Revue Roumaine de Chimie, **2009**, *54*(2), 127–132

SERINOLIC APPROACH IN THE SYNTHESIS OF THE 3-OXA-7-THIA-1-AZABICYCLO[3.3.0]OCTANE SKELETON FUNCTIONALISED AT THE C-5 POSITION

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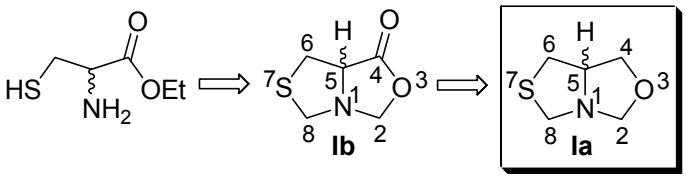
Received June 13, 2008

We report a four steps synthesis of the first term in the title series of compounds, possessing the exploitable hydroxymethyl functionality at the C-5 position, starting from TRIS® [2-amino-2-(hydroxymethyl)propane-1,3-diol, 2-(hydroxymethyl)serinol] *via* its thia analogue, 2-amino-2-(mercaptomethyl)propane-1,3-diol [2-(hydroxymethyl)cysteinol].

INTRODUCTION

The 3-Oxa-7-Thia-1-AzaBicyclo[3.3.0]Octane (OTABO) heterocyclic system **Ia** (**Scheme 1**) is scarcely known as early as the period of 1970' being readily obtainable from *R* or *S* ethyl cysteinate ("cysteine synthetic approach") usually *via* 4-oxo precursors of type **Ib**.[1 - 3]



Scheme 1

Thus, in 1976, just one C-2, -8-disubstituted derivative of **Ia** was prepared by the double cyclocondensation of the *in situ* reduced form of cysteine, namely 2-amino-3-mercaptopropanol ("cysteinol"), upon treatment with *o*-phthaldialdehyde.[1a] Pharmaceutical interest was claimed regarding this synthetic protocol, also directed towards **Ia** itself, one year later.[1 b *]

More recently, Seebach's elegant strategy was also based on *R*-cysteine' diastereoselective cyclisation with trimethylacetaldehyde, then formaldehyde, followed by the asymmetric functionalisation, via metallation, of the resulting **Ib** skeleton, at position C-5, with (hetero)arylaldehydes.[2] It highlighted derivatives of **Ib** to be key as enantiomerically pure intermediates in the total syntheses of Biotin, Micacocidine, Farnesyl Transferase and C-2-functionalised cysteines.[2, 3]

However, one must observe that, in the above "cysteine synthetic approach", no single functionality was present at the C-5 position of an OTABO skeleton **Ia** (**Scheme 1**).

Therefore, our previous expertise in pyrrolizidine' 3,7-dioxa-analogs functionalised at the C-5 position chemistry based on C-2-substituted-2-aminopropane-1,3-diols ("serinols" **IIa-c**, **Scheme 2**),[4] for example *c*-5-hydroxymethyl-3,7-DiOxa-*r*-1-AzaBicyclo[3.3.0]Octane (DOABO-CH_2OH **IIIa**),[5] impelled us to prepare its thia analogue **Va** (OTABO-CH_2OH).

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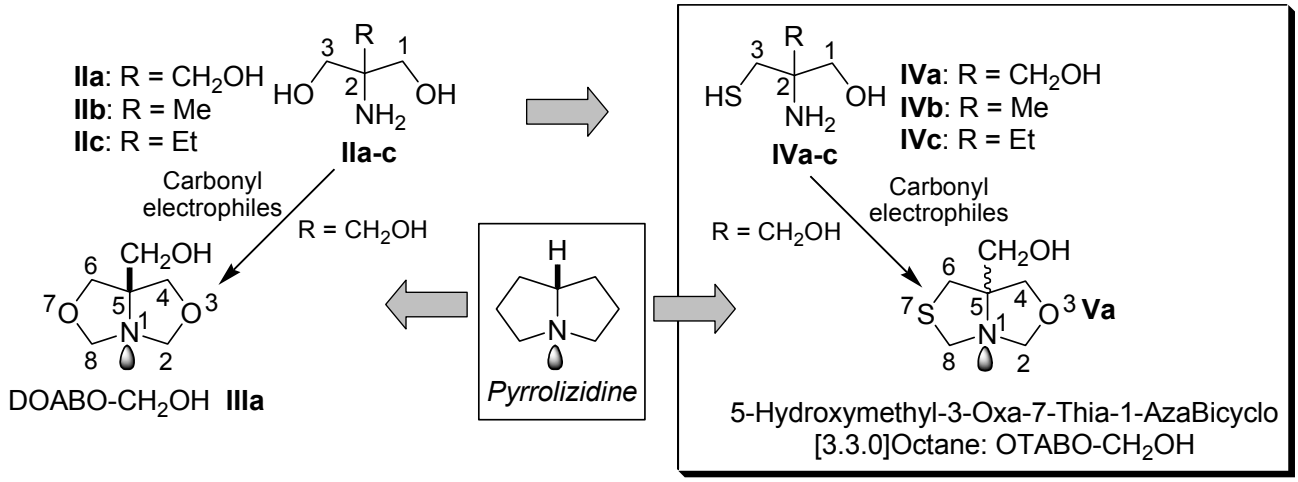


