Published in final edited form as:

Chemistry. 2017 August 10; 23(45): 10738–10743. doi:10.1002/chem.201701944.

β -Hydroxy-tetrahydroquinolines from quinolines using chloroborane: Synthesis of the peptidomimetic FISLE-412

Ahmad S. Altiti^{*,a}, Kai Fan Cheng^a, Mingzhu He^a, and Yousef Al-Abed^{a,*}

^aCenter for Molecular Innovation, The Feinstein Institute for Medical Research, 350 Community Drive, Manhasset, New York 11030, United States

Abstract

A new synthetic protocol provides a simple and direct method to generate functionalized β -hydroxy-tetrahydroquinolines (THQs). Hydroboration of quinolines using chloroboranes followed by oxidation led to the formation of functionalized β -hydroxy-tetrahydroquinolines. High *regio* and diastereoselectivities were observed in α or γ substituted quinolines and the *trans* diastereomer of β -hydroxy-THQ was the major isostere. This new protocol was utilized to build the novel antibody-targeted lupus peptidomimetic **FISLE-412**.

Keywords

Quinoline; β -hydroxy-1,2,3,4 tetrahydroquinoline; Hydroboration of quinolines; Monochloroborane; β -borylated tetrahydro quinolines

1,2,3,4-tetrahydroquinolines (THQ) are abundant scaffolds in many biologically active natural molecules and pharmaceutical drugs. Particularly, β -functionalized-THQs play a vital role in various biologically active compounds (Figure 1).^[1] These compounds are synthetically challenging, they are usually made through multistep synthesis.^[1a, 2] Wide varieties of reducing agents have been used extensively to make THQ,^[3] however, very limited reduction approaches were synchronized with significant functionalization.^[4] Stereoselective silylative reduction of quinolines using $B(C_6F_5)_3$ and Et_2SiH_2 is a good example to access β -silylated THQs,^[4a] which can be used as precursors for wide range of transformations including β -hydroxy-THQs. Yet, this reduction system might suffer from undesired reductive-deoxygenation products.^[5]

Furthermore, activated quinoline systems react readily with borane reagents to give the 1,2-dihydroquinolines or the 1,2,3,4-THQs.^[1a, 6] During the preparation of this report, Ito and co-workers disclosed a *regio*- and *enantio*-enriched borylation of *N*-acetylated 1,2-dihydroquinolines using Cu(I) salts and $B_2(Pin)_2$.^[6b, 6c] Earlier, the reaction of quinoline with BH_3 .THF or its salts was limited to the reduction of the pyridine ring in the quinoline

^{*}Corresponding Authors. aaltiti@northwell.edu; yalabed@northwell.edu.
Dedication ((We Dedicate this work to Professor Wolfgang Voelter on his 80th birthday))

Supporting Information

The Supporting Information is available free of charge. Procedures for reactions and characterization of isolated products, NMR spectra and XRay analysis are available in PDF format files.

system upon protonolysis.^[7] On the other side, Brown and co-workers demonstrated that chloroboranes are superior to $\text{BH}_3\cdot\text{THF}$ in terms of reactivity and *regio*-selectivity.^[8] Vedejs and co-workers also reported the activation of the amine-borane complexes with halides to improve their reactivity and regioselectivity; they demonstrated that halide could act as a good leaving group and facilitate the hydroboration through $\text{S}_{\text{N}}2$ like pathway.^[9] In the light of these findings, we considered the use of chloroborane to reduce the quinoline ring with concomitant borylation of the β -position, which can be readily oxidized to give the corresponding β -hydroxy THQ. Quinoline is a polarized heterocyclic moiety where the pyridine ring is susceptible to hydride nucleophilic attacks at α or γ positions.^[10] Formation of the quinolinium-borane complex is expected to facilitate such reduction leaving the resulting dihydroquinoline prone to further hydroboration under thermodynamic conditions. Herein, we wish to report that β -functionalized THQ and especially β -hydroxy THQ could be accessed directly in a one-step operation using chloroborane reagents followed by appropriate work up.

