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Efficient Synthesis of Piperidine Derivatives. Development of Metal Triflate-Catalyzed Diastereoselective Nucleophilic Substitution Reactions of 2-Methoxy- and 2-Acyloxypiperidines

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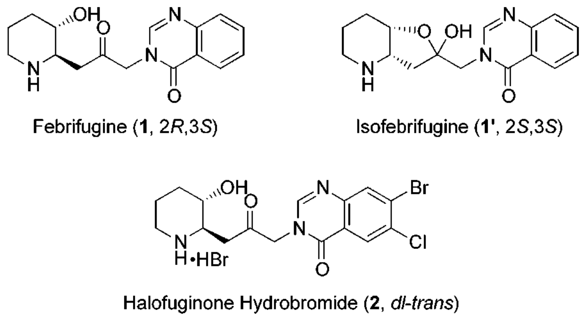
Nucleophilic substitution reactions of 2-methoxy- and 2-acyloxypiperidines were investigated. First, new and efficient methods for the preparation of the starting piperidine derivatives were developed. *N*-Benzyloxycarbonyl-2-methoxypiperidine (**3**) and 3-substituted-2-acyloxy-*N*-benzyloxycarbonylpiperidines (**4a**−**d**), which are recognized as the simplest imino-sugars, were prepared and were examined as substrates for nucleophilic substitution reactions with silyl enolates under the influence of catalytic amounts of metal triflates (Sc(OTf)$_3$, Sn(OTf)$_2$, Cu(OTf)$_2$, Hf(OTf)$_4$, etc). Among the triflates tested, Sc(OTf)$_3$ gave the best results. It was found that 2-acetoxy-3-benzyloxy-*N*-benzyloxycarbonylpiperidine (**4a**) reacted with silyl enolates to afford the 2-alkylated adducts in high *cis*-selectivity, while 2,3-diacyloxy-*N*-benzyloxycarbonylpiperidines (**4b**−**d**) showed *trans*-selectivity. The stereochemical assignments were carefully performed using NMR analysis, X-ray crystallography, and synthetic transformations. Febrifugine (**1**), a potent antimalarial alkaloid, was successfully synthesized from 2,3-diacetoxy-*N*-benzyloxycarbonylpiperidine (**4b**) on the basis of these diastereoselective nucleophilic substitution reactions.

Introduction

Many nitrogen-containing cyclic compounds are widely distributed in biologically important natural products and pharmaceuticals. Febrifugine (**1**) and isofebrifugine (**1′**) are alkaloids first found in the Chinese plant *Dichroa febrifuga*[1] and later in the common hydrangea.[2] These compounds have attracted considerable attention because of their potentially powerful antimalarial activity.[1−3] In addition, halofuginone (**2**) has been used as an antiparasitic feed additive for the prevention of coccidiosis in poultry production.[4] Recently, it has been reported that halofuginone (**2**) inhibits collagen production (collagene synthesis inhibitor) and is now undergoing clinical trials for treatment of scleroderma in human.[4] In relation to our project on antimalarial agents, we previously reported catalytic asymmetric synthesis of febrifugine and isofebrifugine and revised their absolute configurations.[5] The six-membered ring system of febrifugine with an OH group at the 3-position of the piperidine ring is believed to be essential for its antimalarial activity (Chart 1).[6] To prepare a wide variety of febrifugine derivatives for improvement of its properties as an antimalarial agent (increasing its potency and decreasing its toxicity), a new synthetic method using a coupling reaction of the acyliminium cation with the enolate shown in Scheme 1 is desirable.

Chart 1. Bioactive Compounds Having a Febrifugine Skeleton



Febrifugine (**1**, 2*R*,3*S*)

Isofebrifugine (**1'**, 2*S*,3*S*)

Halofuginone Hydrobromide (**2**, *dl-trans*)

The reaction shown in Scheme 1 is regarded as an imino-version of a *C*-glycosylation reaction. Recently, biological properties of carbohydrates[7] have been of great

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(1) (a) Koepfli, J. B.; Mead, J. F.; Brockman, J. A., Jr. *J. Am. Chem. Soc.* **1947**, *69*, 1837. (b) Koepfli, J. B.; Mead, J. F.; Brockman, J. A., Jr. *J. Am. Chem. Soc.* **1949**, *71*, 1048.

(2) (a) Ablondi, F.; Gordon, S.; Morton, J., II; Williams, J. H. *J. Org. Chem.* **1952**, *17*, 14. (b) Kato, M.; Inaba, M.; Itahana, H.; Ohara, E.; Nakamura, K.; Uesato, S.; Inouye, H.; Fujita, T. *Shoyakugaku Zasshi* **1990**, *44*, 288; *Chem. Abstr.* **1991**, *115*, 64012f.

(3) (a) Jang, C. S.; Fu, F. Y.; Wang, C. Y.; Huang, K. C.; Lu, G.; Thou, T. C. *Science* **1946**, *103*, 59. (b) Chou, T. Q.; Fu, F. Y.; Kao, Y. S. *J. Am. Chem. Soc.* **1948**, *70*, 1765. (c) Kuehl, F. A., Jr.; Spencer, C. F.; Folkers, K. *J. Am. Chem. Soc.* **1948**, *70*, 2091.

(4) Rowe, L. D.; Beier, R. C.; Elissalde, M. H.; Stanker, L. H.; Stipanovic, R. D. *Synth. Commun.* **1993**, *23*, 2191 and references therein.

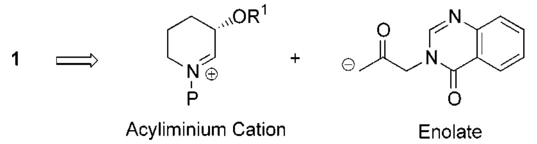
(5) (a) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H.; Kim, H.-S.; Wataya, Y. *J. Org. Chem.* **1999**, *64*, 6833. (b) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H. *Tetrahedron Lett.* **1999**, *40*, 2175.

(6) Recently, some other synthetic studies of febrifugine and its derivatives have been reported. (a) Takeuchi, Y.; Hattori, M.; Abe, H.; Harayama, T. *Synthesis* **1999**, 1814. (b) Takeuchi, Y.; Abe, H.; Harayama, T. *Chem. Pharm. Bull.* **1999**, *47*, 905. (c) Takeuchi, Y.; Tokuda, S.-i.; Takagi, T.; Koike, M.; Abe, H.; Harayama, T.; Shibata, Y.; Kim, H.; Wataya, Y. *Heterocycles* **1999**, *51*, 1869. (d) Takaya, Y.; Tasaka, H.; Chiba, T.; Uwai, K.; Tanitsu, M.; Kim, H.-S.; Wataya, Y.; Miura, M.; Takeshita, M.; Oshima, Y. *J. Med. Chem.* **1999**, *42*, 3163. Cf. (e) Burgess, L. E.; Gross, E. K. M.; Jurka, J. *Tetrahedron Lett.* **1996**, *37*, 3255

(7) For recent reviews on glycobiology, see: (a) St. Hilaire, P. M.; Meldal, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 1162. (b) Petitou, M.; van Boeckel, C. A. A. *Pure Appl. Chem.* **1997**, *69*, 1839, and the following papers in this issue. Olesson, S.

10.1021/jo001297m CCC: $20.00

Scheme 1. Synthetic Strategy of Febrifugine



interest in the fields of chemistry and biology, and various stereoselective glycosylation methods using the anomeric effect and the neighboring group participation have been exploited for the preparation of a wide variety of carbohydrate derivatives.[8] Imino-sugars, nitrogen analogues of carbohydrates, have an interesting juxtaposition of functionality that potentially allows the synthesis of a variety of nitrogen-containing cyclic compounds and can be recognized as bioisosteres of carbohydrates.[9] It has been reported that some Lewis acids (for example, $BF_3\cdot Et_2O$, $TiCl_4$, $SnCl_4$, etc.) activate piperidine and pyrrolidine derivatives to generate acyliminium cations, which react with several carbon nucleophiles at the 2-position. Using this method, 2-substituted piperidine and pyrrolidine derivatives have been prepared.[10−13] While alkylation reactions of simple piperidine and pyrrolidine systems have been reported, there are few reports on 2,3-diastereoselectivity in a piperidine system,[14,15] and successful examples to control diastereoselectivity between the 2- and 3-positions have been limited. Hootele et al. reported that 3-acetoxy-2-methoxy-*N*-methoxycarbonylpiperidine derivatives reacted with the silyl enol ether of acetone in the presence of $TiCl_4$ to afford the corresponding adducts with moderate diastereoselectivities.[16] Correia et al. reported that 3-acetoxy-*N*-ethoxycarbonyl-2-methoxypiperidine reacted with trimethylsilyl cyanide (TMSCN) in the presence of $BF_3\cdot OEt_2$ to afford the corresponding adduct as a 1:1.3 mixture of *cis*/*trans* diastereomers.[17] In related systems, Batey et al. reported the 1,2-*cis* allylation of 2,3-dihydroxy five- and six-membered ring systems using allylboron reagents.[18] Quite recently, Craig et al. independently reported alkylation reactions in an *N*-tosylpiperidine system.[19] In most cases, however, stoichiometric amounts of classical Lewis acids are required, except for a TMSOTf system reported by Pilli et al.[20]

In the course of our investigations to develop new synthetic reactions and catalyst systems, we have found that catalytic amounts of metal triflates ($Sc(OTf)_3$, $Yb(OTf)_3$, $Hf(OTf)_4$, etc.) successfully activate various functional groups such as aldehydes, imines, acylhydrazones, acetals, aminals, etc. to achieve novel carbon−carbon bond-forming reactions.[21] One characteristic of these metal triflates is that catalytic activation of even basic nitrogen-containing compounds is possible. In this paper, we report stereoselective nucleophilic substitution reactions of simple *N*-benzyloxycarbonyl-2-methoxypiperidine (**3**) and 2,3-disubstituted piperidines (**4a**−**d**) with various silyl enolates using these metal triflates as catalysts.[22] The synthesis of febrifugine using a coupling reaction of 2,3-diacetoxy-*N*-benzyloxycarbonylpiperidine (**4b**) with a

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(8) For recent reviews on *C*-glycosylation of carbohydrates, see: (a) Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1. (b) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545. For selected examples of *C*-glycosylation of carbohydrates, see: (c) Nishikawa, T.; Ishikawa, M.; Isobe, M. *Synlett* **1999**, 123. (d) Dondoni, A.; Marra, A.; Massi, A. *Chem. Commun.* **1998**, 1741. (e) Lemaire-Audoire, S. S.; Vogel, P. *Tetrahedron Lett.* **1998**, *39*, 1345. (f) Hung, S.-C.; Lin, C.-C.; Wong, C.-H. *Tetrahedron Lett.* **1997**, *38*, 5419. (g) Komatsu, N.; Uda, M.; Suzuki, H.; Takahashi, T.; Domae, T.; Wada, M. *Tetrahedron Lett.* **1997**, *38*, 7215. (h) Stamos, D. P.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8643. (i) Nakamura, H.; Fujimaki, K.; Murai, A. *Tetrahedron Lett.* **1996**, *37*, 3153. (j) Alvarez, E.; Perez, R.; Rico, M.; Rodriguez, R. M.; Suarez, M. C.; Martin, J. D. *Synlett* **1996**, 1082. (k) Sasaki, M.; Nonomura, T.; Murata, M.; Tachibana, K. *Tetrahedron Lett.* **1994**, *35*, 5023. (l) Levy, D. E.; Dasgupta, F.; Tang, P. C. *Tetrahedron: Asymmetry* **1994**, *5*, 2265. (m) Duan, J. J.-W.; Kishi, Y. *Tetrahedron Lett.* **1993**, *34*, 7541. (n) Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M. D. *Tetrahedron Lett.* **1992**, *33*, 737.

(9) For recent reviews on biological properties of imino-sugars, see: (a) El Ashry, E. S. H.; Rashed, N.; Shobier, A. H. S. *Phamazie* **2000**, *55*, 251. (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645. (c) Asano, N. *Synth. Org. Chem. Soc. Jpn.* **2000**, *58*, 666.

(10) For reviews on *N*-acyliminium cation chemistry, see: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) de Koning, H.; Speckamp, W. N. In *Houben-Weyl, Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; 1995; Vol. E21b, p 1953. (c) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 1047. (d) Volkmann, R. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds; Pergamon: Oxford, 1991; Vol. 1, p 355. (e) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (f) Zaugg, H. E. *Synthesis* **1984**, 85. (g) Zaugg, H. E. *Synthesis* **1984**, 181.

(11) For related C−C bond-forming reactions of pyrrolidine and piperidine systems, see: (a) McAlonan, H.; Potts, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron Lett.* **2000**, *41*, 5411. (b) Matsumura, Y.; Kanda, Y.; Shirai, K.; Onomura, O.; Maki, T. *Org. Lett.* **1999**, *1*, 175. (c) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **1997**, *119*, 3409. (d) Louwrier, S.; Tuynman, A.; Hiemstra, H. *Tetrahedron* **1996**, *52*, 2629. (e) Ponzo, V. L.; Kaufman, T. S. *Synlett* **1995**, 1149. (f) Sato, T.; Mori, T.; Sugiyama, T.; Ishibashi, H.; Ikeda, M. *Heterocycles* **1994**, *37*, 245. (g) Morimoto, Y.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Tetrahedron Lett.* **1993**, *34*, 5773. (h) Narasaka, K.; Kohno, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3456. (i) Ahman, J.; Somfai, P. *Tetrahedron* **1992**, *48*, 9537. (j) Inokuchi, T.; Takagishi, S.; Akahoshi, F.; Torii, S. *Chem. Lett.* **1987**, 1553. (k) Shono, T.; Matsumura, Y.; Ogaki, M.; Onomura, O. *Chem. Lett.* **1987**, 1447. (l) Renaud, P.; Seebach, D. *Synthesis* **1986**, 424. (m) Irie, K.; Aoe, K.; Tanaka, T.; Saito, S. *J. Chem. Soc., Chem. Commun.* **1985**, 633. (n) Palasz, P. D.; Utley, J. H. P.; Hardstone, J. D. *J. Chem. Soc., Perkin Trans. 2* **1984**, 807. (o) Shono, T.; Matsumura, Y.; Onomura, O.; Kanazawa, T.; Habuka, M. *Chem. Lett.* **1984**, 1101. (p) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172.

(12) For alkylation reactions of piperidine derivatives with in situ prepared silyl enolates, see: (a) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717. (b) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *Tetrahedron Lett.* **1993**, *34*, 2729.

(13) For arylation reactions of a tetrahydroisoquinoline system, see: Bianchi, D. A.; Kaufman, T. S. *Synlett* **2000**, 801.

(14) For 2,5- and 2,6-diastereoselective C−C bond-forming reactions of pyrrolidine and piperidine systems, see: (a) Yang, C.-F.; Xu, Y.-M.; Liao, L.-X.; Zhou, W.-S. *Tetrahedron Lett.* **1998**, *39*, 9227. (b) David, M.; Dhimane, H.; Vanucci-Bacque, C.; Lhommet, G. *Synlett* **1998**, 206. (c) Dhimane, H.; Vanucci, C.; Lhommet, G. *Tetrahedron Lett.* **1997**, *38*, 1415. (d) Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3592. (e) Kaufman, T. S.; *J. Chem. Soc., Perkin Trans. 1* **1996**, 2497. (f) Pichon, M.; Figadere, B.; Cave, A. *Tetrahedron Lett.* **1996**, *37*, 7963. (g) Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299. (h) Herdeis, C.; Held, W. A.; Kirfel, A.; Schwabenländer, F. *Liebigs Ann. Chem.* **1995**, 1295. (i) Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S. *Tetrahedron* **1994**, *50*, 6221. (j) Shono, T.; Fujita, T.; Matsumura, Y. *Chem. Lett.* **1991**, 81. (k) Skrinjar, M.; Wistrand, L.-G. *Tetrahedron Lett.* **1990**, *31*, 1775. (l) Shono, T.; Matsumura, Y.; Onomura, O.; Sato, M. *J. Org. Chem.* **1988**, *53*, 4118. (m) Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K. *J. Org. Chem.* **1986**, *51*, 2590. (n) Renaud, P.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1704. (o) Thaning, M.; Wistrand, L. G. *Helv. Chim. Acta* **1986**, *69*, 1711. (p) Kraus, G. A.; Neuenschwander, K. *J. Chem. Soc., Chem. Commun.* **1982**, 134.

