SYNTHESIS OF E- AND Z-1,6-DIOXASPIRO[4.5]DECANES

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Abstract——An efficient synthesis of E- and Z-1,6-dioxaspiro-[4.5]decanes has been achieved via the intramolecular ketallization of 5 bearing a bulky substituent(SPh) at the position α to the carbonyl group.

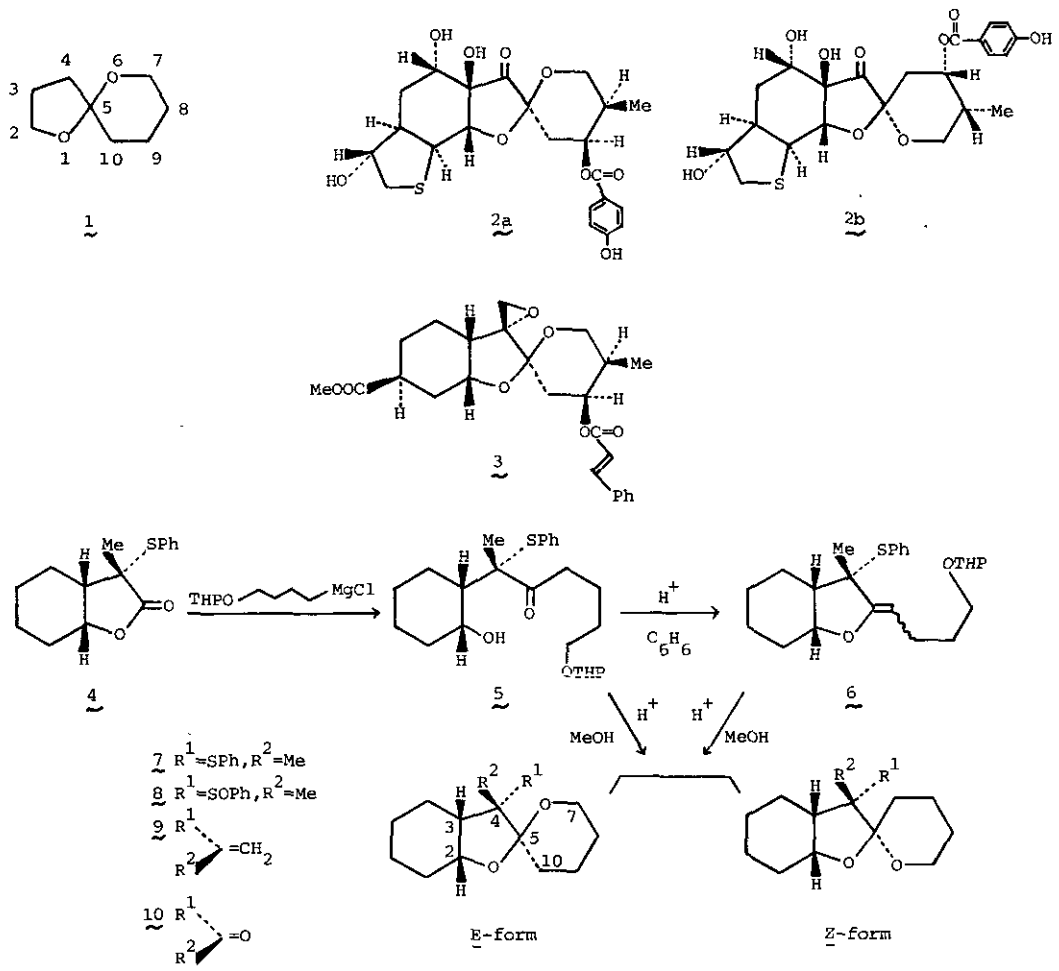
Much attention has been given to the natural products containing a 1,6-dioxaspiro-[4.5]decane skeleton 1 from view point of biological and synthetic interests. Breynogenin 2a and isobreynogenin 2b are genuine and artificial aglycons, derived from an acid hydrolysis of a hypocholesterolemic glycoside, breynin A.[1] The structures of both aglycons, possessing E- and Z-1,6-dioxaspiro[4.5]decane ring systems, were respectively established.

