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Short and Practical Syntheses of (*R*)-(–)-Carnitine and (*R*)-(–)-γ-Amino-β-hydroxybutyric Acid (GABOB)

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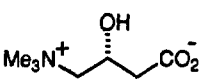
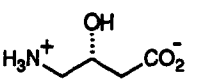
Abstract: Short and practical syntheses of (*R*)-(-)-carnitine and (*R*)-(-)-γ-amino-β-hydroxybutyric acid have been developed, both commencing with the catalytic asymmetric dihydroxylation of allyl bromide.

(*R*)-Carnitine (**1**) and (*R*)-γ-amino-β-hydroxybutyric acid (GABOB) (**2**) have attracted considerable attention in recent years, owing to their interesting biological properties and usefulness as pharmaceuticals. GABOB has found use as an antiepileptic and hypotensive drug[1] and (*R*)-carnitine is a vitamin-like compound (vitamin B_T), which is responsible for the metabolism of long-chain fatty acids, by regulating their transport through mitochondrial membranes.[2] Carnitine has been applied in therapy as a stimulator of fatty acid degradation and also in the treatment of heart disease and other disorders.[3] Since the (*S*)-enantiomer acts as a competitive inhibitor of carnitine acyltransferases,[4] causing depletion of the (*R*)-carnitine level in heart tissue, the preparation of highly enantiomerically enriched material is essential.



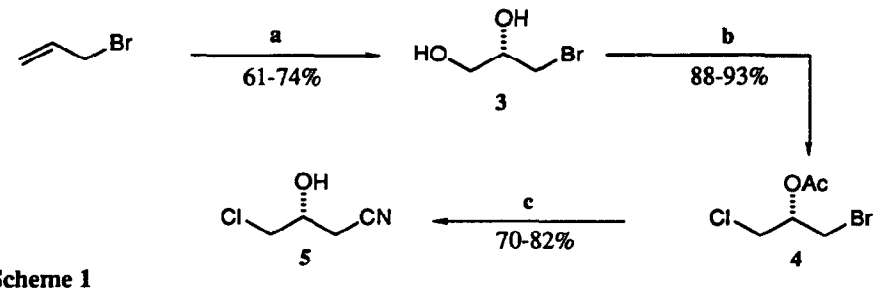
(*R*)-(-)-Carnitine (1)



(*R*)-(-)-GABOB (2)

In recent years, a large number of reports and patents[5] have dealt with the syntheses of (*R*)-carnitine and (*R*)-GABOB employing optical resolution of intermediates,[6] fermentation techniques[7] and asymmetric synthesis. A number of syntheses start with natural products[8] or use *stoichiometric* quantities of chiral auxiliaries to produce optically active intermediates.[9] However, there are still very few syntheses which make use of *catalytic* asymmetric reactions for the preparation of enantiomerically enriched intermediates.[10]

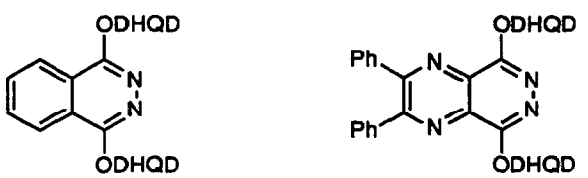
We now report practical enantioselective syntheses of both (*R*)-carnitine and (*R*)-GABOB, commencing with the catalytic asymmetric dihydroxylation of allyl bromide to give enantiomerically enriched (*S*)-(+)-3-bromopropane-1,2-diol (**3**) (Scheme 1). Further elaboration provides the γ-chloro-β-hydroxy nitrile intermediate **5**, which represents the central intermediate for the synthesis of both targets. All intermediates and products can be purified by distillation or recrystallization which makes a scale up feasible.



