Analogous transformations can be performed in the furanosyl series. Carbonylation of manganese complex **10** at 42 psi followed by $MeOH/Na_2CO_3$ 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 ^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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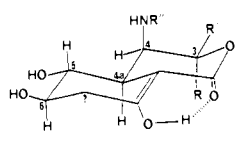
Actinobolin (**1**), a metabolite of *Streptomyces griseoviridis*,[1]



1 ≡ R = H, R'=Me, R''= L-alanine

2 ≡ R = Me, R'=$CHCl_2$, R''= L-alanine

3 ≡ R = H, R'=Me, R''= H_2F

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.

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

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(8) Surprisingly, a variety of other Lewis acid catalysts ($EtAlCl_2$, $BF_3 \cdot Et_2O$, $AlCl_3$, $FeCl_3$, $ZnCl_2$, Me_2AlCl) gave *none* of the desired ene product.

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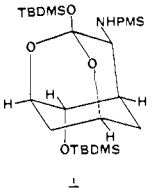
(11) When **10** was treated with TBDMSOTf (2,6-lutidine, DMF, -10 °C) ortho lactone i was produced in 60% yield. Analysis of the ^1H NMR spectrum



i

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

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

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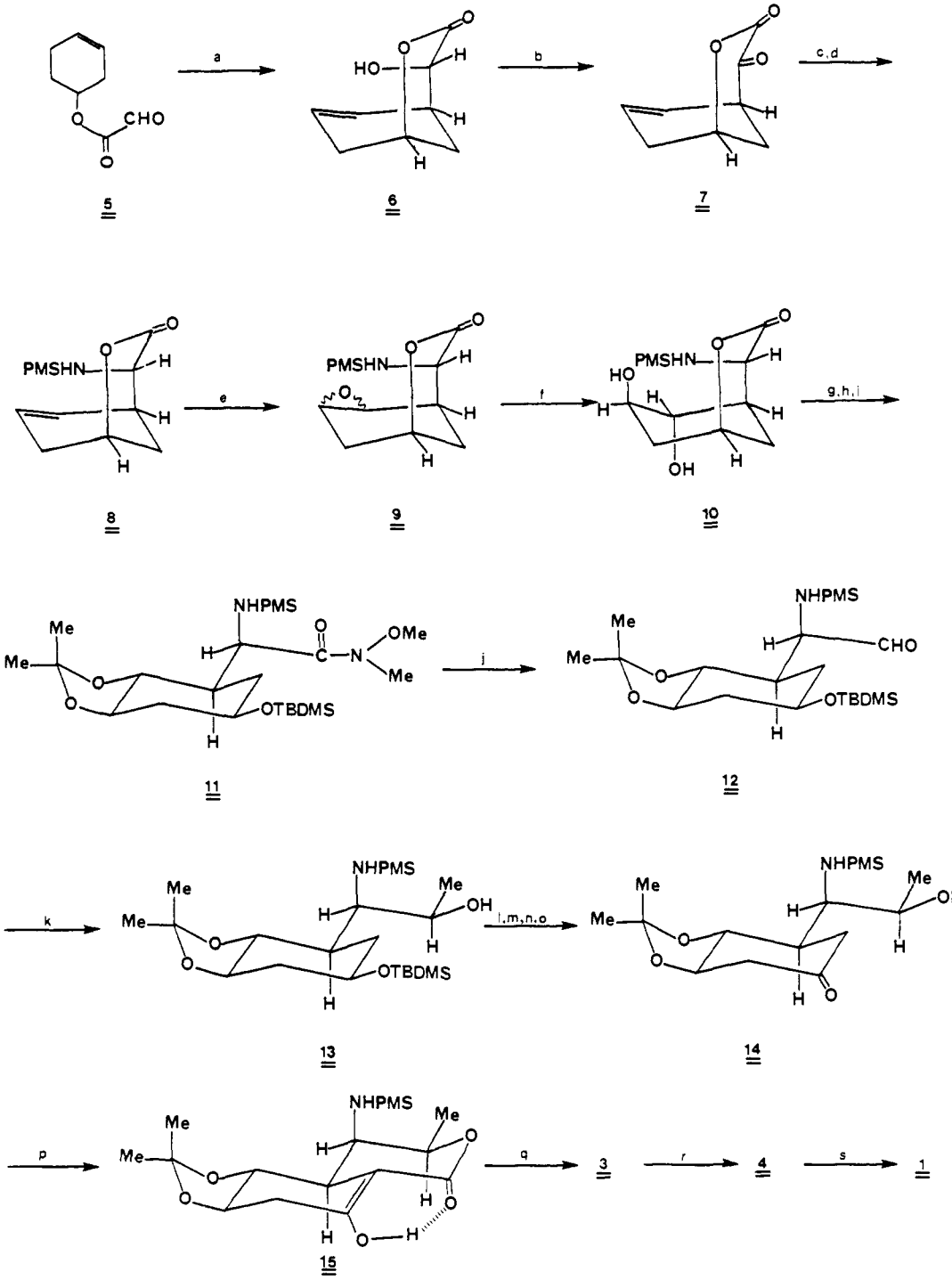
Scheme I[a]



