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SYNTHESIS AND CONFORMATIONAL ANALYSIS OF 6-SUBSTITUTED-3-AZABICYCLO[3,3,1]NONANES

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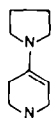
Abstract—6-hydroxy substituted 3-tosyl-3-aza-bicyclo[3,3,1]nonan-9-ones **2a** and **2b** are obtained directly via acrolein addition to N-Ts-piperidine pyrrolidine enamine. From ^{1}H NMR spectral data of a series of derivatives a preferred twin-chair conformation for the adducts is indicated. This conclusion is supported both by studies on the elimination of the 6-OR group and on the reduction of the C_9–oxo function. Anomalous formation of sultone **10** is also noted.

The problem of determining the preferred conformation of the cyclohexane rings in bicyclo[3,3,1]nonanes is attracting considerable attention. Both twin-chair as well as chair-boat forms are known today. In continuation of our studies on the structure and reactivity of N - tosyl - bicyclo[3,3,1]nonanes[1] which may serve as precursors for the preparation of a variety of caged tertiary amines[2] a series of 6- and 7-substituted derivatives has been synthesized. Apart from the planned synthesis of nor-, proto- and homo-1-azaadamantanes the compounds have significance in the evaluation of the pronounced influence of the tertiary sulfonamide moiety on the chemical and conformational behaviour of the 3 - aza - bicyclo[3,3,1]nonane system.

α,α' annelation of piperidine-enamine **1** with acrolein[3] gave a yield of 71% of two stereoisomeric hydroxy-compounds **2a** + **2b** while a small amount of the open product **3** could also be isolated. The formation of *exo*-**2a** and *endo*-**2b** in a ratio of 65:35 (PMR *vide infra*) is remarkable both in contrast to results in the carbocyclic series[4] where in general pyrrolidine adducts are found and in view of the known stereochemical preference for the formation of the *endo*-product in this type of addition. In the carbocyclic series a suggested reaction pathway proceeds via addition of acrolein to the enamine to form an intermediate dihydropyran structure which eventually rearranges to an acyclic immoniumsalt and subsequently ring-closes.[5] Presumably as a consequence of the earlier described[1] zwitter-ionic interaction of the sulfonamide group with the $\overset{\oplus}{N}{=}C$ moiety the intermediate structure **A** is stabilized thus preventing the intermolecular amine exchange and giving rise to intramolecular proton abstraction and addition of the aldehyde C=O to the *endo*cyclic enamine. Recently the occurrence of a zwitter-ionic intermediate was elegantly demonstrated in the carbocyclic series via trapping of the intermediate.[6]



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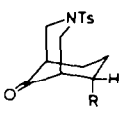
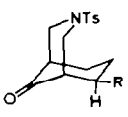
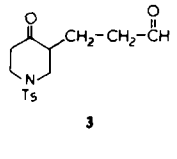


2a R = OH
5a R = OAc
6a R = OMs
7a R = OTs
8a R = Cl
9a R = I



2b R = OH
5b R = OAc
6b R = OMs



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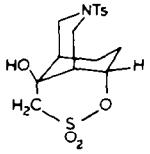

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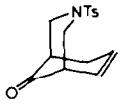

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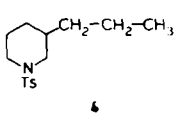
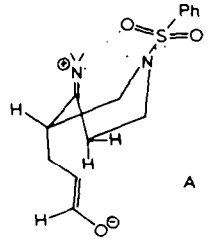


4

Depending on the relative position of the latter C=O with respect to the plane of the heterocyclic ring, the stereo-isomers **2a** and **2b** are formed in a thermodynamically controlled process. Upon crystallization from C_6H_6 the isomer **2a** can be obtained pure.

Additional information on the stabilities of the addition products is found in the observation of a base-catalyzed isomerization[7] via retro-aldolization of pure **2a** to the same **2a** + **2b** mixture. An analogous isomerization process also occurs under acid conditions. Further evidence for the occurrence of an aldolization equilibrium was obtained via the hydrazine-KOH reduction of (**2a** + **2b**) giving a good yield of the 3-propylpiperidine **4**.



A

The ^{1}H NMR of **2a** shows an absorption at δ 4.55, ($W_{1/2}$ = 10 c/s), indicative for an equatorial proton (H_6). The C_6–OH therefore occupies the axial *exo*-position. In the spectrum of **2b** the H_6-absorption coincides with the N–CH_2 signals. One of the latter protons, however, is shifted to lower field (δ 4.86 broadened doublet J = 9 c/s)

which is in accordance with a C_6–OH *endo* position.† To obtain a better structural insight in the stereochemistry of these compounds a series of derivatives was prepared.

The ^{1}H NMR spectrum of the corresponding acetate **5b**, obtained in 20% yield via acetylation $BF_3O(Et)_2$/HOAc of the **2a** + **2b** mixture and separation of the isomers, clearly exhibited the expected pattern for an axial C_6–H δ 5.09 ($W_{1/2}$ = 23 c/s). The isomer **5a** showed δ H_6, 5.46 ppm ($W_{1/2}$ = 7 c/s).

A similar behaviour was noted for the mesylate **6b** (δ H_6 = 5.05, $W_{1/2}$ = 23 c/s) which was prepared via mesylation of the **2a** + **2b** mixture (CH_3SO_2Cl–pyridine–$CHCl_3$, 0°C) and TLC separation of the isomers. The other isomer **6a** δ H_6 = 5.44 ($W_{1/2}$ = 7 c/s) was conveniently obtained from the pure **2a** in 96% yield, via the same procedure.

