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A New Asymmetric Synthesis of *trans*-Hydroisoquinolones

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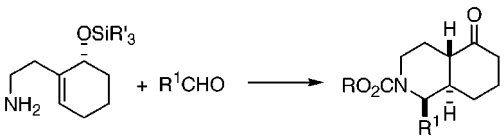
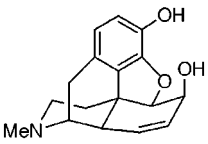
ABSTRACT

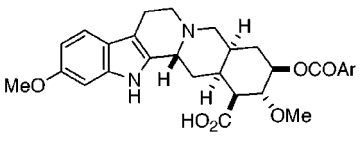


A convenient enantioselective synthesis of *trans*-hydroisoquinolones is described. This synthesis capitalizes on the ready availability of enantioenriched 2-substituted cyclohexenols by exploiting the asymmetry of an allylic carbon−oxygen σ bond to control carbon−carbon bond formation in pinacol-terminated cyclizations of *N*-acyliminium cations.

Decahydroisoquinoline rings are found in structurally diverse isoquinoline alkaloids as well as several important clinical agents.[1,2] Morphine (**1**) and reserpine (**2**) are well-known members of these groups. Because of the wide occurrence and pharmacological importance of *trans*-hydroisoquinolines, the development of new asymmetric routes to this ring system remains an important objective in organic synthesis.



morphine (**1**)



reserpine (**2**) Ar = 3,4,5-trimethoxyphenyl

In recent years, we have invented a suite of carbon−carbon bond-forming ring constructions that couple pinacol rearrangements with cationic cyclization reactions.[3,4] The accompanying communication in this issue details reactions wherein pinacol rearrangement of a ring carbon terminates a cationic cyclization process.[5] Much less developed are cyclization−pinacol reactions concluded by hydride migration.[6] A new sequence of this latter type, which we envisaged

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(1) Bentley, K. W. *Nat. Prod. Rep.* **1999**, *16*, 367−388 and references therein.

(2) Lednicer, D.; Mitscher, L. A. *The Organic Chemistry of Drug Synthesis*; Wiley: New York, 1997; Vol. 7 and earlier volumes in this series.

(3) For brief reviews, see: (a) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352−359. (b) Overman, L. E. *Aldrichim. Acta* **1995**, *28*, 107−120. (c) Overman, L. E. In *Selectivities in Lewis Acid-Promoted Reactions*; NATO ASSI Series 289; Schinzer, D., Ed.; Kluwer Academic: Dordrecht, The Netherlands, 1989; pp 1−20.

(4) Recent illustrative examples include (a) MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391−10392. (b) Minor, K. P.; Overman, L. E. *Tetrahedron* **1997**, *53*, 8927−8940. (c) Hanaki, N.; Link, J. T.; MacMillan, D. W. C.; Overman, L. E.; Trankle, W. G.; Wurster, J. A. *Org. Lett.* **2000**, *2*, 223−226. (d) Overman, L. E.; Pennington, L. D. *Org. Lett.* **2000**, *2*, 2683−2686. (e) Molina-Ponce, A.; Overman, L. E. *J. Am. Chem. Soc.* **2000**, *122*, 8672−8676.

(5) Cohen, F.; MacMillan, D. W. C.; Overman, L. E.; Romero, A. *Org. Lett.* **2001**, *3*, 1225−1228; accompanying paper in this issue.

(6) For other Prins−pinacol reactions that involve hydride migrations, see: (a) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092−1093. (b) Overman, L. E.; Pennington, L. D. *Can. J. Chem.* **2000**, *78*, 732−738.

(7) Several catalytic asymmetric reduction procedures would be possible; at the time this work was initiated, oxazaborolidine-catalyzed borane reduction was particularly attractive.[8]

(8) (a) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Chem. Commun.* **1983**, 469−470. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553. (c) For a review, see: Itsuno, S. *Org. React.* **1998**, *52*, 395−576.

(9) Kamatani, A.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 8743−8744.

(10) For a review of the Suzuki reaction, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(11) For recent reviews of *N*-acyliminium ion chemistry, see: (a) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, Chapter 4.5. (b) de Koning, H.; Speckamp, W. N. In *Methods of Organic Chemistry (Houben-Weyl)*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21b, Chapter D.1.4.5.