(15) For 2,3-diastereoselective C−C bond-forming reactions of pyrrolidine and piperidine systems, see: (a) Pohlit, A. M.; Correia, C. R. *Heterocycles* **1997**, *45*, 2321. (b) Johnson, C. R.; Golebiowski A.; Sundram, H. A.; Miller, M. W.; Dwaihy, R. L. *Tetrahedron Lett.* **1995**, *36*, 653. (c) Thaning, M.; Wistrand, L.-G. *J. Org. Chem.* **1990**, *55*, 1406. (d) Thaning, M.; Wistrand, L.-G. *Acta Chem. Scand.* **1989**, *43*, 290. See also ref 6e.

(16) Plehiers, M.; Hootele, C. *Can. J. Chem.* **1996**, *74*, 2444.

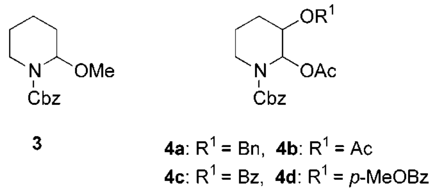
(17) Sugisaki, C. H.; Carroll, P. J.; Correia, C. R. D. *Tetrahedron Lett.* **1998**, *39*, 3413.

(18) Batey, R. A.; MacKay, B.; Santhakumar, V. *J. Am. Chem. Soc.* **1999**, *121*, 5075.

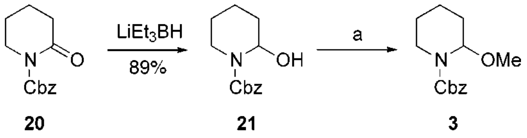
(19) Adelbrecht, J −C.; Craig, D.; Dymock, B. W.; Thorimbert, S. *Synlett* **2000**, 467.

(20) Pilli, R. A.; Dias, L. C. *Synth. Commun.* **1991**, *21*, 2213.

Chart 2. Piperidines as Acyliminium Cation Precursors



Scheme 2. Synthesis of 2-Methoxypiperidine 3



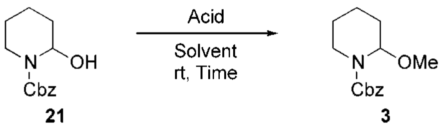
[a] See Table 1.

tin(II) enolate using a catalytic amount of $Sc(OTf)_3$ is also described.

Results and Discussion

Substrate Synthesis. We chose piperidine derivatives **3** and **4** as acyliminium cation precursors (Chart 2). *N*-Benzyloxycarbonyl-2-methoxypiperidine (**3**), which has a cyclic aminal structure and can be recognized as one of the simplest imino-sugars, was prepared from Cbz-protected 2-piperidone (**20**) by partial reduction with lithium triethylborohydride[6c] followed by transacetalization in methanol using a catalytic amount (1 mol %) of $Sc(OTf)_3$ in good yield (Scheme 2).[23] For transacetalization, the use of $Sc(OTf)_3$ was essential, and protonic acids such as *p*-toluenesulfonic acid (PTSA) and its pyridinium salt (PPTSA) decreased the yield as a result of competing dehydroxylation to form ene-carbamate (**24**) as a byproduct (Table 1). Separation of the ene-carbamate and 2-methoxy-*N*-benzyloxycarbonylpiperidine (**3**) by chromatography on silica gel was difficult. One mole % of $Sc(OTf)_3$ was more effective than 2 mol % of $Sc(OTf)_3$ in this reaction.

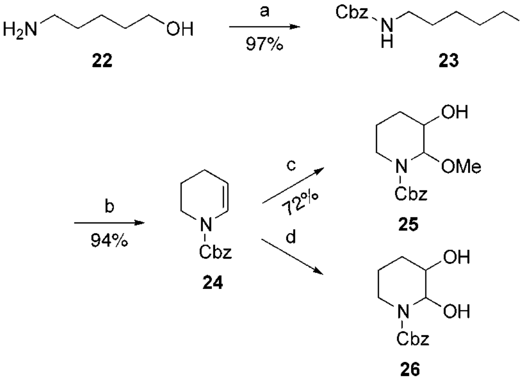
Table 1. Effect of Acids in Transacetalization



entry	acid	solvent	time (h)	yield %
1	PTSA[a] (10 mol %)	MeOH	17	53[c]
2	PPTSA[b] (10 mol %)	MeOH	17	64[c]
3	$Sc(OTf)_3$ (2 mol %)	CH_2Cl_2/MeOH (4:1)	2.5	80
4	$Sc(OTf)_3$ (1 mol %)	CH_2Cl_2/MeOH (4:1)	3	95

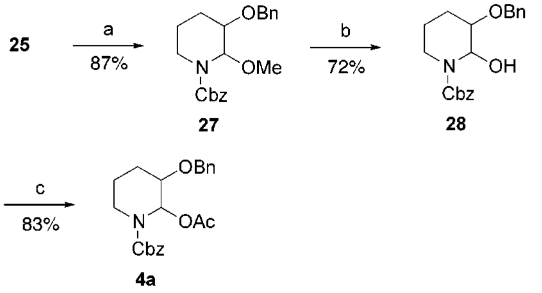
[a] *p*-Toluenesulfonic acid. [b] *p*-Toluenesulfonic acid pyridinium salt. [c] Ene-carbamate (**24**) was formed as a byproduct.

Scheme 3. Synthesis of Ene-Carbamate 24 and Oxidative Introduction of Hydroxyl Groups



[a] CbzCl. [b] Swern Oxidation, then HCl. [c] mCPBA, MeOH. [d] Table 2.

Scheme 4. Synthesis of 2-Acetoxy-3-benzyloxypiperidine



[a] BnBr, NaH, 18-crown-6. [b] $Sc(OTf)_3$ (5 mol %), CH_3CN-H_2O. [c] Ac_2O, DMAP, Et_3N.

It was reported that 2,3-diacetoxy-*N*-methoxycarbonylpiperidine was synthesized using an anodic oxidation method by Shono et al. They suggested that an acetoxy group at the 2-position was easily hydrolyzed in the workup procedure.[11o] In our work, various 2,3-disubstituted piperidines were synthesized by chemical oxidation of the ene-carbamate (**24**) as shown in Schemes 3−5. It was found that these piperidine derivatives were stable, suggesting that the acetoxy groups at the 2-positions were stabilized when the benzyloxycarbonyl group was used as the protecting group of the imino-nitrogen of the piperidine moiety.[24] Swern oxidation of Cbz-protected aminopentanol (**23**)[25] followed by acidic workup using hydrogen chloride afforded cyclic six-membered ene-carbamate (**24**) directly in excellent yield (Scheme 3).[26,27] The ene-carbamate (**24**) is a common key intermediate

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[21] For reviews, see: (a) Kobayashi, S. *Eur. J. Org. Chem.* **1950**, *15*, 5. (b) Kobayashi, S. *Synlett* **1994**, 689. See also: (c) Okitsu, O.; Oyamada, H.; Furuta, T.; Kobayashi, S. *Heterocycles* **2000**, *52*, 1143. (d) Manabe, K.; Oyamada, H.; Sugita, K.; Kobayashi, S. *J. Org. Chem.* **1999**, *64*, 8054. (e) Kawamura, M.; Kobayashi, S. *Tettahedron Lett.* **1999**, *40*, 3213. (f) Kobayashi, S.; Nagayama, S.; Busujima, T. *Tetrahedron* **1999**, *55*, 8739. (g) Kobayashi, S.; Sugita, K.; Oyamada, H. *Synlett* **1999**, 138. (h) Kobayashi, S.; Furuta, T.; Sugita, K.; Okitsu, O.; Oyamada, H. *Tetrahedron Lett.* **1999**, *40*, 1341. (i) Kobayashi, S.; Nagayama, S.; Busujima, T. *Chem. Lett.* **1999**, 71. (j) Kobayashi, S.; Akiyama, R. *Tetrahedron Lett.* **1998**, *39*, 9211. (k) Kobayashi, S.; Furuta, T.; Sugita, K.; Oyamada, H. *Synlett* **1988**, 1019. (l) Nagayama, S.; Kobayashi, S. *Chem. Lett.* **1998**, 685. (m) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840. (n) Oyamada, H.; Kobayashi, S. *Synlett* **1998**, 249.

[22] For a preliminary communication, see: Okitsu, O.; Suzuki, R.; Kobayashi, S. *Synlett* **2000**, 989.

[23] Similarly, ethoxy and *i*-propoxy derivatives were prepared using ethanol and 2-propanol, respectively.

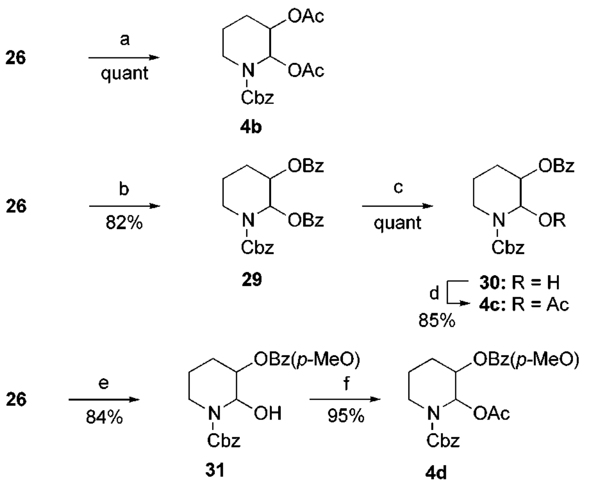
[24] In our preliminary study, it was revealed that *N*-*tert*-butoxycarbonyl-2,3-diacetoxypiperidine was unstable at room temperature and that the acetoxy group at the 2-position was easily converted to a hydroxy group.

[25] Hirai, Y.; Nagatsu, M. *Chem. Lett.* **1994**, 21.

[26] It was reported that oxidation of Cbz-protected 5-amino-1-hexanol using PCC on SiO_2 directly gave the corresponding ene-carbamate: Leclercq, S.; Thirionet, L.; Broeders, F.; Daloze, D.; Vander Meer, R.; Braeckman, J. C. *Tetrahedron* **1994**, *50*, 8465.

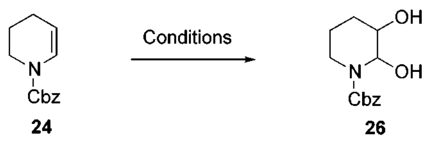
[27] Several ene-carbamates were obtained from lactams via partial reduction followed by dehydration: (a) Oliveira, D. F.; Miranda, P. C. M. L.; Correia, C. R. D. *J. Org. Chem.* **1999**, *64*, 6646. (b) Dieter, R. K.; Sharma, R. R. *J. Org. Chem.* **1996**, *61*, 4180.

Scheme 5. Synthesis of 2-Acetoxy-3-acyloxypiperidines



[a] Ac_2O, DMAP, Et_3N. [b] Bz_2O, DMAP, Et_3N. [c] AcOH−THF−water (quant *trans*/*cis* = 70/30) or 10 mol % of $Sc(OTf)_3$, CH_3CN−water (quant, *tran*/*cis* = 70/30). [d] Ac_2O, DMAP, Et_3N (*trans*/*cis* = 70/30). [e] (i) (*p*-MeO-Bz)$_2$O, DMAP, Et_3N, CH_2Cl_2, (ii) AcOH−THF−water (*trans*/*cis* = 67/33). [f] Ac_2O, DMAP, Et_3N.

Table 2. Osmylation of Ene-Carbamate 24



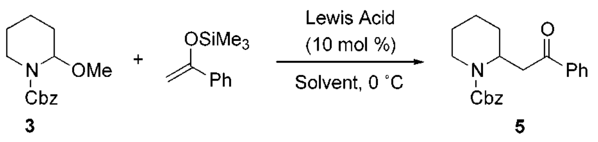
entry	conditions	yield (%)	*cis*/*trans*[a]
1	MC OsO_4 (5 mol %), NMO water/acetone/CH_3CN (1:1:1)	79	100/0
2	$K_2OsO_4 \cdot 2H_2O$ (1.7 mol %), $K_3Fe(CN)_6$, K_2CO_3, ${}^tBuOH$/water (1:1)	73	80/20

[a] Determined by ^1H NMR.

for the synthesis of 3-benzyloxy- and 3-acyloxypiperidine derivatives. The ene-carbamate (**24**) was oxidized to afford *N*-benzyloxycarbonyl-3-hydroxy-2-methoxypiperidine (**25**) using *m*-chloroperbenzoic acid,[17] and to afford *N*-benzyloxycarbonyl-2,3-dihydroxypiperidine (**26**) using osmylation, respectively. In the osmylation procedure,[28] microencapsulated OsO_4,[29] which was developed in this laboratory recently, promised to lead to the *cis*-diol without epimerization at the 2-position, whereas epimerization occurred when $K_2OsO_4 \cdot 2H_2O$ (Table 2) was used.[17]

Benzylation of **25** followed by $Sc(OTf)_3$-catalyzed hydrolysis, which is a reverse reaction of the transacetalization shown in Scheme 2, gave 3-benzyloxy-*N*-benzyloxycarbonyl-2-hydroxypiperidine (**28**) (Scheme 4). Acetylation was easily performed under standard conditions to give 2-acetoxy-3-benzyloxy-*N*-benzyloxycarbonypiperidine (**4a**). *N*-Benzyloxycarbonyl-2,3-dihydroxypiperidine (**26**) was converted to the corresponding diacetate (**4b**) by a standard method using 4-*N*,*N*-(dimethylamino)pyridine (DMAP) (Scheme 5). Slight epimerization (5%) was observed in this acetylation. When benzoic anhydride or *p*-methoxybenzoic anhydride[30] was used as the acylating reagent, the desired adduct was also obtained in high yield. The 2-positions of these diacylated compounds were readily hydrolyzed under the influence of a protonic acid or a Lewis acid in good yield.[31] The monoacylated products (**30** and **31**) thus obtained were successfully acetylated under catalytic DMAP conditions to afford unsymmetrical diacyloxy substituted piperidine derivatives (**4c** and **4d**) without any acyl transfer. In these procedures, DMAP would play an important role to suppress the acyl transfer.

Table 3. Effect of Lewis Acids and Solvents in Nucleophilic Substitution Reactions of 2-Methoxypiperidine 3



entry	Lewis acid	solvent	time (h)	yield (%)
1	$SnCl_4$	CH_2Cl_2	3	trace
2	$BF_3 \cdot Et_2O$	CH_2Cl_2	3	trace
3	$Sn(OTf)_2$	CH_2Cl_2	3	73
4	$Cu(OTf)_2$	CH_2Cl_2	3	81
5[a]	$Sc(OTf)_3$	CH_2Cl_2	1	89
6	$Sc(OTf)_3$	CH_3CN	1.5	95
7	$Sc(OTf)_3$	CH_3NO_2	1.5	92
8	$Hf(OTf)_4$	CH_3CN	40 min	77

[a] 0.5 equiv of $LiClO_4$ was used as an additive.

Alkylation of *N*-Benzyloxycarbonyl-2-methoxypiperidine. The reaction of **3** with the silyl enol ether derived from acetophenone was examined in the presence of a catalytic amount of a Lewis acid, and the results are summarized in Table 3. The desired adduct (**5**) was obtained in high yields when $Sc(OTf)_3$, $Cu(OTf)_2$, $Sn(OTf)_2$, and $Hf(OTf)_4$ were used as Lewis acid catalysts. On the other hand, conventional Lewis acids such as $SnCl_4$ and $BF_3 \cdot Et_2O$ gave only trace amounts of the products. The best result (95% yield) was obtained when 10 mol % of $Sc(OTf)_3$ was used in acetonitrile (entry 6). Acetonitrile and nitromethane were effective solvents when $Sc(OTf)_3$ was used as the catalyst, presumably because of their strong stabilization of the ionic intermediates (entries 6 and 7). Lithium perchlorate ($LiClO_4$) was effective for enhanced reactivity in dichloromethane (entry 5).

Various silyl enolates were then examined as carbon nucleophiles (Table 4). All silyl enol ethers and ketene silyl acetals employed worked well under these alkylation conditions. It was interesting to find that the ketene silyl acetal derived from dimethyl malonate[32] gave the corresponding alkylated product (**10**) in excellent yield (entry 6).

