Abstract: A simple and stereospecific synthesis of both (R)- and (S)-GABOB has been developed. The synthetic approach involves the conversion, through organoselenium intermediates, of commercially available ethyl (R)- and (S)-4-chloro-3-hydroxybutyrate into a protected 1,2-amino alcohol with retention of the original configuration.

Key words: selenium oxidation, ring closure, amino acids, β-hydroxyselenides, 1,3-oxazolidin-2-ones

4-Amino-3-hydroxybutyric acid (GABOB) is a compound of great pharmacological importance due to its biological function as a neuromodulator in the mammalian central nervous system and due to its hypotensive and antiepileptic activity. The (R)-(–)-isomer (Figure 1) has been shown to have a greater biological activity than the (S)-(+) isomer. Furthermore, the trimethylamino analogue of GABOB, i.e. (R)-(–)-carnitine (2), plays a significant role in the human energy metabolism via the transport of long chain fatty acids into the mitochondria. In recent years, a large number of reports and patents dealing with the synthesis of enantiomerically pure (R)-GABOB employing optical resolution of diastereoisomeric salts, enzyme or microbial technique, and asymmetric synthesis, have been published. Moreover, several syntheses which make use of chiral non-racemic starting materials have also appeared. Following our recently proposed stereospecific transformation of β-hydroxyalkyl phenyl selenides into N-benzoyl-1,3-oxazolidin-2-ones we now report a short synthesis of both (R)- and (S)-GABOB.

Figure 1

Thus, ethyl (R)-4-chloro-3-hydroxybutyrate (3) was reacted with phenylselenium anions to give the corresponding β-hydroxyalkyl phenyl selenide 4 in excellent yield (Scheme 1).

Scheme 1

By reaction with benzoyl isocyanate in CH₂Cl₂ at room temperature, this compound was converted into its N-benzoyl-carbamate derivative 5. Treatment of this β-carbamoyloxyalkyl phenyl selenide with an excess of m-chloroperoxybenzoic acid (m-CPBA) in THF, in the presence of potassium hydrogenphosphate, afforded the corresponding selenone intermediate 6. The N-benzoyl-1,3-oxazolidin-2-one 7 was then obtained as a result of the displacement of the selenonyl group by the nitrogen atom of the carbamate. This new cyclization reaction, which represents the crucial step of the entire process, is an intramolecular nucleophilic substitution, which occurs easily because of the great leaving ability of the selenonyl group. During this process no racemization occurred, as demonstrated by HPLC analysis on chiral column. The phenylethynyl moiety, introduced in the first step, was eliminated as benzeneselenenic acid (8) in the oxidation/cyclization step. After addition of K₂CO₃ the water-soluble potassium benzeneseleninate could be separated. From this diphenyl diselenide was recovered in good yield. An attempt to obtain (R)-GABOB by basic hydrolysis of 7 with NaOH in EtOH was unsuccessful because 7 undergoes a rapid β-elimination, giving the ethyl N-benzoyl-4-aminocrotonate as the sole reaction product. An optimization study revealed that the following two-steps sequence gave the best results (Scheme 2).
The N-benzoyl-1,3-oxazolidin-2-one 7 was first hydrolyzed to the corresponding acid 9 by treatment with 4 N HCl at 70 °C. Treatment of 9 with refluxing 6 N HCl then afforded the (R)-GABOB hydrochloride (10). Purification of 10 by ion-exchange chromatography on a cation exchange resin afforded crude (R)-(−)-GABOB (1) in good yield and with spectral data in good agreement with those reported in the literature. The product was contaminated with a by-product (11)-(−)-GABOB ((97% ee) and ethyl (11)-(−)-4-chloro-3-hydroxybutyrate (3); 1.0 g, 6 mmol) was added. After 36 h the reaction was quenched with a 10% solution of NH₄Cl (10 mL). The reaction mixture was extracted with Et₂O (3 × 30 mL) and the combined organic layers were dried over Na₂SO₄ and evaporated. The evaporation product was purified by column chromatography on a silica gel column using a mixture of Et₂O and light petroleum (4:6) as eluent. Pure compound 4 was obtained as a pale yellow oil in 86% yield; [α]D20 = +2.58 (c = 2.23, CHCl₃).

FT-IR (KBr): 3472 (br), 2981, 1730, 1186, 1022 cm⁻¹.

