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Tartaric Acid Amides by the Gabriel Route

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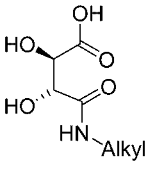
Optically active (3*R*,4*R*)-3,4-diacetoxypyrrolidine-2,5-dione was prepared from L-tartaric acid by ring closure of the ammonium salt of (2*R*,3*R*)-2,3-diacetoxy-3-carbamoylpropanoic acid with thionyl chloride. Mechanistic considerations indicate that the ring closure proceeds through two competing pathways: either direct ring closure of an intermediate acyl chloride or in a parallel route via a ketene intermediate. The cyclic product was further converted into the optically active tartramonoamides and tartradiamides by hydrolysis and reaction with appropriate alkylamines, respectively.

Introduction

Supramolecular assemblies such as cell membranes, nucleic acid multiplexes, proteins and protein complexes with nucleic acids and membranes consist of mesoscopic superstructures in the 10–1000 nm size range. They spontaneously self-assemble in aqueous media into these structures due to interactions such as electrostatic interactions, dipole–dipole interaction, hydrogen bonding, dispersion forces, and hydrophobic association. Chirality is one of the governing factors in determining for if and how they self-assemble into these superstructures. Optically active amphiphiles are therefore components of interest for the use in supramolecular chemistry and for the fabrication of micelles, vesicles and membranes. These find practical use for many applications, like time-controlled delivery of therapeutic agents and transport of genetic material,[1] ultrasound diagnostic,[2] and production of nanoparticles semiconductors, metallic and magnetic materials[3]

We are engaged in studies of the supramolecular chemistry of optically active amphiphiles. The tartaric acids were selected as the general source of chirality for the reason that all the tartaric acid stereoisomers are inexpensive and readily available. Tartaric ester amphiphiles were hydrolytically too labile for all practical applications, and therefore we focused our investigations on the corresponding *N*-alkyltartaric amides which are quite robust in aqueous media. Suitable routes for the synthesis of *N*-alkyl tartaric acid monoamides **1** were required. The synthesis and properties of this *N*-docecyl tartaric acid monoamide, (2*R*,3*R*)-3-dodecylcarbamoyl-2,3-dihydroxypropanoic acid, was reported earlier by Fuhrhop and co-workers.[4] For the construction of vesicles and membranes with specific properties, amphiphiles with one hydrophobic alkyl chain are often used in combination with polychain amphiphiles, in particular if one wants to form vesicles containing double-layer membranes. For these reasons we also tried to find efficient methods to prepare the corresponding diamides, *N*,*N′*-dialkyl-2,3-dihydroxysuccinamides **2**.



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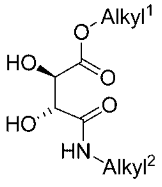

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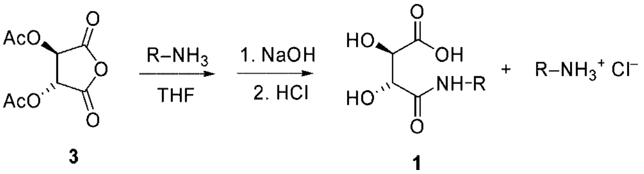
Results and Discussion

Tartaric acid monoamides have usually been prepared by reacting (2*R*,3*R*)-diacetyltartaric anhydride (**3**)[5] with the appropriate amines,[6] Scheme 1. In our hands, however, this procedure had limitations as the use of excess amine (> 2 equiv.) resulted in loss of starting material due to side reactions, because the amine did not only react with the anhydride but also to some extend with the ester functions, which led to the corresponding *N*-alkylacetamides.



Scheme 1. Synthesis of tartaric acid monoamides from anhydride **3**.

The desired amphiphilic monoamides **1** were also formed together with the corresponding alkylammonium chloride salts. We found it difficult to get hold of pure **1** by conven-

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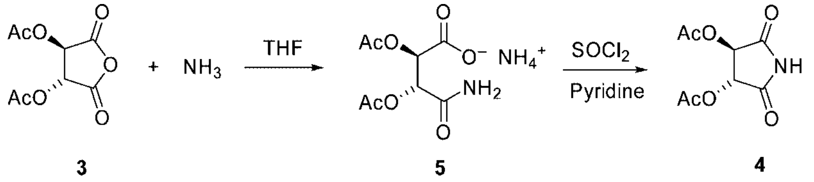


Scheme 2. Formation of imide **4** from tartaric anhydride **3**.

tional work-up procedures, as the long-chain amphiphilic ammonium salts and **1** presumably aggregates into mixed micelles and vesicle structures.

For these reasons we looked for alternative synthetic routes towards **1**. In addition, as many of the structures required for structure–activity studies involved amines not readily available, we also searched for methods that excluded the use of amines. We have developed an alternative general method for synthesis of the amides **1** that satisfy many of these preconditions, as alkyl halides, or alcohols via their corresponding tosylates, were used instead of amines. The procedure is a modification of the classic Gabriel synthesis, where primary amines are obtained after alkylation of potassium phthalimide with an appropriate alkyl halide and subsequent hydrolysis.[7] Instead of phthalimide we used the (2*R*,3*R*)-diacetoxyphthalimide (**4**), readily available from the anhydride **3**[8] (Scheme 2). Known methods involve the reaction of **3** with ammonia, followed by ring closure and re-acetylation in refluxing acetyl chloride. However, reported yields are disappointingly low, 44%.[9] An alternative method applied a four-step reaction sequence from **3** via the monoester acid chloride, reporting formation of **4** in a mere 28% overall yield.[10]

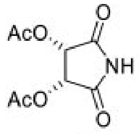
Compound **4** or its enantiomer has found synthetic use for the preparation of antibiotics,[11] potential HIV drugs[12] and alkaloids.[9]

