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Synthetic Study on Naturally Occurring Acetylenic Spiroacetal Enol Ethers: The First Access to Optically Active 3,4-Diacetoxy-2-formylmethylene-1,6-dioxaspiro[4.5]decanes

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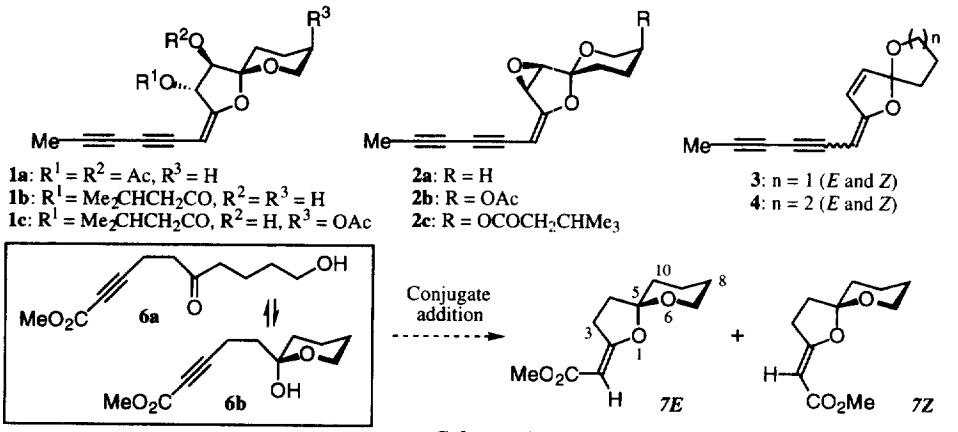
Abstract: Optically active 3,4-diacetoxy-2-formylmethylene-1,6-dioxaspiro[4.5]decanes have been synthesized from an acyclic keto-alcohol possessing an unsaturated aldehyde part *via* intramolecular conjugate addition. The C3- and C4-stereogenic centers were introduced *via* Sharpless asymmetric dihydroxylation of an acyclic conjugated ketone with modified AD-mix-α in high enantioselectivity (96% *e.e.*). This is the first access to optically active spiroacetal 2-enol ethers.

Chrysanthemum lavandulifolium Mak. and the closely related genera produce acetylenic spiroacetal enol ethers, for example, **1**-**4**.[1] Although the biological activities of **1** have not been reported, (*E*)-**3** has been reported to exhibit antifeedant, antiphlogistic, and spasmolitic activities.[2] Recently, **2c** has been reported to be a potent inhibitor against tumor promotion with TPA.[3] Therefore, synthetic approaches are required to examine the biological activities of these unique compounds. We have already reported the highly stereoselective construction of (*E*)- and (*Z*)-2-methoxycarbonylmethylene 1, 6-dioxaspiro[4.5]decanes (**7*E*** and **7*Z***) as racemic model compounds *via* intramolecular conjugate addition of **6a** and **6b** (Scheme 1).[4] In this paper, we describe the first access to optically active spiroacetal 2-enol ethers directed toward total synthesis of naturally occurring acetylenic spiroacetal enol ethers such as **1a**.



Scheme 1

According to our model study, the construction of optically active spiroacetal 2-enol ethers *via* intramolecular conjugate addition was planned, and the optically active precursor corresponding to **6a** is required. However, the first approach to introducing the required dihydroxy-stereogenic centers from L-tartaric acid as the chiral source was suspended because of the inefficiency of the protection, deprotection and carbon-chain elongation steps. Therefore, the next approach using Sharpless asymmetric dihydroxylation (AD)[5] after completion of carbon-chain elongation *via* Horner-Emmons olefination[6] was designed as follows (Scheme 2). 2-Butyne-1,4-diol was treated with sodium hydride and *t*-butyldimethylsilyl chloride (TBDMSCl) to give a