1H NMR (CDCl₃, 25 °C, TMS): δ = 7.58–7.47 (m, 2 H, ArH), 7.30–7.21 (m, 3 H, ArH), 4.14 (q, J = 7.2 Hz, 2 H, OCH₃), 4.24–4.08 (m, 1 H, OCH), 3.24 (d, J = 4.0 Hz, 1 H, OH), 3.17–2.95 (m, 2 H, SeCH₂), 2.74–2.48 (m, 2 H, CH₂), 1.25 (t, J = 7.2 Hz, 3 H, CH₃).

13C NMR (CDCl₃, 25 °C): δ = 172.0 (CO), 132.8 (2 × CH), 129.2 (2 × CH), 127.2, 126.4, 67.1 (OCH), 60.8 (OCH₃), 40.4 (CH₃), 34.7 (SeCH₂), 14.1 (CH₃).

GC–MS: m/z (%): 288 (100) [M⁺], 270 (32), 183 (23), 157 (63), 131 (59), 103 (63), 91 (58), 77 (29).

Anal. Calcd for C₂₃H₂₄O₅Se: C, 55.07; H, 5.19; N, 3.11.

Ethyl (3R)-3-Hydroxy-4-(phenylseleno)butanoate (ent-4)

This compound was prepared as 4. Yield: 89%; pale yellow oil; [α]D20 = +2.63 (c = 4.59, CHCl₃).


Ethyl (3R)-3-[[Benzoylamino]carbonyl]oxy]-4-(phenylseleno)butanoate (5)

Under an inert atmosphere, benzoyl isocyanate (0.83 g, 5.6 mmol) was added to a solution of the β-hydroxyalkyl phenyl selenide 4 (1.48 g, 5.1 mmol) in anhyd CH₂Cl₂ (30 mL) and the reaction was allowed to stir at r.t. until TLC analysis showed that the starting alcohol was completely consumed (14–15 h). The solvent was evaporated and the crude benzoyl carbamate was purified by column chromatography on silica gel with Et₂O–light petroleum (6:4) as eluent. Compound 5 was obtained as an oil in 89% yield; [α]D20 = –24.70 (c = 1.65, CHCl₃).

FT-IR (KBr): 3271 (br), 2982, 1757, 1737, 1508, 1184 cm⁻¹.

1H NMR (CDCl₃, 25 °C, TMS): δ = 8.15 (s, 1 H, NH), 7.91–7.80 (m, 2 H, ArH), 7.60–7.50 (m, 2 H, ArH), 7.30–7.21 (m, 5 H, ArH), 6.48–6.30 (m, 1 H, OCH), 4.11 (q, J = 7.2 Hz, 2 H, OCH₂), 3.35–3.15 (m, 2 H, SeCH₂), 2.88 (dd, J = 16.1, 5.5 Hz, 1 H, CH₂), 2.76 (dd, J = 16.1, 7.1 Hz, 1 H, CH₂), 1.24 (t, J = 7.2 Hz, 3 H, CH₃).

13C NMR (CDCl₃, 25 °C): δ = 169.6 (CO), 164.8 (CO), 146.8 (CO₂), 137.2 (CH), 132.6 (CH), 132.5 (CH), 132.4 (CH₂), 129.0 (2 × CH₂), 128.4 (2 × CH), 127.5 (2 × CH), 127.0 (2 × CH₂), 117.1 (OCH), 60.6 (OCH₃), 38.0 (CH₂), 30.0 (SeCH₂), 13.8 (CH₃).


Ethyl (3S)-3-[[Benzoylamino]carbonyl]oxy]-4-(phenylseleno)butanoate (ent-5)

This compound was prepared as 5. Yield: 88%; oil; [α]D20 = +19.74 (c = 1.70, CHCl₃).

Anal. Calcd for C₂₃H₂₄O₅Se: C, 55.30; H, 4.87; N, 3.22. Found: C, 55.07; H, 5.19; N, 3.11.
Ethyl [(5R)-3-Benzoyl-2-oxo-1,3-oxazolidin-5-yl]acetate (7)

To a solution of N-benzoyl carbamate 5 (1.96 g, 4.5 mmol) in THF (100 mL) at 0 °C powder potassium hydrogenphosphate (3.81 g, 22.5 mmol) and meta-chloroperoxybenzoic acid (3.10 g, 18 mmol) were added. The reaction mixture was allowed to slowly reach room temp. and was stirred until TLC analysis showed that the starting selenide was completely converted into the corresponding selenone (4 h). The solvent was evaporated in vacuo and the residue was suspended in reagent grade acetone (100 mL). Powdered K₂CO₃ (3.10 g, 22.5 mmol) was then added at r.t. The consumption of the selenone was monitored by TLC (20 h). The mixture was then concentrated in vacuo, poured into water (100 mL) and extracted with Et₂O (3 × 60 mL). The organic layer was dried over Na₂SO₄ and evaporated. The reaction product was purified by column chromatography on silica gel using a mixture of Et₂O and light petroleum (6:4) as eluent. Yields, physical and spectral data of pure 7 and ent-7 are reported below.

