CYCLIC DIPEPTIDES. 4.[1] ON THE PUMMERER REARRANGEMENT OF DIASTEREOMERIC DEHYDROCYCLOLANTHIONINE SULFOXIDES

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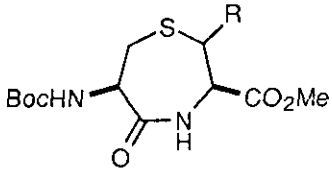
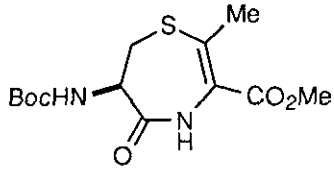
Abstract - Ring transformation and functionalization of dehydrocyclolanthionine sulfoxides by Pummerer rearrangement, leading to different compounds depending on the experimental conditions, are described.

In recent years intensive efforts have been made to develop peptidomimetics, that are agents which can imitate or block the biological functions of bioactive peptides.[2] Generally applicable and successful methods so far for the development of peptidomimetics involve the preparation of peptides containing unusual/unnatural amino acids and/or the formation of conformationally resctricted analogues that imitate the receptor-bound conformation of the endogenous ligands as closely as possible. Conformationally restricted peptidomimetics have been used extensively to probe the topography of enzyme active sites and to generate potent inhibitors devoid of the typical therapeutic shortcomings of peptides.[3]



1a: R = α-Me
1b: R = β-Me



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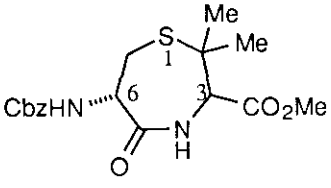
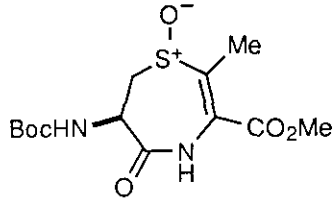


3a: (3*R-trans*)
3b: (3*S-cis*)



4a: (1*R-cis*)
4b: (1*S-trans*)

Lanthionine is an unusual amino acid, composed of two alanine-like residues linked by a thioether bridge (monosulfide cystine analog),[4] present in a family of bioactive polypeptides called "lantibiotics".[5] In the development of peptidomimetics, lanthionine is an effective building block displaying conformational constraint and metabolic stability.[6]

Recently, the design and synthesis of the new constrained dipeptide mimetics (**1**) and (**2**) based on cyclolanthionine has been reported by us,[7] while Goodman and co-workers have studied the β,β-dimethyl analog (**3**).[8]

As an extension of our previous investigations, we conceived the possibility to further functionalize **2** through the Pummerer rearrangement of the corresponding diastereomeric sulfoxides (**4a,b**), whose absolute stereochemistry has been determined by X-Ray crystallography,[1,7a] with the aim to develop new constrained cyclolanthionine analogs. We report herein the results of this study.

