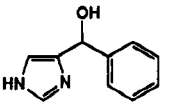
Table I. Reaction of Imidazol-4-yl Anions with Carbonyl Compounds in CH_2Cl_2

starting material	product	R^1	R^2	R^3	isolated yield (%)
1	4	CPh_3	Me	H	83 (66[a])
1	5	CPh_3	Ph	H	79
1	6	CPh_3	$CH{=}CH_2$	H	60
1	7	CPh_3	$(CH_2)_3CO_2Me$	H	63
1	8	CPh_3	4Cl-C_6H_4	4Cl-C_6H_4	69 (53[a])
2	9	SO_2NMe_2	Me	H	80
2	10	SO_2NMe_2	Ph	H	83
2	11	SO_2NMe_2	$(CH_2)_2CH{=}CMe_2$	H	83
2	12	SO_2NMe_2	Ph	Ph	82
2	13	SO_2NMe_2	$-(CH_2)_4-$		77
3	14	$SO_2(CH_2)_2$-$SiMe_3$	Ph	H	66

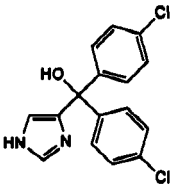
[a] Yield using THF as reaction solvent.

since its use is often accompanied by enhanced results when compared with those obtained in ethereal solvents.[13] We are aware of only one other example of a metal–halogen exchange reaction being performed in dichloromethane.[14]

The trityl,[6,12] dimethylsulfamoyl,[2,4] and [2-(trimethylsilyl)ethyl]sulfonyl[10] protecting groups are removable under a variety of conditions, so that our procedure represents a general method for preparing 4(5)-alkylated NH-imidazoles. For example, treatment of the *N*-trityl-imidazoles **5** and **8** with aqueous 60% CF_3CO_2H at ambient temperature for 1 h yielded the carbinols **15** (84% yield) and **16** (83% yield); both were isolated as their trifluoroacetate salts. The secondary alcohol **15** was also obtained



15



16

by refluxing the dimethylsulfamoylimidazole **10** overnight in 10% sulfuric acid or with an equimolar amount of $LiAlH_4$ in THF (98% and 64% yield, respectively). (Arylhydroxymethyl)imidazoles related to **15**, but with substituents in the aryl ring, exhibit antihypertensive and antiulcerogenic properties,[15] and the tertiary alcohol **16** is a good inhibitor of the P-450 enzyme aromatase.[16]

Finally, it is noted that the reactivity of the magnesio-imidazol-4-yl anions generated via our procedure can be modified by the addition of other metal salts (e.g., $ZnCl_2$, CuCN), so that reaction with a wide variety of noncarbonyl containing electrophiles is also possible.[17]

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A Highly Stereoselective Synthesis of Aryl 2-Deoxy-β-glycosides via the Mitsunobu Reaction

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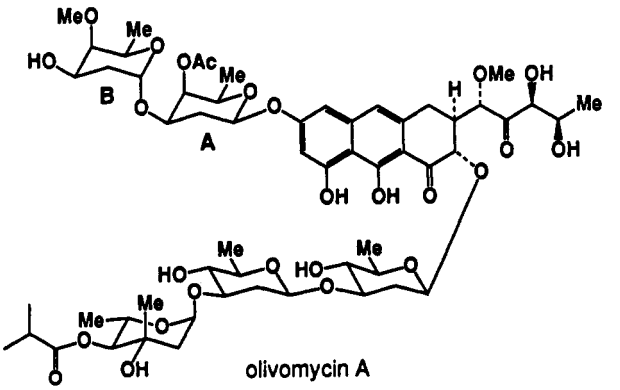
Summary: A highly stereoselective (6.5–>20:1) synthesis of aryl 2-deoxy-β-D-glycosides is described. This method involves the Mitsunobu coupling of phenols and 2α-(thiophenyl)- or 2α-(selenophenyl)-α-D-pyranoses **3–6**, **18**, and **19** followed by Bu_3SnH reduction of the PhS- and PhSe-groups.

