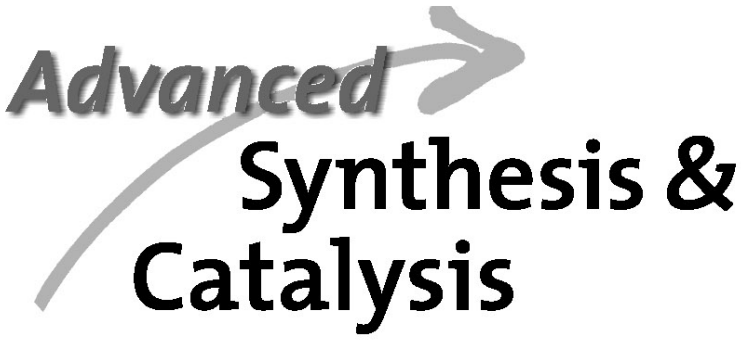


Supporting Information

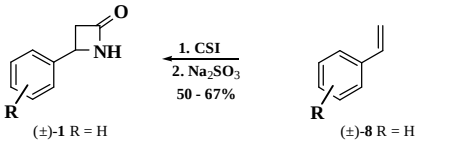
A new route to enantiopure β-aryl-substituted β-amino acids and 4-aryl-substituted β-lactams through lipase-catalyzed enantioselective ring cleavage of β-lactams

Eniko Forró, Ferenc Fülöp*

Institute of Pharmaceutical Chemistry, University of Szeged, H-6701 Szeged, PO Box 427, Hungary

Supporting Information

The spectroscopic and analytical data for compounds (±)-1- (±)-7 (Scheme 1)



(±)-**1** R = H
(±)-**2** R = *p*-Me
(±)-**3** R = *o*-Cl
(±)-**4** R = *m*-Cl
(±)-**5** R = *p*-Cl
(±)-**6** R = *p*-Br
(±)-**7** R = *p*-F

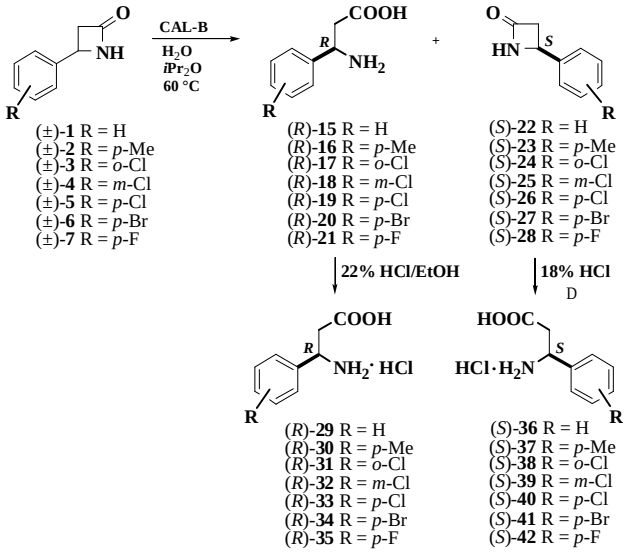
(±)-**8** R = H
(±)-**9** R = *p*-Me
(±)-**10** R = *o*-Cl
(±)-**11** R = *m*-Cl
(±)-**12** R = *p*-Cl
(±)-**13** R = *p*-Br
(±)-**14** R = *p*-F