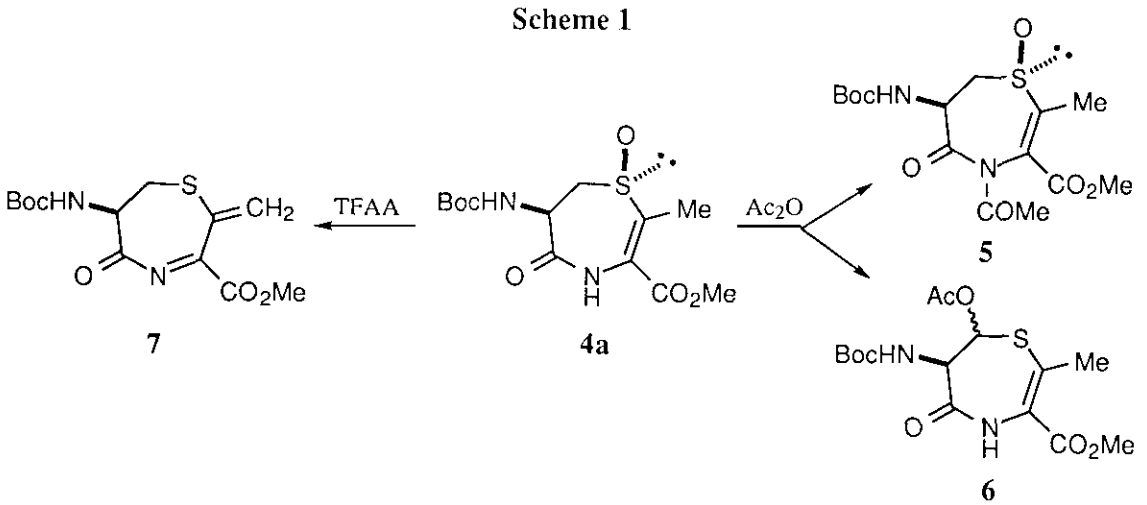
The Pummerer reaction is a well-known method for the preparation of α-substituted sulfides from the corresponding sulfoxides,[9] and it has been widely employed for the synthesis of even complex heterocyclic systems.[10] There have been many reports of reactions (usually referred to as "interrupted"[11] or "non-oxidative"[12] Pummerer reactions) occurring *at sulfur*, by inter- or intramolecular trapping of the intermediate sulfonium cation by strong nucleophiles.[13]

RESULTS AND DISCUSSION

Pummerer reaction of 4a in the presence of Ac_2O.

Heating **4a** at 120 °C for 3 h in excess acetic anhydride led to the formation of a complex reaction mixture, from which only compounds (**5**) and (**6**) (Scheme 1) could be isolated and purified (5% and 34% yields, respectively). Because of their inherent instability, they have been structurally identified only by ^{1}H NMR spectroscopy.

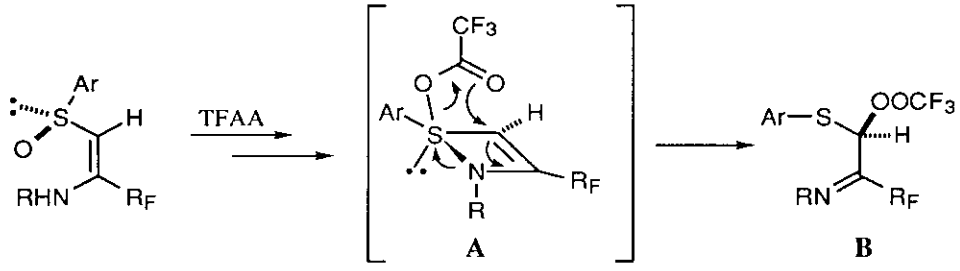
Scheme 1



Pummerer reaction of 4a in the presence of TFAA.

