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Complementary routes to both enantiomers of pipecolic acid and 4,5-dihydroxypipecolic acid derivatives

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Abstract

Complementary new routes to both enantiomers of N-protected pipecolic acid and the corresponding 4,5-dihydroxylated derivatives are developed, which involve stereo-divergent allylation of a chiral *N*-allylimine and ring-closing metathesis as key steps.

Keywords: Imines; Allylation; Ring-closing metathesis; Amino acids

Pipecolic acid **1** (Fig. 1), a naturally occurring[1] but non-proteinogenic amino acid, has found widespread utility as a component of several biologically active secondary metabolites,[2a,b] as a proline mimic and β-turn inducer in many designed peptides and synthetic drug candidates,[2c–e] as a building block in organic synthesis,[2f] as an enzyme inhibitor,[2g] and is receiving current attention[3] for application as an organo-catalyst. These applications have stimulated considerable interest[4] in the synthesis of pipecolic acid[5] and its derivatives.[6] However, only a few general routes to both the enantiomers of pipecolic acid are reported.[7] Herein, we report a stereo-divergent route to N-protected *R*- and *S*-pipecolic acid from readily available[8] *R*-2,3-*O*-cyclohexylideneglyceraldehyde (**2**) based on our efforts to develop stereocontrolled allylation of *N*-allylimine **3** derived from **2**.

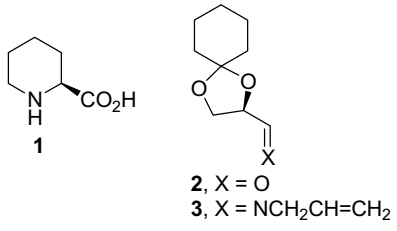

Fig. 1.

Allylation of α-chiral imines has been extensively studied[9] as a route for the preparation of homoallylic amines. A range of allylmetal reagents (wherein, the metal component is either boron, magnesium, zinc, copper, tin, silicon, indium or aluminum) have been shown to be effective for this purpose. However, the more common allylmagnesium or allylzinc reagents have found most applications as they can be used without any additive. We opted to use these in our current efforts towards allylation of **3**.

Thus, imine **3** (Scheme 1) was prepared by straightforward dehydrative condensation of aldehyde **2** with allylamine in the presence of molecular sieves (4 Å). Compound **3** was then reacted with allylmagnesium bromide under optimised conditions to give a mixture of the homoallylic amines **4** (62%) and **5** (16%), which were cleanly separated by silica gel chromatography. On the other hand, treatment of imine **3** with allylzinc bromide (prepared in situ from allyl bromide and zinc powder), under optimised conditions, led to the formation of the *anti*-isomer **5** as the major product (47%) together with **4** (19%).

The complementary mode of these addition reactions is of advantage. However, the predominance of one isomer

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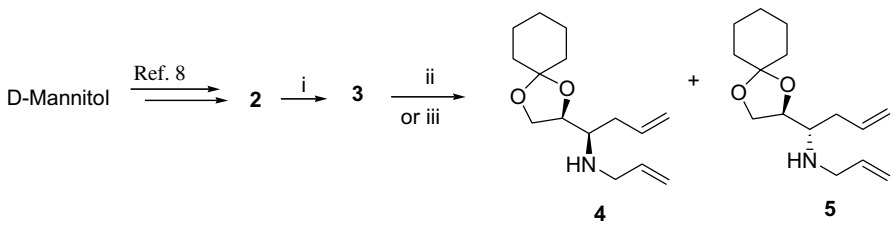
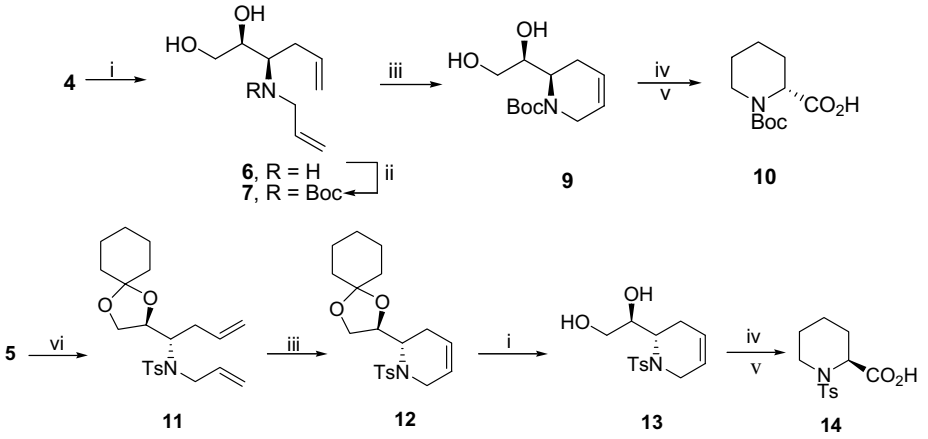


