289 (1.81), 268 (0.78), 246 (2.29), 2.38 (3.07); ^{1}H NMR (400 MHz, acetone-d_6) 3.05 (s, 3 H, CH_3), 7.24 (d, 1 H, $J_{4,3}$ = 5.1 Hz, H4), 7.42 (d, 1 H, $J_{3,4}$ = 5.1 Hz, H3), 7.96 (d, 1 H, $J_{7,6}$ = 7.8 Hz, H7), 8.14 (d, 1 H, $J_{2,1}$ = 7.5 Hz, H2), 8.20 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H1), 8.22 (d, 1 H, $J_{10,9}$ = 9.2 Hz, H10), 8.31 (d, 1 H, $J_{9,10}$ = 9.2 Hz, H9), 8.45 (d, 1 H, $J_{6,7}$ = 7.8 Hz, H6), 8.37 (s, 1 H, H5) ppm; mass spectrum (rel intensity), m/z 240 (100, M^+), 239 (67, M - H), 120 (18, M^{2+}). Anal. Calcd for $C_{19}H_{12}$: C, 94.96; H, 5.04. Found: C, 95.18; H, 4.82.

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New Agents for the Selective Reduction of the Carbon-Carbon Double Bond of α,β-Unsaturated Carbonyl Compounds

Yutaka Nishiyama,* Masanori Yoshida, Shigeo Ohkawa, and Sawako Hamanaka*

Department of Applied Chemistry, Faculty of Engineering, Kansai University, Suita, Osaka 564, Japan

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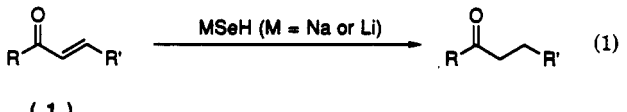
There is increasing interest in the chemistry of organoselenium compounds, and much effort is being devoted to synthesizing new selenium compounds and applying them to organic synthesis.[1] Among such compounds, the alkali metal salts of hydrogen selenide, which can be readily prepared in situ by the reaction of elemental selenium and an appropriate reducing agent (e.g., Li,[2] Na,[2] $NaBH_4$,[3] $LiBEt_3H$,[4] and $NaBEt_3H$[5]), have frequently been used as reagents for introducing of selenium into various organic compounds. However, the utilization of these salts as reducing agents has, so far, been limited to the reduction of organic disulfides and organic thiosulfates[6] and to the reductive dehalogenation of *vic*-dihaloalkanes.[7]

We therefore set out to evaluate the alkali metal salts of hydrogen selenide as reagents for the reduction of various organic functional groups. Here we show that sodium hydrogen selenide (NaSeH) and lithium hydrogen selenide (LiSeH) can be used for the selective reduction of the olefinic linkage of α,β-unsaturated carbonyl compounds (eq 1).[8]



(1)

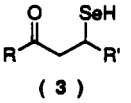
(1) (2)

The results of the reduction of various α,β-unsaturated carbonyl compounds by NaSeH (generated in situ by the reaction of elemental selenium with $NaBH_4$ in ethanol) are shown in Table I. The reduction of 4-phenyl-3-buten-2-one (**1a**) by treatment with a slight excess (1.5 equiv) of NaSeH provided 4-phenylbutan-2-one (**2a**) in 84% yield (entry 5). Under the reaction conditions employed, overreduced products (e.g., alcohols) were not formed (entries 1-5). Decreasing the amount of NaSeH (from 1.5 to 1.0 or 1.2 equiv) or lowering the reaction temperature (from 50 to 25 °C) led to a decrease in the yield of **2a** (entries 1-4). During the reduction of compounds **1d** and **1e**, chloro and methoxy groups were unaffected (entries 8 and 9). The olefinic carbon-carbon double bond of 4-(2-furyl)-3-buten-2-one (**1f**) and 4-(2-thienyl)-3-buten-2-one (**1g**) underwent reduction without affecting the furyl and thienyl groups (entries 10 and 11). α,β-Unsaturated ketones like 3-undecene-2-one (**1h**) and 1-phenyl-3-buten-1-one (**1i**), which possess no aromatic β-substituent, were also reduced by NaSeH in good yields (entries 12 and 13). In the case of dihydrocarvone (**1j**), which possesses both isolated and conjugated carbon-carbon double bonds, the conjugated double bond was reduced selectively (entry 14). The carbon-carbon double bonds of the α,β-unsaturated ester (**1k**) and the α,β-unsaturated dicarboxylic acid ester (**1l**) were also reduced selectively (entries 15 and 16). Unfortunately, however, reduction of the carbon-carbon double bond of the α,β-unsaturated carboxylic acid (**1m**) did not occur to any great extent and, at best, only a small quantity (<10%) of the saturated acid **2m** was produced.

