A Convenient, Scalable Process for the Preparation and Purification of Calcium Acamprosate

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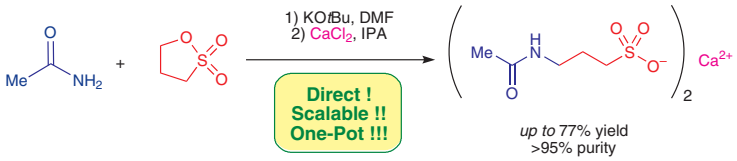

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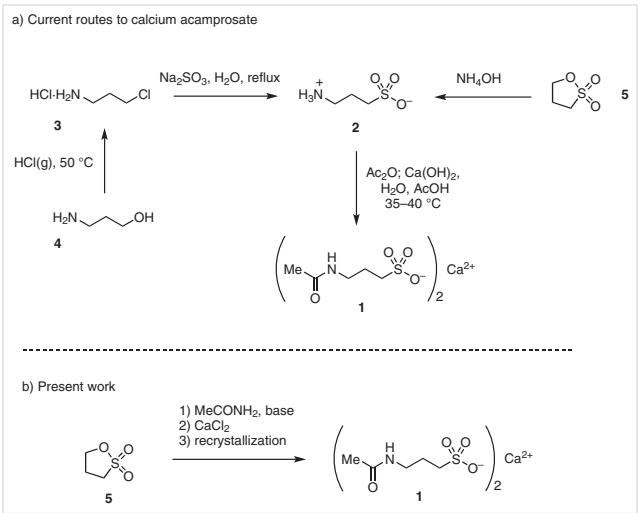
Abstract Calcium acamprosate (Campral, *N*-acetylhomotaurine calcium salt) is a well-established drug for the treatment of alcohol dependence. Its preparation is generally based on a three-step process with some remarkable drawbacks. To avoid these flaws, we have developed a direct, scalable, one-pot procedure for the preparation of calcium acamprosate entailing the nucleophilic opening of readily available 1,3-propanesultone with potassium acetamide (from acetamide and potassium *tert*-butoxide) in *N*,*N*-dimethylformamide solution, followed by in situ cation exchange by addition of calcium chloride at controlled pH, addition of 2-propanol (IPA) as a cosolvent, and removal of potassium chloride by selective precipitation. Calcium acamprosate (purity higher than 95%) is thus obtained in the commercial crystalline form in 74–77% yield.

Key words acetamide, calcium acamprosate, cation exchange, homotaurine, potassium *tert*-butoxide, sultone opening



Scheme 1 Current and proposed routes to calcium acamprosate (**1**)

Calcium acamprosate (*N*-acetylhomotaurine calcium salt, **1**) is a well-established drug for the treatment of alcohol dependence. Acamprosate is thought to stabilize the chemical balance in the brain that would otherwise be disrupted by alcohol withdrawal.[1] Until it became a generic in the US, calcium acamprosate (under the brand name Campral) was manufactured and marketed in the US by Forest Laboratories, and by Merck KGaA in the rest of the world.[2] Legal in Europe since 1989, the FDA approved the drug in July 2004.

Preparation processes for **1** are based on Merck's original patent[3] that implies the acetylation of homotaurine (**2**), followed by in situ formation of the calcium salt (Scheme 1a).[3–5] The chemical procedure performs very well (up to 90% yield), but the final crystallization drops the overall yield to 30%.

Preparation of homotaurine, however, presents remarkable drawbacks. A first approach, starting from 3-aminopropanol (**4**), involves two reaction steps and the use of HCl(g) is required to obtain the reactive chloramine **3** which is transformed to homotaurine (**2**) by sulfonylation.[6] In another approach, starting from 1,3-propanesultone (**5**), the use of ammonia gas or aqueous solution is required and, under these conditions, homotaurine (**2**) is obtained together with the isomeric sulfonamide as byproduct.[7] As a consequence, purification of **2** is mandatory prior to its transformation to **1**.