In continuation of our studies on the synthesis of olivomycin A[1] we required an efficient glycosidation method for establishing the 2-deoxy-β-D-glycosidic linkage between the aglycon, olivin, and the AB disaccharide.[2,3] 2-Deoxy-β-glycosides have been synthesized with good stereoselectivity via the silver silicate mediated glycosylations of alcohols and 2-deoxypyranosyl bromides.[4] However, application of this method to the glycosylation of phenols



has led, at best, to 3:1 mixtures of β/α aryl glycosides.[4b,5] Other successful strategies[6] for the synthesis of β-2-deoxy

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(2) For a review of synthetic efforts through 1987, see: Franck, R. W.; Weinreb, S. M. In *Studies in Natural Product Chemistry*; Rahman, A. U., Ed.; Elsevier: Amsterdam, 1989; pp 173–208.

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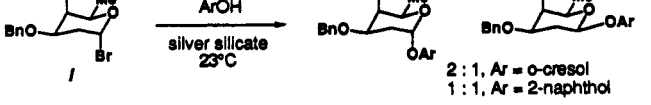
(5) Application of the silver silicate method to bromo sugar **i** provided at best 1:1 mixtures of the β and α glycosides.



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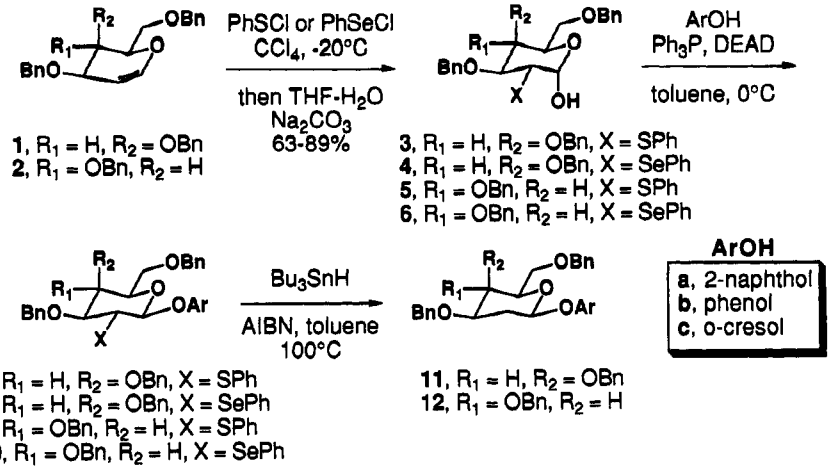
0022-3263/91/1956-5740$02.50/0

Scheme I[a]



1, R_1 = H, R_2 = OBn
2, R_1 = OBn, R_2 = H

3, R_1 = H, R_2 = OBn, X = SPh
4, R_1 = H, R_2 = OBn, X = SePh
5, R_1 = OBn, R_2 = H, X = SPh
6, R_1 = OBn, R_2 = H, X = SePh

7, R_1 = H, R_2 = OBn, X = SPh
8, R_1 = H, R_2 = OBn, X = SePh
9, R_1 = OBn, R_2 = H, X = SPh
10, R_1 = OBn, R_2 = H, X = SePh

11, R_1 = H, R_2 = OBn
12, R_1 = OBn, R_2 = H

		Mitsunobu Glycosidations[a]			Bu$_3$SnH Reductions[d]	
Substrate	Phenol	Product	Selectivity[b]	% Yield[c]	Product	% Yield
3	a	7a	88:12	74	11a	94
3	b	7b	88:12	70	11b	76
3	c	7c	90:10	73	11c	89
4	a	8a	93:7	71	11a	94
4	b	8b	87:13	71	11b	85
4	c	8c	90:10	73	11c	86
5	a	9a	93:7	82	12a	92
6	a	10a	>95:5	80	12a	95
6	c	10c	>95:5	85	12c	92

[a] Key: (a) all glycosidation experiments were performed in tolune at 0 °C as described in text; (b) ratio of $\beta\alpha$ glycosides determined by 500-MHz ^{1}H NMR analysis of the crude mixture. Ratios determined by product isolation were similar; (c) yield of β-glycoside isolated by chromatography; (d) reductions of 7–10 were performed by using 5 equiv of Bu_3SnH in toluene at 100 °C under Ar with catalytic AIBN as initiator. The reductions of 8–10 readily proceeded to completion under these conditions. With PhS-containing glycosides 7 and 9, however, it was necessary to add additional AIBN (catalytic) every 2 h (four additions of AIBN, total) to achieve complete conversion.