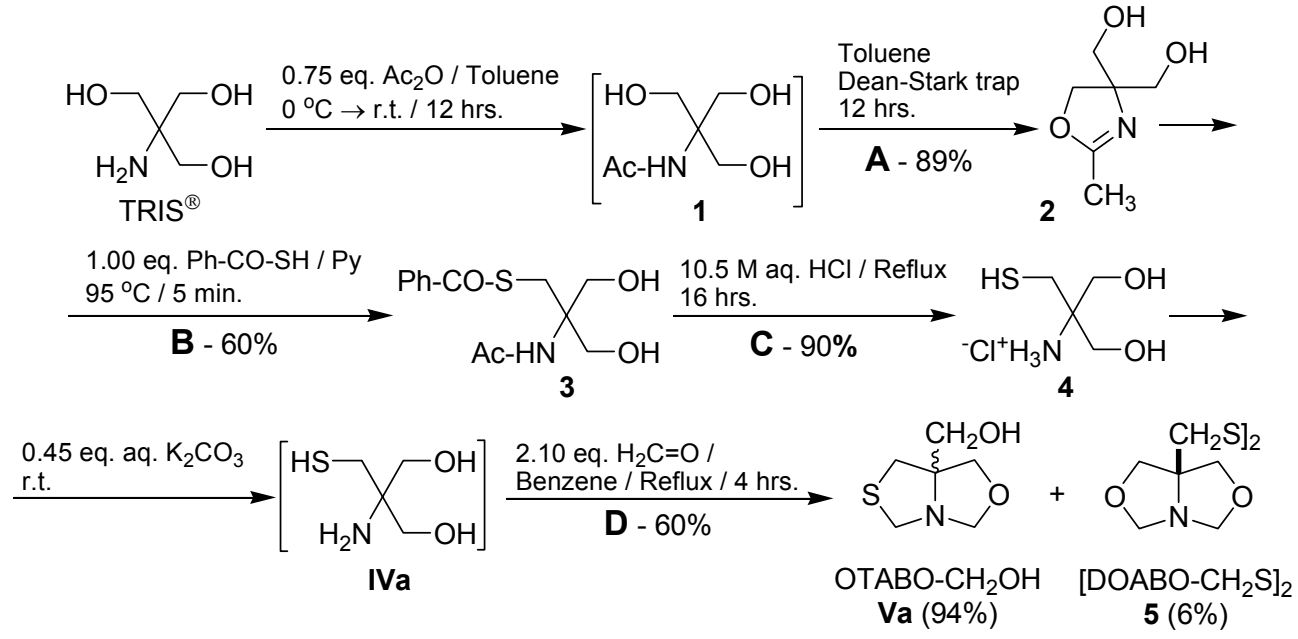
Scheme 2

Thus, the aim of this preliminary report consists of the first synthesis of the previously unknown OTABO-CH_2OH derivative **Va** (**Scheme 2**) starting from the much cheaper TRIS®, 2-(hydroxymethyl)serinol) **IIa**, *via* 2-amino-2-(mercaptomethyl)propane-1,3-diol **IVa** [2-(hydroxymethyl)-cysteinol].

