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A Tandem Conjugate Addition/ Cyclization Protocol for the Asymmetric Synthesis of 2-Aryl-4-aminotetrahydroquinoline-3-carboxylic Acid Derivatives

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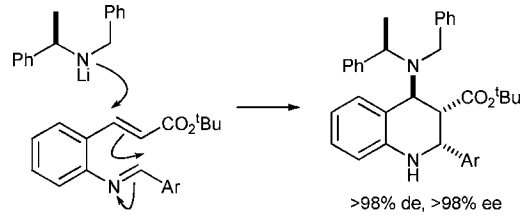
ABSTRACT



Condensation of *tert*-butyl (*E*)-3-(2′-aminophenyl)propenoate with a range of aromatic and heteroaromatic aldehydes gives the corresponding imines as single diastereoisomers (>98% de). Addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide initiates a tandem conjugate addition/ cyclization reaction to generate 2-aryl-4-aminotetrahydroquinoline-3-carboxylic acid derivatives in >98% de, >98% ee and high isolated yield. Hydrogenolysis of an *N*(1)-Boc protected derivative allows selective cleavage of the *N*-benzyl-*N*-α-methylbenzyl protecting groups without compromise of the diastereo- or enantiopurity.

The tetrahydroquinoline subunit is the central motif of several biologically active natural products. Perhaps the most well-known examples comprising this molecular architecture are the *Martinelle* alkaloids martinelline **1** and martinellic acid **2** and the 2-phenyl synthetic analogue **3**[1] (Figure 1).[2] In accord with its importance, the synthesis of the tetrahydroquinoline structural motif has been the subject of intense research, especially concerning examples for clinical use.[3] Several methods have been developed for the preparation of this valuable heterocyclic scaffold, which commonly involve synthesis from aniline precursors (utilizing electrophilic aromatic substitution,[4] aza-Diels−Alder reaction,[5] or nucleophilic displacement[6] to form the tetrahydroquinoline ring system) or the elaboration and reduction of a quinoline precursor.[7] Although these approaches often facilitate the synthesis of diastereoisomerically pure tetrahydroquinolines,

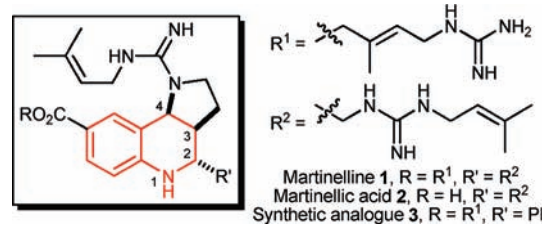


Figure 1. Structures of martinelline **1**, martinellic acid **2**, and the synthetic analogue **3**.

(1) Batey, R. A.; Powell, D. A. *Chem. Commun.* **2001**, 2362.

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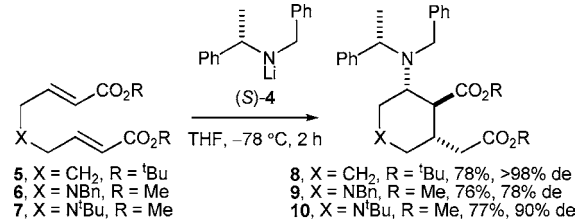
there are relatively few examples which have been demonstrated as synthetic routes to enantiomerically pure targets.

We have previously demonstrated that the conjugate addition of homochiral, secondary lithium amides derived from α-methylbenzylamine to α,β-unsaturated esters represents an efficient and versatile synthesis of β-amino esters and derivatives.[8] This methodology has found application in the total synthesis of natural products,[9] enantiorecognition phenomena,[10] and the initiation of tandem (cascade) processes.[11] For instance, the tandem conjugate addition/cyclization of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **4** to di-*tert*-butyl (*E*,*E*)-nona-2,7-dienedioate **5** and a range of dimethyl 4,4′-(alkylazanediyl)dibut-2-enoates, e.g., **6** and **7**, gives access to the corresponding homochiral, polysubstituted aminocyclohexane **8** and 3-aminopiperidines **9** and **10** in good yield with high diastereoselectivity (Scheme 1).[11a]

Scheme 1. Tandem Conjugate Addition/Cyclization for the Synthesis of Aminocyclohexane and 3-Aminopiperidines **8**−**10**



As a model system en route to derivatives of the *Martinelle* alkaloids, we envisaged that addition of homochiral lithium amide (*R*)-**4** to α,β-unsaturated esters **11** would promote a conjugate addition/cyclization reaction to give access to homochiral 2-aryl-4-aminotetrahydroquinoline-3-carboxylic acid derivatives **12** (Figure 2).[12] We delineate herein the results of these synthetic investigations.

