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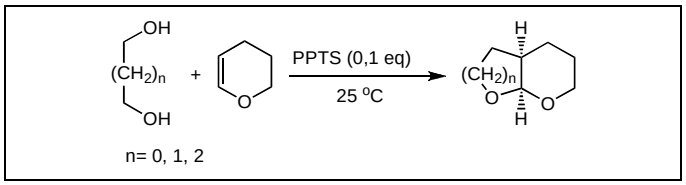

cis-Fused bicyclic acetals were obtained from the unusual cyclization reaction between diols and dihydropyran. Furothiopyran, substituted pyranopyrans, and pyranooxepine and pyranobenzoxepine compounds were obtained with high diastereoselectivity and *cis*-diastereomers were obtained in high yields.

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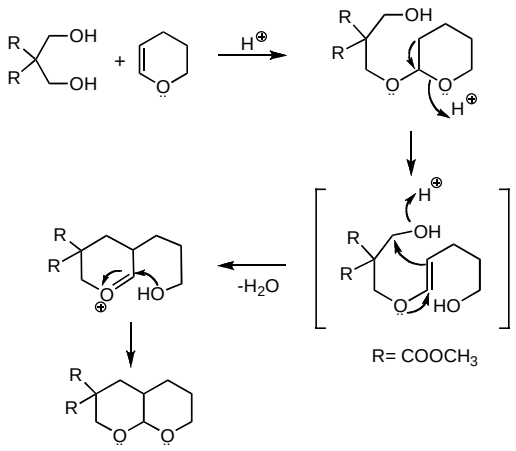
Because the protective groups play important roles in modern multi-step synthetic organic chemistry, in recent years, numerous publications appeared on the selection of the most suitable protecting group for hydroxy functions. In our previous work, we reported selective *o*-benzylation of primary hydroxy groups of di-and tri-hydroxy compounds by using bis(acetylacetonato) copper as catalyst [1]. We showed that bis (acetylacetonato) copper is very efficient in promoting the benzylation of primary aliphatic alcohols versus secondary aliphatic alcohols and phenolic hydroxy groups.

It is known that another common way for the protection of hydroxy groups is to form tetrahydropyranyl ether. Diols in which two hydroxyl groups are far away from each other can be protected as monotetrahydropyranyl ethers in good yields [2]. However, in these reactions formation rate of diprotection products is very low and the reason is not clear. There is no report on the protection of 1,2 and 1,3-diols with 3,4-dihydro-2*H*-pyran (DHP). Therefore, we have been interested in α and β-hydroxy alcohols with DHP because of the possibility of generating bicyclic acetalic products.

In order to investigate the type of the protection products, we decided to begin with bishydroxymethyl-dimethylmalonate which can be easily prepared from dimethylmalonate and formaldehyde. Bishydroxymethyl- dimethylmalonate was reacted with DHP in the presence of *p*-toluen sulfonic acid-pyridin catalyst and surprisingly compound (**I**) was obtained in up to 90 %. Probable reaction mechanism is illustrated in Scheme I. First step is acetal formation by addition of one of the hydroxyl group of the diol to the dihydropyran in the usual way, second step: ring opening of the dihydropyran moiety and generation of an enol ether, third step: acid catalyzed water elimination and recyclization to the oxonium ion, final step: formation of the compound (**I**).

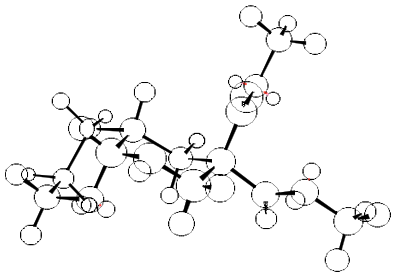
Scheme I



Structure and the stereochemistry of the compound (**I**) were elucidated by spectroscopic and chromatographic experiments. Spectroscopic data showed that the reaction was highly diastreoselective and formation of *cis* isomer was exclusive. The structure was established by nmr studies and compared with the similar studies done before [3,,7,8,9]. Coupling constant 3.6 Hz for the bridgehead protons (dihedral angle of H_{4a} and H_{8a} is 52°) demonstrated the formation of *cis*-fused bicyclic. According to the MM dekstop molecular mechanic calculations, two pyran rings are in the chair conformation (Scheme II).

The acetalic proton is observed approximately at 4.6 ppm. This smaller value is not in accordance with the one given before [3,5]. This difference is attributed to the structure of the compound. Acetalic proton is shielded by the carbonyl group and corresponding peak shifts to lower

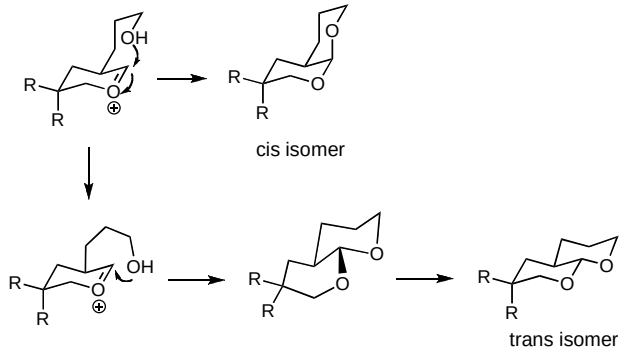
Scheme II



ppm. Although ^2J value of C7 protons is 11.2 Hz, ^{2}J for C2 protons is 9.6 Hz which is unusual for pyran rings. This result is ascribed to the presence of methoxycarbonyl groups at neighbouring carbon atom.