In an early pursuit of optimal hydroborating agents, we settled on borane ($\text{BH}_3\cdot\text{THF}$) and mono-chloroborane ($\text{BH}_2\text{Cl}\cdot\text{THF}$) reagents as promising leads (see supporting information). A 1:3 mixture of BCl_3/BH_3 (4mmol) was capable of converting the quinoline moiety (1mmol) into β -borylated THQ after stirring at rt for 48 h; the reaction progress was monitored by TLC upon simple oxidation of the reaction mixture with NaBO_3 . The corresponding hydroxylated product was isolated in 44% yield in addition to the 1,2,3,4-THQ. The commercially available $\text{Me}_2\text{S}\cdot\text{BH}_2\text{Cl}$ was also effective in obtaining the β -hydroxy THQ in similar yield under similar conditions. Unlike mono-chloroboranes, $\text{BH}_3\cdot\text{THF}$ reacted with quinoline sluggishly at rt and gave much lower yield and slower conversion rate (7 days).^[7a] These results are not in a full agreement with the theoretical calculations that predicted BH_3 and BH_2Cl to have similar reactivity as Lewis acids.^[11] Hence, we explored the potential of this reaction as a synthetic tool to access β -functionalized THQ. In order to cut the reaction time, we considered repeating the reaction under high temperature. Interestingly, 1 equiv of $\text{Me}_2\text{S}\cdot\text{BH}_2\text{Cl}$ was enough to induce the reaction when refluxed at 65 °C for 4 h; however, the reaction did not go to completion. The borane transfer process to the β -carbon under stoichiometric condition indicates that this process might involve a dissociation event of the B-N bond in the borane-dihydroquinolinium complex **II** (eq.1 Scheme 1) especially at high temperature.^[12] We reasoned that such a process could be facilitated by enamine-imine tautomerism eq.1, Scheme 1).^[7e] When 2 equiv $\text{Me}_2\text{S}\cdot\text{BH}_2\text{Cl}$ were used, a complete conversion of the quinoline into products took place in less than 2 h at 65 °C. The borylated intermediate was isolated as a pinacolate ester **V** (eq.2, Scheme 1) upon treatment with pinacol, which was isolated in 31% after purification over basic alumina. Due to the instability of the pinacol ester under the standard extraction and purification procedure, we treated **V** with KHF_2 and isolated the borylated intermediate as trifluoroborate salt **VI** in 41 % from quinoline, **VI** was purified by trituration with ether in order to get rid of the pinacol and the 1,4-butane-diol, a side product that results from opening the THF ring. Besides the borylated intermediate, we isolated the 1,2,3,4-THQ **IX**, which theoretically might be produced from protonolysis of **IV**^[7a]. We were unable to isolate any borylated intermediate at the α -position. However, when the borylated intermediate **IV** was treated with ice-cold water and NaBO_3 , β -hydroxy

THQ **VII** and α -hydroxy THQ **VIII** were isolated as major products with ratio of 7:2 respectively in addition to traces of **IX** (eq.3, Scheme 1). When the isolated trifluoroborate compound **VI** was treated with NaBO₃ under the same work up conditions previously used, only the β -hydroxy THQ **VII** was observed. This indicates that the two hydroxylated products might be formed independently through different pathways. Next, we subjected the quinoline to various sources of chloroboranes in an effort to understand the factors that might affect the ratio of β -hydroxy THQ **VII** and α -hydroxy THQ **VIII** (Table1).

Treatment of quinoline **I** with excess BH₃.THF (8 equiv) resulted in a complete conversion of the starting material into products after 16 h reflux at 65 °C. The products were characterized after oxidative work up as **VII** and **VIII** with 1:1 ratio. Me₂S·BH₂Cl (8 equiv) gave **VII** in 61% (Entry5) in shorter time (2h). Decreasing the amount of Me₂S·BH₂Cl to 4 equiv gave similar results (Entry4), to avoid the malodorous effect of the Me₂S, we considered the preparation of mono-chloroborane following Brown's protocol^[8c] by simply mixing 1 equiv of 1M BCl₃/hexane with 2 equiv of 1M of BH₃.THF. Brown's chloroborane mixture (3 equiv) was effective in reducing the quinoline system, where the β -hydroxy THQ **VII** was isolated in 54% yield. However, the use of 8 equiv of 1:7 mixture of BCl₃/BH₃ gave **VII** in 70% isolated yield (Entry8). Increasing the stoichiometry of BCl₃ did not improve the selectivity or the yield (Entry7). We also considered the use of trichloroisocyanuric acid TCCA as a chlorinating agent (Entry9).^[13] Similarly, **VII** and **VIII** were collected with ratios comparable to the previous chloroboranes systems. As we see from the results in Table1, monochloroborane indeed favors the formation of the β -hydroxy THQ **VII** compare to BH₃. All the examined monochloroboranes had similar effect on the quinoline in terms of reactivity and selectivity, a slight increase in reaction rate was observed when higher concentrations were applied (Entries2 and 3). Controlling the reaction concentration was only possible when Me₂S·BH₂Cl was used because it is supplied as a neat reagent.

