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Asymmetric Synthesis of Functionalized 1,2,3,4-Tetrahydroquinolines

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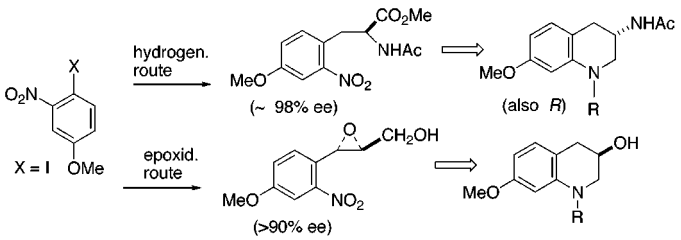
ABSTRACT



Highly enantioselective rhodium-catalyzed asymmetric hydrogenation (>98% ee) and Sharpless epoxidation (>90% ee) of *o*-nitrocinnamyl substrates lead to intermediates that can be transformed into tetrahydroquinoline derivatives. Starting materials are produced in high-yielding Heck reactions of an *o*-nitroaryl iodide and α-acetamidoacrylate or methyl acrylate.

Substituted tetrahydroquinolines (**1**) have attracted considerable attention from organic and medicinal chemists primarily because they display a wide range of physiological activities.[1,2] Several derivatives have been found to elicit potent biological responses leading to analgesic, antiarrhythmic, cardiovascular, immunosuppresent, antitumor, antiallergenic, anticonvulsant, and antifertility and NMDA antagonist activities.[2] Derivatives of tetrahydroquinolines have also been found to be pesticides, antioxidants, photosensitizers, and dyes.[3] In addition, this ring system is present in a number of important natural products as exemplified by 2-methyl-1,2,3,4-tetrahydroquinoline, discorhabdin C,[4a] dynemycin,[4b] and virantmycin.[4c] An important group of antitumor spirocyclopropindoles classified under the broad name duocarmycins (for example, see Duocarmycin SA, **2**) include among them several 1,2,3,4-tetrahydroquinoline congeners.[5] In the total syntheses of various duocarmycins, Natsume[6] and

(1) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 605−618. (b) Balasubramanian, M.; Keay, J. G. In *Comprehensive Heterocyclic Chemistry II*; McKillop, A., Ed.; Pergamon Press: Oxford, 1996; Vol. 5, Chapter 5.06, pp 245−300. (c) Kouznetsov, V.; Palma, A.; Ewert, C.; Varlamov, A. *J. Heterocycl. Chem.* **1998**, *35*, 761−785. For two recent reports, see: (d) De Kempe, N.; Keppens, M. *Tetrahedron* **1996**, *52*, 3705−3718. (e) Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595−3607.

(2) (a) Katritsky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031−15070. (b) Leeson, P. D.; Carling, R. W.; Moore, K. W.; Mosely, A. M.; Smith, J. D.; Stevenson, G.; Chan, T.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R.; Hoogsteen, K. *J. Med. Chem.* **1992**, *35*, 1954−1968. (c) Nagata, R.; Tanno, N.; Kodo, T.; Ae, N.; Yamaguchi, H.; Tamiki, N.; Antoku, F.; Tatsuno, T.; Kato, T.; Tanaka, Y.; Nakamura, M. J. *J. Med. Chem.* **1994**, *37*, 3956−3968.

(3) For an extensive listing, see ref 2a.

(4) (a) Perry, N. B.; Blunt, J. W.; McCombs, J. D.; Munro, H. G. *J. Org. Chem.* **1986**, *51*, 5478−5480. (b) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, I. *J. Am. Chem. Soc.* **1990**, *112*, 3715−3716. (c) Omura, S.; Nakagawa, A. *Tetrahedron Lett.* **1981**, *22*, 2199−2202.

(5) (a) Ohba, K.; Watabe, H.; Sasaki, T.; Takeuchi, Y.; Kodama, Y.; Nakazawa, T.; Yamamoto, H.; Shomura, T.; Sezaki, M.; Kondo, S. *J. Antibiot.* **1988**, *41*, 1515−1519. (b) Ishii, S.; Nagasawa, M.; Kariya, Y.; Yamamoto, H.; Inouye, S.; Kondo, S. *J. Antibiot.* **1989**, *42*, 1713−1717. (c) Ogawa, T.; Ichimura, M.; Katsumata, S.; Morimoto, M. Takahashi, K. *J. Antibiot.* **1989**, *42*, 1299−1301. (d) Yasuzawa, T.; Muroi, K.; Ichimura, M.; Takahashi, I.; Ogawa, T.; Takahashi, K.; Sano, H.; Saitoh, Y. *Chem. Pharm. Bull.* **1988**, *43*, 378−391. (d) Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A. *Chem. Rev.* **1997**, *97*, 787−828, and references therein.