The effectiveness of NaSeH as a reducing agent was compared with that of LiSeH, which was generated in situ by the reaction of Se and $LiEt_3BH$ in the presence of water. The α,β-unsaturated carbonyl compounds **1a**, **1h**, **1i**, and **1j** served as the substrates. Reductions with LiSeH proceeded smoothly and gave the corresponding ketones in fair to good yields (entries 1-4, Table II). Unlike reductions with NaSeH, it was necessary to use only a stoichiometric amount of LiSeH. The α,β-unsaturated carboxylic acid (**1m**) was reduced by LiSeH to the corresponding saturated acid in 57% yield (entry 5, Table II), whereas, as noted above, when NaSeH was the reducing agent, the yield was less than 10%.

To permit a better comparison at the two reagents, NaSeH was also generated in situ in a manner similar to that used to generate LiSeH, i.e., by the reaction of Se, $NaBEt_3H$, and H_2O. Treatment of **1m** with NaSeH prepared in this manner (1.0 equiv) gave **2m** in only 5% yield. Thus, the nature of the cation of the salt does have a significant influence on the extent of reduction. However, the reasons why this is so are not clear.

Although the details of the mechanism remain to be elucidated, it is probable that the reductions proceed through the Micheal adduct **3**.[12,13]



(3)

(1) For example, see: (a) Liotta, D., Ed. *Organoselenium Chemistry*; Wiley: New York, 1987. (b) Paulmier, C. *Organic Chemistry Series: Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon Press: New York, 1986; Vol. 4. (c) Patai, S., Rappoport, Z., Eds. *The Chemistry of Organic Selenium and Tellurium Compounds*; Wiley: New York, 1986; Vol. 1. (d) Patai, S., Ed. *The Chemistry of Organic Selenium and Tellurium Compounds*; Wiley: New York, 1987; Vol. 2.

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(8) The carbon-carbon double bond of α,β-unsaturated carbonyl compounds can also be selectively reduced by PhSeH/$h\nu$,[9] PhSeH/O_2,[10] and Se/CO/H_2O.[11] However, the employment of such reagents suffers from major disadvantages, e.g., the need for cumbersome manipulation, the need to use excess reducing agent (3-5 equiv), low yields, limited applicability, longer reaction times, or the need to employ CO under high (30-atm) pressure.

(9) Perkins, M. J.; Smith, B. V.; Turner, E. S. *J. Chem. Soc., Chem. Commun.* **1980**, 977.

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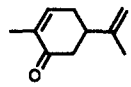
(12) Reports describing the Micheal addition of compounds bearing a Se-H group, e.g., benzeneselenol, to α,β-unsaturated carbonyl compounds have appeared. See: Miyashita, M.; Yoshikoshi, A. *Synthesis* **1980**, 664 and references cited therein.