Synthesis of (3*R*,4*R*)-3,4-Diacetoxypyrrolidine-2,5-dione

We here report a short and improved method for preparation of (2*R*,3*R*)-**4** that combines elements of these reactions. The (2*R*,3*R*)-diacetyltartaric anhydride[8] (**3**) was treated at room temperature with excess ammonia in THF, and the pure crystalline ammonium (2*R*,3*R*)-2,3-diacetoxy-3-carbamoylpropionate (**5**) salt was isolated by filtration in an essentially quantitative yield. Concentration of the mother liquor did not show significant amounts of starting material or by-products such as acetamide. Thus, the ester groups did not react under these conditions. To achieve this selectivity it appeared essential to use THF as solvent. The anhydride **3** was easily soluble in THF, while the monoamide salt **5** was virtually insoluble. Use of other solvents gave low yields and products of poor quality. Conversion of compound **5** to the cyclic imide **4** was next accomplished routinely in 70–85% isolated yields by reaction with thionyl chloride in the presence of ca. 1 equiv. of pyridine for 10 min at 60 °C (Scheme 2). After evaporation of excess reagents, the crude product was worked up by briefly washing a dichloromethane solution of the product with water, affording **4** which could be used directly in subsequent transformations. By-products were efficiently removed by this procedure. The product exhibits NMR, IR data and specific rotation similar to what was reported by Dener et al.[9] The product may further be recrystallized from dichloromethane/hexane to give analytically pure **4**.

By-Products

The NMR spectrum in $CDCl_3$ of the crude product showed the earlier reported signals at $\delta = 2.22$ (s) and 5.56 (s) ppm corresponding to the acetyl CH_3 and the methine protons, respectively.[9] In [D$_6$]DMSO these signals were shifted to $\delta = 2.12$ and $\delta = 5.73$ ppm. However, in this solvent were also observed distinct signals at $\delta = 2.105$ (s) and $\delta = 5.51$ (s) ppm amounting to approximately 3–4% of the product. The corresponding shifts in chloroform for this unknown compound were found at $\delta = 2.15$ and $\delta = 5.58$ ppm. We suggest that this by-product is identical with the corresponding *meso* product (2*R*,3*S*)-diacetoxyphthalimide (**6**). The synthesis of this compound has not been reported before.



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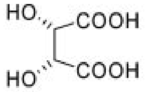

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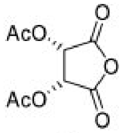

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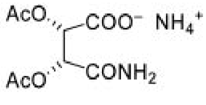

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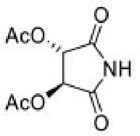

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If the reaction was carried out at room temperature a higher content (ca. 30%) of the *meso* product **6** was obtained. Fortunately, **6** was readily washed out with water of a solution of the crude reaction product dissolved in dichloromethane.

The structural assignment of the by-product is supported by the results of an independent synthesis of compound **6** from *meso*-tartaric acid (**7**) via the anhydride **8**.[13] The same procedure as shown in Scheme 2 was used. The resulting product exhibits NMR and GLC characteristics identical to those observed for the actual by-product **6**. The reaction mixture from synthesis of **6** was shown (GLC, NMR) to contain small amounts (ca. 10%) of racemic **4**.

For reference purposes we also prepared the corresponding enantiomeric product (2*S*,3*S*)-diacetoxyphthalimide (**10**) from D-tartaric acid using the same procedure as shown in Scheme 2.

Selectivity

An important question regarding formation of the *meso* product **6** was if this was due to simple epimerization reactions, in which case partial racemization of the isolate product **4** should be observed. NMR analyses of starting material **3** showed no signs of the corresponding *meso*-anhydride **8**. Similarly, comparing NMR spectroscopic data of **5** and the corresponding racemic *meso*-salt **9** provided no evidence for epimerization during formation of the ammonium salts as indicated by the characteristic NMR peaks for **5** at δ = 5.51 (d, J = 2.5 Hz) and 5.42 (d, J = 2.5 Hz), and for **9** at δ = 5.40 (d, J = 2.5 Hz) and 5.02 (d, J = 2.5 Hz), respectively.

Epimerization during formation of **4** from **5** would result in loss of enantiomeric purity of the isolated product. As a consequence this should be reflected in melting points and specific rotation. However, the product exhibited the same melting point, 147–148 °C, as was reported for the *S*,*S*-enantiomer (lit.: 146–148 °C) and the specific rotation, $[a]_D^{20}$ = +125.1 (c = 0.64, $CHCl_3$), was comparable to that observed for the 2*S*,3*S*-enantiomer **10** (lit.: $[a]_D^{20}$ = –126.5, c = 0.9, $CHCl_3$).[9] Incidentally, we observed that the optical rotation of **4** was strongly concentration dependent. The optical rotation was also measured in acetone, $[a]_D^{20}$ = +113.5 (c = 1.25, acetone) which was comparable to the value reported by Duhamel et al.[10]

NMR studies with an optically active Eu-shift reagent [Eu tris(3-heptafluoropropylhydroxymethylene)-(+)camphorate] in $CDCl_3$ or [D_6]benzene with **4** resulted in shifts of the signals. However, the methine proton signals did not split into multiple signals, indicating that racemization of the main product to form the *meso*-product **6** had not taken place.

Keeping an NMR sample of **4** or **6** or mixtures thereof in chloroform or DMSO with added pyridine for a prolonged period (weeks) did not lead to any changes in the isomer ratios.

Chiral GLC analysis of crude product **4** showed this to be the main product, however, with no signs of the 2*S*,3*S*-enantiomer **10**. An authentic sample of **10** was prepared by using the standard procedure. In addition small amounts of *meso*-**6** were observed. A similar chiral GLC analysis of the crude product from synthesis of authentic **6** proved this to be the major product in addition to ca. 10% of a 1:1 content of products 2*R*,3*R*-**4** and 2*S*,3*S*-**10**, respectively.

The combined evidence of these experiments indicates that racemization does not take place during the formation of 2*R*,3*R*-**4**. The key observation here is that the ring closure of pure *R*,*R*-**5** results in exclusive formation of 2*R*,3*R*-**4** and *meso*-**6** but not 2*S*,3*S*-**10**.

