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A simple enantioselective synthesis of (*R*)- and (*S*)-1,7-dioxaspiro[5.5]undecane via intramolecular asymmetric oxyselenenylation: a new route to optically active spiroketals

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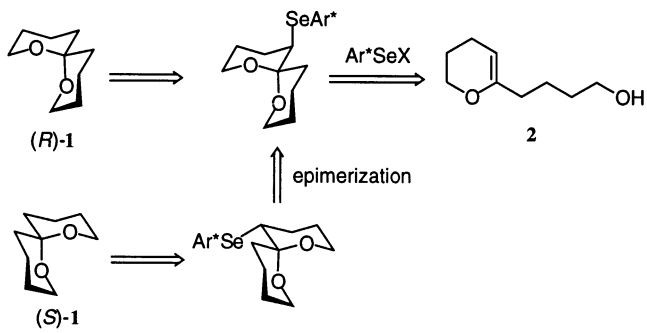
Abstract—Both enantiomers of 1,7-dioxaspiro[5.5]undecane, the major pheromone components of the olive fruit fly (*Bactrocea oleae*), have been synthesized by using a new method based on the intramolecular asymmetric oxyselenenylation of 4-(3,4-dihydro-2*H*-pyran-6-yl)butan-1-ol.

The enantioselective synthesis of chiral spiroketals has attracted considerable attention from organic chemists because they are important subunits of many biologically active natural products and the control of the stereochemistry at their spiro center is challenging.[1] For example, (*R*)- and (*S*)-1,7-dioxaspiro[5.5]undecane (**1**), the major pheromone components of the olive fruit fly (*Bactrocea oleae*),[2] have an interesting feature on bioactivity; the (*R*)-**1** is active against the male insects, whereas the (*S*)-**1** is active against the females.[3] The enantioselective synthesis of (*R*)- and (*S*)-**1**, despite their simple structure, has been achieved by only three groups[4–6] up to now because of difficulty, which is caused by the fact that **1** has no substituent able to control the stereochemistry at the spiro center and the alternative method for stereocontrol at the spiro center is hardly known. Mori and co-workers[5a,b] synthesized both enantiomers of **1** starting from (*S*)-malic acid, and the synthesis by Redlich and Francke[5c] was achieved by using D-glucose as the starting material. However, these two syntheses were based on the chiral pool (chiron) approach and therefore much labor was needed for removal of the substituents remaining after their use. On the other hand, Iwata and co-workers[5d] reported the enantioselective synthesis of (*R*)- and (*S*)-**1** via the intramolecular Michael addition reaction of a hydroxybutylated chiral vinylic sulfoxide. In their synthesis, the stereochemistry at the spiro center was effectively controlled by using a chiral sulfynyl group as the chiral auxiliary, moreover, as the stereodirecting group in the subsequent epimerization step. However, many steps were needed for the preparation of the chiral vinylic sulfoxide.

Recently, we have demonstrated that the asymmetric methoxyselenenylation of alkyl vinyl ethers affords the corresponding acetals or ketals with moderate to good diastereoselectivity.[7] This observation prompted us to undertake the study of enantioselective synthesis of spiroketals via intramolecular asymmetric oxyselenenylation[8] of hydroxyalkylated cyclic vinyl ethers. In order to demonstrate this new synthetic methodology, we planned the synthesis of (*R*)- and (*S*)-**1**, as shown in Scheme 1. The incorporated organoselenium moiety was supposed to induce the inversion of configuration at the spiro center. Therefore, both enantiomers of **1** were presumed to be synthesized in a few steps by using



Scheme 1. Retrosynthetic analysis.

Keywords: spiroketal; insect pheromone; enantioselective synthesis; 1,7-dioxaspiro[5.5]undecane; chiral diselenide; intramolecular asymmetric oxyselenenylation.

