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Organo-Transition-Metal-Based Approach to the Synthesis of C-Glycosides

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Formation of a carbon-carbon bond at the anomeric center of a pyranoside or furanoside is a key transformation in the total synthesis of C-glycosides and polyether antibiotics.¹ Several methods have been developed to affect this transformation including sigmatropic rearrangements,² nucleophilic addition to glycols,³ and addition of allylmetal derivatives to glycosyl derivatives.⁴ Recently, organometallic based approaches to the preparation of C-glycosides have been reported.⁵ In this paper, we report the stereoselective preparation of glycosylmanganese pentacarbonyl complexes. Carbonylation of these complexes with retention of configuration and subsequent ligand incorporation into the acylmanganese bond results in the formation of C-glycosides. The overall transformation replaces the anomeric bromide by an acyl residue in a highly stereoselective fashion (see Scheme I).⁶ This approach to the synthesis of C-glycosides is especially appealing because the acyl residue can carry a diversity of functional groups (see Scheme II).

Glycosyl bromides 1-5⁷ react with sodium pentacarbonylmanganate(I)⁸ (6) in THF at -78 °C to give stable glycosyl-

Scheme I

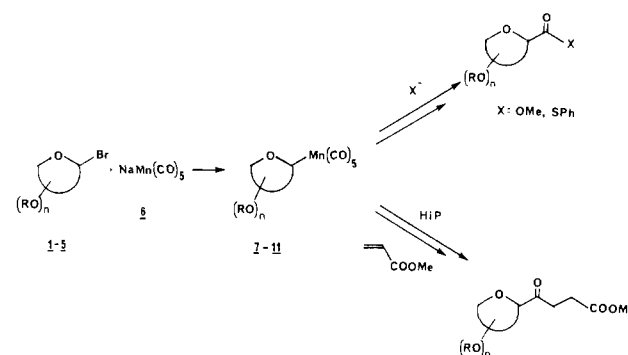


Table I. Preparation of Glycosyl Manganese Pentacarbonyl Complexes

glycosyl bromide	manganese complex	yield, %
 1a: R = Me 1b: R = Bn	 7a: R = Me 7b: R = Bn	75
 2	 8	75
 3	 9 (α:β = 1:2)	80
 4 (α:β = 1:1)	 10	85
 5 (α:β = 1:2)	 11 (1:1)	70

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(7) Glycosyl bromides 1-5 were prepared from the corresponding protected 1-p-nitrobenzoates: Plessars, N. R.; Goldstein, I. J. *Carbohydr. Res.* **1981**, *89*, 211. Koto, S.; Morishima, N.; Miyata, Y.; Zen, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2639. Barker, R.; Fletcher, H. G., Jr. *J. Org. Chem.* **1961**, *26*, 4605.