Yield: 90%; white solid; mp 81–82 °C; [α]D²⁻ = -46.68 (c = 3.36, CHCl₃). Analytical HPLC: Chiralcel OD-H column (250 × 4 mm, Daicel), eluent: i-PrOH-hexane (20:80), flow rate: 0.8 mL/min, UV detection at 240 nm; tR 50.8 min; er > 99:1.

FT-IR (KBr): 2982, 1788, 1736, 1682, 1328, 1205 cm⁻¹.

Yield: 90%; white solid; mp 79–80 °C; [α]D²⁻ = -20.5 (c = 1.75 in H₂O), after recrystallization from aq EtOH. Analytical HPLC of the 4-hydroxy-2-pyrrolidinone derivative: Chirapak AD-H column (250 × 4 mm, Daicel), eluent: EtOH-hexane (5:95), flow rate: 1.0 mL/min, UV detection at 210 nm; tR 85.1 min; er = 96:4.

H NMR (D₂O, 25 °C): δ = 3.99 (ddt, J = 9.6, 8.9, 3.2 Hz, 1 H, OCH), 2.96 (dd, J = 13.1, 3.2 Hz, 1 H, NCH₂), 2.18 (dd, J = 9.1, 3.2 Hz, 1 H, NCH₂).

13C NMR (D₂O, 25 °C): δ = 179.8 (CO), 65.3 (OCH), 44.0 (NCH₂), 41.9 (CH₂).

Anal. Calcd for C₁₄H₁₅NO₅ (277.3): C, 60.64; H, 5.45; N, 5.05. Found: C, 60.82; H, 5.60; N, 5.21.

Ethyl[(5S)-3-Benzoyl-2-oxo-1,3-oxazolidin-5-yl]acetate (ent-7)

This compound was prepared as 7. Yield: 90%; white solid; mp 79–81 °C; [α]D²⁻ = 43.74 (c = 1.83, CHCl₃). Analytical HPLC: Chiralcel OD-H column (250 × 4 mm, Daicel), eluent: i-PrOH-hexane (20:80), flow rate: 0.8 mL/min, UV detection at 240 nm; tR 61.6 min; er > 99:1.

Yield of the crude product: 78%; mp 213–214 °C; [α]D²⁻ = -21–17.51 (c = 0.41 in H₂O). The value reported in the literature is [α]D²⁻ = -20.5 (c = 1.7 in H₂O), after recrystallization.

Hydroxycarbonyl oxazolidinone derivative: Chirapak AD-H column (250 × 4 mm, Daicel), eluent: EtOAc-hexane (4:96), flow rate: 1.0 mL/min, UV detection at 210 nm; tR 85.1 min; er = 96:4.


(3R)-4-Amino-3-hydroxybutanoic Acid (ent-1)

This compound was prepared as 1. Yield of the crude product: 78%; mp 198–201 °C; [α]D¹⁷⁻ = +16.7 (c = 0.41 in H₂O). The value reported in the literature is [α]D¹⁷⁻ = +20.1 (c = 1.7 in H₂O). Analytical HPLC of the 4-hydroxy-2-pyrrolidinone derivative: Chirapak AD-H column (250 × 4 mm, Daicel), eluent: EtOAc-hexane (5:95), flow rate: 1.0 mL/min, UV detection at 210 nm; tR 85.1 min; er = 96:4.


Recovery of Diphenyl Diselenide

The alkaline aqueous extract from the oxidation/cyclization procedure (containing the benzeneulenate anion) was neutralized with concd HCl and then acidified by further addition of the acid. The resulting suspension was evaporated and the residue was suspended in MeOH (50 mL). Hydrazine monohydrate (14.5 mmol, 0.65 mL) was added gradually to the suspension. Stirring was continued until diphenyl diselenide was formed, as indicated by the yellow color. The mixture was then concentrated in vacuo, poured into water (60 mL) and extracted with Et₂O (3 × 30 mL). The organic layer was dried over Na₂SO₄ and evaporated. Diphenyl diselenide was recovered as a pure compound in 62% yield.

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References