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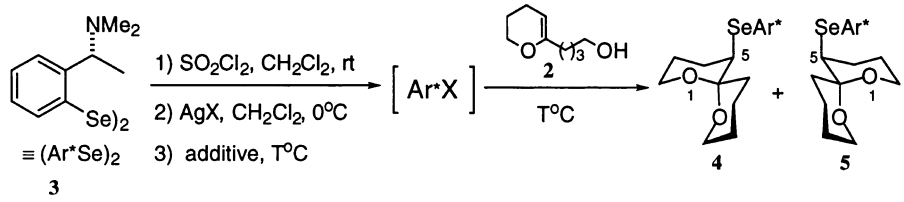


Scheme 2.

the only one chiral source. In this paper, the intramolecular asymmetric oxyselenenylation of 4-(3,4-dihydro-2*H*-pyran-6-yl)butan-1-ol (**2**) and the subsequent transformation into (*R*)- and (*S*)-**1** are described.

The starting material **2** was easily prepared according to the procedure reported in the literature,[9] and the intramolecular asymmetric oxyselenenylation of **2** using chiral diselenide **3**[10] was performed as outlined in Scheme 2. The reaction conditions and the results are summarized in Table 1.

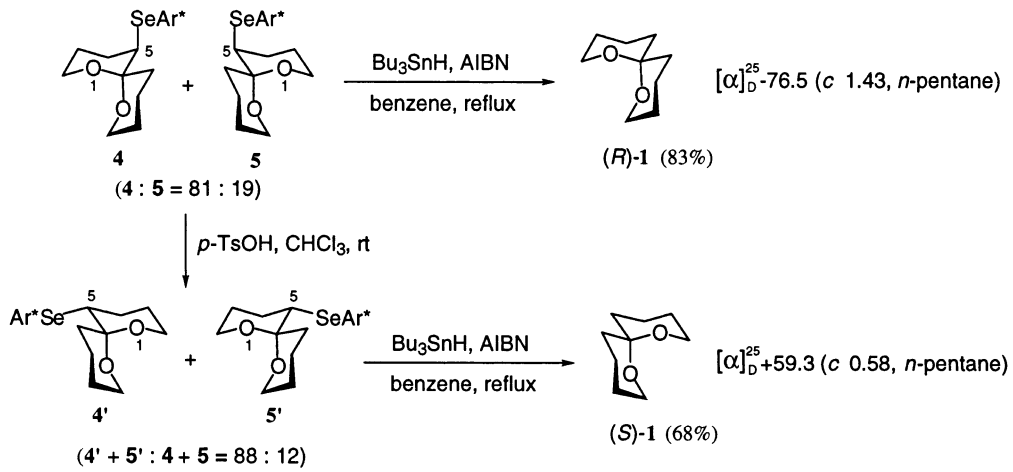
At first, the reaction of **2** with the selenenyl chloride (Ar*Cl) prepared in situ from diselenide **3** was carried out at −78°C, but it gave only a trace amount of an inseparable mixture of **4** and **5** and the other stereoisomers (entry 1). Because this failure was probably due to the low reactivity of the selenenyl chloride and the hydrogen chloride formed during the reaction, we next attempted the reaction in the presence of triethylamine (10 equiv. to **3**) (entry 2). As a result, the reaction proceeded smoothly and *anti*-selectively to give spiro ketals **4** and **5** as an inseparable mixture, which were fully characterized by ^{1}H and ^{13}C NMR, and low and high resolution mass spectroscopy. The axial orientations of the organoselenium moieties in **4** and **5** were determined by their ^{1}H NMR spectra in consideration for their most stable conformations in which each oxygen is axial with respect to the adjacent ring due to the anomeric effect.[11] 5-H in **4** and that in **5** resonated as double doublet (triplet-like) at δ 3.34 (J=3.2 Hz) and δ 3.36 (J=3.2 Hz), respectively. These signal patterns indicated that each 5-H of **4** and **5** was in an equatorial orientation and therefore the organoselenium moiety was in an axial position. The diastereomeric ratio of **4** to **5** was determined to be 67:33 by ^{1}H NMR integration of the protons of the dimethylamino group. Although it was uncertain which diastereomer was major at this stage, further transformation into **1** revealed that the major isomer was **4**.