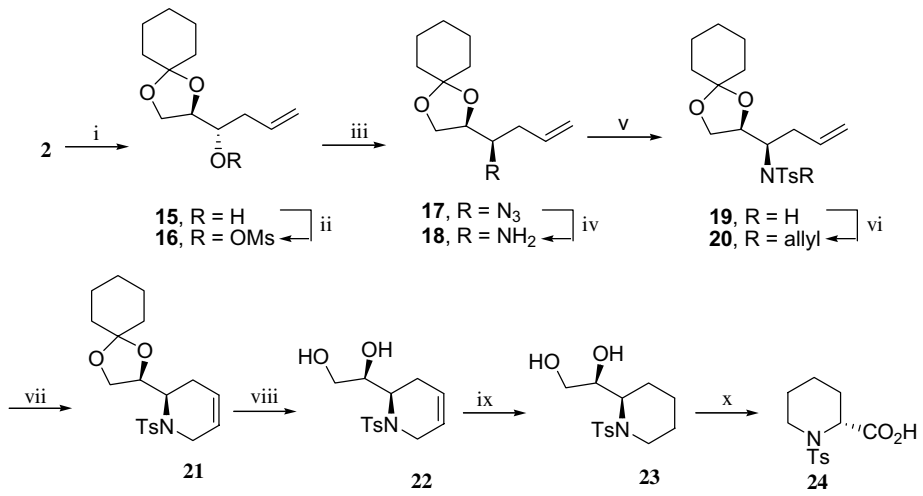
Scheme 1. Reagents and conditions: (i) Allylamine, CH_2Cl_2, powdered molecular sieves (4 Å), 0 °C, 24 h, 95%; (ii) allylmagnesium bromide (1.0 M solution in THF, 2 equiv), Et_2O, −30 °C, 12 h, **4** (62%), **5** (16%); (iii) allylzinc bromide (5 equiv), THF, 0 °C to rt, 12 h, **4** (19%), **5** (47%).

over the other is hard to interpret by classical conformational models since the nature of diastereoselection in imine addition is known[10] to be dependent on several factors. The configuration of the new stereogenic centre in each of the homoallylic amines **4** and **5** was therefore assigned from the following synthetic work. The major product from the allylmagnesium bromide reaction was treated with HCl (6 N) to prepare amino diol **6** (Scheme 2) which, without purification, was treated with Boc_2O to form *N*-tethered diene **7** in good yield. In continuation of our earlier work[11] on ring-closing metathesis[12] (RCM) mediated synthesis of heterocyclic amino acids,[13] we treated **7** with Grubbs' first generation catalyst, benzylidene bis-tricyclohexylphosphinoruthenium(IV) dichloride (**8**), to provide the unsaturated piperidine derivative **9** in good yield.[14] Hydrogenation of the latter followed by oxidative cleavage of the 1,2-diol unit under the Sharpless protocol[15] led to *N*-Boc-pipecolic acid **10** as a colourless crystalline solid, mp 127–128 °C. Comparison of the measured $[\alpha]_D$ values, +63 (*c* 0.06, AcOH), +43 (*c* 1.2, MeOH), with the literature values[16] for (*S*)-*N*-Boc-pipecolic acid (−67.2 in AcOH, −45.1 in MeOH) indicated the product to be of *R*-configuration and of ~93% optical purity. Consequently, the configuration of the starting homoallylic amine **4** was assigned as *syn*. Similarly, the major product from the allylzinc bromide reaction, **5**, was N-tosylated leading to **11** and then subjected to RCM with catalyst **8**. The resulting piperidine derivative **12** was obtained as a colourless solid, mp 110 °C, $[\alpha]_D$ −71 (*c*, 0.13 in $CHCl_3$). Deprotection of the cyclohexylidene moiety in **12** leading to diol **13**, followed by hydrogenation and oxidative cleavage of the 1,2-diol unit then led to the formation of (*S*)-*N*-tosylpipecolic acid **14**, $[\alpha]_D$ −42 (*c*, 0.17 in $CHCl_3$), in an overall yield of 46% over five steps from **5**.

