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Benzylic C-Glycosides via the Ramberg-Backlund Reaction

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Abstract: Easily prepared thioglycosides are oxidized to the sulfone level and then are subjected to Ramberg-Backlund conditions, i.e. a base plus halogenating agent. The products are exo glycals which upon hydrogenation afford C-glycosides

The study of C-glycoside analogs of bioactive natural O- and N-glycosides is a mature field.[1] Since the publication of the two books cited, there have been dozens more articles: a very recent review cites more than 100 newer references.[2] The significance of C-glycosides is that they are essentially inert to degradation because the natural anomeric center has been transformed from a hydrolytically labile O or N acetal link to an ether. The underlying assumption for the use of C-glycoside analogs in glycobiology is that the conformational differences between the O- (or N-) linked natural material and the C-linked analog will be minimal. The corollary to the minimal difference hypothesis is that the recognition and binding of the C-analog will be similar to that of the natural material. In significant papers in 1996 and 1998, Schmidt and Jiminez-Barbaro review the literature and examine these assumptions for the C-lactose / O-lactose case.[3]

Our interest in C-glycosides was focussed on the daunomycin C-analog, first explored by Acton.[4] Our exploration evolved into a search for a method that would link an intact carbohydrate to an existing rather complex aglycone. Wide-ranging model studies made clear to us that an intermolecular method held out little hope for success. Recently, Sinay had overcome problems of low yields in some of his C-glycoside work by tethering the acceptor and donor partners through linkage of spectator hydroxyls. The tether thus rendered a messy intermolecular coupling into a smooth intramolecular one.[5]

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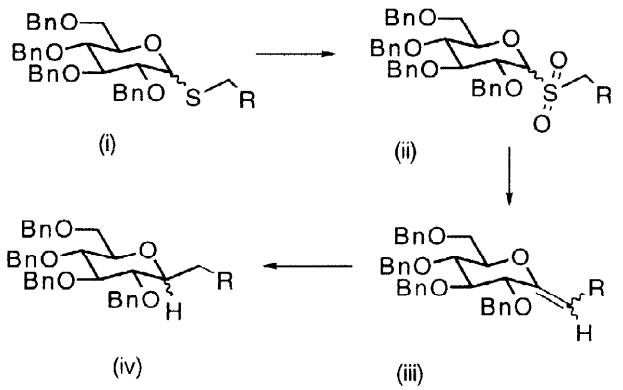
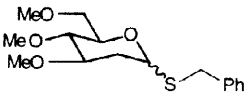
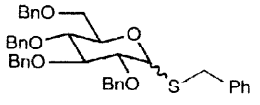
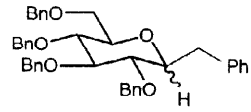
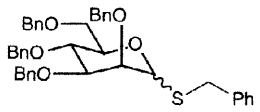
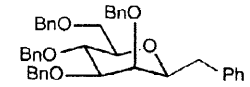
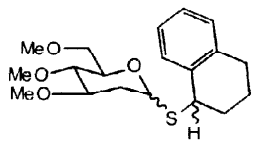
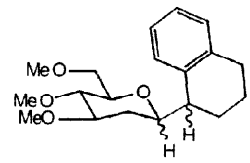
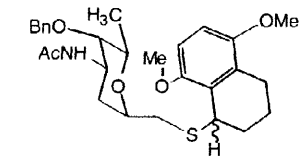
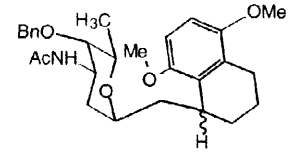
Scheme 1
The Ramberg-Backlund Route to C-glycosides



Since there is an extensive literature on the facile formation of S-glycosides in both the sulfide and sulfone oxidation states, it was our plan to use these functional groups as both tethering agents and C-C bond formers via the Ramberg-Backlund (RB) reaction. A literature survey unearthed no example of this application of the RB reaction, although Hart had use the method to form an acyclic precursor to an aryl C-glycoside.[6] Therefore, a survey of the reaction sequence illustrated in the Scheme : (i) S-glycoside (ii) sulfone glycoside (iii) Ramberg-Backlund (iv) hydrogenation, was undertaken and our preliminary results are presented in the Table.

S-Glycosidation presented no problems with adaptions of either the Falck method[7] in the 2-deoxy series or the Inanaga-Yb(OTf)3-methoxyacetate method[8] in the glucose and mannose series. Overall unoptimized yields for these first two steps were in the 55-78% range. with the products as anomeric mixtures. Sulfone formation was routine with MMPA. The Ramberg-Backlund conditions that we found most useful were those reported by Chan. [9,10] The product enol ethers were fairly sensitive materials so they were normally hydrogenated with Pd catalysis to afford a mixture of C-glycosides with the equatorial product (β-configuration) as the major isomer.[11] As can be seen from the data in the Table, the potential problem of β-elimination of the C-2-alkoxy in the glucose series did not occur (entry 2).[12] To our surprise, in the mannose series (entry 3), the C-glycoside is also obtained with no problem in the elimination of the axial C-2 benzyloxy group. Entry 5 illustrates our model approach to the C-glycoside of daunomycin. In this example, the S-glycoside of daunosamine is not used; the daunosamine was instead functionalized as the axial-1-hydroxymethyl compound using chemistry reported by Bednarski.[13] Then the hydroxymethyl material was converted via the 1-iodomethyl C-glycoside to the benzylic thioether in 85% yield prior to the Ramberg-Backlund chemistry. This C-glycoside was the one case where hydrogenation of the double bond also completely cleaved the benzyl protecting group. In entries 2 and 3 there was minor , partial debenzylation which accounts for some yield decrease. In entry 5, we also observed some epimerization at the daunosamine anomeric carbon, presumably via isomerization of the double bond of the Ramberg-Backlund product. In entries 4 and 5, the hydrogenation creates a new chiral center at the benzylic position as well. It is assumed that the outcome is tied to the E,Z configuration of the alkene, but we have not demonstrated this. The observation is that for entry 4, the final product is approximately a 1:1 mixture of diastereomers at the benzylic carbon and for entry 5, the ratio is 1.75:1.