Scheme 1

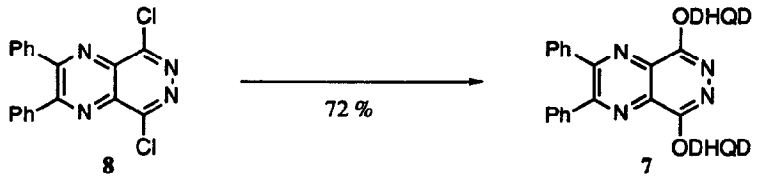
a) $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, ligand **7** (cat.), $K_2OsO_2(OH)_4$ (cat.); **b)** i. $MeC(OMe)_3$, cat. pTSA, r.t., 45 min; ii. Me_3SiCl, r.t., 4 h; **c)** KCN, MeOH, r.t., 17 h.

1. Preparation of the central nitrile intermediate 5. Initially, the asymmetric dihydroxylation of allyl bromide under the previously described biphasic reaction conditions in the presence of 1 mole-% of bis(dihydroquinidine) phthalazine (**6**) as a chiral ligand[11] gave diol **3** in 66% enantiomeric excess and yields between 40 and 50 %. Presumably, the moderate yield was caused by partial loss of the product as water soluble glycidol, formed by cyclization of **3** under the basic reaction conditions. Consequently, a noticable increase in yield was observed when $NaHCO_3$ was added to the reaction mixture as a pH buffer and the diol **3** could now be isolated in yields between 61 and 74 %. Unfortunately, the optimization of the enantioselectivity proved more difficult. Thus, asymmetric dihydroxylation of alternative substrates such as allyl chloride and allyl tosylate afforded the corresponding diols in only 54% ee [$(DHQ)_2$-PHAL] and 40 % ee, respectively, and the reaction of allyl bromide in the presence of the dihydroquinidine 9-phenanthryl ether ligand[12] also gave unsatisfactory results (60 % ee). However, modification of our phthalazine ligand **6** improved the situation. Thus, dihydroxylation of allyl bromide in the presence of 1 mole-% of the sterically more encumbered ligand **7** led to the formation of diol **3** in 72 % ee. The optical purity could be enhanced at a later stage by recrystallization. Further studies revealed that the enantioselectivity did not drop significantly when the amount of chiral ligand employed was reduced to only 0.36 mole-%. Additionally, an acidic work up allowed the recovery of the ligand in 88 % yield, thereby making the process highly efficient.



DHQD = Dihydroquinidine

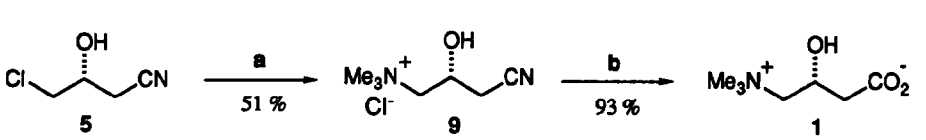
Initial studies in our group indicate that **7** quite generally induces higher enantioselectivity in the dihydroxylation of terminal olefins. Ligand **7** was prepared in good yield by condensation of the sodium alkoxide of dihydroquinidine with dichloride **8** (Scheme 2).[13]



Scheme 2
Dihydroquinidine, NaH, DMF, r.t. to 115°C, 1 h

Conversion of diol **3** into the acetoxy chloride **4** was achieved in excellent yield by reaction with trimethyl orthoacetate, followed by treatment with trimethylsilyl chloride according to our recently published protocol.[14] Halide **4** is a densely functionalized three carbon chiral building block with a different functional group attached to each carbon atom, thereby enabling selective manipulation. Thus, selective displacement of bromide with KCN in methanol afforded the central nitrile intermediate **5** in good yield.