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could provide a concise enantioselective entry to *trans*-hydroisoquinolones having axial substituents at C1, is illustrated in Figure 1. The heart of this plan is to set the

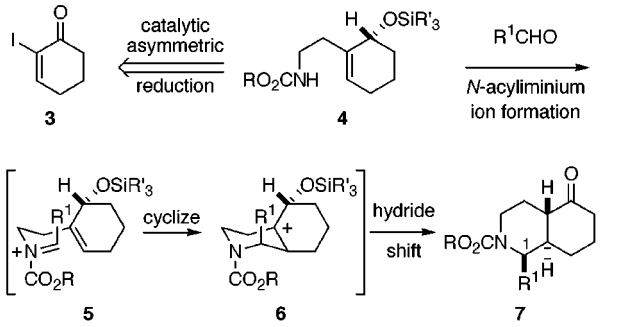
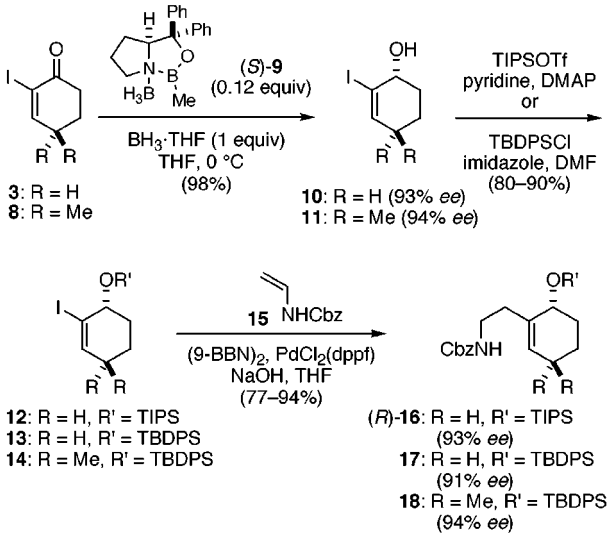


Figure 1. Prins−pinacol synthesis of enantioenriched *trans*-octahydroisoquinolones.

absolute configuration by catalytic asymmetric reduction of 2-iodocyclohexenone (**3**).[7,8] The asymmetry of the allylic carbon−oxygen σ-bond would then be employed to regulate carbon−carbon bond formation in a Prins−pinacol reaction. Specifically, silyl protection of the enantioenriched allylic alcohol, followed by Suzuki β-aminoethylation,[9,10] would provide unsaturated carbamates **4**. Under appropriate conditions, condensation of **4** with an aldehyde should generate *N*-acyliminium intermediates that we expected would cyclize as depicted in **5** to deliver **6**.[11] Hydride migration and loss of the silyl protecting group from **6** would lead to *trans*-5-oxooctahydroisoquinoline **7** having an axial substituent at C1. Stereoselection in the pivotal cyclization step was anticipated to arise from two factors: (a) preferential cyclization of the (*E*)-*N*-acyliminium ion stereoisomer so as to avoid developing A[1,3] interactions in the 1-substituted-2-acylhydroisoquinoline product[12] and (b) preferential approach of the iminium ion electrophile from the cyclohexene face opposite the bulky siloxy group.[13]

To test this sequence, homoallylic carbamates were assembled from 2-iodocyclohexenones **3** and **8** as summarized in Scheme 1 for the *R* cyclization precursors. Enantioselective reduction of **3** or **8** with the oxazaborolidine catalyst (*S*)-**9** introduced by Corey and co-workers provided **10**[14a] and **11**[14b] in nearly quantitative yield and 93−94% enantiomeric purity. Because preliminary survey experiments had shown that the pivotal cyclization step took place in higher yield when a robust silyl protecting group was used, these products were protected with triisopropylsilyl (TIPS)

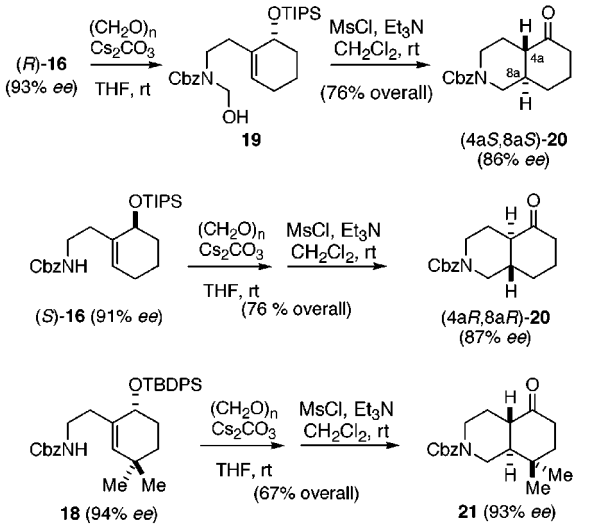
Scheme 1. Enantioselective Synthesis of Homoallylic Carbamate Cyclization Precursors



