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THE DEMJANOV AND TIFFENEAU-DEMJANOV ONE-CARBON RING ENLARGEMENTS OF 2-AMINOMETHYL-7-OXABICYCLO[2.2.1]HEPTANE DERIVATIVES. THE STEREO- AND REGIOSELECTIVE ADDITIONS OF 8-OXABICYCLO[3.2.1]OCT-6-EN-2-ONE TO SOFT ELECTROPHILES.

Daniela Fattori, Sylvie Henry and Pierre Vogel*
Section de chimie de l'Université de Lausanne, 2, rue de la Barre, CH 1005 Lausanne, Switzerland

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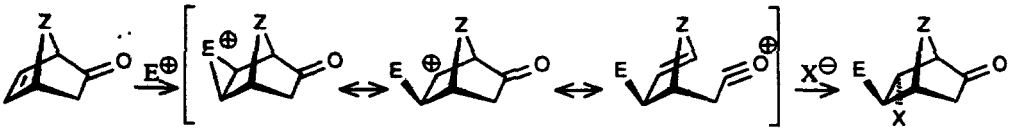
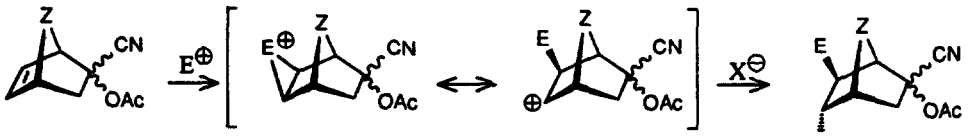
Summary: *Nitrosation of 7-oxabicyclo[2.2.1]hept-5-en-2-*exo*-ylmethyl amine* (**20**) *gave 7-oxabicyclo[2.2.1]hept-5-en-2-*exo*-methanol* (**22**) *whereas 7-oxabicyclo[2.2.1]hept-5-en-2-*endo*-ylmethylamine* (**21**) *afforded a 1.1 mixture of 8-oxabicyclo[3.2.1]oct-6-en-2-ols* (**23**) *and 8-oxabicyclo[3.2.1]oct-3-en-2-ols* (**24**). *Nitrosations of 2-*exo- (**28**) *and 2-*endo*-aminomethyl-7-oxabicyclo[2.2.1]hept-5-en-2-ol* (**29**) *gave mixtures of 8-oxabicyclo[3.2.1]oct-6-en-2-one* (**25**) *and 8-oxabicyclo[3.2.1]oct-6-en-3-one* (**37**). *The preference for the C(3) methylene group migration giving* **25** *was the best (12:1) in the case of the 2-*endo*-aminomethyl alcohol* **29**. *Compared with the nitrosations of bicyclo[2.2.1]heptane analogues, the 7-oxa bridge in* **28** *and* **29** *enhances the preference for the C(3) methylene group migration vs. the C(1) methine group migration. The Tiffeneau-Demjanov one-carbon ring enlargement reactions of 2-*exo*-aminomethyl-7-oxabicyclo[2.2.1]heptan-2-*endo*-ol* (**30**). 2-exo*-aminomethyl-5-chloro* (**32**) *and 2-*exo*-aminomethyl-6-chloro-7-oxabicyclo[2.2.1]hept-5-en-2-*endo*-ol* (**33**) *are also reported. Under kinetically controlled conditions, 8-oxabicyclo[3.2.1]oct-6-en-2-one* (**25**) *adds to electrophiles EX=PhSeCl, PhSeBr, 2,4-*$(NO)_2C_6H_3SCl$ *with high stereo- and regioselectivity giving the corresponding 8-oxabicyclo[3.2.1]-octan-2-ones where E substitutes the* exo *position of C(6) and X the* endo *position of C(7).*

Under kinetically controlled conditions soft electrophiles EX add to the C=C double bond of the homoconjugated bicyclic enones **1** with high stereo- and regioselectivity giving the corresponding adducts **3**, whereas their synthetic precursors **4** furnish the corresponding adducts **6** with opposite regioselectivity.[1] In the case of the additions of **1**, the results were interpreted in terms of the formation of the corresponding bridged-ion intermediates **2**, in which the carbonyl group plays the role of an electron-releasing substituent due to favourable through-bond interactions of the type n(CO) ↔ σC(1,2) ↔ $p^+C(6)$, as illustrated by the limiting structures **2** ↔ **2'** ↔ **2''**, making centre C(6) more electrophilic than centre C(5).[2] In the case of reactions **4** + EX → **6** the corresponding bridged-ion intermediates **5** are engendered which prefer to be attacked at C(5) by the counter-ion $X^{\ominus}$ either for steric reasons or because of an electrostatic factor that favours limiting structures **5'**.[2] The discovery that the regioselectivity of the electrophilic additions of



1 2 2' 2'' 3

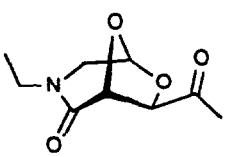
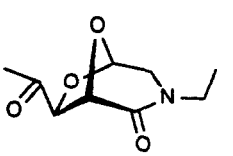
Z=CH_2, CH_2-CH_2



4 5 5' 6

bicyclic olefins such as **1** and **4** depends on the nature of the substituents at C(2) led us to invent the "naked sugars" (optically pure 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives **7** - **12**)[3] that have been shown to be quite powerful chirons in the asymmetric synthesis of rare carbohydrates and analogues, of natural products and compounds of biological interest.[3,4]

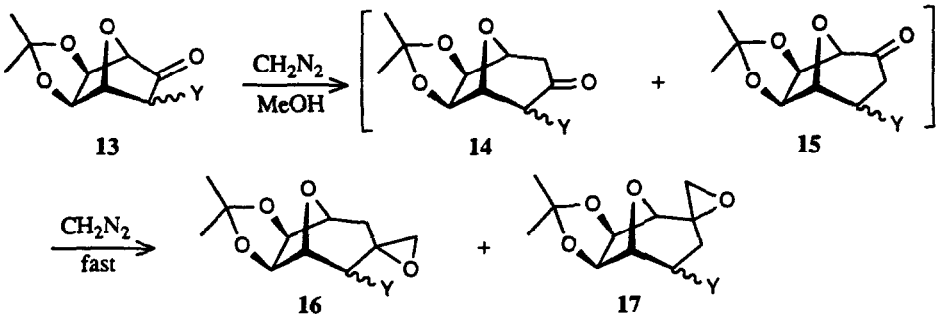
(+)-**7** R*=(1S)-camphanoyl (+)-**9** R'=(1R)-camphanoyl (+)-**11** (+)-**12** (-)-**12**
(+)-**8** R*=RADO(Et)- (+)-**10** R'=SADO(Et)-

RADO(Et):  SADO(Et): 

In this report we describe our studies toward the one-carbon ring enlargement of our "naked sugars". A preliminary study[5] had shown that the reactions of 7-oxabicyclo[2.2.1]heptan-2-ones of type **13** with diazomethane give the corresponding products of one-carbon ring enlargement with a regioselectivity (ratio of products resulting from the C(1) vs. C(3) migration) depending on the nature of the substituent Y at C(3). Unfortunately the expected ketones of type **14** and **15** could not be isolated as they were found to react with CH_2N_2 more rapidly than the corresponding 7-oxabicyclo[2.2.1]heptan-2-ones **13** giving the corresponding epoxides **16** and **17**.

Since the protected cyanohydrines **7**-**11** can, in principle, be reduced to the corresponding 2-aminomethyl-7-oxabicyclo[2.2.1]hept-5-en-2-ols, it was thus logical to explore the regioselectivity of the Tiffeneau-Demjanov rearrangements of these amines and of related derivatives. This has led us to develop a selective synthesis of 8-oxabicyclo[3.2.1]oct-6-en-2-one (**25**). Furthermore, we shall show that this homoconjugated enone adds to soft electrophiles giving, under conditions of kinetic control, adducts with

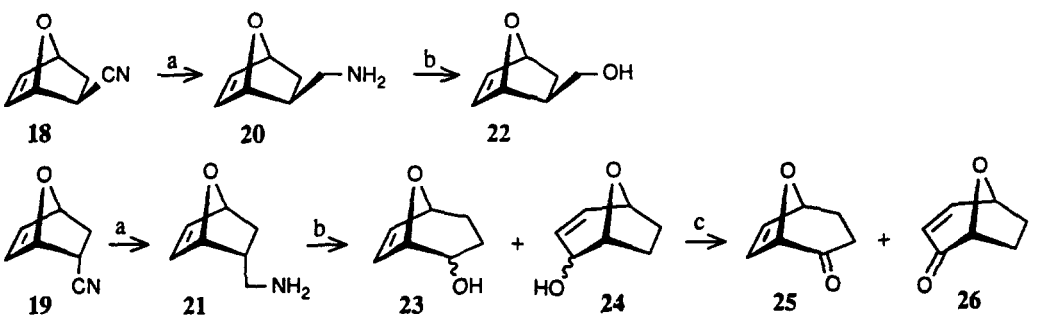
high stereo- (*exo* face attack by E^+, *anti* mode of addition of EX) and regioselectivity. The latter appears to be controlled, as for the additions of **1** to EX, by the electron-releasing ability of the homoconjugated carbonyl group.



