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Synthesis of Methyl *N*-Boc-(2*S*,4*R*)-4-methylpipecolate

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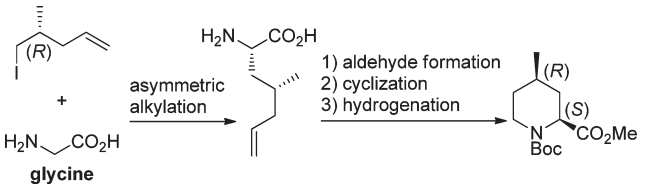
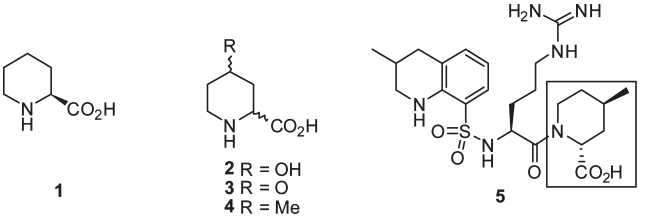


An efficient stereoselective synthesis of fully protected (2*S*,4*R*)-4-methylpipecolic acid has been developed. The synthesis was achieved by initial asymmetric α-alkylation of glycine with a chiral iodide, affording the linear precursor as a single stereoisomer. Subsequent aldehyde formation using $OsO_4/NaIO_4$ followed by immediate intramolecular cyclization afforded an enamine that was then subjected to hydrogenation to give the final compound in 23% yield over 10 steps.

Pipecolic acid **1** is a cyclic nonproteogenic α-amino acid found in plants, fungi, and human physiological fluids.[1] As a metabolite of L-lysine,[2] this naturally occurring homologue of L-proline is an important component in pharmacologically active compounds such as the immunosuppressive agents rapamycin[3] and FK506,[4] the antitumor antibiotic sandramycin,[5] and the anti-HIV cyclodepsipeptide homophymia A.[6] Pipecolic acid, **1**, is also a synthetic precursor to compounds including the amyloglucosidase inhibitor lentiginosine,[7] and the anticonvulsant pipradol.[8] Among the vast variety of pipecolic acid derivatives described to date,[9] 4-substituted pipecolic acids are currently the most prevalent subgroup. Good examples are 4-hydroxy and 4-oxopipecolic acid derivatives **2** and **3** that are present in the highly potent HIV inhibitor palinavir,[10] and the cyclic antibiotic virginiamycin S,[11] respectively. While numerous syntheses of both 4-hydroxy and 4-oxopipecolic acid have been reported, little attention has focused on the formation of the less known 4-methylpipecolic acid, **4**, the key component of the potent and selective thrombin inhibitor argatroban, **5**.[12]



Despite several racemic syntheses of 4-methylpipecolic acid,[13] only a limited number of asymmetric syntheses have been described. Asymmetric synthesis of 4-methylpipecolic acid has been accomplished by aza-Diels−Alder reaction,[14] intramolecular ene-iminium cyclization,[15] and Sharpless epoxidation followed by ring-closing metathesis.[16] Disappointingly, most of these methods proceed with low overall stereoselectivity. Given that the chirality at both the 2- and

(1) (a) Zacharius, R. M.; Thompson, J. F.; Steward, F. C. *J. Am. Chem. Soc.* **1952**, *74*, 2949. (b) Bernasconi, R.; Jones, R. S. G.; Bittiger, H.; Olpe, H. R.; Heid, J.; Martin, P.; Klein, M.; Loo, P.; Braunwalder, A.; Schmutz, M. *J. Neural Transm.* **1986**, *67*, 175–189. (c) Gutierrez, M. C.; Delgado-Coello, B. A. *Neurochem. Res.* **1989**, *14*, 405–408.

(2) Leistner, E.; Spenser, I. D. *J. Am. Chem. Soc.* **1973**, *95*, 4715–4725.

(3) (a) Swindells, D. C. N.; White, P. S.; Findlay, J. A. *Can. J. Chem.* **1978**, *56*, 2491–2492. (b) Smith, A. B., III; Hale, K. J.; Laakso, L. M.; Chen, K.; Riera, A. *Tetrahedron Lett.* **1989**, *30*, 6963–6966. (c) Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L.; Leahy, J. W.; Maleczka, R. E. *J. Am. Chem. Soc.* **1997**, *119*, 962–973. (d) Smith, A. B., III; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365–377.