2. Preparation of (R)-(-)-Carnitine (1). Treatment of the chloro nitrile intermediate **5** with an excess of aqueous trimethyl amine and purification of the crude product by recrystallization from ethanol gave carnitine nitrile (**9**) in 63 % yield and 82 % ee as calculated from the optical rotation (Scheme 3). Two further recrystallizations from the same solvent afforded the product in 51 % overall yield from **5** and an optical purity of greater than 95 % ee. The nitrile was subsequently converted into carnitine hydrochloride by hydrolysis with concentrated hydrochloric acid at temperatures below 75°C to prevent β-elimination of water. Treatment of the crude hydrochloride with basic ion exchange resin afforded enantiomerically pure carnitine as a colorless hygroscopic solid. The physical data, including the specific rotation ($[\alpha]_D^{22}$ -30.0 (c 1.2, H_2O)), were in good agreement with published values[6a] ($[\alpha]_D^{20}$ -31.1 (c 1.0, H_2O)).

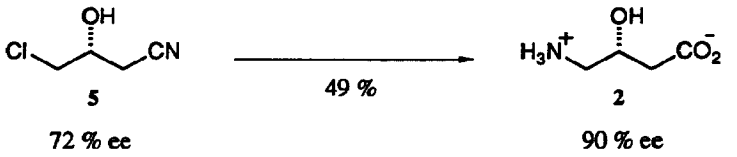


72 % ee >95% ee $[\alpha]_D^{22}$ -30.0 (c 1.2, H_2O)
Lit.:[6a] $[\alpha]_D^{20}$ -31.1 (c 1, H_2O)

Scheme 3
a) i. aq. Me_3N, r.t., 3 h; ii. recrystallization (3x) from EtOH; b) i. conc. HCl, 50 to 75°C, 6 h;
ii. Amberlite IRA 410 (OH^-)

3. Preparation of (R)-γ-amino-β-hydroxybutyric acid (2). Surprisingly, the preparation of GABOB using an analogous reaction sequence was unsuccessful, since treatment of the chloro nitrile intermediate **5** with aqueous ammonia resulted in decomposition and none of the desired γ-amino-β-hydroxy nitrile was obtained. An optimization study revealed the following three-step, 'one-pot' sequence to give the best results

(Scheme 4). Thus, the nitrile **5** was first hydrolyzed to the carboxamide by treatment with concentrated hydrochloric acid at room temperature. Following evaporation of the acid, the resulting residue was dissolved in saturated aqueous ammonia to effect displacement of chloride. Finally, hydrolysis of the carboxamide in refluxing dilute hydrochloric acid and purification by ion exchange on acidic resin, followed by two recrystallizations from ethanol-water gave (*R*)-(-)-GABOB in 49 % yield and 90 % ee as determined from the specific rotation ($[\alpha]_D^{22}$ -18.6 (c 1.5, H_2O); lit.:[15] $[\alpha]_D^{25}$ -20.7 (c 1.8, H_2O)).



5 **2**

72 % ee 90 % ee

$[\alpha]_D^{22}$ -18.6 (c 1.5, H_2O)

Lit.:[15] $[\alpha]_D^{25}$ -20.7 (c 1.8, H_2O)

Scheme 4

i. conc. HCl, r.t., 8.25 h; ii. 28% NH_3/H_2O, r.t., 14 h; iii. 10 % HCl, reflux, 4.5 h; iv. Amberlite IR 120 (H^+); v. recrystallization (x2) from EtOH-H_2O

In summary, the catalytic asymmetric dihydroxylation of allyl bromide provides quick access to the biologically active γ-amino-β-hydroxy amino acids, (*R*)-carnitine and (*R*)-GABOB. Only 0.36 mole-% of the easily recoverable ligand **7** is needed to produce the diol intermediate **3** with 72 % ee, and the final products are obtained in high enantiopurity by recrystallization from suitable solvents. Furthermore, neither synthesis requires purification of intermediates by column chromatography, thereby making scale up feasible.