or *tert*-butyldiphenylsilyl (TBDPS) groups to yield **12**−**14**. Cross-coupling of these products with the 9-borabicyclononane adduct of benzyl vinylcarbamate (**15**) provided homoallylic carbamates (*R*)-**16**, **17**, and **18** in high yields.[9] HPLC analysis of the alcohols derived from **16**−**18** confirmed that there was no loss of enantiomeric purity during the Suzuki coupling step.[14b] Enantioselective reduction of **3** using the *R* enantiomer of **9** delivered (*S*)-**16**, 91% ee, in comparable yield.

We initially examined formation of unsubstituted hydroisoquinolones from acid-promoted reaction of homoallylic carbamate (*R*)-**16** with paraformaldehyde (Scheme 2). When carried out in toluene at room temperature in the presence of 1.6 equiv of trifluoroacetic acid and Na_2SO_4, the reaction of paraformaldehyde and (*R*)-**16** provided a single 5-oxooc-

Scheme 2. Enantioselective Synthesis of *trans*-5-Oxooctahydroisoquinolines



(12) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.

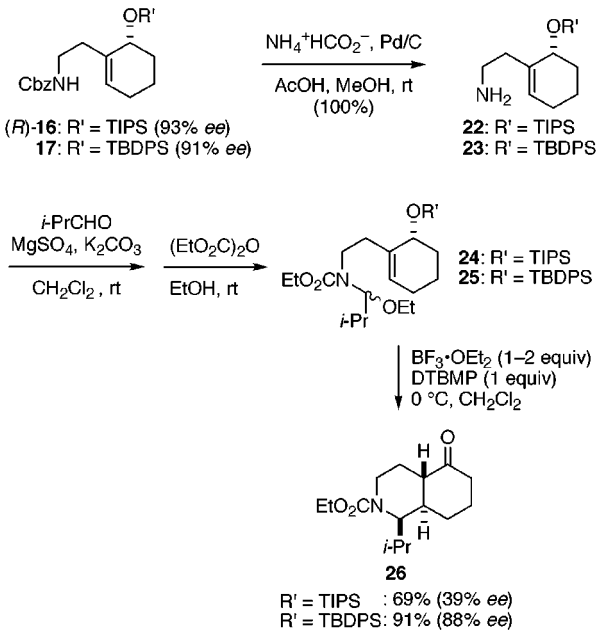
(13) Cyclization from the face of the siloxy substituent, *anti* to the allylic C−H σ-bond, should be favored for electronic reasons.[5] However, destabilizing nonbonded interactions between the developing axial C1 substituent and the bulky siloxy would be severe in such a cyclization transition state.

(14) Enantiomeric purity was determined (a) by capillary GLC analysis using a J&W CyclodexB column or (b) by HPLC analysis using a Daicel OD-H column. In all cases, the analysis was calibrated with a sample of the racemate.

tahydroisoquinoline product **20** in 66% yield. That **20** was the expected *trans* stereoisomer was signaled by the diagonostic triplet of doublets (J = 11.1, 3.2 Hz) observed for H-4a at δ 2.26 ppm in the ^{1}H NMR spectrum.[15] However, the enantiomeric purity of **20** was a disappointing 66% ee.[16] That the 4a*S*,8a*S* enantiomer of **20** had been formed was established unambiguously by Mosher analysis.[17,18] On the assumption that the loss of enantiopurity arose from competing acid-promoted conversion of the starting cyclohexenyl ether to an achiral allyl cation, we turned to the nonacidic conditions first reported by Chamberlin and Chung for generating *N*-acyliminium cations.[19] Reaction of (*R*)-**16** with excess paraformaldehyde and 2 equiv of Cs_2CO_3 in dry THF gave α-hydroxycarbamate **19**, which when activated at room temperature with methanesulfonyl chloride and Et_3N in CH_2Cl_2 delivered (4a*S*,8a*S*)-**20** in 76% overall yield and 86% ee. Under identical conditions, the enantiomeric ketone (4a*R*,8a*R*)-**20** was formed from (*S*)-**16** with a similar high degree of stereospecificity, whereas cyclization of dimethyl derivative **18** took place with complete stereospecificity to give **21** in 67% overall yield.[17]