Results

Reduction of the carbonitriles **18** and **19** (Diels-Alder adducts of furan to acrylonitrile[7] separated by column chromatography) with $LiAlH_4$ in ether afforded the 2-*exo* and 2-*endo*- methylamines **20** (99%) and **21** (78%), respectively. The treatment of **20** with $NaNO_2$ in 0.25 M H_2SO_4 at 0-4°C led to the exclusive formation of alcohol **22**, no trace of product of Demjanov rearrangement[8] could be detected in the crude of the deamination reaction mixture. Strickingly, the *endo* methylamine **21** treated under the same conditions furnished a mixture of rearranged alcohols **23** and **24**, both composed of mixtures of *exo* and *endo* diastereomers, that were oxidized with pyridinium chlorochromate (PCC) to give a 1:1 mixture of the corresponding enones **25** and **26** that could be separated by flash column chromatography on silica gel (Table 1).

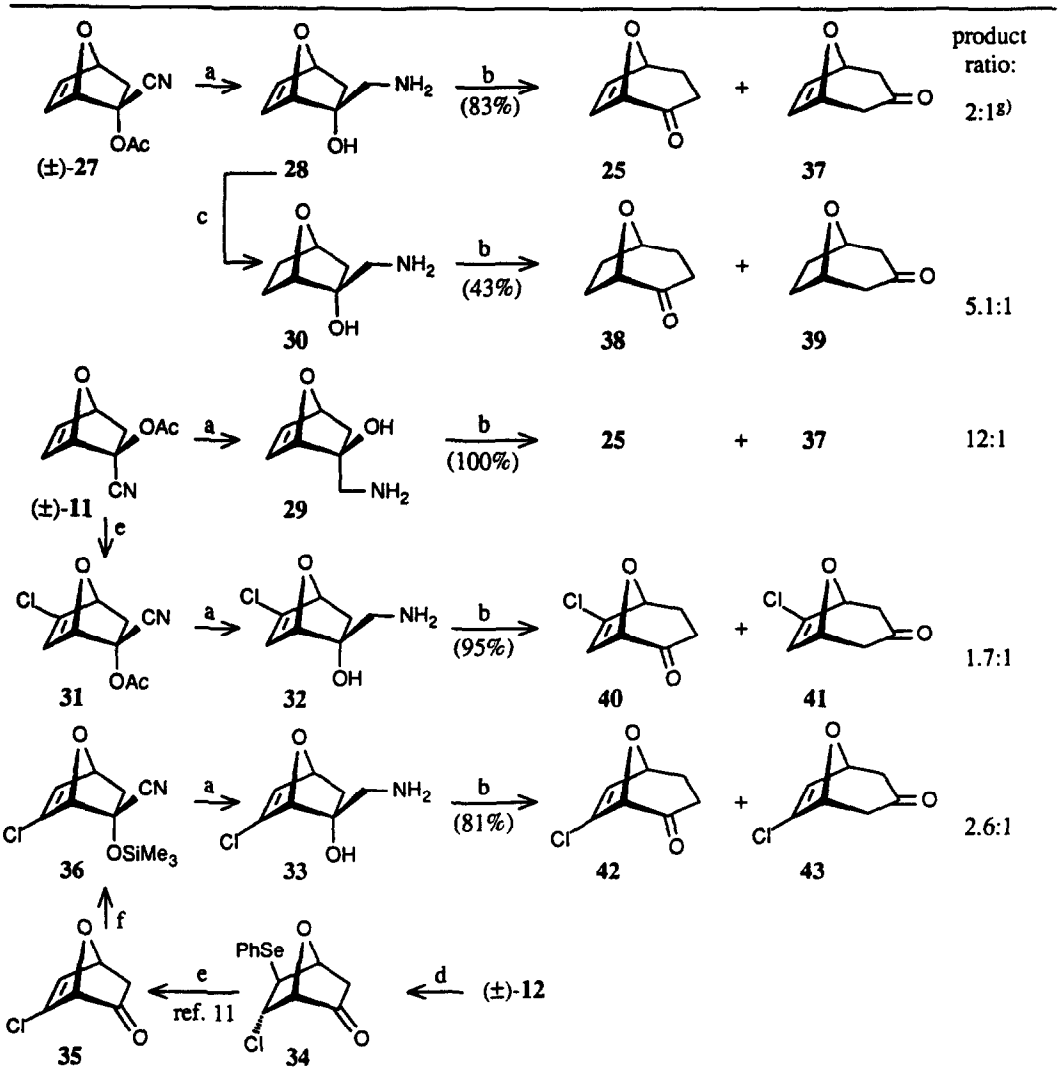
Table 1. Syntheses and deamination products of methylamines **20** and **21**



a) $LiAlH_4/Et_2O$, 0°C; b) $NaNO_2$, 0.25 M H_2SO_4/H_2O, 0-4°C; c) PCC/CH_2Cl_2, 3Å molecular sieves, 20°C

Reduction of the ZnI_2-induced Diels-Alder adducts of furan to 1-cyanovinyl acetate (±)-**27** (major) and (±)-**11** (minor)[9] with $LiAlH_4$ in Et_2O gave the corresponding aminoalcohols **28** (94%) and **29** (75%) (Table 2). Catalytic hydrogenation of the olefinic moiety of **28** furnished **30** (97%). Reduction of the chloroalkene **31**[10] with $LiAlH_4/Et_2O$ provided **32**. The regioisomeric derivative **33** was derived from (±)-7-oxabicyclo[2.2.1]hept-5-en-2-one ((±)-**12**)[11] following the procedure given in Table 2. The amino-

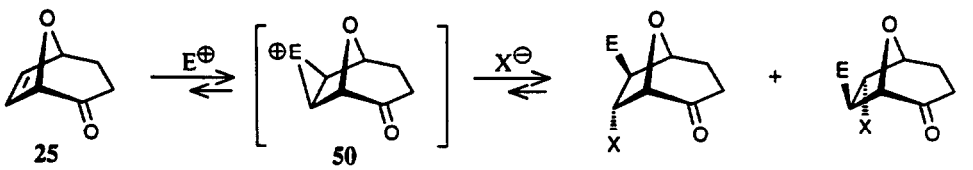
Table 2. Syntheses and products of Tiffeneau-Demjanov reaction of the α-amino-alcohols **28-30, 32-34**.



a) $LiAlH_4/Et_2O$, 0°C; b) $NaNO_2$, 0.25 M H_2SO_4/H_2O, 0-4°C; c) H_2/Pd-C, MeOH, 20°C;
d) $PhSeCl/CH_2Cl_2$; e) $mCPBA/CH_2Cl_2$, -70°C, then 20°C; f) TMSCN, ZnI_2, PhH;
g) No change of this product ratio when H_2SO_4 was replaced by AcOH or on addition of $LiClO_4$. This ratio became 1:1 in 50% aqueous hexafluoroisopropanol.

alcohols **32** and **33** were characterized in the form of the corresponding hydrochlorides (see Experimental Part). Nitrous acid diazotation of α-aminoalcohol **28** gave a 2:1 mixture of the expected products of Tiffeneau-Demjanov rearrangement, the homoconjugated enone **25**, arising from the migration of the methylene group C(3), being slightly preferred over the known symmetrical enone **37**[12] resulting from the migration of the bridgehead C(1) methine group. The product selectivity 2:1 being not satisfactory for synthetic purposes, we examined the Tiffeneau-Demjanov rearrangements of the other aminoalcohols reported in Table 2. The saturated derivative **30** led to a 5.1:1 mixture of the ketones **38** and **39**, suggesting that the olefinic moiety in **28** renders the "unwanted" C(1) migration more competitive. On substituting the endocyclic double bond of **28** with a chloro substituent as in **32** and **33**, we observed only small and insignificant effects on the regioselectivity of the Tiffeneau-Demjanov rearrangements (cf. **32** → **40** + **41**; **33** → **42** + **43**, Table 2). Fortunately, a satisfying selectivity of 12:1 in favour of the unsymmetrical enone **25** was obtained in the case of the nitrous acid deamination of 2-*endo*-aminomethyl-7-oxabicyclo[2.2.1]-hept-5-en-2-*exo*-ol (**29**). Since the precursor of **29** can be prepared readily in one of its optically pure form (+)-**11**,[13] we have realized, in principle, an efficient synthesis of (1R,5R)-8-oxabicyclo[3.2.1]oct-6-en-2-one.[14]

Table 3. Regioselectivity of the additions of 8-oxabicyclo[3.2.1]oct-6-en-2-one (**25**) to soft electrophiles.