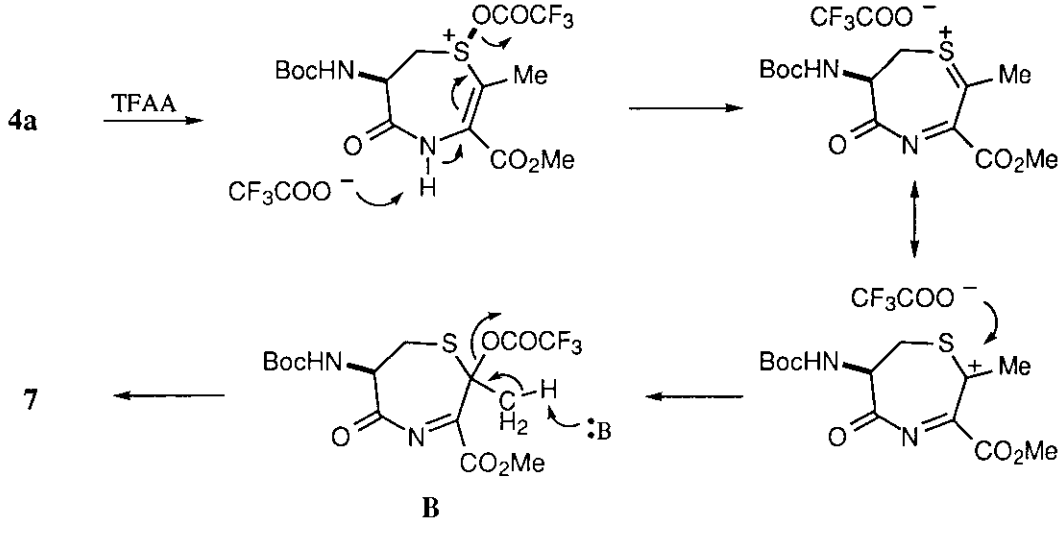
In this case the rearrangement involved the "right hand" of the substrate (**4a**) and led to the isolation of **7** (Scheme 1) in 45% yield after silica gel chromatography. The structure of **7** has been assigned on the basis of its ^{1}H and ^{13}C NMR spectra and EI-MS spectrum. In particular, the ^{1}H NMR spectrum showed the presence of two singlets at 6.04 and 5.57 ppm ($=CH_2$) and the absence of two singlets at 2.42 (allylic methyl) and 7.25 ppm (lactam NH). Accordingly, the ^{13}C NMR spectrum showed a signal relative to a terminal methylene group at 117.7 ppm and the lack of a signal at 23.8 ppm (allylic methyl). Finally, the MS spectrum elicited a peak at *m/z* 314 (M^+).

Scheme 2



Very recently Zanda, Bravo and co-workers have reported that (*Z*)-α-fluoroalkyl-β-sulfinylenamines submitted to Pummerer conditions (TFAA, *sym*-collidine) follow the "interrupted" pathway leading to α-arylthio-α-trifluoroacetoxyimines (**B**) (Scheme 2).[12]

Scheme 3

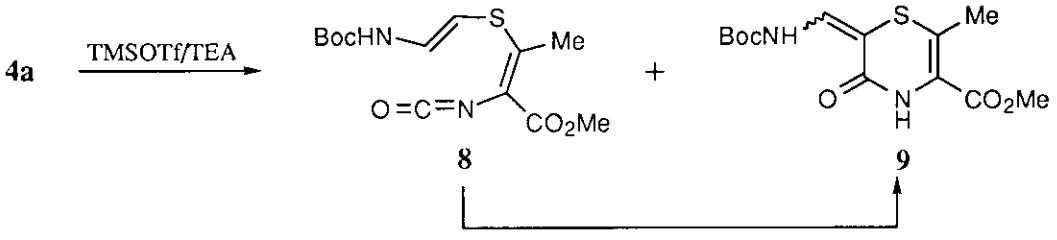


Although **4a** is a (*Z*)-sulfinylenamine and compound (**7**) is most likely formed by spontaneous β-elimination of TFA from an intermediate such as **B** (Scheme 3), we think that the "interrupted" reaction mechanism could hardly account for the formation of **7** on the basis of geometrical (nitrogen lone pair not

directed toward the sulfur atom) and conformational (rigidity of the seven-membered ring) considerations. Therefore, though the intermediacy of highly reactive sulfurane species such as **A** can not be definitely ruled out, we postulate that a reaction path, like that depicted in Scheme 3, may be concerned.

The different results obtained with the use of Ac_2O and TFAA can be explained considering the higher electrophilicity of TFAA and its ability to convert the oxygen atom of sulfoxide into a leaving group better than the acetoxy group.

Scheme 4



Pummerer reaction of 4a and 4b in the presence of TMSOTf/TEA.

