SPIROKETAL SYNTHESIS. PREPARATION OF FUNCTIONALIZED 1,7-DIOXASPIRO[5,5]UNDECANES

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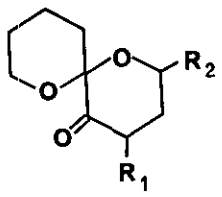
Abstract - 5-Oxo-1,7-dioxaspiro[5,5]undecanes can be prepared from γ-butyrolactones and dihydropyran in a two-step process. Condensation of 2-lithiodihydropyran with the appropriate lactone, followed by acid-catalyzed cyclization, affords the spiroketal.

A number of reports concerning the synthesis of spiroketals have appeared in recent years.[2] These approaches provide entry to a variety of biologically active compounds such as avermectins, milbemycins, insect pheromones, the talaromycins, and polyether antibiotics.

Some of these methodologies make use of lactones[3] to construct the appropriate spiroketals, whereas others require functionalized cyclic ethers.[4] We now wish to report a method that utilizes both a lactone and a cyclic ether for the preparation of spiroketals, and also complements the existing literature. As a result, carbonyl-containing derivatives, such as 5-oxo-1,7-dioxaspiro[5,5]undecanes (1), are amenable by this procedure. The carbonyl moiety should provide a "handle" for further elaboration of the molecule.



1a, R_1 = H, R_2 = H
1b, R_1 = H, R_2 = CH_3
1c, R_1 = H, R_2 = n-C_4H_9
1d, R_1 = CH_3, R_2 = H

The following procedure is typical of the preparation of spiroketals 1a - 1d. To a solution of dihydropyran in THF (ratio of 10 mmoles: 1 ml), cooled to -65°C and under nitrogen, was added 1 equivalent of t-BuLi in pentane such that the temperature did not rise above -55°C. Following the addition, the internal temperature was then allowed to carefully rise to 0°C. The solution is stirred at -5 to 0°C for 1 h and cooled to -65°C. A solution of the γ-butyrolactone (2; 1 equivalent) in THF was added to the 2-lithiodihydropyran (3)[5] while maintaining the temperature below -45°C. After stirring at -65°C for 1 h, the reaction was stirred overnight at room temperature, and then quenched with 20% aq. NH_4Cl. Ethereal work-up and bulb-to-bulb distillation afforded 4 as a clear, viscous oil. Cyclization was effected by stirring a solution of 4, conc. HCl, water, and THF (ratio of 10 mmoles:0.88 ml:4.4 ml:18.4 ml, respectively) at room temperature for 24 to 48 h to provide spiroketal 1. Yields are summarized in the Table.

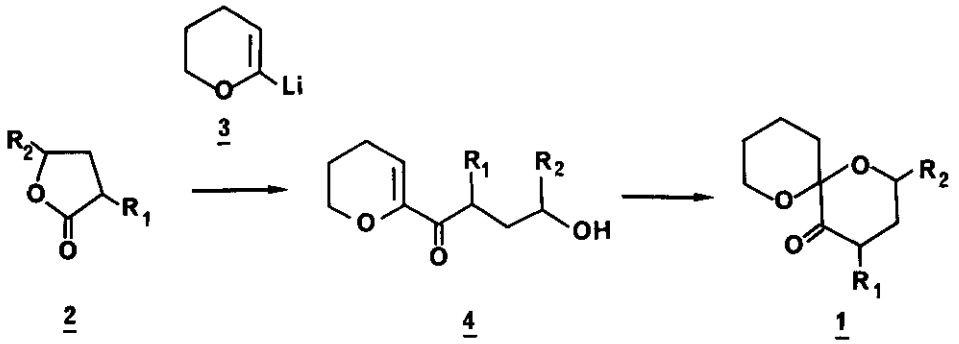


Table. Preparation of 5-oxo-1,7-dioxaspiro[5,5]undecanes (1)

