First Asymmetric Synthesis of Piperidine Alkaloid (–)-Morusimic Acid D

De-Sheng Yu,[a] Wei-Xuan Xu,[a] Liang-Xian Liu,[a] Pei-Qiang Huang*[a,b]

[a] Department of Chemistry and Key Laboratory for Chemical Biology of Fujian Province, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, P. R. of China
Fax +86(592)2186400; E-mail: pqhuang@xmu.edu.cn

[b] The State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. of China

Received 4 January 2008

Abstract: The first asymmetric synthesis of (–)-morusimic acid D, a 2,3-*trans*-2,6-*cis*-2-methyl-6-substituted piperidin-3-ol containing alkaloid is reported. The key steps are the reductive alkylation of N,O-diprotected 3-hydroxyglutarimide, a stepwise reductive alkylation, and an asymmetric aldol-type reaction using a modified Evans chiral auxiliary.

Key words: asymmetric synthesis, *N*-acyliminium ions, imides, aldol reaction, piperidines, alkaloids, morusimic acid D

Substituted, hydroxylated piperidines constitute a class of natural products exhibiting important bioactivities.[1] As a key structural feature shared by many piperidine alkaloids, 2-methyl-6-substituted piperidin-3-ols with different stereochemical patterns have been the targets of numerous synthetic efforts, which have culminated in a number of methods for the synthesis of these molecules.[2–8] Because most of this class of piperidine alkaloids possess a 2,3-*cis* stereochemistry with either a 2,6-*cis*-stereochemical pattern (**A**, Figure 1), or a 2,6-*trans* stereochemistry pattern (**B**), much attention has been devoted to the construction of *cis*-2-methylpiperidin-3-ol skeleton.[3] Only a few methods are available for the synthesis of *trans*-2-methylpiperidin-3-ols,[4] although several methods have been developed for the syntheses of structurally related piperidine alkaloids prosophylline[5] and micropine,[6] quinolizidine alkaloids clavepictines[7] and pictamine,[7a] as well as decahydroquinoline alkaloid lepadin D.[8] In 2002, two 2,3-*trans*-2,6-*cis*-2-methyl-6-substituted piperidin-3-ol containing alkaloids, morusimic acids C (**1**) and D (**2**) were isolated from white ripened fruit of *M. alba* grown in Turkey.[9]

In continuation of our studies on the development of protected 3-hydroxyglutarimide-based synthetic methodology,[10–12] we now report an application of this methodology to the first asymmetric synthesis of morusimic acid D (**2**), an alkaloid having a 2,3,6-*trans*,*trans* stereochemistry.

As displayed retrosynthetically in Scheme 1, both the C2 methyl group and the 2,3-*trans* stereochemistry were envisioned to be introduced by the reductive alkylation method[10,11] starting from the protected 3-hydroxyglutarimide **6**.[12] The C6 side chain with 2,6-*cis* stereochemistry

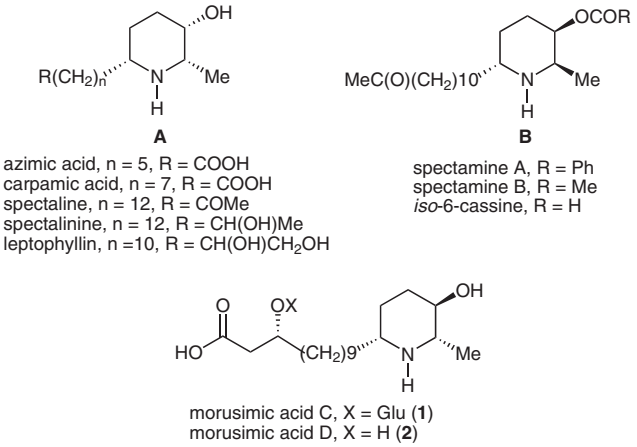
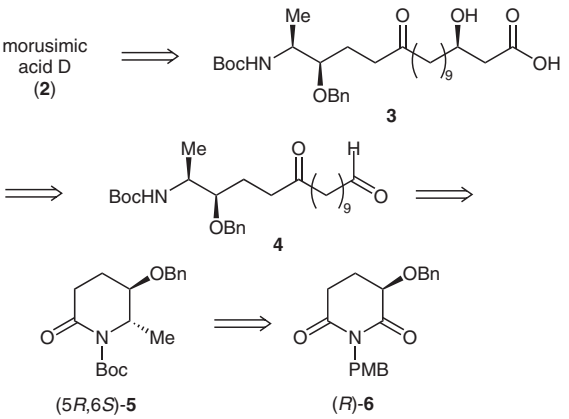