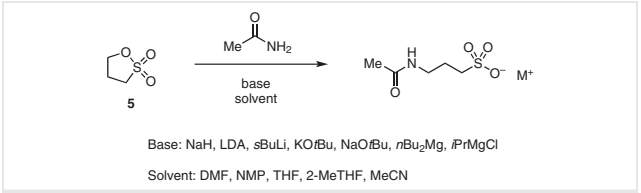
We felt, therefore, that there was ample room for improvement, and we sought to develop an alternative, more straightforward procedure that would obviate the need of the intermediate preparation of homotaurine (**2**) and would allow for the direct precipitation and filtration of the

approved crystalline form of **1**. After careful evaluation of several alternatives, we decided to concentrate our efforts on a previously unknown route, involving the opening of commercially available 1,3-propanesultone (**5**) with acetamide in the presence of a strong base and isolation of the calcium salt **1** from the reaction medium after in situ cation exchange (Scheme 1b). This approach has resulted in the development of a direct, one-pot, and operationally simple procedure for the synthesis of **1**, with industrial applicability. Moreover, it also avoids the use of reactive chloramines. Although this procedure uses the relatively toxic sultone **5**, this compound, due to its high reactivity, was expected to react totally under the set reaction conditions and subsequent workup and, as a consequence, would be not detected in the isolated calcium acamprosate.

Although there are no direct precedents for the nucleophilic ring opening of γ-sultone **5** in the literature, we hoped that suitable conditions would be found based on previous reports of the selective *N*-alkylation of acetamide with primary alkyl bromides[8] or mesylates[9,10] that called for the use of relatively strong bases in aprotic solvents (KOH/Al_2O_3/dioxane[8] or NaH/DMF,[9,10] respectively).

Taking this into account, we set out to find the optimal reaction conditions for the sultone opening step, with regard to the base, solvent, and temperature, by ^1H NMR monitoring of the reaction crude (Scheme 2). Due to the nature of the compounds involved in the process, ^1H NMR spectroscopy was the technique allowing a better assessment of the reaction outcome. All experiments were run with 0.5–1.0 g of **5**.

After an extensive exploration of the reaction variables using NaH as base (Table 1), we reached the following conclusions: Treatment of **5** with 5 equivalents of acetamide and 5 equivalents of NaH in anhydrous *N*,*N*-dimethylformamide (DMF) (14 mL/g of **5**) at 0 °C and warming to room temperature in a 2-hour period (entry 1) led to complete conversion of sultone **5**, with the formation of sodium acamprosate as the major product according to ^1H NMR analysis. Use of less equivalents of acetamide/NaH (entry 2), preformation of sodium acetamide (entry 3), or extended reaction time (entry 4) resulted either in incomplete reaction or in the production of more complex crudes. Tetrahydrofuran and 2-methyltetrahydrofuran were less suitable solvents than DMF (entries 5 and 6).



Scheme 2 Initial exploration of the sultone opening step

Other bases were also tested (Table 2). The use of 2 equivalents of acetamide and 1.8 equivalents of KO*t*Bu (entry 7), but also NaO*t*Bu (entry 8), in anhydrous DMF (16 mL/g of **5**, 0 °C to r.t., 2 h) led to results similar to those of entry 1. Preformation of potassium acetamide (r.t., 1 h) had a beneficial effect on the purity of the reaction crude. LDA or *s*BuLi in DMF can also provide complete conversion of **5**, albeit with more complex reaction crudes (entries 9 and 10, respectively). All attempts with nBu$_2$Mg (entries 11 and 12) or *i*PrMgCl (entry 13) as the base failed to produce pure reaction crudes under the conditions necessary for complete sultone conversion. When weaker bases (K_2CO_3, DIPEA, NaOMe) were used, sultone ring opening did not take place (data not shown).

