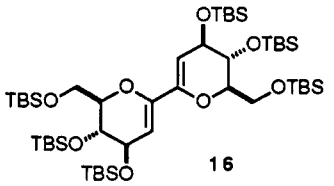
Utilizing these revised "standard" conditions, a wide variety of substituted aryl bromides (entries 5–16) were coupled successfully. A number of points regarding these latter entries deserve mention.

The crude reaction mixtures were quite clean, providing the expected *C*-arylglucals **4–15**[10] in moderate to good yields. Especially satisfying is the observation that oxygenated aromatics, such as are found in many *C*-aryl glycoside antibiotics, can be easily introduced (entries 13–16). It should also be noted that the conditions of choice for the coupling of bromobenzene itself are the original "standard" reaction conditions (compare entries 4 and 12).

Secondly, the isolated yields of the *C*-arylglucals reflect, at least qualitatively, an ordering based on the electron-withdrawing capabilities of the aromatic substituent ortho or para to the bromide.[11]

Finally, a single byproduct (accounting for up to 30% of the starting material **1**; entries 7 and 11) was observed in all cases and was identified as the dimer **16** resulting from the homocoupling of **1**.[12] Various attempts at decreasing the production of **16** by modification of the reaction conditions, including the use of nickel catalysis or the zinc glucal derived from **1**,[13] were not successful. We are investigating the mechanism by which **16** is formed in an effort to reduce the loss of material via this reaction pathway.[14]



16

We feel that the wide range of substituted aromatic moieties that can be appended onto the sugar nucleus, in a single synthetic step, make this an attractive method for the synthesis of *C*-arylglycals. In order to be generally useful as a method for the preparation of *C*-aryl glycosides, the synthetic capabilities of the remaining enol ether double bond of these materials must be addressed. Preliminary work along these lines is very encouraging and will be reported in due course.

Acknowledgment. Financial support from the Natural Sciences and Engineering Research Council of Canada and the University of Toronto is gratefully acknowledged.

Supplementary Material Available: A general procedure for the coupling of **1** and aryl bromides and physical constants for **1** and **4–16** (4 pages). Ordering information is given on any current masthead page.

(10) The purification of these materials was effected by silica gel chromatography of the crude reaction mixtures after evaporation of the reaction solvent. The arylglucals are relatively stable at −5 °C but decompose when stored at room temperature.

(11) A similar ordering, based on electron-withdrawing properties, has been observed in the palladium-catalyzed rate (not yield) of reaction of substituted aryl bromides with vinylstannanes[6a] and terminal acetylenes. (a) Singh, R.; Just, G. *J. Org. Chem.* **1989**, *54*, 4453. (b) Fitton, P.; Rick, A. E. *J. Organomet. Chem.* **1971**, *28*, 287.

(12) The homocoupling of vinylstannanes in the palladium-catalyzed cross-coupling with vinyl iodides has been observed previously. Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813.

(13) Negishi, E.; Luo, F.-T. *J. Org. Chem.* **1983**, *48*, 1562.

(14) The palladium catalyzed dimerizations of vinylsilanes and vinylstannanes have been reported. In these cases, unlike our reaction, an added oxidant such as Cu(II) or ^{t}BuOOH was required to reoxidize Pd(0) to Pd(II). (a) Weber, W. P.; Felix, R. A.; Willard, A. K.; Koenig, K. E. *Tetrahedron Lett.* **1971**, 4701. (b) Kanemoto, S.; Matsubara, S.; Oshima, K. *Chem. Lett.* **1987**, 5.

Asymmetric Synthesis of 2-Alkyl(Aryl)-2,3-dihydro-4-pyridones by Addition of Grignard Reagents to Chiral 1-Acyl-4-methoxypyridinium Salts

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Summary: Grignard addition to a chiral 1-acyl-4-methoxypyridinium salt provides synthetically useful 2-alkyl(aryl)-2,3-dihydro-4-pyridones in high diastereomeric excess.

The reaction of nucleophiles with 1-acylpyridinium salts has proven to be a valuable method for the synthesis of substituted dihydropyridines and pyridines.[2,3] The addition of Grignard reagents to 1-acylpyridinium salts of 4-methoxypyridine is particularly interesting, for synthetically useful 1-acyl-2,3-dihydro-4-pyridones result. These dihydropyridones have been utilized as synthetic intermediates for the synthesis of quinolizidinones.[4,5] For example, we recently reported highly stereocontrolled syntheses of the Lythraceae alkaloid (±)-lasubine II[5a] and the quinolizidine alkaloid (±)-myrtine[5b] from 4-methoxypyridine in four and five steps, respectively. The synthetic potential of 1-acyldihydropyridones prompted us to pursue an enantioselective synthesis of these heterocycles via Grignard addition to chiral 1-acyl-4-methoxypyridinium salts.