In order to account for the substituents effect on the quinoline system and to avoid the malodorous effect of Me₂S, we settled on the procedure used in entry 8 (Table1) to test the scope of this reaction. Using excess borane reagent should not be a burden at this stage, especially as our target is to access the β -hydroxy THQ and the oxidative work up is mild and inexpensive.

We first explored the scope of quinoline derivatives bearing substituents at the benzene ring (Table2). The BCl₃/BH₃ hydroboration system tolerated quinolines with halide substituents on the benzene ring (Entry6), however, halides on the pyridine ring were susceptible to reduction.^[7a] When 2-chloroquinoline was treated with this reduction system, the β -hydroxy-THQ **VII** was isolated as the major product accompanied with traces of **VIII** (results not shown), the methoxy substituent (Entry5) also survived the BCl₃/BH₃ reduction system; the corresponding β -hydroxy-THQ was isolated in 54% yield. The methyl-substituted quinolines (Entries3 and 4) gave good yields of the corresponding β -hydroxy-THQ, on the other hand carboxylic acid moieties suffered from expected partial reduction only and gave the corresponding primary alcohols (Entries2 and 7); these functionalities can be retained with simple oxidations after appropriate functional group manipulation. Interestingly, the unprotected 8-amino quinoline (Entry8) gave the corresponding β -hydroxy-THQ in 74% isolated yield; the borylated intermediate of this quinoline can be

elaborated easily to give the racemic version of Sumanriole (Figure 1).^[6c] Regardless of the modest regioselectivity of some of the quinolines presented here, we believe this protocol has a superior synthetic value compared to the traditionally used protocols to access such substrates using multistep synthesis^[2] (*vide infra*).

Satisfied with the performance of the BCl_3/BH_3 hydroboration system in Table2, we decided to investigate the role of this system on quinolines bearing varied substituents on the pyridine ring (Table3). In general the BCl_3/BH_3 hydroboration system gave greater yields and better *regio*- and diastereoselectivities for quinolines with substituents on the pyridine ring. The diastereoselectivity was confirmed by nOe analysis (see supporting information). As expected, quinolines with available chelating arm at the α position (Entries1 and 5) exhibited faster reactions and higher yields; this behavior can be attributed to an alcohol directed hydroboration effect, the formation of the alkoxy-borane complex facilitates the borylation of the β -position through an intramolecular process.^[14] The α -methyl, α -trifluoromethyl, and α -phenyl-quinolines performed well and gave good *trans*-diastereoselectivity (Entries2, 3, and 4), however, longer reaction time was required. For example, the α -phenyl quinoline was very sluggish under the $\text{BH}_3\cdot\text{THF}$ reduction system (result not shown). After 2 days of reflux, the hydroxylated products were collected in poor selectivity (1:1 *cis/trans*) in addition to recovery of some starting material, however, when subjected to the BCl_3/BH_3 reduction system, the reaction proceeded smoothly and the corresponding β -hydroxy-THQ was generated with 9:91 *cis/trans* selectivity. The γ -substituted quinolines exhibited similar behavior to α -substituted quinolines and gave the β -hydroxy-THQs in good yields and good *trans* diastereoselectivity. Though, these compounds required longer reaction time to achieve full conversion. Interestingly, the α -hydroxy-THQ was not observed as a side product in the case of the γ -substituted quinolines. Instead, the fully reduced 1,2,3,4-THQ was isolated; this indicates that γ -substituted quinolines might undergo a different reduction pathway as a rate-limiting step.^[4b] Further, the electron rich γ -dimethylamino quinoline (Entry9) was expected to form a strong Lewis acid-Lewis base complex and resist the borane reduction. Indeed, the corresponding β -hydroxy-THQ was isolated in 6% yield after 16 h at 65 °C beside the recovered starting material.

