Pyridylseleno Group in Organic Synthesis. Part 4.[1] Oxyseleniation of Olefins using Pyridine-2-selenenyl Bromide as a Selenium Reagent and its Utilization in the Synthesis of 2-Pyridyl Vinylic Selenides

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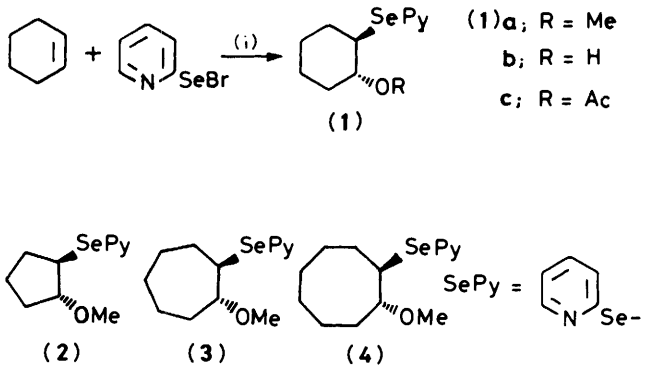
The reaction of olefins with pyridine-2-selenenyl bromide in methanol as solvent affords β-methoxyalkyl 2-pyridyl selenides (A) in good to excellent yields. This reaction also proceeds in acetic acid and aqueous tetrahydrofuran to give acetoxyseleniated and hydroxyseleniated products respectively. Oxidative elimination of (A) proceeds at room temperature, even in the case where the 2-pyridylseleno group is located at a terminal carbon, to afford methyl vinylic ethers in good yield. Treatment of (A) with lithium di-isopropylamide produces 2-pyridyl vinylic selenides (B). Deprotonation of (B) can be carried out under milder conditions than those of the corresponding phenyl vinylic selenides.

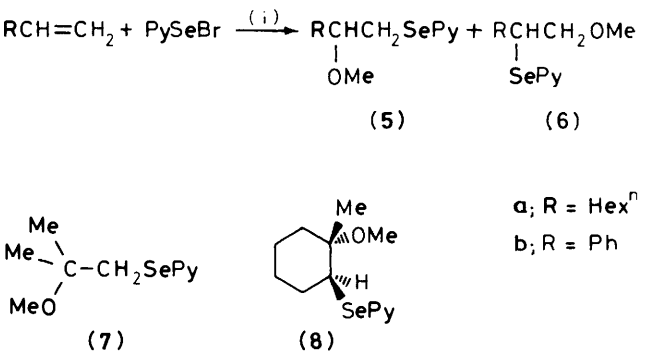
We have already reported that the 2-pyridylseleno group is a better leaving group than the phenylseleno group in selenoxide elimination reactions to form a carbon–carbon double bond in those cases where the products are terminal olefins[1a] and α,β-unsaturated carbonyl compounds.[1b,1c] As a method for introduction of the 2-pyridylseleno group into organic molecules, nucleophilic substitution of alkyl halides by sodium pyridine-2-selenate and the reaction of pyridine-2-selenenyl halides with enols or enolate anion derivatives of carbonyl compounds have been utilized. Another method would be desirable and we succeeded in an electrophilic addition of pyridine-2-selenenyl bromide to olefins in methanol affording β-methoxyalkyl 2-pyridyl selenides in good to excellent yields.

Oxidative elimination of β-methoxyalkyl phenyl selenides has been reported to proceed at room temperature to afford allylic ethers selectively.[2] In the case where the phenylseleno group is situated on the terminal carbon, elimination reaction to afford vinylic alcohol derivatives is slow and drastic conditions (~100 °C) are required.[3] It was disclosed that even in such a case the oxidative elimination of the corresponding β-methoxyalkyl 2-pyridyl selenides proceeds smoothly at ambient temperature to produce methyl vinylic ethers.

Treatment of β-methoxyalkyl 2-pyridyl selenides with lithium di-isopropylamide (LDA) induced the elimination of methanol to produce 2-pyridyl vinylic selenides. A characteristic feature of the resulting selenides is that they possess a nitrogen atom which can work as a chelating site and also reduce the electron density of the double bond. Thus, the deprotonation of these vinylic selenides could be carried out by LDA, while a stronger base such as potassium di-isopropylamide (KDA) is necessary for the deprotonation of the corresponding phenyl vinylic selenides.[4] We describe here these further findings on the characteristics of the 2-pyridylseleno group.