Ramberg-Backlund -benzylic examples

entry	S-glycoside	Glycosidation Method %Yield (β/α)	Sulfone Yield	Ramberg-Backlund Yield	Reduction Product	Yield (β/α)
1		A 71 (45:55) B 77 (45/55)	95 (47:53)	72 (E:Z:endo, 76:15:9)		73 (100:0)
2		B 74 (45/55) C 83 (20:80)	95 (40/60)	85 (Z:E, 91:9)		89 (75:25)
3		B 79 (43/57)	83 (43:57)	62 (Z:E, 95:5)		64 (100:0)
4		B 62(40:60)	90 (40:60)	76 (E:Z, 55:45)		83 (90:10)
5		see text	70	70		70 see text

A = Falck, B = Inanaga methoxyacetic glycoside, C = Inanaga methoxyacetic acid cross-coupling

Table Results for the four-step C-glycosidation sequence using the Ramberg-Backlund reaction for C-C bond formation.

In general, we can say that the ratio of alkene E,Z isomers is not related to the configuration of the anomeric sulfone. We have not yet examined reduction methods other than classical catalytic hydrogenation to discover if the configuration at the anomeric center can be controlled. Even though there remain some unresolved issues, we believe that we have opened a window of opportunity for C-glycoside researchers since the synthesis of the starting S-glycosides is commonplace and the subsequent RB sequence is quite facile.[14]

References and Notes

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10. ***Typical Experimental:*** The modified one-pot Ramberg-Backlund reaction utilized a ~40% KOH/alumina mixture prepared by dissolving 40 g KOH (Certified ACS, 87.5%) in 400 mL MeOH and slurrying with 60 g alumina (Activated, neutral, Brockmann I, standard grade, ~150 mesh). The solvent was removed in vacuo until the alumina mixture was again free flowing, which required some scraping from the inside of the flask. This large batch of basic alumina was protected from the atmosphere and used for all of the R-B reactions. A 100 mL rbf containing 1 g of crude sulfone (Table entry 2) was charged with 5 mL of dry dichloromethane, 5 mL of t-butanol (Certified), and cooled to 5^0 C under nitrogen with stirring. A batch of 4 g of ~40% KOH/alumina was added, followed by 1.25 mL of cold CF_2Br_2. The mixture was stirred at 5^0 C for 1 h. TLC showed some starting material and intermediate bromosulfone, along with product. An additional 3 g of ~40 % KOH/alumina was added followed by 1.25 mL CF_2Br_2. Stirring was continued at 5^0 C for 1 h. The mixture was then filtered through Celite and the solids were washed with EtOAc. Routine workup afforded 1.1 g of a colorless oil . Flash chromatography on 18 g of Silica Gel 60 (230-400 mesh) packed in hexane followed by elution with 5% EtOAc:hexane afforded 0.77 g Z, E alkenes in 85% yield as a colorless oil. NMR showed vinylic singlets at 5.74 and 6.50 ppm in a 91:9, Z:E ratio. The oil was dissolved in 100 ml EtOAc and hydrogenated overnight at rt under atmospheric pressure in the presence of 400 mg of 10% Pd/C. Routine workup gave 0.8 g of an oil which was dissolved in a small amount of toluene and flash chromatographed on a column of 18 g silica gel 60 packed in hexane. Elution with 5% EtOAc:hexane gave a total of 0.69 g (89% yield) of reduced alkene as a colorless oil which slowly solidified, β/α ratio 84/16. Some early fractions from the chromatography allowed for the isolation of 0.24 g of clean β-anomer. (ESMS *m/z* = 637 $[M + Na]^+$).13-C NMR(75 MHz, $CDCl_3$)(carbon type from DEPT) 37.70(t), 68.77(t), 73.24(t), 74.85(t), 75.03(t), 75.45(t), 78.50(d), 78.85(d), 79.91(d), 81.61(d), 87.32(d), 126.11(d), 127.47(d), 127.64(d), 127.69(d), 127.83(d), 127.90(d), 128.07(d), 128.29(d), 128.40(d), 128.45(d), 128.48(d), 129.03(d), 129.64(d), 138.17(s), 138.21(s), 138.37 (s), 138.57(s), 138.82(s).1-H NMR (500 MHz-$CDCl_3$)(assignments from COSY) 7.36-7.19(25H, $5C_6H_5$), 4.94,4.67;4.93,4.88;4.82,4.60 (6H, 3ABq, J=11.3 Hz, PhCH_2), 4.57,4.50 (2H, ABq, J=12.5 Hz, PhCH_2), 3.74-3.62 (4H,m, H-3,H-2,H-1,H-1'),3.49 (1H,dt, J=2,9 Hz, H-6), 3.36-3.33 (2H,m,H-4,H-5), 3.15(1H,dd, J=1.8,14.2 Hz, H7, 2.73(1H,dd,J=8.8,14.2 Hz, H-7').
These conditions afford low yields of Ramberg-Backlund products in non-benzylic sulfones. Our modified method for achieving good yields in non-benzylic carbohydrate sulfones will be described in a future publication.
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14 These results are taken from the Ph.D. thesis of PSB to be submitted to CUNY Graduate School in 1998. The authors thank HLR for support of this project; and thank Drs. Coffen, Manchand, and Wolff for their advice and encouragement.