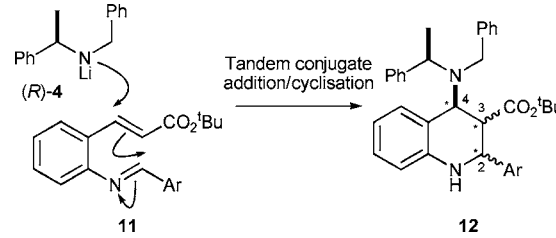


Figure 2. Tandem conjugate addition/cyclization for the synthesis of homochiral 4-aminotetrahydroquinolines **12**.

tert-Butyl (*E*)-3-(2′-aminophenyl)propenoate **13** was prepared in >98% de from Heck coupling of 2-iodoaniline and *tert*-butyl

(2) For selected recent synthetic approaches to the *Martinelle* alkaloids, see: Nyerges, M. *Heterocycles* **2004**, *63*, 1685. Takeda, Y.; Nakabayashi, T.; Shirai, A.; Fukumoto, D.; Kiguchi, T.; Naito, T. *Tetrahedron Lett.* **2004**, *45*, 3481. Hara, O.; Sugimoto, K.; Hamada, Y. *Tetrahedron* **2004**, *60*, 9381. He, Y.; Moningka, R.; Lovely, C. J. *Tetrahedron Lett.* **2005**, *46*, 1251. Ng, P. Y.; Masse, C. E.; Shaw, J. T. *Org. Lett.* **2006**, *8*, 3999. He, Y.; Mahmud, H.; Moningka, R.; Lovely, C. J.; Dias, H. V. R. *Tetrahedron* **2006**, *62*, 8755. Hadden, M.; Nieuwenhuyzen, M.; Osborne, D.; Stevenson, P. J.; Thompson, N.; Walker, A. D. *Tetrahedron* **2006**, *62*, 3977. Zhang, Z.; Zhang, Q.; Yan, Z.; Liu, Q. *J. Org. Chem.* **2007**, *72*, 9808. Badarinarayana, V.; Lovely, C. J. *Tetrahedron Lett.* **2007**, *48*, 2607. Miyata, O.; Shirai, A.; Yoshino, S.; Nakabayashi, T.; Takeda, Y.; Kiguchi, T.; Fukumoto, D.; Ueda, M.; Naito, T. *Tetrahedron* **2007**, *63*, 10092. Shirai, A.; Miyata, O.; Tohnai, N.; Miyata, M.; Procter, D. J.; Sucunza, D.; Naito, T. *J. Org. Chem.* **2008**, *73*, 4464. Lovely, C. J.; Badarinarayana, V. *Curr. Org. Chem.* **2008**, *12*, 1431.

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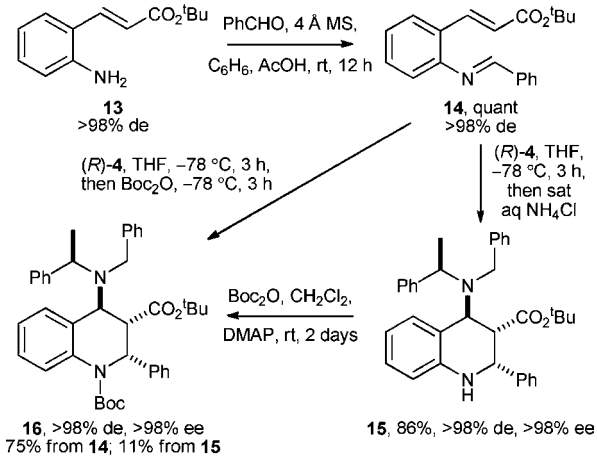
acrylate[13] and isolated in 95% yield and >98% de. Condensation of **13** with benzaldehyde gave benzylidine imine **14** as a single diastereoisomer, which was assigned the (*E*)-configuration.[14] Recrystallization furnished pure **14** in quantitative yield. Benzylidine imine **14** was treated with 1.6 equiv of lithium amide (*R*)-**4** (>98% ee)[15] to give 4-aminotetrahydroquinoline **15** as a single diastereoisomer (>98% de). Chromatographic purification gave **15** in 86% yield, >98% de, and >98% ee.[16] Repeated attempts to grow crystals of **15** for X-ray crystallographic analysis failed. However, treatment of **15** with Boc_2O (20 equiv) gave 17% conversion to the highly crystalline *N*-Boc derivative **16** in >98% de. Alternatively, addition of lithium amide (*R*)-**4** to benzylidene imine **14** and quenching with Boc_2O gave **16** in >98% de, which was isolated in 75% yield, >98% de, and >98% ee[16] after chromatography (Scheme 2).[17] The