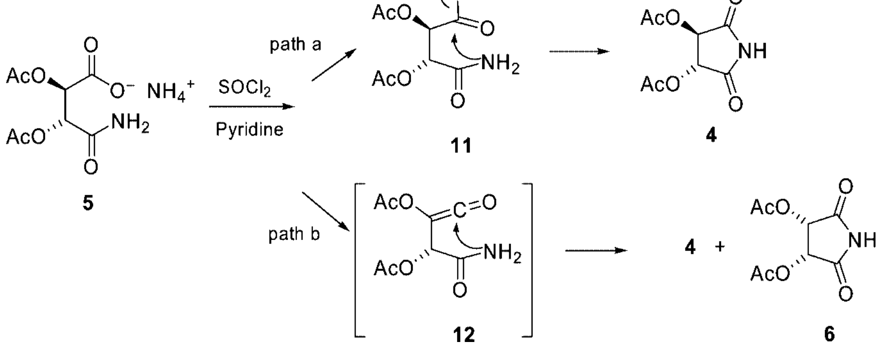
Mechanisms

To rationalize these observations, we propose a reaction scheme involving competing mechanistic pathways (Scheme 3). Treatment of **5** with thionyl chloride gives acid chloride **11**, which ring-closes directly to product **4** (path a). Alternatively, a ketene intermediate like **12**, produced by the reaction of pyridine with the acid chloride or an earlier intermediate, upon ring closure could form exclusively the *R*,*R*-enantiomer of the main product **4**, together with **6** (path b). Molecular modelling studies using PCModel[14] applying the Molecular Mechanics program MMX, showed a number of distinct low-energy conformations of **12** in which the amide NH_2 group was in close proximity to the ketene moiety. This reaction pathway also rationalizes that only the 2*R*,3*R*-**4** is formed as the exclusive enantiomer together with the **6**.

The *R*,*S*-salt **9** with thionyl chloride gave the *R*,*S* product **6** as the major product together with minor amounts of the enantiomers **4** and **10**, indicating that conformational effects were of minor significance in the ring closure reaction.

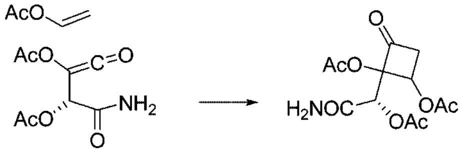
Trapping Experiments

To further investigate the validity of this reaction scheme, trapping of the proposed ketene intermediate was attempted. Thus, the reaction of **5** with thionyl chloride/pyridine was carried out in the presence of vinyl acetate as the



Scheme 3. Proposed mechanism for imide formation by competing pathways.

ketenophile. Under these reaction conditions the characteristic NMR signals of product **4** were observed together with a product which, based on its NMR spectroscopic characteristics, was in agreement with that expected for the ketene addition product **13** (Scheme 4). The reaction mixture contains other interesting cycloaddition products, presumably derived from SO_2 and vinyl acetate, which will be described separately.[15]



12 **13**

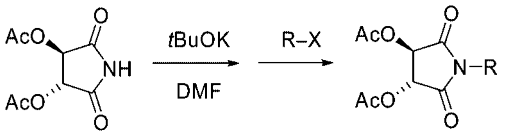
Scheme 4. Trapping of the proposed ketene intermediate **12** with vinyl acetate.

Excess vinyl acetate was removed by evaporation in a nitrogen stream. The resulting product mixture exhibited NMR peaks which can reasonably be ascribed to structure **13** displaying a typical ABX coupling pattern for the cyclobutanone moiety with signals at δ_A = 3.47 ppm (J_{AB} = 13.45 Hz and J_{AX} = 5.25 Hz, 1 H), δ_B = 3.55 ppm (J_{AB} = 13.45 Hz and J_{BX} = 7.67 Hz, 1 H), and δ_X = 6.66 ppm (J_{AX} = 5.25 Hz and J_{BX} = 7.67 Hz, 1 H), and the methine signal at δ_A = 5.68 ppm (s, 1 H).

The proposed cycloaddition product **13** was unstable, all attempts for its isolation failed. Concentration of the sample solution yielded intractable, probably polymeric material. However, after an NMR sample in chloroform or DMSO was allowed to stand overnight at room temperature, the signals corresponding to the cycloaddition product had disappeared completely, and at the same time the intensity of the signals corresponding to **4** and vinyl acetate increased. In agreement with these mechanistic considerations, cyclo-reversion to the ketene intermediate can subsequently may produce by ring closure cyclic imides 2*R*,3*R*-**4** and *meso*-**6** as the exclusive products. Enantiomer *S*,*S*-**10** is not formed.

Synthesis of Tartramides

N-Alkylation of **4** was accomplished by reaction with an appropriate alkyl halide or a tosylate in DMF in the presence of a base, preferably *t*BuOK (Scheme 5). Other solvents such as tetrahydrofuran, for example in combination with other bases like NaH, were not successful. Alkylation of **4** has been attempted before, but failed, and only reactions under Mitsunobu conditions were reported in low yields.[16] Only the dodecyl-alkylated products were studied here, using dodecyl halides or tosylate as alkylation agents. The rate of alkylation increases upon addition of catalytic amounts of potassium iodide. NMR analyses of the crude products indicate that the cyclic imide **14** can be obtained in essentially quantitative yield with *n*-dodecyl iodide, while the other halides and the tosylate ae less effective; results are shown in Table 1. The tosylates were also readily converted into the iodides by the reaction with sodium iodide. Purification of the product by crystallization or chromatography proved in general unsuccessful, presumably because the imides were too unstable in the presence of nucleophiles.



4 **14**

X = OTs, Cl, Br or I R = *n*-dodecyl

Scheme 5. Alkylation of imide **4**.

Table 1. *N*-Alkylation of cyclic imide **4**.