(4) (a) Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. *J. Am. Chem. Soc.* **1987**, *109*, 5031–5033. (b) Romo, D.; Meyer, S. D.; Johnson, D. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 7906–7907. (c) Ireland, R. E.; Gleason, J. L.; Gegnas, L. D.; Highsmith, T. K. A. *J. Org. Chem.* **1996**, *61*, 6856–6872.

(5) Boger, D. L.; Chen, J. H.; Saionz, K. W. *J. Am. Chem. Soc.* **1996**, *118*, 1629–1644.

(6) Zampella, A.; Sepe, V.; Luciano, P.; Bellotta, F.; Monti, M. C.; D'Auria, M. V.; Jepsen, T.; Petek, S.; Adeline, M.-T.; Laprévôte, O.; Aubertin, A.-M.; Debitus, C.; Poupat, C.; Ahond, A. *J. Org. Chem.* **2008**, *73*, 5319–5327.

(7) Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, *29*, 1886–1891.

(8) Portoghese, P. S.; Pazdernik, T. L.; Kuhn, W. L.; Hite, G.; Shafi'ee, A. *J. Med. Chem.* **1968**, *11*, 12–15.

(9) Kadouri-Puchot, C.; Comess, S. *Amino Acids* **2005**, *29*, 101–130.

(10) (a) Lamarre, D.; Croteau, G.; Wardrop, E.; Bourgon, L.; Thibeault, D.; Clouette, C.; Vaillancourt, M.; Cohen, E.; Pargellis, C.; Yoakim, C.; Anderson, P. C. *Antimicrob. Agents Chemother.* **1997**, *41*, 965–971. (b) Beaulieu, P. L.; Lavallée, P.; Abraham, A.; Anderson, P. C.; Boucher, C.; Bousquet, Y.; Duceppe, J.; Gillard, J.; Gorys, V.; Grand-Maître, C.; Grenier, L.; Guindon, Y.; Guse, I.; Plamondon, L.; Soucy, F.; Valois, S.; Wernic, D.; Yoakim, C. *J. Org. Chem.* **1997**, *62*, 3440–3448.

(11) Vanderhaeghe, H.; Janssen, G.; Compernolle, F. *Tetrahedron Lett.* **1971**, *28*, 2687–2688.

(12) (a) Okamoto, S.; Hijikata, A.; Kikumoto, R.; Tonomura, S.; Hara, H.; Ninomiya, K.; Maruyama, A.; Sugano, M.; Tamao, Y. *Biochem. Biophys. Res. Commun.* **1981**, *101*, 440–446. (b) Kikumoto, R.; Tamao, Y.; Tezuka, T.; Tonomura, S.; Hara, H.; Ninomiya, K.; Hijikata, A.; Okamoto, S. *Biochemistry* **1984**, *23*, 85–90. (c) Hilpert, K.; Ackermann, J.; Banner, D. W.; Gast, A.; Gubernator, K.; Hadvary, P.; Labler, L.; Müller, K.; Schmid, G.; Tschopp, T. B.; van de Waterbeemd, H. *J. Med. Chem.* **1994**, *37*, 3889–3901.

(13) (a) Caddy, D. E.; Utley, J. H. P. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1258–1262. (b) Schuman, R. T.; Ornstein, P. L.; Paschal, J. W.; Gesellchen, P. D. *J. Org. Chem.* **1990**, *55*, 738–741. (c) Nazih, A.; Schneider, M. R.; Mann, A. *Synlett* **1998**, 1337–1338. (d) Hu, L. Y.; Ryder, T. R.; Nikam, S. S.; Millerman, E.; Szoke, B. G.; Rafferty, M. F. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1121–1126. (e) Cossy, J.; Belotti, D. *Tetrahedron Lett.* **2001**, *42*, 2119–2120.

(14) (a) Bailey, P. D.; Wilson, R. D.; Brown, G. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1337–1340. (b) Bailey, P. D.; Brown, G. R.; Korber, F.; Reed, A.; Wilson, R. D. *Tetrahedron: Asym.* **1991**, *2*, 1263–1282.