In order to enhance the diastereoselectivity, we examined the effect of the counter anion[12] of the seleniranium cation. When the reaction was carried out using the selenenyl trifluoromethanesulfonate (Ar*OTf) at −78°C, despite the absence of triethylamine, the *anti*-addition products **4** and **5** were obtained in 76% yields with a better diastereoselectivity (entry 4). In the presence of triethylamine, considerable deterioration of the diastereoselectivity was observed[13] (entry 5). The effect of the cosolvent, which was used to make a solution of AgX, was also examined to a small extent. When THF

Table 1. Asymmetric intramolecular oxyselenenylation of dihydropyran **2**

Entry	X	Cosolvent[a] (ca. 4% v/v)	Additive	Temp. (°C)	**4**+**5**[b]	
					Yield (%)[c]	Ratio (**4**:**5**)[d]
1	Cl	–	–	−78	Trace[e]	[f]
2	Cl	–	Et_3N[g]	−78	78	67:33
3	OTf	CH_3CN	–	0	14[e]	[f]
4	OTf	CH_3CN	–	−78	76	79:21
5	OTf	CH_3CN	Et_3N[g]	−78	78	70:30
6	OTf	THF	–	−78	84	75:25
7	OTf	THF	Et_3N[g]	−78	88	70:30
8	OTs	CH_3CN	–	−78	90	76:24
9	ClO_4	CH_3CN	–	−78	44[h]	79:21
10	PF_6	CH_3CN	–	−78	86	75:25
11	BF_4	CH_3CN	–	−78	91	79:21
12	BF_4	CH_3CN	–	−95→−78	91	81:19

[a] Solvent used to make a solution of AgX.
[b] Products **4** and **5** were obtained as an inseparable mixture.
[c] Isolated yield.
[d] Determined by ^{1}H NMR integration.
[e] Contains the epimerization products.
[f] Could not be determined.
[g] 10 equiv. to diselenide **3**.
[h] The diastereomeric mixture (75:25) of the *N*-oxides corresponding to **4** and **5** was also obtained in 19% yield.



Scheme 3.

was used as the cosolvent (entry 6), the diastereoselectivity was lowered in comparison with that observed in the reaction using acetonitrile (entry 4). The deteriorative effect of triethylamine on the diastereoselectivity was shown again in entry 7. The results of entries 1–7 indicate the following trends on the reaction: (i) the more reactive selenenyl trifluoromethanesulfonate enables the reaction to proceed without triethylamine at −78°C and gives a better diastereoselectivity; (ii) triethylamine has a deteriorative effect on the diastereoselectivity;[13] and (iii) acetonitrile is a better cosolvent than THF with respect to the diastereoselectivity. On the basis of the above results, the effect of the counter anion was further examined (entries 8–11). As a result, silver tetrafluoroborate ($AgBF_4$) gave the best results with respect to the chemical yield and the diastereoselectivity. Moreover, when the reaction was carried out at −95°C, a slight enhancement of the diastereoselectivity was observed (entry 12).

Although sufficient diastereoselectivity was not attained, we next attempted the inversion of the stereochemistry at the spiro center of **4** and **5** (Scheme 3). The mixture of **4** and **5** (**4**:**5**=81:19) obtained in entry 12 was treated with 2 equiv. of *p*-toluenesulfonic acid (*p*-TsOH) in $CHCl_3$ at room temperature to give an inseparable mixture of **4′** and **5′**[14] and unreacted **4** and **5** (**4′**+**5′**:**4**+**5**=88:12,[15] **4′**:**5′**=81:19[16]). We searched the reaction conditions which brought the inversion to completion, but unfortunately the attempts were fruitless; neither the prolongation of the reaction time nor the replacement of the solvent and/or the acid were effective, and, besides, the reaction at higher reaction temperature (at 40°C in CH_3CN and reflux in MeOH) caused the epimerization not only at the spiro center but also at C-5.[17] It is thought that the sterically larger organoselenium moiety must complete the inversion at the spiro center.

