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Synthesis and NMR Spectroscopic Analysis of a Conformationally Constrained Selenolactone

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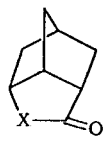
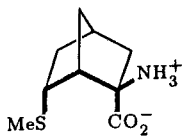
Conformationally constrained selenolactone **1b** was synthesized by intramolecular cyclization of an unsaturated selenocarboxylic acid. The structure of selenolactone **1b** and complete assignment of its ^{1}H NMR spectrum were established by 2D ^{1}H-{^{77}Se} HMQC and COSY NMR spectroscopic methods.

INTRODUCTION

Thiolactone **1a** [1-3] is an invaluable precursor to conformationally constrained derivatives [4] including con-



1a, X = S
b, X = Se



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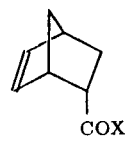

3a, X=OH
b, X=SH
c, X=SeH

formationally constrained methionine **2** [5], the methionine moiety imbedded in this structure is emboldened. Such compounds have proven important in testing the concept of 'orbital steering' and neighboring group participation on oxidation [6,7]. The key idea is that the relatively rigid carbon framework ensures that a 6-endo-thio moiety and a 2-endo-substituent are close to each other favoring direct interaction, including bond formation. However, a 2-exo-substituent is precluded from such interaction and bond formation. In view of the importance of selenium in biological systems [8], studies on the selenium compounds corresponding to the sulfur compounds were warranted. Consequently, the synthesis and NMR spectroscopic structure studies of selenolactone **1b** were undertaken. Thiolactone **1a** is stereospecifically synthesized by intramolecular cyclization of thioacid **3b** obtained from bicyclo [2.2.1] hept-5-ene 2-endo-carboxylic acid **3a**. A comparable route for synthesizing selenolactone **1b** appeared reasonable. Nevertheless, addition of selenocarboxylic acids to alkenes was unknown in contrast to the many examples of both intra- and intermolecular addition of thioacids. This paper presents the synthesis of selenolactone **1b** by cyclization of selenoacid **3a** as well as the structural characterization of **1b**.

RESULTS AND DISCUSSION

Diels-Alder reaction of cyclopentadiene and acrylic acid provides a ready source of 5-norbornene 2-endo-carboxylic acid **3a**. Treatment with thionyl chloride gave the corresponding known acid chloride. Reaction of this acid chloride with sodium hydrogen selenide, generated by treatment of selenium metal with sodium borohydride in methanol [9], followed by acidification resulted in the formation of selenoactone **1b**. After distillation and sublimation, **1b** was obtained as a white solid in 67% yield. Apparently the intermediary selenoacid **3c** underwent intramolecular cyclization. This reaction is the first report of the addition of a selenoacid to an alkene. The structure of selenolactone **1b** was determined by NMR spectroscopic analysis as outlined below.

The ^{1}H and ^{77}Se NMR spectra of **1b** are shown in Figure 1a and b, respectively. The spectroscopic assignments are based on two-dimensional ^{1}H-{^{77}Se} HMQC [10] spectrum shown in Figure 1c and COSY spectrum shown in Figure 2. To assist in the spectroscopic interpretation, the geometry of selenolactone **1** was calculated using the SYBYL force field [11]. There is very little distortion of the norbornyl ring [12] in the structure of minimum energy. Consequently, the ^{1}H,^{1}H-coupling constant ranges reported for norbornanes should be applicable here [13]. The labeling

