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Stereoselective synthesis of optically active perhydrofuro[2,3-*b*]furan derivatives

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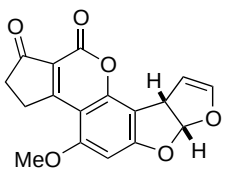
Abstract—(1*R*,5*S*)-2,8-Dioxabicyclo[3.3.0]octan-3-one and its derivatives, important subunits in various biologically active natural products, have been synthesized based on a new approach using the asymmetric oxyselenenylation of 2,3-dihydrofuran as the key step.

Furo[2,3-*b*]furan structure is encountered in various biologically active natural products, such as aflatoxins,[1] dihydroclerodin,[2,3] and norrisolide,[4] Therefore, the synthesis of such furofurans have attracted considerable attention from organic chemists, and many synthetic methods have been reported during the last decade[5]. However, the method for preparation of enantiomerically pure furo[2,3-*b*]furan derivatives is not sufficient yet. For instance, the synthesis of enantiomerically enriched (1*S*,5*R*)-2,8-dioxabicyclo[3.3.0]octan-3-one (**1**), which is considered to be a chiral building block for the synthesis of dihydroclerodin, has been reported by only two groups up to now.[6]



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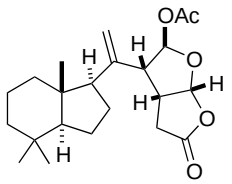
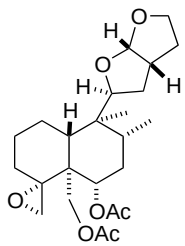
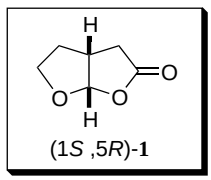


norrisolide



dihydroclerodin



Very recently, we have demonstrated that the asymmetric methoxyselenenylation of alkyl vinyl ethers affords the corresponding acetals or ketals with moderate to good diastereoselectivity.[7] For example, the reaction of 2,3-dihydrofuran (**2**) gave the *anti*-adduct in 87% yield as a 74:26 diastereomeric mixture. This observation prompted us to undertake the stereoselective synthesis of enantiomerically pure **1** using the asymmetric oxyselenenylation of **2** as the key step. Asymmetric synthesis of chiral acetals have been generally based on controlling the stereochemistry at acetal carbon by the other stereocenter(s) in the molecule because direct method of constructing chiral acetal center has not been known to date and acetals easily isomerize under acidic conditions. In contrast with the methods reported before, the absolute configuration at the acetal carbon is directly produced by asymmetric reaction in our approach outlined in Scheme 1. We thought that the asymmetric oxyselenenylation of **2** could introduce not only the asymmetry at the acetal carbon but also a seleno group available for subsequent cyclization and the use of methyl glycolate as an oxygen nucleophile gave an adduct suitable for subsequent transformations. In this paper, we describe the stereoselective synthesis of enantiomerically pure **1** by a new approach based on the asymmetric oxyselenenylation of **2**.

At first, we examined the asymmetric oxyselenenylation of **2** with methyl glycolate according to the procedure reported in our previous paper[7,8] (Scheme 2). When the reaction was carried out at −78°C, the desired *anti*-adduct **4**[9] was obtained in low yield as an inseparable

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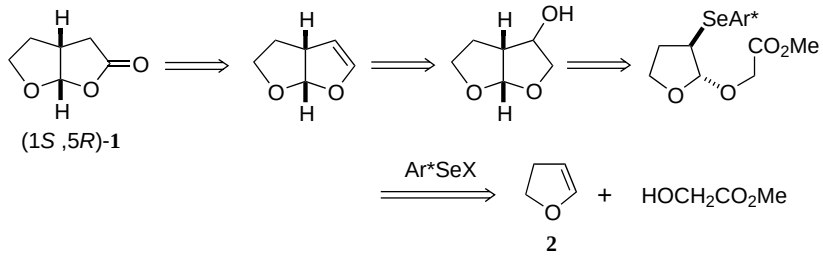
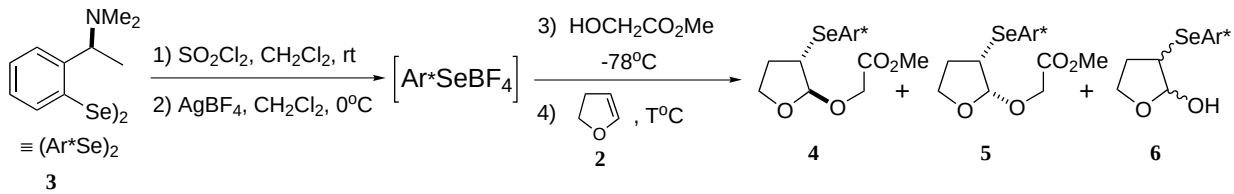


Scheme 1.