In an alternative approach, we prepared the homoallyl alcohol **15** (Scheme 3) from aldehyde **2** following a known procedure.[8] Conversion of alcohol **15** to the corresponding inverted amine **18** was then effected through azide **17** which, in turn, was obtained from mesylate **16** under the conventional conditions. Reduction of the azide moiety in **17** with $LiAlH_4$ followed by treatment of the resulting amine **18** with *p*-toluenesulfonyl chloride smoothly led to the corresponding tosylamide **19**. The latter on N-allylation with allyl bromide in the presence of sodium hydride afforded the desired *N*-tethered diene **20** in good yield. Ring-closing metathesis of compound **20** in the presence of catalyst **8** smoothly led to the unsaturated piperidine derivative **21**. Repetition of the sequence of events adopted for the conversion **12**→**14** on compound **21**, that is, deprotection of the cyclohexylidene unit leading to **22**, saturation of the double bond to form **23** followed by oxidative cleavage of the 1,2-diol unit gave (*R*)-*N*-tosylpipecolic acid **24**, $[\alpha]_D$ +40 (*c*, 0.13 in $CHCl_3$), in an overall yield of 41% over five steps from **20**. The optical purity of each of the



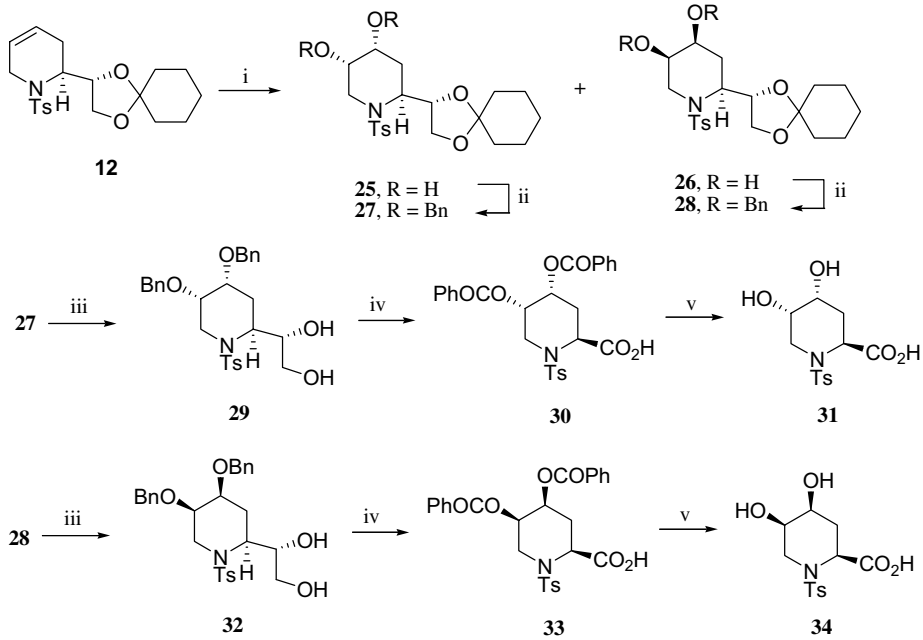
Scheme 2. Reagents and conditions: (i) HCl (6 N), THF, rt, 5 h, 88% (**6**), 91% (**13**): (ii) Boc_2O, MeOH, $NaHCO_3$, rt, 12 h, 77%; (iii) **8** (5 mol %), CH_2Cl_2, rt, 7 h, 91% (**9**), 89% (**12**); (iv) Pd–C (10%), EtOAc, rt, 7 h, quantitative; (v) $NaIO_4$ (4 equiv), $RuCl_3$ (2.5 mol %), CCl_4, CH_3CN, H_2O, rt, 2 h, 76% (**10**), 73% (**14**); (vi) TsCl, Et_3N, CH_2Cl_2, rt, 24 h, 91%.