Our strategy for developing the desired asymmetric synthesis followed the route depicted in Scheme I.

The chiral 1-acylpyridinium salts **2** were prepared in situ from a 4-methoxypyridine **1** and an optically active chlo-

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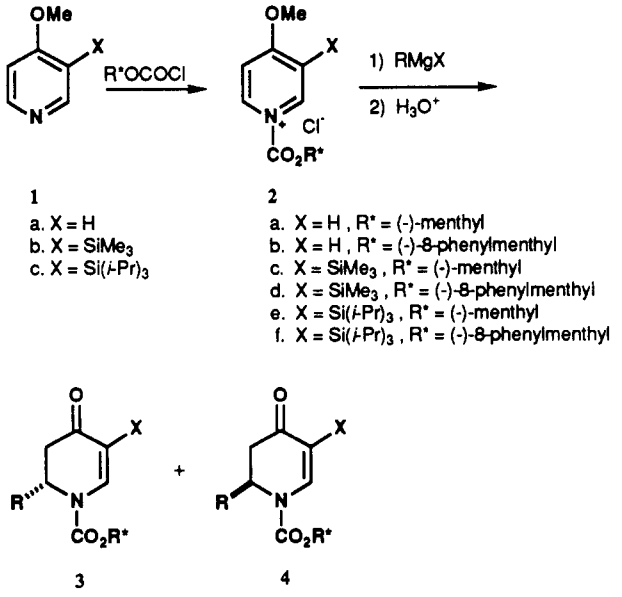
Table I. Addition of Grignard Reagents to Chiral 1-Acylpyridinium Salts

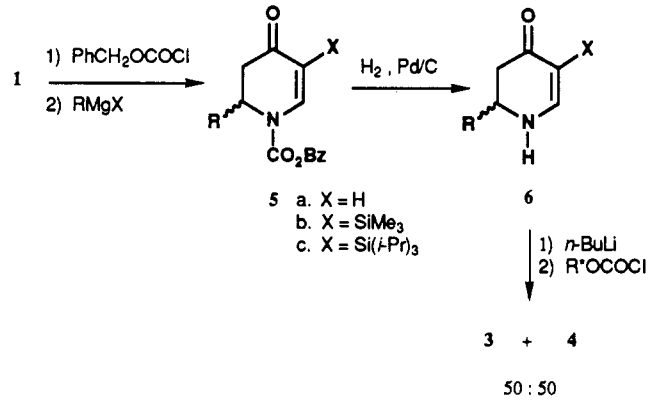
entry[a]	pyridine 1	chiral aux R*OH	RMgX	conditions	yield,[b] %	de[c]
a	**1a**	(−)-menthol	PhMgCl	toluene/THF, −78 °C	79	34
b	**1b**	(−)-menthol	PhMgCl	THF, −78 °C	88	50[d]
c	**1c**	(−)-menthol	PhMgCl	toluene/THF, −78 °C	87	44
d	**1a**	(−)-8-phenylmenthol	PhMgCl	toluene/THF, −78 °C	83	30
e	**1b**	(−)-8-phenylmenthol	PhMgCl	toluene/THF, −78 °C	82	65
f	**1b**	(−)-8-phenylmenthol	*o*-MePhMgCl	toluene/THF, −78 °C	90	30
g	**1b**	(−)-8-phenylmenthol	*p*-MePhMgBr	toluene/Et_2O, −78 °C	79	42
h	**1c**	(−)-8-phenylmenthol	PhMgCl	toluene/THF, −78 °C	88	94
i	**1c**	(−)-8-phenylmenthol	*p*-MePhMgBr	toluene/THF, −78 °C	90	82
j	**1c**	(−)-8-phenylmenthol	*p*-MeOPhMgBr	toluene/THF, −78 °C	77	73
k	**1c**	(−)-8-phenylmenthol	*o*-MePhMgCl	toluene/THF, −78 °C	81	60
l	**1c**	(−)-8-phenylmenthol	*p*-ClPhMgBr	toluene/THF, −78 °C	78	81
m	**1c**	(−)-8-phenylmenthol	MeMgCl	toluene/THF, −78 °C	92	91
n	**1c**	(−)-8-phenylmenthol	*i*-BuMgBr	toluene/THF, −78 °C	95	92
o	**1c**	(−)-8-phenylmenthol	*c*-HexMgBr	toluene/THF, −78 °C	90	81

[a] The reactions were generally performed on a 0.5-mmol scale and quenched with aqueous 10% HCl. [b] Yield of purified product obtained from radial preparative-layer chromatography. [c] Unless indicated the diastereomeric excess (de) was determined by HPLC. [d] The de was determined by 300-MHz ^1H NMR analysis of the crude reaction products.