SERIES	R_1	R_2	4 FROM 2	1 FROM 4
a	H	H	33	82
b	H	CH_3	47	50
c	H	n-C_4H_9	47	54
d	CH_3	H	59	68

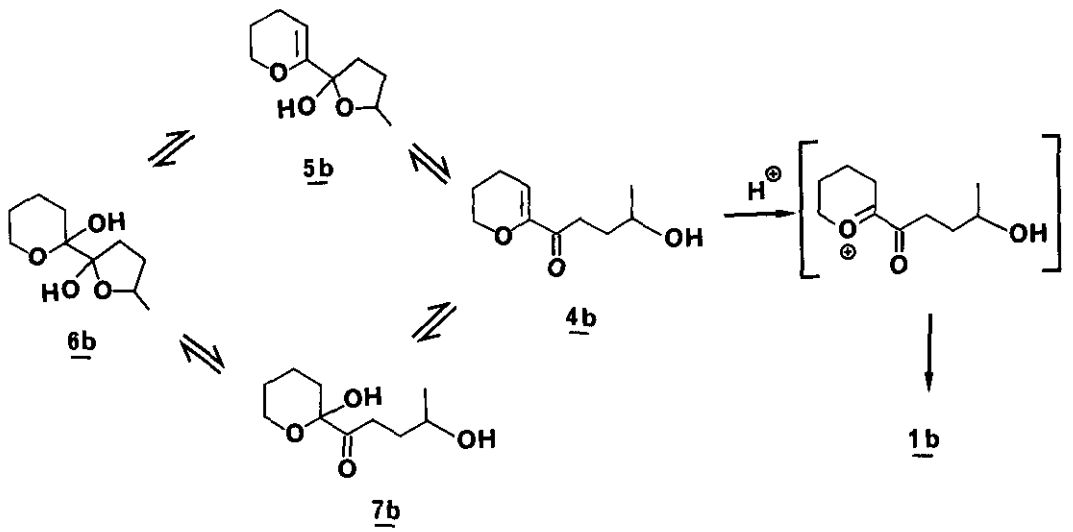
The cyclization of 4a to 1a was slow, requiring 24 h for completion. Cyclization of 4d to 1d occurred at approximately the same rate. However, formation of either 1b or 1c was much slower, requiring twice as long to reach completion. The slower rate of spiroketalization for 1b or 1c as compared to 1a or 1d is likely due to the greater steric hindrance of the secondary alcohols 4b and 4c upon cyclization.

The generally slow rate of conversion for all the alcohols (4a - 4d) to their respective spiroketals (1a - 1d) may be partly due to charge destabilization. The process presumably proceeds through an intermediate with the charge localized on the oxygen of the pyranyl ring (see Scheme). The carbonyl should destabilize this intermediate, resulting in a higher transition state energy and a slower reaction rate. Another factor that may also contribute to the slow cyclization process is the rapid production of other products in the reaction. Production of other components could effectively decrease starting material concentration and thus decrease the rate of conversion of 4 to 1.

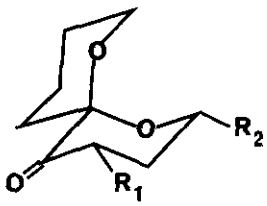
To study this phenomenon the reaction was monitored by capillary GC. For all four cyclizations (a-d) the rapid production of products other than 1 was observed. As the reaction proceeded these materials diminished in amount as the desired spiroketal accumulated. These products were identified by quenching aliquots of the conversion of 4b to 1b with potassium carbonate. Samples obtained 1-4 h after the start of the reaction showed the highest concentrations of these products and were used for analysis by GCMS which was done after trimethylsilylation to prevent dehydration of the tertiary alcohols on GC. The proposed structures (5b, 6b and 7b) are shown in the scheme. The composition of these compounds was established by observation of molecular ions of reasonable intensity in their EI mass spectra. An ion with an m/z of 117 corresponding to $[(CH_3)_3SiOCHCH_3]^+$ was diagnostic for distinguishing the cyclized and uncyclized compounds.

Under aqueous and acidic conditions, the production of such hydrated derivatives and hemiketals is not surprising. To minimize their production we attempted to effect spiroketalization under non-aqueous conditions by treatment of 4b with pyridinium p-toluenesulfonate in dichloromethane. Although 1b was obtained, the yield was low and a large amount of intractable residue also resulted.

SCHEME



Spiroketals 1b, 1c and 1d were each isolated as predominantly one diastereomer as shown by the ^{13}C-nmr spectra (see Figure). The diastereomeric ratios obtained from capillary GC analyses were 95:5, 88:12 and 83:17 for 1b, 1c and 1d, respectively. Stereochemistry was assigned by 200 MHz ^{1}H-nmr[6] using the vicinal coupling constants found for the methine proton of 1b and 1d and is shown below. The result is not unexpected. Under thermodynamic cyclization conditions, the anomeric effect should exclude an equatorial orientation of the ethereal oxygens. This phenomenon, coupled with the sterically preferred equatorial orientation of the methyl group, support the stereochemical assignments for the major diastereomers of 1b, 1c and 1d. This finding is also consistent with the report of Amoroux[4c] concerning the preparation and stereochemistry of a spiroketal similar to 1b but lacking the carbonyl functionality.