Scheme 1. *Reagent:* (i) ROH



Scheme 2. *Reagent:* (i) MeOH

Results and Discussion

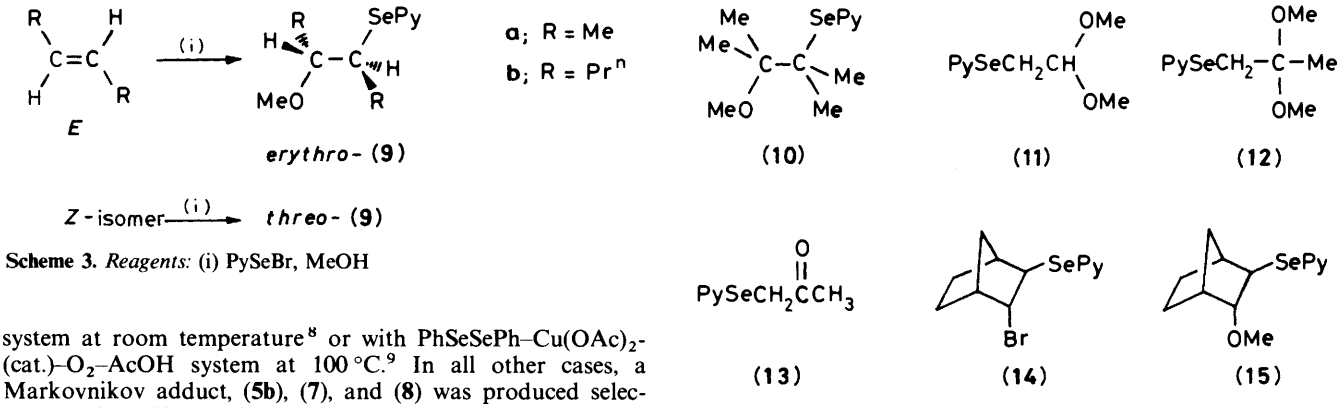
When cyclohexene was added to a suspension of pyridine-2-selenenyl bromide in methanol at ambient temperature, the precipitate disappeared immediately to afford, after the mixture had been stirred for 2 h, *trans*-2-methoxycyclohexyl 2-pyridyl selenide (**1a**) almost quantitatively. The reactions were carried out at a concentration of 0.05M of the reactant, as the yields of (**1a**) were inferior at higher concentrations due to side-reactions. This reaction was also carried out in aqueous tetrahydrofuran (THF) (THF–water 5:1) and acetic acid as the solvent at ambient temperature to give (**1b**) (24 h; 41%) and (**1c**) (3 h; 65%) respectively. From cyclic olefins of other ring size (5, 7, and 8), compounds (**2**)—(**4**) were obtained in almost quantitative yields (Scheme 1). The regioselectivity of this oxyseleniation reaction was examined using oct-1-ene, styrene, 2-methylpropene, and 1-methylcyclohexene as substrates. In the case of oct-1-ene, a mixture of regioisomers,† (**5a**) and (**6a**), was formed in the ratio of 81:19, a Markovnikov adduct, (**5a**), predominating (Scheme 2).[5–9] This isomer ratio is similar to that observed in the oxyseleniation of oct-1-ene with PhSeCN–$CuCl_2$–MeOH

† Regioselectivity of oxyseleniation reaction (*i.e.*, the rate of isomerization and/or position of equilibrium) depends on the nature of the reagents. Typical examples using oct-1-ene or dec-1-ene as the substrate are as follows: > 99 : < 1 (PhSeBr–H_2O–CF_3CH_2OH) (ref. 5); 73:27 (*N*-phenylselenophthalimide–H^+–H_2O–CH_2Cl_2) (ref. 6); a slight excess of a Markovnikov adduct ($PhSeOCOCF_3$–Et_2O) (ref. 7).

Table 1. Methoxyseleniation of various olefins[a]

Entry	Olefin	Temp. (°C)	Time (h)	Product(s) (isomer ratio)	Yield[b] (%)
1	Cyclopentene	20	2	(**2**)	88
2	Cyclopentene	−50 to +20	3	(**2**)	89
3	Cyclohexene	20	2	(**1a**)	98
4	Cycloheptene	20	2	(**3**)	89
5	Cyclo-octene	20	2	(**4**)	93
6	Oct-1-ene	20	2	(**5a**) + (**6a**) (81:19)[c]	67
7	Oct-1-ene	20	24	(**5a**) + (**6a**) (81:19)[c]	70
8	Styrene	20	2	(**5b**)	100
9	2-Methylpropene	25	2	(**7**)	100
10	1-Methylcyclohexene	20	2	(**8**)	72
11	1-Methylcyclohexene[d]	20	2	(**8**)	93
12	*trans*-But-2-ene[e]	−50 to +20	4	*erythro*-(**9a**)	76
13	*cis*-But-2-ene[e]	−50 to +20	4	*threo*-(**9a**)	100
14	*trans*-Oct-4-ene	20	24	*erythro*-(**9b**)	61
15	*trans*-Oct-4-ene	−50 to +10	5.5	*erythro*-(**9b**)	59
16	*trans*-Oct-4-ene[d]	−25 to +25	6	*erythro*-(**9b**)	70
17	*cis*-Oct-4-ene	20	2	*threo*-(**9b**)	94
18	2,3-Dimethylbut-2-ene	−50 to +20	4	(**10**)	55
19	Vinyl acetate	−50 to +20	4	(**11**)	50
20	Vinyl acetate	20	2	(**11**)	36
21	Isopropenyl acetate	−50 to +20	4	(**12**) + (**13**) (28:72)	100
22	Norbornene	20	3	(**14**) + (**15**) (69:31)	74
23	Norbornene	20	24	(**14**) + (**15**) (75:25)	71
24	Norbornene[f]	20	3	(**14**) + (**15**) (79:21)	63

[a] Carried out using olefin (4 mmol) and pyridine-2-selenenyl bromide (4 mmol) in methanol (80 ml). [b] Isolated yield by column chromatography. [c] Determined by g.l.c. analyses. [d] Carried out using olefin (1 mmol) and pyridine-2-selenenyl bromide (1 mmol) in methanol (40 ml). [e] Carried out in a pressure bottle using excess of butenes (*ca.* 12 mmol). [f] Pyridine-2-selenenyl bromide was stirred in methanol at ambient temperature for 24 h prior to the addition of norbornene.