Scheme 3. Reagents and conditions: (i) Allylmagnesium iodide, Et_2O, −50 °C to rt, 18 h, 63%; (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 24 h, 87%; (iii) NaN_3, DMF, 80 °C, 36 h, 71%; (iv) $LiAlH_4$, Et_2O, 0 °C to rt, 8 h, 94%; (v) TsCl, pyridine, CH_2Cl_2, rt, 18 h, 81%; (vi) NaH, allyl bromide, THF–DMSO (5:1), 0 °C to rt, 16 h, 90%; (vii) **8** (5 mol %), CH_2Cl_2, rt, 1.5 h, 92%; (viii) HCl (6 N), THF, rt, 5 h, 76%; (ix) Pd–C (10%), EtOAc, rt, 6 h, 93%; (x) $NaIO_4$ (4 equiv), $RuCl_3$ (2.5 mol %), CCl_4, CH_3CN, H_2O, rt, 3 h, 71%.

enantiomeric *N*-tosylpipecolic acids **14** and **24** was determined by chiral HPLC studies, which indicated the enantiomeric excess values to be 96% and 93%, respectively.[16]

Various hydroxylated pyridine derivatives possess diverse biological activities and therefore have received considerable attention from synthetic organic chemists.[17] Many hydroxylated pipecolic acid derivatives have also been prepared in this regard.[18] We therefore investigated the conversion of the unsaturated piperidine derivative **12** to 4,5-dihydroxypipecolic acid derivatives. Thus, OsO_4 mediated dihydroxylation of compound **12** (Scheme 4) provided an almost 1:1 mixture of the stereoisomeric diols **25** and **26** (stereochemistry not determined at this stage), which were separated by column chromatography, compound **26** eluting first. The hydroxyl groups in compound **25** were then protected as benzyl ethers to form **27**. Cleavage of the cyclohexylidene unit in **27** leading to diol **29** followed by oxidative cleavage using the $RuCl_3$–$NaIO_4$ combination led to the formation of the pipecolic acid derivative **30** with concomitant conversion of the benzyl groups to the corresponding benzoates. The dibenzoate derivative **30** was then hydrolysed to the dihydroxypipecolic acid derivative **31**. The stereochemistry of the C-4 and C-5 centres indicated in compound **25**, and in the



Scheme 4. Reagents and conditions: (i) OsO_4, NMMO, acetone–H_2O (4:1), rt, 12 h, **25** (46%), **26**, 38%; (ii) NaH (3 equiv), BnBr (3 equiv), THF–DMSO (10:1), 0 °C to rt, 18 h, **27** (67%), **28** (66%); (iii) HCl (6 N), THF, rt, 5 h, **29** (81%), **32** (82%); (iv) $NaIO_4$ (4 equiv), $RuCl_3$ (2.5 mol %), CCl_4–CH_3CN–H_2O (1:1:1.5), rt, 2 h, **30** (53%), **33** (59%); (v) KOH (1 M, 10 equiv), MeOH, rt, 10 h, **31** (71%), **34** (68%).

