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Asymmetric Synthesis of Tetrahydroquinolin-3-ols via $CoCl_2$-Catalyzed Reductive Cyclization of Nitro Cyclic Sulfites with $NaBH_4$

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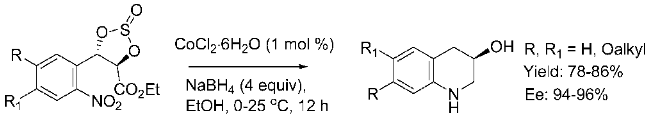
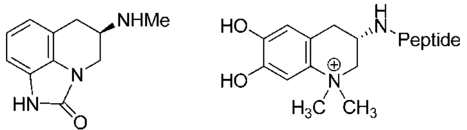
ABSTRACT



A new method for the construction of chiral 3-substituted tetrahydroquinoline derivatives based on asymmetric dihydroxylation and $CoCl_2$-catalyzed reductive cyclization of nitro cyclic sulfites with $NaBH_4$ has been described with high optical purities. This method has been successfully applied in the formal synthesis of PNU 95666E and anachelin H chromophore.

Substituted tetrahydroquinoline derivatives (THQs) bearing various simple and complex substituents are of medicinal and industrial importance due to their pronounced activity in many physiological processes.[1,2] These heterocycles along with their core structures are present in numerous pharmacological agents such as sumanirole maleate (PNU95666 E) (**1**),[3] a selective and high affinity agonist at the dopamine D_2 receptor subtype and a potential agent for the treatment of Parkinson's disease, as well as anachelin H intermediate (**2**), a secondary metabolite recently isolated from the cyanobacterium *Anabaena cylindrica*, which serves as a ligand for iron (siderophores) mediating iron uptake[4] (Figure 1).



1 **2**

Figure 1. PNU 95666 E (**1**) and anachelin H chromophore (**2**).

In addition, THQ-based inhibitors are found to be the most potent among several structural classes of protein farnesyltransferase inhibitors.[5] Among the diverse strategies that have

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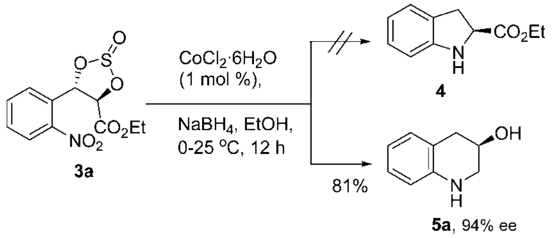
been devised for the synthesis of THQs,[1b,6] the partial reduction of the heteroaromatic ring system has emerged as one of the most useful routes.[7] In contrast, only a few methods exist in the literature for the asymmetric synthesis of 3-substituted THQs, including strategies involving oxidative aza-annulation of chiral amino acids,[8] Rh-catalyzed reduction of α-amino cinnamate,[9] and asymmetric dihydroxylation[10] and epoxidation[9] of olefins followed by cyclization with an aromatic amino group. However, use of chiral starting materials, lengthy reaction sequence, and use of protection and deprotection of various functional groups are some of the drawbacks of the existing routes. Hence, there has been considerable interest in the development of elegant and efficient protocols for the asymmetric synthesis of 3-substituted THQs.[11]

In continuation with our studies on simultaneous reduction of multifunctional moieties,[12] we report in this communication a novel method for the construction of 3-substituted tetrahydroquinoline derivatives **5a−f** using $CoCl_2$ as catalyst and $NaBH_4$ as hydride source, demonstrating its effectiveness in the asymmetric synthesis of PNU 95666 E (**1**) and anachelin H chromophore (**2**).

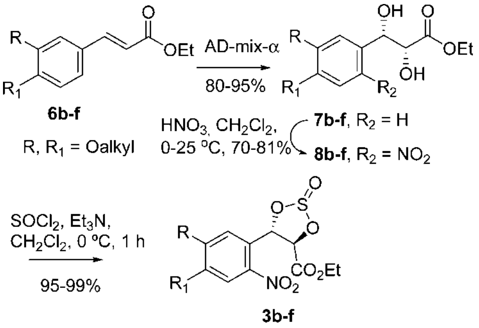
As part of our program on asymmetric synthesis of bioactive molecules,[12] we sought a new enantioselective synthetic route to (*S*)-ethyl indole-2-carboxylate (**4**), a key intermediate required in the synthesis of perindopril,[13] an orally active pharmaceutical for the treatment of hypertension. For this, we reasoned that the required carboxylate **4** could be prepared by Co-catalyzed reductive cyclization of nitro cyclic sulfite **3a**. Surprisingly, when subjected to reduction with $CoCl_2$ (1 mol %) and $NaBH_4$ (4 equiv), compound **3a** underwent reductive cyclization smoothly to provide (*R*)-3-hydroxytetrahydroquinoline (**5a**) exclusively, in 81% yield and 94% ee, instead of the expected ester **4**. This unexpected transformation was comprised of simultaneous reduction of multifunctional groups all occurring in a single step leading to the cyclized 3-substituted THQ **5a** in high optical purity (Scheme 1).