With these results in hand, we shifted our attention to the isolation of calcium acamprosate (**1**) from the reaction mixture, after cation exchange by addition of $CaCl_2$ at a controlled pH. We selected the conditions of entry 1 for sultone opening for the optimization of the process. Firstly, we found that when the sultone opening was performed on a 5 g scale, the equivalents of acetamide and of NaH could be reduced to 2.0 and 1.8, respectively. After careful addition of water to the cold suspension to eliminate the excess sodium acetamide and acidification to pH 6, $CaCl_2$ (1.1 equiv) was added in one portion; cation exchange was complete after 1 hour of stirring at room temperature (a change of the appearance of the suspended solid was observed). At this point, all of our attempts to precipitate selectively **1** from the reaction mixture were unsuccessful. We were delighted

Table 1 Sultone Opening Using Sodium Hydride as Base[a]

Entry	Base	Acetamide	Solvent	Time (h)	Crude analysis[b] (NMR)
1	NaH (5 equiv)	5 equiv	DMF	2	CaAC major
2	NaH (1.8 equiv)	2 equiv	DMF	2	complex crude (CaAC minor)
3	NaH (1.8 equiv)	2 equiv, preformation	DMF	2	complex crude (CaAC minor)
4	NaH (1.1 equiv)	1.2 equiv	DMF	overnight	incomplete reaction
5	NaH (5 equiv)	5 equiv	THF	6	complex crude (CaAC minor)
6	NaH (1.8 equiv)	2 equiv	2-MeTHF	overnight	complex crude (CaAC minor)

[a] Experiments carried out on 0.5–1.0 g scale.
[b] CaAC: calcium acamprosate.

Table 2 Sultone Opening Using Other Bases[a]

Entry	Base	Acetamide	Solvent	Time (h)	Crude analysis[b] (NMR)
1	NaH (5 equiv)	5 equiv	DMF	2	CaAC major
7	KO*t*Bu (1.8 equiv)	2 equiv, preformation	DMF	2	CaAC major
8	NaO*t*Bu (1.8 equiv)	2 equiv, preformation	DMF	2	CaAC major
9	LDA (1.8 equiv)	2 equiv	DMF	2	complex crude
10	sBuLi (1.8 equiv)	2 equiv	DMF	2	complex crude
11	nBu$_2$Mg (1.8 equiv)	2 equiv	THF	5	incomplete reaction
12	nBu$_2$Mg (1.8 equiv)	2 equiv	DMF	5	complex crude
13	iPrMgCl (1.8 equiv)	2 equiv, preformation	THF	overnight	incomplete reaction

[a] Experiments carried out on 0.5–1.0 g scale.
[b] CaAC: calcium acamprosate.

to find, however, that dilution with 2-propanol (IPA) (16 mL/g **5**) allowed us to selectively precipitate NaCl, with a weight content of **1** lower than 2% (most of the theoretical expected amount of NaCl was recovered). This solid was filtered out and the resulting solution was concentrated under vacuum. The resulting residue, containing **1**, less than 10% weight of acetamide, and 50–60% of solvent (DMF) was treated with IPA (33 mL/g **5**), and seeding with **1** allowed the isolation of 86% of the theoretical amount of crude **1** as a readily filterable solid in the commercial crystalline form [by X-ray powder diffraction (XRPD); see the Supporting Information]. The sequence of sultone opening (using 2.0 equiv acetamide and 1.8 equiv NaH) followed by the optimized purification conditions proved to be reproducible on a 5–10 g scale, affording 70–86% of the theoretical amount of **1** with a purity range of 65–78% (by quantitative ^{1}H NMR, maleic acid as internal standard) (Scheme 3, Procedure A).

While Procedure A provided a robust and a quite reproducible method for obtaining good yields of crude calcium acamprosate (**1**), in the commercial crystalline form, there were some concurrent drawbacks that we still wanted to also avoid to increase the consistency of the procedure:

a) The hazards associated with the use of NaH;

b) The need to add Celite in order to clarify the solution and to remove the mineral oil prior to the addition of $CaCl_2$;

c) The purity of crude calcium acamprosate (**1**) was only moderate, and some NaCl was still detected by XRPD.

