Pergamon

Tetrahedron Letters 41 (2000) 4999–5003

TETRAHEDRON LETTERS

From serine to functionalized enantiopure tetrahydroisoquinolines

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Received 22 March 2000; accepted 10 May 2000

Abstract

The reaction of γ-amino-α,β-unsaturated esters prepared from L-serine with diversely substituted arylcuprates affords the corresponding *syn*-adducts. Transformation of the amino group to an isocyanate, followed by Friedel–Crafts intramolecular condensation, leads to enantiopure 3,4-disubstituted tetrahydroisoquinolin-1-ones, which can be reduced to the corresponding tetrahydroisoquinolines.

Keywords: Friedel–Crafts; organocuprate; conjugate addition.

Isoquinoline alkaloids have been a cornerstone in the large collection of naturally occurring substances belonging to the alkaloid family and they figure prominently in the arsenal of pharmacologically active compounds.[1] Tetrahydroisoquinolines are traditionally synthesized from the ring closure of iminium intermediates via the well-known Pictet–Spengler[2] or Bischler–Napieralski[3] reactions. Other methods are also known for the synthesis of 1-substituted 1,2,3,4-tetrahydroisoquinolines in racemic and enantiopure forms.[1]

In contrast, there are fewer methods for the stereocontrolled synthesis of 3- or 3,4-substituted congeners.[4] A recent claim to 3-substituted tetrahydroisoquinolines from *N*,*N*-dibenzylamino alcohols,[5] has been repudiated after careful experimentation by another group.[6] Such compounds could be viewed as versatile scaffolds on which to attach pharmacophore-like groups through the chemical elaboration of existing functionality of the tetrahydroisoquinoline nucleus. An assembly protocol that also allows for the incorporation of substituents on the aromatic portion would greatly enhance the versatility of these molecules as potential pharmacologically important agents, or as probes to study interactions with biological receptors, enzymes, etc.

We report herein a method for the stereocontrolled synthesis of 3,4-disubstituted tetrahydroisoquinolin-1-ones and tetrahydroisoquinolines in enantiopure form starting with L-serine[7] as seen

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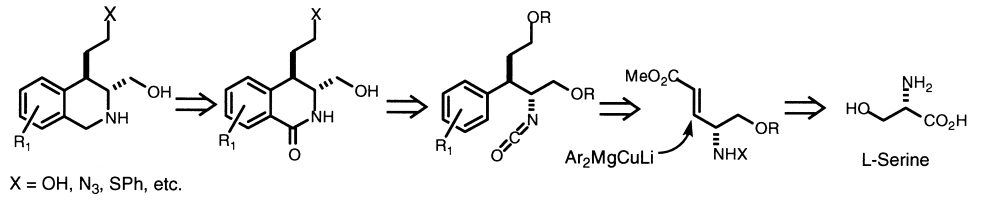
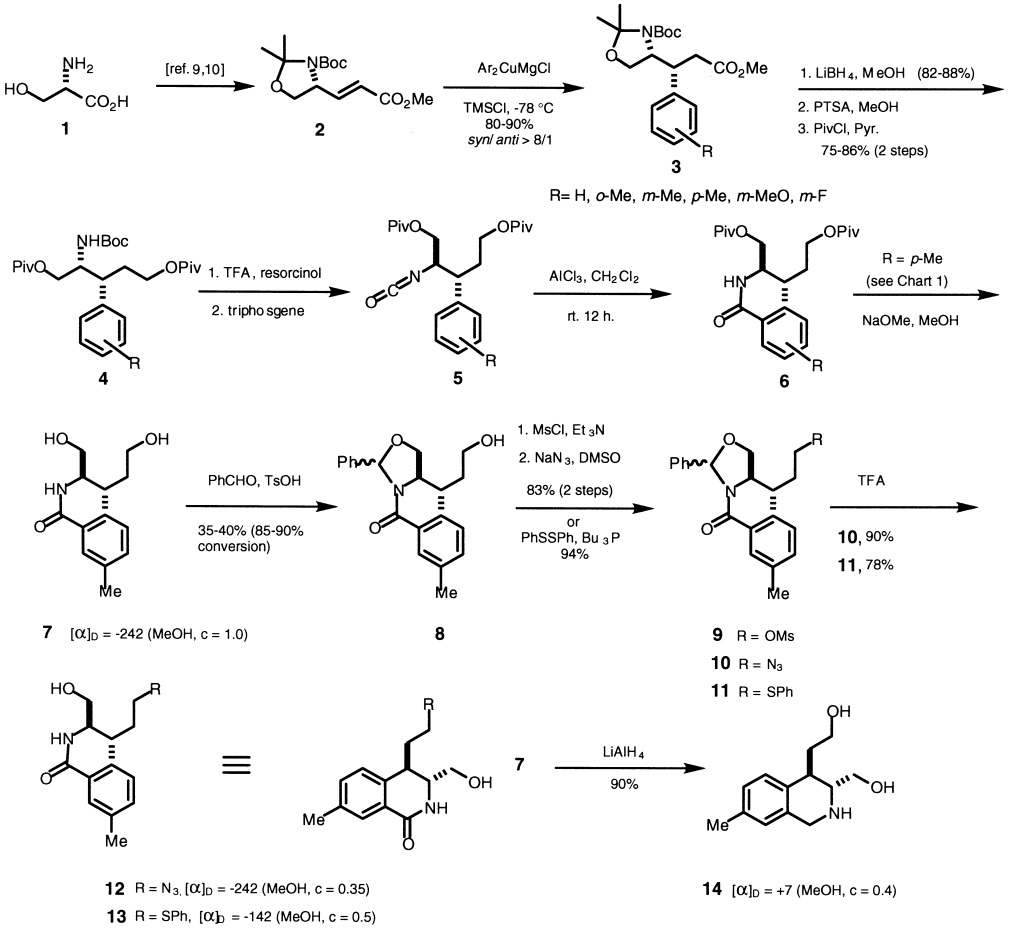
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00765-6