glycosides rely on neighboring group assistance involving C(2α) heteroatom substituents (-Br,[7] -SPh,[6,8] -SePh,[9] -OAc,[10] -NHCHO[10b,11]) that are reductively removed following the successful glycosylation or on the reduction of radical intermediates generated at the anomeric position.[12] Applications of these methods to the synthesis of aryl glycosides, however, have met with limited success. For example, phenyl 2-deoxy-β-D-glucopyranoside has been prepared with 3:1 selectivity (56%) via the phenylbis(phenylthio)sulfonium salt mediated electrophilic functionalization of tribenzyl D-glucal,[6] while 4-cresyl 2-deoxy-β-D-galactopyranoside has been prepared with 16:1 selectivity via the radical reduction of the corresponding ulosonate ester, but in only 18% yield for the two key steps.[12b]

We report herein the synthesis of aryl 2-deoxy-β-D-glycosides via Mitsunobu reactions of 2α-(thiophenyl)- and 2α-(selenophenyl)-α-D sugars (Scheme I).[13,14] The Mitsunobu reaction has previously been utilized for the synthesis of aryl glycosides[14a-c] and glycosyl esters[14d,e] as well as glycosides of alcohols.[14f] However, initial attempts to apply this procedure to the glycosidation of 2,6-dideoxyhexose 13[3b] provided a 2:1 mixture favoring the β-glycoside. Recognizing that 13 is a 2:1 mixture of α/β anomers (in C_6D_6), we anticipated based on Smith's initial report[14d] that substrates with a greater α-anomeric preference might give better β-selectivity in the Mitsunobu reaction, assuming that the rates of oxyphosphonium salt generation and nucleophilic displacement by the phenol are faster than anomerization of the substrate. 2α-(Thiophenyl)- and 2α-(selenophenyl)-α-D-pyranoses 3–6 easily met the first criterion, since the α-anomer is significantly favored in each case.[15] The data summarized in Scheme I show that 3–6 are also excellent substrates for Mitsunobu couplings with phenols, each providing the desired β-D-glycosides with at least 6.5:1 and up to >20:1 selectivity.

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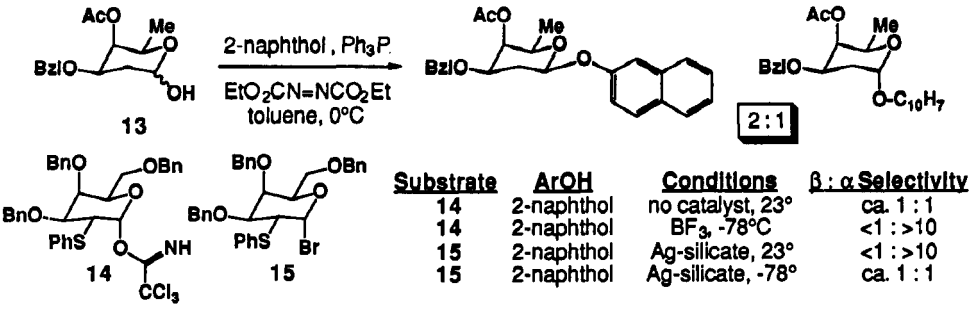
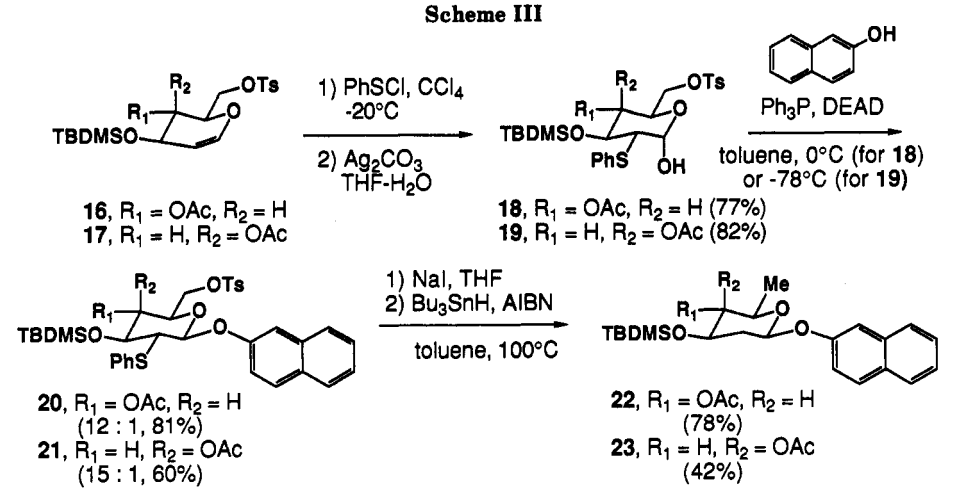
Scheme II