To the best of our knowledge, there are only two old patents[6] from which one entirely focused on the conversion of C-2-substituted-serinols **IIa-c** (**Scheme 2**) into the corresponding C-2-substituted-cysteinols **IVa-c** ("serinolic synthetic approach"), **IVb** and **IVc** being by far much better synthetically documented with respect to **IVa**.[6b] Except elemental analysis, no spectroscopic data of **IVa-c** were reported so far. All **IVa-c** were mentioned to be useful in protection of mammalians against radiation (as free bases or hydrochlorides).

RESULTS AND DISCUSSION

Targeting cysteinol **IVa** (**Scheme 2**) as a key intermediate, our four steps synthetic pathway by which to access the OTABO-CH_2OH derivative **Va** is resumed in **Scheme 3**.



Scheme 3

In all steps **A** – **C**, carried out in usual conditions, only test experiments were based on previous literature description,[6] since they were rapidly mandatory to essential improvements.

Thus, in step **A**, one of the three homotopic methylenes of TRIS® was activated by including it into a 1,3-oxazoline ring **2**. Differently than earlier recommended,[6] rather than operating with excess of boiling anhydrous acetic acid and azeotropic removal of water followed by fractional distillation of crude **2** under reduced pressure, then recrystallisation from THF (52% yield)♣, we opted for a more reactive electrophile, acetic anhydride in toluene, according to the below stoichiometry (Eq. 1, 2).

$$H_2NC(CH_2OH)_3 + Ac_2O \longrightarrow \mathbf{2} + AcOH + H_2O \quad (1)$$

$$H_2NC(CH_2OH)_3 + AcOH \longrightarrow \mathbf{2} + 2\,H_2O \quad (2)$$

$$2\,H_2NC(CH_2OH)_3 + Ac_2O \longrightarrow 2 \times (\mathbf{2}) + 3\,H_2O \quad (1 + 2)$$

Although 0.5 molar equivalents of acetic anhydride theoretically ensured that all acetyl groups were incorporated in the 1,3-oxazoline **2** thus preventing any statistically favoured side *O*-acylation of TRIS®, we anyhow used 0.75 eq. of Ac_2O and removed the resulting water with a Dean-Stark trap. While the yield of crude **2** was 93% (96 % ^{1}H NMR purity and 4% amide **1**), in our hands, **2** was an unstable compound. Indeed, in the crude freshly isolated **2**, the content of TRIS' amide **1** increased to 15% within drying 24 hrs. at room temperature and reached 40% after one week of storage.* ♣Fortunately, in this case, the mixture **1** + **2** could be resubmitted to the dehydrating cyclisation conditions (**1** → **2** + H_2O, **Scheme 3**) affording again, quantitatively, the above crude product **2** (96% ^{1}H NMR purity, 4% **1**).

We therefore used oxazoline **2** as such, directly, in the next step of the synthesis (**B**, **Scheme 3**) with no other purification than a triturating with ether, intended to remove the residual amounts of acetic acid.

In step **B**, we accessed the *S*-, *N*-protected form **3** of the cysteinol **IVa** in 60% yield (previously reported, 57%[6a]). Despite the excellent NMR appearance of crude **3** (71% yield), it required, however, two purifications from EtOH, in order to reach the analytical purity. Both ^{1}H and ^{13}C NMR spectra of crude **3** revealed just a single pair of enantiotopic CH_2O groups located at 60.3 ppm [$\delta_{C(sp3)-S}$ = 30.3 ppm] and just one clear AX geminal coupling pattern between their diastereotopic protons ($\Delta\delta$ = 0.03 – 0.05 ppm, ^2J = 10.3 – 10.6 Hz). Accordingly, we concluded that the ring opening of **2** (**Scheme 3**) consisted of thionation only.

In step **C**, we *N*-, *S*-deprotected the amidoester **3** in boiling 10.5 M aq. HCl with 90% yield (lit. 68%[6b]) and isolated the cysteinol **IVa** as the hydrochloride **4** by applying one of our previous patented protocols[7] (see **EXPERIMENTAL PART**). Compound **4** was stable on storage indefinitely.

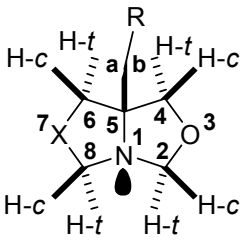
In the final step **D**, cysteinol **IVa** was generated *in situ* from **4**, then trapped with paraformaldehyde in standard conditions, earlier described for the double aminalisation of TRIS®,[4,5] giving the desired OTABO-CH_2OH derivative **Va** in 60% yield after purification by flash column chromatography (**Scheme 3**). The NMR spectra of the crude reaction mixture indicated the presence of the OTABO-CH_2OH derivative **Va** as largely major (94%) against the side product, the disulphide **5** (6%) of type [DOABO-CH_2S]$_2$, issued most likely from the preliminary partial oxidation of **IVa** followed by the double cyclisation involving its remaining nucleophilic sites, the hydroxymethyl groups.