From these results it is concluded that for the carbocyclic part of the 3-aza-[3,3,1]-bicyclo system a chairlike conformation is preferred (*vide infra*). Since the chair form has been generally observed for N-tosylpiperidines the 6-substituted 3-aza-[3,3,1]-bicyclo compounds are likely to possess the twin-chair form. To establish this conclusion also on a chemical basis the elimination of the 6-oxy function was investigated.

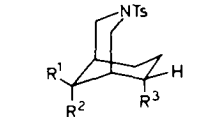
Elimination reactions of **2a** + **2b** *and* **6**

It has been reported that the C-7 position in bicyclo[3,3,1]nonanes possessing the twin-chair form is anomalously inactive towards chemical transformation[8] as a result of back-side sterical hindrance by axial *endo* hydrogen at C-3. It might, therefore be expected that the large N-tosyl substituent is affecting the accessibility of the C-7 *endo* H to a great extent provided that the piperidine ring is in a chair form. The necessity for diaxial positions of C_6–OR and C_7–H in achieving an energetically favorable formation of the olefin has been discussed earlier for analogous carbocyclics.[9] Thus from the behaviour of the hydroxyderivatives **2a** and **2b** and the corresponding mesylates **6a** and **6b** under conditions of elimination some data can be acquired on the conformation of the heterocyclic ring.

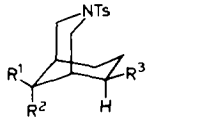
Starting with the hydroxy mixture **2a** + **2b**, it has to be noted that in contrast to other observations[10] no trace of elimination product **11** is formed in the $BF_3O(Et)_2$/HOAc reaction. Upon reaction of **2a** + **2b** with $POCl_3$ pyridine the C_6-*exo* chloro compound **8a** is formed as the only identifiable product. In a similar reaction of **2a** + **2b** with methyl triphenoxyphosphonium iodide in HMPA the C_6-*exo* iodide **9a** is formed. Neither in the first reaction nor in the second reaction a single trace of **11** can be detected. Therefore, we turned our attention to the base catalyzed elimination reactions of the mesylates **6a** and **6b**. As typical sterically demanding bases collidine[11] and KOBt were selected. After refluxing of **6a** in collidine for 2 hr the starting material is recovered unchanged. Reaction of **6a** with KOBt/DMSO leads to the formation of the hydroxy-sultone **10**.[12] The analytical data fully support the structure of **10**; additional evidence for the presence of a C_9-*syn* OH function was obtained from the observed Δ value of 0.5 ppm (*vide infra*). Use of smaller bases such as NaOMe/MeOH did not lead to a noticeable formation of olefin **11** the mesylate **6a** being recovered unchanged.

To prevent the unwanted side reaction of the mesylate **6a** and to directly compare the results in the carbocyclic series[13] similar experiments were carried out with the tosylate **7a** prepared via tosylation of **2a**. Under a variety of conditions—including the KOBt/DMSO reaction leading from **6a** to **10**—no reaction occurred. Under more severe conditions decomposition of **7a** was observed although no trace of **11** could be detected.

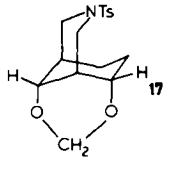
Under modified reaction circumstances—NaOAc/HOAc reflux—it turned out to be possible to induce eliminations, albeit accompanied with substitution. Thus upon reaction of **6a** a mixture of **5b** (38%) and **11** (44%) was obtained, while a similar experiment with **6b** yielded only **11** (50%). Upon lowering of the temperature in the latter reaction the actate **5a** was formed (43%). Since the acetolysis is proceeding via a different reaction type no conclusion can be drawn on the eventual steric influence of the N-tosyl group. However, the base catalyzed eliminations in all probability have to proceed via the E_2 type, thus the first series of experiments provides indirect proof for the marked shielding effect of the N-substituent on the accessibility of the C_7-methylene protons. This conclusion leads also to the acceptance of a twin-chair form for the 6 - *exo* - substituted - 3 - aza - 9 - oxo[3,3,1]bicyclononane.



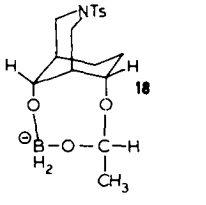
	R^1	R^2	R^3
12a	H	OH	OH
13a	H	OH	OAc
14a	OH	H	OAc
15a	H	OAc	OAc
16a	OAc	H	OAc



	R^1	R^2	R^3
12b	H	OH	OH
13b	H	OH	OAc
14b	OH	H	OAc
15b	H	OAc	OAc
16b	OAc	H	OAc



17



18

Reduction of the C_9*-oxo function*

To evaluate the steric influence of the N–Ts group in a different reaction series and to ascertain the various conformational assignments a series of hydride reductions was carried out,[14] both of the hydroxy-ketones **2a** and **2a** + **2b** and of the acetates **5a** and **5b**.

As stated before[1] a highly useful criterion for the elucidation of the stereochemistry in this type of adduct is the difference in chemical shift—Δ—between the sulfonamide methylene protons. Upon *syn*-substitution‡ at C_9 of a heteroatom the normally observed Δ of 1.0–1.5 ppm decreases to 0.5–0.7 ppm. $NaBH_4$-reduction of **2a** in EtOH aq gave **12a** in almost quantitative yield. Its *syn* H_9-structure was inferred on the basis of spectral considerations: no change in Δ; H_6 equatorial; no deshielding of H_9 by the axial C_6–OH. In addition **12a** was found to undergo acetalisation to **17** upon acid treatment

†Spectra of **2b** and related 6-*endo*-OH derivatives with various amounts of the shift reagent Eu(FOD)$_3$ were recorded. In all cases H_6 turns out to be axial ($W_{1/2}$ > 20 Hz). No evidence was found for the occurrence of an >N···HO interaction resulting in stabilization of the boat conformation.

