Pergamon

Tetrahedron Letters 39 (1998) 3099–3102

TETRAHEDRON LETTERS

SULFINIMINE MEDIATED ASYMMETRIC SYNTHESIS OF 3-SUBSTITUTED -1(2*H*)-ISOQUINOLONES: (3*R*,4*S*)-(-)-4-HYDROXY-3-PHENYLTETRAHYDROISOQUINOLINE

Franklin A. Davis* and Yemane W. Andemichael

Department of Chemistry, Temple University, Philadelphia, PA 19122

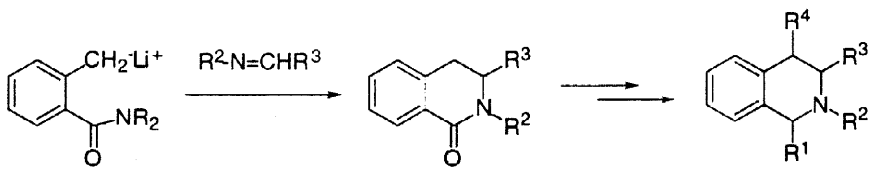
Received 4 February 1998; revised 17 February 1998; accepted 18 February 1998

Summary: A general approach to enantiomerically pure 3-substituted-1(2*H*)-isoquinolones is illustrated by the addition of lateral lithiated amide **7** to sulfinimine **5**. Isoquinolone **8** is readily transformed into (3*R*,4*S*)-(-)-4-hydroxy-3-phenyltetrahydroisoquinoline **15** via hydroxylation and reduction.

The 3-substituted 1,2,3,4-tetrahydroisoquinoline alkaloids **3,** although not as common as their 1-substituted analogs, are of considerable importance because of their unique structure and biological activity. Examples include naphthylisoquinoline,[1] protoberberine[2] and amaryllidaceae[3] families of alkaloids which exhibit a wide range of biological activity; e.g. antimalarial, antitumor and anti-viral activity. The traditional approach to this skeleton has been the cyclization of 1-arylethylamino derivatives using Bishler-Napieralski (B-N) or Pictet-Spengler (P-S) protocols. However, with these procedures the regio- and stereoselective formation of the isoquinoline ring is often an issue,[4] and side reactions resulting from the nitrilium ion intermediate can be a problem.[5] In this regard a modified procedure has been introduced.[6] The enantioselective synthesis of the 1-arylethylamino derivatives and their compatibility with the sometimes harsh B-N and P-S conditions are also problematic.

A potentially important method for the enantioselective synthesis of 3-substituted 1,2,3,4-tetrahydroisoquinoline **3**, illustrated in Scheme 1, is the condensation of lateral lithiated amides **1**[7]with chiral imines. This approach, developed by Clark et. al.[8] with racemic imines,[9] has the potentiality of preparing tetrahydroisoquinolines with substitution patterns not easily accessible by other means because the 3,4-dihydro-1(2*H*)-isoquinolones **2** can be readily manipulated and substituents introduced at the 1- and 4-positions. What has undoubtedly prevented the general application of this method to the asymmetric synthesis of **3** is the unreactivity of imines, the propensity of aliphatic examples to undergo α-deprotonation rather than addition and the lack of suitable chiral examples. Sulfinimines (thiooxime S-oxides, ArS(O)N=CHR) developed in our laboratory offer a solution to this problem.[10,11] The chiral sulfinyl group in sulfinimines is a superior auxiliary in that it activates the imine toward addition to such an extent that α-deprotonation is not