Figure 1 Some alkaloids containing a 2-methyl-6-substituted piperidin-3-ol moiety



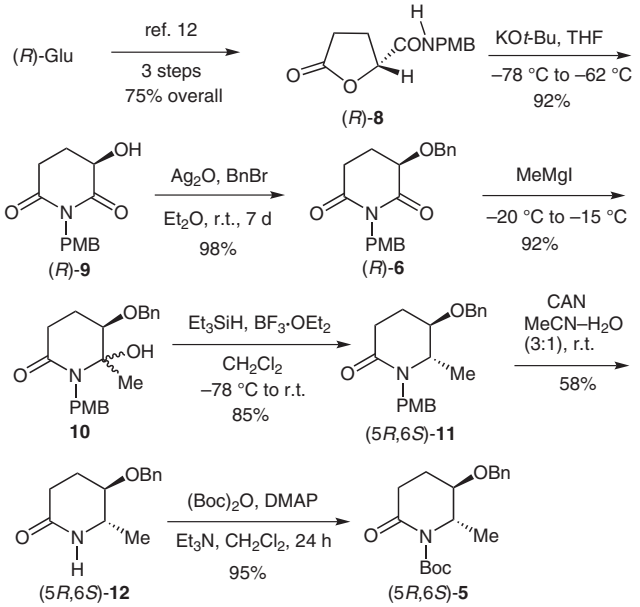
Scheme 1 Retrosynthetic analysis of (–)-morusimic acid D

was considered to be accessible by another diastereoselective reductive alkylation method.[13]

The synthesis commenced with (*R*)-3-benzyloxy-1-(4-methoxybenzyl)glutarimide [(*R*)-**6**],[12] which was prepared from D-glutamic acid following essentially the procedure described for its enantiomer (Scheme 2).[12]

For the reductive methylation, although our previous study showed that the addition of methyl magnesium iodide (3 molar equiv) to (*S*)-3-hydroxyglutarimide derivative (*S*)-**6** in THF at –78 °C yielded a diastereomeric mixture of *N*,*O*-acetal **10** and its C6 adduct in 86:14 C2/C6 regioselectivity, it was found that almost only the C2 addition product was obtained when undertaking the reac-

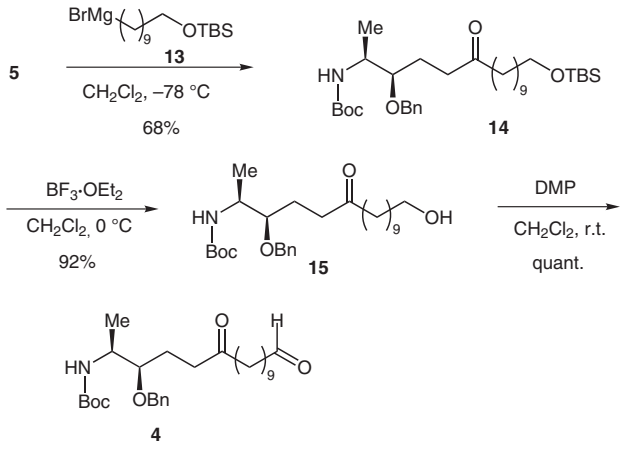
SYNLETT 2008, No. 8, pp 1189–1192
Advanced online publication: 16.04.2008
DOI: 10.1055/s-2008-1072737; Art ID: W00408ST