Scheme I



Scheme II



roformate. Reaction of the 1-acyl salt with an alkyl or aryl Grignard reagent followed by acidic aqueous workup provided chiral dihydropyridones **3** and **4**. We chose to use 4-methoxypyridine (**1a**), 4-methoxy-3-(trimethylsilyl)pyridine (**1b**),[6] 4-methoxy-3-(triisopropylsilyl)pyridine (**1c**),[7] and chloroformates derived from (−)-menthol and (−)-8-phenylmenthol[8] for our initial study. Several reactions were performed using aryl and aliphatic Grignard reagents (Scheme I), and the diastereomeric excess (de) was determined by HPLC or ^1H NMR analyses. For comparison, 50:50 mixtures of diastereomers **3** and **4** were prepared as shown in Scheme II. Racemic **5** was prepared from benzyl chloroformate, substituted pyridine **1**, and a Grignard reagent. Hydrogenation of **5** gave racemic **6**, which was treated with *n*-butyllithium and a chiral chloroformate to give a 50:50 mixture of diastereomers **3** and **4**. In some cases, when 4-methoxypyridine **1b** was used (Scheme I), the de was determined by treating the crude products with HBr/HOAc (6 equiv, CH_2Cl_2, room temperature) to remove the TMS group from C-5, and analyzing the resulting desilylated diastereomers **3a** and **4a** by HPLC. The results of this study are given in Table I.

The use of 4-methoxy-3-(trialkylsilyl)pyridines and (−)-8-phenylmenthyl chloroformate proved to give the best results. It is known from our earlier work that a 3-trialkylsilyl substituent can be effective at blocking the C-2 position of a 1-acylpyridinium salt against attack by Grignard reagents.[9] We anticipated this blocking action would raise the diastereoselectivity of Grignard addition to a chiral 1-acylpyridinium salt by reducing in half the number of α-positions available for nucleophilic attack. When 4-methoxy-3-(trimethylsilyl)pyridine (**1b**) was utilized (entries e–g), the diastereomeric excess ranged from 30 to 65%. A similar reaction with the bulkier 3-(triisopropylsilyl)pyridine derivative **1c** and phenylmagnesium chloride gave an 88% yield of dihydropyridones **3** and **4** in 94% de. The major diastereomer was shown by X-ray single-crystal structure analysis to be **3**, which has the *S* configuration at the newly formed stereogenic center. Other aryl Grignards gave moderate to high de's (entries i–l) although somewhat lower than that observed in the phenyl Grignard case (entry h). The analogous reactions with aliphatic Grignard reagents gave very satisfying diastereoselectivity, ranging from 81 to 92% de (entries m–o). Due to a change in substituent priority, the major diastereomer (**3**) formed from reactions using aliphatic Grignard reagents (entries m–o) contains the newly formed stereogenic center of the *R* configuration. This was determined by comparing NMR spectra of the major dia-

(6) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1988**, *29*, 773.
(7) Lithiation of 4-methoxypyridine using lithium diisopropylamide and in situ trapping with chlorotriisopropylsilane gave a 70% yield of 4-methoxy-3-(triisopropylsilyl)pyridine. See ref 6.
(8) Optically pure (−)-8-phenylmenthol was purchased from Aldrich Chemical Co., Inc., or prepared by a literature procedure. Ort, O. *Org. Synth.* **1987**, *65*, 203.
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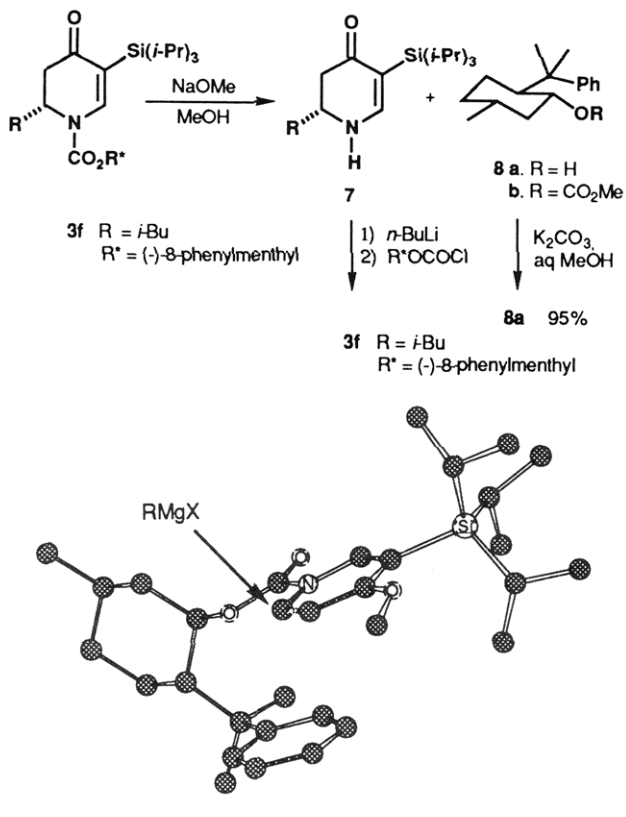
Scheme III



