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Regio- and stereoselective ring opening of epoxide with cyanoguanidine dianions, a facile synthesis of the K_{ATP} opener BMS-180448

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Abstract

BMS-180448, (3S,4R)-**2**, was prepared in 63% yield via a facile method which involved a new regio- and stereoselective ring opening of epoxide (3S,4S)-**12** with the potassium dianion of cyanoguanidine **11**.

Asymmetrically substituted β-hydroxy cyanoguanidines, **1**, are important structural arrays in many biologically active compounds,[1–3] including the new class of potassium channel openers such as BMS-180448, **2**.[2] Three methods have been previously reported for the preparation of β-hydroxy cyanoguanidines, all of which used β-amino alcohols (**3**) as common starting materials. In the first method, the β-amino alcohol was coupled with cyanothiourea **4** using a water soluble coupling reagent, 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDAC). The cyanothiourea **4** was prepared by the reaction of thioisocyanate and preformed monosodium cyanamide.[2,4,5] In the second method, the amino alcohol was condensed with diphenylcyanocarboimidate **5** to give an intermediate, **6**, which was then reacted with amines.[2,6] Although **6** generally reacted smoothly with alkylamines without activation, the use of Lewis acid such as trimethylaluminum was necessary for less active amines such as anilines due to their poor nucleophilicity.[7] In the third method, the amino alcohol was coupled with thioisocyanate to give thiourea **7**. Subsequent treatment of **7** with EDAC afforded oxazolidine **8**, which upon reaction

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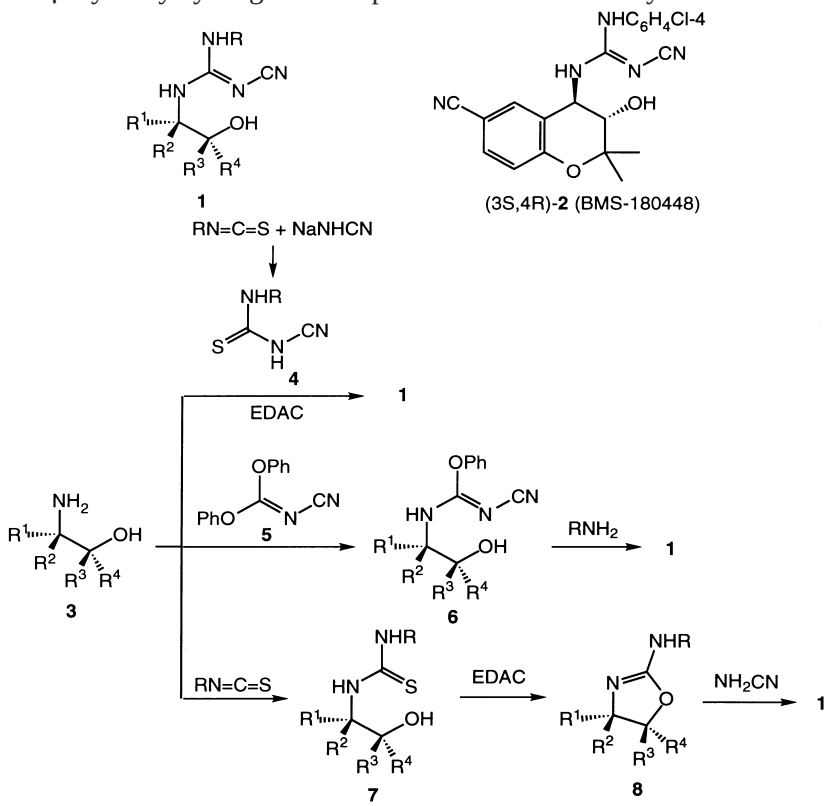
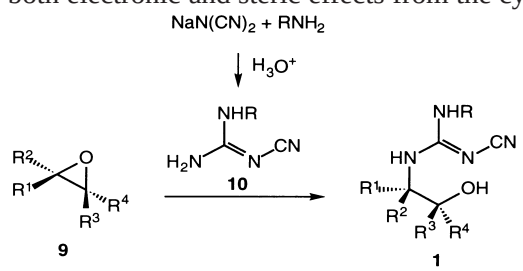
with cyanamide gave β-hydroxy cyanoguanidine.[8] All of these methods were multi-step syntheses and afforded the desired β-hydroxy cyanoguanidine products in low overall yields.