Scheme 2. Tandem Conjugate Addition/Cyclization for the Synthesis of 4-Aminotetrahydroquinolines **15** and **16**



relative configuration within **16** was determined unambiguously by single crystal X-ray analysis, with the absolute (2*R*,3*S*,4*S*,α*R*)-configuration assigned from the known configuration of the (*R*)-α-methylbenzyl stereocenter (Figure 3). This analysis allowed

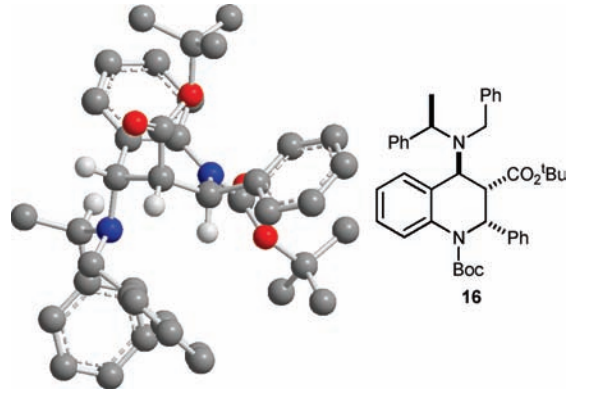


Figure 3. Chem3D representation of the X-ray crystal structure of **16** (some H atoms omitted for clarity).

unambiguous assignment of the absolute (2*R*,3*R*,4*S*,α*R*)-configuration within **15**. The absolute (4*S*)-stereogenic centers of **15** and **16**, formed during the conjugate addition of lithium amide (*R*)-**4**, are in accord with that predicted by the transition-state mnemonic developed by us to rationalize the exceptional stereofacial bias exerted by this class of lithium amide in its conjugate addition reactions.[18]

A simplistic mechanistic rationale to account for the observed stereoselectivity of this process may be proposed. Conjugate addition of lithium amide (*R*)-**4** generates lithium (*Z*)-β-amino enolate **17** and installs the (4*S*)-stereogenic center within tetrahydroquinoline **15**. Alkylation, protonation, or hydroxylation of a range of lithium (*Z*)-β-amino enolates is known to proceed with modest to excellent levels of *anti*-selectivity,[19] which is usually attributed to reaction of the lithium−nitrogen chelated enolate on the least hindered face. In the case of enolate **17**, lithium−nitrogen chelation presents the *Re* face of the enolate to the pendant imine and cyclization proceeds via boat transition state **17A** to give 2,3-*syn*-3,4-*anti*-4-aminotetrahydroquinoline **15** (Figure 4).

The generality of this tandem conjugate addition/cyclization process was next investigated. Aromatic and heteroaromatic (*E*)-configured[14] imines **18**−**21** were prepared as single diastereoisomers (>98% de) from α,β-unsaturated ester **13** and the corresponding aldehydes under dehydrative conditions. Purification of **18** was achieved via recrystallization (95% isolated yield), although **19**−**21** were not amenable to recrystallization and attempted chromatographic purification

(11) For instance, see: (a) Davies, S. G.; Diez, D.; Dominguez, S. H.; Garrido, N. M.; Kruchinin, D.; Price, P. D.; Smith, A. D. *Org. Biomol. Chem.* **2005**, *3*, 1284. (b) Davies, S. G.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2007**, *5*, 1405. (c) Koutsaplis, M.; Andrews, P. C.; Bull, S. D.; Duggan, P. J.; Fraser, B. H.; Jensen, P. *Chem. Commun.* **2007**, 3580. (d) Garrido, N. M.; Garcia, M.; Diez, D.; Sanchez, M. R.; Sanz, F. U.; Julio, G. *Org. Lett.* **2008**, *10*, 1687.