Diastereoselective Alkylation of 2,3-Disubstituted Piperidines. We then examined alkylation reactions of 2,3-disubstituted piperidine derivatives (**4a**−**d**). In our

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(28) For application of osmylation to imino-sugar synthesis, see: (a) Tschamber, T.; Rodriguez-Perez, E.-M.; Wolf, P.; Streith, J. *Heterocycles* **1996**, *42*, 669. (b) Streith, J.; Boiron, A.; Paillaud, J.-L.; Rodriguez-Perez, E.-M.; Strehler, C.; Tschamber, T.; Zehdner, M. *Helv. Chim. Acta* **1995**, *78*, 61. (c) Tschamber, T.; Backenstrass, F.; Neuburger, M.; Zehnder, M.; Streith, J. *Tetrahedron* **1994**, *50*, 1135. (d) Backenstrass, F.; Streith, J.; Tschamber, T. *Tetrahedron Lett.* **1990**, *31*, 2139. See also refs 11f, and 17−19.

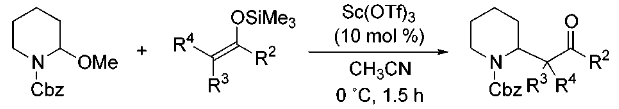
(29) (a) Nagayama, S.; Endo, M.; Kobayashi, S. *J. Org. Chem.* **1998**, *63*, 6094. (b) Kobayashi, S.; Endo, M.; Nagayama, S. *J. Am. Chem. Soc.* **1999**, *121*, 11229.

(30) Nangia, A.; Chandrasekaran, S. *J. Chem. Res. (S)* **1984**, 100.

(31) Epimerization was also observed in these cases.

(32) Ainsworth, C.; Chen, F.; Kuo, Y.-N. *J. Organomet. Chem.* **1972**, *46*, 59.

Table 4. Nucleophilic Substitution Reactions of 2-Methoxypiperidine

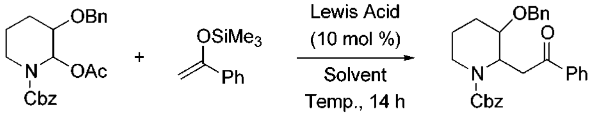


3 **5-10**

entry	R^2	R^3	R^4	product	yield (%)
1	Ph	H	H	**5**	95
2	^{t}Bu	H	H	**6**	89[a]
3	Ph	Me	H	**7**	91[b]
4	OMe	Me	Me	**8**	93
5	S^{t}Bu	H	H	**9**	93
6	OMe	COOMe	H	**10**	91[c]

[a] Room temperature, 18 h. [b] Room temperature, 3 h. Diastereomer ratio was 90/10, determined by ^{1}H NMR analysis. Relative stereochemical assignment was not made. [c] Three hours.

Table 5. Effect of Solvents and Lewis Acids in Nucleophilic Substitution Reactions of 2-Acetoxy-3-benzyloxypiperidine 4a



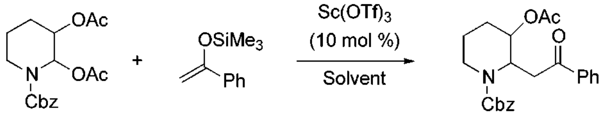
4a **11a**

entry	solvent	Lewis acid	temp (°C)	yield (%)	*trans*/*cis*[a]
1	CH_2Cl_2	$Cu(OTf)_2$	0	90	58/42
2	CH_2Cl_2	$Sc(OTf)_3$	0	99	58/42
3	CH_3CN	$Sc(OTf)_3$	0	93	54/46
4	toluene	$Sc(OTf)_3$	0	68	58/42
5	THF	$Sc(OTf)_3$	0	93	50/50
6	Et_2O	$Sc(OTf)_3$	0	84	43/57
7	Et_2O	$Sc(OTf)_3$	−45	60	28/72
8	DME	$Sc(OTf)_3$	−45	92	29/71
9	DME	$Sc(OTf)_3$	−78	trace	

[a] Determined by HPLC analysis.

preliminary study, it was revealed that acyl substituents (both benzoyloxy and acetoxy groups) at the 3-position of 2-methoxypiperidines decreased the reactivity of the alkylation. Namely, 3-acyloxy-2-methoxypiperidines gave low yields of alkylated adducts in the presence of a catalytic amount of $Sc(OTf)_3$.[33] Thus, we then decided to choose an acetoxy group as a more reactive leaving group at the 2-position in these systems. 2-Acetoxy-3-benzyloxy-*N*-benzyloxycarbonylpiperidine (**4a**) was first selected as a substrate, and the reaction with the silyl enol ether of acetophenone was investigated. The results are summarized in Table 5. It became clear that catalytic amounts of $Sc(OTf)_3$ as well as $Cu(OTf)_2$ were effective for the alkylation to afford the corresponding product (**11a**) in excellent yields and that ethereal solvents enhanced *cis*-selectivity at −45 °C (entries 7 and 8). When 1,2-dimethoxyethane (DME) was used as a solvent at −45 °C, excellent yield (92%) and the best *cis*-selectivity (*trans*/*cis* = 29/71) were obtained (entry 8). While these results would be explained by the anomeric effect, the low *cis*-selectivity compared to that in *C*-glycosylation reactions of carbohydrates[8] would be ascribed to flexibility of the *N*-substituted piperidine ring. 2-Acetoxy-3-benzyloxy-*N*-benzyloxycarbonylpiperidine (**4a**) existed as a mixture of rotamers based on the carbamate structure.

Table 6. Effects of Solvents in Nucleophilic Substitution Reactions of 2,3-Diacetoxypiperidine 4b

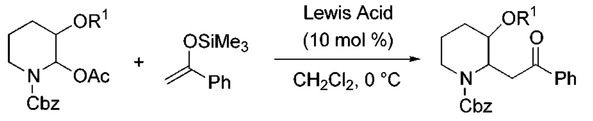


4b **11b**

entry	sovent	temp (°C)	time (h)	yield (%)	*trans*/*cis*[a]
1	CH_2Cl_2	0	3	74	83/17
2	$ClCH_2CH_2Cl$	0	2	70	80/20
3	CH_3CN	−20	40 min	96	65/35
4	toluene	0	4	54	76/24
5	THF	0	1.5	58	74/26
6	Et_2O	0	1.5	36	76/24
7	DME	0	1	80	80/20

[a] Determined by ^{1}H NMR.

Table 7. Effect of Lewis Acids and Substituents at the 3-Position in Nucleophilic Substitution Reactions of 2,3-Diacyloxypiperidine



4b-d **11b-d**

entry	R^1	Lewis acid	time (h)	yield (%)	*trans*/*cis*[a]
1	Ac (**4b**)	$Cu(OTf)_2$	3	60 (**11b**)	81/19
2	Ac (**4b**)	$Sc(OTf)_3$	3	74 (**11b**)	83/17
3	Ac (**4b**)	$Hf(OTf)_4$	0.5	73 (**11b**)	81/19
4	Bz (**4c**)	$Hf(OTf)_4$	0.5	74 (**11c**)	84/16
5	*p*-MeOBz (**4d**)	$Sc(OTf)_3$	3	91 (**11d**)	83/17
6	*p*-MeOBz (**4d**)	$Hf(OTf)_4$	1.5	88 (**11d**)	80/20[b]
7	*p*-MeOBz (**4d**)	$SnCl_4$	3	47 (**11d**)	84/16
8	*p*-MeOBz (**4d**)	$BF_3{\cdot}Et_2O$	3	trace (**11d**)	

[a] Determined by ^{1}H NMR analysis. [b] −45 °C.

On the other hand, it was found that 2,3-diacetoxy-*N*-benzyloxycarbonylpiperidine (**4b**) reacted with the silyl enol ether of acetophenone to afford the corresponding adduct (**11b**) with *trans*-selectivity.[34] Several reaction conditions were examined and the results are summarized in Table 6. The best *trans*-selectivity (*trans*/*cis* = 83/17) was obtained when dichloromethane was used as the solvent (entry 1). The *trans*-selectivity would be explained by neighboring group participation from the acetoxy group at the 3-position. It was found that the reactivity of **4b** (3-acetoxy derivative) in these reactions was lower than that of **4a** (3-benzyloxy derivative). We then examined Lewis acids and various acyloxy groups (acetoxy group (**4b**), a benzoyloxy group (**4c**), and a *p*-methoxybenzoyloxy group (**4d**)) at the 3-position of the substrate in this reaction system (Table 7). Among the catalysts tested, $Cu(OTf)_2$ $Sc(OTf)_3$, and $Hf(OTf)_4$ were effective, and among them $Hf(OTf)_4$ showed the highest activity (entry 3). Similar to the alkylation reaction of **3**, conventional Lewis acids such as $SnCl_4$ and $BF_3{\cdot}Et_2O$ were not effective (entries 7 and 8). It was revealed that higher yields were obtained using the *p*-methoxybenzoyloxy group compared to using the acetoxy or benzoyloxy group (entries 3, 4, and 6). It is presumed that the *p*-methoxybenzoyl group enhanced the electron density

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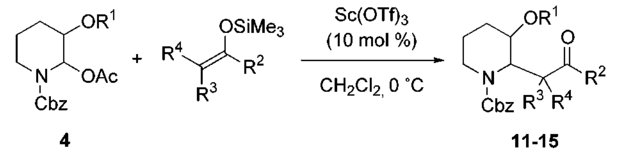
(33) The desired product was obtained in low yield (<20%), and the starting material was recovered. The diastereomer ratio was almost the same as that obtained by the reaction of **4b**.

(34) No isomerization from ***trans*-11b** to ***cis*-11b** occurred in the presence of $Sc(OTf)_3$ (10 mol %). In addition, it was found that the diastereomer ratio of the product was independent of the diastereomer ratio of the starting material.

Table 8. Nucleophilic Substitution Reactions of 3-Substituted 2-Acetoxypiperidines

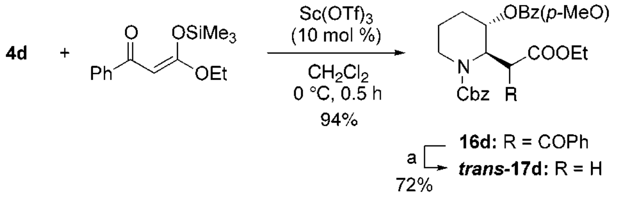


entry	R^1	R^2	R^3	R^4	time (h)	yield (%)	*trans/cis*[b]
1	Ac (**4b**)	Ph	H	H	3	74 (**11b**)	83/17
2	*p*-MeOBz (**4d**)	Ph	H	H	3	91 (**11d**)	83/17
3	Ac (**4b**)	^{t}Bu	H	H	1	84 (**12b**)	73/27
4	*p*-MeOBz (**4d**)	^{t}Bu	H	H	3	91 (**12d**)	74/26[c]
5	Bn (**4a**)	MeO	Me	Me	14[a]	82 (**13a**)	100/0
6	Ac (**4b**)	MeO	Me	Me	1.5	91 (**13b**)	100/0
7	*p*-MeOBz (**4d**)	MeO	Me	Me	1	94 (**13d**)	100/0
8	Ac (**4b**)	S^{t}Bu	H	H	1.5	92 (**14b**)	69/31[c]
9	*p*-MeOBz (**4d**)	S^{t}Bu	H	H	20 min	95 (**14d**)	67/33[c]
10	Ac (**4b**)	MeO	COOMe	H	3	90 (**15b**)	>90/10

[a] −45 °C. [b] Determined by ^{1}H NMR. [c] Determined by HPLC analysis.

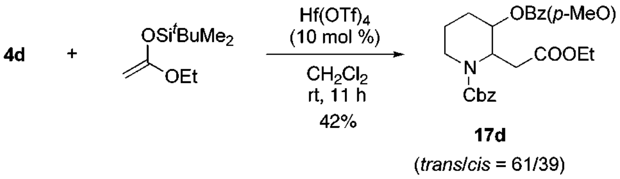
of the piperidine ring to increase the reactivity. While good levels of *trans*-selectivity were obtained in these reactions, the selectivity was lower compared to that observed in *C*-glycosylation reactions of carbohydrates.[8] This would also be explained by flexibility of the *N*-substituted piperidine rings.

Scheme 6. Reaction of 4d with the Silyl Enolate of Ethyl Benzoyl Acetate

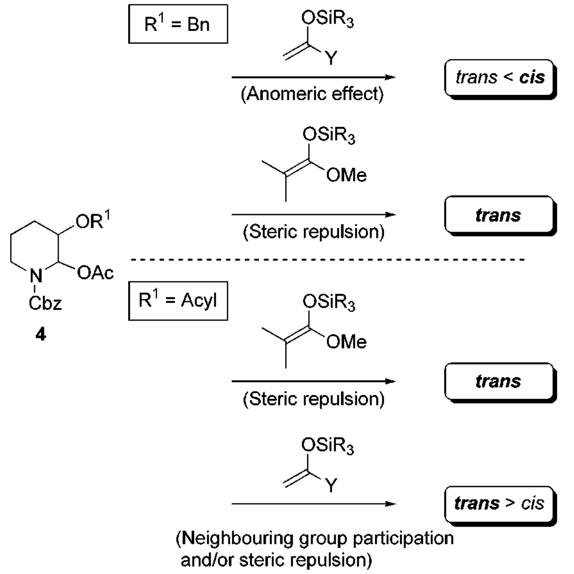


[a] LiOH, THF, reflux, 2 h.

Scheme 7. Reaction of 4d with the Silyl Enolate of Ethyl Acetate



Scheme 8. Diastereoselectivity of Reactions of 2,3-Disubstituted Piperidine Derivatives with Silyl Enolates



Various silyl enolates were next examined as nucleophiles for substitution reactions with 3-substituted 2-acetoxy-*N*-benzyloxypiperidine (**4**), and the results are summarized in Table 8. In all cases, a catalytic amount (10 mol %) of Sc(OTf)$_3$ was enough to complete these reactions, and the desired adducts were obtained in excellent yields. Both 3-acetoxy and 3-*p*-methoxybenzoyloxypiperidines showed good to moderate *trans*-selectivity when the silyl enol ether derived from pinacolone (entries 3 and 4) or the ketene silyl acetals derived from methyl isobutyrate (entries 6 and 7) and *tert*-butyl thioacetate (entries 8 and 9) were used. In particular, the ketene silyl acetal derived from methyl isobutyrate showed perfect *trans*-selectivity (entries 6 and 7). On the other hand, unexpectedly, the *trans*-product (**13a**) was also obtained as the sole diastereomer when a 3-benzyloxypiperidine derivative (**4a**) was used as the substrate (entry 5). This selectivity was opposite to that of the reaction of the same substrate (**4a**) with the silyl enol ether derived from acetophenone (cf. Table 7). Although no clear explanation is available at this stage, this selectivity might be attributed to the steric bulkiness of the nucleophile. The ketene silyl acetal derived from dimethyl malonate[32] also reacted with **4b** to afford the corresponding alkylated adduct (**15b**) in excellent yield with high *trans*-selectivity (entry 10). The ketene sily acetal derived from ethyl benzoyl acetate[35] also reacted with **4d** in excellent yield (Scheme 6). In this case, the diastereomer ratio was not determined at this stage. Retro Claisen condensation of the adduct (**16d**) using LiOH in refluxing THF gave a *trans*-derivative (***trans*-17d**) in 72% yield as the sole diastereomer. This result suggested that the reaction of **4d** with the ketene silyl acetal of ethyl benzoyl acetate proceeded with high *trans*-selectivity. On the other hand, the reaction of **4d** with the ketene silyl acetal of ethyl acetate afforded the corresponding adduct (**17d**) in moderate yield (42%) with moderate *trans*-selectivity (*trans/cis* = 61/39) (Scheme 7). These results also suggested that bulkiness of the nucleophiles influenced the diastereoselectivity in this alkylation.[36] Stereoselectivities in these reactions are summarized in Scheme 8.

Structure Determination. Most of the alkylation products exist as a mixture of rotamers based on the carbamate structure at room temperature. In addition, some diastereomers could not be separated.