(15) Agami, C.; Bisaro, F.; Comesse, S.; Guesne, S.; Kadouri-Puchot, C.; Morgentin, R. *Eur. J. Org. Chem.* **2001**, 2385–2389.

(16) Alegret, C.; Santacana, F.; Riera, A. *J. Org. Chem.* **2007**, *72*, 7688–7692.

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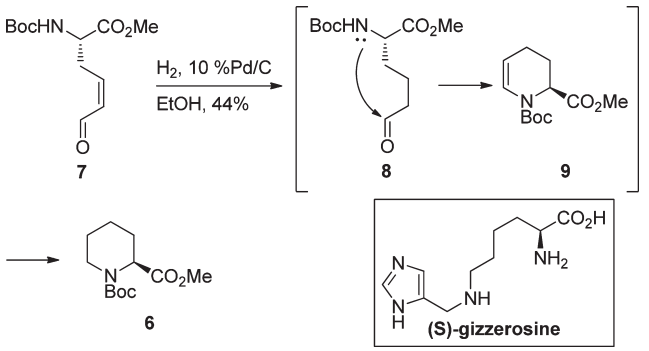
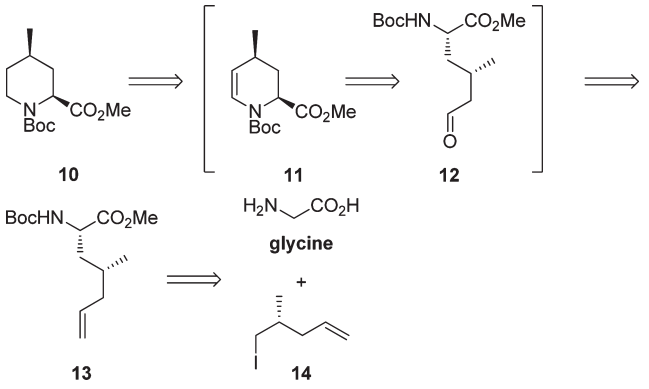
SCHEME 1. Formation of (2*S*)-Pipecolic Acid, 6, upon Hydrogenation of Aldehyde Precursor 7



SCHEME 2. Retrosynthetic analysis of (2*S*,4*R*)-4-methylpipecolic acid



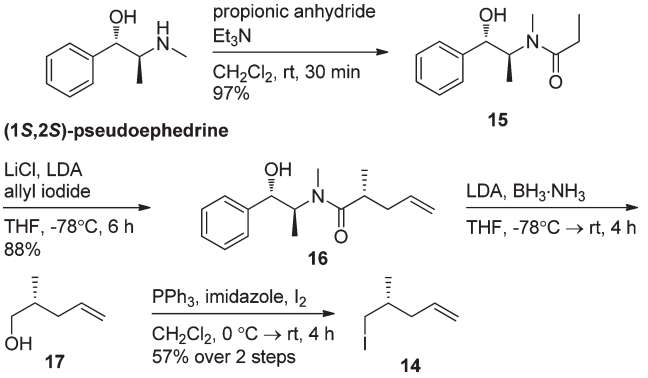
4-position of 4-methylpipecolic acid has a significant effect on the biological activity,[12a,b] our aim was to establish an efficient stereoselective synthesis of 4-methylpipecolic acid.

Recently, Sutherland reported that protected (2*S*)-pipecolic acid, **6**, could be formed in moderate yield upon hydrogenation of its aldehyde precursor **7** in the synthesis of (*S*)-gizzerosine (Scheme 1).[17] The analogues of aldehyde intermediate **8** were shown to be unstable and underwent intramolecular cyclization to give derivatives of the enamine product **9**.[18]

With this idea in mind, a new asymmetric synthesis of 4-methylpipecolic acid based on late-stage cyclization of an aldehyde was proposed. As depicted in scheme 2, the target compound **10** can be obtained from hydrogenation of enamine **11** generated *in situ* from cyclization of the aldehyde intermediate **12**. Aldehyde **12** in turn is derived from olefin **13** which can then be assembled from asymmetric α-alkylation of glycine by iodide **14**. This retrosynthetic strategy was envisaged to provide the desired stereoisomer with excellent stereoselectivity as both the asymmetric synthesis of iodide **14** and asymmetric α-alkylation of glycine are well documented.

