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Synthesis of 2,4-Disubstituted Piperidines via Radical Cyclization: Unexpected Enhancement in Diastereoselectivity with Tris(trimethylsilyl)silane

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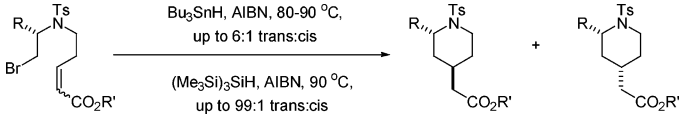

A novel approach to 2,4-disubstituted piperidines is reported, involving the radical cyclization of 7-substituted-6-aza-8-bromooct-2-enoates. Cyclization with tributyltin hydride affords the trans piperidines with trans/cis diastereomeric ratios ranging typically from 3:1 to 6:1. Cyclization with tris(trimethylsilyl)-silane affords the same products with diastereomeric ratios of up to 99:1 in certain cases. The enhancement in diastereoselectivity results from the selective rearrangement of the minor stereoisomer through a cascade process involving radical cyclization to the piperidine radical, 1,5-radical translocation, and attack of the translocated radical onto the sulfonamide with extrusion of SO_2 in a Smiles-type rearrangement. Slower trapping of the piperidine radical by tris(trimethylsilyl)silane compared to tributyltin hydride accounts for the occurrence of the rearrangement cascade in the former case.

Introduction

The piperidine ring is an important structural motif present in natural products[1] and synthetic pharmaceuticals,[2] and this has led to the development of many synthetic approaches to these heterocycles.[3] Nevertheless, the variety of functionality and substitution patterns found in piperidine targets continues to drive the search for new methodologies.[4]

Free-radical cyclization processes occupy an important role in the formation of heterocycles[5] and have found many applications in natural product synthesis.[6] Radical cyclization is well documented in the synthesis of pyrrolidines,[7] but there are fewer reports of radical cyclizations leading to piperidines.[8,9] We now report in full the results of our investigation into the synthesis of 2,4-disubstituted piperidines by radical ring closure.[10]

(1) (a) Findlay, J. A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: London, 1985; Vol. 26, pp 89−183. (b) Pinder, A. R. *Nat. Prod. Rep.* **1986**, *3*, 171−180. (c) Pinder, A. R. *Nat. Prod. Rep.* **1987**, *4*, 527−537. (d) Pinder, A. R. *Nat. Prod. Rep.* **1989**, *6*, 67−78. (e) Pinder, A. R. *Nat. Prod. Rep.* **1990**, *7*, 447−455. (f) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 491−504. (g) Plunkett, A. O. *Nat. Prod. Rep.* **1994**, *11*, 581−590. (h) O'Hagan, D. *Nat. Prod. Rep.* **1997**, *14*, 637−651. (i) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435−446.

(2) Between July 1988 and December 1998 over 12 000 piperidines were mentioned in clinical and preclinical studies. See: Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679−3681.

(3) For reviews see: (a) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781−1813. (b) Weintraub, P. M.; Sabol, J. S.; Kane, J. A.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953−2989. (c) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701−1729. (d) Felpin, F. X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693−3712.

(4) (a) Souers, A. J.; Ellman, J. A. *J. Org. Chem.* **2000**, *65*, 1222−1224. (b) Brooks, C. A.; Comins, D. L. *Tetrahedron Lett.* **2000**, *41*, 3551−3553. (c) Johnson, T. A.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 1004−1005. (d) Shu, C.; Alcudia, A.; Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2001**, *123*, 12477−12487. (e) Harris, J. M.; Padwa, A. *J. Org. Chem.* **2003**, *68*, 4371−4381. (f) Legault, C.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 6360−6361. (g) Angoli, M.; Barilli, A.; Lesma, G.; Passarella, D.; Riva, S.; Silvani, A.; Danieli, B. *J. Org. Chem.* **2003**, *68*, 9525−9527. (h) Amat, M.; Escolano, C.; Lozano, O.; Llor, N.; Bosch, J. *Org. Lett.* **2003**, *5*, 3139−3142. (i) Hedley, S. J.; Moran, W. J.; Price, D. A.; Harrity, J. P. A. *J. Org. Chem.* **2003**, *68*, 4286−4292. (j) Poupon, E.; Francois, D.; Kunesch, N.; Husson, H. P. *J. Org. Chem.* **2004**, *69*, 3836−3841. (k) Toure, B. B.; Hall, D. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 2001−2004. (l) Kuethe, J. T.; Comins, D. L. *J. Org. Chem.* **2004**, *69*, 2863−2866. (m) Davis, F. A.; Zhang, J.; Li, Y.; Xu, H.; DeBrosse, C. *J. Org. Chem.* **2005**, *70*, 5413−5419. (n) Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 8966−8967. (o) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234−12235.

(5) For reviews see: (a) Majumdar, K. C.; Basu, P. K.; Mukhopadhyay, P. P. *Tetrahedron* **2005**, *61*, 10603−10642. (b) Bowman, W. R.; Bridge, C. F.; Brookes, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1−14. (c) Bowman, W. R.; Fletcher, A. J.; Potts, G. B. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2747−2762. (d) Srikanth, G. S. C.; Castle, S. L. *Tetrahedron* **2005**, *61*, 10377−10441.

(6) For reviews see: (a) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237−1286. (b) Bar, G.; Parsons, A. F. *Chem. Soc. Rev.* **2003**, *32*, 251−263.

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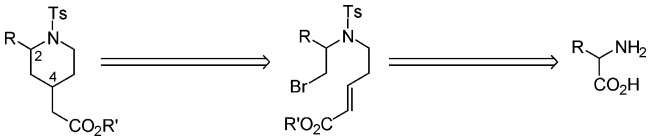


FIGURE 1. Retrosynthetic analysis.

We envisaged ring closure to the piperidine occurring by formation of the C3−C4 bond (Figure 1) with the substituent adjacent to nitrogen exerting stereocontrol over the forming stereogenic center at C4. The C2 substituent of the piperidine can be derived from the wide variety of commercially available natural and unnatural amino acids. Since the relatively slow 6-exo-trig cyclization suffers from competing direct reduction of the acyclic radical and poor exo/endo selectivity, the acceptor double bond was activated as an α,*β*-unsaturated ester.[11]

Results and Discussion

Before commencing on the synthesis of more complex cyclization precursors, we first prepared a model system to investigate the feasibility of using the 6-exo radical cyclization to generate the C3−C4 bond of the piperidine ring (Scheme 1).

Conjugate addition of the diprotected amino ethanol **1**[12] to methyl acrylate, followed by reduction with diisobutylaluminum hydride, afforded aldehyde **2**. Wittig reaction gave the *E*-configured α,*β*-unsaturated ester in 78% yield, along with 6% of the *Z*-isomer, and one-pot desilylation−bromination[13] by dibromotriphenylphosphorane gave the desired *E*-bromide **3** in 84% yield.

Slow addition of tributyltin hydride and AIBN (13 h via syringe pump) to a solution of bromide **3** in refluxing benzene (final concentration 0.01 M) afforded the expected 4-substituted piperidine **4** in a near quantitative yield (90% isolated after chromatography). Careful analysis of the reaction mixture using NMR and GC−MS showed no sign of the acyclic reduction product **5** or the 7-endo cyclization product **6** (Scheme 2).

Encouraged by the successful cyclization of the model system, we set out to use similar methodology to construct analogous cyclization precursors from a variety of 2-substituted amino alcohols **7a**−**g** (Scheme 3). N-Tosylation and O-silylation of the amino alcohols to yield **8a**−**g** was followed by conjugate addition into methyl acrylate as before. Unfortunately, an inseparable mixture of starting material and the desired product was obtained in all cases. Attempts to optimize the reaction by varying the temperature, solvent, and the acrylate ester (Me, Et, ^{t}Bu) proved fruitless, and it appeared that the conjugate addition was reversible with an equilibrium constant that did not favor the product.

Instead, we switched to a route involving alkylation of **8a**−**g** with the dimethyl acetal of 3-iodopropanal, using Cs_2CO_3 as base, to afford the acetals **9a**−**g** (Scheme 4).

Acid-catalyzed acetal hydrolysis with concomitant TBDMS removal gave the lactols **10a**−**g** as a mixture of epimers at the anomeric position. These were directly subjected to a Wittig reaction with methyl- or *tert*-butyl(triphenylphosphoranylidene)-acetate to give the corresponding α,*β*-unsaturated esters **11a**−**n** in good yield but with poor *E*/*Z* selectivity. Performing the reactions at 90 °C in toluene with the inclusion of 20 mol % benzoic acid under the modified conditions of Harcken and Martin[14] led to a significant improvement in the *E*/*Z* ratio.

Bromination of the methyl esters was straightforwardly carried out using carbon tetrabromide and triphenylphosphine to afford the bromides **12** in excellent yield. In the case of the *tert*-butyl esters, bromination under these conditions gave a mixture of the desired bromo ester and the bromo acid resulting from the cleavage of the *tert*-butyl ester. Instead, the alcohols were treated with methanesulfonyl chloride then lithium bromide to give the *tert*-butyl bromides in excellent yield.

The *E* and *Z* esters proved separable at this stage, and so residual *Z* ester was removed by chromatography. We wanted to study the cyclization of the *E* and *Z* esters separately, since, in earlier work on 6-exo-trig cyclizations by Hanessian et al.,[11a] the geometry of the acceptor double bond was found to be an important feature in controlling the stereoselectivity of the cyclization. The *Z* ester experienced greater 1,3-diaxial interactions when it adopted a pseudoaxial position, resulting in preferential cyclization to the trans product (Figure 2).