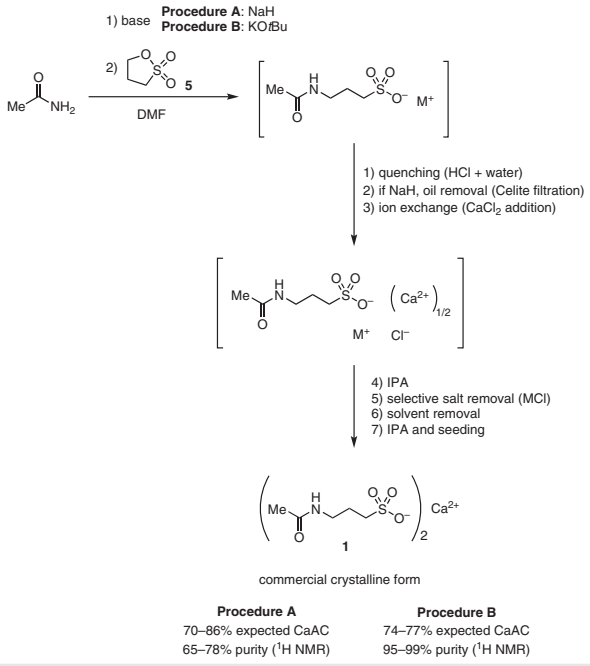
To that end, we applied the cation-exchange and precipitation conditions from Procedure A to the entry 7 reaction conditions (sultone opening with KO*t*Bu, Table 2). We ascertained that NaH could indeed be advantageously replaced by KO*t*Bu, with some methodological modifications:

a) DMF turned out to be the best solvent also for the isolation step, and best results were obtained with slightly more diluted reaction mixtures (final DMF volume 10 mL/g **5** instead of 8 mL/g **5**).

b) NaO*t*Bu was found to be clearly inferior to KO*t*Bu, for the isolation step, and although complete sultone opening can be achieved with both reagents, NaO*t*Bu use affects both the purity (50–59% vs >95% by quantitative ^{1}H NMR) and the crystallinity of the final product. Moreover, precipitation of NaCl was not complete, whereas KCl can be almost quantitatively removed by filtration. After concentration of the mother liquors, addition of IPA, and seeding, crude calcium acamprosate (**1**) was obtained as a readily filterable solid in around 74–77% yield, and with a ^{1}H NMR purity higher than 95%. A KCl content between 0.5% and 1.0% (w/w) was also estimated, by XRPD.

c) The intermediate treatment with Celite (to remove mineral oil from NaH) is avoided with the use of KO*t*Bu.

This process (Scheme 3, Procedure B) has been successfully run with 25 g of sultone **5**, and constitutes a robust, more readily industrializable (with respect to the use of



Scheme 3 Calcium acamprosate developed isolation method

NaH), and reproducible procedure for the preparation of **1**. Table 3 summarizes the main advantages of Procedure B with respect to the initial Procedure A.

Table 3 Comparison of Procedure A and Procedure B

	Procedure A	Procedure B
Base	NaH	KO*t*Bu
Oil removal	required	–
Quenching	H_2 release, exothermic	–
Salt removal	85–87% NaCl recovered	90–98% KCl recovered
Recovery of **1**	70–86%	74–77%
Purity of **1**	65–78% by qNMR	95–99% by qNMR

To achieve a higher calcium acamprosate quality, a further purification step was required and therefore preliminarily investigated (Table 4). Crude **1** was conveniently recrystallized by solubilization in water (1 mL/g crude **1**, 50–60 °C) followed by addition of an antisolvent such as MeOH (9 mL/g crude **1**, stirring overnight at 0–5 °C, and filtration under vacuum; entry 1). The solid was subsequently washed with cold MeOH/H_2O (9:1, 1 mL/g crude **1**) and dried overnight at 100 °C under vacuum. In this way, crystalline calcium acamprosate (**1**) (>95% purity by quantitative ^{1}H NMR, 98% purity by HPLC, containing less than 0.5% KCl according to XRPD) was obtained in 73% yield (entry 1). Moreover, in this case, according to the developed HPLC analysis conditions, acetamide was not detected. Other purification conditions were also tested (Table 4): crystallization time (entry 2), temperature (entry 3), different antisolvents (entries 4–6). However, the final quality of calcium acamprosate was not improved with respect to that of entry 1.