The chirality of the OTABO skeleton in **Va** against the C_S symmetry of the DOABO one in **5** **Scheme 4**, **Figure 1**) and the expected *cis*-fused junction between the two saturated pentaheterocyclic rings essentially discriminated the NMR appearance of **Va** *vs.* **5**.

♣ In both Patents,[6] the use of 1.5 eq. AcOH is recommended for the synthesis of **2**.

* It appeared to us that **2** was sensitive to moisture, especially if residual AcOH was present in the crude material.

Indeed, this stereochemistry is already well-documented with respect to all 3,7-heteroanalogous of pyrrolizidine known so far (to be published).[4,8] Mass Spectrum (CI, *i*-BuH) of **Va** displayed, as basic peak, the protonated form 162 $[M+1]^+$ meanwhile for **5** we found $[M+1]^+ = 132$. In the ^{13}C NMR spectra, the δ values of the carbons adjacent to sulphur were 39.4 and 57.4 ppm (C-6, -8 respectively) in **Va** and 45.9 ppm in **5**.



Va (X = S, R = OH)
(homofacial) nuclei 2 *vs.* 8, 4 *vs.* 6: d i a s t e r e o t o p i c respectively
5 (X = O, R = -S-S-CH_2-DOABO)
(homofacial) nuclei 2 *vs.* 8, 4 *vs.* 6: e n a n t i o t o p i c respectively
[descriptors -*c* (*cis*), -*t* (*trans*) with respect to the lone pair at N-1 and / or the CH_2R group linked at the position C-5]

Scheme 4

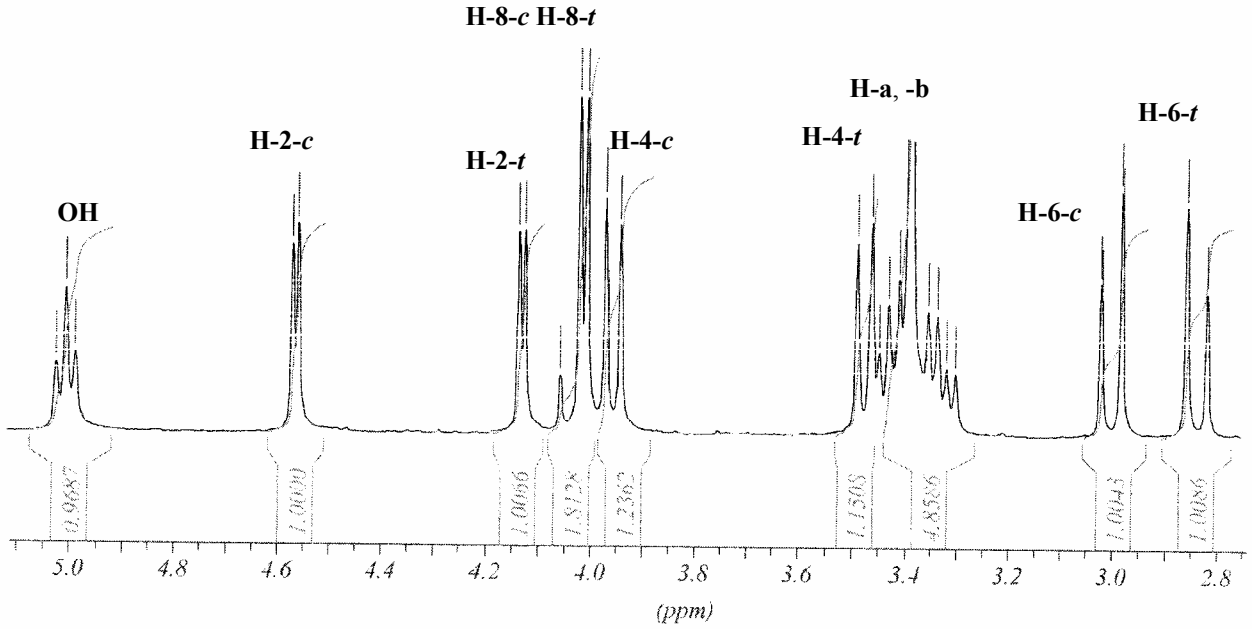


Fig. 1 – ^1H NMR Spectrum of compound **Va** ([D_6]DMSO, 298 K, 300 MHz timescale).