‡*syn* and anti with respect to the piperidine ring.

with formaldehyde, thus confirming its diaxial OH configuration.

$NaBH_4$-reduction of **2a** + **2b** in MeOH aq gave a mixture of stereo-isomeric diols, separated by TLC. As main product **12a** was formed while also a considerable amount of a second isomer proved to be present. The latter structure could be characterized as **12b** because of the presence of an axial C_6–H absorption ($W_{1/2}$ = 20 c/s) and the absence of a significant Δ-effect. Due to experimental difficulties the remaining fraction of 10% could not be further characterized and therefore the hydride reduction of the acetates **5a** and **5b** was separately investigated. The result, however, obtained in the reduction of **2a** and **2b** is in good accord with the preference for *syn* hydride attack.

Reduction of **5a** *and* **5b**

To determine the stereochemistry of the four possible diacetates **15a**, **16a**, **15b** and **16b** and thus indirectly of the four corresponding diols the following series of experiments was carried out. After $NaBH_4$ reduction of **5a** and **5b** the mixture of hydroxy-acetates was acetylated with $BF_3O(Et)_2$/HOAc and the diacetates separated and characterized. Thus upon reduction of **5a** and acetylation it was found that in addition to the H_9-*syn*-product 5% of **14a** was formed, which was characterized as the diacetate **16a**. As an undesired complication a rapid cleavage of the acetate function in the H_9-*syn*-adduct **13a** also occurred upon hydride reduction presumably via the promotion of the ester cleavage[15] as indicated in **18**.

When the $NaBH_4$-reduction of **5a** was carried out in aqueous methanol the diol **12a** was directly obtained. Diacetylation of **12a** proved not possible with $BF_3O(Et)_2$/HOAc: the product being **13a**. Upon treatment with Ac_2O **15a** was obtained. On the other hand, $NaBH_4$-reduction of **5b** gave a non separable mixture of **13b** and **14b** in a ratio of 2:1 (^{1}H NMR). Upon BF_3-acetylation a mixture of the diacetates **15b** and **16b** was obtained which could also not be separated; **15b**, however, could be prepared in 83% yield via $BF_3O(Et)_2$/HOAc acetylation of **12b**. From the ^{1}H NMR data of **15b** and **15b** + **16b** an unambiguous structure determination for the diacetate **16b** proved possible. The axial C_6–H positions in **15b** and **16b** are distinctly recognizable. Furthermore the Δ values of **14b** and **16b** also correspond with the expected figures for C_9 *syn*-OR substitution. A summary of the spectral parameters is presented in Table 1.

From these results it is concluded that in the C_6 *exo*-OR series hydride reduction of the C_9-oxo function almost exclusively occurs from the *syn*-direction. Although this effect may be explained in part as a result of an unfavorable reagent approach from the *anti*-face due to steric interaction with the axial C_6–OR group the experimental outcome is certainly compatible with a chair form for the heterocyclic ring. The clear preference for *syn* hydride transfer to the C_9–CO in the C_6-*endo*-OR series can be argued on a similar basis. Since conformational inversion of the piperidine ring in 3-azabicyclo[3,3,1]nonanes has never been observed the conclusion therefore seems justified as to regard the 6-substituted derivatives as twin-chain forms.

EXPERIMENTAL

All m.ps are uncorrected. Analyses were carried out by Messr. H. Pieters of the Micro-analytical Department of this laboratory. IR spectra were recorded on an Unicam SP-200 and NMR spectra were measured on a Varian Associates Ha-100 instrument.

N - Ts - 4 - *pyrrolodinyl* - 1,2,3,6 - *tetrahydropyridine* (**1**)[1] was obtained as described.

N - Ts - 3 - *aza* - 6 - *hydroxy* - 9 - *oxo* - *bicyclo*[3,3,1]*nonane* (**2a** + **2b**). Acrolein (0.69 g; 11 mmol), freshly distilled and in dry dioxane (10 ml) was added dropwise with stirring at 0° in N_2 to **1** (3.06 g; 10 mmol) and a trace of hydroquinone in dry dioxane

Table 1. NMR spectra of 3-aza-bicyclo[3,3,1]nonanes chemical shift in ppm

Compound	Solvent[a]	$H_{2,4}$ ax	$H_{2,4}$ eq	H_6($W_{1/2}$ in c/s)	H_9-syn	H_9-anti	Δ[b]
2a, **2b**[d]	C	2.70	4.10	4.55 (10)			1.40
		2.70	4.10, 4.48	± 4.10[c]			1.40–1.78
5a	C	2.80	4.14	5.46 (7)			1.34
5b	C	2.80	4.08, 4.38	5.09 (23)			1.28–1.58
6a	C	2.80	4.14	5.44 (7)			1.34
6b	C	2.90	4.14, 4.49	5.05 (23)			1.22–1.59
7a	C	2.75	4.08	5.20 (7)			1.33
8a	C	2.82	4.15	4.82 (9)			1.33
9a	C	2.80	4.13	5.04 (8)			1.33
10	C	3.10	3.59	5.06 (7)			0.49
11	C	2.80	3.97				1.17
12a	P	2.53	3.85	4.22 (8)	3.85		1.32
12b	P	2.60	4.00, 4.74	4.90 (> 15)	4.00		1.40–2.14
13a	C	2.60	3.85	5.28 (9)			1.25
13b, **14b**	C	2.50	3.80, 4.05	5.31 (19)	± 3.80[c]		1.30–1.55
		2.90	3.55, 3.70	4.90 (20)		± 3.70[c]	0.65–0.80
14a	C	2.90	3.55	5.21 (8)		4.04	0.65
15a	C	2.70	3.87	5.12 (9)	4.55		1.17
15b	C	2.60	3.85, 4.12	5.22 (23)	4.77		1.25–1.52
16a	C	2.83	3.65	5.23 (8)		5.09	0.82
16a	C	2.80	3.60, 3.82	4.95 (< 15)		4.68	0.80–1.02
17	C	2.55	3.80	4.34 (8)	3.90		1.25

[a] C = $CDCl_3$; P = C_5D_5N.