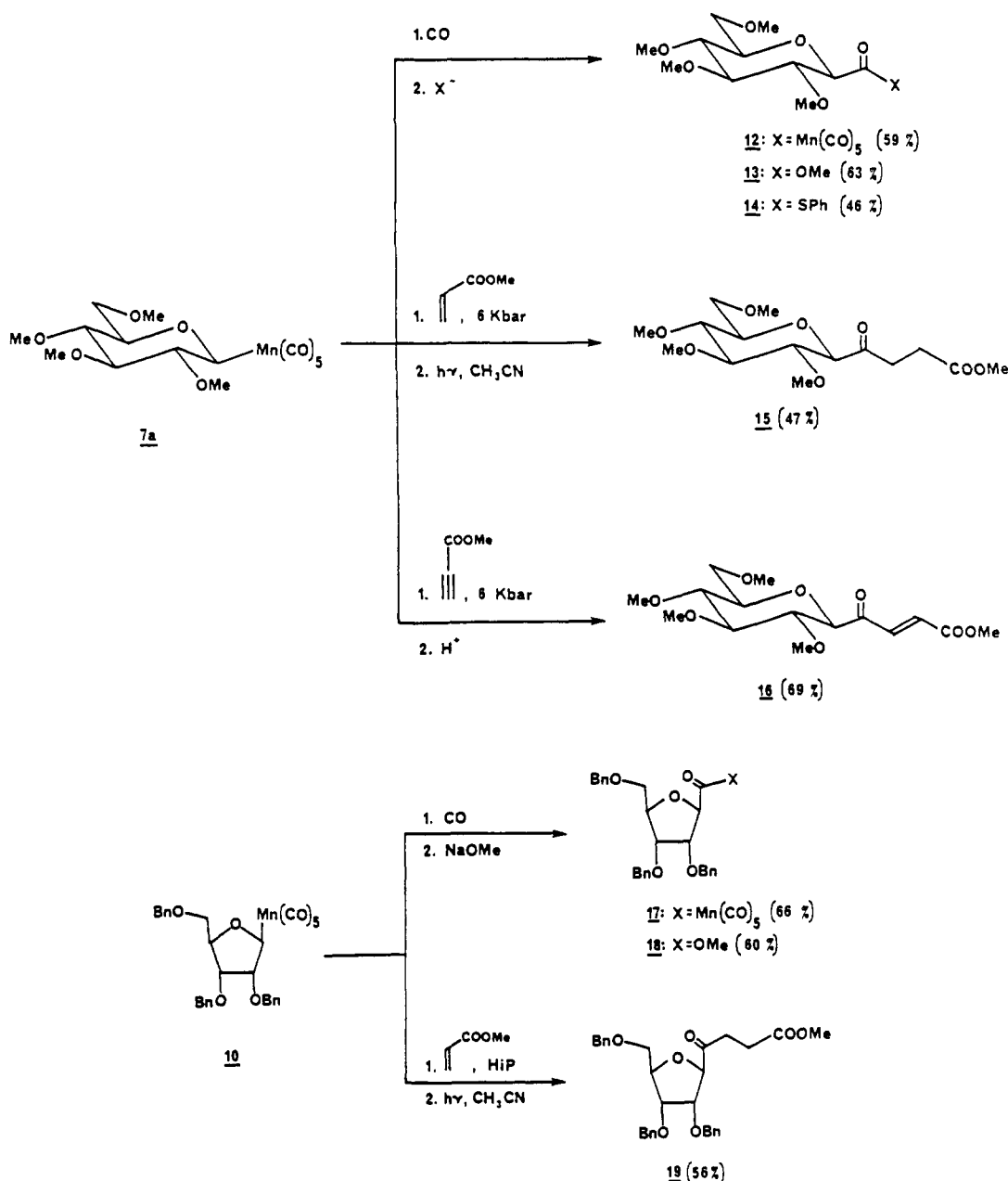
manganese pentacarbonyl complexes 7-11 in good yield (Table I). The displacement occurred with equal facility in either the pyranosyl or furanosyl series and displayed excellent stereoselectivity. α-Bromides 1⁷ and 2⁷ reacted with inversion of configuration to produce exclusively β-manganese complexes 7⁹ and 8⁹, respectively. The stereochemistry of the glucosyl complex 7a was determined by ¹H NMR analysis. The C-1 proton appeared as a doublet at δ 3.94 with J = 10.2 Hz and indicated an axial proton.¹⁰ Alternatively, the stereochemistry at the anomeric center could be determined by subsequent transformations of the complexes (vide infra). Mannosyl bromide 3⁷ gave a 1:2 mixture of

(8) Prepared by reduction of Mn₂(CO)₁₀, according to the procedure of Darensbourg: Drew, D.; Darensbourg, M. Y.; Darensbourg, D. J. *J. Organomet. Chem.* **1975**, *85*, 73.

(9) All compounds gave satisfactory IR, ¹H NMR, ¹³C NMR, MS, and elemental analytical data.