Scheme 1



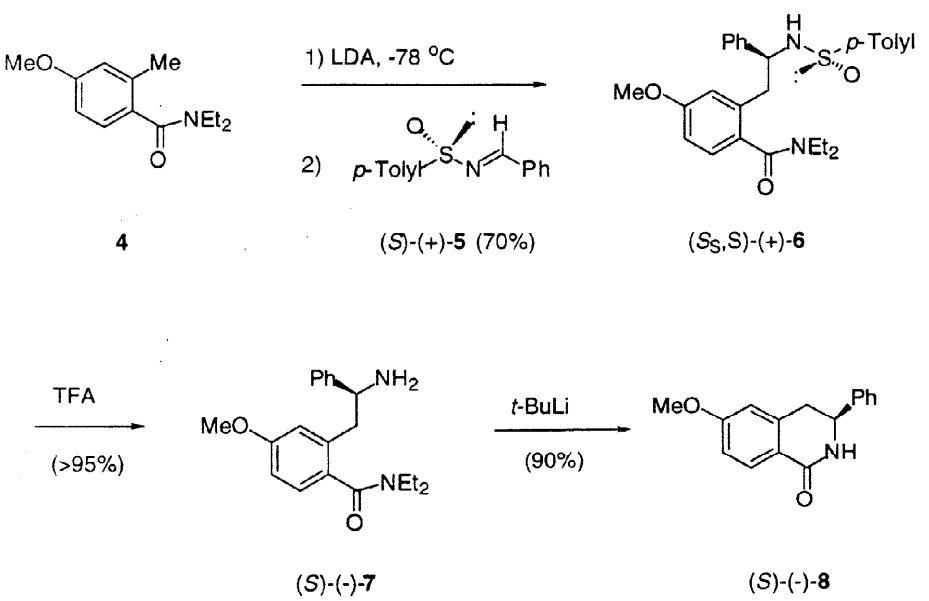
1 **2** **3**

PII: S0040-4039(98)00506-1

an important issue. It is highly stereodirecting and easy to remove. Furthermore, sulfinimines are prepared in "one pot" from commercially available (1*R*,2*S*,5*R*)-(-)-menthyl (*S*)-*p*-toluenesulfinate or (1*S*,2*R*,5*S*)-(+)-menthyl (*R*)-*p*-toluenesulfinate (Andersen reagent) and aromatic or aliphatic aldehydes.[10] Here we illustrate the application of sulfinimines to the asymmetric synthesis of 3,4-dihydro-1(2*H*)-isoquinolones **2** and tetrahydroisoquinolines **3** in the highly diastereoselective synthesis of (3*R*,4*S*)-(-)-6-hydroxy-3-phenyltetetrahydroisoquinoline (**15**). This isoquinoline is a precursor of the 13-hydroxyprotoberberines,[12] and its enantiomer was recently prepared in 7 steps starting from an enzymatically resolved cyanohydrin by Domingues and co-workers.[13]

4-Methoxy-*N*,*N*-diethyl-*o*-toluamide (**4**),[14] [6.0 mmol] was treated with a slight excess of LDA at -78 °C in THF to generate the intensely burgundy colored solution of the lateral lithiated amide (Scheme 2). After a few min, 0.5 equiv of (*S*)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide (**5**)[10] was added and after 15 min. the solution was quenched with sat. NH_4Cl solution. Flash column chromatography afforded (S_S,*S*)-(+)-*N*-[1-phenyl-2-*N*,*N*-diethylbenzamido)ethyl]-*p*-toluenesulfinamide (**6**) in 70% yield as a single diastereoisomer as analyzed by NMR spectroscopy. Attempts to cyclize this material directly to (3*S*)-(-)-3-phenyl-3,4-dihydrol(2*H*)-isoquinolone (**8**) by treatment with excess LDA failed, undoubtedly due to the stability of the N-sulfinyl amine anion. Removal of the sulfinyl auxiliary in **6** was easily accomplished by treatment with 5 equiv of TFA in MeOH to give the amine (-)-**7** in nearly quantitative yield. Preparation of the Mosher amide of **7** with (*S*)-MTPS-Cl indicated that the enantiomeric purity of the amine was >97% ee. At this point it was not possible to establish the configuration of the initially formed chiral center in **6**, subsequently shown to have the (*S*)-configuration (*vide infra*), because suitable crystals for X-ray analysis could not be obtained. Cyclization of **7** to the isoquinolone **8** was easily effected by treatment with 3 equiv of *tert*-butyllithium to give **8** in 90% yield.