R–X	Base	% Conversion (by NMR)	Reaction time (h)	Isolated yield (%) of **14**
n-$C_{12}H_{25}Br$	NaH	40	20	not isolated
n-$C_{12}H_{25}Br$	*t*BuOK	47	2	not isolated
		67	24	
n-$C_{12}H_{25}OTs$	*t*BuOK	31	2	not isolated
		66	24	
n-$C_{12}H_{25}I$	*t*BuOK	84	2	not isolated
		94	24	61%

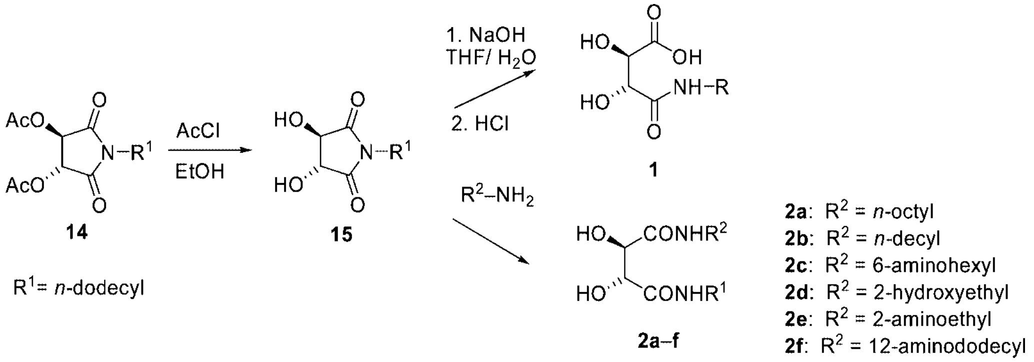
Therefore the crude *N*-alkylimide **14** was reacted without prior purification, and could for example be hydrolyzed directly with sodium hydroxide in water/THF followed by acidification with HCl to afford the pure monoamide acid **1** in good yields (69%) after crystallization.

Compound **14** was also used to synthesize the optically active unsymmetrical tartradiamides. To avoid the use of excess alkylamine and formation of *N*-alkylacetamide through reaction with the acetoxy groups, selective deprotection of **14** was first carried out in ethanol with acetyl chloride[17] to give (2*R*,3*R*)-dihydroxyphthalimide (**15**) which upon reaction with an appropriate alkylamines, gave the desired diamides, **2a**–**f**. These results are shown in Table 2. As is also shown in Scheme 6, compound **15** could also conveniently be hydrolyzed to **1** in 95% yield.

Table 2. Diamides from (2*R*,3*R*)-dihydrophthalimide **15**.

Alkylamine	R^2	Product	Yield (%)
n-Octylamine	*n*-octyl	**2a**	61
n-Decylamine	*n*-decyl	**2b**	43
1,6-Diaminohexane	6-aminohexyl	**2c**	72
2-Aminoethanol	2-hydroxyethyl	**2d**	73
1,2-Diaminoethane	2-aminoethyl	**2e**	81
1,12-Diaminododecane	12-aminododecyl	**2f**	72

In the reactions between **4** and alkyldiamines we were initially interested in obtaining the symmetric geminal amphiphiles. However, we did not observe these products at all, but the aminoalkyl products in satisfactory yields. The reason why the geminals were not formed may be because the initial product form aggregates in the solvent systems we worked with, thus hindering the second amino group to react. The yields were not optimized.



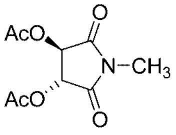
Scheme 6. Conversion of *n*-dodecylimide **14** to amphiphiles **1** and **2**.

Concentration-Dependent Optical Rotation

We briefly studied the concentration dependency of the optical rotation for compound **4**. In these experiments acetonitrile was chosen as the solvent because of its lower hydrogen-bond acceptor properties. Some results are shown in Table 3.

Table 3. Specific rotations, $[\alpha]_D^{20}$, measured for compound **4** and **16** at 589 nm at different concentrations. Measurements were carried out at 20 °C. Concentrations were in g **4**/100 mL acetonitrile.

4 (g/100 mL)	$[\alpha]_D^{20}$	**16** (g/100 mL)	$[\alpha]_D^{20}$
3.181	+114.8	3.390	+111.8
0.636	+116.8	0.678	+113.8
0.127	+120.4	0.135	+116.5



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The specific rotations of **4** decreased with increasing concentrations, Table 3. Initially we assumed this to be due to hydrogen bonding between **4** molcules. However, a similar concentration dependency was also observed for the corresponding (3*R*,4*R*)-3,4-diacetoxy-1-methylpyrrolidine-2,5-dione (**16**), which was prepared according to the literature,[18] but also by alkylation of **4** with methyl iodide. These results indicated that both molecule **4** and **16** associated into molecular complexes, and that hydrogen bonding, to the extend they may play a role for **4**, did not constituted the central mechanism.

Conclusions

Optically active 2*R*,3*R*-**4** was prepared from L-tartaric acid via a thionyl chloride induced ring closure of the ammonium salt **5**. Mechanistic considerations indicated that the ring closure followed two competing pathways, one through direct ring closure of the intermediate acid chloride, in competition with a pathway involving a ketene intermediate. This cyclic product was further converted into optically active tartaric acid monoamide **1**, and optically active diamides **2a**–**2f**. The optically active cyclic imides and the tartramides appeared to be robust under the reaction conditions as racemization reactions were not observed. Therefore **4** were a practical synthon for the syntheses of the planned amphiphiles. The observed concentration dependent optical rotation observed for **4** and **16** indicated that these molecules form aggregate.

Experimental Section

All chemicals and solvents applied were of synthesis quality unless otherwise stated and used as received without further purification. NMR spectra were recorded on a Bruker Avance DPX300 or 400 instruments. TMS was used as an internal standard in samples dissolved in $CDCl_3$ or dioxane for samples dissolved in D_2O. IR spectra were obtained with a Thermo Nicolet Nexus FT-IR Spectrometer, an usually recorded using a Smart Endurance reflexion cell. Mass spectra were obtained on a Thermo Quest MAT95X double focusing high resolution instrument using electron impact ionization using EI at 70 eV. Optical rotations were measured on a Perkin–Elmer Model 341 Polarimeter. Chiral GLC analysis was performed on a Varian 3380 GC with a CP8410 auto-injector equipped with a CP Chirasil-dex CB column (25 m × 0.32 mm ID, 25 µm film thickness), temperature program 110–180 4 °C/min (5 min hold at 180 °C), Retention times were 16.25 min for 2*S*,3*S*-**10**, 16.65 min for 2*R*,3*R*-**4**, and 18.54 min for *meso*-**6** (resolution 3.6). Melting points are uncorrected.

