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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. © 1999 Elsevier Science Ltd. All rights reserved.

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 (7E and 7Z) 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.



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 olefination⁶ was designed as follows (Scheme 2). 2-Butyne-1,4-diol was treated with sodium hydride and *t*-butyldimethylsilyl chloride (TBDMSCI) to give a

0040-4039/99/\$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved. *PII*: S0040-4039(99)00579-1 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 (TBDPSCI) and imidazole in 96% yield, and (3) addition of dimethyl methylphosphonate in 94% yield. Thus, the C_4 -aldehyde (8) and the C_4 phosphonate (9) were prepared. The Horner-Emmons olefination⁶ 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)CH₃ / THF, 94%; (f) *t*-BuOK / THF, 79%, *E*:Z = 59:1; (g) K₂OsO₂(OH)₄ (1.0 mol %), (DHQ)₂PHAL (1.0 mol %), MeSO₂NH₂ (1 eq.), K₂CO₃ (3 eq.), NaHCO₃(3 eq.) / *t*-BuOH-H₂O, 83%, 96% *e.e.*; (h) Ac₂O, pyridine / CH₂Cl₂, 91%; (i) HF pyridine / THF, 99%; (j) MnO₂ / Et₂O, 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, 15S/17 (1.6:1) and 16S/18S (2.8:1) after separation by preparative TLC. On the other hand, treatment with (S)-MTPACI also gave two pairs of an inseparable mixture, 15R/17 (1.7:1) and 16R/18R (1.6:1). The position of the heterodiacyl groups of 15 and 16 was confirmed from the following facts: (1) 15S and 15R provided βelimination-product 17 as a single geometric isomer in the purification process, (2) 16S and 16R provided β elimination-products 18S and 18R, 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 $\Delta\delta$ (δ_s - δ_{p} : 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 (4S, 5R) as predicted from the enantiofacial selectivity for trans-disubstituted olefins and an enyne-system,⁵ and the required asymmetry for 1 was introduced.



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 19E/19Z and 20E/20Z.

Their structures were elucidated from the ¹H-NMR studies including COSY and NOESY. The coupling constants between H-3 and H-4 for 19E 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 19E/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 20E 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 19E/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 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

NaHCO₂, were next examined to improve the product ratio (Table 1). When K₂CO₃ 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 NaHCO₃ 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 NaHCO₃ 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. Spiro	cyclization of 13 under basic c	onditions.
E-4	Conditions	Isolated

Entry	Base (eq.) / Solvent / Temp. / Time	Isolated yield (%)	Product ratio 19E : 19Z : 20E : 20Z (19 : 20)
1	K ₂ CO 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 ₂ CO 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 ₂ O (1:1) / r.t. / 20 min	68	2.0: 1.0: 1.9:1.2 (1.0:1.0)

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Thus, the main core, (2E, 3R, 4R, 5S)-3,4-diadetoxy-2-formylmethylene-1,6-dioxaspiro[4.5]decane (19E) 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 group¹¹ is now in progress.

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- Jarosz, S.; Salanski, P.; Mach, M. *Tetrahedron* **1998**, *54*, 2583-2594. and references cited therein. Satisfactory spectral data (¹H-NMR, ¹³C-NMR, IR, HRMS, $[\alpha]_D$) were obtained for all new compounds. Column: CHIRALCEL OD[®] (ϕ 4.6 x 250 mm), Eluent: hexane/2-propanol = 95/5, Flow rate 1.0 ml/min, 7. 8.
- 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\$'s 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 **19E** may be converted to another protective group to prevent elimination in the process of divnyl part construction.