Herein we report the synthesis of fully protected (2*S*,4*R*)-4-methylpipecolic acid from the readily available and inexpensive starting materials (1*S*,2*S*)-pseudoephedrine and L-proline. As shown in scheme 3, the synthesis of chiral iodide **14** began with simple acylation of (1*S*,2*S*)-pseudoephedrine

SCHEME 3. Synthesis of Iodide 14 from (1*S*,2*S*)-Pseudoephedrine



with propionic anhydride to afford amide **15** in 97% yield.[19] Subsequent asymmetric alkylation of **15** using commercially available allyl iodide afforded olefin **16** in 88% yield.[19] Finally, reduction of **16** by the borane−ammonia complex gave alcohol **17** which was converted to the desired iodide **14** without further purification in 57% yield over two steps.[19,20]

Several methods have been developed for the asymmetric α-alkylation of glycine.[21] Among those reported, use of the Ni(II) complex **18** as a template was deemed a suitable method for the present investigation.[22] It was reported that the Ni(II) complex **18** effects the α-alkylation of glycine with excellent diastereomeric excess. Furthermore, the alkylation reaction can be carried out using inexpensive reagents under mild conditions with simple flash column chromatography employed for the desired product isolation. Also importantly,

(17) Fanning, K. N.; Sutherland, A. *Tetrahedron Lett.* **2007**, *48*, 8479–8481.

(18) (a) Tice, C. M.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 5043–5048. (b) Mori, K.; Sugai, T.; Maeda, Y.; Okazaki, T.; Noguchi, T.; Naito, H. *Tetrahedron* **1985**, *41*, 5307–5311.

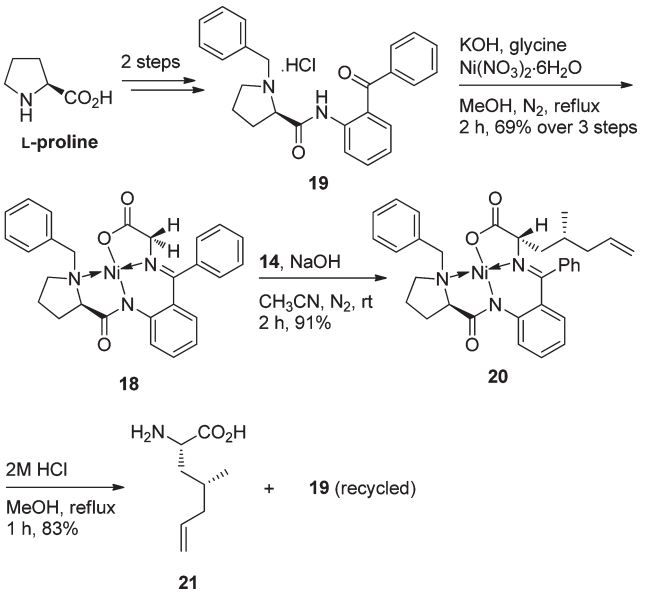
(19) Myers, A. G.; Yang, B. H.; Chen, Y. H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.

(20) Smith, A. B., III; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925–5937.