Scheme 2

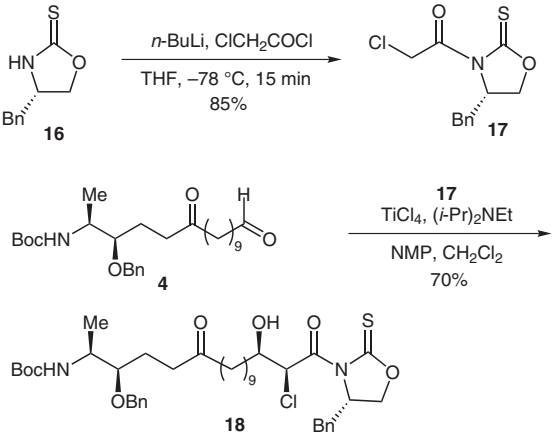
tion in CH_2Cl_2 and at –20 °C. The subsequent reductive dehydroxylation under ionic hydrogenolytic conditions[14] ($Et_3SiH/BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C to r.t.) furnished predominantly *trans*-**11** (*trans*/*cis* = 92:8). Cleavage of the *N*-(4-methoxybenzyl) group by treating (5*R*,6*S*)-**11** with ceric ammonium nitrate (CAN) in MeCN–H_2O (3:1)[15] at room temperature gave lactam (5*R*,6*S*)-**12** in 58% yield (Scheme 2).

Next, we turned our attention to the introduction of the chiral C6 side chain. To this end, another diastereoselective reductive alkylation method[13] was adopted. Thus, lactam **12** was first converted [$(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2, 24 h] to imide (5*R*,6*S*)-**5**, an activated form[13b] of the former (Scheme 2). Reaction of Grignard reagent **13**[16] with imide (5*R*,6*S*)-**5** in CH_2Cl_2 at –78 °C proceeded smoothly to give the ring-opening product **14** in 68% yield. To introduce the ethoxycarbonylmethyl group, the TBS group in compound **14** was cleaved under acidic conditions ($BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C) to give **15** in 92% yield.[17] The resulting alcohol **15** was oxidized with Dess–Martin periodinane (DMP)[18] to give aldehyde **4** in quantitative yield (Scheme 3).



Scheme 3

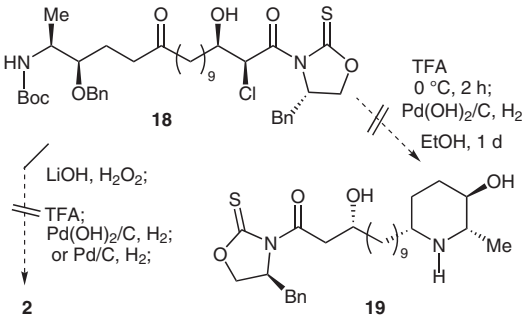
For the asymmetric carboxymethylation, an enzymatic method,[19] Evans asymmetric aldol-type reaction,[20] and Brown's asymmetric allylation reaction[21] were all plausible. We sought to use Evans' aldol chemistry in view of its excellent enantio- and diastereoselectivities, as well as its compatibility with different substituents that may be useful for the synthesis of analogues of (–)-morusimic acid D. To take advantages of the progress in Evans aldol chemistry,[22,23] oxazolidine-2-thione derivative **17** was selected for the asymmetric aldol reaction, where the chloro atom will serve as a stereodirecting group for the asymmetric aldol-type reaction.[20] The starting oxazolidine-2-thione **16** was prepared in 91% yield by the method reported by Wu.[24] Successive treatment of oxazolidine-2-thione **16** with *n*-butyllithium and chloroacetyl chloride gave **17** in 85% yield. Asymmetric aldol reaction of **4** with **17** under Crimmins' conditions [$TiCl_4$, $(i\text{-Pr})_2EtN$, *N*-methylpyrrolidin-2-one (NMP), CH_2Cl_2, 0 °C][23] provided **18** as the only isolable diastereomer in 70% yield (Scheme 4).



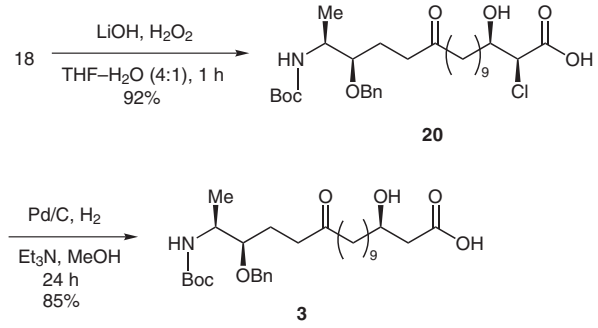
Scheme 4

The subsequent steps required for the synthesis of morusimic acid D (**2**) included *N*-Boc deprotection, one-pot reductive cyclization–debenzylation, dechlorination, and cleavage of the chiral auxiliary. Attempts to cleave the protecting group Boc by TFA, followed by $Pd(OH)_2$ or Pd/C-catalyzed hydrogenolysis to obtain **19** was unsuccessful, and other attempts under the conditions shown in Scheme 5 also failed.

