Complete Retention of Configuration in a Cobaloxime π-Cation-Mediated Cyclization of an (ω-Hydroxy-β-hydroxyalkyl)cobaloxime

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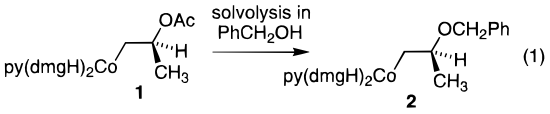
In 1961, Lenhert and Hodgkin reported that the vitamin B_{12} coenzyme contains a novel carbon−cobalt bond.[1] The unusual chemical reactions catalyzed by coenzyme B_{12}-dependent enzymes have stimulated numerous studies of the chemical reactions of the C−Co bond in coenzyme B_{12}, in other cobinamides, and in coenzyme B_{12} model complexes such as the cobaloximes.

Most of the mechanistic studies have focused on the radical chemistry of the C−Co bond.[2] Over the past decade, the radical chemistry of the C−Co bond in B_{12}-like compounds has been used to develop useful synthetic organic methods.[3]

The C−Co bond also displays ionic reactivity. The C−Co bond can provide anchimeric assistance for the departure of a leaving group in the β position to form a hyperconjugated cationic intermediate best described as a cobaloxime π-cation. Several studies have focused on the structure and reactivity of cobaloxime π-cations.[4] It has been known for over 20 years that cobaloxime π-cations can be captured by oxygen and nitrogen nucleophiles. For example, (β-hydroxyalkyl)- and (β-alkoxyalkyl)cobaloximes can undergo acid-catalyzed β-heteroatom exchange with oxygen and nitrogen nucleophiles.[5] Recently, we reported the reaction of cobaloxime π-cations with carbon nucleophiles, the first examples of carbon−carbon bond formation.[6]

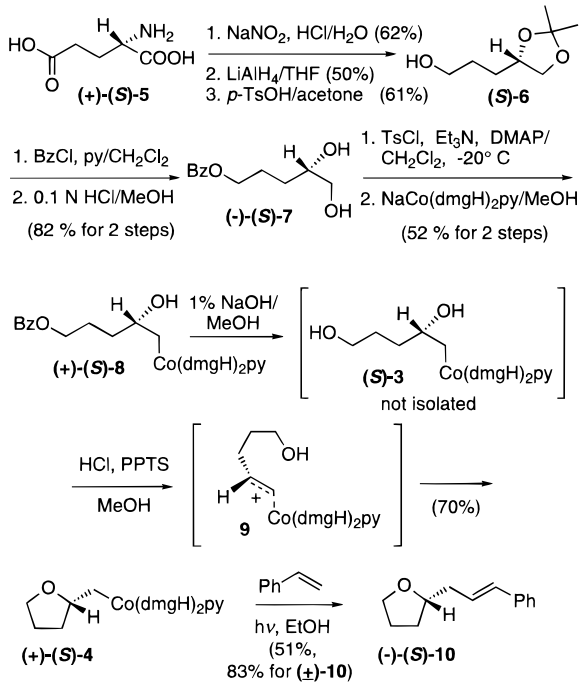
To date there has been only one report of the stereochemistry of reactions of cobaloxime π-cations. In 1972, the solvolysis of homochiral (2-acetoxypropyl)cobaloxime in benzyl alcohol was reported to proceed with retention of configuration (eq 1).[7] This observation supported the



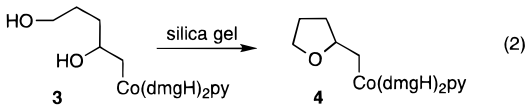
(1)

postulated intermediacy of cobaloxime π-cations in alcoholyses of (2-acetoxyalkyl)cobaloximes. Although the yield of pure, isolated [2-(benzyloxy)propyl]cobaloxime was only 37%,[8] the retention of configuration result in this case and other incisive mechanistic studies of this type of reaction[9] indicated its considerable potential for applications in organic synthesis.

Scheme 1



As part of our research program to explore the reactivity and synthetic potential of cobaloxime π-cations we decided to examine the stereochemistry of a cyclization reaction of an (ω-hydroxy-β-hydroxyalkyl)cobaloxime to form a cyclic ether. Racemic (2,5-dihydroxypentyl)-cobaloxime (**3**) was reported to undergo silica gel-mediated cyclization to form (tetrahydrofurfuryl)cobaloxime (**4**) (eq 2).[10] In this paper, we report the stereochemical



(2)

outcome of that reaction (Scheme 1).