(6) (a) Muratake, H.; Abe, I.; Natsume, M. *Chem. Pharm. Bull.* **1996**, *44*, 67−79. (b) Muratake, H.; Abe, I.; Natsume, M. *Tetrahedron Lett.* **1994**, *35*, 2573−2576. This spirocyclization was initially proposed by Boger et al. in connection with biochemical studies of Duocarmycins, Boger, D. L.; Ishizaki, T.; Zarrinmayeh, M.; Munk, S. A.; Kitos, P. A.; Suntornwat, O. *J. Am. Chem. Soc.* **1990**, *112*, 8961−8971. Boger's synthesis of Duocarmycin A also used the trans-annular cyclization. See ref 7.

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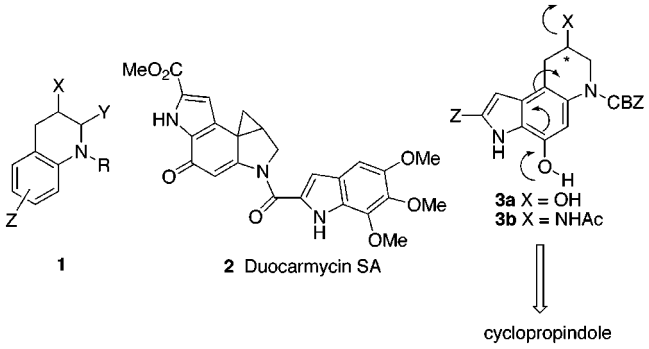
Boger[7] used highly substituted pyrrolotetrahydroquinoline intermediates such as **3a** for the construction of the spirocyclic moiety. In search of a broadly applicable, highly

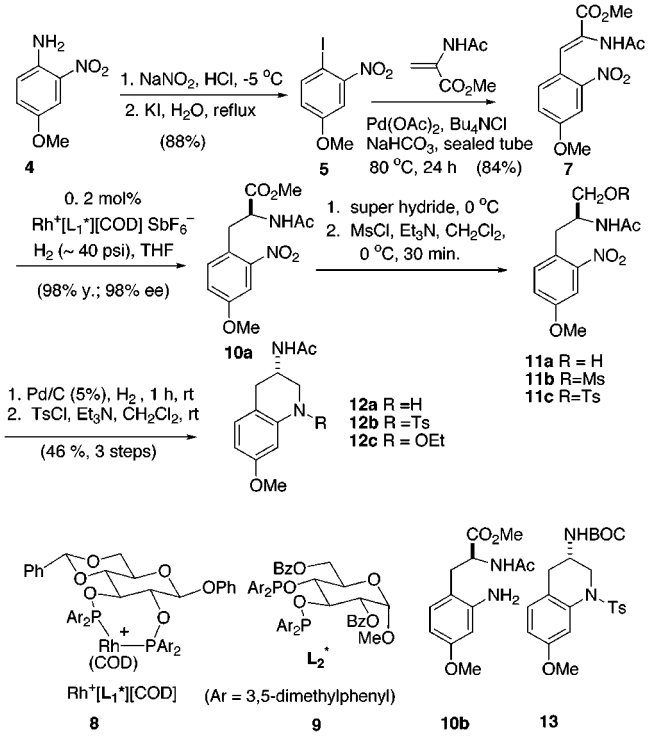


enantioselective synthesis of tetrahydroquinolines, we have explored the utility of Rh-catalyzed asymmetric hydrogenation and Sharpless asymmetric epoxidation as key steps for the installation of asymmetry in these molecules. Apart from the pioneering report by Boger et al.,[7] who used a moderately successful catalytic asymmetric cis-dihydroxylation (78% ee) in a key step, few other useful applications of asymmetric catalysis for the enantioselective synthesis of 3-substituted tetrahydroquinolines have been reported in the literature.[8]

The Asymmetric Hydrogenation Route. Rhodium-catalyzed asymmetric hydrogenation of dehydroamino acids is arguably the most extensively studied[9a] and developed asymmetric catalytic reaction.[9] Yet the full synthetic potential of the substituted aromatic and heteroaromatic alanine derivatives that are readily available by this route, in near 100% enantiomeric excess (ee), remains to be exploited. In our previous work we have reported that abundantly available D-glucose derivatives can be transformed into bis-diarylphosphinite ligands whose cationic Rh complexes (example, **8**) are superb catalysts (substrate/catalyst ratios > 10000) for the asymmetric hydrogenation of dehydroamino acids.[10] Protocols for the synthesis of *both R*- and *S*-enantiomers of several aromatic and heteroaromatic alanine derivatives in greater than 97% ee and near 100% yield have also been recorded.[10b]