Scheme 3. *Reagents:* (i) PySeBr, MeOH

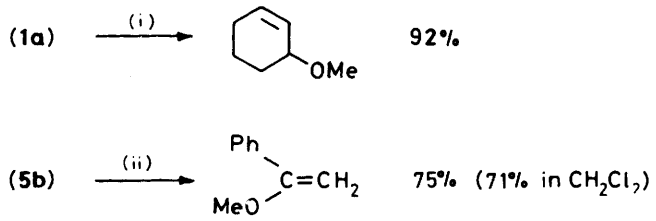
system at room temperature[8] or with PhSeSePh–Cu(OAc)$_2$-(cat.)–O_2–AcOH system at 100 °C.[9] In all other cases, a Markovnikov adduct, (**5b**), (**7**), and (**8**) was produced selectively. When this reaction was applied to *E*- and *Z*-but-2-ene and *E*- and *Z*-oct-4-ene, the addition reaction proceeded stereoselectively and -specifically to afford *erythro*-isomers from *E* olefins and *threo*-isomers from *Z* olefins (Scheme 3). The purity of the products was confirmed by g.l.c. analysis which could not detect the presence of their diastereoisomers (purity >97%). Although the 2-pyridylseleno group would stabilize a carbocationic species less effectively than the phenylseleno group, the regioselectivity and stereoselectivity described above indicate that this reaction proceeds through an episelenonium ion intermediate.

The reaction was also applied to electron-rich olefins such as tetrasubstituted olefins (2,3-dimethylbut-2-ene) and enol acetates (vinyl acetate and isopropenyl acetate) to afford compounds (**10**)—(**13**) in moderate to excellent yields. In these cases better results were obtained when the reactions were carried out at lower temperature (−50 to +20 °C). The oxyseleniated product of vinyl acetate was isolated in the form of the dimethyl acetal of 2-(2-pyridylseleno)acetaldehyde, (**11**), while a mixture of acetal (**12**) and ketone (**13**) was isolated under analogous conditions from isopropenyl acetate. The adduct of pyridine-2-selenenyl bromide to norbornene (**14**) was isolated as a major product accompanied by formation of the methoxyseleniated compound (**15**) (Table 1, entry 22). The ratio (**14**):(**15**) was not decreased by prolongation of the reaction time to 24 h (entry 23), indicating that methanolysis of (**14**) to afford (**15**) does not take place under the present reaction conditions. In almost all cases we have prepared pyridine-2-selenenyl bromide by the reaction of 2,2′-dipyridyl diselenide and bromine in methanol as the solvent at ambient temperature for 2 h. The reaction of pyridine-2-selenenyl bromide with methanol to afford other selenium reagents such as methyl pyridine-2-selenenate (PySeOMe) is, however, unlikely because the ratio of (**14**):(**15**) was not decreased when the suspension of pyridine-2-selenenyl bromide in methanol was stirred for 24 h prior to the addition of norbornene (entry 24). These results suggest that the formation of the mixture of (**14**) and (**15**) is due to a competitive attack of bromide anion and methanol on an

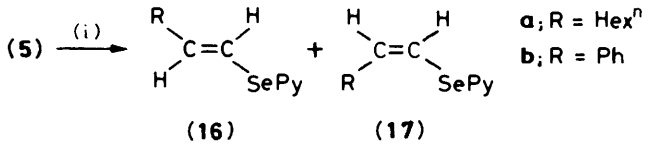
Table 2. Preparation of 2-pyridyl vinylic selenides[a]

Entry	Oxyseleniated compounds	$LiNPr_2^i$ (equiv.)	Temp. (°C)	Time (h)	Product(s)	Yield[b] (%)	(Isomer ratio)[c]
1	(**5a**)	2.5	−78	3	(**16a**) + (**17a**)	77	(39:61)
2	(**5a**)	2.5	0	0.5	(**16a**) + (**17a**)	96	(40:60)
3	(**5b**)	2.5	−78	1	(**16b**) + (**17b**)	76	(70:30)
4	(**5b**)	2.5	−78	3	(**16b**) + (**17b**)	99	(68:32)
5	(**5b**)	1.5	0	1	(**16b**) + (**17b**)	66	(67:33)
6	*erythro*-(**9b**)[d]	2.5	−78 to −65	2	(**18**)	16(74)[e]	
7	*threo*-(**9b**)[d]	2.5	−78 to −65	2	(**18**) + (**19**)	21(43)[e]	(29:71)
8	(**4**)	1.5	0	0.5	(**20**)	97	

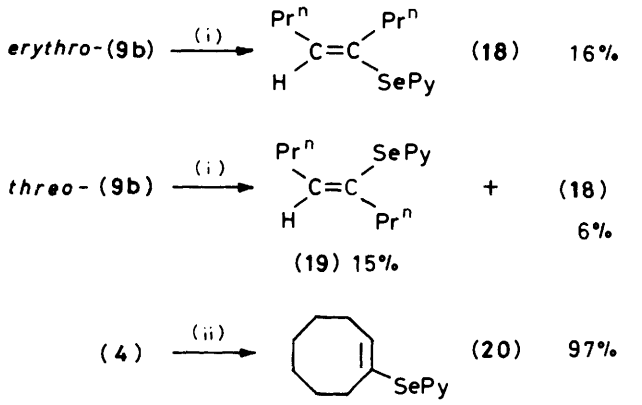
[a] THF containing a small amount of hexane (*ca.* 0.64 ml per 1 mmol of $LiNPr_2^i$) was used as solvent. Concentration of oxyseleniated compounds was *ca.* 0.15M. [b] Isolated yield by column chromatography. [c] Determined by g.l.c. and/or the integration of ^1H n.m.r. signals. [d] Carried out in the presence of HMPA (5 equiv.). [e] Recovered oxyseleniated compound (isolated by column chromatography).