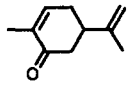
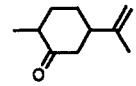
0022-3263/91/1956-6720$02.50/0

Table I. Selective Reduction of the Carbon–Carbon Double Bond of α,β-Unsaturated Carbonyl Compounds by NaSeH

entry	substrate	reagent (equiv)	temp, °C	time, h	yield,[a] %
1	$PhCH{=}CHC(O)CH_3$ (1a)	NaSeH (1.0)	25	3	40
2		NaSeH (1.0)	50	3	61
3		NaSeH (1.0)	50	24	65
4		NaSeH (1.2)	50	3	72
5		NaSeH (1.5)	50	3	84
	$PhCH{=}CHC(O)Ar$				
6	Ar = C_6H_5 (1b)	NaSeH (1.5)	50	3	88
7	Ar = p-$CH_3C_6H_4$ (1c)	NaSeH (1.5)	50	3	81
8	Ar = p-ClC_6H_4 (1d)	NaSeH (1.5)	50	3	82
9	Ar = p-$CH_3OC_6H_4$ (1e)	NaSeH (1.5)	50	3	76
	$ArCH{=}CHC(O)CH_3$				
10	Ar =  (1f)	NaSeH (1.5)	50	3	91
11	Ar =  (1g)	NaSeH (1.5)	50	3	81
12	$C_7H_{15}CH{=}CHC(O)CH_3$ (1h)	NaSeH (1.5)	50	3	78
13	$PhC(O)CH{=}CHCH_3$ (1i)	NaSeH (1.5)	50	3	94
14	 (1j)	NaSeH (1.5)	50	3	78
15	$PhCH{=}CHCOOC_2H_5$ (1k)	NaSeH (1.5)	80	15	90
16	$C_2H_5COOCH{=}CHCOOC_2H_5$ (1l)	NaSeH (1.5)	50	3	80

[a] Isolated yields based on the α,β-unsaturated carbonyl compound.

Table II. Selective Reduction of the Carbon–Carbon Double Bond of α,β-Unsaturated Carbonyl Compounds by LiSeH

entry	substrate	product	yield,[a] %
1	$PhCH{=}CHC(O)CH_3$ (1a)	$PhCH_2CH_2C(O)CH_3$ (2a)	91
2	$C_7H_{15}CCH{=}CHC(O)CH_3$ (1h)	$C_7H_{15}CH_2CH_2C(O)CH_3$ (2h)	97
3	$PhC(O)CH{=}CHCH_3$ (1i)	$PhC(O)CH_2CH_2CH_3$ (2i)	95
4	 (1j)	 (2j)	72
5	PhCH=CHCOOH (1m)	$PhCH_2CH_2COOH$ (2m)	57

[a] Isolated yields.

In summary, described here is not only a new method for the selective reduction of the carbon–carbon double bond of α,β-unsaturated carbonyl compounds,[14] but also a new synthetic application of the alkali metal salts of hydrogen selenide.

Experimental Section

Instruments. ^1H NMR spectra were recorded with a JEOL JNM-PS-100 spectrometer. TMS served as the internal standard. IR spectra were recorded with a JASCO A-202. Mass spectra were recorded with either a Hitachi RMU-8A or a JEOL JMS-QH 100. Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected.

Materials. Elemental Se, $NaBH_4$, $LiBEt_3H$ (1 M solution in THF), and $NaBEt_3H$ (1 M solution in toluene) were commercially available and were used without further purification. The α,β-unsaturated ketones (**1b**,[15] **1c**,[15] **1d**,[15] **1e**,[15] **1f**,[11] **1g**,[11] and **1h**[16]) were prepared by literature methods. Other chemicals were obtained commercially and were purified, if necessary, by distillation or recrystallization.