25 **50**

EX: PhSeCl/$CDCl_3$,	25°C, 1-24 h	**44**	**45**	12:1
	55°C, 24 h			0.6:1
EX: PhSeBr/$CDCl_3$,	25°C, 0.5 h	**46**	**47**	13:1
	25°C, 4 h			8:1
	25°C, 8 days			1:1
EX: 2,4-$(NO_2)_2C_6H_3SCl$/CD_3CN,	25°C, 8 days	**48**	**49**	>20:1
	110°C, 2 days			>20:1

When enone **25** was mixed with PhSeCl in CH_2Cl_2 and allowed to react at 25°C, adduct **44** was isolated in 96% yield. When the reaction was run in a 5 mm NMR tube ($CDCl_3$ as solvent) a 12:1 mixture of adducts **44** and **45** was formed at 25°C. On heating to 55°C, this mixture was equilibrated slowly to a 0.6:1 mixture of **44** and **45** thus demonstrating that the adduct **44** is the favoured regioisomer under conditions of kinetic control, whereas adduct **45** is slightly more stable than **44**. At temperature above 55°C, adducts **44** + **45** regenerated enone **25** (by 250 MHz ^{1}H-NMR). The reaction of PhSeBr with **25** in $CDCl_3$ was somewhat faster than the addition of PhSeCl to **25**, giving a 13:1 mixture of regioisomeric adduct **46** and **47** after 30 min. at 25°C. On staying at 25°C, the 13:1 mixture of **46** + **47** was equilibrated to a 1:1 mixture of **46** + **47**

after a week or so, demonstrating again that the favoured regioisomer **46** corresponds to that obtained under conditions of kinetic control.

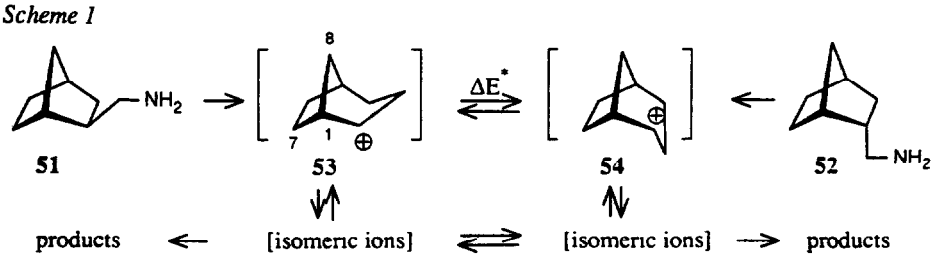
The reaction of 2,4-dinitrobenzenesulfenyl chloride with **25** could not be run in CH_2Cl_2 or $CDCl_3$. A more polar solvent such as CH_3CN was required. When run in a NMR tube and in CD_3CN, only adduct **48** was observed by ^{1}H-NMR, even after prolonged heating to 110°C. No trace of the regioisomeric adduct **49** could be detected under these conditions which are probably not ionizing enough for the formation of the bridged-ion intermediate **50** (E = S-$C_6H_3(NO_2)_2$). By analogy with the results described for the additions of PhSeCl and PhSeBr (Table 3), we propose that **48** corresponds also to the adduct resulting from a kinetic control, i.e., the chloride anion prefers to attack the *endo* position of C(7) rather than that of C(6). In all electrophilic additions of **25** reported here not trace of adducts resulting from a *syn* mode of addition or from *endo* face attack of the endocyclic double bond was detected.

The structures of all the new compounds have been established unambiguously from their mode of formation, mode of reaction, from their spectral data and elemental analyses. In the case of adducts **44** - **48**, distinction between the H-C-Cl and H-C-Se (or H-C-S) ^{1}H-NMR signals was based on their chemical shifts, the former being generally more deshielded than the latter protons. Furthermore, the *exo* and *endo* relative configurations of these protons were readily assigned from their vicinal $^3J_{H,H}$ coupling constants[15] with the adjacent bridgehead protons. When H-C(6) or H-C(7) is in an *exo* position, a coupling of 3-5 Hz was generally observed, whereas it was lower than 1.5 Hz when those protons occupy *endo* positions. When necessary, our NMR signal attributions were confirmed by selective homonuclear decoupling experiments or/and by NOE measurements.

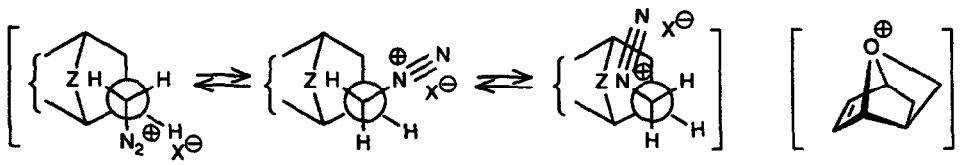
Discussion.

The Demjanov nitrous acid deamination of bicyclo[2.2.1]hept-2-*exo*-ylmethylamine (**51**), of its *endo* stereomer **52** and of optically active derivatives have been studied by Berson and co-workers.[15] They found that most of the products arised from favoured C(3)-methylene group migrations generating the boat-shape and chair-shape bicyclo[3.2.1]oct-2-yl cation intermediates **53** and **54** (Scheme 1), respectively, that undergo further rearrangements involving σC(1,7) and σC(1,8) bond migrations competitively with solvent quenching. Although the more electron-rich C(1)-methine group migration should be favoured in

Scheme 1



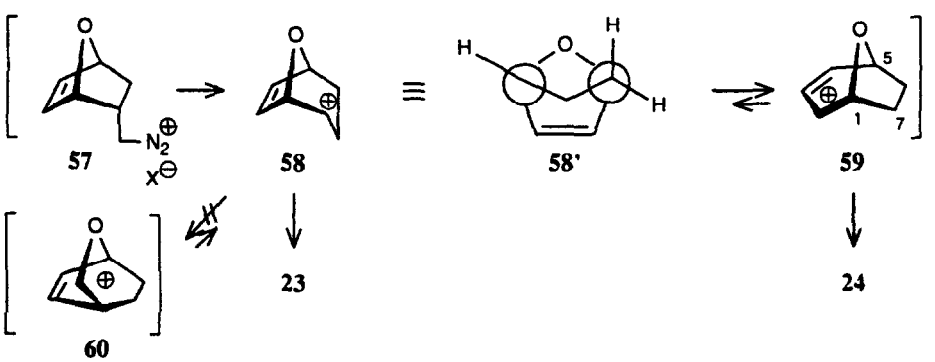
competitive processes involving cationic intermediates, the high exothermicity of the decomposition of aliphatic diazonium ion intermediates generated by nitrosation of the corresponding primary amines requires much less assistance from neighboring groups than, for instance, the heterolysis of halides or sulfonic esters. In the case of diazonium ion intermediates derived from methylamine derivatives such as **20** and **51**, rotamers populations **55A** ⇄ **55B** ⇄ **55C** may determine the regioselectivity of the Demjanov rearrangement. Accordingly, in the case of the nitrous acid deamination of **51**, the favoured rotamer of type **55A** ($Z=CH_2$) would undergo decomposition with migration of C(3) whereas, in the case of the 7-oxabicyclo[2.2.1]heptane analogues **20**, rotamer of type **55C** (Z=O) would be favoured because of a electrostatic factor implying the oxa bridge and the diazonium ion making the migration of C(3) or C(1) retarded processes compared with nucleophilic quenching of the decomposing diazonium ion intermediate.



55A **55B** **55C** **56**

This hypothesis (A) might explain the absence of products of Demjanov rearrangement in the nitrosation of the 2-*exo*-aminomethyl-7-oxabicyclo[2.2.1]hept-5-ene (**20**) whereas its *endo* stereomer **21** and the carba-analogues **51** and **52** do give mostly products of one-carbon ring enlargement. Alternatively one could invoke the formation of an oxonium ion intermediate **56** which would prohibits the alkyl group migrations (hypothesis B). If rotamers of type **55C** (Z=O) should also prevail in the case of the nitrosation of 2-*exo*-aminomethyl-alcohols **28**, **30**, **32** and **33** (Table 2) the corresponding epoxides should have a chance to be formed competitively with the products of Tiffeneau-Demjanov rearrangement. This was not the case! One thus must admit that an α-hydroxy group affects the proportion of the diazonium rotamers of type **55A**, **55B** and **55C**, whether they have the time or not to equilibrate, or/and enhances the Wagner-Meerwein intrinsic migratory aptitudes of the adjacent alkyl groups.