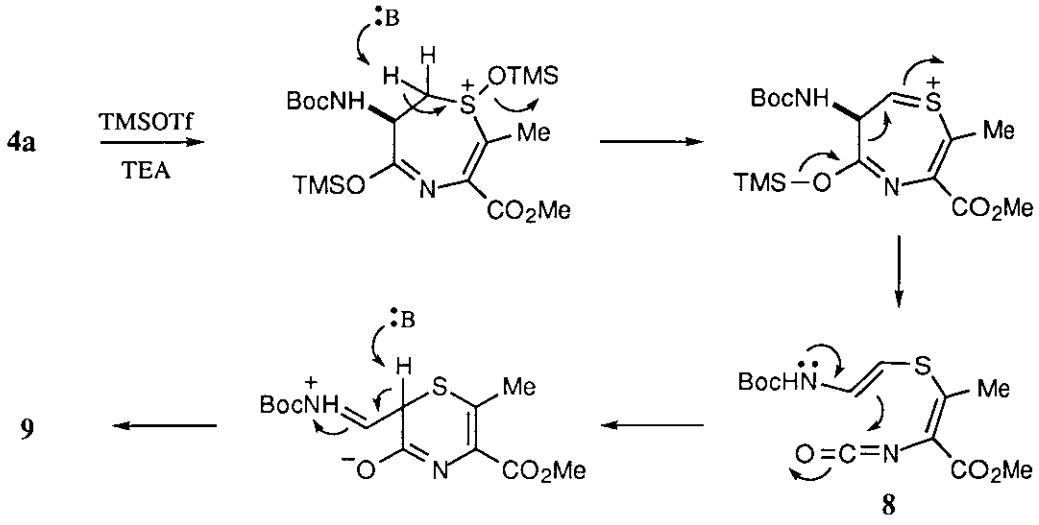
Among the electrophilic reagents capable of bringing about Pummerer rearrangement, the combination of trimethylsilyl triflate (TMSOTf) and a tertiary amine (TEA, DIPEA) has recently attracted much attention.[14] Accordingly, sulfoxide (**4a**) was treated with TMSOTf/TEA in dichloromethane at -20 °C to room temperature for 30 min to give two main reaction products (**8**) and (**9**) in 18% and 47% yields, respectively, along with unchanged starting material (28%) (Scheme 4). On the basis of chromatographic and spectroscopic analyses, **9** proved to be a single stereoisomer (the geometry of the exocyclic double bond was not determined)

The presence in the IR spectrum of **8** of a strong absorption band at ν 2249 cm^{-1}, diagnostic for an isocyanate group, and the presence of signals relative to a CH=CH-NH moiety in the ^1H NMR spectrum supported the structural assignment. When the same reaction conditions were applied to the diastereomeric sulfoxide (**4b**), the same products (**8**) and (**9**) were obtained in comparable yield (40% and 33%, respectively). Performing the reaction at lower temperature (-20 °C to -50 °C) did not influence either the yield or the products ratio, while at -70 °C no reaction occurred. On the other hand, the use of larger amount of TMSOTf/TEA or changing the base to DIPEA afforded complex reaction mixtures due to substrate degradation. However, only compound (**9**) was obtained (57% yield) when the reaction time was prolonged to 4 h, leading to deem compound (**8**) as a possible precursor of **9**. Indeed, storage of **8** under vacuo for three days caused its complete conversion to **9**.

On the basis of the above reported results, we tentatively explained the formation of **8** and **9** according to the reaction path depicted in Scheme 5. Activation of the sulfoxide oxygen by silylation, with concurrent *O*-silylation of the lactam function, is followed by base-promoted abstraction of a proton from the α-carbon to the trivalent sulfonium cation. Desilylation of the lactam causes ring opening, leading to the intermediate isocyanate (**8**), which in turn gives rise to the final thiazinone derivative (**9**) by intramolecular *C*-acylation of the enamino functionality. Silylation of the lactam group prevents its base-promoted deprotonation and

hence structural modification at the "right hand" of the substrate, such as that described in Scheme 3.