9

Figure 1. A working model derived from molecular mechanics (MMX).[12]

stereomers to the NMR spectrum of the 2-methyl derivative, which was subjected to X-ray single-crystal structure analysis. In all cases the dihydropyridones (**3**) prepared from (−)-8-phenylmenthyl chloroformate were crystalline compounds. Purification of the crude products by recrystallization can give high yields of diastereomerically pure dihydropyridones **3** (entries h and n).[10]

(10) All new compounds have been characterized by NMR and IR spectroscopy and elemental analysis.

The chiral auxiliary can be removed and recovered as shown in Scheme III. Treatment of recrystallized **3f** (R = *i*-Bu) (100% de) with sodium methoxide in methanol (4 equiv, reflux, 16 h) gave a 92% yield of dihydropyridone **7** [$[\alpha]^{23}_D$ +216.6° (*c* 1.34, $CHCl_3$); mp 150–152 °C (hexane)] and a mixture of **8a** and **8b** after radial preparative-layer chromatography. The mixture (**8a** and **8b**) was treated with K_2CO_3 in aqueous methanol (room temperature, 2 h) to give a 95% yield of (−)-8-phenylmenthol. The dihydropyridone **7**[11] was deprotonated with *n*-BuLi in THF (−78 °C, 15 min), and the resulting anion was added to (−)-8-phenylmenthyl chloroformate (THF, −78 °C to room temperature) to give **3f** (98%, 100% de), demonstrating that no racemization occurred on removal of the chiral auxiliary.

A working model that rationalizes the formation of **3f** as the major diastereomer is depicted in Figure 1. Attack by a Grignard reagent at C6 on the more accessible face of the pyridinium ring in **9** leads to the observed formation of diastereomer **3f** as the major product. It is not known at this time whether the in situ formed *N*-acyl salt exists mainly in the reaction medium as a nonequilibrating rotamer, i.e. **9**, or if equilibration between rotamers is occurring. Additional studies on the mechanism and scope of this novel asymmetric synthesis and its application toward the enantioselective synthesis of natural products will be reported in due course.

Acknowledgment. We gratefully acknowledge support of this work by the National Institutes of Health and North Carolina State University.

Supplementary Material Available: Experimental details for the preparation of **3f** (R = Ph), physical data for compounds **3f** (R = Ph, Me), ORTEP plots of the X-ray structures, and crystal data of **3d** (R = Ph) and **3f** (R = Me) (7 pages). Ordering information is given on any current masthead page.

(11) Optically active dihydropyridones of this type have been prepared from chiral imines and Danishefsky's diene. Kunz, H.; Pfrengle, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1067; **1989**, *28*, 1068. Pfrengle, W.; Kunz, H. *J. Org. Chem.* **1989**, *54*, 4261. Also see: Danishefsky, S.; Kerwin, J. F. *Tetrahedron Lett.* **1982**, *23*, 3739.

(12) MMX version by K. E. Gilbert and J. J. Gajewski based on MM2 (Allinger, QCPE 395) and MMP1 Pi (Allinger, QCPE 318) modified by K. Steliou.

Installation of the Allylic Trisulfide Functionality of the Enediyne Antibiotics. Thiol-Induced Reductive Actuation of the Bergman Process

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Summary: The title compounds were synthesized through thiosulfenylation. Exposure of the trisulfides to benzyl mercaptan induced reductive cycloaromatization.

Prevailing theory concerning the mode of action of the enediyne antibiotics envisions initial noncovalent binding to double-stranded DNA.[1] It is further assumed that reductive cleavage of the allylic trisulfide initiates a cascade which generates a diyl species strategically disposed to effect cutting of the duplex DNA.[2,3] Recently we have simulated the diyl priming process by recourse to an allylic thioacetate trigger.[4] Actuation involved an S → O acetyl

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