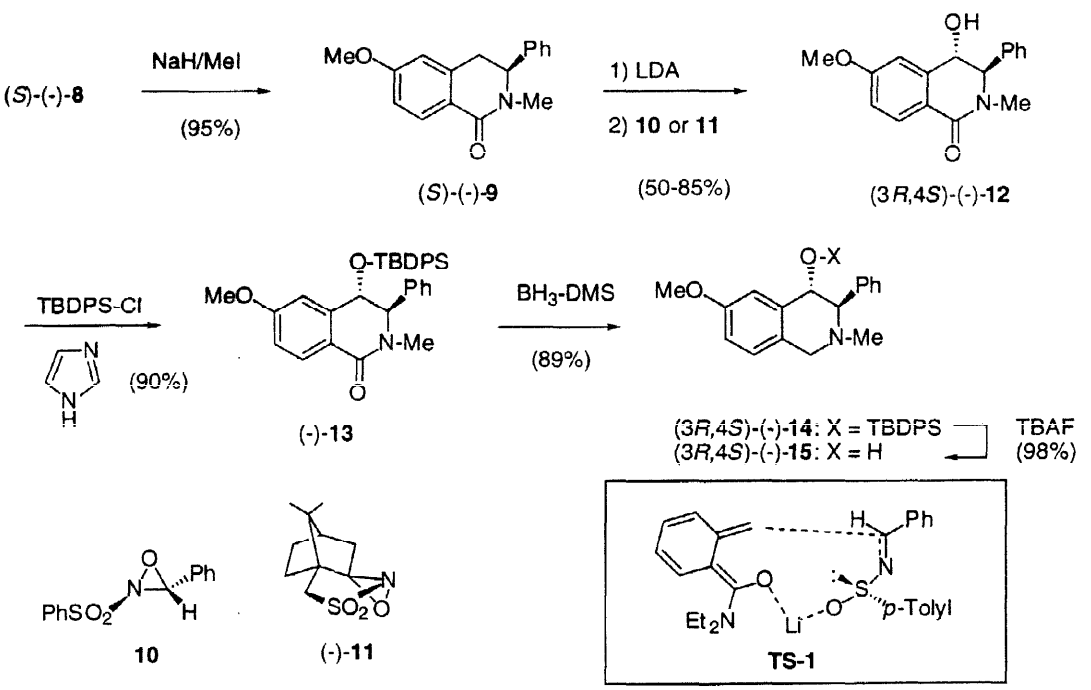
Scheme 2



After N-methylation of the amide nitrogen in **8** with NaH/MeI, we next turned our attention to the introduction of the 4-hydroxyl group into **9** (Scheme 3). This was readily accomplished by the stereoselective

oxaziridine mediated hydroxylation[15] of the anion of **9**, generated by treatment of **8** with 3 equivalents of LDA at -78 °C. Thus reaction of the anion of **9** with 1.5 equivalents of 2-(phenylsulfonyl)-3-phenyloxaziridine (**10**) or (camphorylsulfonyl)oxaziridine (**11**) affords **12** in 56 and 85% yield, respectively. As previously reported, much higher yields with fewer side reactions are observed for carbanion and enolate hydroxylations with **11**.[15a] In each case only a single diastereoisomer of (3*R*,4*S*)-**12** was detected. The *trans* selectivity is consistent with our earlier findings that demonstrated that the hydroxylation stereochemistry is governed by nonbonded steric interactions in the transition state such that **10** or **11** approach from the sterically least hindered direction.[15a] In full agreement with this assignment is the small 3,4-coupling constant (2.1 Hz) in **12**.[16] Silylation with TBDPS-Cl/imidazole, reduction with BH_3·DMS and desilylation with tetrabutylammonium fluoride (TBAF) afforded (3*R*,4*S*)-(-)-4-hydroxy-3-phenyl-6-methoxy-tetrahydroisoquinoline (**15**) in >95% ee (determined using $Eu(hfc)_3$) and in 78% overall yield for the three steps. This establishes that the initially formed stereocenter in **6** has the (*S*)-configuration and results from approach of the lateral lithiated amide anion, thought to exist as an *o*-quinodimethane,[7] at the sterically least congested face of sulfinimine C-N double bond; e.g. **TS-1**.