EXPERIMENTAL PART

General. Melting points are uncorrected; they were carried out on ELECTROTHERMAL® instrument. NMR spectra were recorded on a Bruker® AM 300 instrument operating at 300 and 75 MHz for ^1H and ^{13}C nuclei respectively. All NMR spectra were measured in anhydrous commercially available deuteriated solvents. No $SiMe_4$ was added; chemical shifts were measured against the solvent peak. All chemical shifts (δ values) are given throughout in ppm; all coupling patterns ($^nJ_{H,H}$ values) are given throughout in Hz. TLC was performed by using aluminium sheets with silica gel 60 F_{254} (Merck®); flash column chromatography was conducted on Silica gel Si 60 (40–63 μm, Merck®). IR spectra were performed on a Perkin-Elmer® Paragom FT-IR spectrometer. Only relevant absorptions are listed [throughout in cm^{-1}: weak (w), medium (m) or (s) strong]. Microanalyses were performed on a Carlo Erba® CHNOS 1160 apparatus. Mass spectra (MS) were recorded on a Brucker® Esquire Instrument.

Preparation of 4,4-bis(hydroxymethyl)-2-methyl-1,3-oxazoline **(2).**

To TRIS® (8.48 g, 70 mmol) suspended in cooled (0 °C) dry toluene (125 mL), acetic anhydride (5.00 mL, 5.36 g, 52.5 mmol) was rapidly injected under vigorous stirring. The resulted suspension was stirred and let to reach room temperature overnight (12 hrs.) then heated at reflux for additional 12 hrs. with continuous removal of water in a Dean-Stark trap (TLC monitoring, eluent toluene : ethanol 3/1 v/v, visualisation in a I_2 bath). The reaction was stopped when no more water was separated and no more evolution was observed on TLC. At this step, starting from refluxing toluene, the reaction mixture, as a fine colourless emulsion, was let very gently to reach room temperature under vigorous stirring in order to ensure successfully the obtention of a fine white

suspension. After filtering, well washing with dry ether (× 25 mL) and drying at room temperature within one hour, 9.45 g of the crude title compound **2** were obtained (yield 89% with respect to TRIS®; ^{1}H NMR purity 96%; 4% compound **1**).

2-Acetamido-2-(hydroxymethyl)propane-1,3-diol (1): ^{1}H NMR (300 MHz, [D_6]DMSO):
δ = 1.73 (s, 3
H, CH_3), 3.50 (s, 6 H, C*H*$_2$OH), 4.62 (bs, 3 H, CH_2O*H*), 7.22 (bs, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO) : δ = 24.0 (1 C, CH_3), 60.0 (1 C, Cq., C-2), 60.8 (3 C, CH_2OH), 175.2 (1 C, >C=O) ppm.

4,4-Bis(hydroxymethyl)-2-methyl-1,3-oxazoline (2): yield 89%, (9.45 g, 62.3 mmol **2** starting from 8.48 g, TRIS®) white crystalline powder, m.p. 82–84 °C (Et_2O) [lit.[6a] 95 – 97 °C ($CHCl_3$/Et_2O/AcOEt); lit.[6b] 88 – 89 °C (THF)]. R_f (75% toluene/EtOH) = 0.45. IR (KBr): ν = 3360 (s), 3271 (s), 3108 (s), 2982 (s), 2941 (s), 2872 (s), 1670 (s), 1629 (m), 1572 (m), 1459 (m), 1384 (s), 1270 (s), 1229 (w), 1187 (w), 1143 (w), 1029 (s), 994 (s), 972 (w), 942 (w), 882 (w), 843 (w), 691 (w), 649 (w), 625 (w), 588 (w), 525 (w) cm^{-1}. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 1.84 (s, 3 H, CH_3), 3.29 (d, 2 H, $^2J_{H,H}$ = 11.0 Hz, C*H*$_2$OH), 3.36 (d, 2 H, $^2J_{H,H}$ = 11.0 Hz, C*H*$_2$OH), 4.02 (s, 2 H, H-5), 4.69 (bs, 2 H, CH_2O*H*) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 13.6 (1 C, CH_3), 63.9 (2 C, CH_2OH), 70.3 (1 C, C-4), 76.4 (1 C, C-5), 163.4 (1 C, C-2) ppm. MS (positive CI, isobutane, 200 eV): *m/z* (%) = 202 (17) [M+*i*-BuH-2]$^+$, 188 (7) [M+42]$^+$, 164 (15) [M+18]$^+$, 146 (100) [M+1]$^+$, 114 (6), 73 (< 5); $C_6H_{11}NO_3$ (145.07).