78:22 diastereomeric mixture along with a substantial amount of lactol **6**.[9,10] The absolute stereochemistry of **4** could not been determined at this stage. Because the poor yield of **4** was probably due to the low reactivity of methyl glycolate toward the seleniranium cation intermediate which was formed by the addition of Ar^*SeBF_4 to **2**, in order to improve the yield of **4**, we tried to raise the reaction temperature as shown in Table 1. Raising the reaction temperature from −78°C to −50°C gave no improvement of the yield of **4** (entry 1), however, raising to −20°C fairly improved the yield without the deterioration of the diastereomeric ratio (dr) (entry 2). When the temperature was further raised to 0°C, a slight decrease of the yield of **4** and the formation of *syn*-adduct **5**[9] was observed. The formation of **5** is thought to result from the nucleophilic attack of methyl glycolate to an open oxocarbonium cation rather than a bridged seleniranium cation. We imagined that an unreacted seleniranium cation opened to the oxocarbonium cation through an equilibrium under the reaction conditions in entry 3. This assumption was supported by the result in entry 4, and also by the results of another experiments, namely, that *trans*-adduct **4** did not isomerize to *cis*-adduct **5** under the same reaction conditions as used in entry 3 and 4. Although sufficient diastereoselectivity was not attained and **4** was obtained as an inseparable mixture of two diastereomers, we next set about the transformation of *anti*-adduct **4** to target compound **1** as shown in Scheme 3.[9]

The *anti*-adduct **4** (dr = 78:22) was half-reduced with DIBAL-H to give the corresponding aldehyde, which was subsequently subjected to a radical cyclization by treatment with Bu_3SnH and AIBN to afford *exo* alcohol **7** and *endo* alcohol **8**. *exo* Alcohol **7** could be converted to the desired **8** in two steps. Optical resolution of **8** was carried out by use of (*R*)-1-(1-naphthyl)ethyl isocyanate[11] as a resolving agent; **8** was heated with the isocyanate in benzene at 60°C to afford the corresponding carbamates **9** and **10**, which were separated by preparative TLC. The major diastereomer

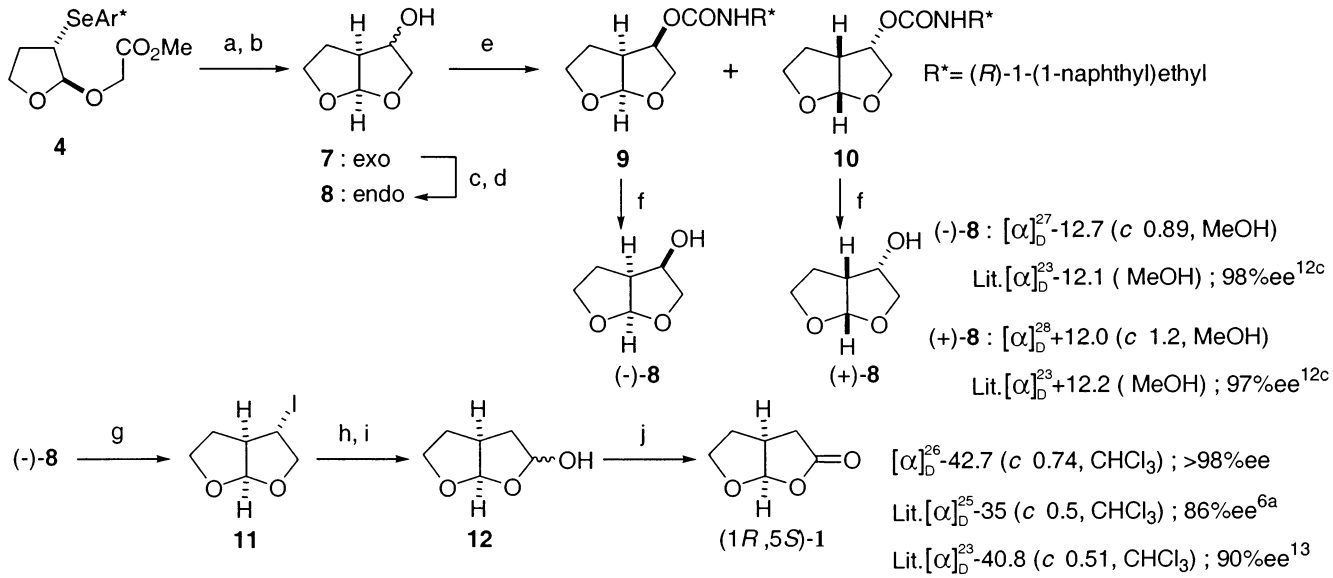


Scheme 2.