To probe the effect of olefin geometry on the stereoselectivity of the cyclization, the *Z* esters were prepared using the Still−Gennari modified Horner−Wadsworth−Emmons reaction.[15] Exposure of lactol **10a** to methyl bis(trifluoroethyl)phosphono-acetate in the presence of K_2CO_3 and 18-crown-6 in toluene led to a quantitative recovery of *N*-tosyl alaninol, presumably as a result of base-induced elimination of acrolein from aldehyde **13** (Scheme 5).

Happily, preforming the phosphonate anion by treatment with KHMDS and 18-crown-6 in THF before adding the lactol resulted in smooth olefination to give **14a** in good yield and with a *Z*/*E* ratio of 12:1. Both the methyl and *tert*-butyl

(7) For examples see: (a) Tsuritani, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2003**, *68*, 3246−3250. (b) Besev, M.; Engman, L. *Org. Lett.* **2002**, *4*, 3023−3025. (c) Bustos, F.; Gorgojo, J. M.; Suero, R.; Aurrecoechea, J. M. *Tetrahedron* **2002**, *58*, 6837−6842. (d) Jahn, U.; Muller, M.; Aussieker, S. *J. Am. Chem. Soc.* **2000**, *122*, 5212−5213.

(8) (a) Katritzky, A. R.; Luo, Z.; Fang, Y.; Feng, D.; Ghiviriga, I. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1375−1380. (b) Koreeda, M.; Wang, Y.; Zhang, L. *Org. Lett.* **2002**, *4*, 3329−3332. (c) Yoo, S. E.; Yi, K. Y.; Lee, S. H.; Jeong, N. *Synlett* **1990**, 575−576. (d) Parsons, A. F.; Pettifer, R. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 651−660. (e) Ihara, M.; Setsu, F.; Shoda, M.; Taniguchi, N.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 5317−5323. (f) Lee, E.; Kang, T. S.; Joo, B. J.; Tae, J. S.; Li, K. S.; Chung, C. K. *Tetrahedron Lett.* **1995**, *36*, 417−420. (g) Lee, E.; Jeong, E. J.; Min, S. J.; Hong, S.; Lim, J.; Kim, S. K.; Kim, H. J.; Choi, B. G.; Koo, K. C. *Org. Lett.* **2000**, *2*, 2169−2171. (h) Prevost, N.; Shipman, M. *Org. Lett.* **2001**, *3*, 2383−2385.

(9) For examples of formation of piperidines within polycyclic natural products by radical ring-closure see: (a) Takayama, H.; Watanabe, F.; Kitajima, M.; Aimi, N. *Tetrahedron Lett.* **1997**, *38*, 5307−5310. (b) Kaoudi, T.; Miranda, L. D.; Zard, S. Z. *Org. Lett.* **2001**, *3*, 3125−3127. (c) Quirante, J.; Escolano, C.; Bosch, J.; Bonjoch, J. *J. Chem. Soc., Chem. Commun.* **1995**, 2141−2142. (d) Ishibashi, H.; Inomata, M.; Ohba, M.; Ikeda, M. *Tetrahedron Lett.* **1999**, *40*, 1149−1152.

(10) For a preliminary account of this work see: Gandon, L. A.; Russell, A. G.; Snaith, J. S. *Org. Biomol. Chem.* **2004**, *2*, 2270−2271.

(11) For earlier examples see: (a) Hanessian, S.; Dhanoa, D. S.; Beaulieu, P. L. *Can. J. Chem.* **1987**, *65*, 1859−1866. (b) Anissa Yeung, B.-W.; Contelles, J. L. M.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1989**, 1160−1162. (c) Marco-Contelles, J.; Pozuelo, C.; Jimeno, M. L.; Martinez, L.; Martinez-Grau, A. *J. Org. Chem.* **1992**, *57*, 2625−2631. (d) Marco-Contelles, J.; Sanchez, B. *J. Org. Chem.* **1993**, *58*, 4293−4297. (e) Pedrosa, R.; Andres, C.; Duque-Soladana, J. P.; Roson, C. D. *Tetrahedron: Asymmetry* **2000**, *11*, 2809−2821. (f) Pedrosa, R.; Andres, C.; Iglesias, J. M.; Obeso, M. A. *Tetrahedron* **2001**, *57*, 4005−4014. (g) Joshi, S. N.; Puranik, V. G.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron: Asymmetry* **2001**, *12*, 3073−3076. (h) Zhang, X.; Guzi, T.; Pettus, L.; Schultz, A. G. *Tetrahedron Lett.* **2002**, *43*, 7605−7608.

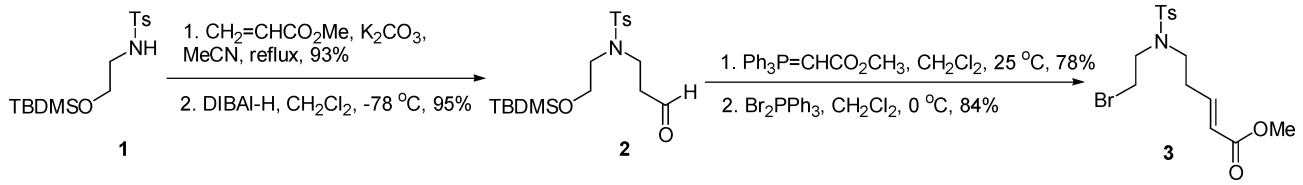
(12) Sato, Y.; Saito, N.; Mori, M. *Tetrahedron* **1998**, *54*, 1153−1168.

(13) Aizpurua, J. M.; Cossio, F. P.; Palomo, C. *J. Org. Chem.* **1986**, *51*, 4941−4943.

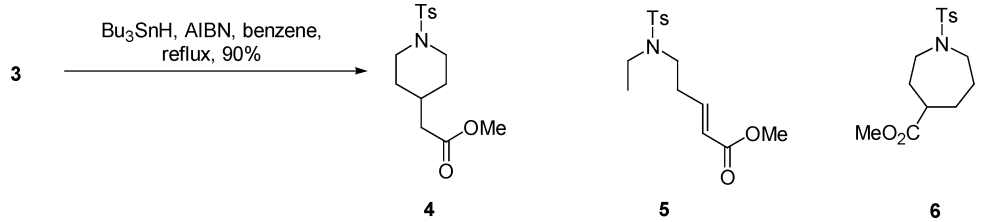
(14) Harcken, C.; Martin, S. F. *Org. Lett.* **2001**, *3*, 3591−3593.

(15) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405−4408.

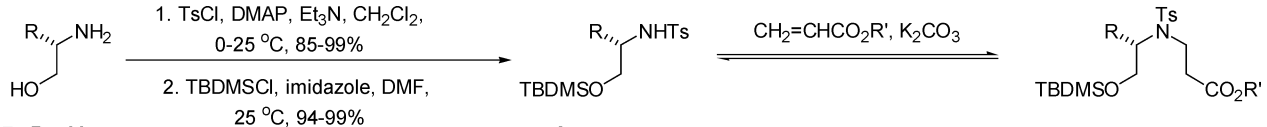
SCHEME 1. Synthesis of the Model Cyclization Precursor



SCHEME 2. Cyclization of Bromide 3

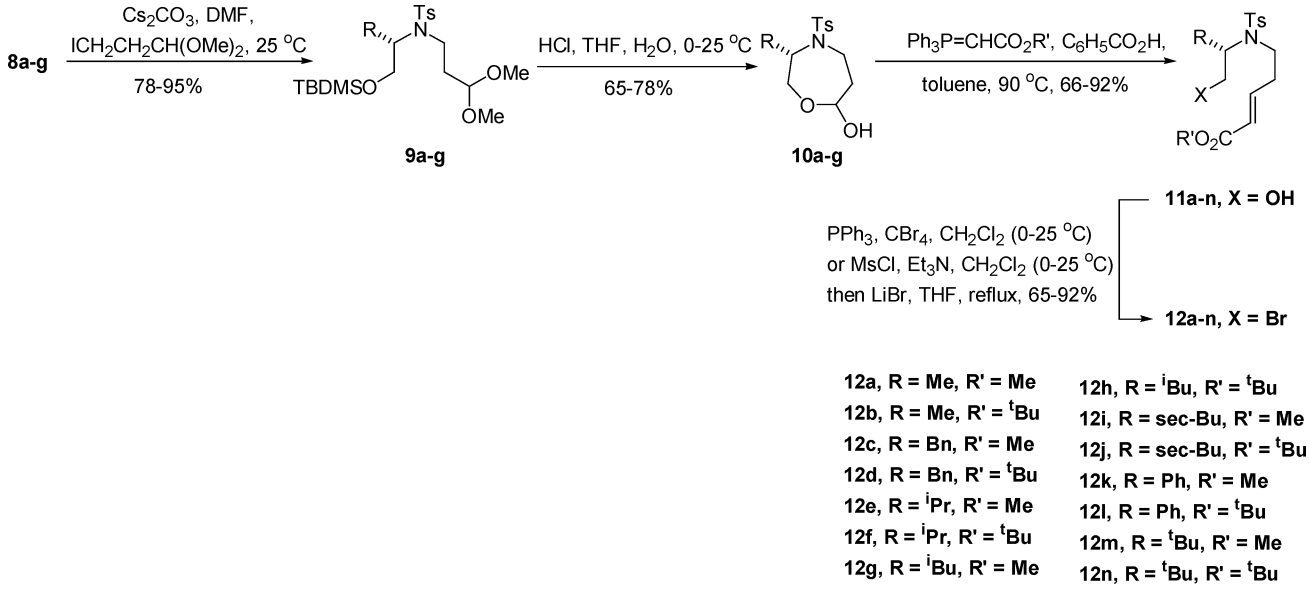


SCHEME 3. Attempted Conjugate Additions of Protected Amino Alcohols



7a R = Me
7b R = Bn
7c R = ^{i}Pr
7d R = ^{i}Bu
7e R = sec-Bu
7f R = Ph
7g R = ^{t}Bu