After extensive trials, it was found that after the cleavage of the chiral auxiliary under Evans' conditions[25] (LiOH, H_2O_2, THF–H_2O, 1 h) selective dechlorination could be achieved by subjecting **20** (colorless oil, yield 92%) to Abushanab's hydrogenation conditions[26] [H_2 (1 atm), 10% Pd/C, Et_3N, MeOH, 24 h, r.t.], which furnished the dechloro product **3** in 85% yield along with 10% of the recovered starting material (Scheme 6).



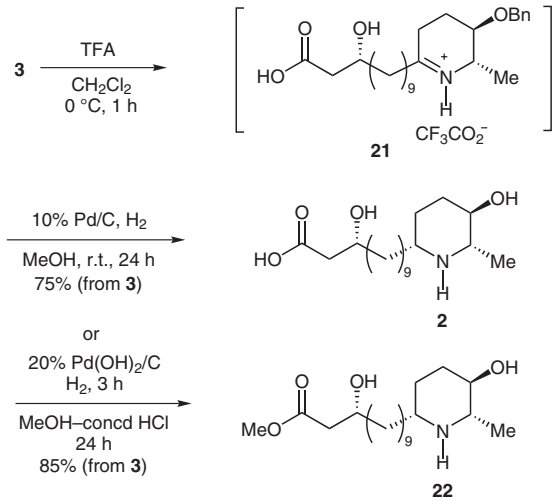
Scheme 5



Scheme 6

Finally, treatment of **3** with trifluoroacetic acid in dichloromethane at 0 °C for one hour, followed by subjecting the resulting crude product to catalytic hydrogenolysis (10% Pd/C, H_2, MeOH, r.t., 24 h) led, in one pot, to the formation of morusimic acid D (**2**) in 75% yield as a white powder {$[\alpha]_D^{20}$ –14.0 (*c* 0.25, MeOH), lit.[9] $[\alpha]_D^{20}$ –14.6 (*c* 0.25, MeOH)}. The ^{1}H NMR and ^{13}C NMR spectral data of the synthetic material are identical with those reported for the natural morusimic acid D (**2**).[9]

Alternatively, morusimic acid D methyl ester (**22**)[27] could be obtained in one pot by treatment of **3** with trifluoroacetic acid, followed by catalytic hydrogenolysis in methanol using Pearlman's catalyst [$Pd(OH)_2$/C (20 mol%), H_2, 1 atm] for three hours, and then stirring with concentrated hydrochloric acid for 24 hours (Scheme 7).



Scheme 7

In summary, by modifying the reaction conditions, the C2/C6 regioselectivity of the addition of methyl magnesium iodide to N,O-diprotected 3-benzyloxyglutarimide **6** was improved from 86:14 to at least 95:5. On the basis of this reaction, the first asymmetric synthesis of (–)-morusimic acid D is achieved in 11 steps with an overall yield of 13% from (*R*)-**6**, with all the three stereocenters established in excellent diastereoselectivities.

Acknowledgment

The authors are grateful to the NSFC (20572088), Qiu Shi Science & Technologies Foundation, and the program for Innovative Research Team in Science & Technology (University) in Fujian Province for financial support. We thank Professor Y. F. Zhao for the use of her Bruker Dalton Esquire 3000 plus LC-MS apparatus.

References and Notes

(1) For reviews on the piperidine alkaloids, see: (a) Strunz, G. M.; Findlay, J. A. *Pyridine and Piperidine Alkaloids, In The Alkaloids*, Vol. 26; Brossi, A., Ed.; Academic Press: New York, **1985**, 89. (b) Numata, A.; Ibuka, T. In *The Alkaloids*, Vol. 31; Brossi, A., Ed.; Academic Press: New York, **1987**. (c) Schneider, M. *Pyridine and Piperidine Alkaloids: An Update*, In *Alkaloids: Chemical and Biochemical Perspectives*, Vol. 10; Pelletier, S. W., Ed.; Elsevier Science: Oxford, **1996**, 155. (d) Michael, J. P. *Nat. Prod. Rep.* **1999**, *16*, 675.