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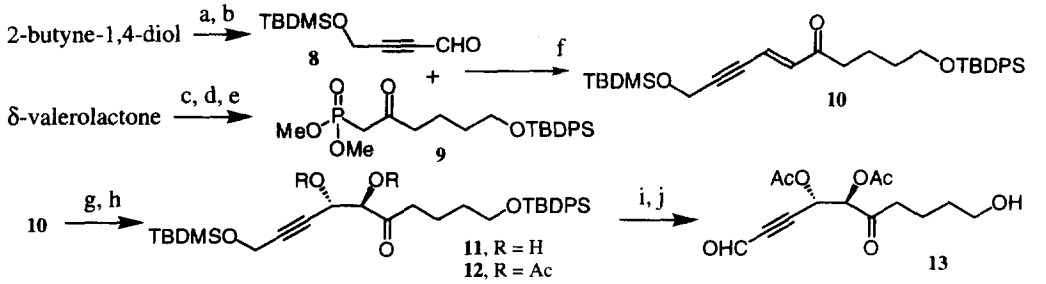
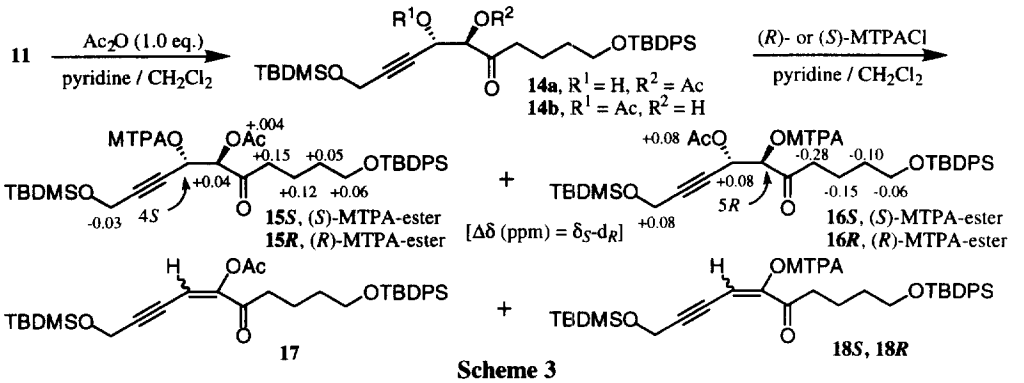
monoprotected alcohol in 81% yield. Swern oxidation of the alcohol gave unsaturated aldehyde **8**[7] in the best yield (55%) among several methods attempted because **8** is unstable and volatile. δ-Valerolactone was converted into β-ketophosphonate **9** by the following three steps: (1) lactone-ring opening with triethylamine in methanol in 83% yield, (2) protection with *t*-butyldiphenylsilyl chloride (TBDPSCl) and imidazole in 96% yield, and (3) addition of dimethyl methylphosphonate in 94% yield. Thus, the C_4-aldehyde (**8**) and the C_6-phosphonate (**9**) were prepared. The Horner-Emmons olefination[6] between **8** and **9** using potassium *t*-butoxide as the base provided the C_{10}-(*E*)-conjugated ketone (**10**) for the substrate of AD in 79% yield and in 59:1 (*E*)-selectivity. In AD of **10**, the modified AD-mix-α was used in order to accelerate the reaction and to prevent the epimerization at the α-position of ketone.[5] As the result of using the modified AD-mix-α, diol **11** was obtained in 83% yield without epimerization. While acetylation of **11** gave diacetate **12** in 91% yield, careful work-up and purification are required to prevent epimerization and β-elimination. Desilylation of **12** with hydrogen fluoride-pyridine complex and subsequent selective oxidation of propargyl alcohol with activated manganese dioxide gave the desired acyclic keto-alcohol (**13**) possessing the unsaturated aldehyde part in 66% yield in 2 steps. Instead of a methoxycarbonyl group as the electron-withdrawing group in the model compound **6a**, **13** possessing a formyl group is in equilibrium with a small amount of its hemiacetal and is considered to be the precursor of intramolecular conjugate addition for construction of optically active spiroacetal 2-enol ethers. Furthermore, the formyl group would be useful for the introduction of the diynyl part.



Scheme 2: (a) NaH, TBDMSCl / THF, 81%; (b) Swern oxid., 55%; (c) Et_3N / MeOH, 83%; (d) TBDPSCl, imidazole / DMF, 95%; (e) *n*-BuLi, $(MeO)_2P(O)CH_3$ / THF, 94%; (f) *t*-BuOK / THF, 79%, *E*:*Z* = 59:1; (g) $K_2OsO_2(OH)_4$ (1.0 mol %), $(DHQ)_2PHAL$ (1.0 mol %), $MeSO_2NH_2$ (1 eq.), K_2CO_3 (3 eq.), $NaHCO_3$ (3 eq.) / *t*-BuOH-H_2O, 83%, 96% *e.e.*; (h) Ac_2O, pyridine / CH_2Cl_2, 91%; (i) HF·pyridine / THF, 99%; (j) MnO_2 / Et_2O, 67%.