[b] Δ = Δ(δ $H_{2,4}$eq−δ $H_{2,4}$ax).

[c] in a number of spectra the signals of the indicated protons are obscured by other absorptions. In such a case the probable region is given.

[d] A mixture of the two compounds.

(50 ml). After 2 hr stirring at rt water (10 ml) was added and the soln was stirred for 1 hr. After evaporation of the solvent, water was added and the aqueous soln was extracted with $CHCl_3$. The combined extracts were washed with 2N HCl, sat $NaHCO_3$ aq and dried over Na_2SO_4. Evaporation of solvent yielded 3.0 g of crude product. The oil was passed through a column of silicagel with EtOAc/cyclohexane = 2/3 as an eluent, yielding 2.2 g (71%) of **2a** + **2b**. Crystallization (C_6H_6) yielded 0.8 g (26%) of **2a**, m.p. 162–165° (sublimation at 150°, 12 mm). IR($CHCl_3$): C=O 1725 cm^{-1}, Ts 1170 and 1360 cm^{-1}, NMR($CDCl_3$) δ: 4.55 ($W_{1/2}$ = 10 Hz) H_6 eq, 4.48(d) N–C<u>H</u> eq, 4.10(d) N–C<u>H</u>$_2$ eq, 2.70(d) N–C<u>H</u>$_2$ ax, NMR(C_6D_5N) δ: 4.86 (d, J = 9 Hz) N–C<u>H</u> eq (35%), 4.65 ($W_{1/2}$ = 10 Hz) H_6 eq (65%). (Found: C, 58.37; H, 6.23; N, 4.41; S, 10.26. Calc. $C_{15}H_{19}O_4N_1S_1$ (M = 309.37): C, 58.24; H, 6.16; N, 4.53; S, 10.35%).

The second fraction yielded 0.1 g (3%) of **3**, m.p. (ether 102–104°. IR($CHCl_3$): C=O 1705 cm^{-1}, Ts 1350 and 1150 cm^{-1}. NMR($CDCl_3$) δ: 9.75 <u>H</u>–C=O, 3.97–4.70 N–C<u>H</u>$_2$ eq, 2.60 N–C<u>H</u>$_2$ ax. (Found: C, 58.15; H, 6.13; N, 4.59; S, 10.33. Calc. $C_{15}H_{19}O_4N_1S_1$ (M = 309.37): C, 58.24; H, 6.16; N, 4.53; S, 10.35%).

Equilibration of **2a** *and* **2b**. In alkaline solution: 100 mg (0.3 mmol) of **2a** was stirred in a 3% KOH soln of MeOH (9 ml) and water (1 ml) for 2 hr. 2N HCl was added till PH = 7, the MeOH was evaporated and the soln extracted with $CHCl_3$. The $CHCl_3$ layers were dried over Na_2SO_4 and evaporated, yield 100%. NMR(C_6D_5N): **2a**:**2b** = 65:35.

In acid solution: 53 mg (0.17 mmol) of **2a** was refluxed in 2N HCl (5 ml) and EtOH (5 ml) for 2 hr to yield 48 mg (91%) of **2a** + **2b**. The NMR spectrum indicates a proportion of **2a**:**2b** = 65:35.

N - Ts - 3 - *propyl* - *piperidine* **4**. **2a** + **2b** (309 mg; 1 mmol) and 80% hydrazine hydrate (186 mg; 3 mmol) was added to a soln of KOH (168 mg; 3 mmol) in glycol (3 ml). The mixture was heated until the initial exothermic reaction was complete (*ca* 110°) and was refluxed for 1 hr. Water and hydrazine was distilled off until the temp. reached 200–210°. Refluxing was continued for 3–5 hr. The soln was poured in water and extracted with $CHCl_3$. The $CHCl_3$ layers were washed with 2N HCl sat $NaHCO_3$ aq and dried over Na_2SO_4. The solvent was evaporated and crystallization (MeOH) yielded 250 mg (89%) of **4**, m.p. 63–64°. IR($CHCl_3$): Ts 1590, 1160 cm^{-1}, NMR($CDCl_3$) δ: 3.55(d) N–C<u>H</u>$_2$ eq, 2.30 N–C<u>H</u>$_2$ax, 0.80 (tr) C<u>H</u>$_3$. (Found: C, 64.17; H, 8.32; N, 4.99; S, 11.22%. Calc. $C_{15}H_{23}O_2N_1S_1$ (M = 281.40): C, 64.03; H, 8.24; N, 4.98; S, 11.37%).