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Experimental Part. *General* — ^1H NMR spectra were recorded in $CDCl_3$ or D_2O at 250 or 400 MHz. Residual protic solvent $C\underline{H}Cl_3$ (δ_H=7.26 ppm) or $\underline{H}OD$ (δ_H=4.65 ppm) was used as internal reference. ^{13}C NMR spectra were recorded in $CDCl_3$ or D_2O at 100 MHz using the resonance of $\underline{C}DCl_3$ (δ_C=77.0 ppm, t) or 1,4-dioxane (δ_C=67.4 ppm), respectively, as internal reference. Analytical thin layer chromatography and reverse phase thin layer chromatography were performed using pre-coated glass-backed plates, Merck Silica gel 60 F_{254} and Merck Silica gel RP-8 F_{254s}, respectively. HPLC was performed on a Chiralcel OD (25 cm x 4.6 mm I.D.) column. The detector was set to 254 nm.

(*S*)-(+)-3-Bromo-1,2-propanediol (3). ^{t}Butanol/H_2O (500 ml of a 1:1 mixture) was added to $K_3Fe(CN)_6$ (49.0 g, 148.8 mmol), K_2CO_3 (20.6 g, 149 mmol), $NaHCO_3$ (12.5 g, 148.8 mmol), ligand **7** (0.17 g, 0.183 mmol) and $K_2OsO_2(OH)_4$ (0.037 g, 0.1 mmol). The mixture was stirred vigorously at room temperature for 10 min and then cooled to 0°C, whereupon allyl bromide (4.3 ml, 49.7 mmol) was added. Stirring was continued for 14.5 h and the reaction was quenched by portionwise addition of $Na_2S_2O_5$ (27 g,

142 mmol) (Caution! Vigorous evolution of CO_2). After warming to room temperature, ethyl acetate (350 ml) was added and stirring was continued for a further 10 min. The aqueous layer was separated and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with 1 N H_2SO_4 (50 ml) to extract the ligand and the aqueous acid was reextracted with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with saturated $NaHCO_3$ (30 ml), dried ($MgSO_4$) and evaporated. Purification of the yellow residue (5.3 g) by vacuum distillation (b.p. 78°C/0.3 mmHg) gave the bromodiol **3** (4.66 g, 61 %) as a colorless oil. The enantiomeric purity was determined to be 72 % ee by HPLC of the bis-MTPA derivative [Chiralcel OD column, 1.5 % 2-propanol/hexane, 1 ml/min, r_t (2*R*) 16.2 min, r_t (2*S*) 29.4 min]; $[\alpha]_D^{22}$ +3.8 (c 1.75, $CHCl_3$); IR (neat film): ν 3367 (bs), 2935 (m), 2887 (m), 1426 (m), 1100 (m), 1065 (s) and 1030 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.98-3.89 (1H, m, H-2), 3.78 (1H, ddd, J_{vic} 3.9, 6.2, J_{gem} 11.3 Hz, H-1), 3.69 (1H, dt, J_{gem} 11.4, J_{vic} 5.7 Hz, H-1), 3.51 (1H, dd, J_{vic} 5.0, J_{gem} 10.5, H-3), 3.46 (1H, dd, J_{vic} 6.5, J_{gem} 10.5 Hz, H-3), 2.83 (1H, d, J 5.2 Hz, 2-OH), 2.31 (1H, t, J 5.9 Hz, 1-OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 71.4 (1 CH, C-2), 64.3 (1 CH_2, C-1), 34.9 (1 CH_2, C-3).

Recovery of ligand 7. The $NaHCO_3$ and H_2SO_4 extracts were combined carefully, basified with 1 M NaOH and extracted with ethyl acetate (3 x 30 ml). The combined organic layers were dried ($MgSO_4$) and evaporated to afford the ligand **7** (0.15 g, 88 %) as a yellow foam.