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Scheme II



manganese complexes in which the β -isomer predominated. The disappointing stereoselectivity observed in the mannose series was preceded since the axial C-2 alkoxy function is known to dramatically affect the stereoselectivity of bond formation at C-1.¹¹

A similar trend of stereoselectivity was found in the furanosyl series. Ribosyl bromide 4 ,⁷ a 1:1 mixture of anomers, gave only β -complex 10 ⁹ upon reaction with manganate anion 6 suggesting that the condensation occurred with significant S_N1 character. However, in the arabinose series, a mixture of anomeric manganese complexes 11 ⁹ was obtained. As was the case with the mannose bromide, arabinosyl bromide 5 ,⁷ tentatively assigned as a 1:2 mixture of the α and β anomers, is known to display modest stereoselectivity in reactions at the anomeric center.¹¹

Manganese complexes 7 – 11 are versatile intermediates for carbon–carbon bond formation to the anomeric center. For example, glucosyl complex $7a$ was stereospecifically carbonylated¹²

to produce an equilibrium mixture of $7a$ and acyl complex 12 .⁹ Cleavage of the acyl group with $MeOH/Na_2CO_3$ or $NaSPh$ gave the corresponding esters 13 ⁹ and 14 ⁹ in 63% and 42% yield, respectively (Scheme II). Analogous treatment of ribosyl complex 10 ⁹ yielded acyl complex 17 ⁹ and methyl ester 18 ,⁹ respectively. The carbonylation reactions occurred with retention of configuration at the anomeric center. For example, analysis of the 1H NMR spectrum of methyl ester 13 ⁹ showed that the proton at C-1 was axial ($J = 9.4$ Hz).¹⁰

Glycosyl complexes $7a$ ⁹ and 10 ⁹ were also found to readily undergo the sequential insertion reaction that has been developed in our laboratory.⁶ Reaction of complex $7a$ with methyl acrylate at 6 Kbar followed by photodemetalation of the manganacycle produced C-glycoside 15 ⁹ in 47% yield.¹⁵ Similarly, high-pressure-induced addition of methyl propiolate into $7a$ followed by demetalation gave unsaturated glycoside 16 ⁹ (69%).

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(14) Srivastava, P. C.; Pickering, M. V.; Allen, L. B.; Streeter, D. G.; Campbell, M. T.; Witkowski, J. T.; Sidwell, R. W.; Robins, R. K. *J. Med. Chem.* **1977**, *20*, 256.

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Analogous transformations can be performed in the furanosyl series. Carbonylation of manganese complex **10** at 42 psi followed by MeOH/Na₂CO₃ treatment produced methyl ester **18**⁹ via manganese acyl complex **17**⁹ (see Scheme II). The β -stereochemistry at the anomeric center of **18** was determined by analysis of the ¹H NMR spectrum. In **18**, the C-1 proton appeared as a doublet with a coupling constant of 3.5 Hz consistent with the assigned β -configuration.¹³ The β -configuration of manganese complex **10** and its transformation products was especially noteworthy because the β -anomer of the ribosyl C-glycoside is required for the synthesis of triazofurin,¹⁴ selenazofurin,¹⁵ and other C-glycosides.

In analogy with the chemistry observed in the pyranosyl series, sequential insertion of carbon monoxide and methyl acrylate into ribosyl complex **10** gave β -glycoside **19** in 56% yield.¹²

The results summarized in this report demonstrate that pyranosyl and furanosyl manganese pentacarbonyl complexes can be prepared stereoselectively from the corresponding glycosyl bromide and that the resulting transition-metal complexes can be transformed into C-glycosides with maintenance of stereochemical integrity. Application of this approach to the total synthesis of representative C-glycosides will be reported in due course.