Different from glycosylation reactions of carbohydrates, no general rules to determine the stereochemistry have been reported, and therefore, the structure of these compounds was determined as follows. The adduct **11b**

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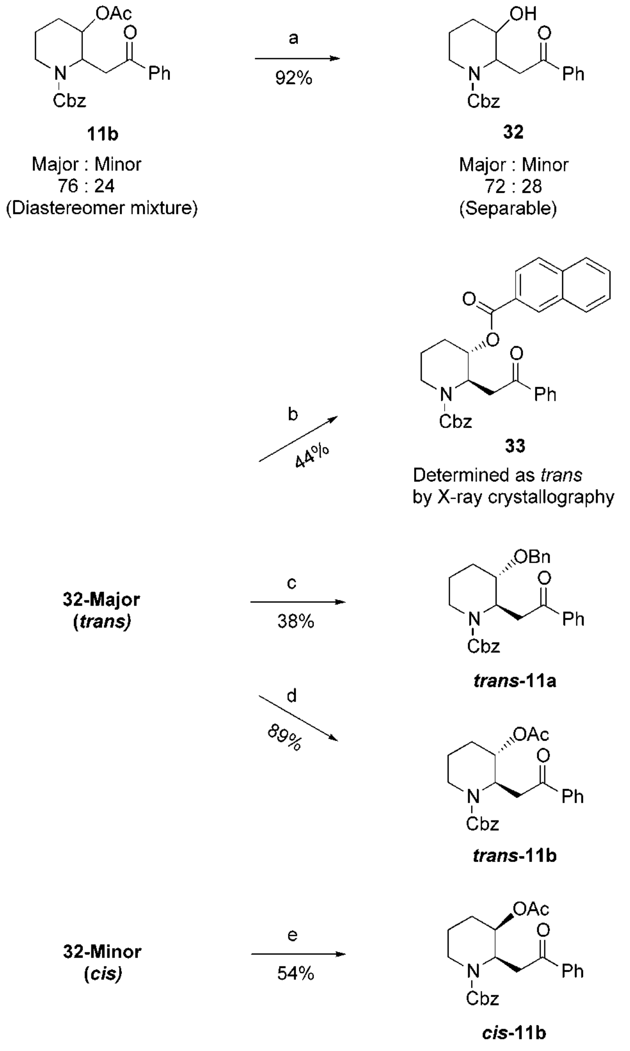
(35) Saigo, K.; Kurihara, H.; Miura, H.; Hongu, A.; Kubota, N.; Nohira, H. *Synth. Commun.* **1984**, *14*, 787.

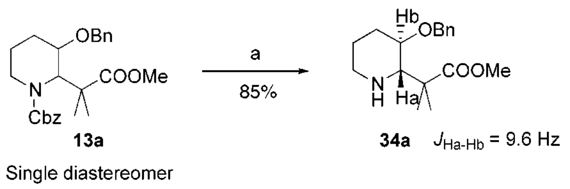
(36) In general, the stereochemistry in *C*-glycosylation as well as *O*-glycosylation of carbohydrates has been controlled using the anomeric effect and neighbouring group participation. On the other hand, there are some examples that the diastereoselectivity in *C*-glycosylation depends on the bulkiness of carbon nucleophiles. In those cases, the bulkiness of carbon nucleophiles enhances the *trans*-selectivity; see: (a) Minehan, T. G.; Kishi, Y. *Tetrahedron Lett.* **1997**, *38*, 6815. (b) Schmidt, R. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 406.

Scheme 9. Structure Determination Based on X-ray Crystallography



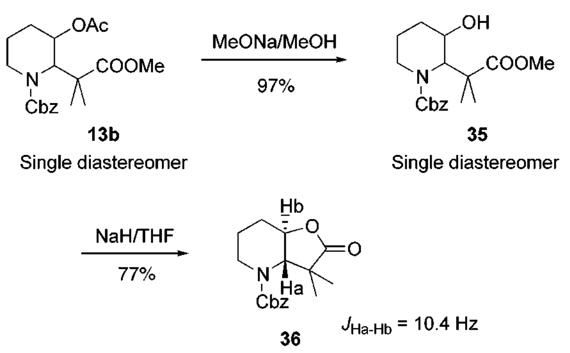
[a] MeONa in MeOH. [b] 2-Naphthoic acid, 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrogen chloride, Et_3N, DMAP (44%, 88% conversion). [c] $Cl_3CC{=}NH(OBn)$, TfOH (38%, 90% conversion). [d] Ac_2O, DMAP. [e] Ac_2O, DMAP.

Scheme 10. Structure Determination of 13a

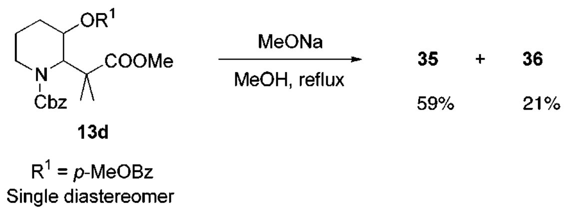


[a] H_2 (1 atm), 10% Pd−C in MeOH, rt.

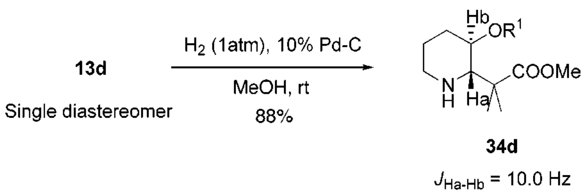
Scheme 11. Structure Determination of 13b



Scheme 12. Structure Determination of 13d



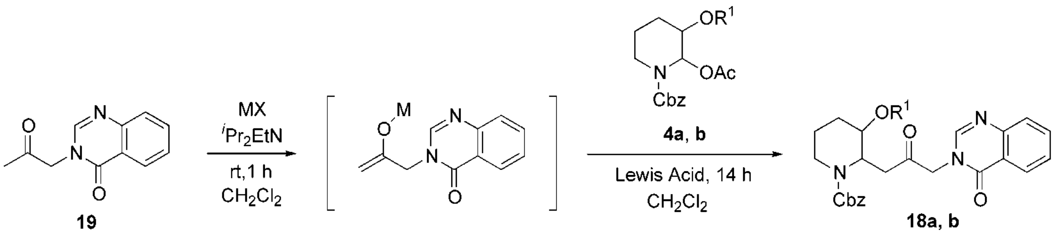
Scheme 13. Structure Determination of 13d



was observed as a diastereomer mixture, which was not separated by chromatography on silica gel. This compound was converted to a 3-hydroxy derivative (**32**), and the diastereomers of **32** were easily separated by chromatography on silica gel (Scheme 9). The separated major compound (highly polar) was derived to a 2-naphthoate derivative (**33**), whose *trans*-configuration was determined by X-ray crystallography. Authentic samples of ***trans*-11a**, ***trans*-11b**, and ***cis*-11b** were prepared from ***trans*-32** and ***cis*-32** according to standard procedures. Compounds **13a**, **13b**, and **13d** were also observed as mixtures of rotamers at room temperature. All of these compounds were determined as sole diastereomers by ^1H NMR analysis at 60−90 °C. *trans*-Configuration of **13a** was confirmed by ^1H NMR analysis after selective removal of the Cbz group by a catalytic hydrogenolysis. A coupling constant between two protons at the 2- and 3-positions of the piperidine ring of **34a** showed 9.6 Hz, which suggested *trans* configuration (Scheme 10). Compound **13b** was converted to a 3-hydroxypiperidine derivative (**35**), which also existed as the sole diastereomer determined by ^1H NMR analysis at 90 °C. Treatment of **35** with NaH induced cyclization to afford a lactone (**36**), whose configuration was determined as *trans* by ^1H NMR analysis (J_{Ha-Hb} = 10.4 Hz) (Scheme 11). Compound **13d** was also treated with NaOMe under refluxing MeOH to afford **35** and **36**, whose structure was determined to be *trans* (Scheme 12). Removal of the Cbz group of **13d** gave **34d**, whose ^1H NMR coupling constant (J_{Ha-Hb} = 10.0 Hz) also supported the *trans* configuration (Scheme 13). According to NMR analysis at 120 °C, it was suggested that **15b** existed as the sole diastereomer and as a mixture of rotamers as a result of the bulkiness of the malonate moiety. Removal of the Cbz group under 25% HBr/AcOH afforded **37**, whose ^1H NMR coupling constant (J_{Ha-Hb} = 10.0 Hz) showed the *trans* configuration (Scheme 14).

Synthesis of Febrifugine. We applied these nucleophilic substitution reactions to the synthesis of febrifugine. Previously, we reported catalytic asymmetric synthesis of febrifugines,[5] based on a tin(II)-mediated catalytic asymmetric aldol reaction[37] and a novel aqueous Mannich-type three-component reaction using a Lewis acid-surfactant combined catalyst (LASC). Our new strategy for the synthesis of febrifugine is shown in Scheme 1. The key steps are the preparation of a chiral piperidine

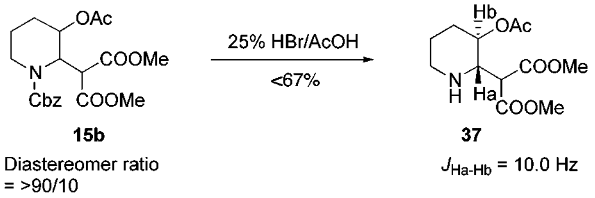
Table 9. Stereoselective Alkylation for the Synthesis of Febrifugine



entry	R^1	MX (equiv)	Lewis acid (equiv)	^{i}Pr$_2$EtN (equiv)	ketone (equiv)	temp	yield (%)	*trans*/*cis*[a]
1	Bn (**4a**)	Me$_3$SiOTf (3.0)	Sc(OTf)$_3$ (0.2)	3.1	1.5	0 °C to rt	71 (**18a**)	46/54
2	Ac (**4b**)	Me$_3$SiOTf (3.0)	Sc(OTf)$_3$ (0.2)	3.1	1.5	0 °C to rt	trace (**18b**)	
3	Ac (**4b**)	Sn(OTf)$_2$ (3.0)	none	3.1	1.5	0 °C to rt	37 (**18b**)	65/35
4	Ac (**4b**)	Sn(OTf)$_2$ (3.0)	Sc(OTf)$_3$ (0.2)	3.1	1.5	0 °C to rt	50 (**18b**)	77/23
5	Ac (**4b**)	Sn(OTf)$_2$ (4.0)	Sc(OTf)$_3$ (0.2)	4.1	2.0	0 °C to rt	63 (**18b**)	72/28
6	Ac (**4b**)	Sn(OTf)$_2$ (4.0)	Sc(OTf)$_3$ (0.2)	4.1	2.0	rt	70 (**18b**)	74/26
8	Ac (**4b**)	Sn(OTf)$_2$ (4.0)	Sc(OTf)$_3$ (0.2)	4.1	2.0	reflux[b]	69 (**18b**)	80/20

[a] Isolated yield. [b] 30 min.

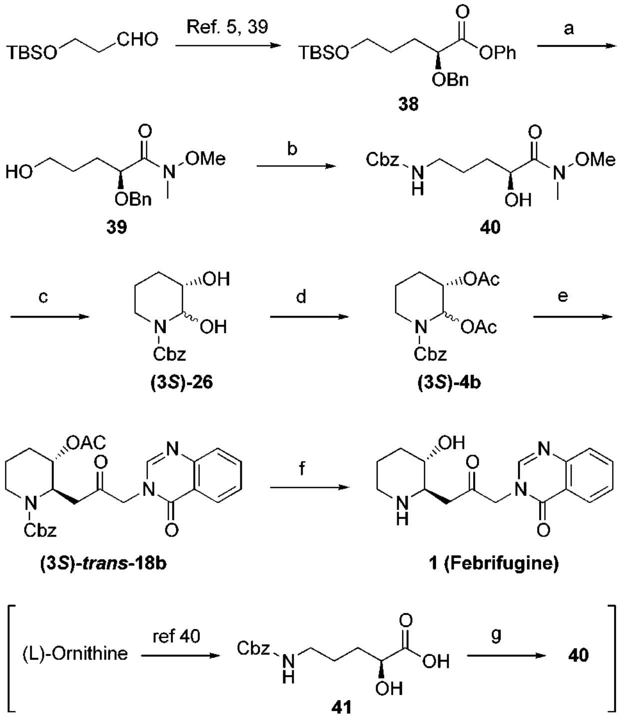
Scheme 14. Structure Determination of 15b



derivative as an acyliminium cation equivalent, and a diastereoselective coupling reaction of the piperidine derivative with a quinazolone (**19**) enolate.

We first examined the coupling reaction of piperidine derivatives with the silyl enol ether derived from **19**. In our preliminary trials, neither 3-benzyloxy nor 3-acetyloxypiperidine derivatives as substrates gave any products under the reaction conditions described in Tables 7 and 8. Next, we examined the use of the silyl enol ether which was freshly prepared in situ,[38] and the results are summarized in Table 9. 2-Acetyloxy-*N*-benzyloxycarbonyl-3-benzyloxypiperidine (**4a**) reacted with the silyl enol ether to afford the corresponding adduct (**18a**) in 71% yield; however, the diastereomer ratio was low (entry 1). On the other hand, the reaction of 2,3-diacetoxy-*N*-benzyloxycarbonylpiperidine (**4b**) with the in situ prepared silyl enol ether did not proceed under the same conditions (entry 2). In addition to the lower reactivity of the silyl enol ether, it was thought that the acetoxy group at the 3-position reduced the reactivity as a result of its electron-withdrawing property, while the benzyloxy group at that position enhanced the reactivity as a result of its electron-donating property. It is noted that these electronic properties of the substituents of the piperidine derivatives influenced the reactivity. We then used a tin(II) enolate,[39] which was considered to be more reactive than the silyl enolate. The tin(II) enolate was prepared in situ from the ketone (**19**), Sn(OTf)$_2$, and diisopropylethylamine (^{i}Pr$_2$EtN). The coupling reaction between **4b** and the tin(II) enolate proceeded smoothly in dichloromethane in the presence of a catalytic amount of Sc(OTf)$_3$ to afford the desired adduct (**18b**) in 69% yield with good *trans*-selectivity (*trans*/*cis* = 80/20) (entry 7).

Scheme 15. Synthesis of Febrifugine



[a] (i) Me$_3$Al, MeNH(OMe), (ii) 1 N HCl (65%, two steps). [b] (i) DEAD, PPh$_3$, DPPA, (ii) H$_2$ (10 atm), 10% Pd/C, (iii) CbzCl (42%, three steps). [c] LiAlH$_4$ in Et$_2$O (91%). [d] Ac$_2$O, DMAP, Et$_3$N (quant). [e] Table 9. [f] (i) 30% HBr/AcOH, (ii) MeONa/MeOH (25%, two steps). [g] 1-Ethyl-3-(dimethylaminopropyl)carbodiimide hydrogen chloride, MeNH(OMe)·HCl, Et$_3$N (89%).

Nonchiral piperidine derivatives were readily synthesized by oxidation of the ene-carbamate (**24**) as shown in Schemes 3−5. On the other hand, chiral 2,3-diacetoxy-*N*-benzyloxycarbonylpiperidine (**3*S*-4b**) was prepared according to Scheme 15. Phenyl (*S*)-2-benzyloxy-5-*tert*-butyldimethylsilyoxypentanoate (**38**) was obtained via

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(37) (a) Kobayashi, S.; Kawasuji, T. *Synlett* **1993**, 911. (b) Kobayashi, S.; Kawasuji, T.; Mori, N. *Chem. Lett.* **1994**, 217. (c) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1990**, 1455. (d) Kobayashi, S.; Horibe, M. *J. Am. Chem. Soc.* **1994**, *116*, 9805. (e) Kobayashi, S.; Hayashi, T. *J. Org. Chem.* **1995**, *60*, 1098. (f) Kobayashi, S.; Horibe, M. *Chem. Eur. J.* **1997**, *3*, 1472.

(38) Pilli et al. synthesized quinolizidin-2-nones using in situ prepared sily enol ethers of α,β-unsaturated ketones; see ref 12.

(39) Mukaiyama, T.; Stevens, R. W.; Iwasawa, N. *Chem. Lett.* **1982**, 353.

the tin(II)-mediated catalytic asymmetric aldol reaction.[5,37] This ester was easily transformed to Weinreb amide (**39**) using trimethyl aluminum. Thus, desilylation under acidic conditions followed by Mitsunobu reaction using diphenylphosporic azide (DPPA) converted the hydroxy group at the 5-position into an azide group. Palladium-catalyzed hydrogenolysis of both the azide and the benzyloxy groups afforded (*S*)-2-hydroxy-5-aminopentanoic acid Weinreb amide. A Cbz protection enabled the easy isolation of (*S*)-5-amino-*N*-benzyloxycarbonyl-2-hydroxypentanoic acid Weinreb amide (**40**), which was also synthesized from L-ornithine.[40] No epimerization was observed during these transformations, which was confirmed by the agreement of the optical rotations. Reduction of **40** using $LiAlH_4$ in ether provided a high yield of (3*S*)-*N*-benzyloxycarbonyl-2,3-dihydroxypiperidine (**(3*S*)-26**). Diacetylation and coupling with the tin(II) enolate of **19** followed by two-step deprotection afforded febrifugine (**1**), which was identical with an authentic sample previously synthesized in this laboratory.