Next, we turned our attention to explore the utility of this protocol in asymmetric synthesis by building the novel peptidomimetic **FISLE-412**; a potent polyamine-alcohol neutralizes *anti*-dsDNA/NMDAR lupus autoantibodies and prevents their pathogenic interaction with tissue antigens.^[11, 1m] this poly amine is very challenging in terms of synthesis, resolution and purification, the only access to this molecule was through global reduction of the corresponding peptide “Saquinavir”, this reduction process was very tedious and gave an inseparable mixture of **FISLE-412** with very low yield after multiple purifications.^[11] We envisaged the synthesis of the complex polyamine **FISLE-412** through the resolution of the β -hydroxy THQ moiety **XI-1** (Entry1, Table3), which could be later integrated in the synthesis of **FISLE-412** through benign reductive-amination steps after simple protecting groups handling.

Accordingly, the *trans* diol **XI-1** was treated with stoichiometric amount of BnBr in aq NaHCO_3 to give the *N*-Bn derivative, which was then treated with benzylaldehyde dimethylacetal and camphorsulphonic acid (CSA) to give only one pair of the racemic acetal

5 in 88% yield over two steps. The stereochemistry was confirmed to be *trans* based on X-ray analysis of **5** (see supporting information), which was isolated as white-needled shaped crystals. Regioselective reductive opening of the acetal **5** using Et₃SiH/EtAlCl₂^[15] gave exclusively the primary alcohol which was oxidized using Dess Martin periodinane (DMP) to give the corresponding racemic aldehyde **6** in 58% yield over two steps (Scheme 2).

Next, we sought a chiral fragment that could resolve the racemic aldehyde and integrate the THQ moieties in the synthesis of the complex peptidomimetics **FISLE-412**. We chose the homologue of Garner's alcohol **7** because it could be converted into the 2,4-diaminobutanol derivative with orthogonal protection of the distal nitrogen. Alcohol **7** was treated with DEAD, Ph₃P, and phthalimide followed by acidic hydrolysis of the Boc and the isopropylidene groups using 6 M HCl to give amino alcohol **8** in 89% yield over two steps. Reductive amination on **6** and amino alcohol **8** followed by selective protection of the nitrogen with Benzyl group through reductive amination using PhCHO/AcOH and Na(OAc)₃BH afforded two separable alcohols by conventional chromatography. The resulting diastomeric alcohols were oxidized respectively using DMP to give aldehydes **9A/9B** in roughly 60% total yield over 4 steps (yield is averaged for both diastereomers because the absolute stereochemistry is not assigned yet) (Scheme 3).

Amino-alcohol **11** was accessed from the known decahydroisoquinoline (DIQ) fragment **10**,^[16] which was reduced with BH₃•THF upon the de-protection of the Boc group to furnish **11** in 40% yield. Reductive-amination on the amino-alcohol **11** and either aldehyde **9A** or **9B** gave the protected **FISLE-412** in 69% for each (the yield is averaged for both isomers). After exhausting several attempts to cleave the benzyl groups safely, we found that the Pd black-formic acid combination^[17] under reflux condition in 75% aqueous EtOH cleaved all benzyl groups orthogonally without affecting the phthalimide group, which was cleaved with hydrazine NH₂NH₂•H₂O under reflux condition to afford **FISLE-412A** and **FISLE-412B** (Scheme 4). Both isomers were isolated as TFA salts after C18 column purification with approximately 50% yield of each over 3 steps (averaged yield), the purity of these compounds was confirmed by HPLC analysis (see supporting information).