in Scheme 1. The method consists in the stereocontrolled conjugate addition of diarylmagnesiocuprates to a readily available α,β-unsaturated ester.[8–10] After transformation of the amino group to the corresponding isocyanate, the products are subjected to a Friedel–Crafts intramolecular cyclization[11] to provide tetrahydroisoquinolin-1-ones.



Scheme 1.

Thus, L-serine was converted to the α,β-unsaturated ester[8–10] **2**, which is known to react with organocuprate reagents in the presence of trimethylsilyl chloride to give predominantly *syn*-adducts[8–10,12] (Scheme 2).



Scheme 2.

Extension of this reaction to a variety of *o*-, *m*-, and *p*-substituted diarylmagnesiocuprates led to the corresponding β-aryl adducts **3** in excellent yields, and diastereoselectivities exceeding 8:1 in favor of the *syn*-isomer.[10] The rationale for the observed stereoselectivity has been discussed in a previous paper from our group.[10] In order to carry out the intramolecular cyclizations en route to the desired tetrahydroisoquinolin-1-ones **6**, it was necessary to introduce functionality and protective groups that would be compatible with the use of aluminum chloride under Friedel–Crafts conditions. The adducts **3** were transformed to the bis-pivaloyl esters of generic structure **4** in good overall yields. Removal of the *N*-Boc group with trifluoroacetic acid in the presence of resorcinol,[13] followed by treatment with triphosgene[14] led to the corresponding isocyanates[15] **5**. In general, the Friedel–Crafts reaction gave single products in good to excellent yields (Fig. 1). In the case of the *m*-methyl isomer corresponding to **5**, the reaction afforded a 2.2:1 mixture of the *o*- and *p*-methyl cyclization products **17a** and **17b** which were separable by column chromatography. The corresponding methoxy analog gave the product of *p*-substitution **19**, only, no doubt due to the activating effect of the methoxy group. Interestingly, the *m*-fluoro isocyanate corresponding to **5** also gave the *p*-substituted product **20** only (Fig. 1).[16]