(2*S*)-(-)-1-Bromo-3-chloro-2-propyl acetate (4). Trimethyl orthoacetate (5.6 ml, 44.6 mmol) was added to a solution of the diol **3** (5.42 g, 34.97 mmol) and pTSA (17 mg, 0.089 mmol) in CH_2Cl_2 (25 ml) at room temperature. After 45 min, the solvent was evaporated and residual methanol was removed under high vacuum (0.1 mmHg) for 1 min. The residue was dissolved in CH_2Cl_2 (25 ml) and trimethylsilyl chloride (5.6 ml, 44.1 mmol) was added with stirring, while the flask was cooled with cold water to keep the temperature below 30°C. The water bath was removed and after 1 h, further trimethyl orthoacetate (0.25 ml, 1.99 mmol) was added, followed by further trimethylsilyl chloride (0.25 ml, 1.97 mmol) 15 min later. After 4 h, a tlc test (35 % ethyl acetate - hexane) showed almost complete absence of hydroxy acetate [formed by hydrolysis of the orthoacetate intermediate on the tlc plate, r_f 0.23, r_f (**4**) 0.67] and the reaction mixture was poured into 1 M HCl (50 ml). The product was extracted with CH_2Cl_2 (3 x 50 ml), the combined extracts were washed with saturated $NaHCO_3$ (30 ml), dried ($MgSO_4$) and evaporated. Purification of the residue by vacuum distillation (b.p. 76°C/6.8 mmHg) gave **4** as a colorless liquid (7.23 g, 96 %); $[\alpha]_D^{23}$ -2.20 (c 3.23, $CHCl_3$); IR (neat film): ν 3035 (m), 2971 (m), 1748 (s), 1432 (m), 1372 (s), 1229 (s), 1034 (s), 934 (m), 760 (m), 602 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 5.16 (1H, quin, J 5.2 Hz, H-2), 3.78 (1H, dd, J_{vic} 5.0, J_{gem} 11.8 Hz, H-3), 3.75 (1H, dd, J_{vic} 5.3, J_{gem} 11.8 Hz, H-3), 3.62 (1H, dd, J_{vic} 5.6, J_{gem} 10.9 Hz, H-1), 3.58 (1H, dd, J_{vic} 5.1, J_{gem} 11.0 Hz, H-1), 2.14 (3H, s, CH_3CO_2R); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8 (1 C_q, CO), 71.3 (1 CH, C-2), 43.3 (1 CH_2, C-3), 30.3 (1 CH_2, C-1), 20.8 (1 CH_3, CH_3CO_2R); MS (EI) m/z 165, 167 (M^+-CH_2Cl), 154, 156 (M^+-HOAc), 135 (M^+-Br), 121 (M^+-CH_2Br), 93, 95 (CH_2Br^+), 43 (100%, CH_3CO^+); found for M^+-CH_2Cl: 164.9555 $C_4H_6BrO_2^+$ requires: 164.9551.

(3*R*)-(+)-4-Chloro-3-hydroxybutyronitrile (5). KCN (2.79 g, 42.84 mmol) was added to a stirred solution of the bromide **4** (6.84 g, 31.74 mmol) in methanol (25 ml). After 12 h, further KCN (0.475 g, 7.29 mmol) was added and stirring was continued for a further 5 h. The mixture was diluted with CH_2Cl_2 (20 ml), filtered and the solid residue washed thoroughly with CH_2Cl_2. After evaporation of the filtrate, the residue was dissolved

in CH_2Cl_2 (100 ml) and washed with saturated aqueous $NaHCO_3$ (75 ml). The aqueous layer was reextracted with CH_2Cl_2 (2 x 75 ml) and the combined organic layers were dried ($MgSO_4$) and evaporated. Purification of the resultant yellowish liquid (3.2 g) by vacuum distillation (b.p. 111-113 °C/ 6.8 mmHg) gave the nitrile **5** (2.65 g, 70 %) as a colorless oil; $[\alpha]_D^{23}$ +6.9 (c 3.0, $CHCl_3$); IR (neat film): ν 3430 (bs), 2964 (m), 2935 (m), 2258 (m), 1416 (s), 1306 (m), 1086 (s), 1055 (s), 754 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 4.19 (1H, br quin, J 5.5 Hz, H-3), 3.64 (2H, d, J 5.3 Hz, 2 x H-4), 3.17 (1H, bs, OH), 2.74 (1H, dd, J_{vic} 5.4, J_{gem} 16.8 Hz, H-2), 2.68 (1H, dd, J_{vic} 6.5, J_{gem} 16.9 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 116.8 (1C_q, C-1), 67.2 (1 CH, C-3), 47.3 (1 CH_2, C-4), 23.2 (1 CH_2, C-2).