Preparation of 2-acetamido-2-(benzoylthiomethyl)propane-1,3-diol **(3)**

In a vigorously stirred solution prepared from 4,4-bis(hydroxymethyl)-2-methyl-1,3-oxazoline **(2)** (3.68 g, 25.35 mmol) dissolved in dry pyridine (10.00 mL, 10.50 g, 133 mmol), thiobenzoic acid (3.30 mL, 3.50 g 100%, 25.35 mmol) was rapidly injected at room temperature. The resulted yellow solution was heated at 95 °C and kept at this temperature for 5 min. A clear orange-reddish solution was obtained which was cooled at 0 °C for 30 min. then poured on aq. HCl (45.00 mL, 47.70 g, 4 M aq. HCl, 179 mmol). Crude **3** crystallised as a yellow mass (pH = 0.5 - 1) which was cooled for additional 12 hrs. at 0 °C. After filtering, washing with cooled water (3 × 15 mL) and drying at r.t., 6.90 g crude **3** were obtained as a yellow amorphous powder. This was twice recrystallised from boiling ethanol (15 mL) to yield 4.30 g pure **3** as a white crystalline powder (60% yield with respect to **2**).

2-Acetamido-2-(benzoylthiomethyl)propane-1,3-diol (3): yield 60% (4.30 g, 15.21 mmol **3** starting from 3.68 g, 25.35 mmol **2**) white crystalline powder, m.p. 143–145 °C (EtOH) [lit.[6a] 147 – 148 °C (-); lit.[6b] 146 – 147 °C (EtOH)]. $C_{13}H_{17}NO_4S$ (283.09): calcd. C 55.11, H 6.05, N 4.94; found C 54.88, H 5.88, N 5.29. R_f (75% toluene/EtOH) = 0.75. IR (KBr): ν = 3380 (s), 3344 (m), 3153 (m), 2942 (m), 2895 (m), 2837 (m), 1662 (s), 1648 (s), 1557 (s), 1450 (m), 1372 (m), 1323 (w), 1205 (s), 1176 (m), 1079 (m), 1064 (s), 969 (w), 913 (s), 774 (m), 690 (m), 645 (m), 596 (w), 554 (m), 533 (w) cm^{-1}. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 1.86 (s, 3 H, CH_3), 3.62 (dd, 2 H, $^2J_{H,H}$ = 10.3 Hz, $^3J_{H,H}$ = 5.7 Hz, C*H*$_2$OH), 3.61 (dd, 2 H, $^2J_{H,H}$ = 10.3 Hz, $^3J_{H,H}$ = 4.6 Hz, C*H*$_2$OH), 4.99 (dd as t, $^3J_{H,H}$ = 5.7 Hz, CH_2O*H*), 7.39 (s, 1 H, NH), 7.59 (t, 2 H, $^3J_{H,H}$ = 7.5 Hz, H-3, Ph), 7.72 (t, 1 H, $^3J_{H,H}$ = 7.4 Hz, H-4, Ph), 7.95 (d, 2 H, $^3J_{H,H}$ = 7.5 Hz, H-2, Ph) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 23.4 (1 C, CH_3), 30.3 (1 C, CH_2S), 60.3 (2 C, CH_2OH), 61.2 (1 C, C-2), 126.8 (2 C, C-2, -6, Ph), 129.0 (2 C, C-3, -5, Ph), 133.7 (1 C, C-4, Ph), 136.5 (1 C, C-1., Ph), 170.3 [1 C, >C(=O)-NH-), 191.1 [1 C, >C(=O)-S-] ppm. MS (positive CI, isobutane, 200 eV): *m/z* (%) = 340 (< 5) [M+*i*-BuH-1]$^+$, 284 [M+1]$^+$ (48), 266 (8), 252(< 5), 236 (5), 218 (7), 180 (100), 162 (10), 148 (8), 130 (< 5), 123 (10), 116 (< 5), 73 (< 5).