N - Ts - 3 - *aza* - 6 - *acetoxy* - 9 - *oxo* - *bicyclo*[3,3,1]*nonanes* **5a** *and* **5b**. $BF_3O(Et)_2$ (6 ml) was added dropwise to a soln of 1.2 g (4 mmol) of a mixture of **2** (65% **2a**, 35% **2b**) in HOAc (20 ml, dried over P_2O_5) and the soln was stirred for 24 hr. After addition of 10 ml water the soln was extracted with $CHCl_3$. The $CHCl_3$ layers were washed with sat $NaHCO_3$ aq (3x) and evaporated. Thick layer chromatography with eluents EtOAc/cyclohexane = 1/1 yielded 590 mg (42%) of **5a**; m.p. (EtOAc/pentane) 133–135° and 280 mg (20%) of **5b**; m.p. (EtOAc/pentane) 143–146°. **5a**: IR($CHCl_3$): C=O 1730–1720 cm^{-1}, Ts 1350 and 1160 cm^{-1}. NMR($CDCl_3$) δ: 5.46 ($W_{1/2}$ = 7 Hz) H_6 eq, 4.14(d) N–C<u>H</u>$_2$ eq, 2.80(d) N–C<u>H</u>$_2$ ax. (Found: C, 58.31; H, 5.89; N, 2.85; S, 9.30. Calc. $C_{17}H_{21}O_5N_1S_1$ (M = 351.41): C, 58.11; H, 6.02; N, 3.99; S, 9.10%). **5b**: IR($CHCl_3$): C=O 1730–1720 cm^{-1}, Ts 1350 and 1160 cm^{-1}. NMR($CDCl_3$) δ: 5.09 ($W_{1/2}$ = 23 Hz) H_6 ax, 4.38(d) N–C<u>H</u> eq, 4.08(d) N–C<u>H</u> eq, 2.80 N–C<u>H</u>$_2$ ax. (Found: C, 57.98; H, 5.94; N, 4.09: S, 9.10. Calc. $C_{17}H_{21}O_5N_1S_1$ (M = 351.41): C, 58.11; H, 6.02; N, 3.99; S, 9.10%).

N - Ts - 3 - *aza* - 6 - *mesyl* - 9 - *oxo* - *bicyclo*[3,3,1]*nonane* **6a**. To **2a** (500 mg; 1.62 mmol) in dry $CHCl_3$ (15 ml) and pyridine (5 ml) was added dropwise at 0° $MeSO_2Cl$ (0.25 ml; 3.26 mmol) in $CHCl_3$ (3 ml). After stirring 32 hr at 0° icewater was added and the soln extracted with $CHCl_3$. The $CHCl_3$ layers were washed with 2N HCl, sat $NaHCO_3$ aq and dried over $MgSO_4$. Evaporation of the solvent and crystallization (MeOH) yielded 600 mg (96%) of **6a**, m.p. 177–179°. IR(KBr): C=O 1720 cm^{-1}; Ts 1600 and 1160 cm^{-1}. NMR ($CDCl_3$) δ: 5.44 ($W_{1/2}$ = 7 Hz) H_6 eq, 4.14(d) N–C<u>H</u>$_2$ eq, 3.01(s) C<u>H</u>$_3$SO$_2$. (Found: C, 49.56; H, 5.37; N, 3.63; S, 16.51. Calc. $C_{16}H_{21}O_6N_1S_2$ (M = 387.46): C, 49.61; H, 5.41; N, 3.62; S, 16.52%).

N - Ts - 3 - *aza* - 6 - *mesyl* - 9 - *oxo* - *bicyclo*[3,3,1]*nonanes* **6a** + **6b**. To **2a** + **2b** (1 g; 3.24 mmol) in CH_2Cl_2 (15 ml) and triethylamine (0.7 ml) was added at −10°–0° CH_3SO_2Cl (0.28 ml; 3.6 mmol). The soln was stirred for 3 hr at 0°. Icewater was added and the soln was extracted with $CHCl_3$. The $CHCl_3$ layers were washed with 2N HCl sat $NaHCO_3$ aq, dried over $MgSO_4$. The solvent was evaporated and the residue was passed through a column with EtOAc/cyclohexane (1/1), yielding two products: 281 mg (22%) of **6a**, m.p. 177–178° (MeOH). 230 mg (18%) of **6b**, m.p. 145–147° (MeOH). IR(KBr): C=O 1720 cm^{-1}, Ts 1590 and 1160 cm^{-1}. NMR($CDCl_3$) δ: 5.05 ($W_{1/2}$ = 23 Hz) H_6 ax, 4.49(d) and 4.12(d) N–C<u>H</u>$_2$ eq, 3.12(s) C<u>H</u>$_3$SO$_2$. (Found: C, 49.53; H, 5.48; N, 3.58; S, 16.32. Calc. $C_{16}H_{21}O_6N_1S_2$ (M = 387.46): C, 49.61; H, 5.41; N, 3.62; S, 16.52%).

N - Ts - 3 - *aza* - 6 - *tosyl* - 9 - *oxo* - *bicyclo*[3,3,1]*nonane* **7a**. To **2a** (384 mg; 1.24 mmol) in pyridine (5 ml) was added TsCl (236 mg; 1.24 mmol) and the soln was stirred for 20 hr. Ice-water was added and the solution was extracted with $CHCl_3$. The $CHCl_3$ layers were washed with 2N HCl, sat $NaHCO_3$ aq and dried over Na_2SO_4. Evaporation of solvent and crystallization (MeOH) yielded 140 mg (24%); m.p. 168–170° Chromatography of the mother liquor afforded 180 mg (47%) of **2a**. IR($CHCl_3$): C=O 1750 cm^{-1}, Ts 1600 and 1160 cm^{-1}. NMR($CDCl_3$) δ: 5.20 ($W_{1/2}$ = 7 Hz) H_6 eq, 4.08(d) N–C<u>H</u>$_2$ eq, 2.75(d) N–C<u>H</u>$_2$ ax, 2.46(s) C<u>H</u>$_3$–ϕ. (Found: C, 56.94; H, 5.44; N, 2.98; S, 13.79. Calc. $C_{22}H_{25}O_6N_1S_2$ (M = 463.55): C, 57.01: H, 5.44; N, 3.02; S, 13.81%).