Recently, Kupchan and co-workers have reported the characterization of phyllanthocin, an aglycon of antileukemic glycoside, phyllanthoside.[2] The structure 3 of the aglycon, carrying an E-1,6-dioxaspiro[4.5]decane ring, was elucidated by an X-ray analysis.

From a biological interest of both E- and Z-forms in simple 1,6-dioxaspiro[4.5]-decanes,[3,4,5] we examined the synthesis of tricyclic spiroketals(E- and Z-forms) via the intramolecular ketallization of a precursor 5.

This paper describes an efficient route to E- and Z-1,6-dioxaspiro[4.5]decane ring systems, simplified models of 2a and 3(E) and 2b(Z), in racemic forms.

Grignard reagent[6](5 equiv.) prepared from tetrahydropyranyl ether of 4-chloro-1-butanol, was added to the readily available cis-lactone 4[7](THF, 60°C, 15 h) and after the usual work-up(satd. aq.NH_4Cl, 0°C) and distillation, the hydroxyketone 5[ν_{max} (CCl_4): 1700 cm^{-1}][8] was obtained as a colorless oil(76%). Cyclization[p-TsOH (1 equiv.), MeOH, r.t., 1.5 h] of 5 gave the E:Z mixture(ca. 1:5 by glc and hplc) of sulfides 7 in nearly quantitative yield.[9] Careful chromatographic separation(mplc, Lober column, hexane:AcOEt=60:1) afforded the pure isomers, E-7[a colorless oil; ν_{max}(CCl_4): 1580, 1070, 1040, 965 cm^{-1}; δ_H(CCl_4): 1.18(3H, s), 3.42-4.16(3H, m);



m/z: 318(M^+, 3.9%), 218(100%)] and Z-7[a colorless oil; $\nu_{max}(CCl_4)$: 1580, 1065, 970 cm^{-1}; $\delta_H(CCl_4)$: 1.08(3H, s), 3.48-4.05(2H, m), 4.16(1H, m); m/z: 318(M^+, 5.7%), 218 (100%)]. When the compound 5 was subjected to cyclization(benzene, r.t., 1 h) in the presence of a catalytic amount of p-TsOH, the dehydration product 6[$\delta_H(C_6D_6)$: 1.32(3H, s), 3.22-4.00(4H, m), 4.08(1H, m), 4.58(1H, m), 4.73(1H, t, J=8 Hz)] could be isolated as an unstable oil(66%), which was cyclized under the same conditions used for 5 to afford the same 1:5 mixture(75%) of E-7 and Z-7.

A tentative assignment of the stereochemistry of these isomers was at this stage made on the basis of the ^{13}C NMR chemical shift(relative low-field resonance at C-2[10] for the Z-isomer)[5a](Table). Final proof was obtained by an X-ray analysis on a compound described in the accompanying paper.

Oxidation($NaIO_4$, MeOH:H_2O=10:1, r.t., 70 h) of Z-7 followed by chromatography on alumina gave the two diastereomeric isomers, Z-8[the major isomer(64%); mp 149-150°C]

and Z-8'[the minor isomer(30%); mp 150-151°C] whereas similar treatment of E-7 furnished the corresponding sulfoxides, E-8[the major isomer(71%); mp 95-96°C] and E-8' [the minor isomer(15%); mp 135-137°C] along with Z-8(8.3%) and Z-8'(3.7%). The E-isomers(E-8 and E-8') obtained above were, after acid-catalyzed isomerization (p-TsOH, MeOH, r.t., 1 h), converted exclusively into the respective Z-isomers(Z-8 and Z-8').