Conclusion

We have developed diastereoselective nucleophilic substitution reactions of 2-methoxy- and 2-acyloxypiperidines using new types of metal triflates as catalysts. Different from carbohydrates and their glycosylation reactions, there have been limited reports on the preparation of piperidine derivatives and their substitution reaction. We have exploited simple and easy synthetic methods for the preparation of 2,3-disubstituted piperidines using chemical oxidation of the ene-carbamate (**24**), which was easily synthesized from commercially available 1-amino-5-pentanol (**22**). In the osmylation procedure, the microencapsulated osmium reagent, which promised an easy and safe osmylation procedure, gave perfect *cis*-selectivity. In addition, it was found that catalytic amounts of metal triflates effectively activated 2-methoxy- and 2-acetoxypiperidine derivatives and that the reactions with various silyl enolates proceeded smoothly to afford the corresponding alkylated adducts in high yields. It has been revealed that the anomeric effect, neighboring participation, and steric bulkiness were crucial factors to determine the stereoselectivity. While the benzyloxy group at the 3-position of piperidine derivatives gave the *cis*-selectivity, the acyloxy group at the same position was effective for obtaining the *trans*-selectivity, when the silyl enol ether derived from acetophenone was used as a nucleophile. These results would be explained by the anomeric effect and neighboring participation, similar to those in *C*-glycosylation of carbohydrates. On the other hand, when bulky nucleophiles were used in this alkylation, *trans*-adducts were obtained as a result of steric bulkiness of the reaction sites. Since no general rules for the determination of the stereochemistry of the products have been established, the relative configuration assignments were carefully performed. These reactions would provide useful information for glycosylation reactions of imino-sugars. Finally, the synthesis of febrifugine (**1**), a potent antimalarial agent, was performed based on the newly developed substitution reactions of piperidine derivatives.

Experimental Section

General Methods. Melting points were uncorrected. Column chromatography was conducted on Silica gel 60 (Merck), and preparative thin-layer chromatography was carried out using Wakogel B-5F. Dichloromethane and acetonitrile were distilled from P_2O_5 and then CaH_2 and dried over MS4A. Toluene was distilled and dried over MS4A. THF and ether were distilled over sodium/benzophenone. 1,2-Dimethoxyethane (DME) and 1,2-dichloroethane were distilled over calcium hydride and dried over MS4A. Methanol was distilled over magnesium and dried over MS3A. $Sn(OTf)_2$,[41] $Sc(OTf)_3$,[42] and $Hf(OTf)_4$[43] were prepared according to reported procedures. Commercially available $Cu(OTf)_2$ (TCI) was used without further purification. $SnCl_4$, $BF_3{\cdot}OEt_2$, and TMSOTf were distilled before use. All silyl enol ethers and ketene silyl acetals were prepared according to the modified House procedure.[44] The ketene silyl acetals of dimethyl malonate[32] and ethyl benzoyl acetate[35] were prepared according to reported procedures. All chemical compounds were purified on the basis of standard procedures.

Typical Procedure for $Sc(OTf)_3$-Catalyzed Substitution. A typical experimental procedure is described in the following reaction of **4d** with the silyl enolate of methyl isobutyrate. To a suspension of $Sc(OTf)_3$ (0.05 mmol, 10 mol %) in dichloromethane (1 mL) was added a mixture of **4d** (0.5 mmol) and the silyl enolate (0.85 mmol) in dichloromethane (1.5 mL). The mixture was stirred at 0 °C for 1 h. Saturated aqueous sodium hydrogen carbonate was then added to quench the reaction, and the aqueous layer was extracted with dichloromethane. After a usual workup, the product was isolated by silica gel column chromatography to afford *trans*-methyl 2-(3′-(*p*-methoxybenzoyl)-*N*-benzyloxycarbonylpiperidin-2′-yl)-2-methylpropionate (**13d**) in 94% yield (tr/c = >99/1, determined by ^1H NMR analysis). Pale yellow oil; IR (neat) 1703 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.28 (s, 1.5H), 1.31 (s, 1.5H), 1.38 (s, 1.5H), 1.42 (s, 1.5H), 1.52 (m, 1H), 1.76−1.96 (m, 3H), 3.03 (m, 1H), 3.68 (s, 3H), 3.85 (s, 1.5H), 3.86 (s, 1.5H), 4.13 (d, 1H, $J = 13.7$ Hz), 4.24 (d, 1H, $J = 12.8$ Hz), 4.43 (s, 0.5H), 4.50 (s, 0.5H), 4.90 (d, 0.5H, $J = 12.5$ Hz), 4.96 (d, 0.5H, $J = 12.5$ Hz), 5.04 (d, 0.5H, $J = 12.5$ Hz), 5.16 (d, 0.5H, $J = 12.5$ Hz), 5.31 (s, 0.5H), 5.38 (s, 0.5H), 6.77 (m, 2H), 7.07−7.19 (m, 9H), 7.27 (m, 2H), 7.80 (m, 2H); ^1H NMR (DMSO-d_6), rotamers, δ 1.29 (s, 3H), 1.37 (s, 1.5H), 1.38 (s, 1.5H), 1.51 (m, 1H), 1.79−1.90 (m, 3H), 2.96−3.13 (m, 1H), 3.69 (s, 3H), 3.90 (s, 3H), 4.20 (d, 1H, $J = 11.9$ Hz), 4.50 (d, 1H, $J = 5.7$ Hz), 5.03 (s, 1H), 5.14 (d, 0.5 H, $J = 12.9$ Hz), 5.24 (d, 0.5H, $J = 12.9$ Hz), 5.35 (d, 1H, $J = 12.6$ Hz), 7.04−7.45 (m, 7H), 7.85−7.92 (m, 2H); ^1H NMR (DMSO-d_6, 90 °C) δ 1.25 (s, 3H), 1.31 (s, 3H), 1.50 (m, 1H), 1.71−1.83 (m, 3H), 3.01 (m, 1H), 3.63 (s, 3H), 3.84 (s, 3H), 4.15 (d, 1H, $J = 13.9$ Hz), 4.49 (s, 1H), 4.87 (s, 2H), 5.30 (s, 1H), 6.98 (d, 2H, $J = 8.8$ Hz), 7.26 (br, 5H), 7.81 (d, 2H, $J = 8.8$ Hz); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.5, 19.9, 23.2, 23.6, 25.2, 25.4, 25.6, 40.2, 40.5, 40.8, 41.3, 45.68, 45.72, 52.13, 52.17, 55.37, 55.40, 61.7, 61.8, 67.2, 67.3, 67.6, 113.5, 113.6, 122.6, 122.7, 127.47, 127.54, 127.72, 127.84, 128.3, 128.4, 131.5, 131.6, 136.3, 137.6, 156.6, 156.7, 163.3, 163.4, 165.1, 176.8, 177.0; ^{13}C NMR (DMSO-d_6), rotamers, δ 19.1, 19.5, 22.9, 23.3, 24.9, 25.0, 45.27, 45.31, 52.1, 55.5, 60.9, 66.3, 66.5, 67.3, 113.97, 114.03, 121.9, 126.96, 127.03, 127.6, 127.7, 128.2, 128.4, 131.2, 136.5, 137.1, 155.6, 156.1, 163.16, 163.24, 164.3, 164.4, 175.98, 176.05; ^{13}C NMR (DMSO-d_6, 90 °C) δ 18.8, 22.8, 24.4, 24.7, 45.2, 51.5, 54.2, 55.1, 60.7, 66.1, 67.2, 113.6, 122.0, 126.7, 127.2, 127.8, 130.7, 136.4, 155.6, 162.9, 164.0, 175.5; HRMS (ESI) calcd for $C_{26}H_{32}NO_7$

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(40) Karanewsky, D. S.; Badia, M. C.; Cushman, D. W.; Deforrest, J. M.; Dejneka, T.; Loots, M. J.; Perri, M. G.; Petrillo, E. W., Jr.; Powell, J. R. *J. Med. Chem.* **1988**, *31*, 204.

(41) (a) Batchelor, R. J.; Ruddick, J. N. R.; Sams, J. R.: Aubke, F. *Inorg. Chem*. **1977**, *16*, 1414. (b) Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381.

(42) Thom, K. F. U.S. Patent 3615169, 1971; *Chem. Abstr.* **1972**, *76*, 5436a.

(43) (a) Hachiya, I.; Moriwaki, M.; Kobayashi, S. *Tetrahedron Lett.* **1995**, *36*, 409. (b) Hachiya, I.; Moriwaki, M.; Kobayashi, S. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 2053.

(44) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.

470.2179, found $(M + H)^+$ 470.2149. Anal. Calcd for $C_{26}H_{31}NO_7$: C, 66.51; H, 6.65; N, 2.98. Found: C, 66.46; H, 6.80; N, 3.00.

2-(*N*-Benzyloxycarbonylpiperidin-2-yl)acetophenone (5). Mp 78−79 °C; IR (KBr) 1684 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.30−1.80 (m, 6H), 2.96 (m, 1H), 3.10−3.40 (m, 2H), 4.11 (m, 1H), 4.91 (m, 1H), 5.09 (m, 2H), 7.26−7.56 (m, 8H), 7.94 (m, 2H); ^{13}C NMR ($CDCl_3$), rotamers, δ 18.7, 25.2, 27.8, 39.2, 39.9, 48.3, 67.1, 127.8, 127.9, 128.2, 128.4, 128.6, 133.1, 136.6, 136.7, 155.3, 198.3; HRMS (ESI) calcd for $C_{21}H_{24}NO_3$ 338.1756, found $(M + H)^+$ 338.1748. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.69; H, 7.02; N, 4.14.

***N*-Benzyloxycarbonyl-2-hydroxypiperidine (21).**[6c] To a solution of *N*-benzyloxycarbonyl piperidone (**20**) (2.54 mmol) in dry THF (4 mL) was added a solution of $LiEt_3BH$ in THF (1 M, 4 mL) at −78 °C. The reaction mixture was stirred for 1 h at the same temperature, and the reaction was quenched with water (1 mL) and warmed to room temperature. To the mixture were added a saturated aqueous $NaHCO_3$ solution (10 mL) and then 30% aqueous H_2O_2 solution (2 mL). After stirring for 1 h, the mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to afford **21** in 89% yield as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.44−1.90 (m, 7H), 3.18 (td, 1H, J = 12.6, 3.0 Hz), 3.89 (d, 1H, J = 11.7 Hz), 5.15 (s, 2H), 5.79 (m, 1H), 7.32−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 17.6, 24.7, 30.5, 39.4, 67.2, 75.0, 125.6, 127.9, 128.1, 136.4, 160.2.

***N*-Benzyloxycarbonyl-2-methoxypiperidine (3)** (Table 1, entry 2). A solution of *p*-toluenesulfonic acid pyridinium salt (0.04 mmol) and **21** (0.4 mmol) in MeOH (2 mL) was stirred for 17 h at room temperature. The solvent was evaporated in vacuo, and the residue was partitioned between ethyl acetate and a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to afford **3** in 64% yield as a colorless oil (Table 1, entry 4). A solution of $Sc(OTf)_3$ (0.04 mmol) and **21** (4.0 mmmol) in a mixture of CH_2Cl_2 (5 mL) and MeOH (2.5 mL) was stirred for 3 h at room temperature. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution, and the mixture was extracted with CH_2Cl_2 (twice). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to afford **3** in 95% yield as a colorless oil. IR (neat) 1702 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.25−2.03 (m, 6H), 2.98 (q, 1H, J = 14.7 Hz), 3.18 (s, 1.5 H), 3.25 (s, 1.5 H), 3.98 (t, 1H, J = 14.7 Hz), 5.16 (m, 2H), 5.34 (s, 0.5H), 5.43 (s, 0.5H), 7.26−7.60 (m, 5H); ^{13}C NMR ($CDCl_3$), rotamers, δ 18.4, 24.97, 25.1, 30.0, 30.3, 38.7, 39.0, 54.3, 55.6, 67.0, 67.2, 82.0, 17.8, 128.0, 128.5, 136.6, 154.1; MS (EI) m/z 249 (M^+). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.39; H, 7.75; N, 5.65.

5-Amino-*N*-benzyloxycarbonylpentanol (23).[25] To a solution of 5-aminopentanol (**22**, 0.184 mol) and $NaHCO_3$ (0.550 mol) in water (100 mL) was added a solution of benzyloxycarbonyl chloride (0.248 mol) in THF (100 mL) at 0 °C. The reaction mixture was warmed to room temperature and then vigorously stirred for 12 h at the same temperature. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was triturated with *n*-hexane. The resulting powder was collected by filtration, washed with ether (3 times), and dried under reduced pressure to afford **23** in 97% yield. This material was used without further purification. Mp 42 °C; IR (KBr) 3332, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36−1.64 (m, 7H), 3.20 (q, 2H, J = 6.5 Hz), 3.63 (s, 2H), 4.78 (s, 1H), 5.09 (s, 2H), 7.26−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.9, 29.8, 32.2, 40.9, 62.7, 66.6, 128.1, 128.2, 128.5, 136.6, 154.4; HRMS (ESI) calcd for $C_{13}H_{20}NO_3$ 238.1443, found $(M + H)^+$ 238.1437.

***N*-Benzyloxycarbonyl-1,2,3,4-tetrahydropyridine (24).** To a solution of oxalyl chloride (44.2 mmol) in CH_2Cl_2 (60 mL) was added dimethyl sulfoxide (6.5 mL, 91.5 mmol) at −78 °C, and the mixture was stirred for 2 min. A solution of **23** (35.5 mmol) in CH_2Cl_2 (50 mL) was added dropwise over 20 min below −60 °C, and the reaction mixture was stirred at −78 °C for 1 h. The reaction was quenched with triethylamine (188 mmol) at the same temperature. The mixture was warmed to 0 °C for 1 h and an aqueous 3 N HCl solution was added. The suspension was warmed to room temperature and stirred vigorously for 15 h at the same temperature. The mixture was extracted with CH_2Cl_2 (twice). The combined organic layers were washed with water, a saturated aqueous $NaHCO_3$ solution, and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by silica gel chromatography to afford **24** in 94% yield as a colorless oil. IR (neat) 1705, 1655 cm^{-1}; ^1H NMR ($CDCl_3$), rotamers, δ 1.81−1.87 (m, 2H), 2.01−2.07 (m, 2H), 3.63 (t, 2H, J = 5.5 Hz), 4.85 (dt, 0.5H, J = 8.4, 4.0 Hz), 4.96 (dt, 0.5H, J = 8.4, 3.8 Hz), 5.18 (s, 2H), 6.79 (d, 0.5 H, J = 8.4 Hz), 6.88 (d, 0.5 H, J = 8.4 Hz), 7.31−7.63 (m, 5H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.7, 21.2, 21.4, 21.6, 42.2, 42.4, 67.3, 67.4, 106.4, 106.7, 124.9, 125.4, 128.0, 128.1, 128.5, 136.4, 151.8; HRMS (ESI) calcd for $C_{13}H_{16}NO_2$ 218.1181, found $(M + H)^+$ 218.1156.

***N*-Benzyloxycarbonyl-3-hydroxy-2-methoxypiperidine (25).** To a solution of **24** (1.17 mmol) in MeOH (4 mL) was added *m*-chloroperbenzoic acid (1.38 mmol) portionwise at 0 °C, and the mixture was stirred for 1 h at the same temperature. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution, and the mixture was extracted with CH_2Cl_2 (three times). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to afford **25** in 72% yield as a colorless oil (a mixture of diastereomers). IR (neat) 3453, 1702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23−1.90 (m, 4H), 2.43 (br, 1H), 2.77−2.96 (m, 1H), 3.20−3.43 (m, 3H), 3.55 (m, 1H), 3.84−3.95 (m, 1H), 5.08−5.29 (m, 2H), 5.32−5.44 (m, 1H), 7.27−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.8, 23.8, 24.1, 25.6, 28.0, 37.5, 37.9, 38.7, 55.0, 66.1, 67.3, 67.5, 69.0, 69.2, 84.2, 84.4, 85.3, 127.8, 128.1, 128.2, 128.50, 128.55, 136.2, 136.4, 155.3, 155.7; HRMS (ESI) calcd for $C_{14}H_{19}NO_4Na$ 288.1212, found $(M + Na)^+$ 288.1205. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.32; N, 5.28. Found: C, 63.29; H, 7.18; N, 5.28.