compounds derived thereof, was followed from extensive one- and two-dimensional ^{1}H NMR spectral data of compound **30** including homonuclear decoupling experiments. In the ^{1}H NMR spectrum of compound **30** the H-5 signal was located at δ 5.01 (ddd, $J = 11.2$, 5.5, 2.7 Hz). One of the C-6 protons at δ 3.81 (dd, $J = 13.8$, 11.6 Hz) exhibited a diaxial coupling of ~11 Hz with H-5, while the second H-6 at δ 4.04 (dd, $J = 13.3$, 5.6 Hz) showed an equatorial–axial coupling of 5.6 Hz indicating that H-5 was axially oriented. Moreover, H-5 showed an nOe with the axial proton at C-3 appearing at δ 2.11 (ddd, $J = 15.0$, 6.9, 2.1 Hz). Other data[19] pointed to a distorted chair-like conformation of **30** in which the lone pair on nitrogen is axially oriented.

Likewise, the isomeric diol **26** was transformed into (*2S, 4S,5R*)-4,5-dihydroxy-*N*-tosylpipecolic acid (**34**) through intermediates **32** and **33** following an analogous sequence of events.

In summary, we have developed complementary syntheses of both the enantiomers of N-protected pipecolic acid and two isomeric 4,5-dihydroxypipecolic acid derivatives from a common starting material. The methodology is expected to be applicable for the synthesis of other piperidine derivatives and the compounds prepared may prove to be of interest.