SCHEME 4. Preparation of Bromide Cyclization Precursors



12a, R = Me, R' = Me
12b, R = Me, R' = ^{t}Bu
12c, R = Bn, R' = Me
12d, R = Bn, R' = ^{t}Bu
12e, R = ^{i}Pr, R' = Me
12f, R = ^{i}Pr, R' = ^{t}Bu
12g, R = ^{i}Bu, R' = Me
12h, R = ^{i}Bu, R' = ^{t}Bu
12i, R = sec-Bu, R' = Me
12j, R = sec-Bu, R' = ^{t}Bu
12k, R = Ph, R' = Me
12l, R = Ph, R' = ^{t}Bu
12m, R = ^{t}Bu, R' = Me
12n, R = ^{t}Bu, R' = ^{t}Bu

Z-configured esters were prepared from a representative range of lactols and brominated as before to afford **15a**−**f** (Scheme 6). The *Z* esters were obtained free from any (*E*)-isomer after chromatography.

With a range of suitable cyclization precursors in hand, radical cyclizations were performed in refluxing benzene, or toluene heated at 90 °C, with slow addition of tributyltin hydride and AIBN, affording excellent yields of the diastereomeric piperidines **16** and **17**. With one exception (entry 10), the diastereoselectivities ranged from 3:1 to 6:1, increasing with the steric bulk of the substituent adjacent to nitrogen (Table 1). Surprisingly, and in contrast to the findings of Hanessian et al., results for the *E* and *Z* esters were essentially identical.

Identification of the major and minor diastereomers was not straightforward; separation of the diastereomers could only be achieved by HPLC, and the ^{1}H NMR data were too complex to allow us to extract coupling constants. The major diastereomer **16** was assumed to have an axial 2-substituent and an equatorial 4-substituent, resulting from cyclization of the radical via transition state **18** (Figure 3); in the chairlike transition state

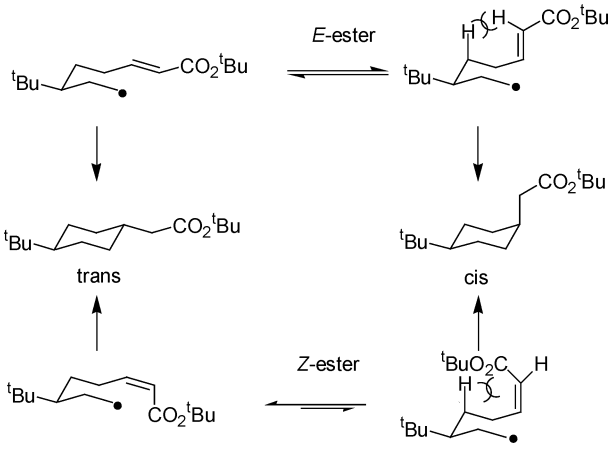


FIGURE 2. Improved selectivity for *Z* esters in Hanessian et al.'s system.

the 2-substituent adopts the energetically more favorable pseudoaxial disposition to minimize pseudo $A^{1,3}$ strain with the sulfonamide,[16] while the acceptor double bond is in the pseudoequatorial position to minimize 1,3-diaxial interactions.

The conformation of the transition state leading to the minor diastereomer **17** was less clear-cut. In earlier work on 6-exo-trig cyclizations by Hanessian et al., the major and minor products resulted from cyclization onto pseudoequatorial and pseudoaxial acceptor double bonds, respectively; *Z*-configured esters gave reduced amounts of the minor product due to an increase in 1,3-diaxial interactions. In our case, the essentially identical results obtained for the *E* and *Z* esters suggested that the minor product did not result from cyclization onto a pseudoaxial double bond but was more likely to have both substituents equatorial.

The identities of the diastereomers were tentatively confirmed by NOE measurements, but crystallographic support was hampered by the low crystallinity of the piperidines and the fact that the diastereomers were often inseparable by flash chromatography. Minor product **17k**, purified by HPLC, did yield X-ray quality crystals, and single-crystal X-ray analysis confirmed the structure.

Piperidine **16d**, also obtained by HPLC purification, was not crystalline, but the brucine salt, prepared by acid-catalyzed removal of the *tert*-butyl ester followed by treatment with brucine dihydrate, yielded X-ray quality crystals from water. Single-crystal X-ray analysis confirmed the structure.

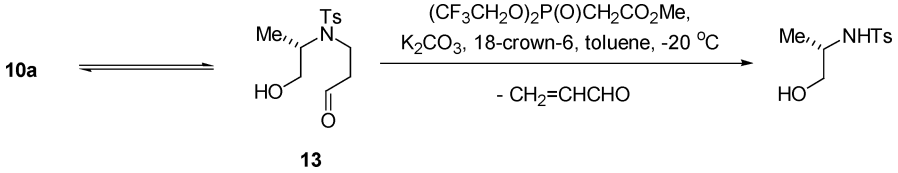
Although the tendency for the 2-substituent of an *N*-tosylpiperidine to lie in an axial position is usually very marked,[17] the fact that the axial/equatorial ratios are more modest in this case is perhaps less surprising given the rather early transition states for radical cyclization which distort the transition state geometry from the idealized chair.[18] This distortion, with the forming bond being rather elongated, means that factors such as the pseudo $A^{1,3}$ strain which are important in the product are of less importance in the transition state, and other conformers are energetically accessible.

The toxicity of TBTH led us to explore the use of tris-(trimethylsilyl)silane (TTMSS) in our cyclizations. As well as lower toxicity, TTMSS also exhibits a lower rate constant than TBTH for hydrogen atom donation as a result of the stronger Si−H bond (79 kcal mol^{-1}, compared with 74 kcal mol^{-1} for the Sn−H bond of TBTH),[19] a factor which can be beneficial in radical cyclization reactions since products of direct reduction of the uncyclized radical are minimized. Cyclization was carried out by slow addition of solutions of TTMSS and AIBN to the bromide in toluene at 90 °C (Table 2).

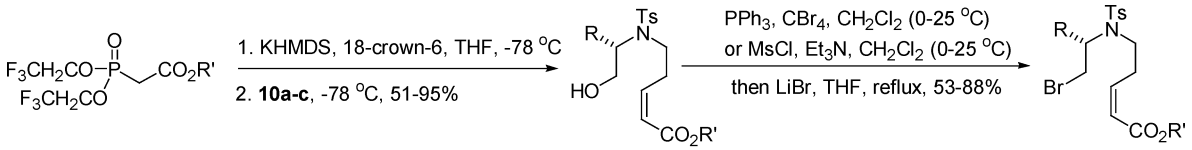
Cyclization yields were a little lower than those obtained with TBTH, but the most striking feature was the improvement in stereoselectivity in a number of cases, with, for example, the product ratio for the cyclization of **12f** increasing from 6:1 (TBTH) to 99:1 (TTMSS). The improvement was not observed in all cases, and there was no correlation between the size of the 2-substituent and the increased stereoselectivity with TTMSS. There did, however, appear to be some correlation between the increased selectivity and the nature of the 2-substituent, with secondary and benzylic substituents affording the highest **16**:**17** ratios.

An enhancement in stereoselectivity on switching from TBTH to TTMSS is remarkable and apparently without precedent. Others have reported increased stereoselectivity in the reduction of halides by TTMSS, a result attributed to the greater steric

SCHEME 5. Attempted Still−Gennari Olefination



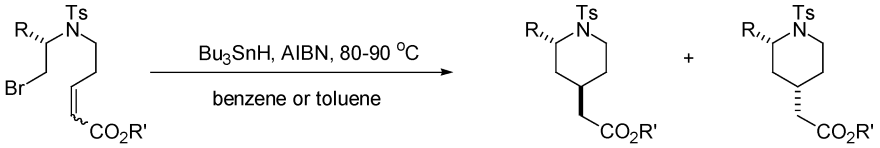
SCHEME 6. Preparation of *Z*-Cyclization Precursors 15a−f



14a, R = Me, R' = Me
14b, R = Me, R' = ^{t}Bu
14c, R = Bn, R' = Me
14d, R = Bn, R' = ^{t}Bu
14e, R = ^{i}Pr, R' = Me
14f, R = ^{i}Pr, R' = ^{t}Bu

15a-f

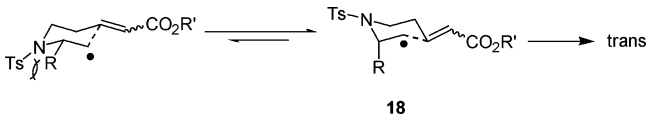
TABLE 1. Cyclizations with TBTH[a]