***N*-Benzyloxycarbonyl-2,3-dihydroxypiperidine (26). Osmylation using microencapsulated OsO_4** (Table 2, entry 1). To a solution of **24** (10.4 mmol) and *N*-methylmorpholine (50% aqueous solution, ca. 16 mmol) in a mixture of acetonitrile (12 mL), acetone (12 mL), and water (12 mL) was added microencapsulated osmium tetraoxide[29] (0.42 mmol/g, 0.52 mmol) at room temperature. The reaction mixture was stirred for 24 h at the same temperature. The catalyst was filtered off and washed with acetonitrile (five times). The filtrate was evaporated in vacuo. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (twice). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to afford **26** in 79% (*cis*/*trans* = 100/0) yield as a colorless oil. **26** (*cis*): IR (neat) 3419, 1682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39−1.83 (m, 4H), 2.71 (s, 1H), 3.03 (dt, 1H, J = 12.9, 2.7 Hz), 3.58 (m, 1H), 3.83 (d, 1H, J = 11.6 Hz), 5.13 (s, 2H), 5.73 (d, 1H, J = 3.3 Hz), 7.26−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.5, 26.8, 38.2, 67.6, 69.0, 76.5, 128.0, 128.2, 128.6, 136.2, 155.9; HRMS (ESI) calcd for $C_{13}H_{17}NO_4Na$ 274.1056, found $(M + Na)^+$ 274.1041. Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.85; H, 7.07; N, 5.54.

Osmylation of 24 by a standard method (Table 2, entry 2). To a solution of **24** (29.9 mmol), methanesulfonyl amide (2.31 mmol), potassium carbonate (91.3 mmol), and potassium ferricyanide (III) (90.2 mmol) in a mixture of water (225 mL) and *tert*-butyl alcohol (225 mmol) was added potassium osmate dihydrate (0.510 mmol) at room temperature. The reaction mixture was stirred for 24 h and the reaction was quenched with an aqueous solution of sodium thiosulfate (10.1 mmol).

The mixture was extracted with ethyl acetate (three times). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to afford **26** in 73% yield as a mixture of diastereomers (*cis*/*trans* = 80/20). The diastereomer ratio was determined by ^{1}H NMR. **26** (*cis*/*trans* = 80/20): ^{1}H NMR ($CDCl_3$) δ 1.39−1.88 (m, 4H), 2.99−3.21 (m, 2H), 3.53−3.63 (m, 1H), 3.79−3.89 (m, 1H), 5.10 (s, 2H), 5.59 (d, 0.2 H, J = 2.4 Hz), 5.71 (d, 0.8 H, J = 3.3 Hz), 7.26−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.6, 23.4, 24.8, 26.5, 27.3, 38.0, 38.8, 66.9, 67.4, 69.0, 76.4, 77.2, 78.0, 127.77, 127.8, 128.03, 128.08, 128.4, 128.5, 136.1, 155.9.

3-Benzyloxy-*N*-benzyloxycarbonyl-2-methoxypiperidine (27). To a suspension of NaH (60% dispersion in mineral oil, 12.0 mmol) in dry THF (10 mL) was added a mixture of 18-crown-6 (0.57 mmol) and **25** (11.4 mmol) in dry THF (10 mL) at room temperature. The mixture was stirred for 30 min at the same temperature and then cooled to 0 °C. Benzyl bromide (17.1 mmol) was added at the same temperature, and the reaction mixture was then stirred for 10 h at room temperature. The reaction was quenched with water, and the mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to afford **27-major** (more polar) and **27-minor** (less polar) in 50% and 37% yields as a colorless oil, respectively. These compounds were used as a mixture of diasereomers in the further transformation. **27-major:** IR (neat) 1702 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.46−1.87 (m, 4H), 2.83−2.96 (m, 1H), 3.22−3.33 (m, 3H) 3.37−3.42 (m, 1H), 3.82−3.93 (m, 1H), 4.51−4.68 (m, 2H), 5.07−5.20 (m, 2H), 5.35−5.58 (m, 1H), 7.25−7.35 (m, 10H); ^{13}C NMR ($CDCl_3$), rotamers, δ 23.8, 24.2, 24.4, 24.7, 37.7, 38.0, 54.8, 55.2, 67.2, 67.3, 70.5, 70.7, 76.0, 76.2, 82.3, 82.8, 127.6, 127.7, 127.8, 127.9, 128.1, 128.3, 128.5, 136.4, 138.2, 138.3, 155.1, 155.6; HRMS (ESI) calcd for $C_{21}H_{25}NO_4$ 355.1784, found $(M + Na)^+$ 378.1659. Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.91; H, 7.07; N, 3.96. **27-minor:** IR (neat) 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.26−1.92 (m, 4H), 2.91−3.02 (m, 1H), 3.93−3.29 (m, 3H) 3.54−3.59 (m, 1H), 3.93−4.06 (m, 1H), 4.48−4.68 (m, 2H), 5.11−5.18 (m, 2H), 5.34−5.52 (m, 1H), 7.10−7.35 (m, 10H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.2, 19.4, 23.6, 23.9, 38.2, 38.6, 54.5, 54.9, 67.1, 70.5, 70.8, 72.8, 73.0, 82.4, 82.9, 127.2, 127.4, 127.5, 127.6, 127.8, 127.9, 128.3, 128.4, 136.6, 136.7, 138.4, 156.0, 156.4; HRMS (ESI) calcd for $C_{21}H_{25}NO_4Na$ 378.1682, found $(M + Na)^+$ 378.1659. Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.91; H, 7.07; N, 3.96.

3-Benzyloxy-*N*-benzyloxycarbonyl-2-hydroxypiperidine (28). To a solution of **27** (a mixture of diastereomers, 10.0 mmol) in a mixture of acetonitrile (80 mL) and water (20 mL) was added $Sc(OTf)_3$ (0.50 mmol) at room temperature. The reaction mixture was stirred for 24 h at the same temperature, and the reaction was quenched with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to afford **28** in 72% yield as colorless oil (a mixture of diastereomers). IR (neat) 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.42−1.47 (m, 1H), 1.70−1.91 (m, 4H), 3.09−3.18 (m, 1H), 3.42−3.61 (m, 1H) 3.54−3.59 (m, 1H), 3.87−3.91 (m, 1H), 4.53−4.61(m, 2H), 5.10−5.17(m, 2H), 5.78−5.89 (m, 1H), 7.25−7.36 (m, 10H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.0, 22.9, 23.9, 38.8, 67.3, 67.4, 70.5, 70.7, 73.5, 75.9, 76.7, 127.4, 127.5, 127.7, 127.8, 128.0, 128.1, 128.3, 128.5, 136.3, 136.4, 137.8, 138.4; HRMS (ESI) calcd for $C_{20}H_{23}NO_4Na$ 364.1525, found $(M + Na)^+$ 364.1564. Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.30; H, 6.86; N, 4.14.

2-Acetoxy-3-benzyloxy-*N*-benzyloxycarbonylpiperidine (4a). To a solution of **28** (1.00 mmol) and 4-*N*,*N*-(dimethylamino)pyridine (0.10 mmol) in triethylamine (5 mL) was added acetic anhydride (4.0 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h at the same temperature. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution at 0 °C. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water (five times), saturated aqueous $NaHCO_3$ solution, and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to afford **4a** in 83% yield as a colorless oil (a mixture of diastereomers). IR (neat) 1745, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.48−1.87 (m, 4H), 2.07 (s, 3H), 2.96−3.02 (m, 1H), 3.43−3.48 (m, 1H), 3.90−3.93 (m, 1H), 4.47−4.50 (m, 2H), 5.12−5.21 (m, 2H), 4.71−4.74 (m, 1H), 7.25−7.36 (m, 10H); ^{13}C NMR ($CDCl_3$), rotamers, δ 20.8, 23.2, 25.1, 39.2, 67.3, 67.6, 70.3, 70.8, 74.7, 74.8, 127.4, 127.5, 127.6, 127.7, 127.9, 128.0, 128.2, 128.4, 136.0, 137.8, 154.8, 159.3; HRMS (ESI) calcd for $C_{22}H_{25}NO_5Na$ 406.1631, found $(M + Na)^+$ 406.1669. Anal. Calcd for $C_{21}H_{25}NO_4$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.86; H, 6.59; N, 3.63.

2,3-Diacetoxy-*N*-benzyloxycarbonylpiperidine (4b). To a solution of **26** (*cis*/*trans* = 100/0, 1.75 mmol) and 4-*N*,*N*-(dimethylamino)pyridine (0.18 mmol) in triethylamine (1.5 mL) was added acetic anhydride (10.6 mmol) at room temperature. The reaction mixture was stirred for 3 h at the same temperature. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution at 0 °C. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water (five times), saturated aqueous $NaHCO_3$ solution, and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to afford **4b** quantitatively as a colorless oil (*cis*/*trans* = 95/5). The diastereomer ratio was determined by ^{1}H NMR. IR (neat) 1744, 1714, 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.60−1.87 (m, 4H), 2.01 (s, 3H), 2.07 (s, 3H), 3.01 (t, 1H, J = 11.6 Hz), 3.96 (d, 1H, J = 9.3 Hz), 4.88 (m, 1H), 5.11 (d, 1H, J = 12.5 Hz), 5.21 (d, 1H, J = 12.5 Hz), 6.69 (d, 0.05H, J = 2.6 Hz), 6.99 (d, 0.95H, J = 3.3 Hz), 7.26−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$), rotamers, δ 20.78, 20.84, 23.0, 39.2, 67.8, 69.4, 75.4, 128.0, 128.1, 128.5, 136.0, 154.8, 169.2, 170.0; HRMS (ESI) calcd for $C_{17}H_{21}NO_6Na$ 358.1267, found $(M + Na)^+$ 358.1231. Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.83; H, 6.34; N, 4.15.

Similarly, **(3*S*)-4b** (*cis*/*trans* = 57/43) was obtained from **(3*S*)-26** (*cis*/*trans* = 56/44). **(3*S*)-4b** (*cis*/*trans* = 57/43): $[\alpha]^{25}_{D}$ +6.1 (c = 0.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$), rotamers, δ 1.56−2.09 (m, 10H), 2.96−3.05 (m, 1H), 3.94−4.08 (m, 1H), 4.84−4.91 (m, 1H), 5.09−5.23 (m, 2H), 6.69 (d, 0.43H, J = 2.6 Hz), 6.99 (d, 0.57H, J = 3.3 Hz), 7.26−7.37 (m, 5H).

***N*-Benzyloxycarbonyl-2,3-dibenzoyloxypiperidine (29).** To a solution of **26** (1.19 mmol) and 4-*N*,*N*-(dimethylamino)pyridine (0.12 mmol) in triethylamine (4 mL) was added benzoic anhydride (2.98 mmol) at room temperature. The reaction mixture was stirred for 20 h at the same temperature. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution at 0 °C. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water (five times), a saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to afford **29** in 82% yield as a colorless oil. IR (neat) 1735, 1715, 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.80−2.13 (m, 4H), 3.21 (t, 1H, J = 13.1 Hz), 4.12 (m, 1H), 5.15−5.24 (m, 3H), 7.26−7.62 (m, 1H), 7.87 (d, 2H, J = 7.7 Hz), 8.06 (d, 2H, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$), rotamers, δ 23.1, 24.4, 39.5, 68.0, 70.6, 76.3, 76.4, 128.0, 18.1, 128.3, 128.5, 129.7, 129.8, 130.0, 133.0, 133.3, 136.0, 154.8, 164.6, 165.5; HRMS (ESI) calcd for $C_{27}H_{25}NO_6Na$ 482.1580, found $(M + Na)^+$ 482.1617. Anal. Calcd for $C_{27}H_{25}NO_6$: C, 70.58; H, 5.48; N, 3.05. Found: C, 70.46; H, 5.70; N, 2.97.

3-Benzoyloxy-*N*-benzyloxycarbonyl-2-hydroxypiperidine (30). Method A. A solution of **29** (0.352 mmol) in a mixture of THF (0.6 mL), water (0.6 mL) and acetic acid (1.8 mL) was stirred for 12 h at room temperature. The reaction was carefully quenched with saturated aqueous $NaHCO_3$ solution at 0 °C, and the mixture was extracted with ethyl acetate (three times). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (five times), water and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to afford **30** quantitatively as a colorless oil (a mixture of diastereomers). **Method B.** To a suspension of **29** (0.12 mmol) in a mixture of acetonitrile (0.8 mL) and water (0.2 mL) was added $Sc(OTf)_3$ (0.012 mmol) at room temperature. The reaction mixture was stirred for 24 h at the same temperature and the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to afford **30** quantitatively as a colorless oil (*cis*/*trans* = 30/70). The diastereomer ratio was determined by ^{1}H NMR. **30** (*cis*/*trans* = 30/70): IR (neat) 3444, 1716, 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.50−2.11 (m, 5H), 3.24 (m, 1H), 4.00 (m, 1H), 5.08−5.18 (m, 3H), 5.84 (s, 0.7H), 5.99 (s, 0.3H), 7.26−7.56 (m, 8H), 7.98 (d, 1.4H, *J* = 7.7 Hz), 8.06 (d, 0.6H, *J* = 7.7 Hz); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.5, 22.9, 23.0, 23.4, 67.3, 67.6, 69.4, 72.0, 74.9, 75.5, 127.7, 128.0, 128.2, 128.37, 128.43, 128.5, 128.7, 129.65, 129.71, 129.9, 130.0, 133.09, 133.14, 136.1, 136.2, 150.0, 165.6, 165.6; HRMS (ESI) calcd for $C_{20}H_{21}NO_5Na$ 378.1318, found (M + Na)$^+$ 378.1345. Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.62; H, 6.14; N, 3.93.

2-Acetoxy-3-benzoyloxy-*N*-benzyloxycarbonylpiperidine (4c). To a solution of **30** (0.505 mmol) and 4-*N*,*N*-(dimethylamino)pyridine (0.06 mmol) in triethylamine (0.7 mL) was added acetic anhydride (2.64 mmol) at room temperature. The reaction mixture was stirred for 1.5 h at the same temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution at 0 °C. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water (five times), saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to afford **4c** in 85% yield as a colorless oil (mixture of diastereomers *cis*/*trans* = 30/70). The diastereomer ratio was determined by ^{1}H NMR. **4c** (*cis*/*trans* = 30/70): IR (neat) 1748, 1738, 1716, 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.58−2.25 (m, 7H), 3.02−3.13 (m, 1H), 4.00−4.15 (m, 1H), 5.07−5.28 (m, 3H), 6.85 (d, 0.7H, *J* = 2.6 Hz), 7.16−7.59 (m, 8.3H), 7.93−7.97 (m, 2H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.2, 20.8, 23.0, 23.4, 24.0, 39.2, 67.3, 67.5, 67.8, 70.4, 75.5, 76.3, 127.6, 128.0, 128.1, 128.3, 128.36, 128.43, 129.5, 129.7, 129.8, 133.07, 133.14, 136.0, 136.1, 154.7, 155.2, 165.1, 165.4, 168.6, 169.0; HRMS (ESI) calcd for $C_{22}H_{23}NO_6Na$ 420.1423, found (M + Na)$^+$ 420.1410. Anal. Calcd for $C_{27}H_{25}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.31; H, 5.92; N, 3.51.

