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Synthesis of Spiroacetal Enol Ethers *via* Intramolecular Conjugate Addition of Hemiacetal Alkoxides to Alkynoates

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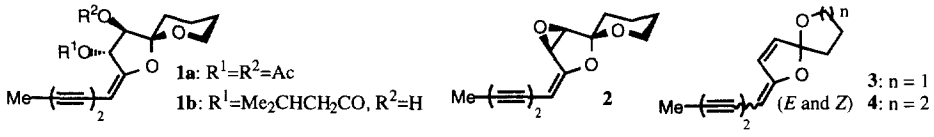
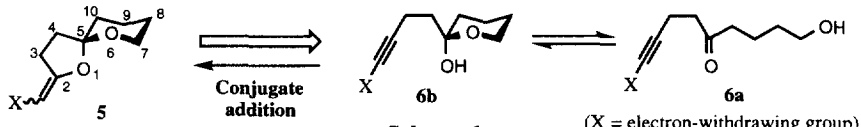
Abstract: (*E*)- and (*Z*)-2-Methoxycarbonylmethylene-1,6-dioxaspiro[4.5]decane (**12*E***, **12*Z***) have been constructed from the acyclic keto alcohol **11a** possessing an alkynoate part under the basic conditions. By the thermodynamic control, **12*E*** could be obtained in high selectivity. Under several basic and acidic conditions, **12*Z*** could be isomerized to **12*E***. Copyright © 1996 Elsevier Science Ltd

Polyacetylenic metabolites are widespread in several plant families and utilized as the chemotaxonomical markers.[1] Within the tribe *Anthemideae* of the family *Asteraceae* (= *Compositae*), the genus *Chrysanthemum* and the closely related genera produce acetylenic spiroacetal enol ethers, for example, **1**-**4**.[2] Polyacetylenes may generally play various ecological roles. Among them, (*E*)-**3** has been reported to exhibit antifeedant, antiphlogistic, and spasmolitic activities.[3] In relation to such a class of compounds, although a few syntheses of **3** and **4** have been reported, the yield and the geometrical selectivity are not always satisfactory.[4] In this paper, we describe the construction of such spiroacetal enol ethers[5] that would be useful in the total synthesis of more oxygenated natural products (**1** and **2**).

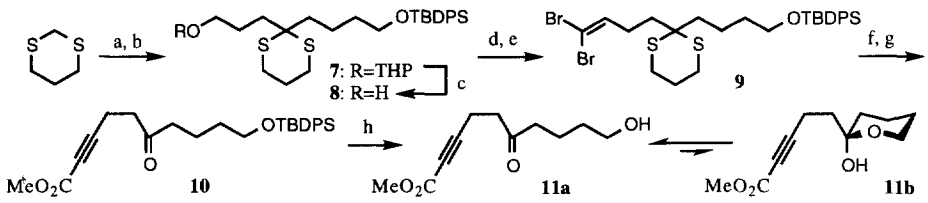


Our strategy to construct of 2-enol ether-type 1, 6-dioxaspiro[4.5]decane **5** is shown in Scheme 1. The substrate **6b** possessing both acceptor part and donor part (hemiacetal hydroxyl group) is in equilibrium with the keto alcohol **6a**. Therefore, hemiacetalization and the following conjugate addition would provide **5**.



Scheme 1

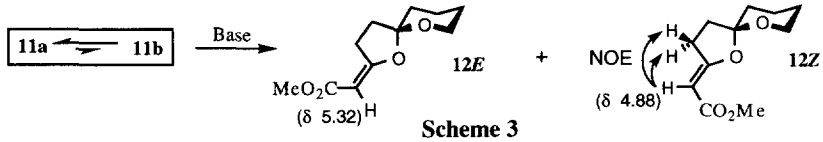
In practice, a methoxycarbonyl group was chosen as the activating group (Scheme 2). 1, 3-Dithianyl anion was successively alkylated by two requisite alkyl halides to give **7** in 84% yield (2 steps).[6] Selective deprotection of the THP group gave alcohol **8** in 96% yield, which was converted to dibromoolefin **9** in 67% yield (2 steps). The lithium acetylide, generated by the treatment of **9** with *n*-BuLi (2 eq.), was trapped by methyl chloroformate to give an alkynoate, whose dithioacetal was deprotected to give ketone **10**. Desilylation of **10** with HF-pyridine gave **11a**, the desired substrate for spirocyclization. ^{1}H-NMR (in $CDCl_3$) showed that **11a** and **11b** are an equilibrium mixture of 8:1.