In one of the previous studies stereoelectronic control in acetal formation was investigated and it is reported that acetal formation is controlled by stereoelectronic effects [3]. During the formation of bicyclic and tricyclic acetals at ambient temperature, first kinetically controlled *cis* product is formed. To form thermodynamically controlled *trans* product, intermediate of *cis* conformer should undergo a conformational change in order to form a more stable conformation of *trans* cyclic acetals (Scheme III).

Scheme III



If conformational changes are restricted due to the structural reasons *cis* isomer formations are favored. The reason of the formation of *cis* and *trans* isomer mixtures could be explained with easy twisting between acetal conformers. In our case, two electron withdrawing methoxycarbonyl groups restricted the twisting and also activated -CH_2 group for nucleophilic attack which is followed by subsequent cyclization of enol ether.

In order to extend this method for the synthesis of different type of bicyclic acetals, several diols were reacted with DHP. Ethylene glycol gave furopyran (**2**) in low yield. This compound was previously obtained from hex-3-en-1,6-diol in good yield [3]. The spectroscopic data of compound (**2**) is in accordance with the one obtained before. When thioethylene glycol was used as diol, only the corresponding thiophenopyran (**3**) was obtained in the higher yield than that of ethylene glycol. *cis*-2-Buten-1,4-diol and 2,3-dihydroxymethylbenzene were reacted with DHP and compound (**4**) and (**5**) yielded respectively. Only *cis* diastereomers were obtained in all reactions as common.

Table I

Products and the yields

Entry	Product	Yields %
	1	92[b]
	2	30[a,3]
	3	70[a]
	4	60[a]
	5	70[a]

a : yields are given from GC analysis, b: yield of isolated product

Another starting material was pentaerythritol. From the GC-MS analysis, it was observed that 3,3-bishydroxy-methyl-pyranopyran formed in the yield of 10% but it could not be separated from the mixture properly. So, its spectroscopic data was not given in the experimental part. However, when the ^{1}H nmr spectrum of the crude product was investigated, two doublets at 3.5 and 3.1 ppm with J=9.6 Hz were observed as seen before compound (**I**). These doublets could not belong to any of other possible acetalic products. This result supported the formation of the bicyclic structure.

All starting materials and products prepared with this novel method are given in the Table 1.

In conclusion, we have described herein a simple reaction pathway for the the synthesis of *cis*-fused bicyclic acetals. Starting from easily accesible diols, bicyclic acetals are obtained with high diastereo-selectivity. In addition to its efficiency and simplicity, this method provides opportunities to obtain interesting target molecules using different substituted diols and dihydropyrans.

EXPERIMENTAL

All general chemicals and starting materials purchased from commercial sources, except 2,2-dihydroxymethyl-dimethyl-malonate. IR spectra were recorded on a Jasco FT-IR 5300 spectrometer using neat compounds as films between NaCl cells or crystalline compound as KBr disks. ^{1}H and ^{13}C NMR spectra were run with Bruker 250 MHz spectrometer and reported as ppm relative to TMS. GC-MS spectra were obtained on Thermo Finnigan Trace DSQ instrument using ZB-5MS capillary column. The products were purified by column chromatography on neutral silicagel 60 (0,040-0,063 mm) from Merck, Darmstadt.

Synthesis of 2,2-Bishydroxymethyl-dimethylmalonate. The solution of 13.2 g (0.10 mole) dimethylmalonate in 100 ml dioxane was cooled to 4-5° and 33 g of 20% formaldehyde solution (0.22 mol) was added. pH was adjusted to 8 with triethylamine and stirred at this temperature for 20 minutes. Then the solution was allowed to warm to room temperature and stirred for 2 hours. The solution was diluted with water and product was extracted with dichloromethane, dried and the solvent was evaporated. The residue was crystallized from dichloromethane/hexane (1/1), yield 13.6g (72%), mp 78-79°; ir (potassium bromide): 3433 (OH), 1732 (CO) cm^{-1} ; 1H nmr ($CDCl_3$): δ 4.12 (s, 4H, CH_2), 3.79 (s, 6H, CH_3), 2.94 (s, 2H, OH); ms: m/z 175, 145, 113, 85, 67, 59.

General Procedure for the Reaction of Diols with 3,4-Dihydro-2*H*-Pyran. 1,5 mmol of Dihydropyran was added to the solution of diol compound (1 mmol) in methylene chloride (10 ml) containing PPTS (0,1 mol). The solution was stirred for 8 hours at 25 ºC, then washed with half-saturated brine in order to remove the catalyst. The solvent is removed and the product was purified by an appropriate method.