[a] (a) $SnCl_4/MeNO_2$, room temperature, 50–60%; (b) CrO_3/pyridine, CH_2Cl_2, room temperature, 86%; (c) PMSNSO, $ClCH_2CH_2Cl$, $BF_3 \cdot Et_2O$, 42 °C; (d) $NaCNBH_3$, *t*-amyl alcohol, room temperature, 85% from **7**; (e) mCPBA, CH_2Cl_2, room temperature, 90%; (f) HCO_2H; MeOH, NEt_3; (g) $Me_2AlNMe(OMe)$, (7 equiv) THF, room temperature; (h) $Me_2C(OMe)_2$, PPTS, DMF; (i) TBDMSOTf, 2,6-lutidine, DMF, −10 °C, 78% from **9**; (j) $LiAlH_4$, THF, −78 °C, 89%; (k) MeMgBr, PhMe, −20 °C, 99%; (l) Ac_2O, pyridine, room temperature; (m) *n*-Bu_4NF, THF, room temperature; (n) CrO_3/pyridine, room temperature; (o) K_2CO_3, MeOH, room temperature, 90% from **13**; (p) carbonyl diimidazole (2 equiv), THF, room temperature; NaH, 80%; (q) anhydrous HF, anisole, room temperature, 99%; (r) Cbz-L-alanine, DCC, Et_3N, DMF, room temperature, 95%; (s) H_2–5% Pd/C, HOAc, MeOH, 0.5 N HCl (2 equiv), room temperature, 98%.

of intramolecular acylation reaction does not appear to be well precedented in the literature.

To complete the synthesis, enol lactone **15** was treated with anhydrous HF containing anisole to remove both the PMS and acetonide protecting groups,[3,10] providing (±)-actinobolyl amine as its hydrofluoride salt **3** (99%). This compound was coupled with Cbz-L-alanine to afford *N*-Cbz-actinobolin (**4**) along with an equal amount of its diastereomer (95% combined yield) which was separated by preparative TLC on silica gel ($MeOH/CHCl_3$, 5/95). Hydrogenolysis[3] of **4** yielded (+)-actinobolin hydrochloride (98%), which was identical with a sample prepared from natural material.[16]

(16) We are grateful to Drs. J. H. Dodd and J. French of Warner-Lambert Co. for a generous sample of (+)-actinobolinsulfate. This material was converted to the chloride salt using Dowex resin AG-1-X8 (chloride form). Natural (+)-actinobolin hydrochloride: $[\alpha]^{20}_D$ +48° (*c* 0.51, H_2O). Synthetic: $[\alpha]^{20}_D$ +44° (*c* 0.40, H_2O).

Thus, we have synthesized actinobolin stereoselectivity in 18 steps from glyoxylate **5**. We are currently in the process of preparing **5** in enantiomerically pure form and hope to use advanced intermediates **11** and/or **12** in the synthesis of bactobolin (**2**).

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An Inhibitor of Chorismate Mutase Resembling the Transition-State Conformation

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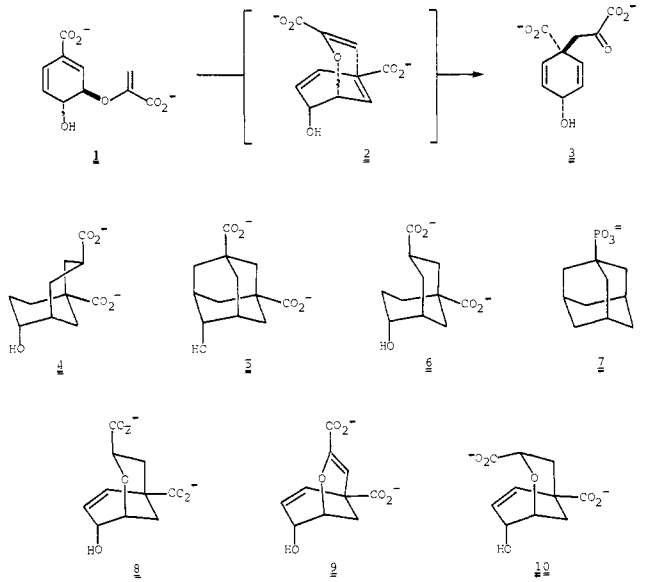
The chorismate mutases are appealing targets for the design of enzyme inhibitors, since they lie on a pathway that is key for the biosynthesis of aromatic amino acids in plants and microorganisms.[1] These enzymes are unique not only for catalyzing what is formally a Claisen rearrangement[2] but also for the fact that the conversion of chorismic acid **1** to prephenic acid **3** has a *unimolecular* solution counterpart. The relationship between substrate binding forces and enzymatic rate acceleration can therefore be explored without the complications that arise from imperfect comparisons of multimolecular (solution) with unimolecular (enzymatic) transformations.[3] Indeed, it can be argued that the chorismate mutases are the ideal targets for transition-state analogue inhibitors, in that the enzymatic rate acceleration should be reflected in enhanced binding of a "perfect" transition-state analogue in comparison to substrate.[4] This factor could be as much as 2×10^6.[5]