(2) For reviews on the syntheses of piperidines, see: (a) Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3493. (b) Zhou, W. S.; Lu, Z. H.; Xu, Y. M.; Liao, L. X.; Wang, Z. M. *Tetrahedron* **1999**, *55*, 11959. (c) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781. (d) Toyooka, N.; Nemoto, H. *Drugs Future* **2002**, *27*, 143. (e) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953. (f) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693. (g) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701.

(3) (a) Lu, Z. H.; Zhou, W. S. *Tetrahedron* **1993**, *49*, 4659. (b) Lee, H. K.; Chun, J. S.; Pak, C. S. *Tetrahedron* **2003**, *59*, 6445. (c) Sato, T.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2003**, *5*, 3839. (d) Randl, S.; Blechert, S. *Tetrahedron Lett.* **2004**, *45*, 1167. (e) Lemire, A.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2747. (f) Leverett, C. A.; Cassidy, M. P.; Padwa, A. *J. Org. Chem.* **2006**, *71*, 8591.

(4) (a) Ha, J. D.; Lee, D.; Cha, J. K. *J. Org. Chem.* **1997**, *62*, 4550. (b) Sengupta, S.; Mondal, S. *Tetrahedron* **2002**, *58*, 7983. (c) Bailey, P.; Smith, P. D.; Morgan, K. M.; Rosair, G. M. *Tetrahedron Lett.* **2002**, *43*, 1071.

(5) (a) Takao, K.-i.; Nigawara, Y.; Nishino, E.; Takagi, I.; Maeda, K.; Tadano, K.-i.; Ogawa, S. *Tetrahedron* **1994**, *50*, 5681. (b) Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3592. (c) Ojima, I.; Vidal, E. S. *J. Org. Chem.* **1998**, *63*, 7999. (d) Toyooka, N.; Yoshida, Y.; Yotssui, Y.; Momose, T. *J. Org. Chem.* **1999**, *64*, 4914. (e) Herdeis, C.; Telser, J. *Eur. J. Org. Chem.* **1999**, 1407. (f) Datta, A.; Kumar, J. S. R.; Roy, S. *Tetrahedron* **2001**, *57*, 1169. (g) Comins, D. L.; Sandelier, M. J.; Grillo, T. A. *J. Org. Chem.* **2001**, *66*, 6829. (h) Cossy, J.; Willis, C.; Bellosta, V.; BouzBouz, S. *J. Org. Chem.* **2002**, *67*, 1982. (i) Dransfield, P. J.; Gore, P. M.; Prokeš, I.; Shipman, M.;

Slawin, A. M. Z. *Org. Biomol. Chem.* **2003**, *1*, 2723. (j) Chavan, S. P.; Praveen, C. *Tetrahedron Lett.* **2004**, *45*, 421. (k) Jourdant, A.; Zhu, J. P. *Heterocycles* **2004**, *64*, 249. (l) Wang, Q.; Sasaki, N. A. *J. Org. Chem.* **2004**, *69*, 4767. (m) Kim, I. S.; Ryu, C. B.; Li, Q. R.; Zee, O. P.; Jung, Y. H. *Tetrahedron Lett.* **2007**, *48*, 6258. (n) Fuhshuku, K.-i.; Mori, K. *Tetrahedron: Asymmetry* **2007**, *18*, 2104.

(6) Bayquen, A. V.; Read, R. W. *Tetrahedron* **1996**, *52*, 13467.

(7) (a) Toyooka, N.; Yotsui, Y.; Yoshida, Y.; Momose, T.; Nemoto, H. *Tetrahedron* **1999**, *55*, 15209. (b) Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 10012. (c) Agami, C.; Couty, F.; Evano, G.; Darro, F.; Kiss, R. *Eur. J. Org. Chem.* **2003**, 2062.

(8) Pu, X. T.; Ma, D. W. *J. Org. Chem.* **2006**, *71*, 6562.

(9) Kusano, G.; Orihara, S.; Tsukamoto, D.; Shibano, M.; Coskun, M.; Guvenc, A.; Erdurak, C. S. *Chem. Pharm. Bull.* **2002**, *50*, 185.

