b**, were made to compete for methanol in the presence of 1 equiv of the promoter. With iodonium dicollidine perchlorate (IDCP), **11a** reacted completely to give **12** (α/β) while **11b** was recovered unchanged. However, when the promoter was changed to NIS/Et_3SiOTf,[11] **11a** and **11b** both reacted, giving **12** and **13** in 5 to 1 ratio.

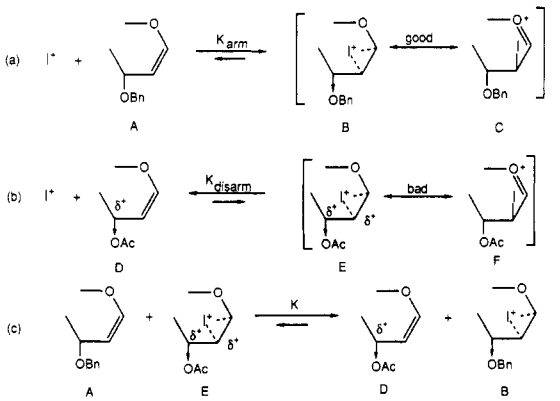
The ability to activate[1] disarmed substrates by changing the electrophile[11] can undoubtedly be extended to other glycosyl donors in view of the rationalization shown in Figure 1. However, NPGs are distinctive in that K_{arm} (or K_{disarm}) is a composite of *two* preequilibrium constants K_1 and K_2 as shown in Scheme III.

Our initial rationalization[4] for the selective coupling of **1** and **2** had focused upon the transformation **15** → **17**.

(8) Feather, M. S.; Harris, J. F. *J. Org. Chem.* **1965**, *30*, 153. BeMiller, J. N.; Doyle, E. R. *Carbohydr. Res.* **1971**, *20*, 23. Cocker, D.; Sinnott, M. L. *J. Chem. Soc., Perkin Trans. 2* **1976**, 618. Fraser-Reid, B.; Boctor, B. *Can. J. Chem.* **1969**, *47*, 393. Buncell, E.; Bradley, P. R. *Can. J. Chem.* **1967**, *45*, 515. Overend, W. G.; Rees, C. W.; Sequeira, J. S. *J. Chem. Soc.* **1962**, 3429.

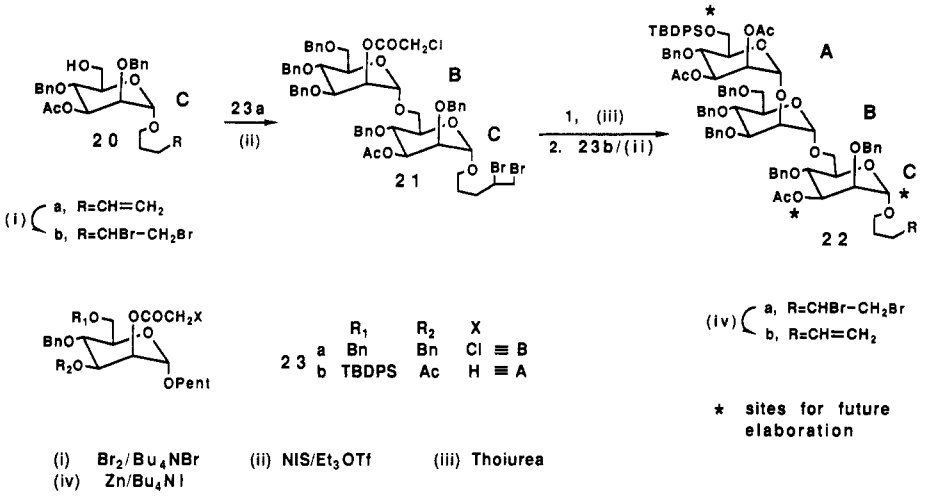
(9) For discussion of a comparable process see: Bochkov, A. F.; Zaikov, G. E. *Chemistry of the O-Glycosidic Bond: Formation and Cleavage*; Pergamon Press: New York, 1979. Igarishi, K. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 243.

(10) The rationalization presented in Figure 1 can be adapted to the observations made by Friesen and Danishefsky on glycal donors[5] as shown below.



(11) Konradsson, P.; Mootoo, D. R.; McDevitt, R. E.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1990**, 270. Konradsson, P.; Udodong, U. E.; Fraser-Reid, B. *Tetrahedron Lett.* **1990**, *31*, 4313.

Scheme IV



Thus we had postulated that the glycosyl oxygen of **15** would be a poorer nucleophile when Y = OAc than when Y = OBn because of the electron-withdrawing effect of the ester. *This is still true.*

However, the bromonium ion **15** has a competitive decomposition pathway available to it, which should become effective when K_2 is slowed down. Indeed in experiments to prepare the glycosyl bromide **19** by treatment of **14** with bromine,[12] the vicinal dibromide **16** was obtained in 10–30% when Y = OAc, but never when Y = OBn.

However, the fate of **15** is affected not only by the electronic nature of Y. Thus, the vicinal dibromide **16** is produced in a bimolecular reaction, and hence an increase in the concentration of bromide ion should enhance its formation. Indeed when the armed substrated **20a** was treated with bromine in the presence of 2 equiv of Et_4NBr (Scheme IV), the dibromide **20b** was obtained in near quantitative yield, without any evidence of the corresponding glycosyl bromide.

This interesting result engendered a new and versatile application of NPGs that, unlike the armed/disarmed coupling, is not readily shared with other glycosyl donors. Thus in the normal case, as exemplified in Scheme I, the alcohol donor carries the C2 ester while the alcohol acceptor carries the C2 ether, **1** and **2**, respectively. The ability to prepare vicinal dibromides gives us the flexibility of reversing this pattern.

This development has facilitated the synthesis of the trimannan **22b**, which is to be elaborated in the A and C rings, at the sites indicated, into a complex oligosaccharide. The 1,2-trans intersaccharide linkages are best ensured by using esters in the A and B units, **23a** and **23b**, respectively. For the C unit, the differentially protected mannoside **20a** was an attractive starting material, but being armed it could not be directly coupled to **23a**. However, conversion first to **20b** followed by coupling with **23a** afforded disaccharide **21**. Reaction with thiourea followed by coupling to **23b** then afforded the trisaccharide **22a**. Reductive debromination now restored the pentenyl residue in the C ring in the target **22b**.

Studies designed to obtain better insight into the armed/disarmed phenomenon in order to better exploit (or sidetrack) it are underway and will be reported in due course.

(12) Konradsson, P.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1989**, 1124. Since this preliminary report on our early work, additional experiments have revealed the formation of vicinal dibromides (**16**) in attempts to prepare glycosyl bromides (**19**) but only when Y = ester.