12a-k or **15a-f** **16a-k** **17a-k**

entry	bromide	R	R′	*E* or *Z*	**16**:**17**[b]	yield (%)[c]
1	**12a**	Me	Me	*E*	72:28	98
2	**12b**	Me	^{t}Bu	*E*	74:26	99
3	**12c**	Bn	Me	*E*	80:20	89
4	**12d**	Bn	^{t}Bu	*E*	83:17	85
5	**12e**	^{i}Pr	Me	*E*	86:14	95
6	**12f**	^{i}Pr	^{t}Bu	*E*	86:14	82
7	**12g**	^{i}Bu	Me	*E*	85:15	85
8	**12h**	^{i}Bu	^{t}Bu	*E*	77:23	92
9	**12i**	*sec*-Bu	Me	*E*	85:15	99
10	**12j**	*sec*-Bu	^{t}Bu	*E*	97:3	66
11	**12k**	Ph	Me	*E*	86:14	66
12	**12l**	Ph	^{t}Bu	*E*	77:23	93
13	**12m**	^{t}Bu	Me	*E*	85:15	81
14	**12n**	^{t}Bu	^{t}Bu	*E*	86:14	86
15	**15a**	Me	Me	*Z*	78:22	85
16	**15b**	Me	^{t}Bu	*Z*	75:25	98
17	**15c**	Bn	Me	*Z*	75:25	88
18	**15d**	Bn	^{t}Bu	*Z*	75:25	80
19	**15e**	^{i}Pr	Me	*Z*	87:13	87
20	**15f**	^{i}Pr	^{t}Bu	*Z*	85:15	85

[a] Reactions performed by syringe pump addition of benzene or toluene solutions of Bu_3SnH and AIBN to a solution of the bromide in benzene or toluene heated at 80−90 °C, final concentration typically 0.01−0.015 M. [b] Ratio determined by HPLC of the crude reaction mixture and/or ^{1}H NMR after chromatography to remove tin residues. [c] Isolated yields following chromatography.



18

FIGURE 3. Proposed transition state leading to the major diastereomer.

demands of TTMSS leading to approach from the less hindered face.[20] However, this explanation cannot account for the enhanced diastereoselectivities observed in our cyclizations.

We suspected that the slightly lower yields obtained when using TTMSS, coupled with the improved diastereoselectivities, resulted from selective loss of the minor stereoisomer. Pure samples of both **16f** and **17f** were heated at reflux in benzene-d_6 with TTMSS/AIBN and monitored by NMR. Even after prolonged heating (up to 48 h), no changes in the ^{1}H NMR spectra were observed, confirming that once the piperidines were formed, stereochemistry was fixed, and exposure to the cyclization conditions did not result in isomerization or preferential decomposition of one diastereomer. This suggested that the differences in selectivity achieved using the tin- and silicon-based reagents were due to side reactions occurring at some point in the radical chain process.

Smiles-type radical rearrangements have been observed for certain aryl sulfonamides, and indeed the formation of biarylamines and sultams from aryl sulfonamides was first observed (as unwanted side products in the Pschorr reaction) by Huppatz and Sasse in the 1960s.[21] Later work from Köhler and Speckamp showed that upon treatment with TBTH/AIBN, sulfonamide-protected 2-halomethyl piperidines could undergo radical Smiles-type rearrangement to yield the products of both ipso and ortho attack of the radical onto the aryl ring, as well as the direct reduction product (Scheme 7).[22] More recently, Tada et al. reported radical Smiles-type rearrangements in systems derived from simple aliphatic amines,[23] while Gheorghe et al. used the rearrangement to assemble a range of cyclization precursors for piperidine synthesis.[24]

To see if such pathways could be competing during the cyclization reactions, we returned to the cyclizations of **12f** and **12i**, since it was for these two substrates that we had observed the greatest improvement in selectivity with TTMSS. If Smiles-type rearrangements were occurring in our system, potential products could include free amines which would form extremely polar ammonium salts with the HBr formed from TTMSS−Br on aqueous work up. Following each reaction the crude products

(16) The phenomenon of pseudo A^{1,3} strain in piperidines is reviewed in: Johnson, F. *Chem. Rev.* **1968**, *68*, 375−413.

(17) For examples of the phenomenon in *N*-acyl, *N*-sulfonyl and related piperidines see: (a) Beak, P.; Zajdel, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 1010−1018. (b) Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445−7447. (c) Heintzelman, G. R.; Weinreb, S. M.; Parvez, M. *J. Org. Chem.* **1996**, *61*, 4594−4599. (d) Lemire, A.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2747−2750. (e) Cariou, C. A. M.; Snaith, J. S. *Org. Biomol. Chem.* **2006**, *4*, 51−53.

(18) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, Germany, 1996; pp 77−78.

(19) Kanabus-Kaminska, J. M.; Hawari, J. A.; Griller, D.; Chatgilialoglu, C. *J. Am. Chem. Soc.* **1987**, *109*, 5267−5268.

(20) (a) Apeloig, Y.; Nakash, M. *J. Am. Chem. Soc.* **1994**, *116*, 10781−10782. (b) Kawashima, E.; Uchida, S.; Miyahara, M.; Ishido, Y. *Tetrahedron Lett.* **1997**, *38*, 7369−7372. (c) Mima, K.; Ishihara, T.; Kuwahata, S.; Konno, T.; Yamanaka, H. *Tetrahedron* **2002**, *58*, 2369−2376.

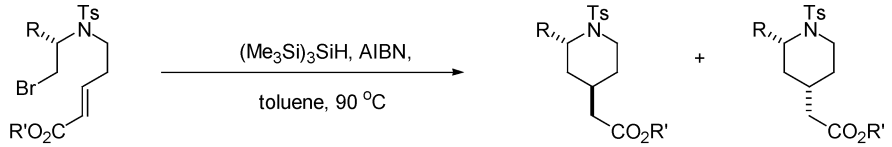
(21) Huppatz, J. L.; Sasse, W. H. F. *Aust. J. Chem.* **1963**, *16*, 417−431.

(22) Köhler, J. J.; Speckamp, W. N. *Tetrahedron Lett.* **1977**, *18*, 631−634.

(23) Tada, M.; Shijima, H.; Nakamura, M. *Org. Biomol. Chem.* **2003**, *1*, 2499−2505.

(24) Gheorghe, A.; Quiclet-Sire, B.; Vila, X.; Zard, S. Z. *Org. Lett.* **2005**, *7*, 1653−1656.

TABLE 2. Cyclizations with TTMSS[a]

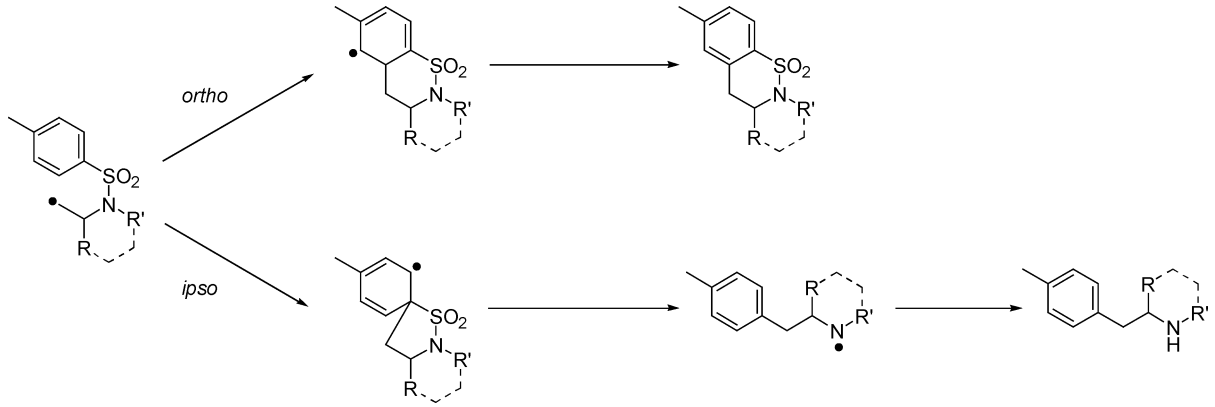


12a-n, **15b** **16a-n** **17a-n**

entry	bromide	R	R′	*E* or *Z*	**16**:**17**[b]	yield (%)[c]
1	**12a**	Me	Me	*E*	73:27	90
2	**12b**	Me	^{t}Bu	*E*	77:23	82
3	**15b**	Me	^{t}Bu	*Z*	77:23	86
4	**12c**	Bn	Me	*E*	92:8	76
5	**12d**	Bn	^{t}Bu	*E*	96:4	62
6	**12e**	^{i}Pr	Me	*E*	97:3	73
7	**12f**	^{i}Pr	^{t}Bu	*E*	99:1	75
8	**12g**	^{i}Bu	Me	*E*	85:15	80
9	**12h**	^{i}Bu	^{t}Bu	*E*	90:10	80
10	**12i**	*sec*-Bu	Me	*E*	98:2	64
11	**12j**	*sec*-Bu	^{t}Bu	*E*	>99:1	60
12	**12k**	Ph	Me	*E*	79:21	75
13	**12l**	Ph	^{t}Bu	*E*	78:22	74
14	**12m**	^{t}Bu	Me	*E*	86:14	72
15	**12n**	^{t}Bu	^{t}Bu	*E*	88:12	75

[a] Reactions performed by syringe pump addition of toluene solutions of $(Me_3Si)_3SiH$ and AIBN to a solution of the bromide in toluene heated at 90 °C, final concentration typically 0.01−0.015 M. [b] Ratio determined by HPLC of the crude reaction mixture and ^{1}H NMR after chromatography to remove silicon residues. [c] Isolated yields following chromatography.

