LETTERS 2009 Vol. 11, No. 4 803–806

ORGANIC

Asymmetric Synthesis of Tetrahydroquinolin-3-ols via CoCl₂-Catalyzed Reductive Cyclization of Nitro Cyclic Sulfites with NaBH₄

Arun R. Jagdale, R. Santhosh Reddy, and Arumugam Sudalai*

Chemical Engineering and Process Development Division, National Chemical Laboratory, Pashan Road, Pune-411 008, INDIA

a.sudalai@ncl.res.in

Received September 26, 2008

ABSTRACT



A new method for the construction of chiral 3-substituted tetrahydroquinoline derivatives based on asymmetric dihydroxylation and CoCl₂catalyzed reductive cyclization of nitro cyclic sulfites with NaBH₄ 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 D₂ 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

10.1021/0l8028109 CCC: \$40.75 © 2009 American Chemical Society Published on Web 01/21/2009 from the cyanobacterium *Anabaena cylindrica*, which serves as a ligand for iron (siderophores) mediating iron uptake⁴ (Figure 1).



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

⁽¹⁾ For reviews, see: (a) Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A. *Chem. Rev.* **1997**, *97*, 787–828. (b) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031–15070.

^{(2) (}a) Yasuzawa, T.; Muroi, K.; Ichimura, M.; Takahashi, I.; Ogawa, T.; Takahashi, K.; Sano, H.; Saitoh, Y. *Chem. Pharm. Bull.* **1995**, *43*, 378–391. (b) Santangelo, F.; Casagrande, C.; Miragoli, G.; Vecchietti, V. *Eur. J. Med. Chem.* **1994**, *29*, 877–882. (c) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, I. J. Am. Chem. Soc. **1990**, *112*, 3715–3716. (d) Ogawa, T.; Ichimura, M.; Katsumata, S.; Morimoto, M.; Takahashi, K. J. Antibiot. **1989**, *42*, 1299–1301. (e) Omura, S.; Nakagawa, A. *Tetrahedron Lett.* **1981**, *22*, 2199–2202.

^{(3) (}a) Heier, R. F.; Dolak, L. A.; Duncan, J. N.; Hyslop, D. K.; Lipton, M. F.; Martin, I. J.; Mauragis, M. A.; Piercey, M. F.; Nichols, N. F.; Schreur, P. J. K. D.; Smith, M. W.; Moon, M. W. *J. Med. Chem.* **1997**, *40*, 639–646. (b) Moon, M. W.; Morris, J. K.; Heier, R. F.; Chidester, C. G.; Hoffmann, W. E.; Piercey, M. F.; Althaus, J. S.; VonVoigtlander, P. F.; Evans, D. L.; Figur, L. M.; Lahtis, R. A *J. Med. Chem.* **1992**, *35*, 1076–1092.

^{(4) (}a) Ito, Y.; Ishida, K.; Okada, S.; Murakami, M. *Tetrahedron* **2004**, *60*, 9075–9080. (b) Gademann, K.; Budzikiewicz, H. *Chimia* **2004**, *58*, 212–214.

⁽⁵⁾ Van Voorhis, W. C.; Rivas, K. L.; Bendale, P.; Nallan, L.; Hornéy, C.; Barrett, L. K.; Bauer, K. D.; Smart, B. P.; Ankala, S.; Hucke, O.; Verlinde, C. L. M. J.; Chakrabarti, D.; Strickland, C.; Yokoyama, K.; Buckner, F. K.; Hamilton, A. D.; Williams, D. K.; Lombardo, L. J.; Floyd, D.; Gelb, M. H. Antimicrob. Agents Chemother. **2007**, 3659–3671.

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 dihydroxylation¹⁰ and epoxidation⁹ 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 CoCl₂ as catalyst and NaBH₄ 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

(7) (a) Ishitani, H.; Kobayashi, S. Tetrahedron Lett. 1996, 37, 7357–7360. (b) Steinhagen, H.; Corey, E. J. Org. Lett. 1999, I, 823–824. (c) Katritzky, A. R.; Rachwal, B.; Rachwal, S. J. Org. Chem. 1995, 60, 2588–2596. (d) Katritzky, A. R.; Rachwal, B.; Rachwal, S. J. Org. Chem. 1995, 60, 7631–7640. (e) Fujita, K.; Yamamoto, K.; Yamaguchi, R. Org. Lett. 2002, 4, 2691–2694. (f) Fujita, K.; Yamamoto, K.; Yamaguchi, R. Org. Lett. 2001, 3, 2053–2056. (g) Tokes, A. L.; Litkei, G.; Szilagyi, L. Synth. Commun. 1992, 22, 2433–2445.

(8) For review, see: Lawrence, A. K.; Gademann, K. Synthesis 2008, 331–351.

(9) Gallou-Dagommer, I.; Gastaud, P.; RajanBabu, T. V. Org. Lett. 2001, 3, 2053–2056.

(10) Boger, D. L.; McKie, J. A.; Nishi, T.; Ogiku, T. J. Am. Chem. Soc. 1997, 119, 311-325.

(11) (a) Dehnhardt, C. M.; Espinal, Y.; Venkatesan, A. M. Synth. Commun. 2008, 38, 796–802. (b) Gao, K.; Li, Y. Z.; Sun, H. X. Synth. Commun. 2007, 37, 4425–4437. (c) Kouznetsov, V. V.; Bohórquez, A. R. R.; Stashenko, E. E. Tetrahedron Lett. 2007, 48, 8855–8860. (d) Fukamizu, K.; Miyake, Y.; Nishibayashi, Y. J. Am. Chem. Soc. 2008, 130, 10498–10499.