Scheme 4. *Reagents:* (i) H_2O_2 (1.5 equiv.), CH_2Cl_2, −PySeOH; (ii) H_2O_2 (1.5 equiv.), THF, −PySeOH



Scheme 5. *Reagents:* (i) $LiNPr_2^i$, THF



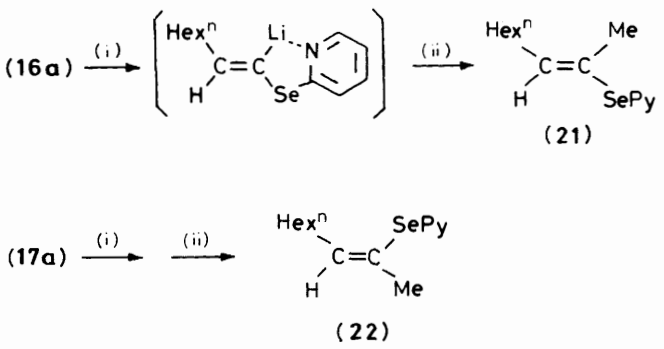
Scheme 6. *Reagents:* (i) LDA (2.5 equiv.), HMPA (5 equiv.), THF; (ii) LDA (1.5 equiv.), THF

episelenonium ion intermediate. We could not detect the products of Wagner-Meerwein rearrangement which were observed in the addition of benzeneselenenyl chloride to norbornene in methanol as solvent.[10] In the cases of other olefins the adducts of pyridine-2-selenenyl bromide would be formed, but they seem to be converted smoothly into the methoxyseleniated compounds under the reaction conditions. The results are summarized in Table 1.

Oxidative elimination of β-methoxyalkyl 2-pyridyl selenides thus prepared were briefly examined using (**1a**) and (**5b**) as substrates. On oxidation of compound (**1a**) with 1.5 equiv. of hydrogen peroxide in dichloromethane as solvent, the elimination 'away from' (attack *meta* to) the methoxy group proceeded to afford 3-methoxycyclohexene in 92% yield (Scheme 4). Its regioisomer, 1-methoxycyclohexene, was not detected by g.l.c. analysis (< 3%). When elimination 'away from' the methoxy group is not possible, as in the case of (**5b**), elimination of the hydrogen atom geminal to the methoxy group occurred to give α-methoxystyrene. The characteristic feature of this reaction is that the elimination proceeded smoothly at ambient temperature using only 1.5 equiv. of H_2O_2.[1a]* Elimination of the phenylseleninyl group with the hydrogen atom geminal to the alkoxy group required heat (100 °C).[3] Even in the oxidative elimination of analogous *o*-nitrophenyl selenides,[11] a large excess (5 equiv.) of H_2O_2 was used in refluxing dichloromethane. This difference clearly indicates that the 2-pyridylseleno group is a better leaving group than others investigated.

Treatment of compounds (**5**) with LDA at −78 to 0 °C in THF as the solvent induced an elimination of methanol to afford 2-pyridyl vinylic selenides, (**16**) and (**17**), in good to excellent yields (Scheme 5).[12] The formation of *Z*-isomer (**17a**) was favoured in the case of (**5a**), while *E*-isomer (**16b**) was the predominant product from (**5b**). The elimination of methanol from (**5a**) requires 0.5 h at 0 °C for completion (entry 2, Table 2) and is slower than the case of (**5b**) which affords the conjugated olefin and reached completion at −78 °C within 3 h (entry 4, Table 2) (See also entry 1 in Table 2). The use of 2.5 equiv. of LDA seems inevitable in this case as the methanol elimination from (**5b**) was not complete when using 1.5 equiv. of LDA at 0 °C for 1 h (entry 5, Table 2). When the reaction was applied to β-methoxy-selenides obtained from 1,2-disubstituted olefins such as *erythro*- and *threo*-(**9b**), it did not proceed under the conditions described above. However, in the presence of hexamethylphosphoric triamide (HMPA) (5 equiv.) the reaction of *erythro*-(**9b**) with 2.5 equiv. of LDA at −78 to −65 °C afforded the *E*-vinyl selenide (**18**) in an isolated yield of 16%, 74% of *erythro*-(**9b**) being recovered. Although the yield of (**18**) was unsatisfactory at this temperature, an unworkable mixture of products was obtained at higher temperature. Under similar conditions, *threo*-(**9b**) afforded a mixture of *Z* and *E* olefins, (**19**) and (**18**), in 15 and 6% yield respectively, 43% of *threo*-(**9b**) being recovered (Scheme 6). The identification of the *E* and *Z* olefins is based on the observation that in the ^1H n.m.r. spectra a

* In a selenoxide elimination of alkyl phenyl selenides 5—10 equiv. of H_2O_2 are normally used.



Scheme 7. *Reagents:* (i) $LiNPr^i_2$, THF; (ii) MeI

vinylic proton *syn* to the heteroatom (*E*-isomer) showed an absorption peak at lower magnetic field (δ 6.22) than that *anti* to the heteroatom (*Z*-isomer; δ 6.02). The selective formation of the *E*-product (**18**) from *erythro*-(**9b**) is a result of *anti* elimination of the methoxy group and the hydrogen atom. Thus, the *trans* addition of the 2-pyridylseleno and methoxy groups followed by *anti* elimination of the hydrogen atom and the methoxy group induced the inversion of the carbon framework of the double bond (*E* ⟶ *Z*). The formation of a mixture of stereoisomers from *threo*-(**9b**) is attributed to the presence of a non-stereoselective course of elimination such as an *E*lcb mechanism.* This seems to be due to a higher energy barrier of *E*2 elimination from *threo*-(**9b**) to give (**19**) than that from *erythro*-(**9b**) to give (**18**), although we have not yet clarified the reason why. The methanol elimination from (**4**) proceeded smoothly on treatment with 1.5 equiv. of LDA at 0 °C for 0.5 h to afford compound (**20**) almost quantitatively. The vinylic proton of compound (**20**) appeared at δ 6.36 in the ^{1}H n.m.r. spectrum, indicating that this proton is situated *syn* to the 2-pyridylseleno group (*vide supra*) and that the stereochemistry of the lone double bond in (**20**) is *Z*. This is the result of *syn* elimination of the hydrogen atom and the methoxy group, again due to non-concerted elimination.