Treatment of L-glutamic acid ((*S*)-**5**) with $NaNO_2$ and HCl in H_2O gave an intermediate lactone[11] that was reduced to (*S*)-1,2,5-pentanetriol using $LiAlH_4$,[12] followed by acetonide protection of the 1,2 diol (catalytic *p*-toluenesulfonic acid (*p*-TsOH) in dry acetone)[13] to give (*S*)-1,2-*O*-isopropylidene-1,2,5-pentanetriol ((*S*)-**6**) in 19% overall yield for three steps from (*S*)-**5**. Treatment of (*S*)-**6** with benzoyl chloride and pyridine in CH_2Cl_2 produced (*S*)-1,2-*O*-isopropylidene-5-*O*-benzoyl-1,2,5-pentanetriol,[14] which was treated with 0.1 N HCl in MeOH/H_2O to remove the acetonide to provide (*S*)-5-*O*-benzoyl-1,2,5-pentanetriol ((*S*)-**7**) in 82% overall yield for two steps from (*S*)-**6**. Treatment of (*S*)-**7** with *p*-toluene-

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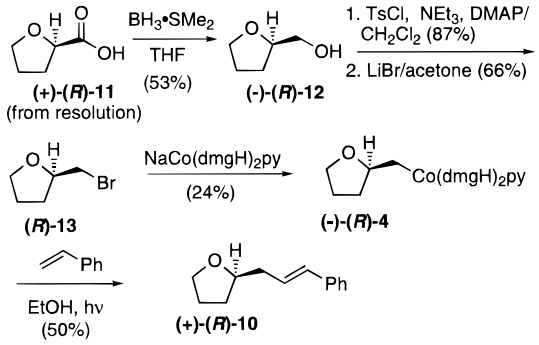
sulfonyl chloride (TsCl), triethylamine, and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in CH_2Cl_2 at −20 °C followed by treatment with $NaCo(dmgH)_2py$ in MeOH under standard conditions to form alkyl cobaloximes[15] provided [(*S*)-2-hydroxy-5-*O*-benzoylpentyl]cobaloxime ((*S*)-**8**) in 52% overall yield for two steps from (*S*)-**7**. The benzoate group in (*S*)-**8** was hydrolyzed with 1% NaOH in MeOH to produce cobaloxime (*S*)-**3**, which was not isolated but was converted directly into cobaloxime (*S*)-**4** by acidification to pH 6.4−6.8 with a standardized HCl solution and solid pyridinium *p*-toluensulfonate (PPTS). The structure of cobaloxime (*S*)-**4** was confirmed by ^1H NMR comparison to an authentic racemic sample, (*R*,*S*)-**4**, prepared from (±)-tetrahydrofurfurylbromide[16] and by comparison to literature data.[17] Cobaloxime (*S*)-**4** was photochemically cross-coupled with styrene in 95% EtOH for 48 h[18] to give alkene (*S*)-**10** in 51% isolated yield after chromatography.

The stereoselectivity of the cyclization of (*S*)-**3** to form (*S*)-**4** was determined by chiral HPLC.[19] Racemic diol (*R*,*S*)-**7** was prepared from racemic 1,2,5-pentanetriol, which was prepared by a literature method.[20] Racemic diol (*R*,*S*)-**7** was used to determine the retention times for each enantiomer of **7** on the chiral HPLC column. The enantiomeric excess of (*S*)-**7** was determined to be 95.9% ee (±0.3%).[21] Racemic alkene (*R*,*S*)-**10** was prepared by cross coupling of racemic (*R*,*S*)-**4** (prepared as described for (*S*)-**10** above) with styrene. Racemic alkene (*R*,*S*)-**10** was used to determine the retention times for each enantiomer of **10** on the chiral HPLC column. Alkene (*S*)-**10** obtained from the cobalt-mediated cyclization shown in Scheme 1 was determined to have an enantiomeric excess of 93.8% (±0.1%).

The data presented in the preceding paragraph establish that the cyclization of cobaloxime π-cation **9** is stereospecific, but they do not establish whether the reaction proceeds with complete retention or with complete inversion of configuration. To determine this it was necessary to obtain an authentic sample of either (*R*)-**10** or (*S*)-**10** by an independent method (Scheme 2). Enantioenriched tetrahydro-2-furoic acid (*R*)-**11** was obtained through a brucine resolution.[22] Borane reduction of (*R*)-**11** using $BH_3{\cdot}SMe_2$ in THF gave (*R*)-**12** in moderate yield.[23] Tosylate formation followed by displacement of the tosylate with LiBr in acetone gave (*R*)-**13**. Reaction of (*R*)-**13** with $NaCo(dmgH)_2py$ in MeOH produced cobaloxime (*R*)-**4.** Cross-coupling of (*R*)-**4** with styrene gave alkene (*R*)-**10**, whose absolute configuration was certain.[24] Alkene (*R*)-**10** was analyzed by chiral HPLC. The major peak in the analysis of (*R*)-**10** was opposite to that observed for alkene (*S*)-**10** obtained by the cobalt-mediated cyclization shown in Scheme 1. This result, combined with the other results reported herein, establishes that the cyclization of cobaloxime (*S*)-**3** to form cobaloxime (*S*)-**4** is stereospecific and proceeds with retention of configuration.

Scheme 2



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Supporting Information Available: Experimental details for synthetic operations and chiral HPLC, and characterization data for all compounds are available (12 pages).

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