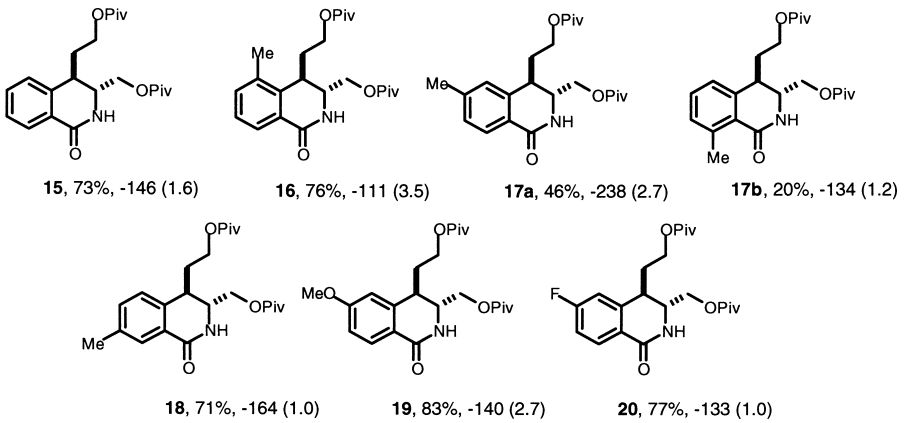


Figure 1. [a]Yields of chromatographically pure product over three steps as in Scheme 2; [b]$[\alpha]_D$ reported in $CHCl_3$ with concentration in brackets; [c]all products were adequately characterized by ^1H, ^{13}C and HRMS

In order to further demonstrate the utility of these compounds, we explored reactions taking the *p*-methyl analog as a prototype (Scheme 2). Hydrolysis of the pivalate esters, gave the corresponding diol **7** which was transformed to a diastereomeric mixture of 2-phenyl-1,3-oxazolidine derivatives **8**, thus allowing for further elaboration of the distal hydroxyethyl group. In a typical example, displacement of the mesylate **9** with azide gave the corresponding azido derivative **10**. The phenylthio ether **11** was also prepared from **8** following known precedents.[17] Acid hydrolysis of **10** and **11** afforded the selectively functionalized azido and phenylthio derivatives **12** and **13**, respectively, in enantiopure form. A prototypical tetrahydroisoquinoline **14** was prepared by reduction of the diol **7** with $LiAlH_4$.

The methodology reported in this paper provides access to diversely functionalized enantiopure 3,4-disubstituted tetrahydroisoquinolines with different aromatic substituents. The azido and phenylthio derivatives **12** and **13** can be subjected to further orthogonally directed chemical manipulations, thus expanding the versatility of this class of heterocycles not only as scaffolds for the deployment of pharmacophores, but also as potential bioactive compounds. In this regard,

recent reports concerning the synthesis of polysubstituted tetrahydroisoquinolines and related compounds on solid-support and by parallel array are noteworthy.[18,19]

Acknowledgements

We thank NSERCC for financial assistance through the Medicinal Chemistry Chair Program.