(a) *n*-BuLi / THF, then $Br(CH_2)_3OTHP$, 96% (b) *n*-BuLi / THF, then $I(CH_2)_4OTBDPS$, 88% (c) PPTS / EtOH, 96% (d) DMSO, SO_3·pyr., Et_3N / CH_2Cl_2, 69% (e) CBr_4, Ph_3P / CH_2Cl_2, 97% (f) *n*-BuLi / THF, then MeO_2CCl (g) NCS, $AgNO_3$ / 10% aq. CH_3CN, 66%, 2 steps (h) HF·pyr. / CH_3CN, 94% [**11a**:**11b**=8:1]

Scheme 2

We expected that the desilylation of **10** with anhydrous TBAF in THF would directly provide spiroacetal enol ethers, **12*E*** and **12*Z***, *via* the resulting ammonium alkoxide. However, in practice, neither **12*E*** and **12*Z*** nor **11a** could be obtained, and the major product was a furan derivative **12a**.[7] Therefore, construction of **12*E*** and **12*Z*** from **11a** was carried out under basic conditions (see Scheme 3 and Table 1).



Scheme 3

Table 1. Construction of Spiroacetal Enol Ethers Under Basic Conditions

Entry	Conditions Base (eq.) / Solvent / Temp. / Time	Yield (%)	Product Ratio 12*E* : 12*Z*
1	NaH (1.0) / THF / 4 °C / 10 min	91	3 : 1[a)]
2	KH (1.0) / THF / 4 °C / 5 min	77	2 : 1[a)]
3	NaOMe (1.0) / MeOH / 4 °C - r.t. / 30 min	95	1 : 1[a)]
4	NaH (1.0) / DMSO / r. t. / 10 min	92	2.3 : 1
5	NaH (1.0) / DMF / 4 °C / 10 min	95	2.5 : 1
6	*t*-BuOK (1.0) / THF / 4 °C / 1 min	73	52 : 1
7	*t*-BuOK (1.0) / *t*-BuOH / r. t. / 5 min	97	25 : 1
8	NaH (0.1) / THF / 4 °C / 10 min	99	1.5 : 1
9	*t*-BuOK (0.1) / THF / 4 °C / 10 min	99	2 : 1
10	*t*-BuOK (0.1) / *t*-BuOH / r. t. / 10 min	96	1 : 1.2
11	Na_2CO_3 (10) / MeOH-H_2O (1:1) / r. t. / 50 min	65	1 : 2.5
12	KOH (1.0) / MeOH / r.t. / 22 h	66	1.1 : 1
13	DBU (1.0) / Toluene / reflux / 3 h	44	3 : 1

a) The ratio was detemined after chromatographic separation. The other cases were based on the integration by ^{1}H-NMR.

The structures of **12*E*** and **12*Z*** were determined by ^{1}H- and ^{13}C-NMR spectra. When the olefinic proton (δ 4.88) of **12*Z*** was irradiated, the two allylic protons were enhanced in ^{1}H-^{1}H NOE experiment. The chemical shift (δ 5.32) of the olefinic proton of **12*E*** was similar to those of naturally occurring spiroacetal enol ethers. In both stoichiometric (base, 1.0 eq., entries 1-7) and catalytic (base, 0.1 eq., entries 8-10) reactions, the reaction proceeded in high yield (73-99%). The geometrical selectivity was poor in entries 1-5 and in catalytic case (entries 8-10). When a stoichiometric amount of NaH was used, the geometrical selectivities rarely varied with the solvents (*E*:*Z*=2.3-3:1, entries 1, 4, 5). The almost same selectivity (*E*:*Z*=2:1) was obtained by using KH in THF (entry 2). By using NaOMe in MeOH, the geometrical selectivity did not appear (*E*:*Z*=1:1, entries 3). However, when a stoichiometric amount of *t*-BuOK in THF or *t*-BuOH was used, the (*E*)-selectivity increased greatly (*E*:*Z*=25-52:1, entries 6, 7). In contrast to the stoichiometric reactions with *t*-BuOK, the catalytic reactions resulted in the poor selectivity (*E*:*Z*=2:1, entries 9; *E*:*Z*=1:1.2, entries 10). The geometrical