Ammonium (3*R*,4*R*)-2,3-Diacetoxy-3-carbamoylpropanoate (5): An approximately 2 M solution of ammonia in THF was prepared by distilling ca. 36 g ammonia into 1 L of cold (ca. –10 °C) THF. This solution was unstable and therefore stored in a closed bottle at –15 to –18 °C. 100 mL of this solution was added drop wise to 21.6 g (0.1 mol) of (2*R*,3*R*)-diacetyltartaric anhydride (**3**), dissolved in 200 mL of dry THF at room temperature. To make sure the presence of excess ammonia, after 2 h another 25 mL of ammonia/THF was added to the reaction mixture to a persistent smell of ammonia. The resulting reaction mixture was stirred overnight (16 h). The precipitated hygroscopic product was isolated as a white solid by filtration, washed with THF and then dried under reduced pressure. The yield of the pure product was 24.5 g (0.098 mol, 98 %) with m.p. 184–185 °C (decomp.) $[\alpha]_D^{25}$ = –29.8 (*c* = 3.0, H_2O). ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 7.43 (s, 1 H, NH_2), 7.17 (s, 1 H, NH_2), 5.40 (d, *J* = 2.6 Hz, 1 H, CH-CO), 5.15 (d, *J* = 2.6 Hz, 1 H, CH-CO-), 2.04 (s, 3 H, CH_3), 1.98 (s, 3 H, CH_3) ppm. ^{13}C-NMR (100 MHz, $[D_6]$DMSO): δ = 169.7, 169.5, 169.3, 73.8, 73.7, 20.9, 20.8 ppm. IR: $\tilde{\nu}$ = 3456, 3358, 2957, 1782, 1736, 1649, 1586, 1418, 1371, 1193, 1108, 1059 cm^{-1}.

Ammonium 2,3-Diacetoxy-3-carbamoylpropanoate (9): This compound was prepared from *meso*-2,3-diacetoxytartaric anhydride **8**, using the same procedure as describe above for **5**. This product was isolated as a white solid in 98% yield, with m.p. 165 °C (decomp.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.45 (s, 1 H, NH$_2$), 7.11 (s, 1 H, NH$_2$), 5.39 (d, J = 2.2 Hz, 1 H, CH-CO), 5.04 (d, J = 2.2 Hz, 1 H, CH-CO), 2.03 (s, 3 H, CH$_3$), 1.97 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 169.7, 169.5, 169.3, 73.8, 73.8, 20.9, 20.8 ppm. IR: $\tilde{\nu}$ = 3160, 1741, 1700, 1604, 1401, 1368, 1222, 1108, 1087, 1054, 764 cm^{-1}.

Ammonium (3*S*,4*S*)-2,3-Diacetoxy-3-carbamoylpropanoate: This enantiomer was prepared from *D*-tartaric acid using the same procedure as describe above for the synthesis of **5**. The product was isolated in 96% yield, and exhibited similar spectroscopic properties as was measured for compound **5**. The Optical rotation: $[\alpha]_{\mathrm{D}}^{25}$ = +29.2 (c = 3.3, H$_2$O).

(3*R*,4*R*)-3,4-Diacetoxypyrrolidine-2,5-dione (4): Compound **5** (18.28 g, 73.1 mmol) was stirred with thionyl chloride (100 mL) and pyridine was added (2 mL). The stirred reaction mixture was heated at 60 °C for 10 min. Thionyl chloride was then evaporated under reduced pressure and dichloromethane was added to the crude product and the precipitated salts separated by filtration. The solvent was then evaporated under reduced pressure to obtain a product containing compound **4** together with small amounts of the isomeric *meso*-product, (3*S*,4*R*)-3,4-diacetoxypyrrolidine-2,5-dione (**6**) (isomer ratio **4**/**6** = 30:1), as a slightly yellow solid (11.9 g, 76%). Compound **6** was removed by washing a solution of the crude product in dichloromethane once with water. An analytical pure sample was obtained by recrystallizing 1 g of the crude product from a 20:80 mixture of dichloromethane/hexane, yielding 0.78 g of product **4** with m.p. 146–147 °C. $[\alpha]_{\mathrm{D}}^{20}$ = +125.1 (c = 0.64, CHCl$_3$). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.91 (s, 1 H, NH), 5.73 (s, 2 H, CH), 2.12 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 170.5, 169.7, 73.1, 20.2 ppm. IR: $\tilde{\nu}$ = 3112, 2950, 1805, 1745, 1722, 1378, 1248, 1213, 1174, 1121, 1075 cm^{-1}. HRMS (70 eV): calcd. for C$_6$H$_7$NO$_5$ [M$^+$ – C$_2$H$_2$O] 173.03242; found 173.03263. C$_8$H$_9$NO$_6$ (215.2): C 44.66, H 4.22, N 6.51; found C 44.07, H 4.22, N 6.47.

(3*S*,4*S*)-3,4-Diacetoxypyrrolidine-2,5-dione (10): This compound was prepared form ammonium (3*S*,4*S*)-2,3-diacetoxy-3-carbamoylpropanoate using the same procedure as described for the synthesis of **4**. The product exhibited the same properties as **4**, except for the specific rotation which was measured to $[\alpha]_{\mathrm{D}}^{20}$ = –124.9 (c = 0.95, CHCl$_3$).

***meso*-3,4-Diacetoxypyrrolidine-2,5-dione (6):** This product was prepared according to the same procedure describe above for the synthesis of **4**. The product was formed together with ca. 10% of a 1:1 mixture of the enantiomers **4** and **10**. Product **6** was isolated as a slightly yellow solid in 65% yield, with m.p. 165 °C (decomp.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.00 (s, 1 H, NH), 5.51 (s, 2 H, CH), 2.10 (s, 3 H, CH$_3$) ppm. IR: $\tilde{\nu}$ = 3160, 1741, 1805, 1700, 1604, 1401, 1368, 1222, 1108, 1087, 1054, 764 cm^{-1}. HRMS (70 eV): calcd. for C$_6$H$_7$NO$_5$ [M$^+$ – C$_2$H$_2$O] 173.03242; found 173.03235.