Scheme 3



In summary, new methodology is introduced for the enantioselective synthesis of 3-substituted-1(2*H*)-isoquinolines via the highly diastereoselective addition of lateral lithiated amides to sulfinimines. The efficient stereoselective conversion of **8** into (3*R*,4*S*)-(-)-4-hydroxy-3-phenyltetrahydroisoquinoline **15** was demonstrated. The application of this protocol in the asymmetric synthesis of 3-substituted 1,2,3,4-tetrahydroisoquinoline alkaloids is under vigorous investigation.

Acknowledgments. This work was supported by Grants from the National Institutes of Health and the SmithKline Beecham Corporation. We thank Dr. Thimma Rawalpally for preliminary results.

REFERENCES AND NOTES

1. For a review of the naphthylisoquinoline alkaloids see: Bringmann, G.; Pokorny in *The Alkaloids*; Cordell, G., Ed. Academic Press: New York, 1995, Vol 46. p 127.
2. For a review of the protoberberine alkaloids see: Bhakuni, D. S.; Jain, S. in *The Alkaloids*; Brossi, A.; Ed. Academic Press: New York, 1986, Vol 28. p 95.
3. For a review of the amaryllidaceae alkaloids see: Martin, S. in *The Alkaloids*; Brossi, A.; Ed. Academic Press: New York, 1987, Vol 30. p 252.
4. Whaley, W. M.; Govindachari, T. R.; *Organic Reactions* **1951**, *6*, 151. Dominguez, E.; Lete, E.; Badia, M. D.; Billa, M. J.; Castedo, L.; Dominguez, D. *Tetrahedron* **1987**, *43*, 1943. Bringmann, G.; Weirich, R.; Reuscher, H.; Jansen, J. R.; Kinzinger, L.; Ortmann, T. *Liebigs Ann. Chem.* **1993**, 877.
5. Nagubandi, S.; Fodor, G. J. *Heterocyclic. Chem.* **1980**, *17*, 1457. Dominguez. E.; Lete, E. *Heterocycles* **1983**, *20*, 1247. Aguirre, J. M.; Alesso, E. N.; Ibanez, A. F.; Tombari, D. G.; Moltrasio Iglesias, G. Y. *Heterocyclic Chem.* **1989**, *26*, 25.
6. Larsen, R. D.; Reamer, R. E.; Corley, E. G.; Davis, P.; Grabowski, E. J. J.; Reider, P. J.; Shinkai, I. *J. Org. Chem.* **1991**, *56*, 6034.
7. For a review on lateral lithiation reactions see: Clark, R. D.; Jahangir, A. *Organic Reactions* **1995**, *47*, 5.
8. Clark, R. D.; Jahangir, A. *J. Org. Chem.* **1987**, *52*, 5378. Clark, R. D.; Jahangir, A. *J. Org. Chem.* **1989**, *54*, 1174.
9. For a chiral example see: Clark, R. D.; Jahangir, A.; Souchet, M.; Kern, J. R. *J. Chem. Soc. Chem. Commun.* **1989**, 930.
10. Davis, F. A.; Reddy, R. E.; Szewcsyk, J. M; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Thimma Reddy, R.; Zhou, P.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 2555.
