Serendipitous Acid-Catalyzed Rearrangement of 13-Methoxy-1,6,8-trioxadispiro[4.1.5.3]pentadecane to 3-Chroman-5-ylpropan-1-ol

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Introduction

The molecular arrangement of trioxadispiroacetals appears in nature in a small number of polyether ionophores.[1] The formation of this three-ring system linked in a spiro fashion at two ketal carbons represents a synthetic challenge. Thus, only a few natural products and simpler models possessing this structure have been synthesized[2] so far. Not surprisingly, the field of the trioxadispiroacetal reactions has not been fully explored. For the less complex dioxaspiro compounds, only a few reactions have been studied,[3] the most noteworthy being the acid-catalyzed spiroisomerization, the opening of spiroacetals to thermodynamically less favored ketones by treatment with mineral acids, and the reductive ring opening to monocyclic compounds[4] or to a 1,6-dioxadecalin system.[5]

We report here on the unexpected rearrangement undergone by the trioxadispiroacetals of type **1**−**4** in the presence of acid to produce a chroman derivative **5** (Chart 1). The removal of the methoxyl group and the aldol condensation reaction play a decisive role in the displacement of the equilibria from the tricyclic structures to the new bicyclic aromatic arrangement.

Results and Discussion

The chiral trioxadispiroacetals **1** and **2** were prepared starting from D-glucopyranose which was homologated at C-1 and C-6 and then underwent intramolecular cyclizations by using alkoxy radical reactions induced by (diacetoxyiodo)benzene as the key steps, with the concomitant formation of the spiroacetal rings.[6] Similarly, the intramolecular H-abstraction of α-hydrogen to the ether function was the strategy used for the construction of trioxadispiro compounds **3** and **4,** starting, this time, from tri-*O*-acetyl-D-glucal and following suitable chemical manipulations.[7]

When compounds **1** and **2** were dissolved separately in aged $CDCl_3$ in an NMR tube, the rapid formation was observed in each case of a complex mixture of products (monitored by TLC and ^{1}H NMR). After 2.5 h each mixture afforded an identical product, the chroman derivative **5**, the structure of which was confirmed by its spectroscopic data: COSY, HMBC, and HMQC experiments.

However, the related diastereomeric compounds **3** and **4** proved to be rather more stable, remaining unaltered after several days in a solution of aged $CDCl_3$, the addition of 1 μL of 35% HCl in 0.5 mL of $CDCl_3$ being required for the transformation to take place. The process was monitored by ^{1}H NMR, the formation of signals corresponding to the chroman derivative **5** being observed after 5 min at room temperature and the total consummation of the trioxaspiroacetals after 30 min under these conditions.

A plausible mechanism for this striking rearrangement could be explained by an acid-water-catalyzed process, as outlined in Scheme 1. The dispiroacetal structure of **1**−**4** exists in equilibrium with its open form A, the protonation of the methyl ether facilitating the elimination of this functional group to give an intermediate B which is in equilibrium with its open form C. An aldolic condensation reaction from the unsaturated enol ether to the ketone would lead to a new cyclohexanone ring (D). The favored hemiacetal is formed by six-membered cyclization, and subsequent aromatization by dehydration of alcoholic groups would give the chroman derivative **5**. Although the elimination of the methoxyl group could give a mixture of the *Z*- and *E*-olefins, under the reaction conditions the α-*β*-unsaturated ketone formed could

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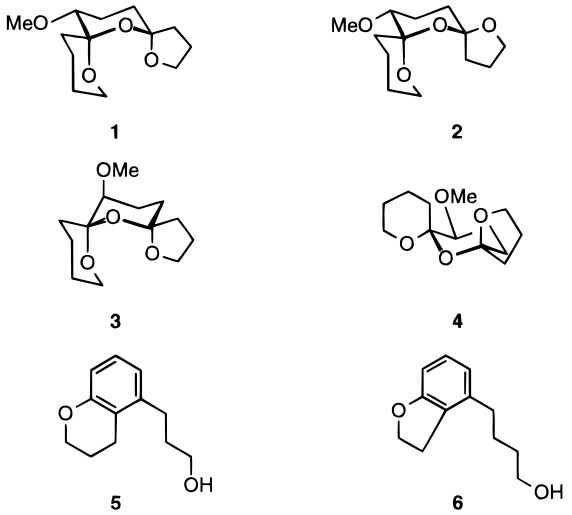
Chart 1



isomerize to the Z-double bond required for the ring closure. Another possibility to be considered is that the methoxyl group elimination could take place after the six-membered ring is closed. An alternative aldolic condensation from the enol ether of the saturated ketone to the unsaturated one, which could produce the thermodynamically less stable compound **6**, was not observed.