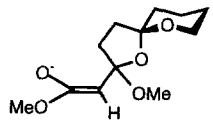
selectivity was also decreased by using a catalytic amount of NaH (*E*:Z=1.5:1, entry 8). Although the several basic conditions to synthesize monocyclic 2-methylene-tetrahydrofurans from alkynoate alcohols[5e] also gave **12*E*** and **12*Z***, the yields were moderate (44-66%) and the geometrical selectivities were poor (see entries 11-13). Such conditions induced the side reaction to form the furan **12a** and unknown products. In contrast to the other conditions, **12*Z*** was preferentially produced by using Na_2CO_3 in MeOH-H_2O (*E*:Z=1:2.5, entry 11).

In order to reveal the mechanism of this spirocyclization, the isomerization process was studied (Table 2). When **12*Z*** was treated with NaH in THF, no isomerization to **12*E*** was observed, and only decomposed products were detected on analytical TLC (entry 1). By treatment with NaOMe in MeOH, **12*Z*** isomerized to **12*E*** over a period of 4 days (*E*:Z=7:1, entry 2). In the reaction starting from **12*E***, **12*Z*** was clearly detected under the same conditions (*E*:Z=15:1, entry 3). It is considered that **12*E*** and **12*Z*** are in equilibrium *via* the enolate anion **13**. By using *t*-BuOK in THF, **12*Z*** underwent isomerization rapidly to **12*E*** to record the highest ratio (*E*:Z=30-70:1, entries 4, 5). In these cases, the dienolate anion **14** would be formed as an intermediate. Therefore, it would be considered that the spirocyclization using NaOMe or *t*-BuOK as the base (entries 3, 6 and 7 in Table 1) would involve the isomerization process. Furthermore, it was proved that the isomerization proceeds smoothly also under acidic conditions (entry 6). The oxonium ion intermediate **15** would be generated by protonation of the enol. Such isomerizations would be based on the thermodynamic satbility of **12*E*** and **12*Z***. The electronic repulsion between the lone pair electrons of the ring oxygen and that of the ester carbonyl oxygen might reduce the thermodynamic stability of **12*Z***.[8] The MOPAC calculation (with PM3 parameter using CAChe™ work system) were carried out for the both *s-cic* and *s-trans* conformers of **12*E*** and **12*Z***. The result shows that the energy (= heat of formation) of **12*E*** (*s-cic*: -167.007 kcal/mol) is lower than that of **12*Z*** (*s-cic*: -164.963 kcal/mol). It supports that **12*E*** is thermodynamically more stable than **12*Z***. The mole fraction, calculated from ΔE (=2.044 kcal/mol) at 298 K, is *E*:Z = *ca.* 30:1. This is approximately identical with the experimental ratio (see entry 7 in Table 1 and entry 4 in Table 2).

Table 2. Isomerization of Spiroacetal Enol Ethers

Entry	SM	Conditions[a] Base or Acid (eq.) / Solvent / Temp. / Time	Product Ratio[b] 12*E* : 12*Z*
1	**12*Z***	NaH (1.0) / THF / r.t. / 10 min	No Isomerization
2	**12*Z***	NaOMe (1.0) / MeOH / r.t. / 4 days	7 : 1
3	**12*E***	NaOMe (1.0) / MeOH / r.t. / 3 days	15 : 1
4	**12*Z***	*t*-BuOK (1.0) / THF / r. t. / 1 min	30 : 1
5	**12*Z***	*t*-BuOK (1.0) / THF / 4 °C / 1 min	70 : 1
6	**12*Z***	CSA (0.2) / $CHCl_3$ / r. t. / 60 min	20 : 1

a) All reactions were carried out at 10-mg scale, and the yields were more than 70% after usual work-up.
b) The ratio was determined based on the integration by ^{1}H-NMR.