General Procedure for the Selective Reduction of the Carbon–Carbon Double Bond of α,β-Unsaturated Carbonyl Compounds with NaSeH (Generated in Situ by the Reaction of Se and $NaBH_4$). To a solution of NaSeH[3] (prepared in situ by the reaction of elemental Se (0.24 g, 3.0 mmol) and $NaBH_4$ (0.14 g, 3.6 mmol, 20 mol % excess) in EtOH (6 mL) at 0 °C under inert atmosphere) was added an EtOH solution (2 mL) of the α,β-unsaturated carbonyl compound **1** (2 mmol). The stirred reaction mixture was warmed to 50 °C and was kept there for 3 h. The mixture was then acidified with 2 N aqueous HCl and was exposed to the air, with stirring, at room temperature. When the solution become clear, it was filtered. The filtrate was extracted with Et_2O (25 mL × 4). The combined extracts were dried over Na_2SO_4 and concentrated. Purification of the residue by column chromatography on silica gel gave the reduced products **2**. All the products were identified by comparing their ^1H NMR, IR, and mass spectra with those of authentic compounds, which either were commercially available or were prepared by independent synthesis.

General Procedure for Reductions with LiSeH (Generated in Situ by the Reaction of Se, $LiBEt_3H$, and H_2O). To a solution of LiSeH[4] (generated in situ by the reaction of elemental Se (0.16 g, 2.0 mmol) and $LiEt_3BH$ (1 M) (2.6 mL of a 1 M THF solution, 2.4 mmol, 20 mol % excess) at 0 °C under inert atmosphere) was added a THF solution (5 mL) of the α,β-unsaturated carbonyl compound **1** (2 mmol) and H_2O (2 mmol). The stirred mixture was warmed to 50 °C and was kept there for 5 h. Workup and isolation of the products was performed in the manner described above.

Reduction of 1m with NaSeH (Generated in Situ by the Reaction of Se, $NaEt_3BH$, and H_2O). To a NaSeH (2 mmol, generated in the manner described[5] at 0 °C under inert atmosphere) was added a THF (5 mL) solution of **1m** (2 mmol) and H_2O (2 mmol). The mixture was warmed, with stirring, to 50 °C and was kept there for 5 h. Workup as described above gave 3-phenylpropionic acid (**2m**) (5%) and **1m** (91%).

Registry No. **1a**, 122-57-6; **1b**, 94-41-7; **1c**, 4224-96-8; **1d**, 956-02-5; **1e**, 959-23-9; **1f**, 623-15-4; **1g**, 874-83-9; **1h**, 10522-37-9;

(13) The intermediacy of **3** (R = PhCH=CH—, R′ = Ph) has been postulated to explain the formation of 2,6-diphenyltetrahydroselenopyran-4-one during the reaction of HSe^- (or Se^{2-}) with dibenzylideneacetone. Here, cyclization, i.e., intramolecular 1,4-addition, of intermediate **3** occurred predominantly to yield 2,6-diphenyltetrahydroselenopyran-4-one. See: Lalezari, I.; Ghanbarpour, F.; Niazi, M.; Jafari-Namin, R. *J. Heterocycl. Chem.* **1974**, *11*, 469.

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Supplementary Material Available: Spectroscopic data (^{1}H NMR, IR, MS) for compounds (2 pages). Ordering information is given on any current masthead page.

Cytotoxic Five-Membered Cyclic Peroxides from a *Plakortis* Sponge

Bradley S. Davidson

Department of Chemistry, University of Hawaii at Manoa, Honolulu, Hawaii 96822

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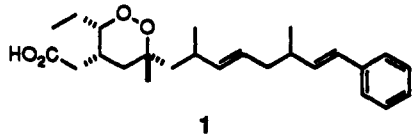
Sponges of the genus *Plakortis* have yielded a number of biosynthetically diverse natural products. For example, a *Plakortis* species was recently reported to contain the novel heteroaromatic pigments the plakinidines.[1] Other members of this genus produce interesting terpenoid[2] or polyketide[3] derived metabolites, many of which contain cyclic peroxides. Examples include plakinic acids A (1) and B (2).[3e] Although secondary metabolites containing



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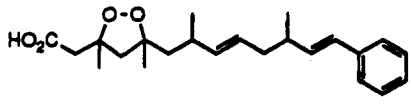
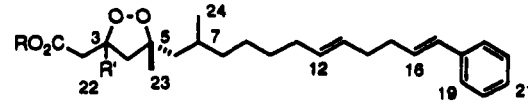