Deprotonation of vinylic selenides to produce α-lithiated derivatives is a synthetically valuable reaction. It has been reported that non-substituted vinyl phenyl selenide is deprotonated with LDA in THF as solvent.[13–15] When an alkyl substituent is introduced into the β position of the vinyl group, however, deprotonation requires more vigorous conditions such as the use of a more active base, *e.g.* KDA,[4] or the use of more reactive vinylic selenides such as *m*-(trifluoromethyl)-phenyl vinyl selenide.[13] We found that oct-1-enyl 2-pyridyl selenides, (**16a**) and (**17a**), are deprotonated quite easily by the reaction with LDA in THF as the solvent at −78 °C and the resulting α-lithiated derivatives react with methyl iodide to afford the methylated products, (**21**) and (**22**), in 100 and 94% yield respectively (Scheme 7). It should be noted that the deprotonation and alkylation shown in Scheme 7 proceeded with retention of configuration. The same sequence using alk-1-enyl *m*-(trifluoromethyl)phenyl selenides has been reported to give a mixture of stereoisomers.[13]† The ready deprotonation and stereoselective alkylation of 2-pyridyl vinylic selenides described above seems to be due to the presence of a nitrogen atom which would reduce the electron density of the double bond and also chelate with a lithium atom as depicted in Scheme 7.‡

Experimental

I.r. spectra were recorded with Hitachi EPI-S2 and JASCO IR-810 spectrophotometers. ^{1}H N.m.r. spectra were obtained with JEOLCO JNM-PFT-100 and Varian EM-360 instruments on solutions in $CDCl_3$ with Me_4Si as internal standard. G.l.c. analyses were carried out with a Shimadzu 4BMPF apparatus with EGSS-X (15%)-Chromosorb W (1, 2, and 3 m) and PEG-6000 (25%)-Shimalite (3 m) columns (N_2 as carrier gas).

2,2′-Dipyridyl diselenide and pyridine-2-selenenyl bromide were prepared by the reported methods.[1c] Authentic samples of 3-methoxycyclohexene[2] and α-methoxystyrene[16] were also prepared by the reported methods. THF was dried over benzophenone ketyl and was distilled just before use. All other organic and inorganic materials were commercial products and were used without purification.

N.m.r. spectral as well as combustion analytical data of new compounds are summarized in Table 3. I.r. spectral data of representative compounds are described here in the Experimental section and are not included in the Table.

Preparation of trans-2-*Methoxycyclohexyl* 2-*Pyridyl Selenide* (**1a**). *General Procedure.*—To a solution of 2,2′-dipyridyl diselenide (0.63 g, 2.0 mmol) in methanol (72 ml) was added a solution of bromine (0.32 g, 2.0 mmol) in methanol (4 ml) and the resulting yellow suspension was stirred at ambient temperature for 2 h. By the addition of cyclohexene (0.33 g, 4.0 mmol) in methanol (4 ml) the precipitate disappeared immediately to give a pale yellow solution which was stirred at ambient temperature for 2 h. The solution was added to saturated aqueous sodium hydrogen carbonate (100 ml) and the products were extracted with chloroform (30 ml × 3). The organic layer was washed with water, dried ($MgSO_4$), and evaporated to leave a yellow oil. Column chromatography on silica gel (Wakogel C-200) with hexane–ethyl acetate (5:1) as eluant yielded compound (**1a**) (1.06 g, 98%); $\nu_{max.}$(film) 1 571, 1 088, 751, and 698 cm^{-1}.

Oxidative Elimination of Selenide (**5b**).—To a solution of compound (**5b**) (0.15 g, 0.5 mmol) in THF (4 ml) was added 30% aqueous H_2O_2 (85 mg, 0.75 mmol) in THF (1 ml) and the resulting solution was stirred at ambient temperature for 2 h. After work-up as described above, g.l.c. analysis of the organic layer using *p*-methylanisole as internal standard showed the presence of α-methoxystyrene (0.38 mmol, 75%).

Preparation of E- *and* Z-*Oct*-1-*enyl* 2-*Pyridyl Selenides* (**16a**) *and* (**17a**).—To a solution of LDA (12.5 mmol) in THF and hexane (24 + 8 ml) was added a solution of compound (**5a**) (1.5 g, 5 mmol) in THF (8 ml) at −78 °C by a syringe and the resulting solution was stirred at 0 °C under nitrogen for 0.5 h. The colour of the solution turned from pale yellow to dark red during this period and then the reaction was quenched by the addition of methanol (2 ml). After being added to saturated aqueous NH_4Cl (20 ml), the products were extracted with dichloromethane (30 ml × 5). The organic layer was washed with brine (10 ml), dried ($MgSO_4$), and analysed by g.l.c. to

* We have confirmed separately that *Z*-selenide (**19**) does not isomerize to the *E*-isomer (**18**) under the reaction conditions.

† Deprotonation and alkylation of alk-1-enyl phenyl selenides using KDA as the base have been reported to proceed with retention of configuration (ref. 4).