Substrate	ArOH	Conditions	β : α Selectivity
14	2-naphthol	no catalyst, 23°	ca. 1 : 1
14	2-naphthol	BF_3, -78°C	<1 : >10
15	2-naphthol	Ag-silicate, 23°	<1 : >10
15	2-naphthol	Ag-silicate, -78°	ca. 1 : 1

Scheme III



16, R_1 = OAc, R_2 = H
17, R_1 = H, R_2 = OAc

18, R_1 = OAc, R_2 = H (77%)
19, R_1 = H, R_2 = OAc (82%)

20, R_1 = OAc, R_2 = H (12 : 1, 81%)
21, R_1 = H, R_2 = OAc (15 : 1, 60%)

22, R_1 = OAc, R_2 = H (78%)
23, R_1 = H, R_2 = OAc (42%)

The Mitsunobu reactions of **3–6** were preformed in toluene (0.2 M) at 0 °C in the presence of molecular sieves typically using 1.4 equiv of Ph_3P, 1.6 equiv of diethyl azodicarboxylate, and 1.2 equiv of the phenol. The reactions were quenched after 30 min with 1 N NaOH and the aryl β-D-glycosides were isolated chromatographically in 70–85% yield. The reaction of **3** and β-naphthol was examined in a variety of solvents: toluene, (88:12,β/α); CH_2Cl_2 (88:12); Et_2O (86:14); THF (82:18); CH_3CN (82:18). These ratios nicely parallel the anomeric composition (500-MHz ^1H NMR analysis) of **3** in similar solvents: C_6D_6, (90:10, α/β); CD_2Cl_2 (89:11); THF-d_8 (90:10); CD_3CN (83:17). Consequently, it appears that very little anomerization of **3** occurs before the S_N2 displacement of the oxyphosphonium salt intermediate.[16] Alternatively, it could be argued that the excellent β-selectivity is the result of neighboring-group assistance by the thiophenyl or selenophenyl substituents.[6,8,9] This mechanistic possibility does not appear valid for the cases at hand, however, since several reactions in which neighboring group assistance might have been anticipated if oxonium ions were generated (glycosyl imidate couplings using **14**;[8c] silver silicate mediated glycosidations of **15**)[4] gave at best 1:1 mixtures of β- and α-aryl glycosides (Scheme II).

The thiophenyl and selenophenyl substituents of β-glycosides **7–10** were removed in high yield by treament with Bu_3SnH and AIBN in toluene at 100 °C.[17] While this is a standard procedure for reduction of phenyl selenides,[9,17] there are many fewer successful examples of Bu_3SnH reductions of phenyl sulfides.[12c,17,18] The reductions of **7** and **9** were noticeably slower than those of **8** and **10**, and it proved necessary to add AIBN several times over the course of an 8–10 h reaction period in order to achieve complete reduction of the PhS-substituted glycosides.

The Mitsunobu glycosidation method also has been applied to differentially functionalized glycals **16**[19] and **17**. Thus, treatment of **16/17** with PhSCl in CCl_4 at −20 °C followed by hydrolysis of the intermediate glycosyl chlorides using Ag_2CO_3 in aqueous THF gave pyranoses **18/19** in 87% and 80% yields, respectively (Scheme III). Mitsunobu couplings with β-naphthol then provided β-D-glycosides **20/21** with excellent selectivity (12–15:1) and in good yield. Treatment of **20/21** with NaI in THF followed by Bu_3SnH reduction (AIBN, toluene, 100 °C) completed the syntheses of the differentially protected aryl 2,6-dideoxy-β-D-glycosides **22** (78%) and **23** (42%).[20]

In summary, an efficient and highly stereoselective method for the synthesis of aryl 2-deoxy-β-D-glycosides has been developed. This procedure seems ideally suited for application toward the synthesis of olivomycin and other members of the aureolic acid antibiotic family.

Acknowledgment. This research was supported by a grant from the National Institute of General Medical Sciences (GM 38907). We also gratefully acknowledge the assistance of Mr. David P. Sebesta for providing the samples of **18** used in these studies.

Supplementary Material Available: Experimental procedures, tabulated spectroscopic data, and copies of ^1H NMR spectra (39 pages). Ordering information is given on any current masthead page.

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(20) The NaI substitution of **21** is the low-yielding step (59% yield) in this sequence.