Although a number of molecules designed or rationalized to mimic the putative transition-state conformation **2** have been



reported,[6-8] none is bound to chorismate mutase significantly more tightly than chorismic acid itself (Table I).[9] The most potent inhibitor reported to date is adamantane-1-phosphonic acid (**7**), which Chao and Berchtold have reported to have a ratio of (inhibitor I_{50})/(chorismate K_m) of 0.05 at pH 9.[7] Since the hydroxybicyclo[3.3.1]nonane- and hydroxybicyclo[3.3.1]-adamantanedicarboxylic acids **5** and **6** incorporate the polar functionality of **2** and yet are not tightly bound, Andrews et al. reasoned that the orientation of these groups is crucial.[6] In this paper, we describe syntheses of the oxabicyclic derivatives **8-10** and our discovery that the endo isomer **10** is the most potent inhibitor of chorismate mutase yet reported.

Table I. Selected Inhibitors of Mutase Activity of Chorismate Mutase/Prephenate Dehydrogenase

inhibitor	I_{50},[a] M (conditns[b])	I_{50}/K_m
4	$>2.5 \times 10^{-3}$ (A)	>20
5	1.3×10^{-3} (A)	12
6	7.8×10^{-4} (A)	7
7	4×10^{-4} (B)[c]	25
	7×10^{-5} (C)	0.05

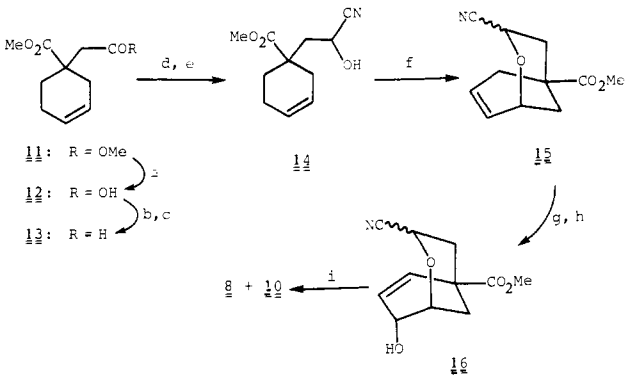
[a] I_{50} is defined as the concentration of inhibitor giving 50% inhibition when substrate concentration equals K_m; for linear competitive inhibitors, $I_{50} = 2K_i$. [b] (A) *E. coli* enzyme, pH 7.5, K_m(chorismate) = 1.1×10^{-4} M; ref 6; (B) *E. coli* enzyme, pH 6.0, K_m(chorismate) = 1.5×10^{-5} M; ref 8; (C) *A. aerogenes* enzyme, pH 9.0, K_m(chorismate) = 1.3×10^{-3} M; ref 7. [c] I_{50} value computed from $K_i = 2 \times 10^{-4}$ M.

Table II. Comparison of Oxabicyclo[3.3.1]nonenes **8-10** and Adamantane-1-phosphonic Acid **7** as Inhibitors of Chorismate Mutase/Prephenate Dehydrogenase[a]

inhibitor	I_{50}, M	I_{50}/K_m
8	5.9×10^{-5}	3.3
9	1.7×10^{-5}	0.9
7	5.5×10^{-6}	0.31
10	1.5×10^{-7}	0.008

[a] *E. coli* enzyme, pH 7.5, K_m(chorismate) = 1.8×10^{-5} M (this value determined in the presence of 0.1 mg/mL of bovine serum albumin[15]).

Scheme I[a]



[a] (a) NaOH/MeOH/H_2O, 92%; (b) ClCOCOCl/CH_2Cl_2, 95%; (c) $(Ph_3P)_2CuBH_4$/acetone, 78%; (d) Me_3SiCN/ZnI_2, 71%; (e) HCl/aqueous THF, 82%; (f) *N*-PhSe-phthalimide/*p*-TSA/CH_2Cl_2/-78 °C, then *t*-BuOOH, 83%; (g) *m*-CPBA/CH_2Cl_2/reflux, 99%; (h) $Me_3SiBr/Ph_3P/CH_2Cl_2$; DBU/MeCN/60 °C; HCl/aqueous THF, 77%; (i) KOH/H_2O/reflux, (100%).

The synthetic route leading to the racemic inhibitors **8** and **10** is outlined in Scheme I. Ester acid **12** obtained from controlled hydrolysis of the Diels-Alder adduct **11** is converted to the aldehyde **13** by the method of Fleet[10] and thence to the cyanohydrin **14** as described by Evans.[11] Selenocyclization[12] of **14** followed

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