To expand this sequence to the formation of 1-substituted 5-oxooctahydroisoquinolines, we turned to cyclizations with other aldehydes. Homoallylic primary amines **22** and **23** were first prepared by selective removal of the benzyloxycarbonyl protecting group from (*R*)-**16** and **17** under transfer hydrogenolysis conditions (Scheme 3). Condensation of these

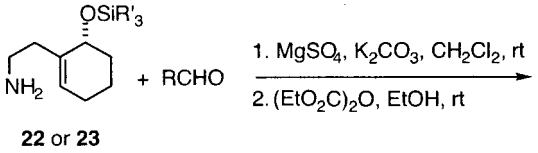
Scheme 3. Enantioselective Synthesis of 1-Substituted *trans*-5-Oxooctahydroisoquinoline **26**

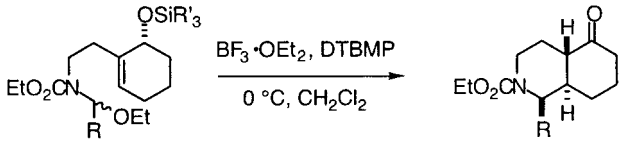


amines with isobutryaldehyde in CH_2Cl_2 at room temperature using a 1:1 mixture of $MgSO_4$ and K_2CO_3 as a water scavenger delivered the corresponding imines. After removal of CH_2Cl_2 and addition of dry ethanol, reaction of these intermediates with 1.2 equiv of diethyl pyrocarbonate[20] at room temperature provided carbamates **24** (80% yield) and **25** (85% yield) as ~1:1 mixtures of ethoxy epimers. After examining several common Lewis acids, it was found that **24** and **25** cyclized in highest yield when exposed to 1 equiv of BF_3·OEt_2 in CH_2Cl_2 at 0 °C in the presence of the protic acid scavenger 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP). Under these conditions, both silyl ether intermediates gave rise to a single 1-substituted 5-oxooctahydroisoquinoline product **26**. Both yield and enantioselection in this conversion were improved by use of the more acid stable *tert*-butyldiphenylsilyl protecting group, with **25** providing **26** in 91% yield and 88% *ee*.[14] The relative configuration of **26** followed unambiguously from ^{1}H NMR studies,[21] whereas the 1*R*,4a*S*,8a*S* absolute configuration of **26** was determined on a derivative by the advanced Mosher method.[17]

Results of our initial survey of this new enantioselective synthesis of 1-substituted *trans*-hydroisoquinolones are summarized in Table 1. Aliphatic, aromatic, or α,β-unsaturated

Table 1. Enantioselective Synthesis of 1-Substituted *trans*-5-Oxooctahydroisoquinolines





			carbamate **27**		5-oxohydroisoquinoline[a]		
entry	amine	R	SiR_3	yield, %	compd	yield, %	ee, %
1	**22**	*n*-Pr	TIPS	72	**28**	87	87
2	*ent*-**23**	*n*-Pr	TBDPS	99	*ent*-**28**	75	87
3	**22**	*i*-Pr	TIPS	80	**26**	69	39
4	**23**	*i*-Pr	TBDPS	85	**26**	91	88
5	**23**	Ph	TBDPS	99	**29**	63	85[b]
6	**23**	*p*-OMeC_6H_4	TBDPS	59	**30**	72	88
7	**23**	(*E*)-MeCH=CH	TBDPS	61	**31**	53	90
8	**23**	*t*-Bu	TBDPS	44	**32**	34	88
9	**23**	CH_2SPh	TBDPS	56[c]	**33**	51	90
10	**23**	CO_2Et	TBDPS	80	**34**	64	0−20
11	**23**	*p*-OMe-*m*-OBn-$C_6H_3CH_2$	TBDPS	60	**35**	0	

[a] Absolute configuration was determined with the *N*-methyl equatorial alcohol derivative by the method of Mosher and Kakisawa (ref 18). [b] Cyclization was conducted at −78 °C; ee was 76% when the cyclization was carried out at 0 °C. [c] Contained unidentified impurities

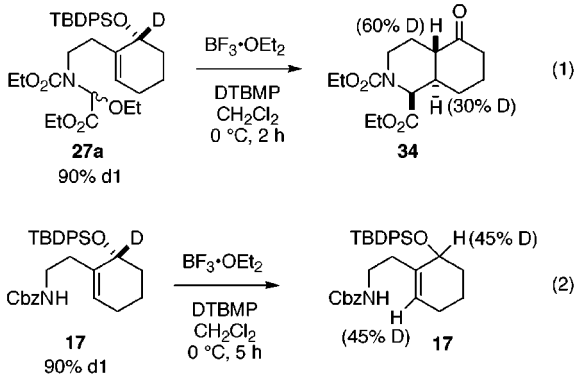
aldehydes can be used to provide, in high enantiopurity (85−90% ee), *trans*-5-oxooctahydroisoquinolines having axial

(15) To collapse carbamate rotamers, this analysis was carried out in DMSO-d_6 at elevated temperature.