A synthetically more appealing strategy for the assembly of asymmetrically substituted chiral non-racemic β-hydroxy cyanoguanidines is the regio- and stereoselective ring opening of epoxides **9** with cyanoguanidines **10**. This approach is particularly attractive as the cyanoguanidines can be readily obtained in high yield by the reaction of amines with an inexpensive and non-toxic reagent, sodium dicyanamide, in water at room temperature.[9] More importantly, a variety of methods are available for the preparation of epoxides (**9**) in chiral nonracemic forms.[10] This approach, however, demands successful differentiation of the three guanidine nitrogen atoms of **10**. The required chemoselectivity was expected based on the consideration of both electronic and steric effects from the cyano and R group.

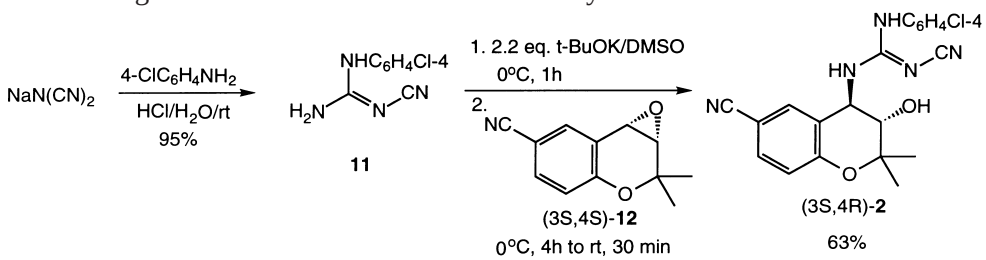


In a project aimed at development of a more efficient synthesis of the cardioselective anti-ischemic ATP-sensitive potassium channel opener BMS-180448,[2,4,11] we examined the coupling of cyanoguanidine **11** with epoxide (3S,4S)-**12** and report herein a facile approach to the assembly of this molecule.

Direct coupling of cyanoguanidine **11**[9] with epoxide (3S,4S)-**12**[12] under a variety of conditions resulted in no reaction, due presumably to the poor nucleophilicity of the cyanoguanidine. Use of Lewis

acids such as boron trifluoride caused decomposition of both starting materials. Attempts to couple the epoxide (3S,4S)-**12** with the more nucleophilic anion of cyanoguanidine **11** also failed. Thus, treatment of **11** with one equivalent of base (LDA, NaHMDS, etc) followed by addition of epoxide (3S,4S)-**12** gave only recovered starting materials. Use of BF_3 to promote this anionic reaction again resulted in decomposition of both starting materials.

In order to overcome this lack of reactivity of cyanoguanidine and its monoanion, an attempt was made to prepare the previously unreported dinitrogen dianion from **11**. Greater reactivity has been previously demonstrated in the case of dianions containing at least one reactive carbanion.[13,14] Indeed, treatment of cyanoguanidine **11** with 2 equivalents of n-BuLi followed by addition of the epoxide (3S,4S)-**12** at 0–25°C for 16 hours gave the desired BMS-180448 in 20% yield.



In the hope of achieving a higher yield in this coupling reaction, several variations of the original conditions were investigated. Use of t-BuMgCl, t-BuOK and Schlosser's base (n-BuLi/t-BuOK) in THF all resulted in only a slight increase in yield (28–30%). Changing the solvent from THF to DME gave inferior results (15–17% yield), while use of DMSO improved the yield to a small degree (35%). The largest improvement by far resulted from the use of the dipotassium salt of cyanoguanidine, formed by treatment of **11** with 2.2 equivalents of potassium t-butoxide in DMSO at 0°C for 1 hour. The coupling reaction was subsequently carried out by adding a solution of **12** in DMSO to the preformed dianion at 0°C. After stirring the reaction mixture for 4 hours at 0°C and 30 minutes at room temperature and quenching the reaction with 6 N HCl at 5°C, the product was extracted into EtOAc at pH 7. Removal of solvents gave a crude product which was purified by crystallization (EtOH/water) affording BMS-180448, (3S,4R)-**2**, in 63% yield. Importantly, other regio- and stereoisomers were not observed in this reaction. It should be pointed out that BMS-180448 was previously prepared in 3–4 steps from (3S,4S)-**12** in 40–50% overall yield.[2,4–8]

In summary, a new approach for the preparation of asymmetrically substituted β-hydroxy cyanoguanidine has been developed as demonstrated in the facile synthesis of BMS-180448. The new approach involved a regio- and stereoselective ring opening of an epoxide with cyanoguanidine dianion. This method is expected to be readily adaptable to the synthesis of other β-hydroxy cyanoguanidines.

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