‡ Although such chelation was suggested to be prevented by the presence of di-isopropylamine (H. J. Reich, *J. Org. Chem.*, 1975, **40**, 2570), we feel it quite attractive to attribute the different results between *m*-(trifluoromethyl)phenylseleno and 2-pyridylseleno cases to the chelation. We are grateful to one of the referees for a valuable comment.

Table 3. Spectral and analytical data of new compounds

Compound (formula)	Chemical shift[a] δ	Found (%)/(required) C	H	N
(**1a**)	1.2—2.4 (8 H, m), 3.34 (3 H, s), 3.2—3.5 (1 H, m), 4.00 (1 H, dt, *J* 4 and 7.5 Hz), 6.96 (1 H, ddd, *J* 3,	53.6	6.4	5.3
$C_{12}H_{17}NOSe$	5, and 6 Hz), 7.3—7.4 (2 H, m), 8.39 (1 H, ddd, *J* 1, 2, and 5 Hz)	(53.3	6.3	5.2)
(**1b**)	0.8—1.9 (6 H, m), 1.9—2.7 (2 H, m), 3.1—4.0 (2 H, m), 5.31 (1 H, br s), 6.8—7.2 (1 H, m),	51.6	5.8	5.3
$C_{11}H_{15}NOSe$	7.2—7.6 (2 H, m), 8.2—8.5 (1 H, m)	(51.6	5.9	5.5)
(**1c**)	1.2—2.6 (8 H, m), 1.87 (3 H, s), 3.95 (1 H, dt, *J* 4 and 9 Hz), 4.8—5.2 (1 H, m), 6.9—7.2 (1 H, m),	52.5	5.8	4.6
$C_{13}H_{17}NO_2Se$	7.2—7.7 (2 H, m), 8.4—8.6 (1 H, m)	(52.35	5.75	4.7)
(**2**)	1.4—2.6 (6 H, m), 3.33 (3 H, s), 3.7—4.0 (1 H, m), 4.0—4.3 (1 H, m), 6.8—7.2 (1 H, m), 7.2—7.6	51.7	6.0	5.6
$C_{11}H_{15}NOSe$	(2 H, m), 8.4—8.5 (1 H, m)	(51.6	5.9	5.5)
(**3**)	1.3—2.2 (10 H, m), 3.49 (3 H, s), 3.3—3.6 (1 H, m), 4.13 (1 H, dt, *J* 4 and 7 Hz), 6.7—7.1 (1 H, m),	55.0	6.9	5.05
$C_{13}H_{19}NOSe$	7.1—7.5 (2 H, m), 8.2—8.5 (1 H, m)	(54.9	6.7	4.9)
(**4**)	1.1—2.4 (12 H, m), 3.29 (3 H, s), 3.2—3.7 (1 H, m), 4.09 (1 H, dt, *J* 3 and 6.5 Hz), 6.8—7.2 (1 H, m),	56.6	7.15	4.7
$C_{14}H_{21}NOSe$	7.2—7.5 (2 H, m), 8.3—8.5 (1 H, m)	(56.4	7.1	4.7)
(**5a**)	0.7—1.0 (3 H, m), 1.0—1.8 (10 H, m), 3.35 (3 H, s), 3.2—3.6 (3 H, m), 6.8—7.1 (1 H, m), 7.1—7.5	55.7	7.95	4.85
$C_{14}H_{23}NOSe$	(2 H, m), 8.2—8.5 (1 H, m)	(56.0	7.7	4.7)
(**6a**)[b] [+ (**5a**)]	3.30 (3 H, s), other signals overlapped with those of (**5a**)	56.2	7.6	4.7
$C_{14}H_{23}NOSe$		(56.0	7.7	4.7)
(**5b**)	3.07 (3 H, s), 3.26 (1 H, d, *J* 8 Hz), 3.29 (1 H, d, *J* 5 Hz), 4.21 (1 H, dd, *J* 5 and 8 Hz), 6.5—6.8 (1 H,	57.8	5.2	4.9
$C_{14}H_{15}NOSe$	m), 6.8—7.2 (7 H, m), 7.9—8.1 (1 H, m)	(57.5	5.2	4.8)
(**7**)	1.30 (6 H, s), 3.19 (3 H, s), 3.44 (2 H, s), 6.8—7.2 (1 H, m), 7.2—7.5 (2 H, m), 8.3—8.5 (1 H, m)	49.5	6.3	5.95
$C_{10}H_{15}NOSe$		(49.2	6.2	5.7)
(**8**)	1.28 (3 H, s), 1.4—2.0 (8 H, m), 3.24 (3 H, s), 4.27 (1 H, dd, *J* 4 and 7.5 Hz), 6.8—7.1 (1 H, m),	55.05	6.7	5.0
$C_{13}H_{19}NOSe$	7.2—7.5 (2 H, m), 8.3—8.5 (1 H, m)	(54.9	6.7	4.9)
threo-(**9a**)	1.24 (3 H, d, *J* 6 Hz), 1.51 (3 H, d, *J* 7 Hz), 3.34 (3 H, s), 3.52 (1 H, dq, *J* 3.2 and 6 Hz), 4.16 (1 H,	49.0	6.3	5.7
$C_{10}H_{15}NOSe$	dq, *J* 3.2 and 7 Hz), 6.7—7.0 (1 H, m), 7.0—7.5 (2 H, m), 8.2—8.4 (1 H, m)	(49.2	6.2	5.7)
erythro-(**9a**)	1.23 (3 H, d, *J* 6 Hz), 1.53 (3 H, d, *J* 7 Hz), 3.34 (3 H, s), 3.61 (1 H, dq, *J* 3.5 and 6 Hz), 4.13 (1 H,	49.3	6.4	5.6
$C_{10}H_{15}NOSe$	dq, *J* 3.5 and 7 Hz), 6.8—7.1 (1 H, m), 7.1—7.5 (2 H, m), 8.3—8.5 (1 H, m)	(49.2	6.2	5.7)
threo-(**9b**)	0.7—1.1 (6 H, m), 1.1—2.0 (8 H, m), 3.31 (3 H, s), 3.1—3.4 (1 H, m), 4.0—4.3 (1 H, m), 6.8—7.1	56.0	7.6	4.85
$C_{14}H_{23}NOSe$	(1 H, m), 7.2—7.4 (2 H, m), 8.2—8.4 (1 H, m)	(56.0	7.7	4.7)
erythro-(**9b**)	0.7—1.1 (6 H, m), 1.2—1.9 (8 H, m), 3.28 (3 H, s), 3.1—3.5 (1 H, m), 4.0—4.3 (1 H, m), 6.7—7.0	56.0	7.6	4.75