(3*R*,4*R*)-3,4-Diacetoxy-1-dodecylpyrrolidine-2,5-dione (14): Compound **4** (0.1 g, 0.46 mmol) and the correspondent alkyl halide or tosylate (0.95 equiv.) was dissolved in 10 mL of dry DMF at 40 °C and potassium *tert*-butoxide (0.060 g, 1.1 equiv.) was added in portions. Upon addition of the base the solution became slightly yellow and transparent. After 24 h at room temperature the mixture was concentrated under reduced pressure. The crude reaction mixture was shown (NMR) to contain unreacted dodecyl halide or tosylate except for dodecyl iodide in which case practically quantitative conversion to product **14** was observed. Extraction with toluene/chloroform (1:10) yielded compound **14** as a slightly yellow oil (0.092 g, 62%). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.50 (s, 2 H, CH-CO-N), 3.61–3.53 (m, 2 H, NCH$_2$-), 2.19 (s, 6 H, -CH$_3$), 1.63–1.48 (m, 2 H, -CH$_2$-), 1.25 (s, 18 H, -CH$_2$-), 0.88 (t, J = 7.14 Hz, 3 H, -CH$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 169.8, 169.3, 72.7, 39.5, 31.8, 29.5, 29.4, 29.3, 29.2, 28.9, 27.2, 26.5, 22.6, 20.3, 14.0 ppm. IR: $\tilde{\nu}$ = 2922, 2853, 1753, 1722.3, 1632, 1439, 1404, 1372, 1215, 1067, 948, 870, 802, 721 cm^{-1}. LRMS (EI): m/z (%): 383 (M$^+$) (1) 323 (20), 281 (100), 264 (19), 173 (32), 168 (17), 166 (19), 157 (21), 126 (21). HRMS (70 eV): calcd. for C$_{18}$H$_{33}$NO$_6$ [M$^+$] 383.23078; found 383.23010.

(3*R*,4*R*)-3,4-Diacetoxy-1-methylpyrrolidine-2,5-dione (16): This compound was prepared by alkylation of **4** with methyl iodide according to the same procedure described for **14**, and isolated in 52% yield as a white solid with m.p. 73–74 °C after crystallization from dichloromethane/hexane (1:3). The product was also prepared using the method described by El-Nezhawy et al.,[18] where, however, the product was described as an oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.52 (s, 2 H, CH-CO-N), 3.10 (s, N-CH$_3$), 2.19 (s, 6 H, -CH$_3$) ppm. IR: $\tilde{\nu}$ = 2980, 1744, 1725, 1439, 1363, 1288, 1259, 1215, 1056, 1026, 926, 870, 798, 712 cm^{-1}. Optical rotation (concentration-dependent): $[\alpha]_{\mathrm{D}}^{20}$ = +111.8 (c = 3.39, CH$_3$CN).

(3*R*,4*R*)-1-Dodecyl-3,4-hydroxypyrrolidine-2,5-dione (15): Compound **14** (0.1861 g, 0.48 mmol) was dissolved in ethanol (20 mL) and acetyl chloride (2 mL) was slowly added at 0 °C, and then allowed to reach room temperature and stirred at this temperature for 1 d. The solvent was then removed under reduced pressure yielding the desired product **15** in a basically quantitative yield, (0.1452 g, 99%) as an off-white powder with m.p.133–135 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 4.58 (s, 2 H, CH-CO-N), 3.57–3.45 (m, 2 H, -*N*-CH$_2$-), 2.19 (s, 6 H, -CH$_3$), 1.63–1.48 (m, 2 H, -CH$_2$-), 1.25 (s, 18 H, -CH$_2$-), 0.88 (t, J = 6.95 Hz, 3 H, -CH$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 174.2, 75.0, 39.5, 32.1, 29.8, 29.7, 29.6, 29.5, 29.2, 27.8, 26.9, 22.9, 14.3 ppm. IR: $\tilde{\nu}$ = 3368, 2945, 2917, 2848, 1701, 1465, 1402, 1345, 1271, 1248, 1219, 1192, 1159, 1143, 1079, 1034, 1000, 973, 855, 839, 808, 783, 721 cm^{-1}. LRMS (EI): m/z (%): 299(3) (M$^+$), 210 (30), 167 (29), 154 (21), 131 (43), 126, (42), 111 (29), 103 (34), 98 (52). HRMS (70 eV): calcd. for C$_{16}$H$_{29}$NO$_4$ [M$^+$] 299.20966; found 299.21011.

(2*R*,3*R*)-3-Dodecylcarbamoyl-2,3-dihydroxypropanoic Acid (1): Compound **15** (0.12 g, 4 mmol) was dissolved in a 1:1 THF/H$_2$O mixture (20 mL) and stirred for a few minutes. Then NaOH (1 M, 4.5 mL, 4.5 mmol) was added slowly and the mixture stirred for 2 h. The reaction mixture was then cooled to 0 °C and the white precipitate that was formed was isolated by filtration. The precipitate was washed first with small amounts of cold water, air-dried and subsequently washed with cold hexane and dried. This product was the sodium salt of **15** [sodium (2*R*,3*R*)-3-dodecylcarbamoyl-2,3-dihydroxypropanoate]. It was obtained as a white powder (0.087 g, 65%) with m.p. 183–184 °C (decomp.). ^{1}H NMR (400 MHz, [D$_4$]Methanol): δ = 4.38 (s, 1 H, CH-CO-N), 4.28 (s, 1 H, CH-CO-N), 3.22 (m, 2 H, -NH-CH$_2$-), 1.5 (m, 2 H, -CH$_2$-), 1.28 (s, 18 H, -CH$_2$-), 0.89 (t, J = 6.9 Hz, 3 H, -CH$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 178.4, 175.1, 74.3, 74.3, 40.3, 32.6, 30.2, 29.9, 23.4, 14.5 ppm. IR: $\tilde{\nu}$ = 3312, 3201, 2953, 2917, 2869, 2847, 1652, 1616, 1542, 1477, 1463, 1427, 1376, 1295, 1277, 1262, 1142, 1087, 1059, 998, 933, 841, 824, 723, 683 cm^{-1}.