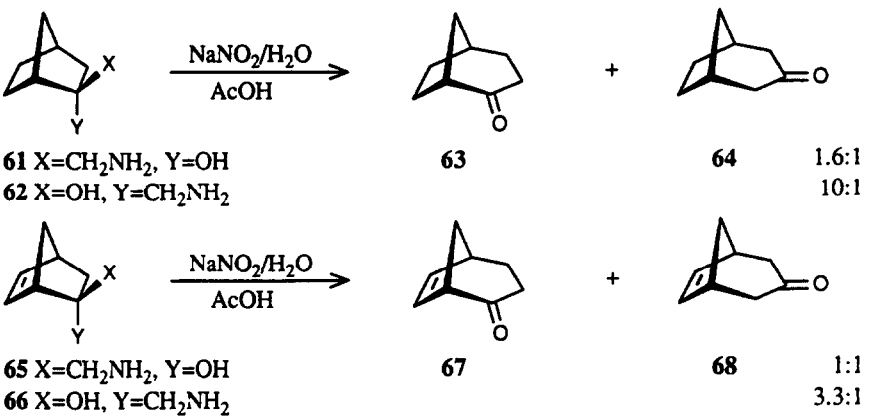
Scheme 2



57 **58** **58'** **59** **60** **23** **24**

The Demjanov reaction of the *endo*-methylamine **21** giving products of one-carbon ring enlargement **23** + **24** (Table 1) can be interpreted in terms of a favoured C(3) methylene group migration that generates the chair 8-oxabicyclo[3.2.1]oct-6-en-2-yl cation intermediate (**58**). Because of a favourable overlap between the 2p empty orbital of this cation and the adjacent σC(1),O(8) bond (see Newman projection **58'**, Scheme 2)[16] the oxa bridge migrates readily to engender the allylic cation intermediate **59** competitively with solvent quenching. This process is faster than the Wagner-Meerwein rearrangement **58** → **60** involving the migration of the σC(1),C(7) bond or/and homoconjugation with the πC(6),C(7) double bond although the oxycarbenium ion intermediate **60** is expected to be more stable than **59** (DH° ($MeOCH_2^+/H^-$) = 243 kcal/mol, DH° (CH_2=CH-CH_2^+/H^-) = 256 kcal/mol, inductive effect of the oxa bridge in **59**).[18] The rearrangement **58** → **60** is retarded probably because there is a significant energy barrier to the conformational change in **58** necessary for a better p^+C(2) orbital with the σC(1),C(7) bond. Alternatively one can invoke a concerted double migration of the C(3) methylene and O(8) oxa group during decomposition of the diazonium ion intermediate **57** (dyotropic rearrangement[19]) giving **59** in one step and thus avoiding the formation of the more stable ion intermediate **60**. It should be noted also that Wagner-Meerwein rearrangement of **59** involving migration of σC(1),C(7) or σC(5),C(6) bond lead to **60** (or its enantiomeric form). This process must be slow compared with water quenching. Although bicyclo[2.2.1]hept-2-yl cation undergoes σC(1),C(6) bond migration with no energy barrier (non-classical norbornyl cation), quantum calculations[2b] have suggested that there is an energy barrier to the related Wagner-Meerwein rearrangement that converts 7-oxabicyclo[2.2.1]hept-2-yl cation into the much more stable 3-oxabicyclo[2.2.1]hept-2-yl cation. This energy barrier, as well as that in a hypothetical exothermic rearrangement **59** → **60**, can be attributed to the destabilizing inductive effect of the oxa bridge intervening at the beginning of the alkyl group migration.

Scheme 3

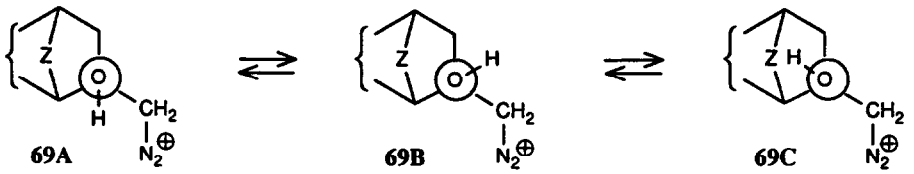


61 X=CH_2NH_2, Y=OH — **63** — **64** — 1.6:1
62 X=OH, Y=CH_2NH_2 — 10:1

65 X=CH_2NH_2, Y=OH — **67** — **68** — 1:1
66 X=OH, Y=CH_2NH_2 — 3.3:1

The regioselectivity of the Tiffeneau-Demjanov reaction of α-amino-alcohols **28** - **30** (Table 2) are parallel with those reported for the carba-analogues **61**, **62**,[20] **65** and **66**[21] (Scheme 3). For both series the

preference for C(3) methylene group migration is enhanced in the case of 2-*endo*-aminomethyl derivatives compared with the corresponding 2-*exo*-aminomethyl stereomers. It is reduced on introducing a C=C double bond at C(5), C(6). The selectivities are in general better for the 7-oxabicyclo[2.2.1]heptane than for the bicyclo[2.2.1]heptane derivatives. The best contrast is seen on comparing reactions **29** → **25** + **37** (product ratio 12:1) and **66** → **67** + **68** (product ratio 3.3:1). Several hypotheses can be invoked to explain this



observation. As already mentionned here-above, the 7-oxa bridge can affect the population of the diazonium ion rotamers of type **55A** ⇄ **55B** ⇄ **55C**; it can also have an influence on the orientation of the hydroxy group (see e.g. **69A** ⇄ **69B** ⇄ **69C**) and because of that modify the relative intrinsic migratory aptitudes[22] of the C(1) and C(3) groups.[5,23] One cannot exclude yet an inductive effect of the 7-oxa bridge that would retard the migration of the C(1) bridgehead group, although, in the case of related Baeyer-Villiger reactions[24] the 7-oxa bridge enhances it.[25] The non-parallelism between the Tiffeneau-Demjanov and Baeyer-Villiger regioselectivities has already been commented.[17,20,26]

The effects due to the introduction of a chloro substituent at C(5) (see **32**) or at C(6) (see **33**) are too small to be discussed; nevertheless they do not weaken the hypotheses proposed above to interprete our results.

Conclusion

The Demjanov reaction of 7-oxabicyclo[2.2.1]hept-5-en-2-*endo*-ylmethylamine gave exclusively products of C(3) methylene group migration. The Tiffeneau-Demjanov rearrangement of 2-*exo*- and 2-*endo*-amino-methyl-7-oxabicyclo[2.2.1]hept-5-en-2-ols gave mixtures of 8-oxabicyclo[3.2.1]oct-6-en-2-one (**25**) and 8-oxabicyclo][3.2.1]oct-6-en-3-one (**37**) resulting from the C(3) methylene and C(1) methine group migration, respectively. The regioselectivity **25/37** was the largest (12:1) for the *endo*-aminomethyl derivative **29**, realizing thus an efficient synthesis of the bicyclic enone **25**. The preference for the C(3) methylene group migration was higher for 2-aminomethyl-7-oxabicyclo[2.2.1]hept-5-en-2-ols and -heptan-2-ols than for the corresponding carba-analogues Under kinetically controlled conditions the additions of soft electrophiles EX to 8-oxabicyclo[3.2.1]oct-6-en-2-one (**25**) were highly stereo- and regioselective giving adducts where E substitutes the *exo* position of centre C(6) and X the *endo* position of centre C(7), in agreement with the hypothesis that the homoconjugated carbonyl group plays the role of an electron-releasing substituent, as in the case of the electrophilic additions of bicyclo[2.2.1]hept-5-en-2-one. 7-oxabicyclo[2.2.1]hept-5-en-2-one and bicyclo[2.2.2]oct-5-en-2-one.

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Experimental Part.

General. Reagents (Fluka, Merck, Aldrich) were used without purification. Solvents were distilled prior use. Anhydrous ether and THF (Na, benzophenone, Ar), CH_2Cl_2 (P_2O_5), pyridine and triethylamine (CaH_2) were prepared just before use. Flash column chromatography (FC) employed Merck silica gel (60, particle size 0.040-0.63 mm). All reactions were monitored by thin layer chromatography (TLC) on 0.25 mm Merck silica gel plates (60F-254) using p-anisaldehyde, UV light or phosphomolybdic acid/heat as developing means. Melting points (m.p.) on SMP-20 Büchi apparatus, were not corrected. IR spectra (solvent) were recorded on Perkin Elmer 1430 spectrometer (ν, in cm^{-1}); ^{1}H-NMR spectra (δ_H in ppm, apparent multiplicity, signal integration, apparent coupling constant in Hz, signal attributions) on Bruker 250 FT (250 MHz), the signal of residual solvent ($\delta_H(CHCl_3)$ = 7.25 ppm, $\delta_H(CHDCl_2)$ = 5.35 ppm, δ_H(MeOH) = 3.35 ppm, $\delta_H(C_6HD_5)$ = 7.20 ppm was used as internal references; ^{13}C-NMR spectra (δ_C in ppm, apparent multiplicity, ^1J(C,H) coupling constant in Hz, signal attributions) on Bruker 250 FT (62.9 MHz), the signal of residual solvent (δ_C ($CHCl_3$) = 77.0 ppm, δ_C (MeOH) = 49.0 ppm, δ_C (CH_2Cl_2) = 53.8 ppm) was used as internal reference; mass spectra (MS) on a Nermag R10-10C machine under chemical ionization (CI-NH_3) or electronic ionization (70 eV) mode. None of the procedures have been optimized.

2-*exo*-Aminomethyl-7-oxabicyclo[2.2.1]hept-5-ene (**20**). A solution of **18**[7] (300 mg, 2.48 mmol) in dry Et_2O (6 mL) was added dropwise to a suspension of $LiAlH_4$ (186 mg, 4.96 mmol) in dry Et_2O (6 mL) under stirring at 0°C and under Ar atmosphere. The resulting mixture was stirred at 0°C for 4 h. Then 15% aq. NaOH (0.5 mL) was added dropwise and the cooling bath was taken away. Stirring was continued until complete disappearance of the grey colour and coagulation of the white precipitate. The solid was filtered off and washed with CH_2Cl_2. The organic layers were collected and the solvents distilled under reduced pressure to afford a colourless oil, 300 mg (99%). IR (film) ν: 3360 (br.), 2990, 2915, 2860, 1600, 1310, 1010, 900 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 6.29 (m, 2H, H-C(5), H-C(6)); 4.98 (d, 1H, J = 4.5 Hz, H-C(4)); 4.75 (s, 1H, H-C(1)); 2.79 (dd, 1H, -C*H*H-, J = 6.5, 12.5 Hz); 2.73 (dd, 1H, -CH*H*-, J = 7.4, 12.5 Hz); 1.58 (dddd, 1H, J 6.5, 7.4, 7.5, 12.5 Hz, H-C(2)); 1.41 (dd, 1H, J = 7.5, 11.5 Hz, H_{endo}-C(3)); 1.32 (ddd, 1H, J = 3.5, 4.5, 11.5 Hz, H_{exo}-C(3)). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C: 135.7, 135.1 (2d, ^1J(C,H) = 175 Hz); 80.0, 78.0 (2d, ^1J(C,H) = 165 Hz); 45.9 (t, ^1J(C,H) = 135 Hz); 41.2 (d, ^1J(C,H) = 135 Hz); 29.8 (t, ^1J(C,H) = 135 Hz). MS (CI, NH_3) m/z: 127 (M^+ + 2, 6), 126 (M^+ + 1, 60), 109 (17), 108 (M^+ - NH_3, 100), 107 (6), 106 (4), 97 (3), 96 (10), 95 (13), 94 (7), 82 (9), 81 (24), 80 (20), 79 (32). Elemental analysis done on the benzamido derivative: calc. for $C_{14}H_{15}NO_2$ (229.28): C 73.34, H 56.59, N 6.11; found: 73.27, H 6.55, N 6.06.