Scheme 5



Pummerer reaction of 4a in the presence of $SOCl_2$ or *O*-methyl-*O*-*tert*-butyldimethylsilylketene acetal.

Treatment of **4a** with $SOCl_2$ in CH_2Cl_2, according to a literature procedure,[15] did not lead to rearrangement products, but only to the reduction product (**2**) in 80% yield. This result is quite surprising, since $SOCl_2$ has been widely used to promote Pummerer rearrangement of sulfoxides, whereas, to the best of our knowledge, it has never been reported as a reducing agent for sulfoxides.

Finally, attempts to react **4a** with *O*-methyl-*O*-*tert*-butyldimethylsilylketene acetal in the presence of catalytic amounts of $ZnCl_2$[16] were completely fruitless, as only the unchanged starting material was recovered, even when forcing experimental conditions were employed.

In conclusion, we have investigated the possibility to apply Pummerer reaction to functionalize and/or modify the 1,4-thiazepinone ring of dehydrocyclolanthionine *en route* to the development of new constrained peptide mimetics. Interestingly, the results of this reaction are strongly dependent on the particular reagent used to activate the oxygen of the sulfoxide toward rearrangement.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 398 spectrophotometer. ^1H NMR spectra were run on Bruker AC 200 (200 MHz). MS spectra were recorded on a Kratos MS 80 spectrometer. Elemental analyses (C, H, N) were performed in house on a Perkin-Elmer 240C Analyzer. Merck silica gel 60 (70-230 mesh) was used for column chromatography. Extracts were dried over Na_2SO_4 and evaporated under reduced pressure with a rotary evaporator. All the reactions were run under an argon atmosphere.

Reaction of 4a with Ac_2O.

A solution of **4a** (0.22 g, 0.66 mmol) in dry Ac_2O (10 mL) is maintained at rt for 2 h, then heated for 3 h at 120 °C. The solution was concentrated and the residue was purified by column chromatography using CH_2Cl_2:Et_2O (15:1) as the mobile phase to afford the following compounds:

Methyl (1*R-cis*)-4-Acetyl-6-(*tert*-butoxycarbonylamino)-4,5,6,7-tetrahydro-2-methyl-5-oxo-1,4-thiazepine-3-carboxylate 1-oxide (**5**) (foam): 0.003 g, 5%; R_f (CH_2Cl_2:Et_2O, 15:1) 0.56; ^{1}H NMR ($CDCl_3$) δ 6.12 (1H, d, J = 5.2 Hz), 4.63 (1H, m), 3.89-3.73 (3H, s, 1H, dd, J = 13.6 and 3.6 Hz), 3.23 (1H, dd, J = 13.6 and 11.0 Hz), 2.64 (3H, s), 2.49 (3H, s), 2.35 (3H, s), 1.42 (9H, s).

Methyl (*R*)-7-Acetoxy-6-(*tert*-butoxycarbonylamino)-4,5,6,7-tetrahydro-2-methyl-5-oxo-1,4-thiazepine-3-carboxylate (**6**) (oil, mixture of two diastereoisomers): 0.084 g, 34%; R_f (CH_2Cl_2:Et_2O, 15:1) 0.33; ^{1}H NMR ($CDCl_3$) δ 6.72 (1H+1H, d, J = 5.4 Hz), 5.49 (1H, s), 5.18 (1H, s), 4.17 (1H+1H, m), 3.82 (3H+3H, s), 3.15 (1H+1H, d, J = 7.4 Hz), 2.06 (3H+3H, s), 1.57 (3H+3H, s), 1.42 (9H, s), 1.38 (9H, s).

Reaction of 4a with TFAA.