Table 1. Asymmetric oxyselenenylation of 2,3-dihydrofuran using methyl glycilate[a]

Entry	Temp. (°C)	**4** (*anti*-adducts)[b]		**5** (*syn*-adducts)[b]		**6**[c]
		Yield (%)[d]	dr[e,f,g]	Yield (%)[d]	dr[e,f,h]	Yield (%)[d]
1	−78→−50	43	78:22	0	–	52
2	−78→−20	73	78:22	0	–	14
3	−78→0	69	78:22	5	76:24	15
4[i]	0	31	69:31	21	68:32	3

[a] All reactions were performed using 6 equiv. of methyl glycolate to diselenide **3**. A solution of $AgBF_4$ in acetonitrile was used.
[b] Obtained as an inseparable mixture of two diastereomers.
[c] Obtained as an inseparable mixture of four diastereomers.
[d] Isolated yield.
[e] Diastereomeric ratio.
[f] Determined by ^1H NMR integration.
[g] The absolute stereostructure of the major diastereomer was determined to be **4** depicted in Scheme 2 by subsequent transformation to **8**.
[h] The absolute stereostructure of the major diastereomer was supposed to be **5** depicted in Scheme 2 in consideration for the mechanism of the reaction.
[i] Methyl glycolate and 2,3-dihydrofuran were successively added at 0°C.



Scheme 3. *Reagents and conditions*: (a) DIBAL-H, toluene, −78°C; (b) Bu_3SnH, AIBN, benzene, reflux, **7**: 13% from **4**, 8: 44% from **4**; (c) PCC, CH_2Cl_2, rt; (d) $NaBH_4$, EtOH, −15°C, 69% from **7**; (e) (*R*)-1-(1-naphthyl)ethyl isocyanate, *N*,*N*-dimethylaminoethanol, benzene, 60°C, **9**: 73%, **10**: 22%; (f) $LiAlH_4$, THF, rt, (−)-**8**: 86% from **9**, (+)-**8**: 78% from **10**; (g) Ph_3P, imidazole, I_2, benzene, 60°C, 87%; (h) DBU, rt ; (i) THF, 40% H_2SO_4, rt, 72% from **11**; (e) PCC, NaOAc, MS 4 Å, CH_2Cl_2, rt, 77%.

9 and minor **10** were separately treated with $LiAlH_4$ to provide optically pure (−)-**8**[12] and (+)-**8**,[12] respectively. Thus, the absolute stereochemistry of the major diastereomer obtained from the reaction in Scheme 2 was confirmed at this stage. Unfortunately, the major product (−)-**8** corresponded with (1*R*,5*S*) antipode instead of our target (1*S*,5*R*)-**1**; however, we proceeded in the transformation of (−)-**8** into (1*R*,5*S*)-**1** in order to demonstrate the synthetic route leading to optically active **1**.

(−)-**8** was converted to *exo* iodide **11**, the iodine atom of which was in the suitable orientation for controlling the regiochemistry in the next elimination step. Treatment of **11** with DBU afforded the 2,3-dihydrofuran intermediate, which was hydrated without isolation because of its volatility to provide lactol **12** as an inseparable mixture of epimers. Oxidation of **12** with PCC gave (1*R*,5*S*)-**1**,[6a,13] the enantiomeric purity of which was determined to be >98% ee by ^1H NMR analysis upon comparison with racemic **1**[14] using (*R*)-(−)-2,2,2-trifluoro-1-(anthryl)ethanol as the chiral solvating reagent.[15] It should be also mentioned that the optical purity of our synthetic (1*R*,5*S*)-**1** is higher than those reported in the literature.[6a,13]

In conclusion, we have accomplished the synthesis of enantiomerically pure (1*R*,5*S*)-**1** and presented herein a new approach to optically active perhydrofuro[2,3-*b*]-furan derivatives using the asymmetric oxyselenenylation of 2,3-dihydrofuran (**2**). Although the diastereoselectivity of the key reaction shown in Scheme 2 is not so high and the obtained (1*R*,5*S*)-**1** is the antipode of our original target, it is supposed that these problems could be solved by optimization of the starting diselenide. Further studies directed towards an improvement of the diastereoselectivity and the total synthesis of dihydroclerodin are currently underway in our laboratory.

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