(21) (a) Sutherland, A.; Willis, C. L. *Nat. Prod. Rep.* **2000**, *17*, 621–631. (b) Beller, M.; Eckert, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1010–1027. (c) Kawabata, T.; Fuji, K. *Synth. Org. Chem. Jpn.* **2000**, *58*, 1095–1099. (d) Kazmaier, U.; Maier, S.; Zumpe, F. L. *Synlett* **2000**, 1523–1535. (e) Yao, S. L.; Saaby, S.; Hazell, R. G.; Jorgensen, K. A. *Chem.—Eur. J.* **2000**, *6*, 2435–2448. (f) Abellan, T.; Chinchilla, R.; Galindo, N.; Guillena, G.; Najera, C.; Sansano, J. M. *Eur. J. Org. Chem.* **2000**, 2689–2697. (g) Rutjes, F. P. J. T.; Wolf, L. B.; Schoemaker, H. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4197–4212. (h) Shioiri, T.; Hamada, Y. *Synlett* **2001**, 184–201. (i) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000. (j)*Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin/Heidelberg, 1999. (k) O'Donnell, M. J. *Aldrichimica Acta* **2001**, *34*, 3–15. (l) Hruby, V. J., Soloshonok, V. A., Guest Eds. Asymmetric Synthesis of Novel Sterically Constrained Amino Acids. Tetrahedron Symposia-in-Print; #88; *Tetrahedron* **2001**, *57* (30). (m) O'Donnell, M. J.; Drew, M. D.; Cooper, J. T.; Delgado, F.; Zhou, C. *J. Am. Chem. Soc.* **2002**, *124*, 9348–9349. (n) Bull, S. D.; Davies, S. G.; Garner, C. A.; O'Shea, M. D.; Savory, E. D.; Snow, E. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2442–2448. (o) O'Donnell, M. J.; Cooper, J. T.; Mader, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 2370–2371.

(22) (a) Belokon', Y. N.; Zeltzer, I. E.; Bakhmutov, V. I.; Saporovskaya, M. B.; Ryzhov, M. G.; Yanovsky, A. I.; Struchkov, Y. T.; Belikov, V. M. *J. Am. Chem. Soc.* **1983**, *105*, 2010–2017. (b) Belokon', Y. N.; Bulychev, A. G.; Vitt, S. V.; Struchkov, Y. T.; Batsanov, A. S.; Timofeeva, T. V.; Tsyryapkin, V. A.; Ryzhov, M. G.; Lysova, L. A.; Bakhmutov, V. I.; Belikov, V. M. *J. Am. Chem. Soc.* **1985**, *107*, 4252–4259. (i) Belokon', Y. N.; Bakhmutov, V. I.; Chernoglazova, N. I.; Kochetkov, K. A.; Vitt, S. V.; Garbalinskaya, N. S.; Belikov, V. M. *J. Chem. Soc.. Perkin Trans. 1* **1988**, 305–312. (c) Belokon', Y. N. *Janssen Chim. Acta* **1992**, *10*, 4. (d) Bolokon', Yu. N. *Pure Appl. Chem.* **1992**, *64*, 1917. (e) Collet, S.; Bauchar, P.; Danion-Bougot, R.; Danion, D. *Tetrahedron: Asymmetry* **1998**, *9*, 2121–2131. (f) Belokon', Y. N.; Tararov, V. I.; Maleev, V. I.; Savel'eva, T. F.; Ryzhov, M. G. *Tetrahedron: Asymmetry* **1998**, *9*, 4249–4252. (g) Ueki, H.; Ellis, T. K.; Martin, C. H.; Boettiger, T. U.; Bolene, S. B.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 7104–7107. (h) Qin, W.; Cao, F.; Li, Z.; Zhou, H.; Wan, H.; Wei, P.; Shi, Y.; Ouyang, P. *J. Chem. Crystal.* **2006**, *36*, 61–65.

SCHEME 4. Synthesis of Linear Backbone of (2*S*,4*R*)-4-Methylpipecolic Acid 21 from Commercially Available L-Proline



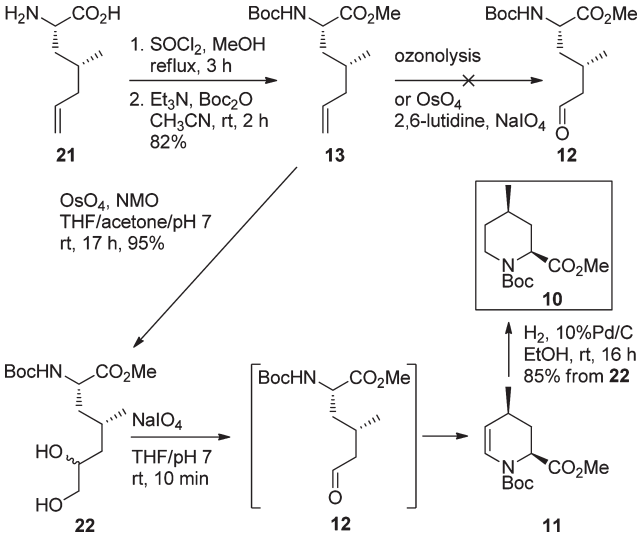
the chiral auxiliary **19** can be recycled following the release of the α-substituted chiral glycine.