11. For recent applications of sulfinimines to asymmetric synthesis see: (α-Amino acids) Davis, F. A..; Portonovo, P. S.; Reddy, R. E.; Chiu, Y.-H. *J. Org. Chem.* **1996**, *61*, 440. Hua, D. H.; Lagneau, N.; Wang, H.; Chen, J. *Tetrahedron: Asymmetry* **1995**, *6* , 349. Lefebvre I. M.; Evans, Jr., S. A. *J. Org. Chem.* **1997**, *62*, 7532. (β-Amino acids) Jiang, J.; Schumacher, K. K.; Joullie, M. M.; Davis, F. A.; Reddy, R. E. *Tetrahedron Lett.* **1994**, *35*, 2121. Davis, F. A.; Reddy, R. E.; Szewczyk, J. *J. Org. Chem.* **1995**, *60*, 7037. Davis, F. A.; Szewczyk, J., Reddy, R. E. *J. Org. Chem.* **1996**, *61*, 2222. Fujisawa, T.; Kooriyama, Y.; Shimizu, M. *Tetrahedron Lett.* **1996**, *37*, 3881. Mikolajczyk, M.; Lyzwa, P.; Drabowicz, J Wieczorek, M. W.; Blaszczyk, J. *J. Chem. Soc. Chem. Commun.* **1996**, 1503. Davis, F. A.; Reddy, R. E. *Tetrahedron: Asymmetry* **1994**, *5*, 955. (Aziridine 2-carboxylate esters): Davis, F. A.; Zhou, P.; Reddy, G. V. *J. Org. Chem.* **1994**, *59*, 3243. Davis, F. A.; Liu, H.; Reddy, G. V. *Tetrahedron Lett.* **1996**, *37*, 5473. Davis, F. A.; Liang, C.-H.; Liu, H. *J. Org. Chem.* **1997**, *62*, 3796. Davis, F. A.; Zhou, P. *Tetrahedron Lett.* **1994**, *35*, 7525. Davis, F. A.; Reddy, G. V. *Tetrahedron Lett.* **1996**, 37, 4349.Davis, F. A.; Reddy, G. V.; Liu, H. *J. Am. Chem. Soc.* **1995**, *117*, 3651. (Amines) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913. Hose, D. R. J.; Mahon, M. F.; Molloy, K. C.; Raynham, T.; Wills, M. *J. Chem. Soc. Perkin I* **1996**, 691. (Heterocycles) Balasubramanian, T.; Hassner, A. *Tetrahedron Lett.* **1996**, *37*, 5755. Viso, A.; de la Pradilla, R. F.; Guerrero-Strachan, C.; Alonso, M.; Martinez-Ripoll, Andre. I. *J. Org. Chem.* **1997**, *62*, 2316.
12. Tellitu, I.; Badia, D.; Dominguez, E.; Carrillo, L. *Heterocycles* **1996**, *43*, 2099.
13. Tellitu, I.; Badia, D.; Dominguez, E.; Garcia, F. J.. *Tetrahedron: Asymmetry* **1994**, *5*, 1567.
14. Mills, R. J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 3153.
15. For reviews on the oxygen transfer reactions of oxaziridines see: (a) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919. (b) Davis, F. A.; Chen, B.-C. in Stereoselective Synthesis, Helmchen, G.; Hoffman, R. W.; Mulzer, J.; Schaumann, E. Eds *Houben-Weyl*, **1995**, *E21e*, 4497. (c) Davis, F. A.; Thimma Reddy, R. *Comp. Heterocycl. Chem. II.* Padwa, A. Ed., Pergamon Press, Oxford, **1996**, 1, 365.
16. Cushman, M.; Choong, T.-C.; Valko, S. T.; Koleck, M. P. *J. Org. Chem.* **1980**, *45*, 5067.
17. Selected properties: (*Ss*,*S*)-**6**, m.p. 143-144 °C, $[\alpha]^{20}_D$ +10.58 (*c* 1.2, $CHCl_3$); (*S*)-(+)-**7**, oil, $[\alpha]^{20}_D$ -4.1 (*c* 1.1, $CHCl_3$); (*S*)-(-)-**8**, mp 127-128 °C, $[\alpha]^{20}_D$ -131.6 (*c* 1.36, $CHCl_3$); (*S*)-(-)-**9**, mp 124-125 °C, $[\alpha]^{20}_D$ -136.5 (*c* 1.0, $CHCl_3$); (3*R*,4*S*)-(-)-**12**; thick oil, $[\alpha]^{20}_D$ +91.9 (*c* 0.86, $CHCl_3$); (-)-**13**, mp. 187-188 °C, $[\alpha]^{20}_D$ +120.5 (*c* 0.6, $CHCl_3$); (3*R*,4*S*)-(-)-**14**, gum, $[\alpha]^{20}_D$ +31.0 (*c* 2.95, $CHCl_3$); (3*R*,4*S*)-(-)-**15**, mp 116-117 °C, $[\alpha]^{20}_D$ -59.8 (*c* 0.80, $CHCl_3$) [Lit.[13] $[\alpha]^{20}_D$ 59 (*c* 1.0, $CHCl_3$) for the (3*S*,4*R* -enantiomer].