The Rh-catalyzed asymmetric hydrogenation of readily accessible α-acetamido-2-nitrocinnamate esters provides a facile entry into enantiomerically pure tetrahydroquinolines. The details are shown in Scheme 1.[11] Commercially available

Scheme 1. Hydrogenation Route to Tetrahydroquinolines



4-methoxy-2-nitroaniline was diazotized at low temperature, and the diazonium salt was converted into the iodide under standard conditions. Heck reaction[12] of the iodide under optimized conditions using α-acetamidoacrylate[13] as the acceptor gave the (*Z*)-acetamidocinnamate substrate **7** in 84% isolated yield in a *Z* to *E* ratio of 86:14. This compound can also be prepared in 90% isolated yield (Z/*E* = 90/10) by Wadsworth−Emmons reaction of 4-methoxy-2-nitrobenzaldehyde using methyl *N*-acetyl diethylphosphonoglycinate.[14] Catalytic asymmetric hydrogenation of **7** using 0.2 mol %

(7) Boger, D. L.; McKie, J. A.; Nishi, T.; Ogiku, T. Goldberg, J. A. *J. Am. Chem. Soc*. **1997**, *119*, 311−325. The low enantioselectivity (78% ee) of the reaction necessitated preparative HPLC purification of the intermediates before further steps in the synthesis of Duocarmycin A. For the synthesis of related molecules using asymmetric epoxidation see: Boger, D. L.; McKie, J. A.; Boyce, C. W. *Synlett* **1997**, 515−517.

(8) For other reports of the use of asymmetric catalysis in the construction of tetrahydroquinolines see: (a) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357−7360. (b) Katayama, S.; Nagata, T. Japan Patent JP 08333345 A2, 1996; *Chem. Abstr*. **1997**, *126*, 157407. (c) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327−6328. (d) Morimoto, Y.; Oda, K.; Shirahama, H.; Matsumoto, T.; Omura, S. *Chem. Lett.* **1988**, 909−912.

(9) For recent reviews see: (a) Brown, J. M. *Chem. Soc. Rev.* **1993**, 25−41. (b) Brown, J. M. Hydrogenation of Carbon-Carbon Double Bonds. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, pp 121−182. (c) Ohkuma, T.; Kitamura, M.; Noyori, R. Asymmetric Hydrogenation. In *Catalytic Asymmetric Syntheis*; Ojima, I., Ed.; John Wiley: New York, 2000; pp 1−110.

(10) (a) RajanBabu, T. V.; Ayers, T. A.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 4101−4102. (b) RajanBabu, T. V.; Ayers, T. A.; Halliday, G. A.; You, K. K.; Calabrese, J. C. *J. Org. Chem.* **1997**, *62*, 6012−6028.

(11) See Supporting Information for details of experimental procedures, characterization of intermediates, and chromatographic determinations of enantiomeric excesses. The nitro compound **10a** can be reduced quantitatively (5% Pd/C, 15 mol %, THF/MeOH) to the amino compound **10b**, potentially useful for the synthesis of 3-aminoquinolones.

(12) (a) Cutolo, M.; Fiandanese, V.; Naso, F.; Sciacovelli, O. *Tetrahedron Lett.* **1983**, *24*, 4603**.** (b) Harrington, P. H.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657−2662. (c) Bozell, J. J.; Vogt, C. E.; Gozum, J. *J. Org. Chem.* **1991**, *56*, 2584−2587.

(13) This valuable intermediate was synthesized from DL-serine methyl ester hydrochloride and acetic anhydride using a procedure similar to the one reported by Nugent (U.S. Patent 340781, 1984). We found that the reaction in the presence of diisopropylethylamine at reflux gave a mixture of methyl *N*-acetyl-2-aminopropenoate and methyl *N*,*N*-diacetyl-2-aminopropenoate. The mixture of the mono- and diacetyl compounds was dissolved in a minimum amount of anhydrous methanol and was treated with of 1 equiv of $NaHCO_3$ overnight. Filtration of the bicarbonate and evaporation of the solvent gave a 38% yield of methyl 2-*N*-acetyl-2-aminopropenoate.[11]