N - Ts - 3 - *aza* - 6 - *chloro* - 9 - *oxo* - *bicyclo*[3,3,1]*nonane* **8a**. To **2a** + **2b** (500 mg; 1.62 mmol) in pyridine (10 ml) was added at 0° $POCl_3$ (5 ml). After 24 hr at rt water was added and extracted with $CHCl_3$. The organic layer was washed with 2N HCl sat $NaHCO_3$ aq, dried over Na_2SO_4 and evaporated. Thick layer chromatography with EtOAc/cyclohexane (1/1) yielded 145 mg (26%) of **8a**; m.p. 153–155° (MeOH). IR($CHCl_3$): C=O 1730 cm^{-1}, Ts 1600 and 1160 cm^{-1}; NMR($CDCl_3$) δ: 4.82 ($W_{1/2}$ = 10 Hz) H_6 eq, 4.15(d) N–C<u>H</u>$_2$ eq, 2.82(d) N–C<u>H</u>$_2$ ax. (Found: C, 54.92; H, 5.58; N, 4.26; S, 9.73; Cl, 10.72. Calc. $C_{15}H_{18}O_3N_1S_1Cl_1$ (M = 327.82): C, 54.95; H, 5.53; N, 4.27; S, 9.78; Cl, 10.82%).

N - Ts - 3 - *aza* - 6 - *iodo* - 9 - *oxo* - *bicyclo*[3,3,1]*nonane* **9a**. **2a** + **2b** (500 mg; 1.62 mmol) and methyltriphenoxyphosphoniumiodide (1.4 g; 3.3 mmol) in HMPA (20 ml) were stirred for 2 hr at 70°. The soln was poured in 10% NaOH (30 ml) and extracted with $CHCl_3$. The organic layers were washed with 2N HCl, sat $NaHCO_3$ soln, dried over Na_2SO_4 and evaporated. Crystallization (MeOH) yielded 145 mg (22%); m.p. 187–190°. IR($CHCl_3$): C=O 1730 cm^{-1}, Ts 1595 and 1160 cm^{-1}. NMR($CDCl_3$) δ: 5.04 ($W_{1/2}$ = 8 Hz) H_6 eq, 4.13(d) N–C<u>H</u>$_2$ eq, 2.80(d) N–C<u>H</u>$_2$ ax. (Found: C, 43.12; H, 4.44; N, 3.51; S, 7.79; I, 30.24. Calc. $C_{15}H_{18}O_3N_1S_1I_1$ (M = 419.29): C, 42.97; H, 4.33; N, 3.34; S, 7.65; I, 30.27%.

N - Ts - 3 - *aza* - 9 - *hydroxy* - *bicyclo*[3,3,1]*nonane* - 6,9 - *sultone* **10**. **6a** (200 mg; 0.51 mmol) in DMSO (2 ml) was added dropwise to KOBt (115 mg; 1 mmol) in DMSO (3 ml). The soln was stirred for 30 min at rt and poured in icewater (20 ml) and extracted with $CHCl_3$. The organic layers were washed with 2N HCl, sat $NaHCO_3$ aq, dried over $NaSO_4$ and evaporated. Crystallization (MeOH/diisopropylether) yielded 87 mg (43%) of **10**, m.p. 177–179°. IR(KBr): OH 3500 cm^{-1}, Ts 1600 and 1160 cm^{-1}. NMR($CDCl_3$) δ: 5.06 ($W_{1/2}$ = 7 Hz) H_6 eq, 3.59 (2 × d) N–C<u>H</u>$_2$ eq, 3.50 H_5, 3.39 (s) C<u>H</u>$_2$–SO$_2$, 3.10(d) N–C<u>H</u>$_2$ ax. (Found: C, 49.69; H, 5.39; N, 3.50; S, 16.67. Calc. $C_{16}H_{21}O_6N_1S_1$ (M = 387.46): C, 49.61; H, 5.41; N, 3.62; S, 16.52%).

N - Ts - 3 - *aza* - 9 - *oxo* - *bicyclo*[3,3,1]*nonan* - 6 - *ene* **11**. **6a** (400 mg; 1.03 mmol) and NaOAc (5 g) was refluxed for 5½ hr in HOAc (50 ml). The solvent was evaporated, water was added and the soln was extracted with $CHCl_3$. The organic layers were washed with sat $NaHCO_3$ aq, dried over Na_2SO_4 and the solvent was evaporated. Thick layer chromatography with EtOAc/cyclohexane (1/1) yielded 101 mg (44%) of **11** and 104 mg (38%) of **5b**.

11: m.p. 143–145° (isopropanol). IR($CHCl_3$): C=O 1725 cm^{-1}, C=C 1650 cm^{-1}, Ts 1590 and 1160 cm^{-1}. NMR($CDCl_3$)δ: 5.98 (d + m) C = C<u>H</u>, 5.64 (tr) C=C<u>H</u>, 3.97 N–C<u>H</u>$_2$ eq, 2.80 N–C<u>H</u>$_2$ ax. (Found: C, 61.80; H, 6.01; N, 4.68; S, 11.08. Calc. $C_{15}H_{17}O_3N_1S_1$ (M = 291.35): C, 61.85; H, 5.88; N, 4.81; S, 10.98%). 265 mg (0.68 mmol) of **6b** and 3 g of NaOAc was refluxed for 5.5 h in HOAc (30 ml). The solvent was evaporated, water was added and the solution was extracted with $CHCl_3$. The $CHCl_3$ layers were

washed with sat $NaHCO_3$aq, dried over Na_2SO_4 and the solvent was evaporated. Thick layer chromatography with EtOAc/cyclohexane yielded 100 mg (50%) of **11** and 28 mg (11%) of **6b**. The reaction was repeated with 103 mg (0.26 mmol) of **6b** at 110°. The yield was 40 mg (43%) of **5a** and 10 mg (10%) of **6b**.