SCHEME 7. Smiles-Type Rearrangement in Aryl Sulfonamides



were purified by chromatography. After elution of the silicon-containing byproducts (arising from TTMSS and TTMSSBr), followed by the piperidines, the column was flushed with CH_2Cl_2/MeOH (80:20), whereupon a small amount of highly polar material was recovered in both cases.

Analytical HPLC of the material obtained from the cyclization of **12f** showed it to be a mixture of several compounds, but with one major component, and purification by preparative HPLC gave a small amount of a white solid. 2D NMR experiments confirmed the structure as the ammonium ion **24f**, and NOE experiments showed a cis relationship between the 2- and 4-substituents, with both lying in equatorial positions. The side product from the cyclization of **12i** was similarly purified by HPLC, affording a small amount of piperidinium salt **24i** as a 3:1 mixture of epimers at the stereocenter in the 2-substituent.

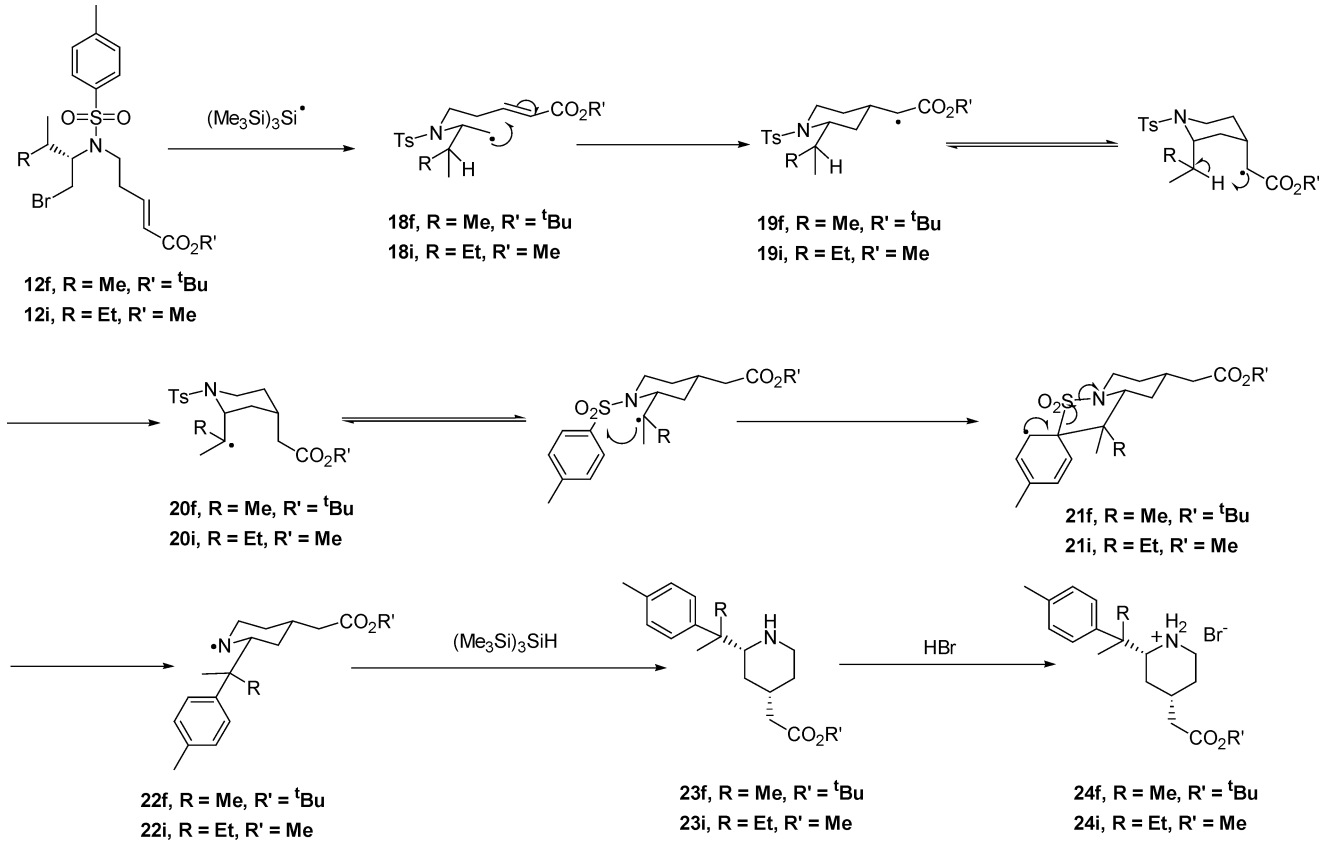
We propose that compounds **24f** and **24i** are formed as shown in Scheme 8.

The initial primary alkyl radical **18** undergoes cyclization to generate the secondary piperidine radical **19**. After ring inversion, this radical then undergoes a 1,5-radical translocation to abstract the methine proton from the axial isopropyl or *sec*-butyl group, giving a tertiary radical **20**.[25] Translocation is only geometrically favorable for 2,4-cis piperidine radicals and, further, depends on the formation of a stable translocated radical, with the amount of rearranged product (and hence the stereoselectivity for the unrearranged trans product) being greatest for tertiary and benzylic 2-substituents.

Another ring inversion occurs to restore the translocated radical to an equatorial position. This can now attack the aromatic ring in the ipso position resulting in the spiro-fused radical **21**, which then extrudes sulfur dioxide to give the N-centered radical **22**. Upon quenching with a hydrogen atom from TTMSS, the piperidine **23** is formed.[26] The rearranged products are isolated as the piperidinium salts since the piperidines react with the HBr arising from the hydrolysis of the TTMSS−Br side product.

(25) For a review of radical translocations in synthesis see: Robertson, J.; Pillai, J.; Lush, R. K. *Chem. Soc. Rev.* **2001**, *30*, 94−103.

SCHEME 8. Proposed Cascade of Rearrangements Leading to 24f and 24i

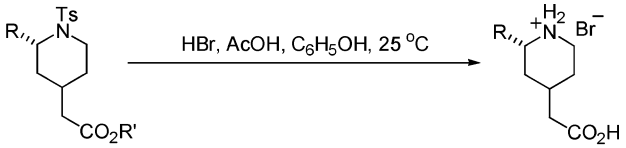


Slower hydrogen atom donation by TTMSS allows the rearrangement cascade to compete with trapping of the piperidine radical **19** to yield **17**. With TBTH the rate of trapping of **19** is rapid, and so rearrangement is much less significant, although a difference in stereoselectivity can still be observed between slow and rapid addition of TBTH. Thus, cyclization of bromide **12d** by adding the TBTH in one portion afforded the piperidines in a 70:30 trans/cis ratio (without any detectable reduction product), while dropwise addition of TBTH over 12 h gave the products in an 83:17 diastereomeric ratio; longer addition periods resulted in recovery of unreacted starting materials due to breakdown of the chain process.

The more bulky *tert*-butyl esters reduce the rate of trapping of the piperidine radical even further by sterically hindering the approach of the bulky TTMSS. This was further emphasized on moving to a more sterically demanding silane. Tris(phenyldimethylsilyl)silane was first prepared by Gilman et al.,[27] but its use in radical reactions has not been reported. Employing this bulky silane in the cyclization of **12c** afforded the expected piperidines with a diastereomeric ratio of 98:2 (59% yield), compared with 92:8 (76%) with TTMSS and 80:20 (89%) with TBTH.

Removal of the *p*-toluenesulfonyl protecting group was carried out on a representative range of examples by stirring the *N*-tosylpiperidines with phenol and HBr in acetic acid (Scheme 9). Deprotection (performed on cis/trans mixtures) proceeded cleanly with simultaneous ester hydrolysis to afford essentially quantitative yields of the piperidine acids **25** with unchanged cis/trans ratios.

SCHEME 9. Deprotection of Piperidines



16/17b, R = Me, R' = tBu
16/17c, R = Bn, R' = Me
16/17d, R = Bn, R' = tBu
16/17f, R = iPr, R' = tBu
16/17g, R = iBu, R' = Me

25a, R = Me
25b, R = Bn
25c, R = iPr
25d, R = iBu

Conclusion

In summary, we have demonstrated a diastereoselective radical route to 2,4-disubstituted piperidines. Cyclization with tributyltin hydride affords predominantly the trans piperidines in excellent yield, with diastereomeric ratios typically ranging from 3:1 to 6:1. Cyclization with tris(trimethylsilyl)silane leads to an enhancement in diastereoselectivity in cases where the 2-substituent is secondary or benzylic, resulting from the selective rearrangement of the minor stereoisomer through a cascade process involving radical cyclization to the piperidine radical, 1,5-radical translocation, and attack of the translocated radical onto the sulfonamide with extrusion of SO_2 in a Smiles-

(26) Work by Studer and Zard suggests that sulfur dioxide extrusion from aminosulfonyl radicals is a slow process, so another possibility is that **21** undergoes C−S bond cleavage to give an aminosulfonyl radical which is trapped by TTMSS before undergoing sulfur dioxide extrusion to afford **23**. See ref 24 and also: Bossart, M.; Fassler, R.; Schoenberger, J.; Studer, A. *Eur. J. Org. Chem.* **2002**, 2742−2757.

(27) Gilman, H.; Atwell, W. H.; Sen, P. K.; Smith, C. L. *J. Organomet. Chem.* **1965**, *4*, 163−167.

type rearrangement. Slow trapping of the piperidine radical by tris(trimethylsilyl)silane accounts for the occurrence of the rearrangement cascade with this reagent. The methodology should find application to the synthesis of more complex molecules.