3,3-Dimethoxycarbonyl-(4a*R*,8a*S*)-perhydropyrano[2,3-*b*]-pyran (1). This compound was crystallized from acetone/water mixture (1/1), mp 83°C; ir (potassium bromide): 1741 (CO), 1226 (OCO) cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 4.6 (d, 1H, acetalic H, J= 3.6 Hz), 4.2 (d, 1H, H-2 eq, J= 9.6), 3.8 (d, 1H, H-2_{ax}, J=9.7), 3.75 (ddd, 1H, H-7_{eq}, J= 11.1, 7.2, 2.3), 3.72 (s, 6H, OCH_3), 3.49 (dt, 1H, 7-H_{ax}, J=11.2, 2.2), 1.8-1.4 (m, 7H, ring protons); ^{13}C nmr ($CDCl_3$, proton decoupled): δ 169.04, 99.7, 65.8, 63.6, 59.3, 52.4, 30.4, 25.4, 19.9, 18.9 ; ms: m/z. 258 (M^+), 245, 193, 145, 113, 85. *Anal*. Calcd. For $C_{12}H_{18}O_6$: C, 55.81; H, 7.02. Found: C, 56.14; H, 7.31

4a*R*,7a*S*-Perhydrothiopheno[2,3-*b*]pyran (3). This compound was purified by column chromatography, using (20/ 80) ethyl acetate/ hexane as the eluent and obtained as a colorless oil, ^{1}H nmr($CDCl_3$): δ 4.62 (d, 1H, acetalic H, J=3.6), 3.84 (ddd, 1H, H-2_{ax}, J=11.2, 6.5, 3.6), 3.52 (dt, 1H, H-2_{eq}, J=11.2, J=6.5), 2.72 (ddd, 1-H_{ax}, J= 9.3,8.2, 6.4), 2.68 (ddd, 1-H_{eq} ,J=8.2, 8.1,6.4), 1.81-1.50 (m, 7H, ring protons); ^{13}C nmr ($CDCl_3$, proton decoupled): δ 99.9, 69.4,62.4,30.8, 25.6, 24.8, 19.6; ms m/z 144 (M^+),103, 101, 89, 85, 61, 60, 41. *Anal*. Calcd. For $C_7H_{12}OS$: C, 58.29; H, 8.39. Found: C, 58.74; H, 8.51

9a*S*,5a*R*-Tetrahydropyrano[2,3-*b*]-2*H*-5,5a, 9a-tetrahydro-oxepine (4). This compound was obtained as a colorless oil after purification with column chromatogrphy by using ethyl acetate/hexane (20/80) as the eluent, ir (NaCl cell): 1614 (C=C), 1201 (O-C-O) cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 5.57-5.53 (m, 2H, olefinic H), 4.52 (d, 1H, ,H-9a, J=2.9), 4.11(dd, 1H, 2-H_{ax},J= 11.4, 2.9), 4.04 (dd, 1H, 2-$H_{eq,}$ J=10.9, 7.8), 3.78 (td, 1H, 8-H_{eq}, J=10.7, 3.6), 3.4 (ddd, 1H, 8-H_{ax} J=11.3, 6.8, 4.7), 1.74-1.44 (m, 7H, ring protons); ^{13}C nmr ($CDCl_3$, proton decoupled): δ 128.4, 126.8, 100.2, 63.8, 62.0, 55.4, 31.2, 26.1, 19.9, ms (CI): m/z 155 (M^+), 101, 85, 67, 57. *Anal*. Calcd. For $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.38; H, 9.38.

11a*S*,7a*R*-Tetrahydropyrano[2,3-*b*]-4,5-dihydro-1*H*-2-benzoxepine (5). This compound was purified by column chromatography using ethyl acetate/ hexane (20/80) as the eluent and gained as a colorless oil, ^{1}H nmr ($CDCl_3$): δ 7.33-7.16 (m, 4H, ar), 4.86 (d, 1H, 2-$H_{ax(eq)}$, J= 11.7), 4.82(d, 1H, H-11a, J=3.5), 4.54 (d, 1H, 2-$H_{eq(ax)}$ J= 11.7), 3.85 (td, 1H, H-10_{ax} J=11.4, 3.6,), 3.54 (dt, 1H, H-$10_{eq,}$ J=11.3, 6.9, 3.5), 3.4 (m, 2H, H-5), 1.8-1.4 (m, 5H, pyran ring protons); ^{13}C nmr ($CDCl_3$, proton decoupled): δ 138.4, 137.8, 128.4, 127.6, 127.4, 125.6, 98.2, 72.0, 63.8, 36.0, 32.2, 26.1, 19.9; ms: m/z 204 (M^+), 143, 121, 120, 93, 85, 77, 67. *Anal*. Calcd. For $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.64; H, 7.61.

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