2-*endo*-Aminomethyl-7-oxabicyclo[2.2.1]hept-5-ene (**21**). Same procedure as for **20**, starting with **19**.[7] Yield 243 mg (78%). IR (film) ν: 3350 (br.), 2990, 2940, 2860, 1600, 1315, 1020, 905 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 6.38 (dd, 1H, J = 1.5, 6.0 Hz, H-C(6)); 6.24 (dd, 1H, J = 1.5, 6.0 Hz, H-C(5)); 4.96 (dd, 1H, J = 1.5, 4.5 Hz, H-C(4)); 4.91 (dd, 1H, J = 1.5, 5.0 Hz, H-C(1)); 2.55 (dd, 1H, J = 7.0, 12.5 Hz), 2.40 (dd, 1H, J = 8.5, 12.0 Hz. CH_2-C(2)); 2.25 (dddd, 1H, J = 4.0, 7.0, 8.5, 9.0 Hz, H-C(2)); 2.02 (ddd, 1H, J = 5.0, 9.0, 11.0 Hz, H_{exo}-C(3)); 0.73 (dd, 1H, J = 4.0, 11.0 Hz, H_{endo}-C(3)). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C: 136.5, 131.9 (2d, ^1J(C,H) = 175 Hz); 79.4, 78.4 (2d, ^1J(C,H) = 165 Hz); 45.1 (t, ^1J(C,H) = 140 Hz); 41.5 (d, ^1J(C,H) = 135 Hz); 29.3 (t, ^1J(C,H) = 135 Hz). MS (CI, NH_3) m/z: 126 (M^+ + 1, 100), 109 (6), 108 (M^+ - NH_3, 31), 106 (2), 105 (3), 97 (3), 96 (7), 95 (3), 94 (4), 82 (5), 80 (6), 79 (7). Elemental analysis done on the benzamido derivative; calc. for $C_{14}H_{15}NO_2$ (229.28): C 73.34, H 6.59, N 6.11; found: 73.38, H 6.52, N 6.07

2-*exo*-Aminomethyl-7-oxabicyclo[2.2.1]hept-5-en-2-*endo*-ol (**28**). A solution of (±)-**27** (10.0 g, 55.8 mmol) in dry Et_2O (200 mL) was added dropwise to a suspension of $LiAlH_4$ (6.0 g, 158 mmol) in dry Et_2O (200 mL) under stirring at 0°C under Ar atmosphere. The resulting mixture was stirred at 0°C for 5 h. Then 15% aq. NaOH (23 mL) was added dropwise and the cooling bath was taken away. Stirring was continued until

complete disappearance of grey colour and coagulation of the white precipitate. The solid was filtered off and washed with CH_2Cl_2. The organic layers were collected and the solvents distilled at reduced pressure to afford 7.45 g (94%), white solid, m.p. 88-91°C. IR (KBr) ν: 3420-2500, 1640, 1560, 1485, 1440, 1370, 1320, 1225, 1190, 1140, 1090, 1060, 1015, 910, 890, 873, 850, 825, 800, 760, 720 cm^{-1}. ^1H-NMR (250 MHz, $CDCl_3$) δ_H: 6.60 (dd, 1H, ^3J = 2.0, 6.0 Hz, H-C(6)); 6.48 (dd, 1H, ^3J = 2.0, 6.0 Hz, H-C(5)); 4.94 (ddd, 1H, ^3J = 0.5, 2.0, 5.0 Hz, H-C(4)); 4.59 (dd, 1H, J = 0.5, 2.0 Hz, H-C(1)); 3.06, 2.90 (2d, ^2J = 13.0 Hz, CH_2-C(2)); 1.83 (dd, 1H, ^3J = 5.0 Hz, ^2J = 12.0 Hz, H_{exo}-C(3)); 1.32 (d, 1H, ^2J = 12.0 Hz, H_{endo}-C(3)). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C: 137.4, 133.7 (2d, ^1J(C,H) = 180 Hz); 80.9, 79.5 (2d, ^1J(C,H) = 165 Hz); 77.7 (s); 49.3, 39.8 (2t, ^1J(C,H) = 135 Hz). MS (CI, NH_3) m/z: 159 (M^+ + 18, 1), 143 (M^+ + 2, 8), 142 (M^+ + 1, 100), 141 (M^+, 1), 125 (M^+ - NH_2, 2), 113 (4), 107 (2), 95 (3), 94 (2), 81 (3), 74 (7), 73 (66), 72 (15), 71 (13), 70 (5). Anal. calc. for $C_7H_{11}NO_2$ (141.17): C 59.55, H 7.85, N 9.92; found: C 59.55, H 7.77, N 9.91.

2-*endo*-Aminomethyl-7-oxabicyclo[2.2.1]hept-5-en-2-*exo*-ol (**29**). A solution of (±)-**11** (200 mg, 1.12 mmol) in dry Et_2O (4 mL) was added dropwise to a suspension of $LiAlH_4$ (120 mg, 3.1 mmol) in dry Et_2O (4 mL) under stirring at 0°C and under Ar atmosphere. The resulting mixture was stirred at 0°C for 5 h. Then 15% NaOH (0.5 mL) was added dropwise and the cooling bath was taken away. The mixture was stirred until disappearance of the grey colour and coagulation of the resulting white precipitate. The solid was filtered off and washed with CH_2Cl_2. The organic layers were collected and the solvent distilled under reduced pressure to afford a pale yellow solid. Trituration of it with Et_2O afforded 118 mg (75%), white solid, m.p. 121-122°C. IR (KBr) ν: 3360, 3300, 3100 (br.), 3010, 2980, 2940, 1580, 1430, 1085, 995, 910 cm^{-1}. ^1H-NMR (250 MHz, $CDCl_3$) δ_H: 6.42 (dd, 1H, ^3J = 1.5 7.0 Hz, H-C(5)); 6.37 (dd, 1H, ^3J = 2.0, 7.0 Hz, H-C(6)); 5.02 (ddd, 1H, ^4J = 1.4 Hz, ^3J = 1.5, 5.0 Hz, H-C(4)); 4.63 (dd, 1H, ^4J = 1.4 Hz, ^3J = 2.0 Hz, H-C(1)); 2.81, 2.61 (2d, 2H, ^2J = 13.0 Hz, $CH_2C(2)$); 1.81 (dd, 1H, ^3J = 5.0 Hz, ^2J = 12.0 Hz, H_{exo}-C(3)); 1.40 (d, 1H, ^2J = 12.0 Hz, H_{endo}-C(3)). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C: 138.4, 132.8 (2d, ^1J(C,H) = 175 Hz); 85.8, 78.1 (2d, ^1J(C,H) = 170 Hz); 77.4 (s); 48.4, 40.1 (2t, ^1J(C,H) = 135 Hz). MS (EI) m/z: 142 (M^+ + 1, 2), 115 (3), 97 (1), 96 (2), 95 (4), 84 (4), 83 (4), 82 (2), 81 (5), 74 (4), 73 (100), 72 (44), 68 (41). Anal. calc. for $C_7H_{11}NO_2$ (141.17): C 59.55, H 7.85, N 9.92; found: C 59.49, H 7.78, N 10.00.

2-*exo*-Aminomethyl-7-oxabicyclo[2.2.1]heptan-2-*endo*-ol (**30**). A solution of **28** (200 mg, 1.41 mmol) in MeOH (4 mL) was stirred at 20°C under H_2 atmosphere for 12 h. After solvent evaporation 197 mg (97%) of a colourless oil was isolated. An analytical sample was obtained by sublimation under 0.1 Torr at 30°C Colourless crystals, m.p. 55-60°C. IR (KBr) ν: 3360 (br.), 2970, 2870, 1580, 1465, 1330, 1235, 1205, 990 cm^{-1}. ^1H-NMR (250 MHz, $CDCl_3$) δ_H: 4.36 (dd, ^3J = 5.0, 5.0 Hz, H-C(4)); 4.00 (d, 1H, ^3J = 5.0 Hz, H-C(1)); 2.79, 2.48 (2d, ^2J = 13.0, CH_2-C(2)); 2.19-1.53 (m, 5H, $H_2C(6)$, $H_2C(5)$, H_{exo}-C(3)); 1.24 (d, 1H, ^2J = 12.5 Hz, H_{endo}-C(3)). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C: 80.0 (d, ^1J(C,H) = 150 Hz); 78.9 (s); 77.6 (d, ^1J(C,H) = 150 Hz); 49 1, 42.7, 29.8, 22.9 (4t, ^1J(C,H) = 135 Hz). MS (CI, NH_3) m/z: 144 ($M+H^+$, 44), 126 (M^+ - NH_3, 25), 115 (3), 114 (8), 113 (5), 100 (100), 98 (7), 97 (16), 96 (36), 86 (32), 84 (8), 83 (11), 82 (9), 81 (5). Anal. calc. for $C_7H_{13}NO_2$ (143.18): C 58.72, H 9.15, N 9.78; found: C 58.68, H 9.10, N 9.71.