$C_{14}H_{23}NOSe$	(1 H, m), 7.2—7.4 (2 H, m), 8.2—8.4 (1 H, m)	(56.0	7.7	4.7)
(**10**)	1.30 (6 H, s), 1.53 (6 H, s), 3.20 (3 H, s), 7.0—7.4 (1 H, m), 7.4—7.7 (2 H, m), 8.4—8.6 (1 H, m)	52.8	6.9	5.3
$C_{12}H_{19}NOSe$		(52.9	7.0	5.1)
(**11**)	3.36 (6 H, s), 3.3—3.5 (2 H, m), 4.61 (1 H, t, *J* 6 Hz), 6.9—7.2 (1 H, m), 7.2—7.5 (2 H, m), 8.3—8.5 (1 H, m)	44.1	5.3	5.7
$C_9H_{13}NO_2Se$		(43.9	5.3	5.7)
(**12**)[c]	1.42 (3 H, s), 3.21 (6 H, s), 3.53 (2 H, s), 6.8—7.3 (1 H, m), 7.3—7.5 (2 H, m), 8.3—8.5 (1 H, m)	45.8	5.7	5.2
$C_{10}H_{15}NO_2Se$		(46.2	5.8	5.4)
(**13**)[c]	2.28 (3 H, s), 3.96 (2 H, s), 6.8—7.1 (1 H, m), 7.1—7.6 (2 H, m), 8.3—8.5 (1 H, m)	44.7	4.25	6.6
C_8H_9NOSe		(44.9	4.2	6.5)
(**14**)	0.8—2.2 (6 H, m), 2.2—2.7 (2 H, m), 3.74 (1 H, dd, *J* 3 and 4 Hz), 4.28 (1 H, br t, *J* 4 Hz), 6.9—7.2	43.85	4.4	4.3
$C_{12}H_{14}BrNSe$	(1 H, m), 7.2—7.7 (2 H, m), 8.3—8.6 (1 H, m)	(43.5	4.3	4.2)
(**15**)	0.7—2.2 (6 H, m), 2.2—2.7 (2 H, m), 3.31 (3 H, s), 3.2—3.5 (1 H, m), 3.6—4.0 (1 H, m), 6.8—7.2	54.9	6.1	5.0
$C_{13}H_{17}NOSe$	(1 H, m), 7.2—7.7 (2 H, m), 8.3—8.5 (1 H, m)	(55.3	6.1	5.0)
(**16a**)[d]	0.7—1.0 (3 H, m), 1.0—1.6 (8 H, m), 2.29 (2 H, br q, *J* 6.6 Hz), 6.24 (1 H, dt, *J* 15.4 and 6.6 Hz), 6.65	58.3	7.4	5.2
$C_{13}H_{19}NSe$	(1 H, dt, *J* 15.4 and 1.1 Hz), 7.03 (1 H, ddd, *J* 7.1, 4.9, and 1.7 Hz), 7.30 (1 H, ddd, *J* 7.8, 1.7, and 1.0 Hz), 7.47 (1 H, ddd, *J* 7.8, 7.1, and 2.0 Hz), 8.44 (1 H, ddd, *J* 4.9, 2.0, and 1.0 Hz)	(58.2	7.1	5.2)
(**17a**)[d]	0.7—1.0 (3 H, m), 1.0—1.6 (8 H, m), 2.19 (2 H, br q, *J* 7 Hz), 6.15 (1 H, dt, *J* 9.0 and 7.1 Hz), 6.87	58.3	7.4	5.0
$C_{13}H_{19}NSe$	(1 H, dt, *J* 9.0 and 1.2 Hz), 7.04 (1 H, ddd, *J* 6.9, 4.8, and 1.7 Hz), 7.33 (1 H, ddd, *J* 7.9, 1.7, and 1.0 Hz), 7.47 (1 H, ddd, *J* 7.9, 6.9, and 1.8 Hz), 8.46 (1 H, ddd, *J* 4.8, 1.8, and 1.0 Hz)	(58.2	7.1	5.2)
(**16b**)[d]	7.04 (1 H, d, *J* 15.9 Hz), 7.07 (1 H, ddd, *J* 6.8, 4.9, and 1.7 Hz), 7.2—7.6 (7 H, m), 7.57 (1 H, d, *J*	60.0	4.2	5.6
$C_{13}H_{11}NSe$	15.9 Hz) 8.49 (1 H, ddd, *J* 4.9, 2.0, and 1.0 Hz)	(60.0	4.3	5.4)
(**17b**)	7.08 (1 H, ddd, *J* 6.7, 4.9, and 1.8 Hz), 7.11 (1 H, d, *J* 10.5 Hz), 7.2—7.6 (7 H, m), 7.52 (1 H, d, *J*	60.3	4.2	5.4
$C_{13}H_{11}NSe$	10.5 Hz), 8.52 (1 H, ddd, *J* 4.9, 2.0, and 1.0 Hz)	(60.0	4.3	5.4)
(**18**)[d]	0.7—1.1 (6 H, m), 1.2—1.8 (4 H, m), 2.1—2.5 (4 H, m), 6.22 (1 H, t, *J* 7.3 Hz), 6.9—7.1 (1 H, m).	58.3	7.2	5.05
$C_{13}H_{19}NSe$	7.1—7.6 (2 H, m), 8.3—8.5 (1 H, m)	(58.2	7.1	5.2)
(**19**)[d]	0.7—1.1 (6 H, m), 1.2—1.8 (4 H, m), 2.1—2.5 (4 H, m), 6.02 (1 H, t, *J* 6.8 Hz), 6.9—7.1 (1 H, m), 7.1—7.6	58.3	7.1	5.25
$C_{13}H_{19}NSe$	(2 H, m), 8.3—8.5 (1 H, m)	(58.2	7.1	5.2)
(**20**)[d]	1.54 (8 H, br s), 2.1—2.4 (2 H, m), 2.5—2.7 (2 H, m), 6.36 (1 H, t, *J* 8.3 Hz), 7.03 (1 H, ddd, *J* 6.8,	58.35	6.5	5.4
$C_{13}H_{17}NSe$	4.9, and 1.7 Hz), 7.35 (1 H, ddd, *J* 7.9, 1.7, and 1.0 Hz), 7.48 (1 H, ddd, *J* 7.9, 6.8, and 2.0 Hz), 8.46 (1 H, ddd, *J* 4.9, 2.0, and 1.0 Hz)	(58.65	6.4	5.3)
(**21**)	0.7—1.0 (3 H, m), 1.1—1.6 (8 H, m), 1.9—2.3 (5 H, m), 6.15 (1 H, tq, *J* 6 and 1.5 Hz), 6.9—7.1	60.0	7.6	5.3
$C_{14}H_{21}NSe$	(1 H, m), 7.2—7.6 (2 H, m), 8.3—8.5 (1 H, m)	(59.6	7.5	5.0)
(**22**)	0.7—1.0 (3 H, m), 1.1—1.6 (8 H, m), 2.1—2.7 (5 H, m), 5.94 (1 H, tq, *J* 7 and 1.5 Hz), 6.9—7.1	59.2	7.9	4.8
$C_{14}H_{21}NSe$	(1 H, m), 7.2—7.5 (2 H, m), 8.3—8.5 (1 H, m)	(59.6	7.5	5.0)