Experimental Section

Typical Procedure for the Preparation of *N*-Tosyl *O*-Silyl Amino Alcohols: (*S*)-*O*-(*tert*-Butyldimethylsilyl)-*N*-(*p*-toluenesulfonyl) Valinol (8c). Tosyl chloride (17.43 g, 91.4 mmol) in CH_2Cl_2 (100 mL) was added dropwise over 2 h to a solution of (*S*)-valinol (8.97 g, 87.1 mmol), DMAP (1.06 g, 8.7 mmol), and Et_3N (24.3 mL, 174.2 mmol) in CH_2Cl_2 (200 mL) at 0 °C. After stirring overnight at room temperature, the reaction mixture was poured into water and extracted with CH_2Cl_2. The combined organic phases were washed with water and brine and dried over $MgSO_4$ before the solvents were removed in vacuo to give the crude tosylate as a white solid. Purification by column chromatography (CH_2Cl_2/MeOH, 95:5) gave the *N*-(*p*-toluenesulfonyl)valinol as a white solid (19.6 g, 88%): R_f = 0.45; mp 87−89 °C (from hexane/EtOAc) (lit.[28] mp 86 °C, from Et_2O); $[\alpha]^{18}_D = -29.5°$ (*c* 1.0, $CHCl_3$) (lit.[26] $[\alpha]^{20}_D = -27.4°$, *c* 1.0, $CHCl_3$); IR (film) 3493, 3282, 3026, 2962, 2874, 1598, 1494 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.75 (d, *J* = 6.6 Hz, 6H), 1.67−1.81 (m, 1H), 2.40 (s, 3H), 2.56 (br s, 1H), 2.96−3.05 (m, 1H), 3.47−3.61 (m, 2H), 5.35 (d, *J* = 8.5 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.77 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 19.2, 21.6, 29.5, 61.2, 63.0, 127.2, 129.7, 137.8, 143.5; MS (electrospray) *m*/*z* 280 (100%, $[M + Na]^+$). HRMS (electrospray) Calcd for $C_{12}H_{19}NO_3SNa$: 280.0983. Found: 280.0973. Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.00; H, 7.44; N, 5.44. Found: C, 56.14; H, 7.41; N, 5.31.

To a solution of the *N*-tosyl amino alcohol (15.00 g, 58.4 mmol) in anhydrous DMF (50 mL) at 0 °C were added imidazole (7.94 g, 116.7 mmol) and TBDMSCl (10.56 g, 70.0 mmol). After stirring overnight at room temperature, the reaction mixture was poured into water and extracted with diethyl ether. The combined organic phases were washed with water and brine and dried over $MgSO_4$ before the solvents were removed in vacuo to give the crude silyl ether as an oil. Purification by column chromatography (petrol/Et_2O, 9:1) gave **8c** as a colorless solid (21.10 g, 97%): R_f = 0.23; mp 54−56 °C (from hexane/Et_2O); $[\alpha]^{20}_D = -22.1°$ (*c* 1.0, $CHCl_3$); IR (film) 3285, 3027, 2957, 2929, 2882, 2857, 1599, 1495 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −0.10 (s, 3H), −0.07 (s, 3H), 0.80 (d, *J* = 6.2 Hz, 3H), 0.81 (s, 9H), 0.86 (d, *J* = 7.0 Hz, 3H), 1.75−1.93 (m, 1H), 2.40 (s, 3H), 2.89−2.99 (m, 1H), 3.20 (dd, *J* = 4.6, 10.2 Hz, 1H), 3.50 (dd, *J* = 2.9, 10.2 Hz, 1H), 4.80 (d, *J* = 8.8 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.6, −5.5, 18.3, 18.7, 19.3, 21.6, 25.9, 29.5, 60.2, 62.0, 127.1, 129.7, 138.5, 143.2; MS (electrospray) *m*/*z* 394 (100%, $[M + Na]^+$). HRMS (electrospray) Calcd for $C_{18}H_{33}NO_3SSiNa$: 394.1848. Found: 394.1840. Anal. Calcd for $C_{18}H_{33}NO_3SSi$: C, 58.18; H, 8.95; N, 3.77. Found: C, 57.93; H, 9.17; N, 3.78.

Typical Procedure for the Alkylation of Protected Amino Alcohols: (*S*)-4-Aza-6-(*tert*-butyldimethylsilanyloxy)-5-isopropyl-4-(*p*-toluenesulfonyl)hexanal Dimethyl Acetal (9c). To a solution of the protected amino alcohol **8c** (18.1 g, 48.8 mmol) in anhydrous DMF (100 mL) was added Cs_2CO_3 (23.85 g, 73.2 mmol) followed by 3-iodopropanal dimethyl acetal[29] (16.83 g, 73.2 mmol). The reaction mixture was stirred for 96 h at room temperature, with further additions of Cs_2CO_3 (11.92 g, 36.6 mmol) and iodoacetal (4.50 g, 36.6 mmol) at 24 h intervals. The reaction mixture was poured into water and extracted with diethyl ether. The combined organic phases were washed with water and brine and dried over $MgSO_4$ before the solvents were removed in vacuo to give the crude acetal as an oil. Purification by column chromatography (hexane/Et_2O, 9:1) provided **9c** as a colorless oil (21.08 g, 91%): R_f = 0.25; $[\alpha]^{24}_D = -20.3°$ (*c* 1.0, $CHCl_3$); IR (film) 2956, 2929, 2882, 2857, 1598, 1494 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −0.10 (s, 3H), −0.09 (s, 3H), 0.80 (s, 9H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 1.80−2.20 (m, 3H), 2.39 (s, 3H), 3.10−3.50 (m, 10H), 3.61 (dd, *J* = 4.8, 11.4 Hz, 1H), 4.33 (t, *J* = 5.5 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.8, −5.7, 18.2, 20.0, 20.8, 21.5, 25.9, 27.9, 34.0, 41.3, 52.8, 52.9, 63.4, 65.8, 102.9, 127.4, 129.6, 138.4, 142.9; MS (electrospray) *m*/*z* 496 (100%, $[M + Na]^+$). HRMS (electrospray) Calcd for $C_{23}H_{43}NO_5SSiNa$: 496.2529. Found: 496.2524. Anal. Calcd for $C_{23}H_{43}NO_5SSi$: C, 58.31; H, 9.15; N, 2.96. Found: C, 58.28; H, 9.29; N, 2.89.

Typical Procedure for the Hydrolysis of Acetals: (5*S*)-4-Aza-1-hydroxy-5-isopropyl-6-oxa-4-(*p*-toluenesulfonyl)cycloheptane (10c). To a solution of the acetal **9c** (14.00 g, 29.6 mmol) in THF/water (2:1, 80 mL) was added 2 M HCl (10 mL), and the solution was stirred at room temperature for 36 h. THF was removed in vacuo, and the aqueous residue was extracted with EtOAc. The combined organic phases were washed with saturated $NaHCO_3$ solution, water, and brine before being dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (CH_2Cl_2/MeOH, 19:1) yielded the lactol **10c** as a white solid (7.24 g, 78%): R_f = 0.43; mp 104−106 °C (from EtOAc); IR (film) 3431, 3021, 2963, 2873, 1598, 1494 cm^{-1}; MS (electrospray) *m*/*z* 368 (81%, $[M + Na + MeOH]^+$), 336 (100%, $[M + Na]^+$). HRMS (electrospray) Calcd for $C_{15}H_{23}NO_4SNa$: 336.1245. Found: 336.1237. Anal. Calcd for $C_{15}H_{23}NO_4S$: C, 57.48; H, 7.40; N, 4.47. Found: C, 57.58; H, 7.58; N, 4.36. The ^1H and ^{13}C NMR spectra of the sample were complex due to the presence of both anomers of the lactol in solution along with a small amount of the open chain aldehyde.

Typical Procedure for Wittig Reactions: Methyl (*S*)-6-Aza-8-hydroxy-7-isopropyl-6-(*p*-toluenesulfonyl)oct-2-enoate (11e). To a solution of lactol **10c** (1.50 g, 4.8 mmol) and benzoic acid (0.12 g, 1.0 mmol) in toluene (40 mL) at 90 °C was added methyltriphenylphosphoranylidene acetate (2.08 g, 6.2 mmol), and the solution was stirred at 90 °C for 1 h. Toluene was removed in vacuo, and the residue dissolved in ethyl acetate and extracted with saturated $NaHCO_3$ solution. The aqueous phase was further extracted with EtOAc, and the combined organic phases were washed with brine before being dried over $MgSO_4$. The solvents were removed in vacuo to yield the crude olefin as a pink oil. Purification by column chromatography (hexane/EtOAc, 3:2) yielded the ester **11e** in an 8:1 (*E*)/(*Z*) ratio as a colorless oil (1.58 g, 89%). The stereoisomers were very difficult to separate by column chromatography, so data were recorded on the mixture. In the case of the NMR spectra, while some signals arising from the minor isomer were observed, only those signals resulting from the major (*E*)-isomer are reported: R_f = 0.55; IR (film) 3526, 2961, 1723, 1656, 1598, 1494 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.61 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.3 Hz, 3H), 1.66−1.83 (m, 1H), 2.07 (t, *J* = 5.1 Hz, 1H), 2.39 (s, 3H), 2.52−2.70 (m, 2H), 3.12−3.45 (m, 3H), 3.49−3.60 (m, 1H), 3.68−3.80 (m, 4H), 5.81 (d, *J* = 15.5 Hz, 1H), 6.83 (dt, *J* = 7.3, 15.5 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 20.6, 21.6, 28.4, 33.7, 43.6, 51.6, 62.4, 66.5, 122.8, 127.5, 129.7, 137.9, 143.6, 145.4, 166.8; MS (electrospray) 392 (100%, $[M + Na]^+$). HRMS (electrospray) Calcd for $C_{18}H_{27}NO_5SNa$: 392.1508. Found: 392.1503. Anal. Calcd for $C_{18}H_{27}NO_5S$: C, 58.51; H, 7.37; N, 3.79. Found: C, 58.47; H, 7.38; N, 3.56.