(16) Enantiomeric purity was determined by chromatographic analysis[14a] of the *N*-methyl derivative obtained by reduction of the Prins−pinacol product with $LiAlH_4$, followed by Swern oxidation of the resulting amino alcohol product.

alkyl, aryl, or alkenyl substituents at C1. When R was primary alkyl, secondary alkyl, or aryl (entries 1−6), overall yields from amine **23** (or *ent*-**23**) ranged from 43% to 74%. Yields for both steps were somewhat lower in reactions with *trans*-crotonaldehyde, pivaldehyde, or 2-(phenylthio)acetaldehyde (entries 7−9). In favorable cases, the TIPS- and TBDPS-protected allylic alcohols performed comparably (entries 1 and 2); however, the TBDPS derivative is generally preferred. In one case (entry 5) it was demonstrated that chirality transfer was slightly higher when the cyclization step was carried out at −78 °C. It is likely that cyclization at lower temperature will be preferred in many cases.

Several limitations of the sequence summarized in Table 1 were also revealed. For example, ethyl glyoxylate (entry 10) provided a single *trans*-5-oxooctahydroisoquinoline **34** in useful yield. However, this product was nearly racemic (0−20% ee). To pursue the origin of racemization in this case, a 1:1 mixture of α-ethoxy carbamate **25** and the analogous intermediate derived from ethyl glyoxylate was cyclized under standard conditions for 30 s at 0 °C to provide **26** in 64% yield; **34** was not detected. That racemization in the glyoxylate case involves to a significant extent formation of an achiral cyclohexenyl carbocation is consistent with the deuterium scrambling observed in the reactions reported in eqs 1 and 2. The slow conversion of ethyl glyoxylate-derived



α-ethoxy carbamate **27a** to hydroisoquinolone **34**, which must reflect the relative instability of the highly electron-deficient *N*-acyliminium cation in this case, apparently allows "background" racemization of the starting material to occur at a competitive rate. Although α-alkoxycarbamates formed from **23** and acetone or 2-(3-benzyloxy-4-methoxyphenyl)-acetaldehyde (Table 1, entry 11) could be generated in useful yield, neither intermediate was converted to the corresponding *trans*-5-oxooctahydroisoquinoline when exposed to BF_3•OEt_2. Unfortunately, this latter failure precludes direct use of this chemistry for enantioselective synthesis of opium alkaloids.

In summary, this communication discloses a conceptually new strategy for asymmetric construction of *trans*-hydroisoquinolines. The synthesis exploits the wide availability of enantioenriched 2-substituted cyclohexenols by catalytic asymmetric reduction of cyclohexenone precursors. The central step in this sequence translates the asymmetry of the allylic C−O σ bond of the cyclohexenol precursors by a Prins−pinacol sequence to three adjacent stereocenters of the hydroisoquinoline products. Using this chemistry, a variety of *trans*-5-oxooctahydroisoquinolines having axial alkyl, aryl, or alkenyl substituents at C1 can be prepared in high enantiopurity.

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Supporting Information Available: Representative experimental procedures and characterization data; details of the determination of absolute configuration of **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Absolute configuration was determined by the advanced Mosher method using the *N*-methyl equatorial alcohol formed by sequential reduction of the Prins−pinacol product with $NaBH_4$ (EtOH, −30 °C) and $LiAlH_4$; details are provided in Supporting Information.

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(19) Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653−3656.

(20) Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N. *Tetrahedron Lett.* **1985**, *26*, 3155−3158.

(21) The ^{1}H NMR spectrum at 100 °C (DMSO-d_6) exhibited a diagnostic triplet of doublets (J = 11.8, 3.8 Hz) for H-4a at δ 2.47 ppm, and the NOESY spectrum showed a strong correlation between H-1 and H-8a. Similar experiments established the structure of the other 1-substituted 5-oxooctahydroisoquinolines reported in Table 1.