(2*R*)-(-)-3-Cyano-2-hydroxypropyltrimethylammonium chloride (9). Trimethyl amine (4.6 ml of a 23 wt-% aqueous solution) was added to chloride **5** (1.0 g, 8.36 mmol) at room temperature. After 3 h, the solution was evaporated *in vacuo* at 30°C to obtain the crude product as an orange solid, which was dried over P_2O_5 under vacuum until the weight was constant (1.4 g, 94 %). The crude product was dissolved in the minimum amount of dry ethanol (46 ml) at reflux temperature and the clear solution was allowed to cool slowly to room temperature. After ca. 3 hours, the mixture was cooled further to 0°C and left at that temperature overnight. The mother liquor was then removed and the residue washed with cold ethanol (1 x 3 ml, 1 x 2 ml), then dried under vacuum to obtain the ammonium salt **9** (942 mg, 63 %) as long needles; $[\alpha]_D^{22}$ -21.5 (c 2.1, H_2O), corresponding to an optical purity of 82 % ee [lit:[8g] $[\alpha]_D^{22}$ -26.07 (c 1.99, H_2O), 100 % ee]. The product was recrystallized twice more from ethanol as described above to obtain **9** in 51 % overall yield and >98 % ee; $[\alpha]_D^{22}$ -25.7 (c 2.1, H_2O); m.p. 247-249°C, dec; IR (KBr disk): ν 3261 (bs), 3203 (bs), 3020 (m), 2981 (m), 2962 (m), 2242 (m), 1492 (m), 1478 (s), 1092 (s), 972 (s), 961 (s), 936 (s), 687 (m) cm^{-1}; ^1H NMR (250 MHz, D_2O) δ 4.60-4.49 (1H, m, H-2), 3.50-3.32 (2H, m, 2 x H-1), 3.11 (9H, s, 3 x CH_3), 2.76 (1H, dd, J_{vic} 5.0, J_{gem} 17.2 Hz, H-3), 2.64 (1H, dd, J_{vic} 6.3, J_{gem} 17.2 Hz, H-3).

(*R*)-(-)-Carnitine (1). A solution of nitrile **9** (0.4 g, 2.24 mmol) in concentrated HCl (1.0 ml) was heated to 50°C and the temperature was slowly increased to 75°C over 2.5 h. After 6 h, the mixture was cooled to 0°C and the mother liquor was removed from the NH_4Cl crystals which had separated from the reaction mixture. The residue was washed with cold concentrated HCl (ca. 2 ml) and the combined mother liquor and washing liquid was evaporated *in vacuo* below 70°C. A solution of the residue in water (2 ml) was applied on an anion exchange column (Amberlite IRA 410/OH^-, 120 mm x 10 mm I.D.) and the column washed with water until the filtrate contained no more product. Evaporation of the filtrate gave crude carnitine (**1**) as a colorless syrup, which crystallized upon addition of 2-propanol/acetone (1:1, 4 ml). The mother liquor was removed, the residue washed with acetone and then dried under vacuum over P_2O_5 at 60°C for 1 h to obtain (*R*)-carnitine (337 mg, 93 %) as a colorless, very hygroscopic solid; $[\alpha]_D^{22}$ -30.0 (c 1.16, H_2O) [lit:[6a] $[\alpha]_D^{20}$ -31.1 (c 1.0, H_2O)]; m.p. 195°C, dec. (lit:[16] 197 - 198°C); ^1H NMR (250 MHz, D_2O) δ 4.42 (1H, br quin, J 6.0 Hz, H-3), 3.34-3.22 (2H, m, 2 x H-4), 3.08 (9H, s, 3 x CH_3), 2.32 (1H, dd, J_{vic} 6.8, J_{gem} 15.4 Hz, H-2), 2.25 (1H, dd, J_{vic} 6.6, J_{gem} 15.4 Hz, H-2); ^{13}C NMR (100 MHz, D_2O) δ 178.9 (1 C_q, C-1), 70.9 (1 CH_2, C-4), 64.9 (1 CH, C-3), 54.9 (3 CH_3, NMe_3), 43.80 (1 CH_2, C-2).