The sodium salt (0.05 g, 0.14 mmol) was next dissolved in THF (20 mL) and HCl (0.01 M, 14 mL, 0.14 mmol) was added. THF was the removed under reduced pressure and the resulting white solid washed first with cold water (10 mL), air-dried and then washed with cold hexane (10 mL) to yield **1** as a white powder (0.046, 99%) with a m.p.148–150 °C. ^{1}H NMR (400 MHz, [D$_4$]methanol): δ = 7.84 (s, 1 H, NH), 4.52 (s, 1 H, CH-CO-N), 4.42 (s, 1 H, CH-CO-N), 3.23 (m, 2 H, -NH-CH$_2$), 1.53 (m, 2 H, -CH$_2$-), 1.28 (s, 18 H, -CH$_2$-), 0.89 (t, J = 6.9 Hz, 3 H, -CH$_3$) ppm. ^{13}C NMR (400 MHz, MeOD): δ = 174.2, 74.4, 40.3, 33.2, 31.0, 30.93, 30.90, 30.8, 30.6, 30.6, 28.0, 23.8, 14.5 ppm. IR: $\tilde{\nu}$ = 3511, 3302, 2954, 2917, 2849, 1738, 1646, 1535, 1469, 1269, 1239, 1197, 1158, 1118, 1069, 918, 860, 773, 720, 670 cm^{-1}.

(2*R*,3*R*)-*N*-Alkyl-*N*′-dodecyl-2,3-dihydroxysuccinamides 2a–f. General Procedure: Compound **15** (1.0 g, 3.3 mmol) was dissolved in a dry toluene/acetonitrile/chloroform solvent mixture. Then a solution of the appropriate amine (3.3 mmol, 1.1 equiv. for the monoamines or 10 mmol, 3 equiv. of hydroxy- or diamine) in small amounts of chloroform was added and the reaction mixture was refluxed for 18 h. Solvents were then removed in vacuo. The diamide products were in general obtained as oils, which upon recrystallization from acetonitrile/toluene (1:1) gave the diamides as crystalline materials.

(2*R*,3*R*)-*N*-Dodecyl-2,3-dihydroxy-*N*′-octylsuccinamide (2a): Here was used as solvent a (3:1:3) mixture of toluene/acetonitrile/chloroform for the reaction with 1-aminooctane (1.1 equiv.). After recrystallization compound **2a** was isolated as an off-white powder in 61% yield with m.p. 157–159 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.07 (m, 2 H, NH), 5.48 (d, J = 7.5 Hz, 2 H, OH), 4.23 (d, J = 7.5 Hz, 2 H, O-CH-CO), 3.27–3.22 (m, 4 H, NH-CH$_2$-), 1.51–1.46 (m, 4 H, CH$_2$), 1.25 (br. s, 25 H, CH$_2$, aliphatic), 0.88 (t, J = 6.9 Hz, 6 H, CH$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 174.1, 70.1, 39.3, 32.1, 31.9, 29.8, 29.8, 29.8, 29.74, 29.5, 29.4, 29.4, 29.3, 26.9, 22.9, 22.8, 14.3, 14.2 ppm. LRMS (EI): m/z (%): 429 [M$^+$ + 1] (1), 272 (36), 216 (43), 212 (60), 199 (18), 198 (16), 156 (100). HRMS (70 eV): calcd. for C$_{24}$H$_{48}$N$_2$O$_4$ [M$^+$] 428.36141; found 428.36164.

(2*R*,3*R*)-*N*-Decyl-*N*′-dodecyl-2,3-dihydroxysuccinamide (2b): For the reaction with 1-aminodecane was used a toluene/acetonitrile/chloroform (20:1:20) mixture as the solvent. After recrystallization compound **2b** was obtained as a white powder in 43.4% yield with m.p. 165–166 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.08 (br. t, J = 5.8 Hz, 2 H, -NH), 5.48 (br. s, 2 H, -OH), 4.23 (s, 2 H,O-CH-CO), 3.24 (m, 4 H, NH-CH$_2$-), 1.49 (m, 4 H, -CH$_2$-), 1.27 (m, 32 H, -CH$_2$-, aliphatic), 0.88 (t, J = 7.0 Hz, 6 H, -CH$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 174.1, 70.1, 39.3, 32.1, 31.9, 29.8, 29.8, 29.8, 29.7, 29.5, 29.45, 29.4, 29.3, 26.98, 22.90, 22.8, 14.3, 14.29 ppm. IR: $\tilde{\nu}$ = 3321, 2956, 2918, 2849, 1642, 1541, 1466, 1430, 1377, 1310, 273, 1129, 1088, 1059, 828, 721, 674 cm^{-1}. LRMS (EI): m/z (%): 456 (M$^+$) (1), 272 (61), 244 (39), 212 (23), 184 (30), 131 (20), 99 (29), 85 (32), 71 (45), 69 (41), 57(100). HRMS (70 eV): calcd. for C$_{26}$H$_{52}$N$_2$O$_4$ [M$^+$] 456.39271; found 456.39325.

(2*R*,3*R*)-*N*-(6-Aminohexyl)-*N*′-dodecyl-2,3-dihydroxysuccinamide (2c): For the reaction with 1,6-diaminohexane (3 equiv.) was used a toluene/acetonitrile/chloroform (6:1:6) as the solvent. Recrystallization gave product **2c** as a white powder in 72.4% yield with m.p. 152–154 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.07 (t, -NH, 2 H, br.), 4.30 (s, 2 H,O-CH-CO), 3.30 (m, 4 H, -NH-CH$_2$-), 2.73, (t, J = 6.5 Hz, 2 H, -NH$_2$), 1.79–1.37 (m, 12 H, -CH$_2$-), 1.26 (m, 24 H, -CH$_2$-, aliphatic), 0.88 (t, J = 6.5 Hz, 3 H, -CH$_3$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$/[D$_6$]DMSO, 10:1): δ = 172.6, 171.6, 71.4, 71.3, 40.8, 38.2, 37.9, 32.3, 31.0, 28.7, 28.7, 28.6, 28.49, 28.48, 28.47, 26.08, 26.6, 26.2, 21.8, 13.3 ppm. IR: $\tilde{\nu}$ = 3317, 2917, 2848, 1643, 1536, 1465, 1379, 1311, 1257, 1136, 1087, 1066, 1045, 1014, 984, 889, 828, 802, 722 cm^{-1}. LRMS (EI): m/z (%): 415 (1) [M$^+$], 382 (13), 380 (28), 378 (38), 376 (18), 308 (13), 203 (19), 105 (17), 70 (15), 30(100). HRMS (70 eV): calcd. for C$_{22}$H$_{45}$N$_3$O$_4$ [M$^+$] 415.34101; found 415.34179.