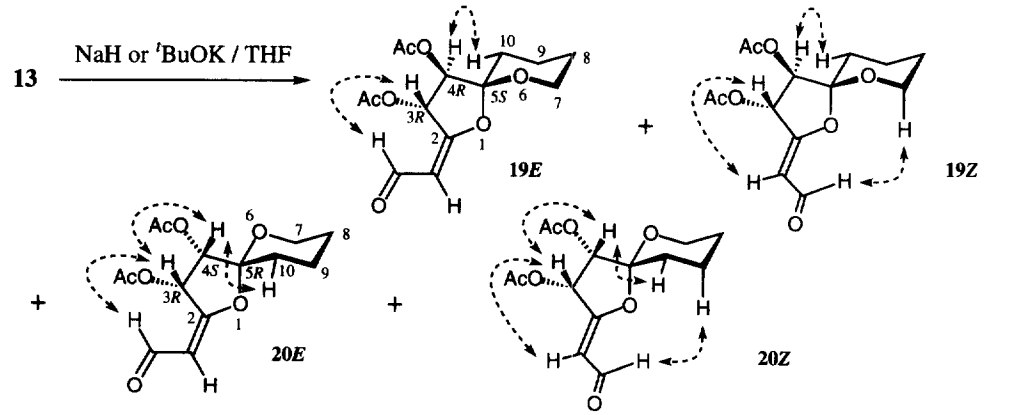
The optical purity of **11** was determined by HPLC-analysis using a chiral column.[8] Racemic **11**, which was prepared *via* osmium oxidation of **10**, appeared as two separate peaks (retention time: 11.3 and 13.6 min). The major enantiomer of chiral **11** showed the latter retention time and the optical purity was calculated to be 96% *e.e.* The absolute configuration of **11** was determined by application of the modified Mosher's method (Scheme 3).[9] Treatment of **11** with 1 eq. of acetic anhydride and pyridine gave an inseparable mixture of the corresponding monoactates (**14a**:**14b** = 1:1.6, 70%) along with unreacted **11** and a diacetate. Treatment of the mixture of **14a** and **14b** with (*R*)-MTPACl gave two pairs of an inseparable mixture, **15*S*/17** (1.6:1) and **16*S*/18*S*** (2.8:1) after separation by preparative TLC. On the other hand, treatment with (*S*)-MTPACl also gave two pairs of an inseparable mixture, **15*R*/17** (1.7:1) and **16*R*/18*R*** (1.6:1). The position of the heterodiacyl groups of **15** and **16** was confirmed from the following facts: (1) **15*S*** and **15*R*** provided β-elimination-product **17** as a single geomertic isomer in the purification process, (2) **16*S*** and **16*R*** provided β-elimination-products **18*S*** and **18*R***, respectively,[10] and (3) the chemical shifts of the acetoxymethine protons of **15** and **16** are in good agreement with those of the corresponding diacetate. The signs of Δδ (δ_S-δ_R: ppm) values of **15** and **16** were completely opposite across the stereogenic centers to be determined.[9] Therefore, the absolute configuration of **11** was determined to be (4*S*,5*R*) as predicted from the enantiofacial selectivity for *trans*-disubstituted olefins and an enyne-system,[5] and the required asymmetry for **1** was introduced.



Scheme 3

In the process of chromatographic purification of **13** on silica gel, we found that cyclization to spiroacetal 2-enol ethers proceeded slightly. Although the acidity might cause **13** to cyclize, various acidic conditions resulted in essentially no increase of the yield. Next, we examined some conditions used for cyclization of the achiral model compound **6a**.[4] While cyclization with a palladium system gave none of the desired products because of decomposition, cyclization under basic conditions (Scheme 4 and Table 1) gave four spiroacetal 2-enol ethers as two pairs of an inseparable mixture of **19*E*/19Z** and **20*E*/20Z**.

Their structures were elucidated from the ^{1}H-NMR studies including COSY and NOESY. The coupling constants between H-3 and H-4 for **19*E*** and **19Z** are 5.9 and 7.8 Hz, respectively, and are closely similar to those (7.0-7.5 Hz) of a *trans*-disubstituted type such as **1a-1c**.[1b] The geometry of the enol-part and the stereochemistry of the spiro-center (C-5) in **19*E*/19Z** are reasonably explained by the NOESY experiment. Especially, the NOESY correlations between H-4 and H-10 were also observed in the same position as that of natural products **1a-1c**.