2-*exo*-Aminomethyl-5-chloro-7-oxabicyclo[2.2.1]hept-5-en-2-*endo*-ol (**32**). A solution of **31**[10] (500 mg, 2.34 mmol) in dry Et_2O (8 mL) was added dropwise to a suspension of $LiAlH_4$ (252 mg, 7.90 mmol) in dry Et_2O (8 mL) stirred at 0°C under Ar atmosphere. The resulting mixture was stirred at 0°C for 5 h. Then 15% aq. NaOH (0.5 mL) was added dropwise and the mixture was stirred until it became completely white. It was filtered and the solid residue was washed with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated to obtain 408 mg (99%) of a pale yellow oil The oil was crystallized from CH_2Cl_2/Et_2O giving 97 mg (24%), white crystals. Treatment of the mother liquor with HCl followed by crystallization from Et_2O/MeOH afforded 67 mg (14%) of the corresponding chlorhydrate. Analytical data are reported for the chlorhydrate **32**·HCl, m.p. 197-201°C. IR (KBr) ν: 3300, 3000 (br.), 1590, 1495, 1440, 1400, 1380, 1310, 1280, 1225, 1200, 1135, 1080, 1040, 1000, 940, 890, 860, 835, 795, 675, 630 cm^{-1}. ^1H-NMR (250 MHz, d^4-MeOH) δ_H: 6.33 (d, 1H, ^3J = 2.5 Hz, H-C(6)). 4.77 (d, 1H, ^3J = 2.5 Hz, H-C(1)); 4.76 (d, 1H, ^3J = 4.5 Hz, H-C(4)); 3.21 (s, 2H, CH_2-C(2)); 2.12 (dd, 1H, ^3J = 4.5, 12.5 Hz, H_{exo}-C(3)); 1.56 (d, 1H, ^2J = 12 5 Hz, H_{endo}-C(3)). ^{13}C-NMR (62.9 MHz, d^4-MeOH) δ_C: 142.6 (s); 129.5 (d, ^1J(C,H) = 180 Hz); 85.0 (d, ^1J(C,H) = 165 Hz); 78.9 (s); 49.4 (t, ^1J(C,H) = 145 Hz); 40.8 (t, ^1J(C,H) = 135 Hz). MS (CI, NH_3) m/z: 178 (M^+ -

$H^{35}Cl$, 0.5), 176 (M^+ - $H^{37}Cl$, 1.3), 123 (2), 111 (2), 115 (2), 104 (8), 103 (1), 102 (25), 81 (4), 73 (100). Anal. calc. for $C_7H_{11}Cl_2NO_2$ (212.07): C 39.64, H 5.23, Cl 33.43; found: C 39.57, H 5.14, Cl 33.45.

2-*exo*-Aminomethyl-6-chloro-7-oxabicyclo[2.2.1]hept-5-en-2-*endo*-ol chlorhydrate (**33**·HCl). Same procedure as for **32**, starting with **36** (2.11 g, 8.6 mmol). Yield: 506 mg (27%) of chlorhydrate **33**·HCl, white crystals, m.p. 185°C (dec.). (IR (KBr) ν: 3350, 3000 (br.), 2640, 2580, 2540, 1995, 1592, 1505, 1450, 1430, 1405, 1390, 1310, 1275, 1230, 1215, 1200, 1130, 1080, 1035, 1040, 990, 935, 890, 820, 790, 675, 620 cm^{-1}. ^{1}H-NMR (250 MHz, d^4-MeOH) δ_H: 6.53 (d, 1H, ^3J = 2.0 Hz, H-C(5)); 5.02 (ddd, 1H, ^3J = 2.0, 5.0 Hz, ^4J = 1 Hz, H-C(4)); 4.57 (d, 1H, ^4J = 1 Hz, H-C(1)); 3.24 (s, 2H, H_2C-C(2)); 2.12 (dd, 1H, ^3J = 5.0 Hz, ^2J = 12.0 Hz, H_{exo}-C(3)); 1.57 (d, ^2J = 12.0 Hz, H_{endo}-C(3)). ^{13}C-NMR (62.9 MHz, d^4-MeOH) δ_C: 138.3 (s); 132.9 (d, ^1J(C,H) = 180 Hz); 85.8, 82.0 (2d, ^1J(C,H) = 170 Hz); 76.8 (s); 48.7 (t, ^1J(C,H) = 145 Hz); 39.9 (t, ^1J(C,H) = 135 Hz). MS (CI, NH_3) m/z: 178 (M^+ - $H^{35}Cl$, 0.8), 176 (M^+ - $H^{37}Cl$, 1.1), 142 (4), 140 (10), 122 (10), 112 (110), 104 (13), 102 (39), 78 (18), 77 (30), 75 (11), 73 (100). Anal. calc. for $C_7H_{11}Cl_2NO_2$ (212.07): C 39.64, H 5.23, Cl 33.43; found: C 39.60, H 5.20, Cl 33.37.

6-Chloro-2-*endo*-(trimethylsilyl)oxy-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*-carbonitrile (**36**). A solution of trimethylsilyl cyanide (TMSCN, 1.6 mL, 12.8 mmol) in C_6H_6 (20 mL) was added dropwise to a stirred solution of 6-chloro-7-oxabicyclo[2.2.1]hept-5-en-2-one (**35**)[11] (1.4 g, 9.7 mmol) and ZnI_2 (50 mg) in C_6H_6 (20 mL) under Ar atmosphere. After stirring at 20°C for 24 h, the mixture was filtered through a pad of silica gel, rinsing with CH_2Cl_2. The solution was washed with 5% aqueous solution of sodium thiosulfate, then with H_2O and brine. After drying ($MgSO_4$), the solvent was evaporated in vacuo, yielding 2.11 g (89%), brown oil that was used without further purification in the synthesis of **33**.

General method for the Demjanov and the Tiffeneau-Demjanov reactions. A solution of the amine or of the α-amino alcohol (0.71 mmol) in 0.25 M H_2SO_4 (2 mL) was stirred at 0-4°C (ice bath). $NaNO_2$ (1.1 mmol) was added portionwise under stirring. The mixture was stirred an additional 4 h. Then the solution was saturated with solid NaCl and extracted with Et_2O. The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under atmospheric pressure (Vigreux column). ^{1}H-NMR determination of the product ratio (Table 1, 2) was done on this crude. The two ketones were separated by flash chromatography (silica gel, CH_2Cl_2).

Characteristics of 7-oxabicyclo[2.2.1]hept-5-en-2-*exo*-ylmethanol (**22**). IR (Film): 3400 (br.), 3000, 2940, 2870, 1680, 1555, 1310, 1080, 1030, 980 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 6.32 (AB syst., 2 H, H-C(5), H-C(6)); 4.95 (m, 1H, H-C(4)); 4.87 (s, 1H, H-C(1)); 3 77 (dd, 1H, ^3J = 5.0, ^2J = 11.5 Hz), 3.60 (dd, 1H, ^3J = 8.0, ^2J = 11.5 Hz, CH_2-C(2)); 1.79 (dddd, 1H, ^3J = 5.0, 5.1, 6.5, 8.0 Hz, CH_2-C(2)); 1.37 (m, 2H, H_2C(3)) ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C: 136.1, 134.8 (2d, ^1J(C,H) = 175 Hz); 79.9, 77.9 (2d, ^1J(C,H) = 165 Hz), 65.3 (t, ^1J(C,H) = 140 Hz); 39.5 (d, ^1J(C,H) = 135 Hz); 28.1 (t, ^1J(C,H) = 135 Hz)

Oxidation of alcohol mixture **23** + **24**. The crude reaction mixture resulting from the Demjanov reaction of **21** was purified and separated by column chromatography (silica gel, CH_2Cl_2/Et_2O 4:1, then CH_2Cl_2/Et_2O 7:3) giving 25 mg of alcohols **23** and 25 mg of alcohol **24**. A mixture of **23** (or (**24**) (25 mg), PCC (30 mg), freshly activated molecular sieves 3 Å and dry CH_2Cl_2 (1 mL) was stirred at 20°C for 3 h. After addition of Et_2O (1 mL), the mixture was stirred for 15 min and filtered through a pad of silica gel giving after solvent evaporation 25 mg of ketone **25** (or **26**).