N - Ts - 3 - *aza* - 6,9 - *dihydroxy* - *bicyclo*[3,3,1]*nonane* **12a**. A soln of **2a** (500 mg; 1.62 mmol) and $NaBH_4$ (350 mg; 9.25 mmol) in EtOH (30 ml) and H_2O (2 ml) was stirred for 18 hr. The soln was cooled and AcOH was added slowly till PH = 5, the solvent was evaporated and H_2O was added and extracted with $CHCl_3$. The $CHCl_3$ layers were washed with sat $NaHCO_3$aq. Evaporation of solvent and crystallization yielded 450 mg (90%) of **12a**, m.p. (MeOH/diisopropylether) 147–150° IR(KBr): OH 3400 cm^{-1}, Ts 1340 and 1160 cm^{-1}. NMR(C_6D_5N) δ: 4.22 ($W_{1/2}$ = 8 Hz) H_6 eq, 3.85(d) N–CH_2 eq, 3.85 H_9, 2.53 (tr) N–CH_2 ax. (Found: C, 57.97; H, 6.69; N, 4.33; S, 10.14. Calc. $C_{15}H_{21}O_4N_1S_1$ (M = 311.39): C, 57.86; H, 6.80; N, 4.50; S, 10.28%).

N - Ts - 3 - *aza* - 6,9 - *dihydroxy-bicyclo*[3,3,1]*nonanes* **12a** + **12b**. A soln of (1 g; 3.24 mmol) of a mixture of **2** (65% **2a** and 35% **2b**) and 0.7 g (18.5 mmol) of $NaBH_4$ in MeOH (50 ml) and H_2O (3 ml) was stirred for 18 hr. Work up yielded 1 g (99%) of a mixture of **12a** and **12b**. Thick layer chromatography with EtOAc/cyclohexane = 1/1 yielded: 360 mg (36%) of **12a**, m.p. (MeOH/diisopropylether) 147–150° and 250 mg (25%) of **12b**, m.p. (MeOH) 208–210°.

12b: IR(KBr): OH 3400 cm^{-1}, Ts 1340 and 1160 cm^{-1}. NMR(C_6D_5N) δ: 4.90 ($W_{1/2}$ > 15 Hz) H_6 ax, 4.74(d) and 4.00(d) N–CH_2 eq, 4.00 H_9, 2.60(d) N–CH_2 ax. (Found: C, 57.93; H, 6.87; N, 4.38; S, 10.33%. Calc. $C_{15}H_{21}O_4N_1S_1$ (M = 311.39): C, 57.86; H, 6.80; N, 4.50; S, 10.28%)

N - Ts - 3 - *aza* - 6,9 - *diacetoxy* - *bicyclo*[3,3,1]*nonane* **15a**. **12a** (350 mg; 1.12 mmol) was heated at reflux in AC_2O for 2 hr. The solvent was evaporated and the residue dissolved in $CHCl_3$ and the organic layer was washed with sat $NaHCO_3$ aq and evaporated yielding 270 mg (62%) of **15a**, m.p. (MeOH/pentane): 144–146°. IR($CHCl_3$): C=O 1715 cm^{-1}, Ts 1350 and 1160 cm^{-1}. NMR($CDCl_3$) δ: 5.15 ($W_{1/2}$ = 10 Hz) H_6 eq, 4.58 ($W_{1/2}$ = 8 Hz) H_9, 3.80(d) N–CH_2 eq, 2.60 N–CH_2 ax, 2.08(s) and 2.04(s) CH_3CO_2. (Found: C, 57.76; H, 6.25; N, 3.53; S, 8.13. Calc. $C_{19}H_{25}O_6N_1S_1$ (M = 395.46): C, 57.71; H, 6.37; N, 3.54; S, 8.08%).

N - Ts - 3 - *aza* - 6,9 - *diacetoxy* - *bicyclo*[3,3,1]*nonane* **15b**. $BF_3O(Et)_2$ (2 ml) was added dropwise to **12b** (100 mg; 0.30 mmol) in HOAc (4 ml) and the soln was stirred for 60 hr. H_2O (5 ml) was added and the soln was extracted with $CHCl_3$. The $CHCl_3$ layers were washed with sat $NaHCO_3$ aq (3x) and evaporated. Yield: 105 mg (83%), m.p. (EtOAc/pentane): 136–138°. IR($CHCl_3$): C=O 1715 cm^{-1}, Ts 1350 and 1160 cm^{-1}. NMR($CDCl_3$) δ: 5.22 ($W_{1/2}$ = 23 Hz) H_6 ax, 4.77 ($W_{1/2}$ = 9 Hz) H_9, 4.12(d) and 3.85(d) N–CH_2eq, 2.60 N–CH_2ax, 2.05(s) CH_3CO_2. (Found: C, 57.56; H, 6.22; N, 3.45; S, 8.26. Calc. $C_{19}H_{25}O_6N_1S_1$ (M = 395.46): C, 57.71; H, 6.37; N, 3.54; S, 8.08%).

N - Ts - 3 - *aza* - 6,9 - *dioxymethylene* - *bicyclo*[3,3,1]*nonane* **17**. A soln of **12a** (150 mg; 0.48 mmol) paraformaldehyde (150 mg; 1.67 mmol) and *p*-TsOH (10 mg) in C_6H_6 (20 ml) was refluxed for 16 hr in a Dean stark apparatus over molsieves 3A. The soln was washed with sat $NaHCO_3$ aq and evaporated yielding 90 mg (56%) of **17**; m.p. (EtOAc/pentane) 162–163°. IR($CHCl_3$): Ts 1350 and 1160 cm^{-1}; NMR($CDCl_3$) δ: 5.20 (d, J = 5.5 Hz) O–CH–O, 4.87 (d, J = 5.5 Hz) O–CH–O, 4.34 (s, $W_{1/2}$ = 8 Hz) H_6 eq, 3.90 H_9, 3.80 N–CH_2 eq, 2.55 N–CH_2 ax. (Found: C, 59.26; H, 6.44; N, 4.34; S, 9.84. Calc. $C_{16}H_{21}O_4N_1S_1$ (M = 323.40): C, 59.43; H, 6.55; N, 4.33; S, 9.90%).