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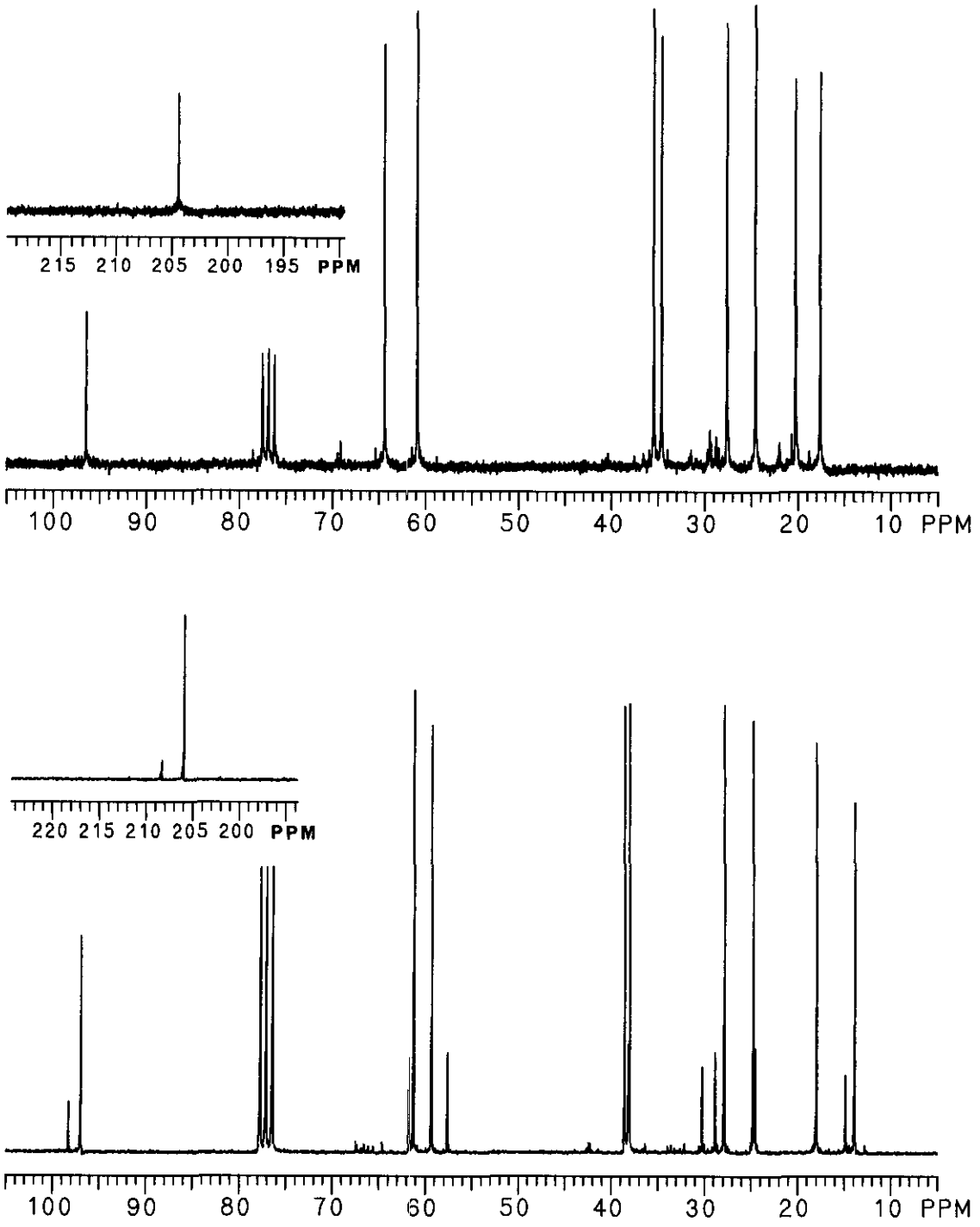
1c, R_1 = H, R_2 = n-C_4H_9

1d, R_1 = CH_3, R_2 = H

FIGURE. ^{13}C-NMR SPECTRA OF 1b (TOP) AND 1d (BOTTOM)



In conclusion, we have developed a ready synthesis of substituted 1,7-dioxaspiro[5,5]undecanes which may be added to the growing arsenal of synthetic methodologies for the preparation of spiroketals.

REFERENCES

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6. (a) 200 MHz ^{1}H-nmr spectral data for 1b (major diastereomer): ($CDCl_3$) δ 4.24 (ddq, J = 11.1, 2.8, 6.3 Hz, 1H), 3.72 (m, 2H), 2.82 (ddd, J = 14.3, 13.4, 6.6 Hz, 1H), 2.19 (ddd, J = 14.3, 4.7, 2.5 Hz, 1H), 2.03 (m, 1H), 1.72-1.89 (m, 3H), 1.49-1.62 (m, 4H), 1.20 (d, J = 6.3 Hz, 3H). The vicinal coupling constants (11.1 and 2.8 Hz) of the methine proton (4.24 ppm) are consistent with an axial orientation of the methine proton and an equatorial orientation of the methyl group. (b) 200 MHZ ^{1}H-NMR spectral data for 1d: The methine proton of the major diastereomer appears as a doublet of quintets (J = 12.8 and 6.4 Hz) at 2.99 ppm which suggests an axial proton and an equatorial methyl group. The methine proton of the minor diastereomer appears at 2.68 ppm as a doublet of quintets (J = 9.3 and 6.9 Hz). The magnitude of these coupling constants suggests a distorted chair conformation.

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