(2*R*,3*R*)-*N*-Dodecyl-2,3-dihydroxy-*N*′-(2-hydroxyethyl)succinamide (2d): For the reaction with 2-aminoethanol (3 equiv.) was used a toluene/acetonitrile/chloroform (6:1:6) as the solvent system. Recrystallization gave 73% of compound **2d** as a white powder with m.p. 170–172 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.6 (t, J = 5.5 Hz, 2 H, -NH), 5.56 (d, J = 6.8 Hz, 1 H, -OH), 5.54 (d, J = 6.8 Hz, 1 H, -OH), 4.70 (br. t, J = 5.5 Hz, 1 H, -OH), 4.20 (br. s, 2 H, O-CH-CO), 3.40 (m, 2 H, O-CH$_2$), 3.18 (m, 2 H, -NH-CH$_2$), 3.11 (m, 2 H, -NH-CH$_2$), 1.41 (m, 2 H, -CH$_2$), 1.23 (m, 20 H, -CH$_2$-, aliphatic), 0.88 (t, 3 H, -CH$_3$, J = 6.8 Hz). ^{13}C NMR (75 MHz, CDCl$_3$/[D$_6$]DMSO, 10:1): δ = 172.1, 171.2, 71.6, 71.5, 60.1, 41.2, 38.2, 31.0, 28.77, 28.74, 28.69, 28.45, 26.07, 21.80, 13.3 ppm. IR: $\tilde{\nu}$ = 3321, 3175, 2954, 2916, 2847, 1644, 1540, 1464, 1442, 1378, 1314, 1276, 1214, 1129, 1079, 1058, 1035, 926, 834, 721 cm^{-1}. LRMS (EI): m/z (%): 361 [M$^+$ + 19] (1), 272 (100), 254 (24), 212 (71), 148 (86), 131 (37). HRMS (70 eV): calcd. for C$_{18}$H$_{36}$N$_2$O$_5$ [M$^+$] 360.26242; found 360.26251.

(2*R*,3*R*)-*N*-(2-Aminoethyl)-*N*′-dodecyl-2,3-dihydroxysuccinamide (2e): For the reaction with 1,2-diaminoethane (2 equiv.) was used a toluene/acetonitrile/chloroform (6:1:6) as the solvent system. Recrystallization gave 82.1% of compound **2e** as a white powder with m.p. 166 °C (decomp.). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.69 (br. t, J = 5.9 Hz, 1 H, -NH-), 7.60 (br. t, J = 5.9 Hz, 1 H, -NH-), 4.21 (br. s, 1 H, O-CH-CO), 4.19 (br. s, 1 H, O-CH-CO), 3.09 (m, 4 H, -NH-CH$_2$), 2.59 (t, J = 5.9 Hz, 2 H, -NH$_2$), 1.40 (m, 2 H, -CH$_2$-), 1.23 (m, 18 H, -CH$_2$-, aliphatic), 0.88 (t, J = 6.5 Hz, 3 H, -CH$_3$) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 172.1, 171.2, 71.6, 71.5, 60.1, 41.2, 38.2, 31.0, 28.77, 28.74, 28.69, 28.45, 26.07, 21.80, 13.3 ppm. IR: $\tilde{\nu}$ = 3321, 3175, 2954, 2916, 2847, 1644, 1540, 1464, 1442, 1378, 1314, 1276, 1214, 1129, 1079, 1058, 1035, 926, 834, 721 cm^{-1}. LRMS (EI): m/z (%): 359 [M$^+$] (9), 330 (24), 316 (28), 271 (64), 260 (21), 243 (12), 212 (46), 184 (15), 146 (24), 112 (21), 98 (27), 71 (43). HRMS (70 eV): calcd. for C$_{18}$H$_{37}$N$_3$O$_4$ [M$^+$)] 359.27841 found 359.27725.

(2*R*,3*R*)-*N*-(12-Aminododecyl)-*N*′-dodecyl-2,3-dihydroxysuccinamide (2f): For the reaction with 1,12-diaminododecane (3 equiv.) was used a toluene/acetonitrile/chloroform (6:1:6) as the solvent system. Recrystallization gave 72.3% of compound **2f** as a white powder with m.p.156–160 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.07 (br. t, 2 H, -NH), 4.30 (s, 2 H,O-CH-CO), 3.30 (m, 4 H, -NH-CH$_2$-), 2.73 (t, J = 6.5 Hz, 2 H, -NH$_2$), 1.79–1.37 (m, 12 H, -CH$_2$), 1.26 (m, 24 H, -CH$_2$-, aliphatic), 0.88 (t, J = 6.5 Hz, 3 H, -CH$_3$) ppm. ^{13}C NMR (100 MHz, CD$_3$OD): δ = 174.6, 74.1, 33.2, 30.97, 30.96, 30.91, 30.88, 30.80, 30.65, 23.9, 14.6 ppm (some carbons are not observed due to relation time and solubility problems). IR: $\tilde{\nu}$ = 3319, 2915, 2848, 1643, 1541, 1467, 1377, 1315, 1157, 1129, 1064, 820, 721 cm^{-1}. LRMS (EI): m/z (%): 499 [M$^+$] (4), 287 (100), 272 (33), 269 (24), 228 (53), 227 (28), 201 (27), 170 (22). HRMS (70 eV): calcd. for C$_{28}$H$_{57}$N$_3$O$_4$ [M$^+$] 499.43491; found 499.43616.

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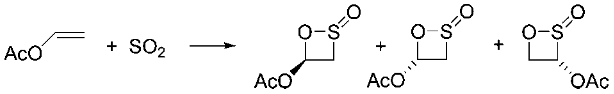
[15] Incidentally, in the reaction mixture with vinyl acetate, two sets of strong signals consisting of distinct ABX-coupling patterns were observed. They could not be assigned to any of the expected products. We propose these signals to be due to three different substituted β-sultine products, formed in concerted or stepwise cycloaddition reactions between sulfur dioxide and vinyl acetate. The proposed structures are as follows. A study dealing with this unusual reaction will be reported separately.



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