Scheme 4: Arrows between protons indicate some important NOESY-correlations.

On the other hand, the coupling constants between H-3 and H-4 for **20*E*** and **20Z** are 0.8 and 2.0 Hz, respectively, and are close to those (2.8-3.0 Hz) of a *cis*-disubstituted type such as epoxides **2a-2c**.[1d,1e] The NOESY correlations between H-3 and H-4 also supported the *cis*-relationship. The stereochemistry of the spiro-center (C-5) was deduced to be *R* from the NOESY correlations between H-4 and H-10 as observed in **19*E*/19Z**. Therefore, the C-5 stereogenic center (the α-position of the carbonyl group) of **13** would be considered to epimerize under basic conditions before cyclization.

When NaH, KH, or ^{t}BuOK were used in anhydrous THF, the reactions gave **19** and **20** in the range of 30 to 50% yield and 1:1 to 1:2.6 ratio. Cyclizations under more weakly basic conditions, using K_2CO_3 or

$NaHCO_3$, were next examined to improve the product ratio (Table 1). When K_2CO_3 was used in anhydrous toluene in the presence of 18-crown-6, the product ratio was not improved (entry 1). However, the reaction using K_2CO_3 in the absence of 18-crown-6 gave the best result with respect to the product ratio of **19/20** (entry 2). Although the reaction using $NaHCO_3$ in anhydrous benzene (entry 3) or in anhydrous THF in the presence of 18-crown-6 (entry 4) took a long time, **19** was predominantly produced. While the *E/Z* ratio was different in entries 3 and 4, the product ratio of **19/20** was almost the same. When $NaHCO_3$ was used in aqueous heterogeneous medium, the reaction proceeded rapidly in contrast to in anhydrous solvents but the product ratio of **19/20** decreased (entry 5). From these results, the basicity due to the solubility of bases in used solvents would greatly influence the product ratio. A search for cyclization conditions to prevent or to minimize epimerization is currently under way.

Table 1. Spirocyclization of **13** under basic conditions.

Entry	Conditions Base (eq.) / Solvent / Temp. / Time	Isolated yield (%)	Product ratio **19*E*** : **19*Z*** : **20*E*** : **20*Z*** (**19** : **20**)
1	K_2CO_3 (1.0), 18-crown-6 / toluene / r.t. / 10 min	51	7.0 : 1.0 : 9.4 : 2.0 (1.0 : 1.4)
2	K_2CO_3 (1.0) / toluene / r.t. / 10 min	60	53.1 : 12.7 : 19.7 : 1.0 (3.2 : 1.0)
3	$NaHCO_3$ (1.0) / benzene / r.t. / 24 h	58	15.4 : 1.6 : 9.0 : 1.0 (1.7 : 1.0)
4	$NaHCO_3$ (1.0), 18-crown-6 / THF / r.t. / 30 h	50	8.8 : 1.7 : 5.0 : 1.0 (1.8 : 1.0)
5	$NaHCO_3$ (1.0), / benzene-H_2O (1:1) / r.t. / 20 min	68	2.0 : 1.0 : 1.9 : 1.2 (1.0 : 1.0)

Thus, the main core, (2*E*,3*R*,4*R*,5*S*)-3,4-diadetoxy-2-formylmethylene-1,6-dioxaspiro[4.5]decane (**19*E***) possessing the same absolute configuration as that of **1c**, which is considered to be an important intermediate for the total synthesis of **1c**, was first constructed *via* intramolecular conjugate addition. The introduction of the remaining diynyl group[11] is now in progress.

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7. Satisfactory spectral data (^{1}H-NMR, ^{13}C-NMR, IR, HRMS, $[\alpha]_D$) were obtained for all new compounds.
8. Column: CHIRALCEL OD® (ϕ4.6 x 250 mm), Eluent: hexane/2-propanol = 95/5, Flow rate 1.0 ml/min, Detection: UV 254 nm.
9. Kusumi, T. *J. Synth. Org. Chem. Jpn.* **1993**, *51*, 462-470 (in Japanese).
10. Although β-elimination-products **18*S*** and **18*R*** as well as **17** were obtained as single geometric isomers, respectively, the geometry was not determined by spectroscopic method.
11. From the results up to date, the diacetyl groups of **19*E*** may be converted to another protective group to prevent elimination in the process of diynyl part construction.