Thus, the Ni(II) complex **18** was synthesized in 69% overall yield over three steps starting from L-proline (Scheme 4).[22e−g] The key asymmetric alkylation was carried out using sodium hydroxide in acetonitrile, affording olefin **20** as a single diastereomer in 91% yield. Subsequent acid hydrolysis of **20** using 2 M HCl solution afforded olefin **21** in 83% yield and recovered the chiral auxiliary **19** quantitatively.

Prior to aldehyde formation and further cyclization of the key acyclic precursor **21**, the amine and acid functionality were both protected as a Boc group (Boc_2O in MeCN) and methyl ester ($SOCl_2$ in MeOH), respectively, affording protected olefin **13** in 82% yield over two steps (Scheme 5).[23] Initial attempts to synthesize aldehyde **12** followed by intramolecular cyclization from olefin **13** using ozonolysis[24] or OsO_4, 2,6-lutidine/$NaIO_4$[25] were unsuccessful. Pleasingly, formation of diol **22** from olefin **13** using OsO_4 and NMO followed by treatment with $NaIO_4$[26] afforded enamine **11** via aldehyde intermediate **12** in almost quantitative yield. Enamine **11** was subjected to hydrogenation to give the target compound **10** in 85% yield over two steps without further purification.[17]

In summary, an efficient stereoselective synthesis of Boc protected methyl (2*S*,4*R*)-4-methylpipecolate has been developed via asymmetric α-alkylation of glycine with a chiral unsaturated iodide followed by intramolecular cyclization of the derived aldehyde. The key asymmetric α-alkylation of glycine afforded the linear backbone **21** of (2*S*,4*R*)-4-methylpipecolic acid in 91% yield as a single stereoisomer. Following oxidative cleavage of diol **22**, intramolecular cyclization of the

SCHEME 5. Synthesis of *N*-Boc (2*S*,4*R*)-4-Methylpipecolic Methyl Ester 10



aldehyde intermediate **12** and hydrogenation of the enamine **11** proceeded smoothly, affording the target compound **10** in 10 steps in 23% overall yield. The synthesis employed allows for versatile access to a range of analogues, by varying the nature of the alkyl iodide[20,27] and the chirality of the Ni(II) complex.[22b]

Experimental section

(*R*)-1-Iodo-2-methylpent-4-en 14.[20]**.** To a solution of alcohol **17** (1.89 g, 18.88 mmol) in dry dichloromethane (35 mL) at 0 °C under nitrogen was added triphenylphosphine (5.47 g, 20.86 mmol), imidazole (1.43 g, 20.98 mmol), and iodine in three portions (5.35 g, 21.07 mmol). The resulting suspension was warmed to room temperature and stirred for 4 h. The reaction mixture was passed through a sintered funnel packed with silica gel using a mixture of pentane/diethyl ether (5:1). After removal of the solvent under reduced pressure (750 mmHg, 40 °C), bulb-to-bulb distillation (20 mmHg, 50−80 °C) afforded compound **14** (2.26 g, 57% from amide **16**) as a colorless liquid; TLC (hexane/ethyl acetate 3:1) R_f = 0.9; $[\alpha]_D^{20}$ −6.7 (*c* 1.40, $CHCl_3$);[28] ν_{max} (neat)/cm^{-1} 2960, 1640, 1437, 1194, 993, 914, 721, 694; δ_H(300 MHz; $CDCl_3$) 1.00 (3H, d, *J* = 6.6 Hz, $CHCH_3$), 1.51−1.66 (1H, m, $CHCH_3$), 1.98−2.19 (2H, m, $CHCH_2CH{=}CH_2$), 3.13−3.26 (2H, m, ICH_2CH), 5.03−5.13 (2H, m, $CH_2CH{=}CH_2$), 5.66−5.80 (1H, m, $CH_2CH{=}CH_2$); δ_C (75 MHz; $CDCl_3$) 16.7 (CH_2, ICH_2CH), 20.3 (CH_3, $CHCH_3$), 34.6 (CH, $CHCH_3$), 40.6 (CH_2, $CHCH_2CH{=}CH_2$), 116.9 (CH_2, $CH_2CH{=}CH_2$), 135.8 (CH, $CH_2CH{=}CH_2$).