In summary, we have successfully developed a rapid and inexpensive protocol to access β -hydroxy-THQs. The new procedure features a hydroboration-oxidation reaction using chloroboranes. High *regio*- and *trans* diastereoselectivities were observed for the α - and γ -substituted quinolines. This methodology was used to build an interesting library of β -hydroxy-1,2,3,4-tetrahydroquinolines. We assert that this protocol has superior synthetic value compared with other synthetic approaches used to build β -hydroxy-1,2,3,4-THQ scaffolds. We are currently investigating the utility of this method in the synthesis of other biologically relevant alkaloids of interest.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by grants from NIH (RO1AR057084) and STTR (R41 AR060620-01). We also thank Dr. Matthew Devany the director of NMR facility at Hunter College and Dr. Barney Yoo for collecting the HRMASS data. Yousef Alabed thanks Dr. Nanette M. Wachter-Jurcsak, Professor of Chemistry at Hofstra University.

References

1. a) Sridharan V, Suryavanshi PA, Menéndez JC. Chemical reviews. 2011; 111:7157–7259. [PubMed: 21830756] b) Nammalwar B, Bunce R. Molecules. 2014; 19:204.c) Katritzky AR, Rachwal S, Rachwal B. Tetrahedron. 1996; 52:15031–15070.d) Nakagawa A, Iwai Y, Hashimoto H, Miyazaki N, Oiwa R, Takahashi Y, Hirano A, Shibukawa N, Kojima Y, Omura S. J. Antibiot. 1981; 34:1408–1415. [PubMed: 7319904] e) Kim W-G, Kim J-P, Kim C-J, Lee K-H, Yoo I-D. J. Antibiot. 1996; 49:20–25. [PubMed: 8609080] f) Dunlop J, Watts SW, Barrett JE, Coupet J, Harrison B, Mazandarani H, Nawoschik S, Pangalos MN, Ramamoorthy S, Schechter L, Smith D, Stack G, Zhang J, Zhang G, Rosenzweig-Lipson S. J Pharmacol Exp Ther. 2011; 337:673–680. [PubMed: 21402690] g) Dragan V, McWilliams JC, Miller R, Sutherland K, Dillon JL, O'Brien MK. Org. Lett. 2013; 15:2942–2945. [PubMed: 23751116] h) Dziechciejewski WJ, Weber R, Sowada O, Boysen MMK. Org Lett. 2015; 17:4132–4135. [PubMed: 26274890] i) Heier RF, Dolak LA, Duncan JN, Hyslop DK, Lipton MF, Martin IJ, Mauragis MA, Piercey MF, Nichols NF, Schreur PJKD, Smith MW, Moon MW. J. Med. Chem. 1997; 40:639–646. [PubMed: 9057850] j) Zou, M-f, Keck, TM., Kumar, V., Donthamsetti, P., Michino, M., Burzynski, C., Schweppe, C., Bonifazi, A., Free, RB., Sibley, DR., Janowsky, A., Shi, L., Javitch, JA., Newman, AH. J. Med. Chem. 2016; 59:2973–2988. [PubMed: 27035329] k) McCall RB, Lookingland KJ, Be PJ, Huff RM. J. Pharmacol. Exp. Ther. 2005; 314:1248–1256. [PubMed: 15980060] l) Bloom O, Cheng KF, He M, Papatheodorou A, Volpe BT, Diamond B, Al-Abed Y. Proc Natl Acad Sci U S A. 2011; 108:10255–10259. [PubMed: 21646518] m) VanPatten S, Sun S, He M, Cheng KF, Altiti A, Papatheodorou A, Kowal C, Jeganathan V, Crawford JM, Bloom O, Volpe BT, Grant C, Meurice N, Coleman TR, Diamond B, Al-Abed Y. J. Med. Chem. 2016; 59:8859–8867. [PubMed: 27603688]
2. a) Jagdale AR, Reddy RS, Sudalai A. Tetrahedron Asymmetry. 2009; 20:335–339.b) Khadem S, Joseph R, Rastegar M, Leek DM, Oudatchin KA, Arya P. Journal of Combinatorial Chemistry. 2004; 6:724–734. [PubMed: 15360207] c) Ganton MD, Kerr MA. J. Org. Chem. 2007; 72:574–582. [PubMed: 17221976] d) Gallou-Dagommer I, Gastaud P, RajanBabu TV. Org. Lett. 2001; 3:2053–2056. [PubMed: 11418047] e) Jagdale AR, Reddy RS, Sudalai A. Org Lett. 2009; 11:803–806. [PubMed: 19159276] f) Back TG, Wulff JE. Angewandte Chemie International Edition. 2004; 43:6493–6496. [PubMed: 15578771] g) Degutyte R, Daskeviciene M, Stumbraite J, Getautis V. ARKIVOC (Gainesville, FL, U S.). 2009:115–122.h) Kratzel M, Hiessbock R. Heterocycles. 2000; 52:853–862.i) Morimoto Y, Shirahama H. Tetrahedron. 1996; 52:10631–10652.j) Hiessböck R, Wolf C, Richter E, Hitzler M, Chiba P, Kratzel M, Ecker G. J. Med. Chem. 1999; 42:1921–1926. [PubMed: 10354400] k) Anderson JC, Barham JP, Rundell CD. Org Lett. 2015; 17:4090–4093. [PubMed: 26270567]
3. a) Wang, D-s, Chen, Q-a, Lu, S-m, Zhou, Y-g. Chem. Rev. 2012; 112:2557–2590. [PubMed: 22098109] b) Zhang Z, Du H. Org. Lett. 2015; 17:6266–6269. [PubMed: 26652046] c) Zurro M, Asmus S, Beckendorf S, Mu C, Garc O. J. Am. Chem. Soc. 2014; 139:13999–14002.d) Chen F, Surkus A-e, He L, Pohl M-m, Radnik J, Topf C, Junge K, Beller M. J. Am. Chem. Soc. 2015; 137:11718–11724. [PubMed: 26293483]
4. a) Gandhamsett N, Joung S, Park S-W, Park S, Chang S. J. Am. Chem. Soc. 2014; 136:16780–16783. [PubMed: 25412033] b) Gandhamsetty N, Park S, Chang S. J. Am. Chem. Soc. 2015; 137:15176–15184. [PubMed: 26580152] c) Zhang Q, Wei D, Cui X, Zhang D, Wang H. Tetrahedron. 2015; 71:6087–6093.
5. a) Arakawa N, Aluwihare L. Environ. Sci. Technol. 2015; 49:4097–4105–4097–4105. [PubMed: 25769031] b) Mahdi T, Stephan DW. Angew. Chem., Int. Ed. 2015; 54:8511–8514.c) Bajracharya GB, Nogami T, Jin T, Matsuda K, Gevorgyan V, Yamamoto Y. synthesis. 2004:308–311.d) Tan M, Zhang Y. Tetrahedron Letters. 2009; 50:4912–4915.e) Oestreich M, Hermeke J, Mohr J. Chem. Soc. Rev. 2015; 44:2202–2220. [PubMed: 25679769]