Characteristics of 8-oxabicyclo[3.2.1]oct-6-en-2-one (**25**). Colourless oil. IR (film) ν: 2960-2870, 1722, 1447, 1411, 1345, 1330, 1304, 1260, 1226, 1188, 1155, 1054, 1036, 1015, 905, 880, 820, 765, 756, 708 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 6.37 (dd, 1H, ^3J = 2.0, 7.0 Hz, H-C(6)); 6.25 (dd, 1H, ^3J = 2.0, 7.0 Hz, H-C(7)); 5.00 (br.d, 1H, ^3J = 5.0 Hz, H-C(5)); 4.63 (br.s, 1H, H-C(1)); 2.72 (m, 1H, H_{endo}-C(3)); 2.38 (m, 2H, H_{exo}-C(3), H_{exo}-C(4)); 1.72 (m, 1H, H_{endo}-C(4)). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C: 202.4 (s), 134.8, 129.6 (2d, ^1J(C,H) = 175 Hz); 86.2, 78.9 (2d, ^1J(C,H) = 160 Hz); 32.2, 24.9 (2t, ^1J(C,H) = 130 Hz). MS (CI, NH_3) m/z: 125 (M^+ + 1, 14), 128 (M^+, 68), 108 (11), 107 (27), 97 (83), 96 (62), 95 (68), 93 (20), 85 (42), 82 (27), 81 (100), 80 (25), 79 (31), 73 (14), 70 (73). Elemental analysis done on the 2,4-dinitrophenylhydrazone

derivative; calc. for $C_{13}H_{12}N_4O_5$ (306.26): C 51.32, H 3.97, N 18.41; found: C 51.42, H 4.17, N 18.32.

Characteristics of 8-oxabicyclo[3.2.1]oct-3-en-2-one (**26**). UV (95% EtOH) λ_{max}: 221 nm ($\epsilon \cong 10000$). IR (film) v: 2960, 1690, 1380, 1250, 1125, 1055, 1030, 1010 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 7.23 (dd, 1H, ^3J = 4.5, 10.0 Hz, H-C(4)); 5.97 (dd, 1H, ^4J = 1.5 Hz, ^3J = 10.0 Hz, H-C(3)); 4.82 (dd, 1H, ^3J = 4.5, 7.0 Hz, H-C(5)); 4.58 (ddd, 1H, ^4J = 1.5 Hz, ^3J = 1.5, 8.5 Hz, H-C(1)); 2.36 (dddd, 1H, ^3J = 2.5, 8.5, 11.0 Hz, ^2J = 12.5 Hz, H_{exo}-C(6)); 2.11 (dddd, 1H, ^3J = 5.0, 7.0, 11.9 Hz, ^2J = 12.0 Hz, H_{exo}-C(6)); 1.83 (ddd, 1H, ^3J = 2.5, 9.5 Hz, ^2J = 12.0 Hz, H_{endo}-C(6)); 1.82 (ddd, 1H, ^3J = 1.5, 5.0, 9.5 Hz, ^2J = 12.5 Hz, H_{endo}-C(7)). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C: 197.1 (s); 152.9 (d, ^1J(C,H) = 165 Hz); 125.8 (d, ^1J(C,H) = 170 Hz); 81.4, 73.1 (2d, ^1J(C,H) = 160 Hz); 27.9 (t, ^1J(C,H) = 135 Hz); 24.3 (t, ^1J(C,H) = 140 Hz). MS (CI, NH_3) m/z: 126 (M^+ + 2, 24), 125 (M^+ + 1, 13), 124 (M^+, 81), 123 (M^+ - 1, 11), 120 (47), 115 (10), 97 (45), 96 (87), 95 (38), 94 (34), 93 (21), 91 (39), 81 (100).

Characteristics of 8-oxabicyclo[3.2.1]heptan-2-one (**38**). Colourless oil. IR (film) v: 2980, 2890, 1730, 1635, 1555, 1470, 1450, 1290, 1260, 1240, 1125, 1190, 1145, 1070, 1045, 1020, 990, 905, 880, 830, 790, 695 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 4.57 (m, 1H, H-C(5)); 4.24 (dd, 1H, J = 3.0, 5.0 Hz); 2.33, 2.24, 2.12, 1.86-1.67 (m, 8H, H_2C(3), H_2C(4), H_2C(6), H_2C(7)). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C: 207.7 (s); 82.0 (d, ^1J(C,H) = 160 Hz); 74.0 (d, ^1J(C,H) = 150 Hz); 31.7 (t, ^1J(C,H) = 125 Hz); 31.1, 28.3, 27.7 (3t, ^1J(C,H) = 130 Hz). MS (CI, NH_3) m/z: 144 (M^+ + 18, 60), 127 (M^+ + 1, 16), 126 (M^+, 100), 115 (6), 109 (6), 108 (14), 99 (4), 98 (61), 83 (11), 81 (15), 79 (7), 71 (4), 70 (14). Elemental analysis done on the 2,4-dinitrophenylhydrazone derivative; calc. for $C_{13}H_{14}N_4O_5$ (306.28): C 50.98, H 4.61, N 18.29; found: C 51.02, H 4.67, N 18.22.

Characteristics of 8-oxabicyclo[3.2.1]octan-3-one (**39**). Colourless oil. IR ($CDCl_3$) v: 2980, 2890, 1720, 1470, 1350, 1300, 1265, 1200, 1140, 1070, 1000, 980, 870, 830 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 4.96 (m, 2H, H-C(1), H-C(5)); 2.68 (br. d, 2H, ^2J = 16.5 Hz, H_{exo}-C(2), H_{exo}-C(4)); 2.26 (d, 2H, ^2J = 16.5 Hz, H_{endo}-C(2), H_{endo}-C(4)); 2.05 (m, 2H, H_{exo}-C(6), H_{exo}-C(7)); 1.72 (m, 2H, H_{endo}-C(6), H_{endo}-C(7)). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C: 207.3 (s); 74.8 (d, ^1J(C,H) = 150 Hz); 49.7, 29.4 (2t, ^1J(C,H) = 130 Hz). MS (CI, NH_3) m/z: 127 (M^+ + 1, 10), 126 (M^+, 60), 98 (23), 97 (19), 95 (15), 84 (28), 83 (36), 82 (11), 81 (25), 79 (14), 71 (25), 70 (100). Elemental analysis done on the 2,4-dinitrophenylhydrazone derivative; calc. for $C_{13}H_{14}N_4O_5$ (306.28): C 50.98, H 4.61, N 18.29; found: C 51.17, H 4.64, N 18.16.

Characteristics of 6-chloro-8-oxabicyclo[3.2.1]oct-6-en-2-one (**40**). Colourless oil. IR (film) v: 3100, 2960-2930, 2870, 1765, 1730, 1610, 1445, 1410, 1270, 1245-1235, 1185, 1155, 1090, 1060, 1010. 950, 940, 885, 870, 800, 750, 670 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 6.12 (d, 1H, ^3J = 2.0 Hz, H-C(7)); 4.74 (br.d, 1H, ^3J = 5.0 Hz, H-C(5)); 4.59 (dd, 1H, ^3J = 1.0, 2.0 Hz, H-C(1)); 2.76 (ddd, 1H, ^3J = 8.0, 9.0 Hz, ^2J = 17.0 Hz, H_{endo}-C(3)); 2.50 (ddd, 1H, ^3J = 2.0, 9.0 Hz, ^2J = 17.0 Hz, H_{exo}-C(3)); 2.20 (dddd, 1H, ^3J = 2.0. 5.0, 8.0. 9.0 Hz, ^2J = 14.0 Hz, H_{exo}-C(4)); 2.00 (dddd, 1H, ^3J = 1.0, 2.0, 9.0 Hz, ^2J = 14.0 Hz, H_{endo}-C(4)). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C: 200.6 (s); 138.1 (s); 123.9 (d, ^1J(C,H) = 180 Hz); 86.5 (d, ^1J(C,H) = 165 Hz); 81.4 (d, ^1J(C,H) = 160 Hz); 32.2, 23.4 (2t, ^1J(C,H) = 130 Hz). MS (CI, NH_3) m/z: 160 (M^+ + 2, 12), 158 (M^+, 4), 115 (4), 104 (33), 103 (4), 102 (100), 81 (5), 75 (4), 73 (9), 71 (5). Elemental analysis done on the 2,4-dinitrophenylhydrazone derivative; calc. for $C_{13}H_{11}ClN_4O_5$ (338.66): C 46.10, H 3.27, N 16.54; found: C 46.30, H 3.38, N 16.67.

Characteristics of 6-chloro-8-oxabicyclo[3.2.1]oct-6-en-3-one (**41**). Colourless oil. IR ($CDCl_3$): 3095, 2960, 1720, 1610, 1400, 1320, 1290, 1250, 1180, 1125, 1085, 1050, 1015, 970, 945, 930, 870, 850, 790, 680 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 6.14 (d, 1H, ^3J = 2.0 Hz, H-C(7)); 5.05 (ddd, 1H, ^4J = 1.0 Hz, ^3J = 2.0, 5.0 Hz, H-C(1)); 4.76 (dd, 1H, ^4J = 1.0, ^3J = 5.0 Hz); 2.75 (dd, 1H, ^3J = 5.0 Hz, ^2J = 16.5 Hz, H_{exo}-C(2)); 2.71 (dd, 1H, ^3J = 5.0 Hz, ^2J = 16.5 Hz, H_{exo}-C(4)); 2.56 (br.d, 1H, ^2J = 16.5 Hz, H_{endo}-C(4)); 2.33 (br.d. 1 H, ^2J = 16.5 Hz, H_{endo}-C(2)). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C: 203.6 (s); 136.4 (s); 127.6 (d, ^1J(C,H) = 180 Hz); 79.2, 77.7 (2d, ^1J(C,H) = 165 Hz); 45.2, 4.47 (2t, ^1J(C,H) = 130 Hz). MS (CI, NH_3) m/z: 123 (M^+ + 2. 4), 121 (M^+, 7), 97 (14), 95 (13), 85 (31), 83 (45), 71 (50), 70 (16). 69 (48), 57 (100), 56 (15), 55 (62). Elemental analysis done on the 2,4-dinitrophenylhydrazone derivative; calc. for $C_{13}H_{11}ClN_4O_5$ (338.66): C 46.10, H 3.27, N 16.54; found: C 45.97, H 3.18, N 16.47.