Typical Procedure for Still−Gennari Modified Horner−Wadsworth−Emmons Reactions: Methyl (*S*)-(*Z*)-6-Aza-8-hydroxy-7-methyl-6-(*p*-toluenesulfonyl)oct-2-enoate (14a). A mixture of 18-crown-6 (3.40 g, 12.9 mmol), recrystallized from acetonitrile, and bis(2,2,2-trifluoroethyl) methoxycarbonylmethyl

(28) Hoppe, I.; Hoffmann, H.; Gaertner, I.; Krettek, T.; Hoppe, D. *Synthesis* **1991**, 1157−1162.

(29) Clive, D. L. J.; Paul, C. C.; Wang, Z. *J. Org. Chem.* **1997**, *62*, 7028−7032.

phosphonate (0.60 mL, 2.84 mmol) in THF (20 mL) was stirred at −78 °C, and KHMDS (5.7 mL of a 0.5 M solution in toluene, 2.8 mmol) was added dropwise over 5 min. Stirring was continued for 1 h. Lactol **10a** (0.73 g, 2.56 mmol) was then added portionwise over 30 min, and the solution was stirred at −78 °C for 3 days. The reaction mixture was quenched with saturated NH_4Cl solution and allowed to warm to room temperature before being extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography (petrol/EtOAc, 6:4) provided a 12:1 (*Z*)/(*E*) mixture of isomers as a colorless oil (0.72 g, 82%). Repeated chromatography allowed the isolation of a sample of pure **14a** as a colorless oil. Data for the (*Z*)-isomer: $R_f = 0.34$; $[\alpha]^{19}_D = +17.7$ (*c* 1.11, $CHCl_3$); IR (film) 3522, 2951, 2881, 1721, 1646, 1598, 1495 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, J = 7.0 Hz, 3H), 2.41 (s, 3H), 2.88−3.10 (m, 2H), 3.13−3.26 (m, 1H), 3.30−3.44 (m, 1H), 3.53 (dd, J = 5.0, 11.6 Hz, 1H), 3.61 (dd, J = 8.3, 11.6 Hz, 1H), 3.70 (s, 3H), 3.85−4.00 (m, 1H), 5.87 (d, J = 11.6 Hz, 1H), 6.30 (dt, J = 7.7, 11.6 Hz, 1H), 7.28 (d, J = 8.3 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 21.4, 30.7, 42.3, 51.2, 55.5, 64.7, 121.3, 127.0, 129.6, 137.5, 143.2, 145.7, 166.5; MS (electrospray) *m*/*z* 364 (100%, $[M + Na]^+$). HRMS (electrospray) Calcd for $C_{16}H_{23}NO_5SNa$: 364.1195. Found: 364.1187. Anal. Calcd for $C_{16}H_{23}NO_5S$: C, 56.29; H, 6.79; N, 4.10. Found: C, 56.26; H, 6.77; N, 4.06.

Data for the (*E*)-isomer: $R_f = 0.32$. For further data see the Supporting Information.

Typical Procedure for the Bromination of Methyl Esters: Methyl (*S*)-(*E*)-6-Aza-8-bromo-7-isopropyl-6-(*p*-toluenesulfonyl)-oct-2-enoate (12e). Triphenylphosphine (1.183 g, 4.51 mmol) and carbon tetrabromide (1.497 g, 4.51 mmol) were added to a stirred solution of an 8:1 (*E*)/(*Z*) mixture of alcohols **11e:14e** (1.390 g, 3.76 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The solution was allowed to warm to room temperature and was stirred for 24 h after which TLC showed some remaining starting material, so further portions of PPh_3 (0.493 g, 1.88 mmol) and CBr_4 (0.623 g, 1.88 mmol) were added, and the reaction mixture stirred a further 15 h. The crude reaction mixture was adsorbed onto silica and purified by column chromatography (petrol/Et_2O, 7:3) to yield first **15e** as a colorless oil (0.144 g, 9%), followed by **12e** as a colorless oil (1.249 g, 77%). Overall yield: 86%. Data for the (*Z*)-isomer **15e**: $R_f = 0.30$; $[\alpha]^{19}_D = +22.0°$ (*c* 1.0, $CHCl_3$); IR (film) 2965, 2875, 1720, 1644, 1598, 1494 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, J = 7.0 Hz, 3H), 1.00 (d, J = 6.2 Hz, 3H), 1.90−2.04 (m, 1H), 2.39 (s, 3H), 2.87−3.08 (m, 2H), 3.13−3.35 (m, 2H), 3.48 (dd, J = 7.4, 11.4 Hz, 1H), 3.56 (dd, J = 3.9, 11.4 Hz, 1H), 3.65−3.77 (m, 4H), 5.81 (d, J = 11.4 Hz, 1H), 6.83 (dt, J = 7.7, 11.4 Hz, 1H), 7.26 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 20.9, 21.6, 30.5, 31.4, 33.8, 43.6, 51.3, 65.8, 121.6, 127.8, 129.5, 137.9, 143.4, 145.5, 166.4; MS (electrospray) *m*/*z* 456 (100%, $[M(^{81}Br) + Na]^+$), 454 (85%, $[M(^{79}Br) + Na]^+$). HRMS (electrospray) Calcd for $C_{18}H_{26}NO_4S^{79}BrNa$: 454.0664. Found: 454.0674; Anal. Calcd for $C_{18}H_{26}NO_4SBr$: C, 50.00; H, 6.06; N, 3.24. Found: C, 49.74; H, 6.03; N, 3.19.

Data for the (*E*)-isomer **12e**: $R_f = 0.21$; $[\alpha]^{14}_D = -12.0°$ (*c* 1.0, $CHCl_3$); IR (film) 2968, 1723, 1658, 1598, 1493 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 1.88−2.01 (m, 1H), 2.41 (s, 3H), 2.57−2.75 (m, 2H), 3.10−3.21 (m, 1H), 3.25−3.35 (m, 1H), 3.43 (dd, J = 6.6, 11.4 Hz, 1H), 3.52 (dd, J = 3.3, 11.4 Hz, 1H), 3.61−3.70 (m, 1H), 3.71 (s, 3H), 5.84 (d, J = 15.6 Hz, 1H), 6.83 (dt, J = 7.2, 15.6 Hz, 1H), 7.28 (d, J = 8.1 Hz, 2H), 7.72 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 20.4, 21.6, 30.7, 33.9, 34.9, 43.6, 51.6, 65.0, 122.9, 127.6, 129.7, 137.5, 143.7, 145.1, 166.7; MS (electrospray) *m*/*z* 456 (96%, $[M(^{81}Br) + Na]^+$), 454 (100%, $[M(^{79}Br) + Na]^+$). HRMS (electrospray) Calcd for $C_{18}H_{26}NO_4S^{79}BrNa$: 454.0664. Found: 454.0666. Anal. Calcd for $C_{18}H_{26}NO_4SBr$: C, 50.00; H, 6.06; N, 3.24. Found: C, 50.18; H, 6.13; N, 3.09.

Typical Procedure for the Bromination of *t*-Butyl Esters: *tert*-Butyl (*S*)-(*E*)-6-Aza-8-bromo-7-isopropyl-6-(*p*-toluenesulfonyl)-oct-2-enoate (12f). Triethylamine (0.529 mL, 3.80 mmol) followed by methane sulfonyl chloride (0.196 mL, 2.53 mmol) was added to a stirred solution of the alcohol **11f** (1.040 g, 2.53 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The solution was stirred for 1 h and then poured into aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvent was removed in vacuo to yield the mesylate as a sticky oil. The crude mesylate was dissolved in THF (30 mL), and anhydrous LiBr (0.880 g, 10.13 mmol) was added. The suspension was heated at reflux for 48 h. THF was removed in vacuo, and the residue dissolved in CH_2Cl_2/water, 1:1. The aqueous layer was extracted with CH_2Cl_2, the combined organic layers dried over $MgSO_4$, and the solvent was removed in vacuo. Purification by column chromatography (petrol/Et_2O, 7:3) yielded **12f** as a colorless oil (1.009 g, 84%): $R_f = 0.53$; $[\alpha]^{16}_D = -10.3$ ° (*c* 1.0, $CHCl_3$); IR (film) 2975, 2932, 1711, 1656, 1598, 1494 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 1.47 (s, 9H), 1.88−2.01 (m, 1H), 2.41 (s, 3H), 2.53−2.71 (m, 2H), 3.09−3.21 (m, 1H), 3.23−3.35 (m, 1H), 3.42 (dd, J = 6.6, 11.4 Hz, 1H), 3.52 (dd, J = 3.3, 11.4 Hz, 1H), 3.63−3.71 (m, 1H), 5.75 (d, J = 15.8 Hz, 1H), 6.71 (dt, J = 7.1, 15.8 Hz, 1H), 7.30 (d, J = 8.3 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 20.5, 21.6, 28.3, 30.8, 33.7, 34.8, 43.7, 65.1, 80.5, 125.1, 127.7, 129.7, 137.6, 143.5, 143.6, 165.7; MS (electrospray) *m*/*z* 498 (97%, $[M(^{81}Br) + Na]^+$), 496 (100%, $[M(^{79}Br) + Na]^+$). HRMS (electrospray) Calcd for $C_{21}H_{32}NO_4S^{79}BrNa$: 496.1133. Found: 496.1138. Calcd for $C_{21}H_{32}NO_4S^{81}BrNa$: 498.1113. Found: 498.1113. Anal. Calcd for $C_{21}H_{32}NO_4SBr$: C, 53.16; H, 6.80; N, 2.95. Found: C, 53.20; H, 6.92; N, 2.81.