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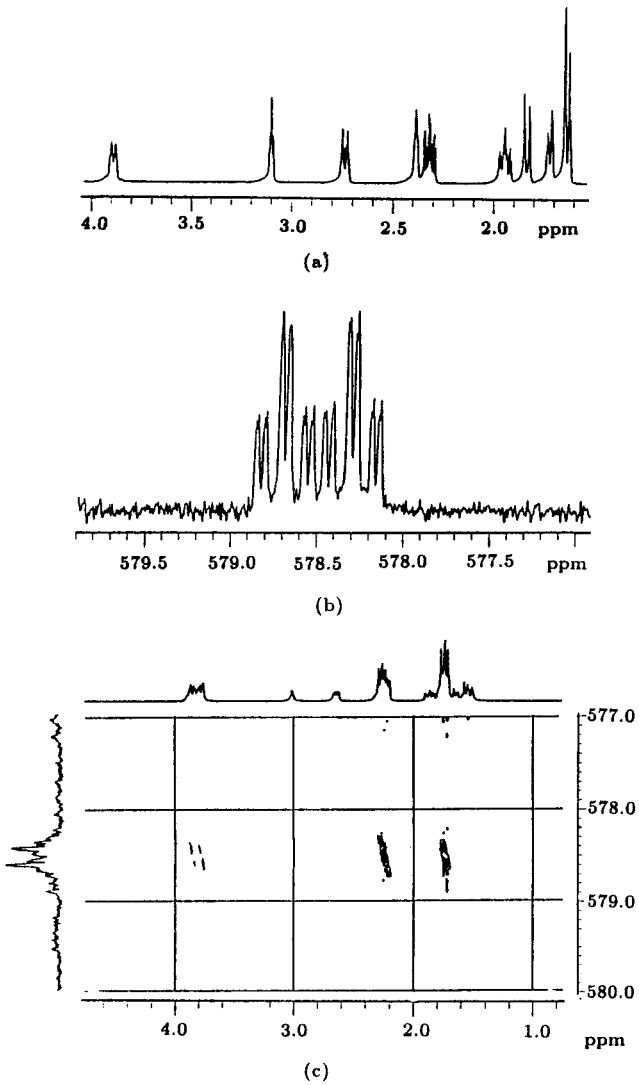

Figure 1. (a) ^{1}H NMR spectrum, (b) ^{77}Se NMR spectrum and (c) 2D ^{1}H-{^{77}Se} HMQC spectrum of selenolactone **1b**.

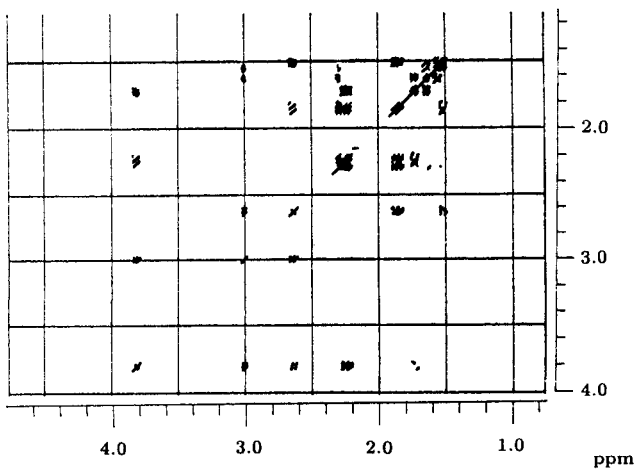

Figure 2. COSY spectrum of selenolactone **1b**.

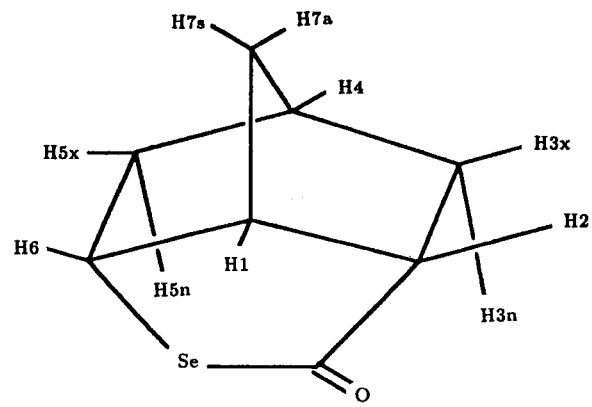

Figure 3. Labeling of the hydrogen atoms in selenolactone **1b**.

of the hydrogen atoms is shown in Figure 3. The assignments are shown in Table 1 and the basis for their assignment is presented below.

The signal at δ3.88 ppm, based on its chemical shift, is assigned to H6. This assignment is confirmed by the two dimensional ^{1}H-{^{77}Se} HMQC spectrum which shows correlation between the resonances centered at 3.88, 2.31 and 1.82 ppm with ^{77}Se. Furthermore, the largest scalar coupling constant is between ^{77}Se and the ^{1}H, giving rise to the signal at 3.88 [$^{2}J(^{1}\mathrm{H},^{77}\mathrm{Se})$ = 29.8 Hz] as expected for a two bond, as opposed to three bond, coupling. There are three hydrogens three bonds away from ^{77}Se. Two of these are coupled with ^{77}Se but one is not. The dihedral angle Se-C6-C1-H1 calculated using SYBYL is 84°. Consequently, it is suggested that the coupling constant between ^{77}Se and H1 is close to zero. Thus, the signals due to the H5 protons are at 2.31 and 1.82 ppm which have $^{3}J(^{1}\mathrm{H},\ ^{77}\mathrm{Se})$ = 3.8 and 10.7 Hz, respectively. Since this is the first report of an angular dependence on ^{1}H-^{77}Se coupling constants, it is important to confirm this interpretation. Inspection of the COSY spectrum reveals that the protons resonating at 2.31 and 1.82 ppm are strongly coupled with each other as expected for geminal protons, supporting their assignment as H5 protons.