Preparation of 2-amino-2-(mercaptomethyl)propane-1,3-diol hydrochloride **(4)**

2-Acetamido-2-(benzoylthiomethyl)propane-1,3-diol **(3)** (2.41 g, 8.50 mmol) was suspended in aq. HCl (7.40 mL, 8.57 g, 10.5 M aq. HCl, 77.8 mmol) and the reaction mixture was heated at reflux with stirring for 16 hrs. After cooling at room temperature, benzoic acid crystallised abundantly and was filtered off, washed with aq. HCl (3 × 5 mL, 10.5 M aq. HCl) to yield 0.93g pure by product (90% with respect to the theoretical amount). The combined aqueous filtrate was added to benzene (100 mL) and the resulted mixture was heated with stirring at reflux with azeotropic removal of water (Dean-Stark trap). During anhydrification, compound **4** precipitated as an oily mass. When no more water was separated, the mixture was kept at reflux for additional 2 hrs. in order to eliminate thes excess of hydrochloric acid. After cooling at room temperature, benzene was decanted and crude oily **4** was crystallised at 0 °C from 10 mL 1:1 v/v isopropanol : ether to give 1.32 g pure **4** (90% yield with respect to **3**).

2-Amino-2-(mercaptomethyl)propane-1,3-diol hydrochloride (4): yield 90% (1.32 g, 7.65 mmol **4** starting from 2.41 g, 8.50 mmol **3**) white crystalline powder, m.p. 102 - 104 °C (*i*-PrOH/Et_2O 1:1 v/v) [lit.[6b] 104 – 105 °C (*i*-PrOH)]. $C_4H_{12}ClNO_2S$ (173.03): calcd. C 27.66, H 6.96, N 8.07; found C 28.02, H 6.88, N 7.99. IR (KBr): ν = 3344 (s), 3265 (s), 3008 (s), 2554 (m), 1602 (m), 1542 (m), 1514 (s), 1458 (m), 1399 (m), 1277 (m), 1247 (m), 1112 (m), 1062 (s), 918 (m), 671 (m), 546 9w) cm^{-1}. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 2.74 (d, 2 H, $^3J_{H,H}$ = 9.1 Hz, C*H*$_2$SH), 3.03 (d, 1 H, $^3J_{H,H}$ = 9.1 Hz, CH_2S*H*), 3.52 (d, 2 H, $^2J_{H,H}$ = 11.6 Hz, C*H*$_2$OH), 3.58 (d, 2 H, $^2J_{H,H}$ = 11.6 Hz, C*H*$_2$OH), 5.40 (bs, 2 H, CH_2O*H*), 8.03 (s, 3 H, NH_3^+) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 24.5 (1 C, CH_2S), 59.7 (1 C, C-2), 61.0 (2 C, CH_2OH) ppm. MS (positive CI, isobutane, 200 eV): *m/z* (%) = 176 [M+3]$^+$, 152 (7), 138 (100), 103 (9), 90 (6).

Preparation of *c*-5-hydroxymethyl-3-oxa-7-thia-*r*-1-azabicyclo[3.3.0]octane (**Va**)

2-Amino-2-(mercaptomethyl)propane-1,3-diol hydrochloride **(4)** (1.00 g, 5.78 mmol) was dissolved in water (3.00 mL) and the resulted solution was added to anh. potasssium carbonate (0.380 g, 2.75 mmol) and paraformaldehyde (0.38 g, 12.72 mmol) suspended in benzene (40 mL). The reaction mixture was heated with stirring at reflux with continuous removal of water (Dean-Stark trap). When no more water separated (about. 4 hrs.), the reactoion

mixture was cooled at room temperature then the benzenic solution was decanted and evaporated under reduced presure to give crude **Va** as an oily mass. This was purified by flash column chromatography (eluent ligroin : acetone 2:1 v/v) to yield pure **Va** (0.567 g, 60% yield withy respect to **4**) as the first fraction; complete elution of the column provided additional 0.100g as a equimolar mixture mixture **Va** : **5** (^{1}H NMR monitoring).