(12) For a related conjugate addition/cyclisation protocol for the synthesis of tetrahydroquinoline derivatives, see: Youn, S. W.; Song, J.-H.; Jung, D.-I. *J. Org. Chem.* **2008**, *73*, 5658.

(13) Lizos, D. E.; Murphy, J. A. *Org. Biomol. Chem.* **2003**, *1*, 117.

(14) The condensation of a range of aniline derivatives with a range of aldehydes is known to give the corresponding (*E*)-configured imines with good to excellent levels of diastereoselectivity; see: Tennant, G. *Comprehensive Organic Chemistry*; Barton, D. E., Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol. 2, Chapter 8. Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*; John Wiley and Sons: Chichester, 1970. For some very recent examples, see: Shen, M.; Driver, T. G. *Org. Lett.* **2008**, *10*, 3367. Albert, J.; D'Andrea, L.; Bautista, J.; Gonzalez, A.; Granell, J.; Font-Bardia, M.; Calvet, T. *Organometallics* **2008**, *27*, 5108.

(15) The parent amine (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine was assessed to be >98% ee by ^{1}H NMR chiral shift experiments using (*S*)-*O*-acetylmandelic acid and comparison with an authentic racemic sample.

(16) Given the known enantiomeric purity (i.e., >98% ee) of the lithium amide (*R*)-**4** used to initiate the tandem conjugate addition/cyclization process, the enantiomeric purity of **15**, **16**, and **22**−**27** was assigned from the diastereoisomeric purity (determined by peak integration of the ^{1}H NMR spectrum of the crude reaction mixture and the pure product).

(17) (*R*)-*N*-*tert*-Butoxycarbonyl-*N*-benzyl-*N*-(α-methylbenzyl)amine, formed by reaction of the excess lithium amide (*R*)-**4** with $(Boc)_2O$, was also isolated.

(18) Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1999.

(19) Davies, S. G.; Garrido, N. M.; Ichihara, O.; Walters, I. A. S. *Chem. Commun.* **1993**, 1153. Davies, S. G.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1129. Davies, S. G.; Ichihara, O.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1141. Bunnage, M. E.; Chernega, A. N.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2373.

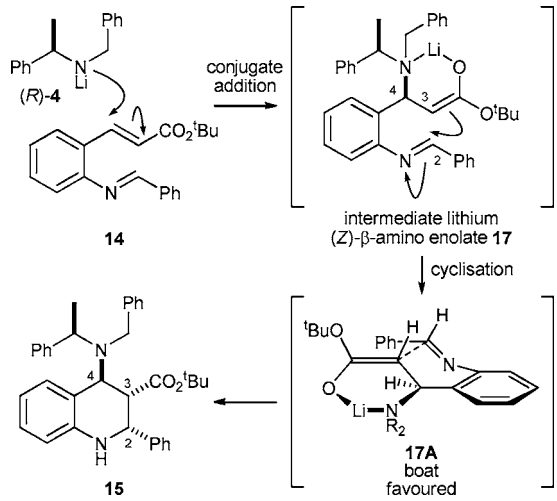
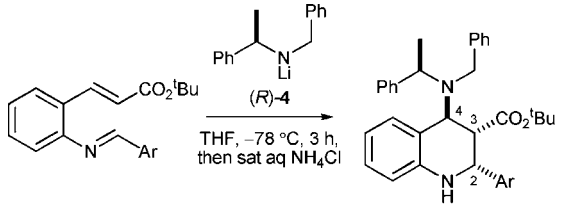


Figure 4. Postulated transition-state model for cyclization of lithium (*Z*)-*β*-amino enolate **17** (numbered atoms correspond to the stereocenters within tetrahydroquinoline **15**).

promoted hydrolysis of the imine functionality; therefore, **19**−**21** were utilized without prior purification. Addition of lithium amide (*R*)-**4** to imines **18**−**21** gave, in each case, the corresponding 4-aminotetrahydroquinolines **22**−**25** as the sole reaction products in >98% de. Chromatographic purification gave **22**−**25** in good yield (≥72%) and in >98% de and >98% ee[16] in each case (Scheme 3). The relative 2,3-