[a] 60 MHz N.m.r. unless otherwise stated. [b] Identified as a mixture with (**5a**). [c] These compounds were isolated from the aqueous layer resulting from the work-up procedure. [d] 100 MHz N.m.r.

show that the isomer ratio (**16a**):(**17a**) was 40:60. After removal of the solvent, column chromatography [silica gel (200 mesh); hexane–ethyl acetate (20:1) as eluant] of the residual oil afforded a mixture of (**16a**) + (**17a**) (1.31 g, 4.8 mmol, 96%). Separation of (**16a**) and (**17a**) was carried out by column chromatography under medium pressure (2—5 kg cm^{-2}) [silica gel (230—400 mesh); hexane–ethyl acetate (40:1) as eluant] to afford pure isomer (**17a**) (0.43 g, 1.6 mmol), a mixture of (**16a**) and (**17a**) (0.60 g, 2.2 mmol), and pure (**16a**) (0.19 g, 0.7 mmol). *E*-Isomer (**16a**); $\nu_{max.}$(film) 3 060, 2 940, 2 870, 1 572, 1 557sh, 1 450, 1 411, 1 111, 950, 752, and 698 cm^{-1} *Z*-isomer (**17a**); $\nu_{max.}$ (film) 3 070, 2 940, 2 880, 1 572, 1 559sh, 1 451, 1 411, 1 111, 752, and 700 cm^{-1}.

Deprotonation and Methylation of Selenides (**16a**) *and* (**17a**).—To a solution of LDA (1 mmol) in THF and hexane (4 + 0.7 ml) was added a solution of compound (**16a**) (0.19 g, 0.7 mmol) in THF (1 ml) at −78 °C under nitrogen. After 0.5 h, methyl iodide (1 mmol) was added and the temperature of the solution was allowed to rise from −78 °C to 10 °C during 5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 ml) and the products were extracted with dichloromethane (20 ml × 5). The organic layer was washed with brine (10 ml), dried ($MgSO_4$), and evaporated under reduced pressure. Column chromatography [silica gel (200 mesh); hexane–ethyl acetate (20:1) as eluant] of the residual oil afforded pure methylation product (**21**) (0.20 g, 0.7 mmol, 100%); $\nu_{max.}$(film) 3 030, 2 945, 2 920, 2 850, 1 570, 1 550, 1 445, 1 410, 1 105, 745, and 695 cm^{-1}. The same procedure using compound (**17a**) (0.43 g, 1.6 mmol) as starting material afforded the *Z*-product (**22**) (0.424 g, 1.5 mmol, 94%); $\nu_{max.}$(film) 3 030, 2 950, 2 920, 2 850, 1 570, 1 555, 1 445, 1 415, 1 110, 750, and 695 cm^{-1}.

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