Acknowledgements

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References and notes

1. Zacharius, R. M.; Thompson, J. F.; Steward, J. C. *J. Am. Chem. Soc.* **1952**, *74*, 2949.
2. (a) Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419–4420; (b) Ireland, R. E.; Gleason, J. L.; Gegnas, L. D.; Highsmith, T. K. *J. Org. Chem.* **1996**, *61*, 6856–6872; (c) Hanessian, S.; Papeo, G.; Angiolini, M.; Fettis, K.; Baretta, M.; Munro, A. *J. Org. Chem.* **2003**, *68*, 7204–7218; (d) Copeland, T. D.; Wondrak, E. M.; Tozser, J.; Roberts, M. M.; Oroszlan, S. *Biochem. Biophys. Res. Commun.* **1990**, *169*, 310–314; (e) Beil, E. A. *J. Agric. Food Chem.* **2003**, *51*, 2854–2865; (f) Sardine, F. J.; Rapoport, H. *Chem. Rev.* **1999**, *99*, 3329–3366; (g) Flynn, G. A.; Giroux, E. L.; Dage, R. C. *J. Am. Chem. Soc.* **1987**, *109*, 7914–7915.
3. (a) Cheoug, P. H.-Y.; Zhang, H.; Thayumanavan, R.; Tanaka, F.; Houk, K. N.; Barbas, C. F., III. *Org. Lett.* **2006**, *8*, 811–814; (b) Aroyan, C. E.; Vasbinder, M. M.; Miller, S. *Org. Lett.* **2005**, *7*, 3849–3851.
4. For a recent review, see: Kadouri-Puchot, C.; Comesse, S. *Amino Acids* **2005**, *29*, 101–130.
5. (a) Fadel, A.; Lahrache, N. *J. Org. Chem.* **2007**, *72*, 1780–1784; (b) Wilkinson, T. J.; Stehle, N. W.; Beak, P. *Org. Lett.* **2000**, *2*, 155–158; (c) Teoh, E.; Campi, E. M.; Jackson, W. R.; Robinson, A. J. *Chem. Commun.* **2002**, 978–979; (d) Pal, B.; Ikeda, S.; Kominami, H.; Kera, Y.; Ohtani, B. *J. Catal.* **2003**, *217*, 152–159; (e) Rogers, L. M.-A.; Rouden, J.; Lecomte, L.; Lasne, M.-C. *Tetrahedron Lett.* **2003**, *44*, 3047–3050; (f) Calmes, M.; Escale, F.; Rolland, M.; Martinez, J. *Tetrahedron: Asymmetry* **2003**, *14*, 1685–1689.
6. (a) Agami, C.; Comesse, S.; Kadouri-Puchot, C. *J. Org. Chem.* **2002**, *67*, 2424–2428; (b) Tjen, K. C. M. F.; Kinderman, S. S.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Chem. Commun.* **2000**, 699–700; (c) Maison, W.; Adiwidjaja, G. *Tetrahedron Lett.* **2002**, *43*, 5957–5960; (d) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762–766; (e) Souers, A. J.; Ellman, J. A. *J. Org. Chem.* **2000**, *65*, 1222–1224; (f) Kanayama, T.; Yoshida, K.; Miyabe, H.; Kimachi, T.; Takemoto, Y. *J. Org. Chem.* **2003**, *68*, 6197–6201; (g) Varray, S.; Lazaro, R.; Martinez, J.; Lamaty, F. *Eur. J. Org. Chem.* **2002**, 2308–2316; (h) Kim, I. S.; Ji, Y. J.; Jung, Y. H. *Tetrahedron Lett.* **2006**, *47*, 7289–7293.
7. (a) Greek, C.; Ferreira, F.; Genet, G. P. *Tetrahedron Lett.* **1996**, *37*, 2031–2034; (b) Chenevert, R.; Morin, M.-P. *Tetrahedron: Asymmetry* **1996**, *7*, 2161–2164; (c) Meyers, A. G.; Gleason, J. L.; Yoon, T. *J. Am. Chem. Soc.* **1995**, *117*, 8488–8489; (d) Aketa, K.; Terashima, S.; Yamada, S. *Chem. Pharm. Bull.* **1976**, *24*, 621–630.
8. Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem.* **1995**, *60*, 585–587.
9. For reviews, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293; (b) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895–1946; (c) Thomas, E. J. *Chem. Commun.* **1997**, 411–418; (d) Block, R. *Chem. Rev.* **1998**, *98*, 1407–1438; (e) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094.
10. Adams, J. P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 125–139.
11. (a) Chattopadhyay, S. K.; Sarkar, K.; Karmakar, S. *Synlett* **2005**, 2083–2085; (b) Chattopadhyay, S. K.; Sarkar, K.; Thander, L.; Roy, S. P. *Tetrahedron Lett.* **2007**, *48*, 6113–6116.
12. For reviews on RCM, see: (a) Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K. C.; Rahaman, H.; Roy, B. *Tetrahedron* **2007**, *63*, 3919–3952; (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140; (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238; (d) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141–8153; (e) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450; (f) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388.
13. (a) Barret, G. C. *Amino Acids, Peptides and Proteins*; Springer: London, 2001, Vol. 32; (b) Adlington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J.; Tang, L. M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 303–305; (c) Bunnage, M. E.; Davies, S. G.; Roberts, P. M.; Smith, A. D.; Withey, J. M. *Org. Biomol. Chem.* **2004**, *2*, 2763–2776; (d) Jones, R. C. F.; Berthelot, D. J. C.; Iley, J. N. *Tetrahedron* **2001**, *57*, 6539–6555; (e) Lygo, B.; Slack, D.; Wilson, C. *Tetrahedron Lett.* **2005**, *46*, 6629–6632; (f) Hale, K. J.; Cai, J.; Delisser, V.; Manaviazar, S.; Peak, S. A.; Bhatia, G. S.; Collins, T. C.; Jogia, N. *Tetrahedron* **1996**, *52*, 1047–1068.
14. All new compounds reported here gave satisfactory spectroscopic and/or analytical data. Data for **31**: Mp: 197–198 °C. $[\alpha]_D$ +54 (*c* 0.1, MeOH). IR (KBr): 3347, 1710, 1328, 1159 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.64 (2H, d, $J = 8.1$), 7.36 (2H, d, $J = 7.8$), 4.88 (1H, d, $J = 4.0$, D_2O exchangeable), 4.32 (1H, d, $J = 7.2$), 3.67 (1H, quin, $J = 1.8$), 3.30 (1H, dd, $J = 12.6$, 5.6), 3.23 (1H, t, $J = 11.0$), 3.10 (1H, ddd, $J = 11.0$, 5.4, 2.4), 2.34 (3H, s), 2.22 (1H, ddd, $J = 14.4$, 3.6, 1.8), 1.65 (1H, ddd, $J = 13.8$, 7.2, 2.4). ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.7 (s), 142.8 (s), 137.8 (s), 129.6 (d), 128.7 (d), 66.8 (d), 65.7 (d), 50.7 (d), 42.0 (t), 33.1 (t), 20.9 (q). HRMS (TOF MS ES$^+$): obsd 338.0679 (M+Na); calcd 338.0674. Data for **34**: Mp: 189–190 °C $[\alpha]_D$ +96 (*c* 0.12, MeOH). IR (KBr): 3418, 1346, 1727, 1324, 1159 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.64 (2H, d, $J = 7.8$), 7.32 (2H, d, $J = 8.1$), 4.78 (1H, br s, D_2O exchangeable) 4.62 (1H, br s, D_2O exchangeable), 4.37 (1H, d, $J = 6.0$), 3.65 (1H, br s), 3.63–3.60 (1H, m), 3.37 (1H, dt, $J = 11.0$, 3.6), 3.30 (1H, dd, $J = 13.8$, 1.8), 2.33 (3H, s), 1.88 (1H, dt, $J = 12.6$, 6.6), 1.77 (1H, dt, $J = 12.6$, 3.0). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0 (s), 142.7 (s), 137.2 (s), 129.3 (d), 127.1 (d), 66.0 (d), 65.7 (d), 54.8 (d), 47.9 (t), 29.0 (t), 21.0 (q). HRMS (TOF MS ES$^+$): obsd 338.0670 (M+Na); calcd 338.0674.
15. (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938; (b) Poch, M.; Alcon, M.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron Lett.* **1993**, *34*, 7781–7784.

