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 glycals,[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 **1–5**[7] react with sodium pentacarbonylmanganate(I)[8] (**6**) in THF at −78 °C to give stable glycosyl-
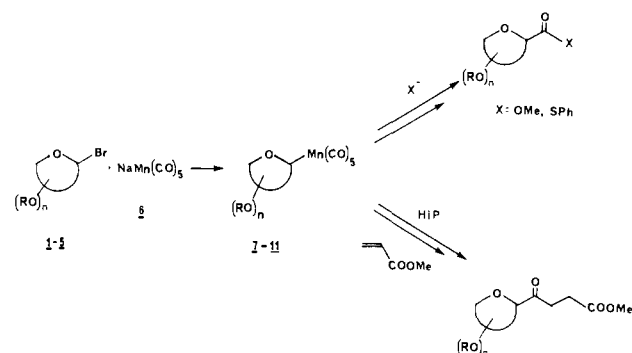
(1) For an excellent review of this topic, see: Hanessian, S. "Total Synthesis of Natural Products: The 'Chiron' Approach"; Pergamon Press: New York, 1983.

(2) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48. Ireland, R. E.; McGarvey, G. J.; Anderson, R. C.; Badond, R.; Fitzsimmons, B.; Thaisrivongs, S. *J. Am. Chem. Soc.* **1980**, *102*, 6178. Curran, C. P.; Suh, Y.-G. *Ibid.* **1984**, *106*, 5002 and references cited therein.

(3) Dawe, R. D.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1981**, 1180.

(4) Posner, G. H.; Haines, S. R. *Tetrahedron Lett.* **1985**, *26*, 1823. Keck, G. E.; Enholm, E. J.; Kachensky, D. F. *Ibid.* **1984**, *25*, 1867. Hosomi, A.; Sakata, y.; Sakurai, H. *Ibid.* **1984**, *25*, 2383. Kunz, H.; Weissmuller, J.; Muller, B. *Ibid.* **1984**, *25*, 3571. Kozikowski, A. P.; Sorgi, K. L. *Ibid.* **1984**, *25*, 2085. Wilcox, C. S.; Long, G. W.; Suh, H. *Ibid.* **1984**, *25*, 395. Hanessian, S.; Sato, K.; Liak, T. J.; Danh, N.; Dixit, D.; Cheney, B. V. *J. Am. Chem. Soc.* **1984**, *106*, 6114. Nicholau, K. C.; Dolle, R. E.; Chucholowski, A.; Randall, J. L. *J. Chem. Soc., Chem. Commun.* **1984**, *1153*.

(5) For an excellent review of the application of the Oxo reaction to carbohydrate chemistry, see: Rosenthal, A. *Adv. Carbohydr. Chem.* **1968**, *23*, 59. See also: Trainor, G. L.; Smart, B. E. *J. Org. Chem.* **1983**, *48*, 2447. Dunkerton, L. V.; Serino, A. J. *J. Org. Chem.* **1982**, *47*, 2812. Arai, I.; Daves, G. D., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 287. Arai, I.; Lee T. D.; Hanna, R.; Daves, G. D., Jr. *Organometallics* **1982**, *1*, 742.

(6) We have reported the use of alkylmanganese pentacarbonyl complexes for the preparation of a variety of functional groups; see: (a) DeShong, P.; Slough, G. A. *Organometallics* **1984**, *3*, 636. (b) DeShong, P.; Slough, G. A. *J. Am. Chem. Soc.*, submitted for publication.