Scheme 1

(±)-4-Phenyl-2-azetidinone, (±)-1: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.85-2.89 (1H, dd, *J* = 2, 14.8, C*H*$_A$H) 3.41-3.46 (1H, ddd, *J* = 2.4; 5.2; 7.6, C*H*$_B$H), 4.71-4.73 (1H, dd, *J* = 2.5; 5.3, CH), 6.34 (1H, bs, NH) 7.26-7.40 (5H, m, Ph). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ (ppm) 48.6, 51.0, 126.3, 128.8, 129.5, 140.9, 168.8. Analysis: calculated for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52; found: C, 73.42; H, 6.00; N, 9.62.
(±)-4-(*p*-Tolyl)-2-azetidinone, (±)-2: (1.73 g, 63%; mp 87-88 °C, lit.[7] mp 85-86 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.35 (3H, s, CH_3) 2.83-2.87 (1H, dd, *J* = 1.7; 14.8, C*H*$_A$H) 3.39-3.44 (1H, ddd, *J* = 2.4; 5.2; 7.6, C*H*$_B$H), 4.67-4.69 (1H, dd, *J* = 2.3; 5.2, CH), 6.13 (1H, bs, NH) 7.17-7.27 (4H, m, Ph). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ (ppm) 21.8, 48.7, 50.9, 126.3, 130.2, 137.8, 138.7, 168.9. Analysis: calculated for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69; found: C, 74.66; H, 6.83; N, 8.68.
(±)-4-(2-Chlorophenyl)-2-azetidinone, (±)-3: ^{1}H NMR (400 MHz, $CDCl_3$) d (ppm): 2.81-2.85 (1H, dd, *J* = 2.6; 14.9, C*H*$_A$H), 3.52-3.58 (1H, ddd, *J* = 2.9; 5.4; 8.3, C*H*$_B$H), 5.05-5.07 (1H, dd, *J* = 2.6; 5.4, CH), 6.33 (1H, bs, NH), 7.26-7.47 (4H, m, Ph). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ (ppm) 47.4, 48.7, 126.6, 127.8, 129.7, 130.3, 133.2, 138.4, 168.6. Analysis: calculated for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71; found: C, 59.34; H, 4.41; N, 7.58.
(±)-4-(3-Chlorophenyl)-2-azetidinone, (±)-4: ^{1}H NMR (400 MHz, $CDCl_3$) d (ppm): 2.85-2.89 (1H, dd, *J* = 2.0; 14.9, C*H*$_A$H), 3.43-3.49 (1H, ddd, *J* = 2.6; 5.3; 14.9, C*H*$_B$H), 4.69-4.71 (1H, dd, *J* = 2.4; 5.3, CH), 6.20 (1H, bs, NH), 7.24-7.37 (4H, m, Ph). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ (ppm) 48.6, 50.5, 124.4, 126.5, 128.9, 130.8, 135.5, 143.1, 168.5. Analysis: calculated for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71; found: C, 59.51; H, 4.30 N, 7.52.
(±)-4-(4-Chlorophenyl)-2-azetidinone, (±)-5: ^{1}H NMR (400 MHz, $CDCl_3$) d (ppm): 2.82-2.86 (1H, dd, *J* = 1.8; 14.9, C*H*$_A$H), 3.42-3.48 (1H, ddd, *J* = 2.6; 5.3; 14.9, C*H*$_B$H), 4.70-4.72 (1H, dd, *J* = 2.4; 5.2, CH), 6.30 (1H, bs, NH), 7.26-7.36 (4H, m, Ph). ^{13}C NMR (100.62 MHz,

$CDCl_3$) δ (ppm) 48.7, 50.4, 127.7, 129.7, 134.6, 139.4, 168.6. Analysis: calculated for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71; found: C, 59.50; H, 4.35; N, 7.82.
(±)-4-(4-Bromophenyl)-2-azetidinone, (±)-6: ^{1}H NMR (400 MHz, $CDCl_3$) d (ppm): 2.81-2.86 (1H, dd, *J* = 2.0; 14.9, C*H*$_A$H), 3.42-3.48 (1H, ddd, *J* = 2.6; 5.3; 7.9, C*H*$_B$H), 4.68-4.70 (1H, dd, *J* = 2.5; 5.3, CH), 6.24 (1H, bs, NH), 7.24-7.51 (4H, m, Ph). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ (ppm) 48.6, 50.5, 122.7, 128.0, 132.6, 139.9, 168.6. Analysis: calculated for C_9H_8BrNO: C, 47.82; H, 3.57; N, 6.20; found: C, 47.76; H, 3.47; N, 76.11.
(±)-4-(4-Fluorophenyl)-2-azetidinone, (±)-7: ^{1}H NMR (400 MHz, $CDCl_3$) d (ppm): 2.82-2.87 (1H, ddd, *J* = 0.8; 2.5; 14.9, C*H*$_A$H), 3.41-3.47 (1H, ddd, *J* = 2.6; 5.3; 14.9, C*H*$_B$H), 4.71-4.73 (1H, dd, *J* = 2.5; 5.3, CH), 6.26 (1H, bs, NH), 7.05-7.36 (4H, m, Ph). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ (ppm) 48.7, 50.4, 116.3, 116.5, 127.9, 128.0, 136.6, 164.4, 168.8. Analysis: calculated for C_9H_8FNO: C, 65.45; H, 4.88; N, 8.48; found: C, 65.34; H, 4.85; N, 8.30.