***N*-Benzyloxycarbonyl-2-hydroxy-3-(*p*-methoxybenzoyl)oxypiperidine (31).** To a solution of **26** (4.89 mmol) and 4-*N*,*N*-(dimethylamino)pyridine (0.49 mmol) in a mixture of triethylamine (15 mL) and CH_2Cl_2 (10 mL) was added *p*-methoxybenzoic anhydride[30] (14.6 mmol) at room temperature, and the reaction mixture was stirred for 24 h at the same temperature. The reaction was quenched with water at the same temperature. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water (five times), a saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was dissolved in a mixture of THF (5 mL), water (5 mL) and acetic acid (15 mL), and was stirred for 24 h at room temperature. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution at 0 °C. The mixture was extracted with ethyl acetate (three times). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution (five times), water and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to afford **31** in 84% yield as a colorless oil (*cis*/*trans* = 33/67). The diastereomer ratio was determined by ^{1}H NMR. IR (neat) 1715, 1700, 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.53−2.09 (m, 4H), 3.17−3.29 (m, 1H), 3.80−3.99 (m, 4H), 4.95−5.14 (m, 3H), 5.82 (s, 0.67 H), 5.97 (s, 0.33 H), 6.88 (d, 2H, *J* = 8.7 Hz), 7.00−7.33 (m, 5H), 7.92 (d, 1.3 H, *J* = 8.7 Hz), 8.00 (d, 0.7 H, *J* = 8.7 Hz); ^{13}CNMR ($CDCl_3$), rotamers, δ 19.5, 22.9, 23.2, 23.4, 38.1, 38.5, 55.2, 55.37, 55.39, 67.2, 67.5, 69.1, 71.6, 75.0, 75.5, 77.2, 113.57, 113.59, 122.2, 122.4, 127.6, 128.0, 128.1, 128.4, 128.5, 131.7, 131.8, 136.1, 136.2, 155.5, 163.4, 163.5, 165.27, 165.34; HRMS (ESI) calcd for $C_{21}H_{23}NO_6Na$ 408.1423, found (M + Na)$^+$ 408.1448. Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.15; H, 6.22; N, 3.58.

2-Acetoxy-*N*-benzyloxycarbonyl-3-(*p*-methoxybenzoyl)oxypiperidine (4d). To a solution of **31** (3.45 mmol) and 4-*N*,*N*-(dimethylamino)pyridine (0.35 mmol) in triethylamine (5 mL) was added acetic anhydride (10.6 mmol) at room temperature. The reaction mixture was stirred for 2.5 h at the same temperature. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution at 0 °C. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water (five times), a saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to afford **4d** in 95% yield as a white solid. Mp 108−110 °C; IR (KBr) 1748, 1707 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.61−2.17 (m, 7H), 3.06 (m, 1H), 3.85 (m, 1H), 4.13 (m, 1H), 5.03−5.30 (m, 3H), 6.84−6.91 (m, 3H), 7.15−7.37 (m, 5H), 7.89−7.92 (m, 2H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.2, 20.8, 23.5, 24.1, 55.40, 55.43, 64.9, 65.0, 67.0, 67.5, 67.8, 70.1, 75.6, 113.6, 122.1, 122.2, 127.6, 127.9, 18.0, 128.1, 128.4, 128.5, 131.6, 131.7, 131.8, 136.0, 136.2, 155.1, 155.2, 163.48, 163.53, 164.8, 165.1, 168.6, 169.0; HRMS (ESI) calcd for $C_{23}H_{25}NO_7Na$ 450.1529, found (M + Na)$^+$ 450.1524. Anal. Calcd for $C_{23}H_{25}NO_7$: C, 64.63; H, 5.90; N, 3.28. Found: C, 64.46; H, 5.84; N, 3.26.

2-(*N*-Benzyloxycarbonyl-3-hydroxypiperidin-2-yl)acetophenone (32). A solution of **11b** (major/minor = 76/24, 1.78 mmol) and MeONa (2.41 mmol) in MeOH (7 mL) was stirred for 4 h at room temperature. The solvent was evaporated in vacuo. The residue was partitioned between ethyl acetate and a saturated aqueous NH_4Cl solution. The aqueous layer was extracted with ethyl acetate (twice). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The resulting crude product was purified by silica gel chromatography to afford **32-major** (more polar) and **32-minor** (less polar) as colorless oils in 66% and 26% yields, respectively (a mixture of diastereomers). The configuration of **32-major** was determined as *trans* by X-ray crystallography of its 2-naphthoate derivative. **32-major (*trans*):** IR (neat) 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.46 (d, 1H, *J* = 12.7 Hz), 1.71−2.04 (m, 3H), 2.23 (s, 1H), 2.97 (t, 1H, *J* = 12.1 Hz), 3.19 (d, 2H, *J* = 7.3 Hz), 3.90 (s, 1H), 4.13 (t, 1H, *J* = 6.2 Hz), 4.86 (s, 1H), 5.04 (d, 1H, *J* = 12.4 Hz), 5.10 (d, 1H, *J* = 12.4 Hz), 7.26−7.41 (m, 7H), 7.53−7.58 (m, 1H), 7.91 (m, 2H); ^{13}C NMR ($CDCl_3$), rotamers, δ 18.8, 25.7, 38.7, 39.6, 54.6, 66.6, 67.3, 127.8, 127.9, 128.2, 128.4, 128.7, 133.4, 136.3, 136.5, 156.2, 197.5; MS (EI) *m*/*z* 353 (M$^+$). Anal. Calcd for $C_{21}H_{23}NO_4 \cdot 0.5H_2O$: C, 69.60; H, 6.67; N, 3.86. Found: C, 69.95; H, 6.50; N, 3.96. **32-minor (*cis*):** IR (neat) 1688 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.32−1.91 (m, 4H), 2.85 (t, 1H, *J* = 11.7 Hz), 2.90 (s, 1H), 2.99 (dd, 1H, *J* = 15.6, 6.0 Hz), 3.82 (s, 1H), 4.03 (d, 1H, *J* = 13.0 Hz), 4.80−5.20 (m, 3H9, 7.12−7.63 (m, 8H), 7.92 (m, 2H); ^{13}C NMR ($CDCl_3$), rotamers, δ 23.6, 27.2, 34.9, 38.7, 52.5, 67.2, 68.2, 127.7, 127.8, 128.2, 128.3, 128.4, 133.1, 136.3, 136.6, 155.2, 199.6; MS (EI) *m*/*z* 353 (M$^+$). Anal. Calcd for $C_{21}H_{23}NO_4 \cdot 0.5H_2O$: C, 69.60; H, 6.67; N, 3.86. Found: C, 69.78; H, 6.48; N, 3.86.

***trans*-2-[*N*-Benzyloxycarbonyl-3-(2-naphthoyloxy)piperidin-2-yl]acetophenone (33).** To a solution of **32-major** (0.342 mmol), 2-naphthoic acid (0.350 mmol), triethylamine (0.820 mmol) and 4-*N*,*N*-(dimethylamino)pyridine (0.035 mmol) in CH_2Cl_2 (5 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrogen chloride (0.417 mmol) at room temperature. The reaction mixture was stirred for 24 h, and the reaction was quenched with an aqueous 1 M hydrogen chloride solution. The mixture was extracted with CH_2Cl_2 (twice). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by silica gel chromatography to afford **33** in 44% yield as a syrup, and the starting material (**32-major**) was recovered (50%, 88% conversion). X-ray quality single crystals were obtained by crystallization from ether/*n*-hexane in 86% yield as colorless plates. The configuration was determined as *trans* by X-ray crystallography. Mp 88−89 °C; IR (KBr) 1708, 1688 cm^{-1}; ^{1}H NMR (CDCl$_3$), rotamers, δ 1.26−1.12 (m, 4H), 3.10 (t, 1H, J = 11.0 Hz), 3.26−3.38 (m, 2H), 4.29 (s, 1H), 4.87−5.25 (m, 4H), 7.00−7.97 (m, 16H), 8.50 (s, 1H); ^{13}C NMR (CDCl$_3$), rotamers, δ 19.8, 23.8, 38.4, 51.9, 67.1, 69.9, 125.1, 126.5, 127.4, 127.7, 128.1, 128.2, 128.7, 129.4, 131.1, 132.3, 133.3, 135.5, 136.2, 155.7, 165.6, 196.5; HRMS (ESI) calcd for $C_{32}H_{30}NO_5$ 508.2124, found (M + H)$^+$ 508.2111. Anal. Calcd for $C_{32}H_{29}NO_5$: C, 75.72; H, 5.76; N, 2.76. Found: C, 75.45; H, 5.92; N, 2.78.

***trans*-2-(3-Benzyloxy-*N*-benzyloxycarbonylpiperidin-2-yl)acetophenone (*trans*-11a).** To a solution of **32-major** (0.250 mmol) and benzyl trichloroacetoimidate (1.00 mmol) in ether (2 mL) was added a solution of trifluoromethanesulfonic acid in ether (0.17 M, 0.1 mL) at room temperature. After the reaction mixture was stirred for 20 h at the same temperature, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. After silica gel chromatography of the residue, ***trans*-11a** was obtained in 38% yield as a colorless oil (2% of epimerization was observed by HPLC analysis. However, ***cis*-11a** was not observed by ^{1}H NMR analysis). The starting material (**32-major**) was recovered without epimerization (58%, 90% conversion). ***trans*-11a:** IR (neat) 1690 cm^{-1}; ^{1}H NMR (CDCl$_3$), rotamers, δ 1.48−2.05 (m, 4H), 2.95−3.38 (m, 3H), 3.54 (s, 1H), 4.24 (br, 1H), 4.45−5.19 (m, 5H), 7.01−7.59 (m, 13H), 7.80−7.96 (m, 2H); ^{13}C NMR (CDCl$_3$), rotamers, δ 19.5, 19.8, 23.8, 24.4, 38.4, 38.9, 39.1, 39.7, 50.2, 51.9, 67.1, 67.5, 69.7, 70.2, 73.0, 76.6, 127.3, 127.5, 127.7, 127.8, 128.1, 128.2, 128.3, 128.4, 128.7, 129.6, 130.1, 133.0, 133.4, 136.3, 136.4, 136.7, 138.6, 141.1, 155.7, 155.9, 196.6, 197.5; HRMS (ESI) calcd for $C_{28}H_{30}NO_4$ 444.2175, found (M + H)$^+$ 444.2207

***trans*-2-(3-Acetoxy-*N*-benzyloxycarbonylpiperidin-2-yl)acetophenone (*trans*-11b).** A solution of **32-major** (0.203 mmol), triethylamine (0.494 mmol), 4-*N*,*N*-(dimethylamino)-pyridine (0.0221 mmol) and acetic anhydride (0.353 mmol) in CH_2Cl_2 (5 mL) was stirred for 4 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford ***trans*-11b** in 89% yield as a colorless oil. IR (neat) 1734, 1695 cm^{-1}; ^{1}H NMR (CDCl$_3$), rotamers, δ 1.45 (m, 1H), 1.73−1.99 (m, 6H), 2.92 (s, 1H), 3.12−3.20 (m, 2H), 4.11 (s, 1H), 4.83−5.03 (m, 4H), 7.12−7.49 (m, 8H), 7.84 (m, 2H); ^{13}C NMR (CDCl$_3$), rotamers, δ 19.5, 21.0, 13.6, 38.4, 39.0, 51.7, 67.0, 69.1, 127.6, 127.8, 128.2, 128.4, 128.6, 133.3, 136.2, 155.6, 170.2, 196.6; HRMS (ESI) calcd for $C_{23}H_{26}NO_5$ 396.1810, found (M + H)$^+$ 396.1835.

***cis*-2-(3-Acetoxy-*N*-benzyloxycarbonylpiperidin-2-yl)-acetophenone (*cis*-11b).** Similarly, ***cis*-11b** was obtained from **32-minor** in 54% yield as colorless oil. IR (neat) 1739, 1697 cm^{-1}; ^{1}H NMR (CDCl$_3$), rotamers, δ 1.58−2.01 (m, 7H), 2.97 (m, 2H), 3.48 (dd, 1H, J = 15.2, 6.6 Hz), 4.07 (s, 1H), 4.92−5.09 (m, 3H), 5.24 (q, 1H, J = 6.3 Hz), 7.26−7.58 (m, 8H), 7.91 (m, 2H); ^{13}C NMR (CDCl$_3$), rotamers, δ 21.0, 23.6, 24.8, 35.4, 38.8, 50.3, 67.3, 70.1, 127.8, 127.9, 128.1, 128.4, 128.6, 133.1, 136.4, 136.7, 155.1, 169.6, 197.2; HRMS (ESI) calcd for $C_{23}H_{26}NO_5$ 396.1811, found (M + H)$^+$ 396.1790.

***trans*-Methyl 1-(3-Benzyloxypiperidin-2-yl)-1-methylpropionate (34a).** Compound **13a** (0.428 mmol) was dissolved in MeOH (5 mL) and hydrogenated (10% Pd−C, 1atm) for 2.5 days at room temperature. After purification by silica gel chromatography, **34a** was obtained in 85% yield as a colorless oil. IR (neat) 3363, 1731 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.16−1.41 (m, 9H), 1.72−1.76 (m, 1H), 2.28 (m, 1H), 2.95 (d, 1H, J = 9.6 Hz), 3.05 (m, 1H), 3.16 (dt, 1H, J = 9.6, 4.0 Hz), 3.31 (s, 3H), 4.30 (d, 1H, J = 10.8 Hz), 4.50 (d, 1H, J = 10.8 Hz), 7.24−7.32 (m, 5H); ^{13}C NMR (CDCl$_3$) δ 18.2, 24.6, 26.2, 30.2, 43.6, 46.9, 51.3, 66.2, 70.5, 77.4, 127.4, 128.0, 128.4, 138.1, 177.7; HRMS (ESI) calcd for $C_{17}H_{26}NO_3$ 292.1912, found (M + H)$^+$ 292.1913.

***trans*-Methyl 1-(*N*-Benzyloxycarbonyl-3-hydroxypiperidin-2-yl)-1-methylpropionate (35).** A solution of **13b** (0.130 mmol) and NaOMe (0.259 mmol) in MeOH (1.5 mL) was stirred for 10 h at room temperature. The reaction was quenched with an aqueous 1 N HCl solution (0.27 mL) and the solvent was evaporated in vacuo. The residue was purified by silica gel chromatography to afford **35** in 97% yield as a pale yellow oil (a single diastereomer). IR (neat) 1726, 1676 cm^{-1}; ^{1}H NMR (CDCl$_3$), rotamers, δ 1.14−1.60 (m, 7H), 1.63−1.86 (m, 3H), 2.43 (br, 1H), 2.84 (t, 0.5H, J = 12.3 Hz), 2.92 (t, 0.5H, J = 13.1 Hz), 3.58 (s, 3H), 3.95−4.04 (m, 1.5 H), 4.16 (d, 0.5 H, J = 12.3 Hz), 4.31 (d, 1 H, J = 14.3 Hz), 4.99−5.14 (m, 2H), 7.20−7.28 (m, 5H); ^{1}H NMR (DMSO-d_6), rotamers, δ 1.14−1.30 (m, 7H), 1.53−1.70 (m, 3H), 2.81 (t, 0.5 H, J = 12.8 Hz), 2.90 (t, 0.5 H, J = 13.4 Hz), 3.56 (s, 3H), 3.84 (d, 1H, J = 9.4 Hz), 4.00 (t, 1H, J = 16.3 Hz), 4.19 (d, 1H, J = 10.8 Hz), 4.81 (d, 1H, J = 11.9 Hz), 5.07−5.13 (m, 2H), 7.34 (m, 5H); ^{1}H NMR (DMSO-d_6, 90 °C) δ 1.17 (s, 3H), 1.21 (s, 3H), 1.26−1.42 (m, 1H), 1.55−1.81 (m, 3H), 2.88 (t, 1H, J = 11.3 Hz), 3.58 (s, 3H), 3.87 (s, 1H), 4.01 (d, 1H, J = 13.6 Hz), 4.24 (s, 1H), 4.51 (s, 1H), 5.09 (s, 2H), 7.28−7.61 (m, 5H); ^{13}C NMR (CDCl$_3$), rotamers, δ 18.6, 19.0, 22.9, 25.5, 25.7, 27.3, 27.6, 40.3, 40.6, 45.8, 52.0, 64.2, 64.4, 64.6, 64.9, 67.3, 127.6, 127.7, 127.8, 128.4, 136.7, 156.9, 157.2, 177.2; ^{13}C NMR (DMSO-d_6), rotamers, δ 18.4, 18.8, 22.8, 23.1, 25.1, 25.3, 27.45, 27.54, 45.26, 45.35, 51.8, 62.7, 62.8, 64.0, 66.2, 66.4, 127.3, 127.4, 127.7, 128.3, 128.4, 136.9, 137.2, 156.1, 156.3, 176.5; ^{13}C NMR (DMSO-d_6, 90 °C) δ 18.2, 22.6, 24.6, 27.3, 45.2, 51.1, 62.8, 63.9, 65.9, 126.9, 127.2, 127.8, 136.7, 155.9, 175.9; HRMS (ESI) calcd for $C_{18}H_{26}NO_5$ 336.1811, found (M + H)$^+$ 336.1811.