(*S*)-Glycine-nickel-(*S*)-2-[*N*-(*N*′-benzylpropyl)amino]benzophenone-(*R*)-2-methyl-pent-4-en complex 20.[22g]**.** To a suspension of compound **18** (3.52 g, 7.08 mmol) and powdered sodium hydroxide (0.71 g, 17.69 mmol) in acetonitrile (60 mL) was added iodide 14 (2.23 g, 10.61 mmol) under nitrogen. After stirring at room temperature for 2 h, 0.1 M aqueous hydrochloric acid (55 mL) was added, and the solution mixture was stirred for 30 min. Following extraction with dichloromethane (3 × 100 mL), the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purified by

(23) Kokotos, G.; Padróon, J. M.; Martín, T.; Gibbons, W. A.; Martín, V. S. *J. Org. Chem.* **1998**, *63*, 3741–3744.
(24) Xu, L. F.; Huang, W. F.; Wei, B. G.; Lin, G. Q. *Synlett* **2009**, *8*, 1307–1310.
(25) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217–3219.
(26) Roush, W. R.; Bannister, T. D.; Wendt, M. D.; Jablonowski, J. A.; Scheidt, K. A. *J. Org. Chem.* **2002**, *67*, 4275–4283.
(27) (a) Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, *68*, 9274–9283. (b) Smith, A. B., III; Kozmin, S. A.; Adams, C. M.; Paone, D. V. *J. Am. Chem. Soc.* **2000**, *122*, 4984–4985.
(28) The optical rotation for (*S*)-1-iodo-2-methylpent-4-en was found to be +6.3 (*c* 1.4, $CHCl_3$).[20]

silica gel column chromatography using dichloromethane/acetone (4:1) as eluent afforded compound **20** (3.74 g, 91%) as a blood-red amorphous solid; TLC (dichloromethane/acetone 4:1) R_f = 0.38; $[\alpha]_D^{20}$ +2266.4 (*c* 0.12, MeOH); mp 89.4−93.7 °C; ν_{max} (neat)/cm^{-1} 2957, 1671, 1637, 1589, 1439, 1330, 1256, 1165, 1063, 913, 752, 702; δ_H (300 MHz; $CDCl_3$) 0.84 (3H, d, *J* = 6.7 Hz, $CHCH_3$), 1.36−1.45 (1H, m, CH_2CHCH_3), 1.64−1.74 (2H, m, $CHCH_2CHCH_3$), 1.85−1.95 (2H, m, $CHCH_2CH{=}CH_2$), 2.01−2.21 (2H, m, Proδ-H, Proγ-H), 2.34−2.43 (1H, m, Proβ-H), 2.46−2.61 (1H, m, Proβ-H), 2.71−2.81 (1H, m, Proγ-H), 3.43−3.72 (4H, m, Proδ-H, NCH_2Ph, Glyα-H), 3.92−3.96 (1H, dd, *J* = 9.8, 4.7 Hz, Proα-H), 4.43 (1H, d, *J* = 12.6 Hz, NCH_2Ph), 4.71−4.86 (2H, m, $CH_2CH{=}CH_2$), 5.34−5.48 (1H, m, $CH_2CH{=}CH_2$), 6.58−6.68 (2H, m, Ph), 6.92 (1H, d, *J* = 5.3 Hz, Ph), 7.09−7.15 (2H, m, Ph), 7.17−7.20 (1H, d, *J* = 7.5 Hz, Ph), 7.26−7.36 (4H, m, Ph), 7.42−7.54 (4H, m, Ph), 8.06 (3H, d, *J* = 7.4 Hz, Ph); δ_C(75 MHz; $CDCl_3$) 20.5 (CH_3, $CHCH_3$), 23.9 (CH_2, Proγ-C), 28.9 (CH, CH_2CHCH_3), 30.7 (CH_2, Proβ-C), 39.5 (CH_2, $CHCH_2CHCH_3$), 43.9 (CH_2, $CHCH_2CH{=}CH_2$), 57.1 (CH_2, Proδ-C), 62.9 (CH_2, NCH_2Ph), 69.0 (CH, Proα-C), 70.3 (CH, Glyα-C), 116.1 (CH_2, $CH_2CH{=}CH_2$), 120.7 (CH, Ph), 123.7 (CH, Ph), 126.6 (C, Ph), 127.6 (CH, Ph), 127.9 (CH, Ph), 128.8 (CH, Ph), 128.9 (CH, Ph), 128.9 (CH, Ph), 129.0 (CH, Ph), 129.7 (CH, Ph), 131.5 (CH, Ph), 131.9 (CH, Ph), 133.1 (CH, Ph), 133.2 (C, Ph), 133.5 (C, Ph), 136.2 (CH, $CH_2CH{=}CH_2$), 142.1 (C, Ph), 169.6 (C, Ph_2CN), 179.1 (C, *C*O), 180.2 (C, Pro-*C*ON); *m*/*z* (EI) 602 (10%, M^+ + Na), 584 (10), 583 (16), 582 (45), 581 (38), 580 (100) and 366 (6); HRMS (EI, M^+ + Na) found 602.1906, calcd for $C_{33}H_{35}N_3NaNiO_3$ 602.1924.