With the signal at 3.88 ppm unequivocally assigned to H6, the COSY spectrum facilitates further assigments. The resonance at 3.88 ppm correlates with those at 3.09, 2.31 and 1.82 ppm. Furthermore, there is also a weak correlation with the signal at 2.72 ppm. The resonances at 2.31 and 1.82 ppm have been assigned to the H5 protons. Consequently, that at 3.09 ppm is assigned to H1. The small coupling constant that gives rise to the weak correlation between the resonances at 3.88 and 2.72 ppm is ascribed to a long-range W-coupling between H6 and H2.

The COSY spectrum shows that H1, centered at 3.09 ppm, correlates with the signals at 3.88, 2.72, 1.71 and 1.62 ppm. Furthermore, the resonances at

Table 1. Analysis of the ^{1}H NMR spectrum[a] of selenolactone **1b**.

δ (ppm)	Assignment	Coupling Constant	J (Hz)	Coupling Constant	J (Hz)
3.88 [b]	H6	$J_{1,2}$	4.6	$J_{2,6}$	2.6
3.09	H1	$J_{2,3n}$	1.6	$J_{5n,6}$	2.2
2.72	H2	$J_{2,3x}$	11.9	$J_{5x,6}$	10.5
2.37	H4	$J_{3n,3x}$	12.4	$J_{1,7a}$	1.5
2.31	H5x	$J_{1,4}$	1.0	$J_{4,7a}$	1.6
1.93	H3x	$J_{3x,4}$	4.1	$J_{5n,7a}$	2.5
1.82	H5n	$J_{3x,5x}$	3.2	$J_{1,7s}$	1.4
1.71	H7a	$J_{4,5x}$	3.9	$J_{4,7s}$	1.5
1.62 [c]	H7s	$J_{5n,5x}$	13.2	$J_{7a,7s}$	10.4
1.62 [c]	H3n	$J_{1,6}$	4.4		

[a] See Figure 1 for ^{1}H NMR spectrum. [b] J (^{1}H, ^{77}Se) = 29.8 Hz.

[c] These absorptions overlap rending determination of the chemical shifts imprecise.

1.62 and 1.71 ppm are strongly coupled to each other (J= 10.4 Hz). These results confirm the assignment of the signal at 2.72 ppm to H2 and suggests that the absorbances at 1.62 and 1.71 ppm are due to the H7 protons.

Inspection of the COSY spectrum further shows that the peak at 2.72 ppm, assigned to H2, is correlated with those at 3.88, 3.09, 1.93 and 1.62 ppm. Since the signals at 3.88 and 3.09 ppm have already been assigned, the resonances centered at 1.93 and 1.62 ppm must be due to H3x and H3n.

The only unassigned absorption, thus far, is that at 2.37 ppm which must be due to H4. Furthermore, the correlation of this signal with those assigned to H3 and H5 in the COSY spectrum confirms this assignment. Once H4 has been assigned, it is now possible to distinguish the exo and endo hydrogens at C3 and C5. The dihedral angle between the bridgehead hydrogen and an adjacent exo hydrogen is small but nears 90° for an adjacent endo hydrogen. Consequently, for exo hydrogens the coupling constant with the bridgehead hydrogen is substantially larger than that for endo hydrogens. Thus, in selenolactone **1b**, $J_{1,2x}$ = 4.6 Hz and $J_{1,6x}$ = 4.4 Hz fall in the expected range for exo-hydrogen coupling constants with the adjacent bridgehead hydrogen [13]. Since the H4 resonance show good correlation with those at 1.93 and 2.31 ppm in the COSY spectrum, these signals are due to H3x and H5x, respectively. Therefore, resonances at 1.62 and 1.82 ppm are due to H3n and H5n, respectively. This is confirmed by the measured coupling constants: $J_{3x,4}$ = 4.1 Hz and $J_{4,5x}$ = 3.9 Hz which are in the exo hydrogen range as well as $J_{3n,4}$ = 0 Hz and $J_{4,5n}$ = 0 Hz which are in the endo hydrogen range [13]. The assignment of H_{7a} and H_{7s} was obtained in the following way. The COSY spectrum shows a long range (four bond W-coupling) between H_{7s} (1.71 ppm) and H_{3n} (1.62 ppm) as well as H_{7a} (1.71 ppm) and H_{5n} (1.82 ppm). Such long range scalar coupling of 3-4 Hz is well-known in norbornyl derivatives.