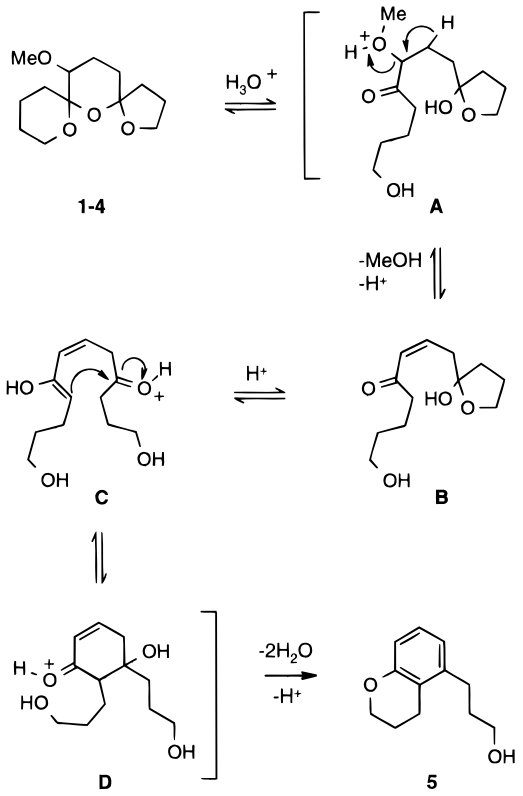
Due to the instability of the models shown in this paper, natural product chemists should be aware of these results during the isolation and purification of this type of compounds.

Experimental Section

General. Melting point was determined with a hot-stage apparatus and is uncorrected. NMR spectrum was determined at 500 MHz for ^{1}H and 50.3 MHz for ^{13}C for $CDCl_3$ solution in the presence of TMS as internal standard. Mass spectrum was determined at 70 eV. Merck silica gel 60 PF_{254} and 60 (0.063−0.2 mm) were used for preparative thin-layer chromatography (TLC) and column chromatography, respectively. Circular layers of 1 mm of Merck silica gel 60 PF_{254} were used on a Chromatotron for centrifugally assisted chromatography. Commercial reagents and solvents were analytical grade or were purified by standard procedures prior to use. The spray reagent for TLC was vanillin (1 g) in H_2SO_4−EtOH (4:1, 200 mL).

3-Chroman-5-ylpropan-1-ol (5). To a solution of dispiroacetal **3** (6 mg, 0.025 mmol) in $CDCl_3$ was added 35% HCl (1 μL) with stirring at rt for 30 min. The reaction mixture was then poured into water and extracted with CH_2Cl_2. The combined extracts were washed with aqueous saturated $NaCO_3H$ and brine, dried over Na_2SO_4, and concentrated. Chromatotron chromatography of the residue (hexanes−EtOAc, 80:20) afforded the title compound **5** (3 mg, 0.016 mmol, 63%): mp 57.4−58.5 °C (from *n*-hexane); IR ($CHCl_3$) 3626, 3070 cm^{-1}; ^{1}H NMR 1.82−1.88 (2H, m), 2.00−2.05 (2H, m), 2.64 (2H, dd, J = 7.8, 7.8 Hz), 2.73 (2H, t, J = 6.6 Hz), 3.72 (2H, t, J = 6.3 Hz), 4.14 (2H, dd, J = 5.2, 5.2 Hz), 6.67 (1H, d, J = 8.0 Hz), 6.74 (1H, d, J = 7.3 Hz), 7.03 (1H, t, J = 7.8 Hz); ^{13}C NMR 22.0 (t), 22.4 (t), 28.6 (t), 32.8 (t), 62.6 (t), 65.8 (t, C-2), 114.8 (d), 120.5 (s), 120.6 (d), 126.8 (d), 141.1 (s), 155.1 (s); MS *m*/*z* (rel intensity) 192 (M^+, 68), 175 (2), 161 (6), 148 (100), 133 (41), 91 (17). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.23; H, 8.21.

Scheme 1



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