Thermolysis(toluene, reflux, 23 h) of Z-8 in the presence of trimethylphosphite (5 equiv.) afforded the olefin Z-9[a colorless oil(60%); bp 120°C/0.004 mmHg] as a sigle product. The product was equilibrated with an acid(pyridinium p-toluenesulfonate, CH_2Cl_2, 0°C, 2 h) to furnish an E:Z mixture(3:1 by ^1H NMR). This epimeric mixture was separated by chromatography on alumina and purified on distillation to give E-9[11](bp 100°C/0.002 mmHg), and the repeated runs of recovered Z-9 gave a further amount of E-9.

Ozonolysis(MeOH, -78°C) of E-9 and Z-9 and subsequent removal of the solvent yielded the corresponding ketones, E-10[a colorless oil(66%)] and Z-10(63%; mp 57-58°C), respectively. Isomerization(p-TsOH, CH_2Cl_2, r.t., 10 days) of each isomer resulted in an inseparable mixture(6:1) of E-10 and Z-10.

In general, the E-isomer is more stable thermodynamically than the corresponding Z-isomer in 1,6-dioxaspiro[4.5]decanes.[2b,5] In fact, the respective E-isomers were preferentially obtained in the dioxaspirane ring isomerization of 9 and 10. However, in the cases of 7 and 8, the respective Z-isomers were obtained preferentially(in 7) or exclusively(in 8). This phenomenon would be attributable to the steric interaction between the bulky substituent(SPh or SOPh) at C-4 and the C-10 methylene. Much cleaner structural information about the spirane juncture of a series of the spiroketals obtained above can be diagnostically available from the comparison of the ^{13}C NMR chemical shifts at C-2 of the isomeric pairs: its carbon resonance in the Z-series is uniformly low-field from the corresponding carbon in the E-series (Table).[12]

Table. Selected ^{13}C NMR($CDCl_3$, δ_{ppm}, TMS=0) spectral data of 7, 8, 9, and 10

Carbon	7		8		9		10	
	E	Z	E	Z	E	Z	E	Z
2	73.7	76.4	73.1	74.9	73.7	77.5	71.3	75.5
3	48.3	48.1	50.8	47.3	42.5	42.2	44.0	46.1
4	65.7	63.9	77.2	75.1	158.2	154.8	211.4	211.4
5	107.0	107.5	103.9	106.2	103.7	105.0	99.1	99.1
7	62.3	61.2	62.8	61.5	61.8	62.5	61.9	62.2

In conclusion, E- and Z-1,6-dioxaspiro[4.5]decane ring systems found in breynogenin and phyllanthocin(E) and isobreynogenin(Z) could be obtained from 5 or 6 via 7 in the reaction sequence(E:Z-7 → E:Z-8 → Z-8 → Z-9 → Z-10 or E-9 → E-10)[13] involving the isomerization of E-8 and Z-9 to the corresponding isomers. Work is currently in progress to utilize this approach in the synthesis of a variety of spiroketals including natural products

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3. Simple spiroketals such as 2-methyl- and 7-methyl-1,6-dioxaspiro[4.5]decanes exist in nature[4] as an E:Z mixture, both isomers of which are pheromone components. Various attempts[5] of syntheses of these spiroketals resulted in an E:Z mixture with predominance of E-isomer. From this mixture, the isolation of each isomer is very difficult on a preparative scale.
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8. The carbonyl band shows the presence of the keto-form in compound 5. The co-existence of the corresponding hemiacetal-form in 5 may be possible but has not been confirmed by our present spectral data.
9. This is a thermodynamically controlled ketallization: identical product distributions could be obtained by the equilibration experiment[p-TsOH, MeOH, r.t., 5 min] of E-7 or Z-7.
10. 1,6-Dioxaspiro[4.5]decane numbering system is used in this paper for clarity.
11. The same product E-9(69%) was also obtained by thermolysis(toluene, reflux, 3 h) of E-8.
12. This trend is found and discussed in 2- and/or 7-alkylated 1,6-dioxaspiro[4.5]-decanes: see ref. 5a.
13. For the introduction of epoxide ring found in phyllanthocin, see accompanying paper.

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