Similarly, **13d** (0.319 mmol) was treated with NaOMe (0.555 mmol) in THF−MeOH (2/1, 15 mL) for 6 h under reflux. After the usual workup and purification by silica gel chromatography, **35** and **36** were obtained in 59% and 21% yields, respectively.

Lactone 36. To a suspension of NaH (60% dispersion in mineral oil, 0.51 mmol) in dry THF (2 mL) was added a solution of 18-crown-6 (0.04 mmol) and **35** (0.43 mmol) in dry THF (5 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 24 h at the same temperature. The reaction was quenched with a saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to afford **36** in 77% yield as a single diastereomer. Colorless needles; mp 115 °C; IR (KBr) 1777, 1717 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.29 (s, 3H), 1.57 (s, 3H), 1.59−1.92 (m, 2H), 2.29−2.36 (m, 1H), 3.09 (d, 1H, J = 10.4 Hz), 3.16 (ddd, 1H, J = 13.5, 9.8, 3.7 Hz), 3.98 (dt, 1H, J = 13.5, 4.9 Hz), 4.09 (ddd, 1H, J = 11.0, 10.4, 4.8 Hz), 5.12 (s, 2H), 7.32−7.39 (m, 5H); ^{13}C NMR (CDCl$_3$) δ 17.3, 22.0, 25.1, 26.9, 45.5, 45.8, 67.5, 69.1, 75.7, 128.26, 128.32, 128.6, 136.0, 155.5, 180.2; MS (EI) *m*/*z* 303. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.34; H, 7.16; N, 4.57.

***trans*-Methyl 1-(3-Benzyloxypiperidin-2-yl)-1-methylpropionate (34d).** Compound **13d** (0.328 mmol) was dissolved in MeOH (3 mL) and hydrogenated (10% Pd−C, 1atm) for 5 days at room temperature. After purification by silica gel chromatography, **34d** was obtained in 88% yield as a pale yellow oil (a single diastereomer). IR (neat) 1726, 1649 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.09 (s, 3H), 1.13 (s, 3H), 1.41−1.51 (m, 3H), 1.66−1.69 (m, 1H), 2.08−2.11 (m, 1H), 2.54 (td, 1H, J = 12.2, 2.9 Hz), 3.03 (dt, 1H, J = 12.7, 2.0 Hz), 3.15 (d, 2H, J = 10.0 Hz), 3.34 (s, 3H), 3.78 (s, 3H), 4.83 (dt, 1H, J = 10.0, 4.8 Hz), 6.82−6.86 (m, 2H), 7.85−7.89 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 19.6, 23.9, 26.4, 31.4, 44.7, 46.6, 51.8, 55.4, 64.7, 72.0, 113.5, 122.6, 131.7, 163.4, 165.1, 177.6; HRMS (ESI) calcd for $C_{18}H_{26}NO_5$ 336.1811, found (M + H)$^+$ 336.1839.

***trans*-Dimethyl 2-(3-Benzyloxypiperidin-2-yl)malonate (37).** Compound **15b** (0.196 mmol) was dissolved in 25% HBr/AcOH (3 mL) at 0 °C, and the reaction mixture was stirred for 1.5 h at room temperature. To the solution was added piperidine (2 mL), and the resulting mixture was basified with a saturated aqueous $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (three times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by silica gel chromatography to afford the desired compound (**37**) in <67% yield as a pale yellow oil. A little contamination was not separated by this procedure. IR (neat) 1739 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28−1.73 (m, 4H), 2.04 (s, 3H), 2.15−2.25 (m, 1H), 2.54 (td, 1H, J = 12.3, 2.9 Hz), 3.01 (dq, 1H, J = 12.8, 2.0 Hz), 3.21 (dd, 1H, J = 10.0, 4.1 Hz), 3.68 (d, 0.8H, J = 5.0 Hz), 3.70 (s, 0.2H), 3.75 (s, 3H), 3.77 (s, 3H), 4.66 (ddd, 1H, J = 10.1, 10.0, 4.5 Hz); ^{13}C NMR ($CDCl_3$) δ 21.0, 25.8, 30.6, 45.9, 52.1, 52.4, 52.6, 59.9, 71.7, 168.3, 168.9, 169.9; MS (APCI) *m*/*z* 273 (M$^+$).

***O*-Benzyl-*N*-benzyloxycarbonylfebrifugines (18a). In situ prepared silyl enolate method** (Table 9, entry 1). To a suspension of **19**^{6e} (0.220 mmol) and diisopropylethylamine (0.451 mmol) in CH_2Cl_2 (0.3 mL) was added a solution of trimethylsilyl triflate (0.435 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 1 h and cooled again to 0 °C. To this mixture were added $Sc(OTf)_3$ (0.029 mmol) and then a solution of **4a** (0.145 mmo) in CH_2Cl_2 (0.3 mL). The mixture was warmed to room temperature and stirred for 14 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution and the mixture was extracted with CH_2Cl_2 (twice). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. After purification by silica gel chromatography, ***trans*-18a** (more polar) and ***cis*-18a** (less polar) were obtained in 33% and 38% yields, respectively. ***trans*-18a:** pale yellow oil; IR (neat) 1730, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.40 (d, 1H, J = 10.5 Hz), 1.60−1.66 (m, 1H), 1.86−1.93 (m, 2H), 2.74−2.95 (m, 3H), 3.50 (s, 1H), 4.05 (br, 1H), 4.50−5.25 (m, 7H), 7.24−7.31 (m, 10H), 7.46−7.49 (m, 1H), 7.70−7.90 (m, 4H), 8.24−8.26 (m, 1H); ^{13}C NMR ($CDCl_3$), rotamers, δ 19.3, 24.1, 39.4, 40.7, 50.5, 50.6, 53.8, 67.2, 70.3, 73.5, 121.7, 126.5, 127.2, 127.4, 127.5, 127.6, 127.9, 128.2, 128.4, 134.3, 136.4, 138.2, 146.4, 148.1, 160.8, 200.0; HRMS (ESI) calcd for $C_{31}H_{32}N_3O_5$ 526.2342, found (M + H)$^+$ 526.2324. ***cis*-18a:** pale yellow oil; IR (neat) 1732, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.25−1.92 (m, 7H), 2.78−2.89 (m, 2H), 3.51 (m, 1H), 4.24 (m, 1H), 4.51−4.66 (m, 2H), 5.07−5.86 (m 3H) 7.25−7.81 (m, 14H), 8.25−8.28 (m, 1H); ^{13}C NMR ($CDCl_3$), rotamers, δ 23.8, 25.2, 36.7, 38.8, 50.9, 53.7, 67.6, 71.1, 75.4, 121.9, 126.7, 127.6, 127.7, 127.9, 128.1, 128.5, 128.7, 134.4, 136.4, 137.9, 146.8, 146.9, 148.2, 200.9; HRMS (ESI) calcd for $C_{31}H_{32}N_3O_5$ 526.2342, found (M + H)$^+$ 526.2391. Anal. Calcd for $C_{28}H_{29}NO_4$: C, 70.84; H, 5.94; N, 7.99. Found: C, 70.56; H, 6.25; N, 7.68.

***O*-Acetyl-*N*-benzyloxycarbonylfebrifugines (18b).** ***In situ* prepared tin(II) enolate method** (Table 9, entry 7)**.** To a suspension of tin(II) triflate (0.367 mmol) and **19**^{6e} (0.184 mmol) in CH_2Cl_2 (0.5 mL) was added a solution of diisopropylethylamine (0.377 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 1 h and then heated to reflux. To the refluxing solution were added $Sc(OTf)_3$ (0.018 mmol) and then a solution of **4b** (0.092 mmol) in CH_2Cl_2 (0.3 mL). The mixture was heated under reflux for 30 min and cooled to room temperature. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution and the mixture was extracted with CH_2Cl_2 (twice). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. After silica gel chromatography of the residue, ***trans*-18b** (more polar) and ***cis*-18b** (less polar) were obtained in 55% and 14% yields, respectively. ***trans*-18b:** colorless powder; mp 179−181 °C (*n*-hexane/AcOEt); IR (KBr) 1733, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.25−2.10 (m, 8H), 2.85−2.98 (m, 3H), 4.09 (br, 2H), 4.70−4.98 (m, 2H), 5.16 (m, 2H), 7.26−7.80 (m, 9H), 8.26−8.28 (m, 1H); ^{13}C NMR ($CDCl_3$), rotamers, δ 21.1, 23.6, 25.2, 34.4, 39.1, 45.2, 53.6, 67.6, 69.1, 121.8, 126.8, 127.3, 127.6, 127.8, 128.0, 128.1, 128.5, 132.4, 133.8, 134.5, 136.1, 136.3, 170.4, 199.4; HRMS (ESI) calcd for $C_{26}H_{28}N_3O_6$ 478.1978, found (M + H)$^+$ 478.1983. Anal. Calcd for $C_{26}H_{27}N_3O_6$: C, 65.40; H, 5.70; N, 8.80. Found: C, 65.43; H, 5.79; N, 8.84. ***cis*-18b:** colorless oil; IR (neat) 1738, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.21−2.07 (m, 7H), 2.81−2.96 (m, 2.75H), 3.46 (s, 0.75 H), 3.68−3.72 (m, 0.25H), 3.96 (br, 1H), 4.61−5.70 (m, 5.25H), 7.28−7.33 (m, 5H), 7.48−7.97 (m, 4H), 8.25−8.27 (m, 1H); ^{13}C NMR ($CDCl_3$), rotamers, δ 18.3, 19.2, 20.9, 22.7, 23.1, 23.4, 24.5, 37.1, 38.7, 50.1, 50.6, 53.7, 58.2, 67.1, 67.4, 67.7, 68.0, 69.8, 75.2, 121.7, 126.6, 127.2, 127.5, 127.6, 127.8, 128.0, 128.1, 128.4, 128.5, 134.4, 136.1, 136.4, 146.6, 148.2, 160.9, 169.7, 200.5; HRMS (ESI) calcd for $C_{26}H_{28}N_3O_6$ 478.1978, found (M + H)$^+$ 478.1993. **(3*S*)-*trans*-18b** was prepared according to the same method. **(3*S*)-*trans*-18b:** $[\alpha]^{25}_D$ −51.3 (c = 0.80, $CHCl_3$).

(*S*)-2-Benzyloxy-5-hydroxy-*N*-methoxy-*N*-methylpentanamide (39). To a solution of *N*,*O*-dimethylhyldroxyamine hydrogen chloride (0.42 mmol) in CH_2Cl_2 (1.5 mL) was added a solution of trimethylaluminum in *n*-hexane (0.98 M, 0.42 mL) at −15 °C. The mixture was warmed to room temperature, stirred for 1 h and then cooled to −15 °C. To the reaction mixture was added a solution of **38**^{5,37} (0.14 mmol) in CH_2Cl_2 (1.5 mL) at −15 °C. The reaction mixture was warmed to room temperature and stirred for 24 h. To the resulting mixture was added a 15% aqueous potassium sodium tartrate solution. After being stirred for 1 h, the mixture was filtered through a Celite pad. The filtrate was extracted with CH_2Cl_2 (twice). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was dissolved in a mixture of aqueous 1 N hydrogen chloride solution and THF (1/5, 3 mL) and the solution was stirred for 5 h at room temperature. After neutralization, the mixture was extracted with CH_2Cl_2 (twice). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by silica gel chromatography to afford **39** in 65% yield (two steps) as a colorless oil. IR (neat) 3749, 1651 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.62−1.95 (m, 5H), 3.22 (s, 3H), 3.58 (s, 3H), 3.60−3.77 (m, 2H), 4.32 (s, 1H), 4.37 (d, 1H, J = 8.8 Hz), 4.71 (d, 1H, J = 8.8 Hz), 7.23−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.8, 28.8, 32.3, 49.8, 61.3, 62.3, 71.5, 75.1, 127.9, 128.1, 137.5.

(*S*)-2-Benzyloxy-5-hydroxy-*N*-methoxy-*N*-methylpentanamide (40). Method A. To a solution of **39** (0.117 mmol), triphenylphosphine (0.467 mmol) and diphenylphosphoryl azide (0.233 mmol) in dry THF (0.8 mL) was successively added a solution of DEAD (0.467 mmol) in dry THF (0.3 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h at the same temperature. The solvent was evaporated in vacuo. The residue was purified by silica gel chromatography to afford the corresponding azide. This azide was dissolved in EtOH (5 mL) and treated with few drops of aqueous 1 N HCl solution. Catalytic hydrogenation was then performed (10% Pd−C, 10 atm) for 3 h. The catalyst was filtered off, and the solvent was evaporated in vacuo. The resulting residue was dissolved in a mixture of THF and water (2/1, 15 mL). To this solution were added $NaHCO_3$ (0.584 mmol) and then benzyloxycarbonyl chloride (0.467 mmol). The mixture was stirred for 1 h at 0 °C and extracted with CH_2Cl_2 (three times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by silica gel chromatography to afford **40** in 42% yield (3 steps) as a colorless oil. **Method B.** To a solution of **41**^{40} (0.78 mmol), *N*,*O*-dimethylhyldroxyamine hydrogen chloride (0.83 mmol) and triethylamine (0.82 mmol) in CH_2Cl_2 (2 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrogen chloride (0.94 mmol) at room temperature. The mixture was stirred for 3 h at the same temperature and the reaction was quenched with water. The mixture was extracted with CH_2Cl_2 (three times). The combined organic layers were washed with an aqueous 1 N HCl solution, water and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by silica gel chromatography to afford **40** in 89% yield as a colorless oil. $[\alpha]^{25}_D$ −29.8 (c = 0.76, $CHCl_3$); IR (neat) 3338, 1712, 1656 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19−1.79 (m, 4H), 3.24 (s, 3H), 3.69 (s, 3H), 3.71−4.92 (s, 2H), 5.08 (s, 2H), 7.23−7.38 (m, 5H); ^{13}C

NMR ($CDCl_3$) δ 25.6, 31.6, 32.4, 40.6, 61.3, 66.6, 68.2, 128.1, 128.5, 136.6, 156.4, 174.6; HRMS (ESI) calcd for $C_{15}H_{22}N_2O_5$-Na 333.1427, found $(M + Na)^+$ 333.1438. Anal. Calcd for $C_{15}H_{22}N_2O$: C, 58.05; H, 7.15; N, 9.03. Found: C, 57.76; H, 7.11; N, 8.93.

(3*S*)-*N*-Benzyloxycarbonyl-2,3-dihydroxypiperidine ((3*S*)-26). To a solution of **40** (0.493 mmol) in dry ether (2 mL) was added $LiAlH_4$ (1.77 mmol) at 0 °C. The reaction mixture was stirred for 1.5 h at the same temperature and the reaction was quenched with water. The mixture was filtered through a Celite pad, and the filtrate was extracted with ethyl acetate (twice). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by silica gel chromatography to afford **(3*S*)-26** in 91% yield as a colorless oil (a mixture of diastereomers). Diastereomer ratio was determined by ^{1}H NMR, and it was found that the ratio depended on workup procedures. The ratio of *cis*/*trans* = 56/44 was obtained by this workup procedure, and the ratio of *cis*/*trans* = 34/66 was obtained when the reaction was quenched by an aqueous potassium sodium tartrate solution. **(3*S*)-26** (*cis*/*trans* = 56/44): colorless oil; ^{1}H NMR ($CDCl_3$), rotamers, δ 1.38−1.95 (m, 4H), 2.94−3.40 (m, 2H), 3.51−3.88 (m, 2H), 5.02−5.14 (m, 2H), 5.58 (d, 0.44H, $J = 2.4$ Hz), 5.71 (d, 0.56H, $J = 3.3$ Hz), 7.26−7.37 (m, 5H).

Febrifugine (1). Compound **(3*S*)-*trans*-18b** (0.052 mmol) was dissolved in 25% HBr/AcOH (3 mL) at 0 °C, and the reaction mixture was stirred for 30 min at the same temperature. To this solution was added piperidine (2 mL), and the resulting mixture was basified with a saturated aqueous $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (three times). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was dissolved in MeOH (5 mL). To the solution was added NaOMe (0.065 mmol) and the reaction mixture was stirred for 1 h at room temperature. The mixture was partitioned between water and CH_2Cl_2, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. After purification by silica gel chromatography, **1** was obtained in 25% yield (two steps). This material was identified with the authentic sample previously synthesized in our laboratory.[5]

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Supporting Information Available: Full experimentl and details of X-ray analysis of **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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