In summary, we have developed a new, direct, robust procedure suitable for the preparation of calcium acamprosate (**1**) on industrial scale. This one-pot methodology is based on the nucleophilic opening of the available 1,3-propanesultone (**5**) by potassium acetamidate, followed by cation exchange with Ca^{2+} ion at controlled pH and selective precipitation of **1** as a readily filterable solid in the commercial crystalline form (74–77% yield, >95% purity). This new procedure compares favorably with previously described methods both in terms of number of reaction steps (one-step reaction) and workup procedures (very simple and suitable for scale-up). Moreover, it also avoids the use of reactive chloramines and although the relatively toxic sultone **5** is used, due to its high reactivity, sultone **5** is not detected in the isolated calcium acamprosate. Crude **1** can be further purified by recrystallization from water/methanol.

Nuclear magnetic resonance analyses (^{1}H NMR) were recorded in D_2O on a Varian Mercury 400 MHz spectrometer, equipped with a broadband probe ATB 1H/19F/X of 5 mm. Spectra were acquired on sample (5–10 mg) dissolved in deuterated solvent (0.7 mL). X-ray powder diffraction measurements of the starting material and the samples were performed under ambient conditions on a PANalytical X'Pert PRO θ-θ diffractometer of 240 mm radius in reflection geometry, equipped with Cu Kα radiation and a PIXcel detector, operated at 45 kV and 40 mA. Each sample was mounted on a zero-background silicon holder and allowed to spin at 0.25 rev/s during the data collection. The measurement angular range was 3.0–50.0° (2θ) with a step size of 0.013°. The scanning speed was 0.328°/s or 0.082°/s.

Acamprosate calcium [CAS Reg. No. 77337-73-6] is a well-known, active pharmaceutical ingredient described in several patents and articles.[2,11] All analytical quality determinations were carried out by comparing samples with a commercially available reference standard.

Preparation of Calcium Acamprosate (1) from Sultone 5 and Sodium Acetamide (from Acetamide/Sodium Hydride); Procedure A

To an ice-cooled solution of acetamide (4.84 g, 82 mmol) in anhydrous DMF (30 mL) under inert atmosphere, NaH (60% w/w in mineral oil; 2.95 g, 73.7 mmol) was added in one portion. The mixture was stirred for 1 h at r.t. before cooling (ice bath). A solution of 1,3-propanesultone (**5**; 5.0 g, 40.9 mmol) in anhydrous DMF (10 mL) was added dropwise to the cooled mixture. The mixture was stirred for 2 h at r.t. H_2O (4 mL) was carefully added dropwise to the ice-cooled mixture which was stirred overnight at r.t. Then, the pH was adjusted

Table 4 Purification Conditions[a]

Entry	CaAC (weight, HPLC[b] purity)	Antisolvent[c]	Temp, time	CaAC (**1**) obtained (weight, HPLC[b] purity)	Yield (%)[d]
1	3 g, 90%	MeOH (9 V)	0–5 °C, overnight	1.98 g, 98% (acetamide not detected)	73
2	0.5 g, 84%	MeOH (5 V)	0–5 °C, 2 h	0.17 g, 95% (0.1% acetamide)	40
3	0.5 g, 85%	MeOH (5 V)	r.t., overnight	0.25 g, 96% (0.2% acetamide)	59
4	1 g, 78%	EtOH (9 V)	r.t., overnight	0.71 g, 88% (0.2% acetamide)	80
5	1 g, 89%	MeOH (9 V), MEK (0.5 V)	r.t., overnight	0.68 g, 97% (0.2% acetamide)	76
6	3 g, 90%	MeOH (9 V), *i*BuOAc (0.5 V)	r.t., overnight	1.74 g, 97% (0.1% acetamide)	64

[a] All experiments were carried out using 1 V of hot water to dissolve calcium acamprosate (CaAC).
[b] Gemini NX C18, 250 × 4.6 mm, 3 µm, 10 mL potassium dihydrogen phosphate, pH 3/acetonitrile. Given values corresponding to area%.
[c] V = mL of solvent per gram of crude material.
[d] Yield corrected considering purity of starting CaAC.