16. Johnson, R. L.; Rajakumar, G.; Yu, K.-L.; Mishra, R. K. *J. Med. Chem.* **1986**, *29*, 2104–2107. Reported $[\alpha]_D$ values for (*S*)- and (*R*)-*N*-Boc-piperidine-2-carboxylic acid, of equal optical purity, in Aldrich Chemical catalogue are −63.2 (*c* 1.0, AcOH), +68 (*c* 1.0, AcOH), respectively. The enantiomeric excess values for compounds **14** and **24** were determined by HPLC using a CHIRALPAK AD-H column and 20% 2-propanol in hexane as eluent with a flow rate of 0.5;ml/min. The retention times for **14** and **24** were 15.8 and 13.4 min, respectively.
17. (a) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 17–23; (b) Nadin, A. *Contemp. Org. Synth.* **1997**, *4*, 387–414; (c) Bashyal, B. P.; Chow, H. F.; Fleet, G. W. J. *Tetrahedron Lett.* **1986**, *27*, 3205–3208.
18. For some recent reports, see: (a) Jourdant, A.; Zhu, J. *Tetrahedron Lett.* **2000**, *41*, 7033–7036; (b) Brooks, C. A.; Comins, D. L. *Tetrahedron Lett.* **2000**, *41*, 3551–3553; (c) Sabat, M.; Johnson, C. R. *Tetrahedron Lett.* **2001**, *42*, 1209–1212; (d) Haddad, M.; Larcheveque, M. *Tetrahedron Lett.* **2001**, *42*, 5223–5225; (e) Bodas, M. S.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 8461–8463; (f) Liang, N.; Datta, A. *J. Org. Chem.* **2005**, *70*, 10182–10185; (g) Kim, I. S.; Ji, Y. J.; Jung, Y. H. *Tetrahedron Lett.* **2006**, *47*, 7289–7293.
19. These data will be disclosed in a full account of this work.