Characteristics of 7-chloro-8-oxabicyclo[3.2.1]oct-6-en-2-one (**42**). Colourless oil. IR ($CDCl_3$) ν: 2960, 2250, 1730, 1610, 1450, 1410, 1275, 1180, 1090, 1050, 1015, 850, 810 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 6.26 (d, ^3J = 2.0 Hz, H-C(6)); 5.02 (dd, ^3J = 2.0, 4.5 Hz, H-C(5)); 2.96 (m, 1H); 2.50 (m, 2H, H-C(3), H-C(4)); 1.86 (m, 1H). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C: 200.1 (s); 128.8 (d, ^1J(C,H) = 180 Hz); 87.7 (d, ^1J(C,H) = 165 Hz); 80.2 (d, ^1J(C,H) = 160 Hz); 32.5, 26.7 (2t, ^1J(C,H) = 130 Hz). MS (CI, NH_3) m/z: 160 (M^+ + 2, 4), 158 (M^+, 13), 116 (8), 115 (10), 104 (35), 103 (7), 102 (100), 95 (7), 88 (7), 84 (6), 81 (7), 75 (6), 73 (12). Elemental analysis done on the 2,4-dinitrophenylhydrazone derivative; calc. for $C_{13}H_{11}ClN_4O_5$ (338.66): C 46.10, H 3.27, N 16.54; found: C 46.20, H 3.47, N 16.44.

6-*exo*-Benzeneselenenyl-7-chloro-8-oxabicyclo[3.2.1]octan-2-one (**44**). A solution of **25** (1.08 g, 8.70 mmol) in CH_2Cl_2 (10 mL) was cooled to 0°C. A solution of PhSeCl (1.70 g, ~97%, ~8.70 mmol) in CH_2Cl_2 (20 mL) was added dropwise under stirring. The cooling bath was taken away. At the end of the reaction (2-3 h, TLC control, silica gel, light petroleum/ EtOAc 7:3) the solvent was distilled off under reduced pressure and the resulting yellow oil was purified by flash chromatography (light petroleum/EtOAc 95:5), yielding 2.64 g, (96%), pale yellow crystals, m.p. 38-41°C. IR (KBr) ν: 3060, 2950, 1730, 1575, 1480, 1440, 1415, 1210, 1185, 1050, 1020, 945, 890, 810, 740, 690 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 7.64 (m, 2H, Ph); 7.35 (m, 3H, Ph); 4.55 (dd, 1H, ^3J = 1.5, 5.0 Hz, H-C(5)); 4.45 (dd, 1H, ^3J = 5.0, 7.5 Hz, H-C(7)); 4.36 (d, 1H, ^3J = 7.5 Hz, H-C(1)); 3.69 (dd, 1H, ^3J = 1.5, 5.0 Hz, H-C(6)); 2.62-2.53 (m, 2H, $H_2C(3)$); 2.36-2.21 (m, 1H, H_{exo}-C(4)); 2.00 (m, 1H, H_{endo}-C(4)). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C: 200.9 (s); 134.9 (d, ^1J(C,H) = 165 Hz); 129.5, 128.7 (2d, ^1J(C,H) = 160 Hz); 85.5 (d, ^1J(C,H) = 165 Hz); 82.4 (d, ^1J(C,H) = 160 Hz); 60.5 (d, ^1J(C,H) = 165 Hz); 49.7 (d, ^1J(C,H) = 150 Hz); 33.2, 30.9 (2t, ^1J(C,H) = 130 Hz). MS (CI, NH_3) m/z: 318 (2), 316 (4), 123 (8), 115 (3), 95 (12), 82 (3), 81 (100), 78 (14), 77 (15), 76 (3), 75 (6), 74 (3). Anal. calc. for $C_{13}H_{13}ClO_2Se$ (315.66): C 49.46, H 4.15, Cl 11.23; found: C 49.47, H 4.17, Cl 11.20.

6-*exo*-Benzeneselenenyl-7-bromo-8-oxabicyclo[3.2.1]octan-2-one (**46**). A solution of **25** (41 mg, 0.32 mmol) in $CHCl_3$ (2 mL) was cooled to -10°C. A solution of PhSeBr (80 mg, 0.32 mmol) in $CHCl_3$ (2 mL) was added dropwise. At the end of the reaction (30 min, TLC control, light petroleum /EtOAc 7:3) the solvent was distilled off under reduced pressure and the residue was crystallized from light petroleum/Et_2O to obtain 192 mg of brown crystals. Another crystallization afforded 55 mg (47%), colourless crystals, m.p. 65-67°C. IR (KBr) ν: 2940, 2930, 1720, 1470, 1420, 1230, 1210, 1150, 1020, 940, 920, 885, 750, 700 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 7.45 (m, 2H, Ph); 7.00 (m, 3H, Ph); 4.17 (dd, 1H, ^3J = 4.5, 1.5 Hz, H-C(5)); 4.12 (d, 1H, ^3J = 7.0 Hz, H-C(1)); 3.97 (dd, 1H, ^3J = 5.0, 7.0 Hz, H-C(7)); 3.38 (dd, 1H, ^3J = 1.5, 5.0 Hz, H-C(6)); 2.12-2.06 (m, 2H, $H_2C(3)$); 1.48 (m, 1H, H_{exo}-C(4)); 1.02 (m, 1H, H_{endo}-C(4)). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C: 201.7 (s); 135.2 (d, ^1J(C,H) = 170 Hz), 135.1 (s), 129.7 (d, ^1J(C,H) = 160 Hz); 129.5, 85.7, 82.6 (3d, ^1J(C,H) = 160 Hz); 49.9 (d, ^1J(C,H) = 150 Hz); 48.1 (d, ^1J(C,H) = 165 Hz); 33.1, 31.0 (2d, ^1J(C,H) = 130 Hz). MS (CI, NH_3) m/z: 362 (M^+ + 2, 4), 360 (M^+, 6), 314 (4), 157 (5), 124 (10), 123 (23), 117 (5), 115 (4), 96 (6), 95 (18), 93 (4), 82 (10), 81 (100), 78 (18), 77 (27), 74 (4). Anal. calc. for $C_{13}H_{13}BrO_2Se$ (360.12): C 43.35, H 3.64, found: C 43.27, H 3.72.

7-*endo*-Chloro-6-*exo*-(2',4'-dinitrobenzenesulfenyl)-8-oxabicyclo[3.2.1]octan-2-one (**48**). A solution of 2,4-dinitrobenzenesulfenyl chloride (85 mg, 0.36 mmol) in CH_3CN (1 mL), was added dropwise to a solution of **25** (45 mg, 0.36 mmol) stirred at 25°C. After 2 days at 25°C, the mixture was filtered (washing with CH_2Cl_2), concentrated under reduced pressure and crystallized from Et_2O to obtain 76 mg (58%), yellow crystals, m.p. 145-146°C. IR (KBr) ν: 3110, 2960, 1730, 1590, 1515, 1340, 1300, 1250, 1050, 1020, 920, 830, 750, 730 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 9.12 (d, 1H, J = 2.0 Hz), 8.45 (dd, 1H, J = 2.0, 9.0 Hz), 7.76 (d, 1H, J = 9.0 Hz, Harom.); 4.60 (d, 1H, ^3J = 7.0 Hz, H-C(1)); 4.58 (d, 1H, ^3J = 4.0 Hz, H-C(5)); 4.48 (dd, 1H, ^3J = 4.0, 7.0 Hz, H-C(7)); 4.02 (d, 1H, ^3J = 4.0 Hz, H-C(6)); 2.76 (m, 2H, $H_2C(3)$); 2.51 (m, 1H, H_{exo}-C(4)); 2.26 (m, 1H, H_{endo}-C(4)). ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C: 206.2 (s); 130.2, 128.5, 122.2 (3d, ^1J(C,H) = 170 Hz); 86.0 (d, ^1J(C,H) = 165 Hz); 82.6 (d, ^1J(C,H) = 170 Hz); 59.8 (d, ^1J(C,H) = 150 Hz), 34.1, 31.1 (2t, ^1J(C,H) = 130 Hz). MS (CI, NH_3) m/z: 161 (1), 159 (M^+ - $(NO_2)_2C_6H_3S$, 4), 123 (13), 102 (5), 96 (4), 95 (16), 85 (4), 82 (6), 81 (100), 79 (4), 77 (6), 75 (7). Anal. calc. for $C_{13}H_{11}ClN_2O_6S$ (358.76): C 43.52, H 3.09, N 7.81; found: C 43.55, H 3.13, N 7.85.

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