with 6 M aq HCl (9.3 mL, pH 6.1). Celite (250 mg) was added and the mixture was stirred for 30 min at r.t. before filtering (Büchner, Whatman paper, vacuum). The filtrate was washed with cyclohexane (2 × 5 mL) and the aqueous layer was concentrated to dryness (Rotavapor, 45 °C, 25 mbar). To the resulting oil was added anhydrous $CaCl_2$ (5 g, 45 mmol). The mixture was stirred for 1 h at r.t. and IPA (82 mL) was added dropwise while cooling with ice. The mixture was stirred for 1 h at 0–5 °C and filtered (vacuum, filter pore 2). The filtrate was concentrated to an oil and IPA (165 mL) was added dropwise. The solution was seeded twice with pure calcium acamprosate before solid was formed. Then, the suspension was stirred overnight at r.t. The mixture was filtered (vacuum, filter pore 2) and the solid was washed with IPA (10 mL). The wet solid was dried (100 °C, vacuum, overnight) to obtain crude calcium acamprosate (**1**); yield: 7.1 g (86%). Quantitative ^{1}H NMR (maleic acid as internal standard) indicated a purity of 70% for this product.

Preparation of Calcium Acamprosate (1) from Sultone (5) and Potassium Acetamidate (from Acetamide/Potassium *tert*-Butoxide); Procedure B

To an ice-cold solution of acetamide (24.18 g, 409 mmol) in anhydrous DMF (200 mL) under inert atmosphere, KO*t*Bu (41.3 g, 368 mmol) was added in one portion (no exotherm was observed). The mixture was stirred for 1 h at r.t. before cooling (ice bath). A solution of 1,3-propanesultone (**5**; 25.0 g, 205 mmol) in anhydrous DMF (50 mL) was added dropwise over 15 min to the cooled mixture. The resultant dense mixture was vigorously stirred for 4 h at r.t. H_2O (20 mL) and 6 M aq HCl (20 mL) were added to the ice-cooled mixture which was stirred overnight at r.t. Then, the pH was adjusted with 6 M aq HCl (14.5 mL, pH >3 to <6) and H_2O (8 mL) was added to achieve a final DMF/H_2O ratio of 4:1. Anhydrous $CaCl_2$ (25.0 g, 225 mmol) was added and, after stirring for 1 h at r.t., IPA (825 mL) was added dropwise over 20 min while cooling (ice bath). The mixture was stirred for 1 h at 0–5 °C and filtered (vacuum, filter pore 2). The filtrate was concentrated in vacuo (distillation at 40–50 °C, 20–24 mbar for 1 h) to an oil before the dropwise addition of IPA (825 mL) at r.t. over 20 min. The resulting solution was seeded twice with pure calcium acamprosate before solid was formed. Then, the suspension was stirred overnight at r.t. The mixture was filtered (vacuum, filter pore 2) and the solid was washed with IPA (50 mL). The wet solid was dried (100 °C, vacuum, overnight) to obtain crude calcium acamprosate (**1**); yield: 31.73 g (77%). Quantitative ^{1}H NMR (maleic acid as internal standard) indicated a purity of >95% for this product.

Recrystallization of Calcium Acamprosate (1)

A stirred aqueous suspension of crude calcium acamprosate (**1**; 3.0 g, 7.49 mmol, 90% HPLC purity) in H_2O (3 mL) was heated to 50–60 °C until a clear solution was obtained. At this point, MeOH (27 mL) was added dropwise, upon which the formation of an opalescent solution was observed. After overnight stirring at 0–5 °C (previous seeding with pure **1** is sometimes needed to induce crystallization), the precipitate was collected by filtration (vacuum, filter pore 2), washed with cold MeOH/H_2O (9:1, 3 mL/g), and dried overnight at 100 °C under vacuum to afford calcium acamprosate (**1**) of 98% HPLC purity; yield: 1.98 g (66%).

^{1}H NMR (400 MHz, D_2O): δ = 3.26 (t, *J* = 6.8 Hz, 2 H), 2.89 (t, *J* = 8.0 Hz, 2 H), 1.96 (s, 3 H), 1.90 (m, 2 H).

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707399.

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