Scheme 1. Synthesis of (*R*)-3-Hydroxytetrahydroquinoline (**5a**)



Encouraged by this result, we examined the scope of this reaction by subjecting several chiral nitro cyclic sulfites **3b−f** to reductive cyclization. While compound **3a** was prepared from *o*-nitrobenzaldehyde (Wittig followed by AD-mix-α), other substrates **3b−f** were efficiently prepared in three steps starting from the corresponding α,*β*-unsaturated esters **6b−f**: (i) Os-catalyzed asymmetric dihydroxylation (AD-mix-α) of cinnamates **6b−f** using $(DHQ)_2$-PHAL ligand;[15] (ii) regiospecific aromatic nitration of diols **7b−f** using HNO_3,[2a] and (iii) protection of diols **8a−f** with $SOCl_2$[16] (Scheme 2).

Scheme 2. Synthesis of Nitro Cyclic Sulfites **3b−f**



When subjected to the $CoCl_2$-catalyzed reduction[14] with 4 equiv of $NaBH_4$, chiral nitro cyclic sulfites **3a−f** gave the corresponding (*R*)-3-hydroxytetrahydro-quinoline derivatives **5a−f** in 78−86% yields with excellent enantioselectivities. Results of such studies are presented in Table 1. As can be seen, various cyclic sulfites underwent reductive cyclization

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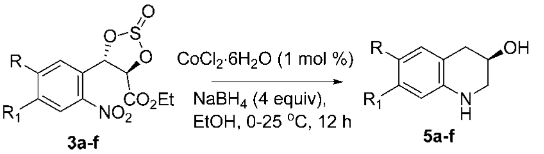
Table 1. Co-Catalyzed Reductive Cyclization of Nitro Cyclic Sulfites with $NaBH_4$



		products **5a−f**	
entry	substrates **3a−f**	yield (%)[a]	ee (%)
a	R = R^1 = H	81	94[c]
b	R = R^1 = OMe	78	96[b]
c	R = R^1 = OBn	85	96[c]
d	R = OBn; R^1 = OMe	83	95[c]
e	R, R^1 = −O−CH_2−O−	81	96[c]
f	R = *O*-pentyl; R^1 = OMe	82	94[c]

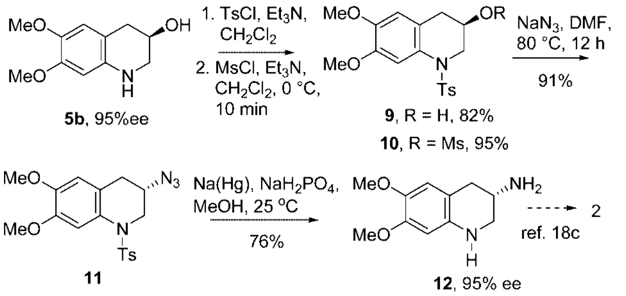
[a] Isolated yield after column chromatographic purification. [b] ee determined by chiral HPLC analysis. [c] ee determined by Mosher's ester analysis.

smoothly, at ambient conditions, to provide **5a−f** in a one-pot reaction.

The optimization showed a mixture of products were obtained with lower equiv of $NaBH_4$, thus requiring a minimum of 4 equiv of $NaBH_4$ to achieve excellent yields; ethanol or a combination of EtOH and DMF could be used as solvent. However, other metal catalysts such as $NiCl_2$ and MnO_2 were found to show catalytic activity under the reduction conditions to give poor yields (33% and 21%, respectively) of **5a**. The formation of the tetrahydroquinolin-3-ols **5a−f** was confirmed by their spectra, which displayed characteristic signals in the range of δ 4.15−4.30 as multiplets in their ^1H NMR and δ 63.1−63.4 in their ^{13}C NMR spectra corresponding to the presence of the CHOH moiety in THQ.

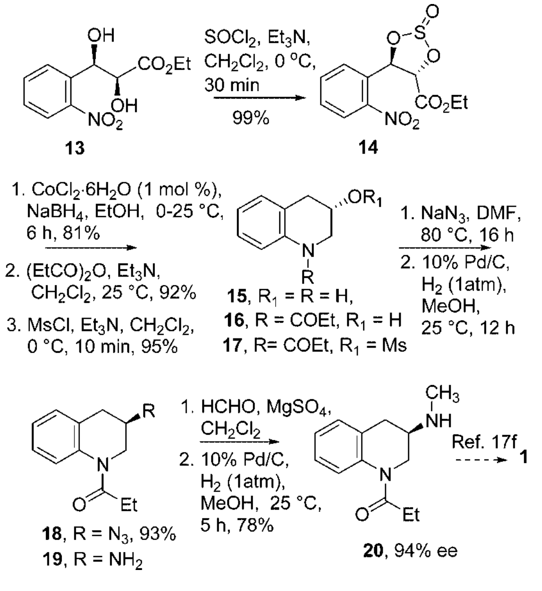
Next, the Co-catalyzed one-pot reductive cyclization of nitro cyclic sulfites has been successfully demonstrated in the formal synthesis of sumanirole maleate (PNU95666 E)[17] and anachelin H.[18] First, the synthesis of anachelin H chromophore **2** with the (*S*)-configuration in the THQ core was undertaken. Both the amine and hydroxyl functions in **5b** were protected sequentially as tosylate **9** and mesylate **10**, respectively. Displacement of the mesylate **10** with azide anion gave azido THQ **11**, which was subjected to reduction with sodium amalgam in NaH_2PO_4 whereby reduction of both azide and tosylate functions took place efficiently to afford (*S*)-3-aminotetrahydroquinoline **12** in 76% yield and 95% ee[18c] (Scheme 3).