TFAA (48 μL, 0.34 mmol) was added at 3 °C to a solution of **4a** (0.057 g, 0.17 mmol) in dry CH_2Cl_2 (4 mL). After 30 min of stirring at 3 °C, toluene (4 mL) was added and the solution was warmed at 50 °C in an oil bath. CH_2Cl_2 was evaporated under a stream of argon and the resulting solution was heated to 110 °C for 30 min. After the solution was cooled, saturated $NaHCO_3$ solution was added and the organic layer diluted with EtOAc. The organic layer was washed with water, dried and evaporated. Chromatography on silica gel (hexanes:EtOAc, 1.5:1) of the residue gave methyl (*R*)-6-(*tert*-butoxycarbonylamino)-6,7-dihydro-2-methenyl-5-oxo-5*H*-1,4-thiazepine-3-carboxylate (**7**) (0.024 g, 45%) as a yellowish oil; R_f (hexanes:EtOAc, 1.5:1) 0.43; $[\alpha]^{20}_D$ -62.5 ° (*c* 0.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.38 (1H, s), 6.04 (1H, s), 5.57 (1H, s), 4.52 (1H, m), 3.89 (3H, s), 3.55 (1H, dd, J = 12.1 and 4.0 Hz) 2.68 (1H, d, J = 12.1 Hz,), 1.49 (9H, s); ^{13}C NMR ($CDCl_3$) δ 171.17, 165.22, 162.82, 151.12, 133.41, 117.72, 82.78, 58.31, 53.11, 36.15, 28.18; IR ($CHCl_3$) ν 3269, 2963, 1719, 1367, 1115, 1034, 752 cm^{-1}; EI-MS *m/z* 314 (M^+). Anal. Calcd for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91. Found: C, 49.44; H, 5.90; N, 8.77.

Reaction of 4a with TMSOTf.

To a cooled (-20 °C) solution of **4a** (0.05 g, 0.15 mmol) in dry CH_2Cl_2 (6 mL) was added Et_3N (70 μL, 0.54 mmol) and, after 5 min, TMSOTf (98 μL, 0.54 mmol). After stirring at -20 °C for 20 min, the reaction mixture was slowly warmed to rt, washed successively with 5% aqueous $NaHCO_3$, 0.5 N HCl, brine, then dried and evaporated. The residue was separated by chromatography on silica gel (CH_2Cl_2:Et_2O, 15:1 as eluent) to give **8** (0.009 g, 18%) and **9** (0.022 g, 47%). Further elution with EtOAc afforded **4a** (0.014 g, 28%).

(2*Z*)-3-[2-[(*tert*-Butoxycarbonylamino)ethenyl]thio]-2-isocyanato-2-butenoic Acid Methyl Ester (**8**): oil; R_f (CH_2Cl_2:Et_2O, 15:1) 0.55; ^{1}H NMR ($CDCl_3$) δ 6.99 (1H, dd, J = 13.4 and 11.4 Hz), 6.59 (1H, d, J = 11.4 Hz), 5.46 (1H, d, J = 13.4 Hz), 3.82 (3H, s), 2.33 (3H, s), 1.46 (9H, s); IR ($CHCl_3$) ν 3318, 2942, 2249, 1725, 1631 cm^{-1}.

2-[2-(*tert*-Butoxycarbonylamino)ethenyl]-3,4-dihydro-6-methyl-3-oxo-2*H*-1,4-thiazepine-5-carboxylic Acid Methyl Ester (**9**): yellow powder, mp 165-167 °C; R_f (CH_2Cl_2:Et_2O, 15:1) 0.27; ^1H NMR ($CDCl_3$) δ 7.77-7.83 (1H+1H, s, d, J = 12.5 Hz), 6.39 (1H, d, J = 12.5 Hz), 3.82 (3H, s), 2.38 (3H, s), 1.52 (9H, s); IR ($CHCl_3$) ν 3396, 2950, 1720, 1664, 1608, 1492, 1436, 1237, 1136 cm^{-1}; FAB-MS *m/z* 315 (M^++1). Anal. Calcd for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91. Found: C, 49.86; H, 5.88; N, 8.69.

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