(2*S*,4*R*)-1-*tert*-Butyl-2-(carbonylmethyl)-4-methylpiperid ine-1,2-dicarboxylate 10.[17] Sodium (*meta*)periodate (0.13 g, 0.59 mmol) was added to a solution of compound **22** (45.2 mg, 0.15 mmol) in a mixture of THF/pH 7 buffer solution (5:1, v/v, 6 mL). After stirring vigorously at room temperature for 10 min, the solvent was removed and the solid residue was dissolved in water (10 mL) and ethyl acetate (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford an oily residue. To this residue dissolved in ethanol (20 mL) under hydrogen was added 10% Pd/C (33.9 mg, 0.03 mmol) and the mixture was stirred for 16 h. The reaction mixture was passed through a thin layer of Celite and washed with ethanol. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using hexane/ethyl acetate (9:1) as eluent to afford compound **10** (32.2 mg, 85%) as a yellow oil; TLC (hexane/ethyl acetate 9:1) R_f = 0.34; $[\alpha]_D^{20}$ −23.6 (*c* 0.66, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2954, 2929, 1745, 1695, 1393, 1366, 1155, 1130.20, 1070, 865, 777; δ_H(300 MHz; $CDCl_3$) 0.91 (3H, d, *J* = 6.6 Hz, $CHCH_3$), 1.23−1.34 (1H, m, $CH_2CH_2CHCH_3$), 1.42 [9H, s, $(CH_3)_3C$], 1.66−1.84 (3H, m, $CHCH_2CHCH_3$, $CH_2CHCH_3CH_2$, $CH_2CH_2CHCH_3$), 1.91−1.97 (1H, m, $CHCH_2CHCH_3$), 3.32−3.41 (1H, m, CH_2CH_2N), 3.52−3.58 (1H, m, CH_2CH_2N), 3.70 (3H, s, OCH_3), 4.31 (1H, t, *J* = 6.3 Hz, $NCHCO$); δ_C (75 MHz; $CDCl_3$) 18.9 (CH_3, $CHCH_3$), 26.0 (CH, $CH_2CHCH_3CH_2$), 28.2 [CH_3, $(CH_3)_3C$], 30.8 (CH_2, $CH_2CH_2CHCH_3$), 33.2 (CH_2, $CHCH_2CHCH_3$), 38.9 (CH_2, CH_2CH_2N), 51.9 (CH_3, OCH_3), 54.2 (CH, $NCHCO$), 80.1 [C, $(CH_3)_3C$], 155.8 (C, *C*ON), 173.4 (C, CO_2Me); *m*/*z* (EI) 280 (100%, M^+ + Na), 258 (3), 224 (19), 180 (20), 158 (64), 128 (4) and 98 (9); HRMS (EI, M^+ + Na) found 280.1523, calcd for $C_{13}H_{23}NNaO_4$ 280.1519'.

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Supporting Information Available: General experimental procedures, and ^1H and ^{13}C spectra for individual compounds can be obtained in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.