CONCLUSIONS

Selenolactone **1b** has been prepared by a new method for making selenolactones and its structure is established by 2D ^{1}H-{^{77}Se} HMQC and COSY NMR spectroscopic methods.

EXPERIMENTAL

Synthesis of Selenolactone 1b

To a suspension of powdered elemental selenium (0.60 g, 7.6 mmol) in dry degassed methanol (15 mL), sodium borohydride (0.320 g, 8.4 mmol) was added over 2-3 hrs with stirring under an argon atmosphere. A vigorous reaction started immediately and a red colored solution was obtained. After completion of the addition, the solution was colorless. To this solution of sodium hydrogen selenide 5-norbornene 2-endo-carboxylic acid chloride (1.18 g, 7.6 mmol) was added over a 10 min period. A white precipitate formed. After stirring overnight at room temperature, water (~10 mL) was added and the pH of the solution was adjusted to 4-6 by the addition of dilute sulfuric acid. Argon was bubbled through the solution for 30 min and then it was extracted with ethyl ether (4 × 50 mL). The combined organic extracts were washed successively with water (2 × 25 mL), saturated aqueous sodium bicarbonate solution (2 × 30 mL) and again water (2 × 30 mL) and then dried over anhydrous sodium sulfate. The mixture was filtered and concentrated on a rotary evaporator to a yellow oil which was distilled under oil pump pressure and then sublimed to afford a white solid (1.02 g, 67% yield): mp 99-101°C; IR (neat) 2955, 2866, 1712 (C = O), 1466 cm^{-1}; ^{1}H NMR (400 MHz,

$CDCl_3$) see Figure 1a and Table 1; MS *m/z* 204 (26), 202 (100), 200 (67), 199 (19), 198 (25), 196 (2.3).

Calcd for $C_8H_{10}OSe$: C, 47.76; H, 4.98. Found: C, 48.13, H, 5.06.

NMR Spectroscopy

All NMR spectra were taken on an Bruker AMX400 pulsed Fourier transform NMR spectrometer and processed using the X32 computer on the spectrometer. The ^1H frequency was centered at 400.13 MHz and the ^{77}Se at 76.355 MHz. The ^1H NMR spectra of a 1.9M solution of selenolactone **1b** were referenced relative to the internal lock solvent C^2HCl_3 (7.24 ppm) and the ^{77}Se NMR spectrum was referenced relative to a 60% (v/v) external standard of dimethyl selenide in C^2HCl_3 (76.31145 MHz).

The ^1H NMR spectrum was acquired using 32 transients, a spectral window of 5000 Hz, 16 K data points, a 4 μs pulse and no recycle delay. The digital resolution was $\pm$ 0.3 Hz. The ^{77}Se NMR spectrum was run using 1024 transients, a spectral window of 2000 Hz, 8 K data points and a recycle delay of 1 s. The DQF-COSY spectrum was run in a phase sensitive mode using 16 transients and spectral windows of 2500 Hz in both $\omega 1$ and $\omega 2$ dimensions. 2 K points were used for 512 experiments and the spectrum was processed by a 1K by 1K matrix. The two-dimensional ^1H-$\{^{77}Se\}$ HMQC spectrum was performed as described in [10]. In the two dimensional ^1H-$\{^{77}Se\}$HMQC spectrum, a spectral window of 2000 Hz and 4 K data points for the $\omega 2$ dimension and a 2000 Hz spectral window and 512 experiments for the $\omega 1$ dimension were used. An inverse probe was utilized for all experiments, configured such that the inner coil was used for the direct detection of the proton and the indirect detection of selenium and the outer coil for the direct detection of selenium. 90°pulses were determined to be 7 μs for selenium and 8 μs for the proton. The two-dimensional spectra were acquired without spinning to reduce the amount of t_1 spectrometer noise.

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