The spectroscopic and analytical data for enantiopure compounds 15 - 42 (Scheme 2)



Scheme 2

(*R*)-**15**: ^{1}H NMR (400 MHz, D_2O) δ (ppm): 2.80-2.95 (2H, m, CH_2), 4.64-4.68 (1H, m, CH), 7.46-7.52 (5H, m, Ph). Analysis: calculated for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48; found: C, 65.41; H, 6.58; N, 8.49.
(*R*)-**16**: ^{1}H NMR (400 MHz, D_2O) δ (ppm): 2.35 (3H, s, CH_3), 2.77-2.93 (2H, m, CH_2), 4.60-4.64 (1H, m, CH), 7.31-7.37 (4H, m, Ph). Analysis: calculated for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82; found: C, 66.83; H, 7.33; N, 7.64.
(*R*)-**17**: ^{1}H NMR (400 MHz, D_2O) δ (ppm): 2.85-2.88 (2H, m, CH_2), 5.09-5.14 (1H, m, CH), 7.41-7.54 (4H, m, Ph). Analysis: calculated for $C_9H_{10}ClNO_2$: C, 54.15; H, 5.05; N, 7.02; found: C, 54.06; H, 5.17; N, 7.00.
(*R*)-**18**: ^{1}H NMR (400 MHz, D_2O) δ (ppm): ^{1}H NMR (400 MHz, D_2O) d (ppm): 2.79-2.93 (2H, m, CH_2), 4.64-4.68 (1H, m, CH), 7.39-7.51 (4H, m, Ph). Analysis: calculated for $C_9H_{10}ClNO_2$: C, 54.15; H, 5.05; N, 7.02; found: C, 54.37; H, 5.27; N, 7.37.
(*R*)-**19**: ^{1}H NMR (400 MHz, D_2O) δ (ppm): ^{1}H NMR (400 MHz, D_2O) d (ppm): 2.79-2.94 (2H, m, CH_2), 4.64-4.68 (1H, m, CH), 7.43-7.51 (4H, m, Ph). Analysis: calculated for $C_9H_{10}ClNO_2$: C, 54.15; H, 5.05; N, 7.02; found: C, 54.23; H, 4.88; N, 6.94.