(10) For accounts on the methodologies, see: (a) Huang, P.-Q. *Recent Advances on the Asymmetric Synthesis of Bioactive 2-Pyrrolidinone-Related Compounds Starting from Enantiomeric Malic Acid*, In *New Methods for the Asymmetric Synthesis of Nitrogen Heterocycles*; Vicario, J. L.; Badia, D.; Carrillo, L., Eds.; Research Signpost: Kerala, **2005**, 197. (b) Huang, P.-Q. *Synlett* **2006**, 1133.

(11) Huang, P.-Q.; Guo, Z.-Q.; Ruan, Y.-P. *Org. Lett.* **2006**, *8*, 1435.

(12) Ruan, Y.-P.; Wei, B.-G.; Xu, X.-Q.; Liu, G.; Yu, D.-S.; Liu, L.-X.; Huang, P.-Q. *Chirality* **2005**, *17*, 595.

(13) For a recent example, see: (a) Jourdant, A.; Zhu, J. *Tetrahedron Lett.* **2001**, *42*, 3431. (b) For amide activation by Boc, see: Giovannini, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, *54*, 228.

(14) For a review on Et_3SiH-mediated ionic hydrogenation, see: (a) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633. For selected examples, see: (b) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656. (c) Yoda, H.; Kitayama, H.; Yamada, W.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1451. (d) Drage, J. S.; Earl, R. A.; Vollhardt, K. P. C. *J. Heterocycl. Chem.* **1982**, *19*, 701.

(15) Yamaura, M.; Suzuki, T.; Hashimoto, H.; Yoshimura, J.; Okamoto, T.; Shin, C. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1413.

(16) McDougal, P. G.; Rico, J. G.; Oh, Y. I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388.

(17) Kelly, D. R.; Roberts, S. M.; Newton, R. F. *Synth. Commun.* **1979**, *9*, 295.

(18) (a) Dess, D. M.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Frigerio, M.; Santagostino, M.; Sputores, S. *J. Org. Chem.* **1999**, *64*, 4537.

(19) (a) Oetting, J.; Holzkamp, J.; Meyer, H. H.; Pahl, A. *Tetrahedron: Asymmetry* **1997**, *8*, 477. (b) Singh, R.; Ghosh, S. K. *Tetrahedron Lett.* **2002**, *43*, 7711.

(20) For the use of halogen as a stereodirecting group for the asymmetric ethoxycarbonylmethylation, see: (a) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39. (b) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033.

(21) (a) Jadhav, P. K.; Bhat, K. S. P.; Perumal, T.; Brown, H. C. *J. Am. Chem. Soc.* **1986**, *51*, 432. (b) Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewicz, M.; Racherla, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389. (c) See also: Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 4109.

(22) For recent reviews on the asymmetric aldol reaction, see: (a) Arya, P.; Qin, H. P. *Tetrahedron* **2000**, *56*, 917. (b) Csákÿ, A. G.; Plumet, J. *Chem. Soc. Rev.* **2001**, *30*, 313.

(23) (a) Crimmins, M. T.; She, J. *Synlett* **2004**, 1371. See also: (b) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894. (c) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883.

(24) Wu, Y. K.; Yang, Y. Q.; Hu, Q. *J. Org. Chem.* **2004**, *69*, 3990.

(25) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

(26) Saibaba, R.; Sarma, M. S.; Abushanab, E. *Synth. Commun.* **1989**, *19*, 3077.

(27) All new compounds gave satisfactory analytical and spectral data. Selected physical and spectral data for morusimic acid D methyl ester (**22**): pale yellow powder; mp 132–135 °C; $[\alpha]_D^{20}$ –11.3 (*c* 0.4, $CHCl_3$). IR (film): 3387, 2929, 2854, 1731, 1438, 1380, 1305, 1165, 1061 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 1.40 (s, 3 H), 1.22–1.68 (m, 20 H), 2.09 (m, 2 H), 2.30–2.50 (m, 2 H), 2.92 (m, 1 H), 3.08 (m, 1 H), 3.42 (s, 1 H), 3.64 (s, 3 H), 3.95 (m, 1 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 16.00, 26.52, 26.56, 28.33, 30.43, 30.48, 30.52, 30.56, 30.59, 32.92, 34.26, 38.05, 43.25, 52.15, 58.49, 59.24, 69.23, 70.70, 173.92. ESI-HRMS: *m/z* calcd for $C_{19}H_{38}NO_4$ $[M + H]^+$: 344.2795; found: 344.2798.