Scheme 3. Tandem Conjugate Addition/Cyclization for the Synthesis of 4-Aminotetrahydroquinolines **22**−**25**



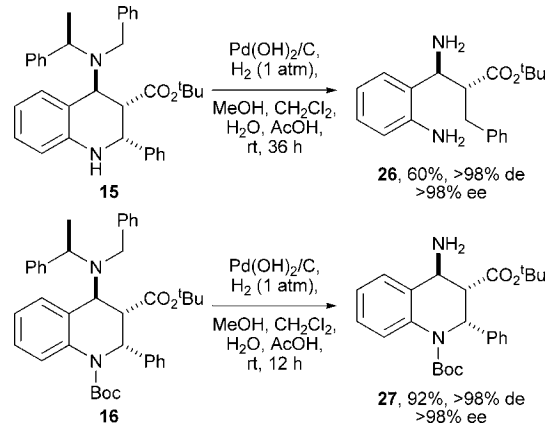
18-21, >98% de
18, Ar = 4-$C_6H_4CF_3$
19, Ar = 4-C_6H_4OMe
20, Ar = 2-$C_6H_4CH_3$
21, Ar = furan-2-yl

22-25, >98% de, >98% ee
22, Ar = 4-$C_6H_4CF_3$, 82%
23, Ar = 4-C_6H_4OMe, 72%
24, Ar = 2-$C_6H_4CH_3$, 72%
25, Ar = furan-2-yl, 80%

syn-3,4-*anti*-configurations within **22**−**25** were assigned by analogy to that unambiguously established for **15** and **16** and were supported by NOE data. The absolute (2*R*,3*R*,4*S*,α*R*)-configurations within **22**−**25** were thus assigned by reference to the transition state mnemonic described by us to rationalize the highly diastereoselective conjugate addition of lithium amide (*R*)-**4** to achiral α,*β*-unsaturated esters.[18]

Hydrogenolysis of 4-aminotetrahydroquinoline **15** gave quantitative conversion to α-benzyl-*β*-amino ester **26** as the only product, in which cleavage of the *N*-benzyl-*N*-α-methylbenzyl protecting groups and the N(1)−C(2) benzylic bond of the tetrahydroquinoline ring had occurred.[20] Hydrogenolysis of *N*-Boc protected 4-aminotetrahydroquinoline **16** gave **27** in 92% isolated yield, >98% de, and >98% ee,[16] consistent with our previous reports that hydrogenolysis of *N*-benzyl-*N*-α-methylbenzyl-protected *β*-amino esters proceeds with no loss of stereochemical integrity[8a] (Scheme 4).

Scheme 4. Hydrogenolysis of 4-Aminotetrahydroquinolines **15** and **16**



In conclusion, condensation of *tert*-butyl 3-(2′-aminophenyl)propenoate with a range of aromatic and heteroaromatic aldehydes generates the corresponding diastereoisomerically pure imines. Addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide initiates a tandem conjugate addition/cyclization reaction, generating 2-aryl-4-aminotetrahydroquinoline-3-carboxylic acid derivatives in >98% de and >98% ee. Hydrogenolysis of a 2-phenyl-4-aminotetrahydroquinoline-3-carboxylic acid derivative gives a diamino ester scaffold, while hydrogenolysis of the corresponding *N*(1)-Boc-protected compound allows selective cleavage of the *N*-benzyl-*N*-α-methylbenzyl protecting groups without compromising the diastereo- or enantiopurity. This procedure represents a very operationally simple yet powerful method for the construction of three contiguous stereogenic centers within a homochiral 4-aminotetrahydroquinoline nucleus in a single step. This approach should be readily applicable to the preparation of libraries of 4-aminotetrahydroquinolines for biological screening.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The remarkable resistance of *β*-aryl-*β*-amino ester derivatives to undergo cleavage of the N−C(*β*) bond has been attributed to the presence of an intramolecular hydrogen bond between the *β*-amino substituents and the carbonyl oxygen atom that holds the C(*β*)-aryl group in a conformation that disfavors hydrogenolysis of the benzylic N−C(*β*) bond; see ref 8a.