(12) (a) Jagdale, A. R.; Sudalai, A. *Tetrahedron Lett.* 2008, 49, 3790–3793.
(b) Paraskar, A. S.; Sudalai, A. *Tetrahedron* 2006, 62, 5756–5762.
(13) Vincent, M.; Remond, G.; Portevin, B.; Laubie, S. M. *Tetrahedron*

Lett. **1982**, 23, 1677–1680. (14) (a) For review, see: Periasamy, M.; Thirumalaikumar, M. J.

Organomet. Chem. 2000, 609, 137–151. (b) Ganem, B.; Osby, J. O. Chem. Rev. 1986, 86, 763–780. (c) Satoh, T.; Suzuki, S. Tetrahedron Lett. 1969, 10, 4555–4558. reduction with CoCl₂ (1 mol %) and NaBH₄ (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 HNO₃,^{2a} and (iii) protection of diols **8a**-**f** with SOCl₂¹⁶ (Scheme 2).

Scheme 2. Synthesis of Nitro Cyclic Sulfites 3b-f



When subjected to the CoCl₂-catalyzed reduction¹⁴ with 4 equiv of NaBH₄, chiral nitro cyclic sulfites $3\mathbf{a}-\mathbf{f}$ gave the corresponding (*R*)-3-hydroxytetrahydro-quinoline derivatives $5\mathbf{a}-\mathbf{f}$ 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

^{(6) (}a) Zhu, G.; Pang, K.; Parkin, G. J. Am. Chem. Soc. 2008, 130, 1564– 1565. (b) Kinney, W. A.; Teleha, C. A.; Thompson, A. S.; Newport, M.; Hansen, R.; Ballentine, S.; Ghosh, S.; Mahan, A.; Grasa, G.; Zanotti-Gerosa, A.; Dingenen, J.; Schubert, C.; Zhou, Y.; Leo, G. C.; McComsey, D. F.; Santulli, R. J; Maryanoff, B. E. J. Org. Chem. 2008, 73, 2302–2310. (c) Fujita, K.; Kitatsuji, C.; Furukawa, S.; Yamaguchi, R. Tetrahedron Lett. 2004, 45, 3215–3217. (d) Bouyssou, P.; Le Goff, C.; Chenault, J. J. Heterocycl. Chem. 1992, 29, 895–898. (e) Schaus, J. M.; Huser, D. L.; Titus, R. D. Synth. Commun. 1990, 20, 3553–3562. (f) Gracheva, I. N.; Tochilkin, A. I. Chem. Heterocycl. Comp. (Eng. Trans.) 1988, 65–67. (g) Murahashi, S.-I.; Imada, Y.; Hirai, Y. Tetrahedron Lett. 1987, 28, 77–80.

⁽¹⁵⁾ For review, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Chem. Rev. 1994, 94, 2483–2547.

^{(16) (}a) Gao, Y.; Sharpless, K. B. J. Am. Chem. Soc. 1988, 110, 7538–7539.
(b) Lohray, B. B.; Jayachandran, B.; Bhushan, V.; Nandanan, N.; Ravindranathan, T. J. Org. Chem. 1995, 60, 5983–5985.

Table 1. Co-Catalyzed Reductive Cyclization of Nitro CyclicSulfites with NaBH4



^{*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 NaBH₄, thus requiring a minimum of 4 equiv of NaBH₄ to achieve excellent yields; ethanol or a combination of EtOH and DMF could be used as solvent. However, other metal catalysts such as NiCl₂ and MnO₂ 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 ¹³C 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 NaH₂PO₄ whereby reduction of both azide and tosylate functions took place efficiently to

afford (S)-3-aminotetrahydroquinoline **12** in 76% yield and 95% e^{18c} (Scheme 3).





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 CoCl₂·6H₂O (1 mol %) and NaBH₄ (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

^{(17) (}a) Joshi, D. K.; Sutton, J. W.; Carver, S.; Blanchard, J. P. Org. Process Res. Dev. 2005, 9, 997–1002. (b) Jian, Z. J. Labelled Compd. Radiopharm. 2004, 47, 609–614. (c) Hulin, B.; Lopaze, M. G. Tetrahedron: Asymmetry 2004, 15, 1957–1958. (d) Wuts, P. G. M.; Gu, R. L.; Northuis, J. M.; Kwan, T. A.; Beck, D. M.; White, M. J. Pure Appl. Chem. 2002, 74, 1359–1368. (e) Wuts, P. G. M. Curr. Opin. Drug Discovery Dev. 1999, 2, 557–564. (f) Romero, A. G.; Darlington, W. H.; McMillan, M. W. J. Org. Chem. 1997, 62, 6582–6587.

^{(18) (}a) Gademann, K.; Bethuel, Y.; Locher, H. H.; Hubschwerlen, C. J. Org. Chem. 2007, 72, 8361–8370. (b) Zurcher, S.; Wackerlin, D.; Bethuel, Y.; Malisova, B.; Textor, M.; Tosatti, S.; Gademann, K. J. Am. Chem. Soc. 2006, 128, 1064–1065. (c) Bethuel, Y.; Gademann, K. J. Org. Chem. 2005, 70, 6258–6264. (d) Gademann, K.; Bethuel, Y. Org. Lett. 2004, 6, 4707–4710. (e) Gademann, K.; Bethuel, Y. Angew. Chem., Int. Ed. 2004, 43, 3327–3329.

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 Cocatalyzed 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).





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 CoCl₂ as catalyst and NaBH₄ 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.

Acknowledgment. A.R.J. and R.S.R. thank CSIR, New Delhi, for the award of research fellowships. The authors are also thankful to Dr. B. D. Kulkarni, Head, CEPD, for his constant support and encouragement.

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

OL8028109