(*R*)-**20**: ^{1}H NMR (400 MHz, D_2O) δ (ppm): ^{1}H NMR (400 MHz, D_2O) d (ppm): 2.83-2.89 (2H, m, CH_2), 4.63-4.66 (1H, m, CH), 6.37-7.67 (4H, m, Ph). Analysis: calculated for $C_9H_{10}BrNO_2$: C, 44.29; H, 4.13; N 5.74; found: C, 44.08; H, 4.13; N 5.67.
(*R*)-**21**: ^{1}H NMR (400 MHz, D_2O) δ (ppm): ^{1}H NMR (400 MHz, D_2O) d (ppm): 2.53-2.69 (2H, m, CH_2), 4.39-4.42 (1H, m, CH), 6.94-7.22 (4H, m, Ph). Analysis: calculated for $C_9H_{10}FNO_2$: C, 59.01; H, 5.50; N 7.65; found: C, 58.88; H, 5.54; N 7.69.
(*S*)-**22**: The ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data are similar to those for (±)-**1**. Analysis: calculated for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52; found: 73.37; H, 6.08; N, 9.60.
(*S*)-**23**: The ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data are similar to those for (±)-**2**. Analysis: calculated for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69; found: C, 74.55; H, 6.65; N, 8.70.
(*S*)-**24**: The ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data are similar to those for (±)-**3**. Analysis: calculated for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71; found: C, 59.66; H, 4.35; N, 7.66.
(*S*)-**25**: The ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data are similar to those for (±)-**4**. Analysis: calculated for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71; found: C, 59.61; H, 4.38; N, 7.80.
(*S*)-**26**: The ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data are similar to those for (±)-**5**. Analysis: calculated for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71; found: C, 59.59; H, 4.39; N, 7.72.
(*S*)-**27**: The ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data are similar to those for (±)-**6**. Analysis: calculated for C_9H_8BrNO: C, 47.82; H, 3.57; N, 6.20; found: C, 47.97; H, 3.55; N, 6.08.
(*S*)-**28**: The ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data are similar to those for (±)-**7**. Analysis: calculated for C_9H_8FNO: C, 65.45; H, 4.88; N, 8.48; found: C, 65.59; H, 4.67; N, 8.51.
(*R*)-**29**: ^{1}H NMR (400 MHz, D_2O) d (ppm): 3.05-3.20 (2H, m, CH_2), 4.78-4.80 (1H, m, CH), 7.48-7.49 (5H, m, Ph). Analysis: calculated for $C_9H_{11}NO_2$·HCl: C, 53.61; H, 6.00; N, 6.95; found: C, 53.47; H, 6.09; N, 7.15.
(*R*)-**30**: ^{1}H NMR (400 MHz, D_2O) δ (ppm): 2.34 (3H, s, CH_3), 3.02-3.18 (2H, m, CH_2), 4.72-4.76 (1H, m, CH), 7.32-7.37 (4H, m, Ph). Analysis: calculated for $C_{10}H_{13}NO_2$·HCl: C, 55.69; H, 6.54; N, 6.49; found: C, 55.72; H, 6.50; N, 6.38.
(*R*)-**31**: ^{1}H NMR (400 MHz, D_2O) δ (ppm): ^{1}H NMR (400 MHz, D_2O) d (ppm): 3.12-3.25 (2H, m, CH_2), 5.25-5.28 (1H, m, CH), 7.46-7.56 (4H, m, Ph). Analysis: calculated for $C_9H_{10}ClNO_2$·HCl: C, 45.79; H, 4.70; N, 5.93; found: C, 45.65; H, 4.74; N, 6.20.
(*R*)-**32**: ^{1}H NMR (400 MHz, D_2O) δ (ppm): 3.05-3.20 (2H, m, CH_2), 4.73-4.80 (1H, m, CH), 7.41-7.52 (4H, m, Ph). Analysis: calculated for $C_9H_{10}ClNO_2$·HCl: C, 45.79; H, 4.70; N, 5.93; found: C, 45.64; H, 4.60; N, 6.19.
(*R*)-**33**: ^{1}H NMR (400 MHz, D_2O) d (ppm): 3.04-3.19 (2H, m, CH_2), 4.76-4.80 (1H, m, CH), 7.44-7.52 (4H, m, Ph). Analysis: calculated for $C_9H_{10}ClNO_2$·HCl: C, 45.79; H, 4.70; N, 5.93; found: C, 45.76; H, 4.66; N, 5.88.
(*R*)-**34**: ^{1}H NMR (400 MHz, D_2O) δ (ppm): ^{1}H NMR (400 MHz, D_2O) d (ppm): 3.10-3.14 (2H, m, CH_2), 4.71-4.77 (1H, m, CH), 7.40-7.68 (4H, m, Ph). Analysis: calculated for $C_9H_{10}BrNO_2$·HCl: C, 38.53; H, 3.95; N, 4.99; found: C, 38.68; H, 4.10; N, 5.05.
(*R*)-**35**: ^{1}H NMR (400 MHz, D_2O) δ (ppm): ^{1}H NMR (400 MHz, D_2O) d (ppm): 3.04-3.19 (2H, m, CH_2), 4.78-4.80 (1H, m, CH), 7.20-7.51 (4H, m, Ph). Analysis: calculated for $C_9H_{10}FNO_2$·HCl: C, 49.22; H, 5.05; N, 6.38; found: C, 49.10; H, 5.16; N, 6.31.
(*S*)-**36**: The ^{1}H NMR (400 MHz, H_2O) δ (ppm) data are similar to those for (*R*)-**29**. Analysis: calculated for $C_9H_{11}NO_2$·HCl: C, 53.61; H, 6.00; N, 6.95; found: C, 53.43; H, 6.01; N, 6.93.
(*S*)-**37**: The ^{1}H NMR (400 MHz, H_2O) δ (ppm) data are similar to those for (*R*)-**30**. Analysis: calculated for $C_{10}H_{13}NO_2$·HCl: C, 55.69; H, 6.54; N, 6.49; found: C, 55.64; H, 6.37; N, 6.40.
(*S*)-**38**: The ^{1}H NMR (400 MHz, H_2O) δ (ppm) data are similar to those for (*R*)-**31**. Analysis: calculated for $C_9H_{10}ClNO_2$·HCl: C, 45.79; H, 4.70; N, 5.93; found: C, 45.61; H, 4.70; N, 5.65.

(*S*)-**39**: The ^{1}H NMR (400 MHz, H_2O) δ (ppm) data are similar to those for (*R*)-**32**. Analysis: calculated for $C_9H_{10}ClNO_2$·HCl: C, 45.79; H, 4.70; N, 5.93; found: C, 45.68; H, 4.55; N, 5.89.
(*S*)-**40**: The ^{1}H NMR (400 MHz, H_2O) δ (ppm) data are similar to those for (*R*)-**33**. Analysis: calculated for $C_9H_{10}ClNO_2$·HCl: C, 45.79; H, 4.70; N, 5.93; found: C, 45.77; H, 4.61; N, 6.12.
(*S*)-**41**: The ^{1}H NMR (400 MHz, H_2O) δ (ppm) data are similar to those for (*R*)-**34**. Analysis: calculated for $C_9H_{10}BrNO_2$·HCl: C, 38.53; H, 3.95; N, 4.99; found: C, 38.37; H, 3.90; N, 4.92.
(*S*)-**42**: The ^{1}H NMR (400 MHz, H_2O) δ (ppm) data were similar to those for (*R*)-**35**. Analysis: calculated for $C_9H_{10}FNO_2$·HCl: C, 49.22; H, 5.05; N, 6.38; found: C, 49.07; H, 4.92; N, 6.40.