(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.
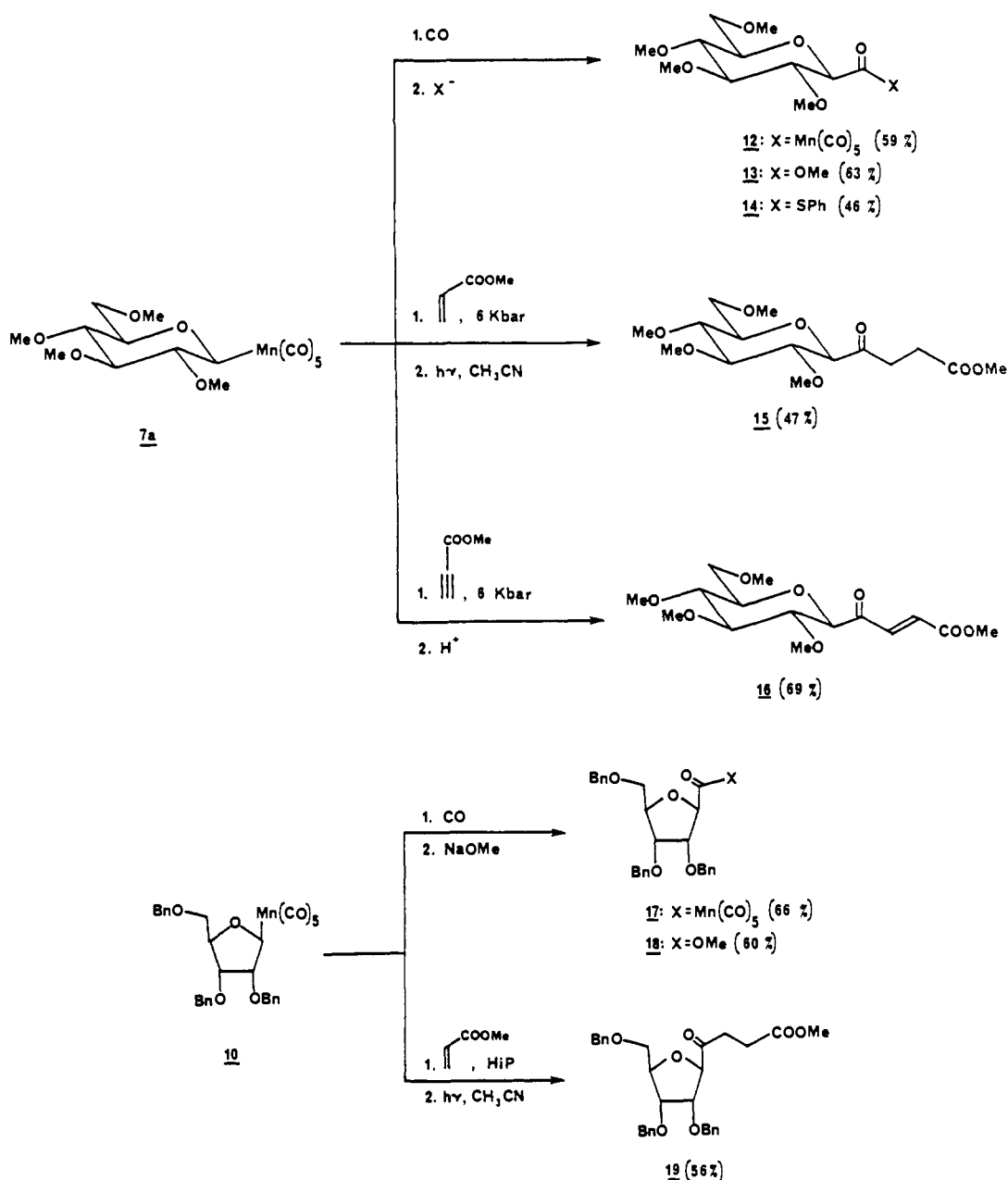
Scheme I

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)	60
4 (α:β ≈ 1:1)	**10**	65
5 (α:β ≈ 1:2)	**11** (1.7:1)	70

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 **1**[7] and **2**[7] reacted with inversion of configuration to produce exclusively β-manganese complexes **7**[9] and **8**,[9] 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 **3**[7] 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.

(10) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Oxford, 1969; pp 280–298.

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Scheme II

12: X = Mn(CO)₅ (59 %)

13: X = OMe (63 %)

14: X = SPh (46 %)

15 (47 %)

16 (69 %)

17: X = Mn(CO)₅ (66 %)

18: X = OMe (60 %)

19 (56 %)

manganese complexes in which the β-isomer predominated. The disappointing stereoselectivity observed in the mannose series was precedented 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 mannosyl 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 carbonylated[12]

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 ^{1}H 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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(11) Bochkov, A. F.; Zaikov, G. E. "Chemistry of the O-Glycosidic Bond: Formation and Cleavage"; Pergamon Press: Oxford, 1979, pp 51–55 and references cited therein.

(12) For references relating to carbonylation of alkyl manganese pentacarbonyl complexes, see: Noack, K.; Calderazzo, F. *J. Organomet. Chem.* **1967**, *10*, 101. Calderazzo, F. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 299.