Typical Procedure for the Cyclization of Bromides Using TTMSS: Preparation of (2*R*,4*R*)-4-(*tert*-Butoxycarbonylmethyl)-2-isopropyl-1-(*p*-toluenesulfonyl)piperidine (16f), (2*R*,4*S*)-4-(*tert*-Butoxycarbonylmethyl)-2-isopropyl-1-(*p*-toluenesulfonyl)-piperidine (17f), and 4-*tert*-Butoxycarbonylmethyl-2-(1′-methyl-1′-*p*-tolylethyl)piperidinium Bromide (24f). A solution of the bromide (**12f**) (222 mg, 0.47 mmol) in toluene (10 mL) was deoxygenated by bubbling argon through it for 30 min. The solution was heated to 90 °C, and deoxygenated solutions of TTMSS (260 μL, 0.84 mmol) in toluene (10 mL) and AIBN (8 mg, 0.05 mmol) in toluene (10 mL) were added simultaneously via syringe pump over 12 h, followed by a further addition of TTMSS (144 μL, 0.47 mmol) in toluene (10 mL) and AIBN (8 mg, 0.05 mmol) in toluene (10 mL) over another 12 h. After this addition was complete, the reaction mixture was maintained at 90 °C for 15 h. Purification by column chromatography (gradient, 100% hexane to 100% EtOAc) yielded a 99:1 (determined by analytical HPLC on the crude reaction mixture) trans/cis mixture of piperidines **16f** and **17f** (petrol/EtOAc, 4:1, $R_f = 0.45$) as a colorless oil (139 mg, 75%). Data for trans isomer **16f** (recorded on trans/cis mixture): analytical HPLC (from 100% water to 100% methanol over 60 min): $t_r = 53.63$ min; $[\alpha]^{18}_D = +34.9°$ (*c* 0.64, $CHCl_3$); IR (film) 3024, 2973, 2933, 2874, 1726, 1599, 1494 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.67−0.94 (m, 8H), 1.30−1.45 (m, 10H), 1.71 (d, J = 12.1 Hz, 1H), 1.78−2.10 (m, 4H), 2.39 (s, 3H), 2.91−3.04 (m, 1H), 3.57 (dd, J = 4.4, 10.7 Hz 1H), 3.80 (dd, J = 4.1, 14.7 Hz, 1H), 7.24 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 19.6, 20.9, 26.0, 26.8, 27.4, 29.7, 30.9, 40.1, 42.0, 58.9, 79.8, 126.3, 128.9, 138.4, 142.1, 170.8; MS (electrospray) *m*/*z* 418 (100%, $[M + Na]^+$). HRMS (electrospray) Calcd for $C_{21}H_{33}NO_4SNa$: 418.2028. Found: 418.2032. Anal. Calcd for $C_{21}H_{33}NO_4S$: C, 63.76; H, 8.41; N, 3.54. Found: C, 63.71; H, 8.46; N, 3.49.

Separation of the cis and trans isomers was possible by HPLC. Data for the cis isomer **17f**: Analytical HPLC (100% water to 100% methanol over 60 min): $t_r = 53.10$ min; MS (electrospray) *m*/*z* 418 (100%, $[M + Na]^+$). For further data vide infra.

After elution from the column of the silane-derived byproducts, followed by the piperidines, the column was flushed with CH_2Cl_2/MeOH (4:1). Evaporation of the solvent in vacuo gave a yellow solid (38 mg), a portion of which was purified by HPLC to afford **24f** as a white solid: mp 186−189 °C (from CH_2Cl_2); $[\alpha]^{15}_D$ = 8.3° (*c* = 0.3, $CHCl_3$, *l* = 0.25 dm); IR (film) 2921, 2764, 1782, 1579, 1516, 1477 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.25−1.39 (m, 10H), 1.43−1.51 (m, 1H), 1.57 (s, 3H), 1.67 (s, 3H), 1.81−1.93 (m, 3H), 2.06 (dd, *J* = 5.8, 15.2 Hz, 1H), 2.16 (dd, *J* = 5.8, 15.2 Hz, 1H), 2.31 (s, 3H), 2.91−2.99 (m, 1H), 3.16 (t, *J* = 11.5 Hz, 1H), 3.81 (d, *J* = 12.2 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 8.33 (br s, 1H), 8.57 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8, 22.4, 27.9, 28.1, 28.2, 30.4, 32.3, 40.4, 41.7, 46.7, 67.5, 80.8, 125.8, 129.6, 136.8, 141.7, 170.8; MS (electrospray) *m*/*z* 332 (100%, [ammonium ion]$^+$). HRMS (electrospray) Calcd for $C_{21}H_{34}NO_2$: 332.2590. Found: 332.2595.

Typical Procedure for the Cyclization of Bromides Using TBTH: Preparation of (2*R*,4*R*)-4-(*tert*-Butoxycarbonylmethyl)-2-isopropyl-1-(*p*-toluenesulfonyl)piperidine (16f) and (2*R*,4*S*)-4-(*tert*-Butoxycarbonylmethyl)-2-isopropyl-1-(*p*-toluenesulfonyl)-piperidine (17f). A solution of the bromide **12f** (188 mg, 0.40 mmol) in toluene (10 mL) was deoxygenated by bubbling argon through it for 30 min. The solution was heated to 90 °C, and deoxygenated solutions of TBTH (192 μL, 0.71 mmol) in toluene (10 mL) and AIBN (7 mg, 0.04 mmol) in toluene (10 mL) were added simultaneously via syringe pump over 12 h, followed by heating at 90 °C for a further 6 h. Purification by column chromatography gave an 86:14 (determined by analytical HPLC on the crude reaction mixture) trans/cis mixture of piperidines **16f** and **17f** (petrol/EtOAc, 4:1, R_f = 0.45) as a colorless oil (129 mg, 82%). Further purification of a small sample of this material by semipreparative HPLC (100% water to 100% methanol over 60 min) allowed separation of the diastereomers. Data for trans isomer **16f** as before. Data for cis isomer **17f**: Analytical HPLC (100% water to 100% methanol over 60 min): t_r = 53.10 min; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88−0.96 (m, 6H), 1.05−1.10 (m, 1H), 1.24−1.32 (m, 1H), 1.39 (s, 9H), 1.51−1.66 (m, 3H), 2.05−2.13 (m, 3H), 2.41 (s, 3H), 3.13−3.21 (m, 1H), 3.52 (q, *J* = 7.4 Hz, 1H), 3.61 (ddd, *J* = 2.7, 7.1, 15.0 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.74 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 20.1, 21.6, 27.9, 28.1, 28.2, 28.3, 32.5, 40.0, 41.7, 60.7, 80.5, 127.3, 129.7, 138.4, 143.1, 171.6; MS (electrospray) *m*/*z* 418 (100%, [M + Na]$^+$). HRMS (electrospray) Calcd for $C_{21}H_{33}NO_4SNa$: 418.2028. Found: 418.2033.

Typical Procedure for the Deprotection with HBr: Preparation of (2*R*,4*R*)-2-Benzyl-4-carboxymethylpiperidine (25b). Piperidine **16d** (as a 96:4 trans/cis mixture, 62 mg, 0.14 mmol) was dissolved in 48% HBr in acetic acid (2 mL). Phenol (26 mg, 0.28 mmol) was added, and the solution was stirred at room temperature for 4 days. Solvents were removed in vacuo to leave a dark residue which was washed with diethyl ether (5 × 2 mL). NMR showed the resulting gum (50 mg) to be essentially pure piperidinium salt **25b**. This was further purified by preparative HPLC (99.95% water + 0.05% trifluoroacetic acid to 100% acetonitrile over 40 min, flow rate 10 mL/min) to give **25b**, presumably with trifluoroacetate as the counterion, as a colorless film (39 mg, 80%). ^1H NMR (300 MHz, D_2O) δ 1.47−1.77 (m, 3H), 1.82−2.00 (m, 1H), 2.25−2.45 (m, 3H), 2.84−3.12 (m, 3H), 3.14−3.26 (m, 1H), 3.54−3.66 (m, 1H), 7.19−7.38 (m, 5H); ^{13}C NMR (100 MHz, D_2O) δ 27.0, 27.7, 32.2, 37.9, 38.5, 40.7, 54.7, 129.3, 130.9, 131.2, 137.3, 178.7; MS (electrospray) *m*/*z* 234 (100%, [M + H]$^+$). HRMS (electrospray) Calcd for $C_{14}H_{20}NO_2$: 234.1494. Found: 234.1482.

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Supporting Information Available: Experimental procedures, NMR spectra, and full characterization for all compounds, as well as CIF files and ORTEP diagrams for the X-ray structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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