Finally, a mixture of **4** and **5** (**4**:**5**=81:19) was treated with *n*-Bu_3SnH in refluxing benzene to afford (*R*)-**1** in 83% yield. On the other hand, a mixture of **4′** and **5′** containing **4** and **5** (**4′**+**5′**:**4**+**5**=88:12,[15] **4′**:**5′**=81:19[16]) gave (*S*)-**1** in 68% yield by the same treatment as described above. The spectral data (^1H and ^{13}C NMR and IR) of the synthetic (*R*)- and (*S*)-**1** were in accordance with those reported in the literature.[2,5] The specific optical rotations of the synthetic (*R*)- and (*S*)-**1** were $[\alpha]_D^{25}$ −76.5 (*c* 1.43, *n*-pentane) and $[\alpha]_D^{25}$ +59.3 (*c* 0.58, *n*-pentane), respectively. By comparison of these values with those reported in the literature,[18] the optical purities of the synthetic (*R*)- and (*S*)-**1** were estimated to be approximately 63 and 46%, respectively. These optical purities are in fair agreement with the values calculated from the diastereomeric ratios of the precursors.

In conclusion, we have accomplished a short synthesis of (*R*)- and (*S*)-1,7-dioxaspiro[5.5]undecane using the intramolecular asymmetric oxyselenenylation of 3,4-dihydro-2*H*-pyran derivative **2**. Although the optical purities of the synthetic (*R*)- and (*S*)-**1** are not so high, they could be improved by the optimization of the starting diselenide. The strategy used in the present synthesis provides a new route to optically active spiroketals.

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14. **4′** and **5′** were characterized by ^{1}H and ^{13}C NMR, and low and high resolution mass spectroscopy. In the ^{1}H NMR spectrum, the signal patterns of 5-H of **4′** and **5′** indicated that each 5-H was in an axial orientation: **4′**; 3.06 (dd, $J=4.7$, 12.7 Hz), **5′**; 3.11 (dd, $J=4.7$, 12.8 Hz).
15. The ratio was determined by ^{1}H NMR integration of 5-H.
16. In the ^{1}H NMR spectrum of the isomeric mixture (**4**, **4′**, **5**, **5′**), the signals of 5-H of **4′** and **5′** partially overlapped each other, therefore, the ratio was determined by integration of 5-H of the iodomethylates which were prepared by treatment of the mixture with an excess of iodomethane.
17. The epimerization at C-5 was suggested by a change of the diastereomeric ratio of **4′** to **5′** under these reaction conditions: the ratio of **4′** to **5′** changed from 81:19 to ca. 1:1 by exposure to these reaction conditions. It is supposed that the epimerization at C-5 proceeds via the reversible pathway of the oxyselenenylation.
18. (*R*)-**1**: lit. $[\alpha]_D^{23}$ −121.6 (*c* 0.1, *n*-pentane), 73% ee;[5a] $[\alpha]_D^{21}$ −121.0 (*c* 1.84, *n*-pentane), >99.5% ee;[5b] $[\alpha]_D^{19}$ −122.8 (*c* 3.2, *n*-pentane), >95% ee;[5c] $[\alpha]_D^{25}$ −128 (*c* 0.503, *n*-pentane);[5d] $[\alpha]_D$ −118.0 (*c* 0.2, *n*-pentane), 94.5% ee;[5e] (*S*)-**1**: lit. $[\alpha]_D^{23}$ +109.3 (*c* 0.28, *n*-pentane), 100% ee;[5a] $[\alpha]_D^{21}$ +119 (*c* 1.41, *n*-pentane), 92% ee;[5b] $[\alpha]_D^{24}$ +123 (*c* 0.234, *n*-pentane);[5d] $[\alpha]_D$ +97.0 (*c* 0.25, *n*-pentane), 80% ee;[5e] $[\alpha]_D^{22}$ +118 (*c* 0.026, *n*-pentane), 96% ee.[6b]