(*R*)-(-)-4-Amino-3-hydroxybutyric acid (2). The nitrile **5** (955 mg, 7.99 mmol) was dissolved in concentrated HCl (8.5 ml) and the solution was allowed to stand at room temperature for 8.25 h. The acid was then evaporated *in vacuo* below 40°C and the oily residue taken up in 28% ammonium hydroxide (8.5 ml) at room temperature. After 14 h, the solution was evaporated *in vacuo*, the white, solid residue dissolved in 10% HCl (16 ml) and heated to reflux for 4.5 h. After evaporation of the acid, the residue was taken up repeatedly in H_2O (7 ml) and evaporated to remove remaining acid. A solution of the crude product in H_2O (5 ml) was applied on a cation exchange column (Amberlite IR 120 (plus)/H^+, 180 mm x 28 mm I.D.) and the column was washed with H_2O until the pH of the filtrate was neutral. The product was then eluted with 5% ammonium hydroxide (ca. 150 ml), followed by 10% ammonium hydroxide until reverse phase tlc (40% MeOH/H_2O, Ninhydrin stain) indicated absence of product in the filtrate (ca 250 ml). The product containing fractions were combined, evaporated, then dissolved in H_2O (5 ml) and treated with activated charcoal (120 mg) for 30 min. Filtration of the mixture and evaporation afforded crude GABOB (**2**) as a colorless solid (760 mg, 80 %). The crude product was recrystallized from H_2O/EtOH by dissolving it in H_2O (1 ml) at 80°C and adding EtOH (ca. 1 ml) until the solution became cloudy. The mixture was allowed to cool to room temperature for 2 h, then further EtOH (0.3 ml) was added and the mixture cooled further to 0°C over night. The mother liquor was removed and the residue washed with cold EtOH/H_2O (2:1, 1 ml), EtOH (1 ml) and finally Et_2O (3 ml). The residue was dried for 2 h over P_2O_5 at 60°C under vacuum to obtain GABOB (**2**) (539 mg, 57 %) as a colorless solid; $[\alpha]_D^{22}$ -17.1 (c 1.56, H_2O), corresponding to an optical purity of 82 % [lit:[15] $[\alpha]_D^{25}$ -20.7 (c 1.8, H_2O), 100 % ee]; m.p. 211-212°C, dec. (lit:[15] 216-217°C, dec); a second recrystallization from EtOH/H_2O provided **2** in 49 % overall yield and 90 % ee; $[\alpha]_D^{22}$ -18.6 (c 1.52, H_2O); m.p. 214°C, dec; IR (KBr disk): ν 3500-2350 (bs), 2188 (bm), 1659 (m), 1578 (s), 1499 (m), 1451 (m), 1395 (s), 1055 (m) cm^{-1}; ^1H NMR (250 MHz, D_2O) δ 4.13-4.00 (1H, m, H-3), 3.03 (1H,. dd, J_{vic} 3.3, J_{gem} 13.1Hz, H-4), 2.81 (1H, dd, J_{vic} 9.4, J_{gem} 13.1 Hz, H-4), 2.29 (2H, d, J_{vic} 6.6 Hz, 2 x H-2); ^{13}C NMR (100 MHz, D_2O) δ 179.5 (1 C_q, C-1), 66.4 (1 CH, C-3), 45.0 (1 CH_2, C-4), 43.2 (1 CH_2, C-2).