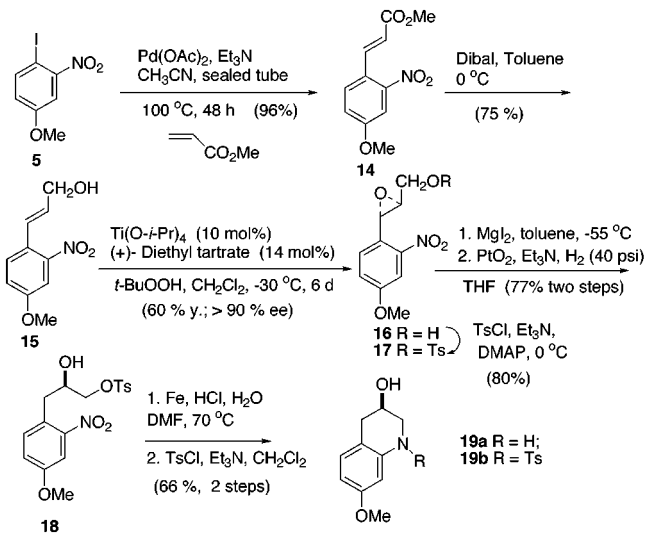
(14) Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487−490.

of the rhodium catalyst **8** $[SbF_6]^-$ under 40 psi of hydrogen pressure gave the (*S*)-2-(2-nitro-4-methoxyphenyl)alanine derivative **10a** in 98% yield and ~98% ee.[11] The enantioselectivity of this product can be enhanced, if desired, by further recrystallization. Reduction of the ester with $LiHB(Et)_3$ (Super hydride), conversion of the resulting primary alcohol (**11a**) to the mesylate (**11b**),[15] and its subsequent hydrogenation using 10% palladium on carbon in THF gave the unstable 3-acetamido-1,2,3,4-tetrahydroquinoline (**12a**). This compound was protected as its tosylamide by treatment with TsCl in the presence of Et_3N.[16] The catalytic hydrogenation of intermediate nitro-mesylate **11b** is a capricious reaction, leading to, for example, the corresponding *N*-ethoxy compound **12c** when the reaction was carried out in ethanol.

Catalytic hydrogenation of **7** using the catalyst Rh^+(**9**)-(COD) SbF_6^- gave the opposite enantiomer (*R*) of the 2-nitrophenylalanine derivative in >96% ee and 99% yield, thus providing access to both enantiomers of the heterocyclic system in excellent yields and selectivity.

The Asymmetric Epoxidation Route. The iodide **5** was subjected to Heck reaction using the classical procedure[17] published by Heck ($Pd(OAc)_2$, Et_3N, acetonitrile, methyl acrylate, sealed tube at 100 °C, 48 h) to obtain a 94% yield of the cinnamate **14**. In this reaction, no trace of the *Z*-isomer was observed in the NMR or GC. Reduction of **14** with 2 equiv of DIBAL at 0 °C gave the expected allylic alcohol **15** in 75% isolated yield (Scheme 2). Initial attempts to carry

Scheme 2 The Asymmetric Epoxidation Route



out the Sharpless asymmetric epoxidation using the catalytic protocol (5 mol % of Ti(O-*i*-Pr)$_4$ and L(+)-diethyl tartrate, 4 Å molecular sieve, 24 h) gave consistently poor results.[18] When the reaction was performed at −20 °C, with 5 to 20 mol % of catalyst, a nearly constant ratio of product to starting material was observed at 6, 12, and 24 h. Prompted by reports[19] that 3-aryl-2,3-epoxypropanols were prone to facile ring opening mediated by Ti(IV), we concluded that lower temperatures and higher catalyst loadings would be needed for this substrate. In the event, the asymmetric epoxidation reaction was carried out at −30 °C using ~10 mol % of the catalyst for 6 days to obtain the desired epoxyalcohol **16** in >90% ee and an isolated yield of 60%. The enantiomeric excess was determined by ^{19}F NMR of the Mosher ester of the epoxyalcohol. To confirm this high selectivity, authentic samples of the racemic epoxyalcohols and the corresponding diastereomeric Mosher esters were prepared via *m*-CPBA epoxidation of the allylic alcohol **15**. Attempts to separate the diastereomeric esters by chiral GC and HPLC have not been successful.