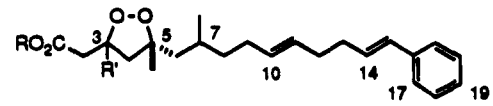
2

six-membered peroxide rings are not uncommon from marine sponges, compound 2 is the sole example of a naturally occurring five-membered-ring peroxide; furthermore, the relative stereochemistry of plakinic acid A (2) was never established. This paper now reports the structures of four new five-membered-ring peroxides, including assignment of the relative stereochemistry of the ring substituents. The compounds, isolated from a *Plakortis* sp. collected in the Fiji Islands,[4] have been named plakinic acids C (3) and D (5) and epiplakinic acids C (4) and D (6).

A methanolic extract (2.9 g concentrated), obtained by soaking homogenized, freeze-dried sponge tissue, exhibited cytotoxicity toward L1210 murine leukemia cells in vitro



3 R = H; R' = β-CH_3
3a R = CH_3; R' = β-CH_3
4 R = H; R' = α-CH_3
4a R = CH_3; R' = α-CH_3



5 R = H; R' = β-CH_3
5a R = CH_3; R' = β-CH_3
6 R = H; R' = α-CH_3
6a R = CH_3; R' = α-CH_3

with an ID_{50} of 0.26 μg/mL. The bioactive, hexane-soluble material, obtained by solvent partition, was subjected to silica gel flash chromatography. Treatment of an impure fraction with diazomethane yielded the methyl esters of plakinic acids C (3a, 11.8 mg) and D (5a, 9.2 mg) and the methyl esters of epiplakinic acids C (4a, 13.0 mg) and D (6a, 10.6 mg), as a mixture, which were then purified by normal-phase and reverse-phase HPLC.

The IR spectrum of plakinic acid C methyl ester (3a) showed an absorption at 1738 cm^{-1}, typical of a methyl ester, while the UV spectrum [249 nm (ε 12000), shoulders at 282 and 292 nm] was characteristic of a styrene unit.[5] A molecular formula of $C_{27}H_{40}O_4$ was establish on the basis of ^{13}C NMR and a high-resolution mass measurement of the M^+ ion. The ^{13}C NMR spectrum (Table I) displayed 25 distinct signals, of which two were assigned to the degenerate positions of a monosubstituted benzene ring. The ^{13}C NMR data, together with the results of ^{1}H NMR and HMQC[6] experiments, indicated the presence of 10 CH's, nine CH_2's, and four CH_3's, of which one was the methyl ester, two were singlets in the proton spectrum, and one was a doublet. The remaining quaternary carbons were assigned as an ipso aromatic carbon (137.80 ppm), an ester carbonyl (171.19 ppm), and two oxygenated quaternary carbons observed at δ 83.39 and 87.04.

A COSY experiment, along with the data presented above, allowed the construction of several partial structures, which could then be interconnected using long-range heteronuclear correlations obtained from HMBC data.[7] Key long-range correlation are as follows: H4A/H4B correlate to C2, C3, C5, C6, C22, and C23; H22 exhibits coupling to C2, C3, and C4; and H23 correlates to C4, C5, and C6. These results are consistent with a five-membered peroxide ring as reported for 2.[3e] The placement of isolated methyl group C24 at C7 was based on HMBC correlations from H6A/H6B to C24, as well as on the coupling, observed in the COSY spectrum, of H6A/H6B to H7, and H7 to H24. The terminal styrene unit was confirmed by the three-bond coupling of H16 to C18 and H17 to C19. The Δ16 double bond was assigned a trans configuration from the proton-proton coupling constant ($J_{16,17}$ = 15.5 Hz). The signals for H12 and H13 are overlapping at 200 MHz and only partially resolved at 500 MHz; however, irradiation of the H14 signal collapsed H13 to a broad

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