6. a) Tiwari VK, Pawar GG, Das R, Adhikary A, Kapur M. *Org Lett.* 2013; 15:3310–3313. [PubMed: 23789894] b) Kubota K, Watanabe Y, Hayama K, Ito H. *J. Am. Chem. Soc.* 2016; 138:4338. [PubMed: 26967578] c) Kubota K, Watanabe Y, Ito H. *Adv. Synth. Catal.* 2016; 358:2379–2384.
7. a) Keller PC, Marks RL, Rund JV. *Polyhedron.* 1983; 2:595–602. b) Nose A, Kudo T. *Chem. Pharm. Bull.* 1986; 34:3905–3909. c) Nose A, Kudo T. *Chem. Pharm. Bull.* 1988; 36:1529–1533. d) Srikrishna A, Reddy TJ, Viswajanani R. *Tetrahedron.* 1996; 52:1631–1636. e) Kikugawa Y, Kuramoto M, Saito I, Yamada S-I. *Chem. Pharm. Bull.* 1973; 21:1914–1926. f) Foret CJ, Chiusano MA, OB JD, Martin DR. *J. Inorg. Nucl. Chem.* 1980; 42:165–169.
8. a) Brown, JVBKaHC. *Organic Letters.* 1999; 1:315–317. b) Brown, JVBKaHC. *J. Org. Chem.* 2001; 66:5359–5365. [PubMed: 11485456] c) Brown HC, Ravindran N. *J. Am. Chem. Soc.* 1976; 98:1785–1798. d) Brown HC, Ravindran N, Surendra UK. *J. org. chem.* 1980; 45:384–389.
9. a) Matthew Scheideman GW, Vedejs Edwin. *J. Am. Chem. Soc.* 2008; 130:8669–8676. [PubMed: 18549217] b) Vedejs, JMCaE. *J. Am. Chem. Soc.* 2005; 127:5766–5767. [PubMed: 15839656]
10. a) Bull JA, Mousseau JJ, Pelletier G, Charette AB. *chemical reviews.* 2012; 112:2642–2713. [PubMed: 22352938] b) Dudnik AS, Weidner VL, Motta A, Delferro M, Marks TJ. *Nat Chem.* 2014; 6:1100–1107. [PubMed: 25411889]
11. Evanseck, JAPaJD. *J. Phys. Chem. A.* 2009; 113:5985–5992. [PubMed: 19388700]
12. Chandrasekharan, HCBaJ. *J. Am. Chem. Soc.* 1984; 106:1863–1865.
13. Varaprath S, Stutts DH. *J Organomet Chem.* 2007; 692:1892–1897.
14. a) James SP, Xu F. *J. Org. Chem.* 1992; 57:5288–5290. b) Welch MC, Bryson TA. *Tetrahedron Letters.* 1989; 30:523–526. c) Panek JS, Xu F, Rondo AC. *J. Am. Chem. Soc.* 1998; 120:4113–4122.
15. Kumar PS, Baskaran S. *Tetrahedron Letters.* 2009; 50:3489–3492.
16. Ghosh AK, Hussain KA, Fidanze S. *J. Org. Chem.* 1997; 62:6080–6082.
17. Kozioł A, Lendzion-Paluch A, Manikowski A. *Org. Process Res. Dev.* 2013; 17:869–875.