$NaBH_4$-*reduction of* **5a**. A soln of **5a** (700 mg; 2 mmol) and $NaBH_4$ (70 mg; 1.85 mmol) was stirred in dry MeOH (50 ml) for 1 hr. With cooling HOAc was added until PH = 5 and the solvent was evaporated. The residue was dissolved in $CHCl_3$ and the soln washed with sat $NaHCO_3$ aq. Evaporation of solvent yielded 700 mg (99%) of crude product. TLC with eluent EtOAc/cyclohexane = 1/1 yielded 35 mg (5%) of **14a** and a mixture of **13a** (40%) and **12a** (55%) (620 mg, 100%).

14a: NMR($CDCl_3$) δ: 5.21 (tr, $W_{1/2}$ = 8 Hz) H_6 eq, 4.04 (tr, $W_{1/2}$ = 8 Hz) H_9, 3.55(d) N–CH_2 eq, 2.90(d) N–CH_2 ax, 2.00(s) CH_3CO_2. Mixture of **12a** and **13a** NMR($CDCl_3$) δ: 5.28 (s, $W_{1/2}$ = 9 Hz) H_6 (40%) **13a**; 4.20 (s, $W_{1/2}$ = 9 Hz) H_6 (55%) **12a**.

N - Ts - 3 - *aza* - 6,9 - *diacetoxy* - *bicyclo*[3,3,1]*nonane* **15a**. The mixture of **12a** and **13a** (60 mg) was heated at reflux in Ac_2O for 2 hr and yielded after isolation and crystallization (EtOAc/pentane) 52 mg (66%) of **15a**; NMR($CDCl_3$) δ: 5.12 ($W_{1/2}$ = 9 Hz) H_6 eq, 4.55 ($W_{1/2}$ = 7 Hz) H_9, 3.87 (d) N–CH_2eq, 2.60–2.80 N–CH_2 ax, 2.04 CH_3CO_2, 2.00 CH_3CO_2.

N - Ts - 3 - *aza* - 6,9 - *diacetoxy* - *bicyclo*[3,3,1]*nonane* **16a**. **14a** (35 mg; 0.1 mmol) was stirred in HOAc(2 ml) and $BF_3O(Et)_2$ (1 ml) for 3 days. Work-up yielded 35 mg (88%) of **16a**. NMR($CDCl_3$) δ: 5.23 ($W_{1/2}$ = 9 Hz) H_6 eq, 5.09 ($W_{1/2}$ = 8 Hz) H_9, 3.65 (d) N–CH_2 eq, 2.83(d) N–CH_2 ax, 2.05 CH_3CO_2–C_6, 1.87 CH_3CO_2–C_9.

$NaBH_4$-*reduction of* **5b**

N - Ts - 3 - *aza* - 6 - *acetoxy* - 9 - *hydroxy* - *bicyclo*[3,3,1]*nonanes* **13b** *and* **14b**. A soln of **5b** (220 mg; 0.63 mmol) and $NaBH_4$ (30 mg; 0.91 mmol) was stirred in dry MeOH (10 ml) for 1 hr. HOAc was added with cooling till PH = 5 and the solvent was evaporated. The residue was dissolved in $CHCl_3$ and the soln washed with sat $NaHCO_3$ aq. Evaporation of solvent yielded 222 mg (100%) crude product consisting of **13b** (65%) and **14b** (35%). NMR($CDCl_3$) **13b** δ: 5.31 ($W_{1/2}$ = 19 Hz) H_6 ax, 4.05(d) and 3.80 N–CH_2 eq, 2.50 N–CH_2 ax, 2.05(s) CH_3CO_2, **14b** δ: 4.90 ($W_{1/2}$ = 20 Hz) H_6 ax, 3.70 and 3.55(d) N–CH_2 eq, 2.90(d) N–CH_2 ax, 2.05(s) CH_3CO_2.

N - Ts - 3 - *aza* - 6,9 - *diacetoxy* - *bicyclo*[3,3,1]*nonanes* **15b** *and* **16b**. $BF_3O(Et)_2$ (2 ml) was added dropwise to a soln of a mixture of **13b** and **14b** (222 mg; 0.63 mmol) in HOAc (8 ml) and the soln was stirred for 20 hr. H_2O (5 ml) was added and the soln was extracted with $CHCl_3$. The $CHCl_3$ layers were washed with sat $NaHCO_3$aq and evaporated yielding 250 mg (100%) crude product consisting of **15b** (65%) and **16b** (35%). NMR($CDCl_3$) **15b** δ: 5.22 ($W_{1/2}$ = 23 Hz) H_6 ax, 4.77 ($W_{1/2}$ = 9 Hz) H_9, 4.12(d) and 3.85(d) N–CH_2eq, 2.60 N–CH_2ax, 2.05(s) CH_3CO_2. **16b** δ: 4.95 ($W_{1/2}$ > 15 Hz) H_6 ax, 4.68 H_9, 3.82(d) and 3.60(d) N–CH_2 eq, 2.80(d) N–CH_2 ax, 2.05(s) CH_3CO_2, 1.87(s) CH_3CO_2–C_9.

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