The epoxyalcohol **16** was readily converted into the corresponding tosylate **17** at low temperature in 80% yield. Two well-precedented reactions, viz., the regioselective benzylic C−O cleavage of 1-phenyl-1,2-epoxy-3-tosyloxypropane[20] and the reductive cyclization of a (2-nitrophenyl)-propoan-1-yl methanesulfonate,[21] prompted us to explore the tandem reduction−cyclization strategy for the conversion of the epoxytosylate to the final tetrahydroquinoline **19**.[21c] However, catalytic hydrogenation under a variety of conditions, using Pd and Pt, led to none of the expected products. Regioselective opening of the allylic alcohols using DIBAL[22] or $LiBH_4$[23] in the presence of of Ti(O-*i*-Pr)$_4$ have also been reported. Reaction of **16** with $LiBH_4$ gave small amounts of the desired alcohol, whereas the DIBAL gave mixtures of products. The regioselective opening of the epoxide in **17** was accomplished by treatment with MgI_2[24] in toluene at −55 °C. The sensitive iodotosylate was not isolated, nor purified; it was immediately reduced under mild catalytic hydrogenation conditions in the presence of PtO_2. The resulting tosylate (**18**) was reduced with iron and HCl.[25]

(15) Attempted conversion of **11a** to the corresponding tosylate **11c** led mostly to an oxazoline.[11]

(16) Mesylation leads to a mixture of the mono- and di-*N*-mesyl compounds. Also see ref 26. (b) To facilitate further transformations, the *N*-Ac group could be exchanged for an *N*-BOC group (**13**) by the method published by Burk et al. Burk, M. J.; Allen, J. G. *J. Org. Chem.* **1997**, *62*, 7054−7057.[11]

(17) Plevyak, J. E.; Dickerson, J. E.; Heck, R. F. *J. Org. Chem.* **1979**, *44*, 4078−4080.

(18) Examples of Sharpless epoxidation of *o*-substituted cinnamyl alcohol derivatives are rare; no examples of the especially valuable 2-nitrocinnamyl alcohols have been reported previously. Yields and selectivities for these reactions are generally low. See for example: (a) Medina, E.; Vidal-Ferran, A.; Moyano, A.; Pericás, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1581−1586. (b) Takahashi, K.; Ogata, M. *J. Org. Chem.* **1987**, *52*, 1877−1880.

(19) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

(20) Goument, B.; Duhamel, L.; Mauge, R. *Tetrahedron* **1994**, *50*, 171−188.

(21) Wierenga, W. *J. Am. Chem. Soc.* **1981**, *103*, 5621−5623. See also: (b) Fukuda, Y.; Itoh, Y.; Nakatani, K.; Terashima, S. *Tetrahedron* **1994**, *50*, 2793−2807. (c) This and the subsequent experiments were conducted in the racemic series.

(22) Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719−2722.

(23) Dai, L.; Lou, B.; Zhang, Y.; Guo, G. *Tetrahedron Lett.* **1986**, *27*, 4343−4346.

(24) Bonini, C.; Righi, G.; Sotgiu, G. *J. Org. Chem.* **1991**, *56*, 6206−6209.

(25) (a) Rewcastle, G. W.; Baguley, B. C.; Cain, B. F. *J. Med. Chem.* **1982**, *25*, 1231−1235. (b) Verboom, W.; Orlemans, E. O. M.; Berga, H. J.; Scheltinga, M. W.; Reinhoudt, D. N. *Tetrahedron* **1986**, *42*, 5053−5064. (c) Le Corre, M.; Hercouet, A.; Le Stanc, Y.; Le Baron, H. *Tetrahedron* **1985**, *41*, 5313−5320.

Neutralization of the reaction mixture by addition of ammonia led to the 3-hydroxy-1,2,3,4-tetrahydroquinoline (**19a**), which was rapidly protected as an *N*-tosylamide (**19b**).[26]

In summary, two independent routes to enantiomerically enriched 3-substituted tetrahydroquinolines based on highly selective catalytic reactions are reported. The hydrogenation route, which is operationally simpler to execute, provides nearly optically pure materials. In addition, the scope of this reactions is much broader, and synthesis of various substituted aromatic and heteroaromatic nuclei can be envisioned from the starting *o*-nitro derivatives. Both the amino and the hydroxy moieties provide excellent handles for further elaboration of the tetrahydroquinolines. Further applications of these and related intermediates for the construction of biologically important molecules will be disclosed in due course.

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Supporting Information Available: Experimental procedures and spectroscopic and chromatographic (HPLC and GC) data of key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) Coutts, I. G. C.; Culbert, N. J.; Edwards, M.; Hadfield, J. A.; Musto, D. R.; Pavlidis, V. H.; Richards, D. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1829−1836.