***c*-5-Hydroxymethyl-3-oxa-7-thia-*r*-1-azabicyclo[3.3.0]octane (Va)**: yield 60% (0.567g, 3.52 mmol **Va** starting from 1.00 g, 5.78 mmol **4**) yellowish oil (flash column chromatography, eluent ligroin : acetone 2:1 v/v). R_f (66% ligroin/acetone) = 0.75. $C_6H_{11}NO_2S$ (161.05): calcd. C 44.70, H 6.88, N 8.69; found C 45.03, H 6.68, N 8.82. IR (KBr): ν = 3417 (s), 2931 (s), 2868 (s), 1715 (w), 1644 (w), 1455 (m), 1434 (m), 1398 (m), 1239 (m), 1208 (m), 1156 (m), 1122 (s), 1069 (s), 959 (s), 919 (m), 779 (w), 738 (m), 708 (m), 654 (m), 615 (w), 572 (w) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.84 (d, 1 H, $^2J_{H,H}$ = 11.8 Hz, H-6-*t*), 3.00 (d, 1 H, $^3J_{H,H}$ = 11.8 Hz, H-6-*c*), 3.42 (dd, 1 H, $^2J_{H,H}$ = 11.7 Hz, $^3J_{H,H}$ = 5.5 Hz, C*H*$_2$OH), 3.33 (dd, 1 H, $^2J_{H,H}$ = 11.7 Hz, $^3J_{H,H}$ = 5.5 Hz, C*H*$_2$OH), 3.48 (d, 1 H, $^2J_{H,H}$ = 8.5 Hz, H-4-*t*), 3.96 (d, 1 H, $^2J_{H,H}$ = 8.5 Hz, H-4-*c*), 3.99 (d, 1 H, $^2J_{H,H}$ = 10.8 Hz, H-8-*t*), 4.04 (1 H, d, $^2J_{H,H}$ = 10.8 Hz, H-8-*c*), 4.13 (1 H, d, $^2J_{H,H}$ = 3.3 Hz, H-2-*t*), 4.57 (d, 1 H, $^2J_{H,H}$ = 3.3 Hz, H-2-*c*), 5.01 (1 H, dd as t, $^3J_{H,H}$ = 5.5 Hz, CH$_2$O*H*) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 39.4 (1 C, C-6), 57.4 (1 C, C-8), 65.3 (1 C, CH$_2$OH), 73.9 (1 C, C-4), 77.8 (1 C, C-5), 86.9 (1 C, C-2) ppm. MS (positive CI, isobutane, 200 eV): *m/z* (%) = 218 [M+*i*-BuH-1]$^+$ (13), 204 [M+43]$^+$ (7), 178 [M+17]$^+$ (<5), 162 [M+1]$^+$ (100), 144 [M-17]$^+$ (<5), 130 (10).

Bis(3,7-dioxa-*r*-1-azabicyclo[3.3.0]octan-*c*-5-yl)-disulphide (5). R_f (66% ligroin/acetone) = 0.65. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.21 (s, 4 H, C*H*$_2$S), 3.73 (d, 4 H, $^2J_{H,H}$ = 9.0 Hz, H-4, -4', -6, -6'-*t*), 3.85 (d, 4 H, $^2J_{H,H}$ = 9.0 Hz, H-4, -4', -6, -6'-*c*), 4.35 (d, 4 H, $^2J_{H,H}$ = 5.5 Hz, H-2, -2', -8, -8'-*t*), 4.48 (d, 4 H, $^2J_{H,H}$ = 5.5 Hz, H-2, -2', -8, -8' -*c*) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 45.9 (2 C, CH$_2$S), 72.0 (4 C, C-4, -4', -6, -6'), 74.6 (2 C, C-5, -5'), 87.7 (4 C, C-2, -2' -8, -8') ppm. MS (positive CI, isobutane, 200 eV): *m/z* (%) = 377 [M+*i*-BuH-1]$^+$ (15), 321 [M+1]$^+$ (80).

CONCLUSIONS

Starting from TRIS®, a four steps methodology provided the first 3-oxa-7-thia-1 azabicyclo[3.3.0]octane derivative possessing the hydroxymethyl functionality at the position C-5 in 29% overall yield. For the key intermediate, 2-amino-2-(mercaptomethyl)propane-1,3-diol hydrochloride, an essentially improved protocol, occurring in 48 % overall yield, was described (lit. 20%[6b]).

Acknowledgements: Financial support from the Grant provided by the National Council of Scientific Research (C.N.C.S.I.S., 1482) is gratefully acknowledged.

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