References

1. Rozwadowska, M. D. *Heterocycles* **1994**, *39*, 903, and references cited therein; Herbert, R. B. In *The Chemistry and Biology of Isoquinoline Alkaloids*; Philipson, J. D.; Roberts, M. F.; Zenk, M. H., Eds.; Springer-Verlag: Berlin, 1985; p. 213; Shamma, M. In *Isoquinoline Alkaloids, Chemistry and Pharmacology*; Academic: New York, 1972.
2. Cox, A. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.
3. For a recent example, see: Morimoto, T.; Suzuki, N.; Achiwa, K. *Tetrahedron: Asymmetry* **1998**, *9*, 183.
4. For leading references, see: Vicario, J. L.; Badía, D.; Domínguez, E.; Carrillo, L. *J. Org. Chem.* **1999**, *64*, 4610; Monsees, A.; Laschat, S.; Dix, I. *J. Org. Chem.* **1998**, *63*, 10018.
5. Chandrasekhar, S.; Mohanty, P. K.; Harikishan, K.; Sasmal, P. K. *Org. Lett.* **1999**, *1*, 877.
6. Weber, K.; Kuklinski, S.; Gmeiner, P. *Org. Lett.* **2000**, *2*, 647.
7. For the synthesis of heterocycles from amino acids, see: Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825; for early seminal work in asymmetric synthesis, see: Meyers, A. I.; Fuentes, L. M. *J. Am. Chem. Soc.* **1983**, *105*, 117.
8. Hanessian, S.; Wang, W.; Gai, Y. *Tetrahedron Lett.* **1996**, *37*, 7477.
9. Jako, I.; Uiber, P.; Mann, A.; Taddei, M.; Wermuth, C.-G. *Tetrahedron Lett.* **1990**, *31*, 1011.
10. Hanessian, S.; Sumi, K. *Synthesis* **1991**, 1083.
11. Effenberger, F.; Gleiter, R. *Chem. Ber.* **1964**, *97*, 472.
12. For a review on α-amino acid aldehydes, their derivatives, and further transformations, see: Reetz, M. T.; Röhrig, D. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1706; Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121.
13. Wünsch, E.; Jaeger, E.; Kisfaludy, L.; Löw, M. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 317; Schmidt, U.; Lieberknecht, A.; Bökens, H.; Griesser, H. *J. Org. Chem.* **1983**, *48,* 2680.
14. Eckert, H.; Forster, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 894.
15. Nowick, J. S.; Powell, N. A.; Nguyen, T. M.; Noronha, G. *J. Org. Chem.* **1992**, *57*, 7364.
16. *Typical procedure for cuprate addition*: A suspension of magnesium chips (535 mg, 22 mmol, 1.1 equiv.) with a trace of iodine in 6 mL of THF was heated at reflux until colorless. After cooling to room temperature, 2-bromotoluene (3.4 g, 20 mmol), in 34 mL of THF was added dropwise over 30 min so that the temperature was kept below 40°C. Stirring was maintained for 30 min and after 12 h the supernatant was cannulated into a flask, affording a 0.5 M solution of the Grignard reagent. To a suspension of CuI (1.9 g, 10 mmol) in 10 mL of THF at –78°C was added dropwise 40 mL of the preceding solution of Grignard reagent (0.5 M in THF, 20 mmol). The resulting mixture was allowed to warm to –20°C over 1 h, then recooled to –78°C. To the reaction mixture were added trimethylsilyl chloride (3 mL, 22 mmol) and a solution of **2** (712 mg, 2.5 mmol) in 5 mL of THF dropwise. The resulting mixture was stirred at this temperature for 12 h, then quenched with 30 mL of a saturated aqueous NH_4Cl solution. After dilution with AcOEt, the layers were separated. The aqueous layer was extracted twice with AcOEt and the combined organic phases were washed twice with NH_4OH (5% in solution), brine, dried over Na_2SO_4 and concentrated in vacuo to give after flash chromatography on silica gel (petroleum ether:AcOEt, 9:1 then 8:2) 760 mg (81%) of **3** as a pale yellow oil. *Typical procedure for the Friedel–Crafts cyclization*: To a solution of **4** (680 mg, 1.42 mmol) and resorcinol (157 mg, 1.42 mmol) in 5 mL of toluene at 0°C was added 1 mL of CF_3COOH. The resulting mixture was stirred at this temperature for 6 h, then concentrated in vacuo. The resulting material was diluted in AcOEt, washed twice with 1 M NaOH, brine, dried over Na_2SO_4 and concentrated in vacuo to give **5** (520 mg, 97%) as a pale yellow oil which was used in the next reaction without purification. To a solution of triphosgene (143 mg, 0.48 mmol) in 5 mL of CH_2Cl_2 at 0°C was added dropwise by cannula a solution of **4** (520 mg, 1.38 mmol) and pyridine (280 μl, 3.45 mmol) in 5 mL of CH_2Cl_2. The resulting yellow solution was

stirred at this temperature for 2 h, diluted in AcOEt and washed rapidly with water (pH 3). The aqueous layer was extracted with AcOEt and the combined organic phases washed rapidly with a saturated aqueous $NaHCO_3$ solution, brine, then dried over Na_2SO_4 and concentrated in vacuo to give isocyanate **5** (520 mg, 93%) as a brown oil which was used in the next reaction without purification. To a suspension of $AlCl_3$ (860 mg, 6.45 mmol) in 5 mL of CH_2Cl_2 at 0°C was added a solution of **5** (520 mg, 1.29 mmol) in 3 mL of CH_2Cl_2. The mixture was allowed to warm to room temperature and stirred overnight, then partitioned between AcOEt and 10% aqueous HCl. The layers were separated and the aqueous layer was extracted with AcOEt. The combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution, brine, then dried over Na_2SO_4 and concentrated in vacuo to give after flash chromatography (petroleum ether:AcOEt. 3:1 then 1:1) 370 mg (72%) of **6** as a colorless oil.

17. See, for example: Hanessian, S.; Tyler, P. C.; Demailly, G.; Chapleur, Y. *J. Am. Chem. Soc.* **1981**, *103*, 6243; Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1409.
18. Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1996**, *118*, 8977.
19. Baudelle, R.; Melnyk, P.; Déprez, B.; Tartar, A. *Tetrahedron* **1998**, *54*, 4125.