2,3-Diphenyl-5,8-dichloropyrazino[2,3-*d*]pyridazine (8). A mixture of 2,3-diphenyl-5,8-dihydroxy pyrazino[2,3-*d*]pyridazine[13] (2.83 g, 8.955 mmol), phosphorus pentachloride (3.75 g, 17.92 mmol), phosphorus oxychloride (35.0 ml) and DMF (1 drop) was heated at 125°C for 1 h. The clear solution was cooled to room temperature and evaporated to dryness. The solid residue was dried under high vacuum (0.5 mmHg) for 1 h, dissolved in CH_2Cl_2 (ca. 3 ml) and purified by silica gel chromatography using CH_2Cl_2 as eluent to obtain **8** as a light yellow solid (2.78 g, 87 %); the product is very moisture sensitive and should be stored under argon; r_f 0.45 (CH_2Cl_2); mp 202-204°C; ^1H NMR (250 MHz, $CDCl_3$): δ 7.75-7.30 (m, Ar. H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.31, 157.66, 136.49, 134.70, 131.02, 130.09, 128.72; IR (KBr): ν 1595 (w), 1533 (m), 1371 (s), 1234 (s), 1095 (m), 1016 (s), 976 (s), 771 (s) cm^{-1}; MS (FAB): found ($M+Cs^+$) 484.9337, $C_{18}H_{10}Cl_2N_4Cs$ requires 484.9337.

2,3-Diphenyl-5,8-bis-(9-*O*-dihydroquinidine)pyrazino[2,3-*d*]pyridazine (7). A solution of dihydroquinidine (4.0 g, 12.25 mmol) in anhydrous DMF (50 ml) was added to a suspension of NaH (95%, 0.324 g, 13.5 mmol) in DMF (30 ml) at 25°C over 20 min. Stirring was continued for an additional 60 min, then 2,3-diphenyl-5,8-dichloropyrazino[2,3-*d*]pyridazine (**8**) (2.16 g, 6.11 mmol) was added at once and the mixture heated for 60 min at 115°C (bath temp.). The mixture was cooled to room temprature, then H_2O (50 ml) was

added, followed by EtOAc (200 ml). The organic layer was washed with H_2O (4 x 50 ml), brine (2 x 20 ml), dried ($MgSO_4$) and evaporated to dryness. The yellow residue was purified on silica gel chromatography using a gradient of EtOAc:MeOH (9:1 to 8:2) to give **7** (3.98 g, 72 %) as a yellow solid; r_f 0.25 (EtOAc:MeOH 2:1); mp 168-174°C; $[\alpha]_D^{22}$ -316.0 (c 1.22, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (2 H, d, J 4.5 Hz), 7.97 (2 H, d, J 9.2 Hz), 7.59 (6 H, m), 7.49 (4 H, m), 7.40 (4 H, m), 7.31 (2 H, dd, J 9.2, 2.5 Hz), 7.01 (2 H, d, J 4.0 Hz), 3.75 (6 H, s, 2 x OCH_3), 3.42 (2 H, m), 2.79 (6 H, m), 2.69 (2 H, m), 2.16 (2 H, t, J 1.3 Hz), 1.71 (2 H, br s), 1.44 (12 H, m), 0.65 (6 H, t, J 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.73, 157.57, 156.50, 147.26, 144.66, 143.79, 137.68, 131.48, 131.21, 130.05, 129.88, 128.33, 126.79, 121.81, 119.19, 102.06, 78.24, 59.50, 55.49, 50.91, 50.08, 37.46, 27.09, 26.08, 25.10, 22.46, 11.79; IR ($CHCl_3$): ν 3150 (w), 2940 (m), 2770 (m), 2260 (s), 1480 (m), 1385 (m), 1100 (m), 920 (s), 840 (s); MS (FAB): found ($M+Cs^+$) 1065.3780, $C_{58}H_{60}N_8O_4Cs$ requires 1065.3792.

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