Scheme 3. Synthesis of Anachelin H Chromophore **2**



In a similar manner, a formal synthesis of PNU95666E (**1**) with the (*R*)-configuration in the THQ core was undertaken. The chiral nitrodiol **13**, prepared by AD-mix-β oxidation of nitro cinnamate using $(DHQD)_2$-PHAL as ligand, was transformed into the corresponding cyclic sulfite **14**. The one-pot reductive cyclization of **14** using $CoCl_2 \cdot 6H_2O$ (1 mol %) and $NaBH_4$ (4 equiv) gave the (*S*)-tetrahydroquinolin-3-ol (**15**) in 81% yield. Selective protection of the amine in **15** with propionic anhydride gave amide **16** in 92% yield. Mesylation of the hydroxyl group in **16** followed by treatment with sodium azide gave **18**, which was catalytically hydrogenated to yield amine **19**. The reductive methylation of amine **19** gave the methylamine **20** in two steps with an overall yield of 78% and 94% ee (Scheme 4).

Scheme 4. Formal Synthesis of PNU 95666 E (**1**)



To have a better understanding of the reaction mechanism, we have subjected diols **21** and **8a** to Co-catalyzed reduction

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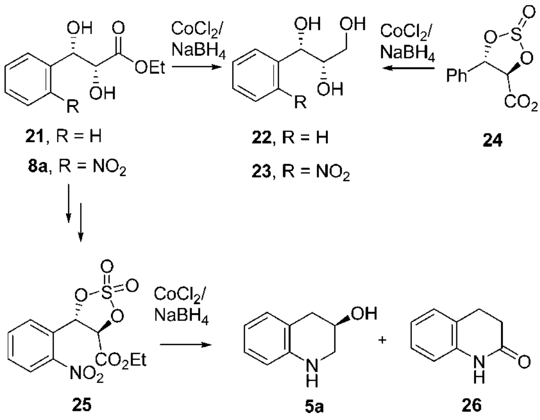
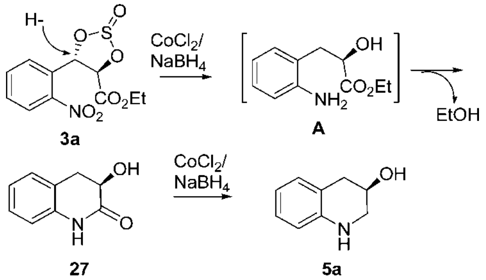
that proceeded to give high yields of the corresponding triols **22** and **23**, respectively. Also, when nitro cyclic sulfate **25**, obtained from **8a** in two steps, was subjected to reduction, a mixture of **5a** (34%) and **26** (41%) was obtained. However, cyclic sulfite **24**, under the reduction condition, gave only triol **22** in 55% yield (Scheme 5). This indicates that both nitro and cyclic sulfite moieties are required in the Co-catalyzed reductions of **3a−f**. Thus, we believe that simultaneous reduction of both nitro and cyclic sulfite groups takes place to give the unstable species **A**, which underwent cyclization to afford hydroxylactam **27**. Compound **27** was indeed isolated and characterized when the reaction was terminated before completion. Finally, the reduction of the lactam carbonyl in **27**, assisted by the α-hydroxyl group, resulted in the formation of THQs (**5a−f**) (Scheme 6).

Scheme 5. Co-Catalyzed Reduction of Esters, Sulfites, and Sulfate with $NaBH_4$



Scheme 6. Mechanistic Pathway for the Co-Catalyzed Reduction of Nitro Cyclic Sulfite



In conclusion, we believe this reductive cyclization strategy to be novel for the construction of 3-substituted THQ cores with both (*R*)- and (*S*)-configurations in a single step. This unprecedented multifunctional transformation in a single step employs $CoCl_2$ as catalyst and $NaBH_4$ as an easily handled reducing agent. The formal synthesis of two important drugs, namely, PNU95666 E (**1**) and anachelin H core (**2**), has been further demonstrated.

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Supporting Information Available: Detailed experimental procedures and ^{1}H NMR and ^{13}CNMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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