Figure 1.
Important β -functionalized tetrahydroquinolines

Scheme 1.
Hydroboration of the quinolone ring

Scheme 2.
Synthesis of the racemic aldehyde **6**

Scheme 3.
Synthesis and resolution of Aldehydes **9A** & **9B**

Scheme 4.
Synthesis of the FISLE-412 compounds **4a** and **4b**

Table 1

Hydroboration-oxidation of quinoline using mono-chloroborane

Entry	Hydroboration System	Conc. (M)	Time (h)	VII%	VIII%
1	BH ₃ .THF (8 equiv)	0.13	16	48	49
2	Me ₂ S.BH ₂ Cl (2 equiv)	1.0	1.0	65	18
3	Me ₂ S.BH ₂ Cl (2 equiv)	0.5	1.5	69	19
4	Me ₂ S.BH ₂ Cl (4 equiv)	0.13	2	64	32
5	Me ₂ S.BH ₂ Cl (8 equiv)	0.13	2	61	33
6	BCl ₃ /BH ₃ (1equiv+2equiv)	0.33	4	54	33
7	BCl ₃ /BH ₃ (2equiv+6equiv)	0.13	4	59	31
8	BCl ₃ /BH ₃ (1equiv+7equiv)	0.13	4	70	23
9	TCCA/BH ₃ (0.5equiv/8 equiv)	0.13	4	63	29

Table 2

Hydroboration-oxidation of quinolines bearing substituents at the benzene ring

Entry	Substrates	Time (h)	VII %	VIII%
1		4	70	21
2		3	38	45
3		8	73	13
4		7	68	24
5		6	54	13
6		6	44	48
7		6	47	38
8		8	74	17

Table 3

Hydroboration of quinolines bearing substituents at the pyridine ring.

Entry	Substrates	Products*	Time (h)	Isolated yield%	Diastereos. selectivity (cis/trans)
1			1	94	9:91
2			6	65	11:89
3			16	55	11:89
4			8	82	9:91
5			0.5	84	> 98 trans
6			16	70	> 98 trans
7			16	91	> 98 trans

Entry	Substrates	Products *	Time (h)	Isolated yield%	Diastereos. selectivity (<i>cis/trans</i>)
8			16	46	> 98 <i>trans</i>
9			24	6	> 98 <i>trans</i>
10			4	72	> 98 <i>trans</i>

* The depicted structural formulas do not reflect the absolute stereochemistry