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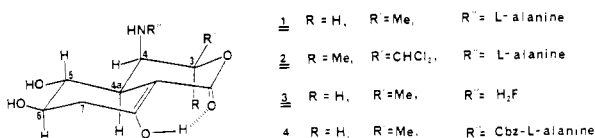
Total Synthesis of (+)-Actinobolin

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Actinobolin (**1**), a metabolite of *Streptomyces griseoviridis*,¹



has broad spectrum antibiotic and moderate antitumor activity. More recently, a structurally related, dichlorinated metabolite, bactobolin (**2**), was isolated from a *Pseudomonas* strain and was found to possess more potent antibiotic and antitumor activity than actinobolin.² The promising biological activity and unique chemical structures of these natural products have spurred interest by synthetic chemists. Ohno et al.³ have reported a total synthesis of actinobolin in 29 steps from L-threonine using an intramolecular Diels-Alder cycloaddition of a Z diene as the key synthetic operation. We now describe a significantly shorter, conceptually different route to actinobolin which should be amenable to late-stage modification to also efficiently produce bactobolin.

Our synthesis commenced with glyoxylate **5**, which was prepared in 75% overall yield from cyclohexen-3-ol⁴ using the Kornblum procedure.^{5,6} An intramolecular ene reaction of **5** could be effected by using stannic chloride in nitromethane to afford bicyclic hydroxy lactone **6** as a single stereoisomer (50–60% yield).^{7,8} Oxidation of **6** with Collins reagent yielded keto lactone **7** (86%). The functionality and relative stereochemistry corresponding to C-4/4a in **1** and **2** were established by converting **7** to the N-sulfonyl imine with N-sulfinyl(*p*-methylbenzyl)sulfonamide⁹ followed by treatment with sodium cyanoborohydride. This imine reduction occurs from the less congested face of the molecule to afford **8** as the exclusive product (85%). The (*p*-methylbenzyl)sulfonyl (PMS) N-protecting group¹⁰ was chosen since Ohno et al. demonstrated that it could be successfully removed late in their actinobolin synthesis.³ Treatment of **8** with *m*-chloroperbenzoic acid gave epoxides **9** as a 1.5:1 stereoisomer mixture (100%). It was of no consequence that a mixture was formed here since the two epoxides underwent diaxial opening with formic acid in opposite regiochemical senses to give the same diol **10**.¹¹ This strategy thus efficiently provides a compound which possesses four of the five stereocenters (C-4/4a/5/6) of the natural products.

The next stage of the synthesis involved elaboration of the lactone carbonyl group of **10** into the C-3 chiral center of actinobolin. Accordingly, treatment of **10** with the dimethylaluminum amide reagent¹² derived from *N,O*-dimethylhydroxylamine gave an amido triol, which on acetone formation and O-silylation yielded **11** (78% from **9**). By use of our reported methodology, the *N*-methoxy-*N*-methyl amide function of **11** was cleanly reduced to aldehyde **12** with lithium aluminum hydride (89%).¹³ Addition of methylmagnesium bromide in toluene to **12** at –20 °C produced the desired threo alcohol **13** with 12:1 stereoselectivity in quantitative yield. Other solvents and lower temperatures resulted in significantly reduced selectivity. Although this transformation can be viewed as a Cram “chelation controlled” addition involving the α -sulfonamido group,¹⁴ other coordination and conformational factors may well be in operation here.

In order to introduce the final carbon needed to produce the actinobolin bicyclic enol lactone system, alcohol **13** was converted to ketone **14** as shown in Scheme I (90%). The critical transformation of **14** to **15** could be effected regioselectively by an intramolecular C-acylation using carbonyl diimidazole to first form an activated carbonate derivative at C-3, followed by enolate formation with sodium hydride (80%).¹⁵ Interestingly, this type

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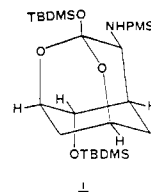
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(11) When **10** was treated with TBDMSOTf (2,6-lutidine, DMF, –10 °C) ortho lactone **i** was produced in 60% yield. Analysis of the ¹H NMR spectrum



of **i** supported the structural assignment of diol **10**.

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