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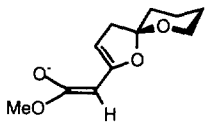

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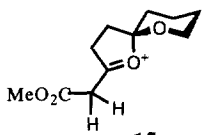

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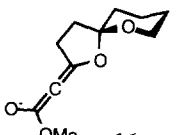
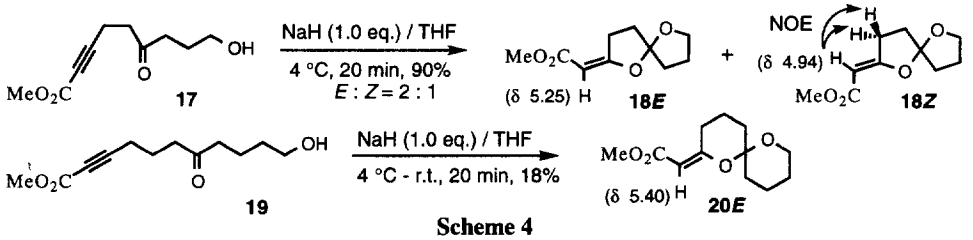


16

The primary alkoxide derived from **11a** forms the hemiacetal alkoxide (derived from **11b**), and then the intramolecular conjugate addition would provide the allenolate anion **16**. The diastereofacial selectivity of protonation in **16** reflects the geometrical selectivity under the kinetic conditions. The proton source is aq. NH_4Cl (used upon the work-up of the reactions), MeOH, or *t*-BuOH. It is also clear from the result of catalytic reactions that the starting material itself acts as the proton source for **16**. The difference of the counter cation (Na^+ / K^+) might influence on the geometrical selectivity. After the formation of **12*E*** and **12*Z*** by the kinetic control, the geometrical selectivity is made to vary by the thermodynamic control under the paticular conditions (entries 6 and 7 in Table 1). The study to prove the intermediates (**13-16**), and to reveal the effect of the counter cation, is progress.

This spirocyclization could be applied to the synthesis of other homologues, 2-methoxycarbonylmethylene-1, 6-dioxaspiro[4.4]nonane and 1, 7-dioxaspiro[5.5]undecane (Scheme 4). Acyclic compounds **17** and **19** were prepared by the almost similar manner as shown in Scheme 2. The compound **17** was converted to spiroacetal enol ethers **18*E*** and **18*Z*** in 90% yield. The structures of **18*E*** and **18*Z*** were determined by ^{1}H-NMR spectrum and ^{1}H-^{1}H NOE experiment. Only **20*E*** was obtained from **19** in 18% yield along with a complex mixture of unknown products. The geometry of **20*E*** was deduced from the chemical shift (δ 5.40) of the olefinic proton by comparing with the other (*E*)-isomers. In a preliminary experiment, it was also found that a formyl group is also an effective activating group to give spiroacetal enol ethers under acidic conditions.[9] Application to a chiral substrate directed toward total synthesis of natural products is now in progress.



Scheme 4

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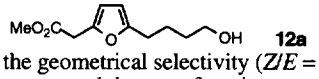
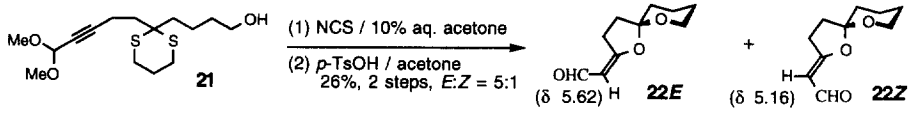
5. There are many synthetic studies on monocyclic enol ethers and lactones starting from acetylenic alcohols and carboxylic acids, respectively. Several examples are shown in following: (a) Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron Lett.* **1992**, *33*, 4905-4908. (b) Pale, P.; Chuche, J. *Tetrahedron Lett.* **1987**, *28*, 6447-6448. (c) Dai, W.; Katzenellenbogen, J. A. *J. Org. Chem.* **1991**, *56*, 6893-6896. (d) Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pietroni, B. R. *J. Org. Chem.* **1992**, *57*, 976-982. (e) Pflieger, D.; Muckensturm, B. *Tetrahedron* **1989**, *45*, 2031-2040.
6. Satisfactory spectroscopic data were obtained for all new compounds.
7. When **10** was treated with anhydrous TBAF in THF, furan **12a** was obtained in 30-50% yield. A similar anionic cyclization (using NaH) starting from keto alkynoates to give furan derivatives has recently been reported. (Vieser, R.; Eberbach, W. *Tetrahedron Lett.* **1995**, *36*, 4405-4408.)



8. In ref. 5e, the authors explain that the geometrical selectivity (*Z*/*E* = 10/90) can be related to the steric hindarance between the furanoic oxygen and the ester function.
9. After dethioacetalization of **21**, the following acid treatment provided spiroacetal enol ethers **22*E*** and **22*Z*** in one pot. The low yield may be due to the volatility of the products.



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