(13) Jain, T. C.; Simolike, G. C.; Jackman, L. M. *Tetrahedron* **1983**, *39*, 599. Hall, L. D.; Steiner, P. R.; Pederson, C. *Can. J. Chem.* **1970**, *48*, 1155.

(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.

(15) Srivastava, P. C. Robins, P. K. *J. Med. Chem.* **1983**, *26*, 445.

Analogous transformations can be performed in the furanosyl series. Carbonylation of manganese complex 10 at 42 psi followed by MeOH/Na$_2$CO$_3$ 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 ^{1}H 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.
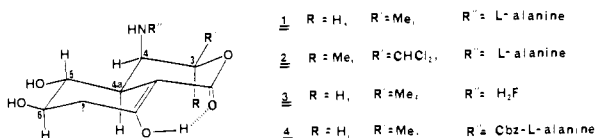
Total Synthesis of (+)-Actinobolin

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

1	R = H,	R' = Me,	R'' = L-alanine
2	R = Me,	R' = CHCl$_2$,	R'' = L-alanine
3	R = H,	R' = Me,	R'' = H$_2$F
4	R = H,	R' = Me.	R'' = Cbz-L-alanine

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.

(1) Isolation: Haskell, T. H.; Bartz, Q., R. *Antibiot. Annu.* **1959**, 505. Structure: Antotz, F. J.; Nelson, D. B.; Herald, D. L., Jr.; Munk, M. E. *J. Am. Chem. Soc.* **1970**, *92*, 4933 and references cited therein. Absolute configuration: Wetherington, J. B.; Moncrief, J. W. *Acta Crystallogr., Sect. B* **1975**, *B31*, 501.

(2) Kondo, S.; Horiuchi, Y.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1979**, *32*, 1069. Ueda, I.; Munakata, T.; Sakai, J. *Acta Crystallogr. Sect. B* **1980**, *B36*, 3128.

(3) (a) Yoshioka, M.; Nakai, H., Ohno, M. *J. Am. Chem. Soc.* **1984**, *106*, 1133. (b) Yoshioka, M.; Nakai, H.; Ohno, M. *Heterocycles* **1984**, *21*, 151. (c) A carbohydrate-based synthesis of N-acetyldesalanylactinobolin has recently appeared: Rahman, M. A.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1985**, *107*, 5576.

Our synthesis commenced with glyoxylate 5, which was prepared in 75% overall yield from cyclohexen-3-ol[4] 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)sulfonamide[9] 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 group[10] 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 reagent[12] derived from N,O-dimethylhydroxylamine gave an amido triol, which on acetonide 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 signficantly 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

(4) Pearlman, B. A. *J. Am. Chem. Soc.* **1979**, *101*, 6398.

(5) Kornblum, N.; Frazier, H. W. *J. Am. Chem. Soc.* **1966**, *88*, 865. See also: Emmons, W. D.; Freeman, J. P. *J. Am. Chem. Soc.* **1955**, *77*, 4415.

(6) Tschaen, D. M. Ph.D. Thesis, The Pennsylvania State University, 1984.

(7) cf Lindner, D. L.; Doherty, J. B.; Shoham, G.; Woodward, R. B. *Tetrahedron Lett.* **1982**, *23*, 5111.

(8) Surprisingly, a variety of other Lewis acid catalysts (EtAlCl$_2$, BF$_3$·Et$_2$O, AlCl$_3$, FeCl$_3$, ZnCl$_2$, Me$_2$AlCl) gave *none* of the desired ene product.

(9) For a discussion of this reaction, see: Bussas, R.; Kresze, G.; Munsterer, H.; Schwobel, A. *Sulfur Rep.* **1983**, *2*, 215.

(10) Fukuda, T.; Kitada, C.; Ffujino, M. *J. Chem. Soc., Chem. Commun.* **1978**, 220.

(11) When 10 was treated with TBDMSOTf (2,6-lutidine, DMF, −10 °C) ortho lactone i was produced in 60% yield. Analysis of the ^{1}H NMR spectrum
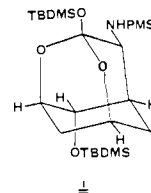
of i supported the structural assignment of diol 10.

(12) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.

(13) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(14) For a review of additions of organometallics to α-amino ketones and related compounds, see: Tramontini, M. *Synthesis* **1982**, 605.

(15) β-Elimination of the acetonide oxygen of the C-7 enolate (actinobolin numbering) is precluded on stereoelectronic grounds.