Pergamon

Tetrahedron Letters, Vol. 37, No. 20, pp. 3521-3524, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00602-8

Stereoselective Synthesis of Spiroethers and Spiroketals *via* Photoaddition of Dihydro-4-pyrones to 1,3-Dioxin-4-ones#

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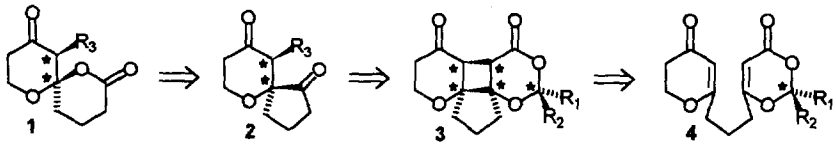
Abstract: A versatile and stereoselective synthesis of spiroethers and spiroketals is presented. The key step based on an intramolecular photoaddition of dihydro-4-pyrones to 1,3-dioxin-4-ones, followed by subsequent fragmentation affording a spiroether which provides, after Baeyer-Villager oxidation, the corresponding spiroketal with complete retention of configuration at the spirocenter. The configuration of this center is defined by the facial selectivity of the chiral dioxinone at the photoaddition step. Thus, this method enables stereoselective synthesis of less thermodynamically stable spiroketals, which are usually produced as isomeric mixtures by most conventional methods that rely on equilibration. Synthesis of a less thermodynamically stable spiroketal, followed by controlled epimerization, in the presence of internal standard, was demonstrated on **19**.

The spiroketal unit can be found in a wide variety of natural products[1], for example, in the Milbemycin/ Avermectin macrolides which possess significant antibiotic as well as insecticidal activity[2], and have been the target of much synthetic effort[3]. A number of antitumor toxic metabolites from blue-green algae also have unique spiroketal substructures[4]. Most of the synthetic approaches to spiroketal systems involve intramolecular cyclization of acyclic keto-diols or their equivalents[1]. The stereochemistry in such cases results from a balance between anomeric stabilization and the preference of substituents for equatorial orientation in six membered rings. Mixtures of products were obtained and tedious separations were required when these factors were in conflict[5]. Thus, an approach to the formation of spiro systems which can preclude such conflict and will not risk hydrolysis of the spiroketal unit might be of great interest.

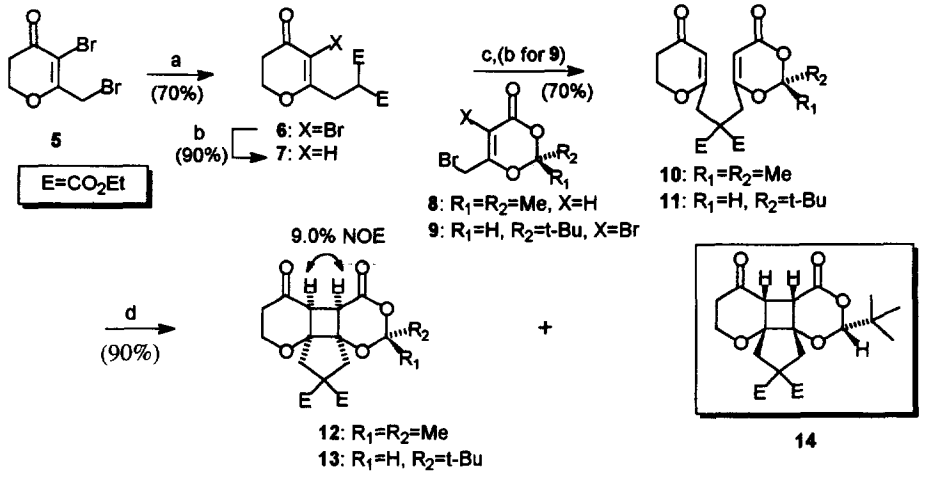
We present herein a versatile method for the construction of spiroketals, which allows preparation of less thermodynamically stable ketals. The method is based on the [2+2] photocycloaddition of dihydropyrones with chiral 1,3-dioxin-4-ones of type **4** ($R_1 \neq R_2$) described in the following retrosynthetic scheme:



Scheme 1

The photocyclization introduces four stereogenic centers with the corresponding configurations defined by the approach of the chiral dioxinone towards the dihydropyrone. Irradiation of achiral compounds **4** ($R_1=R_2$) affords a racemic mixture of spiroketals **1** after manipulation of the first formed photoproducts **3**.

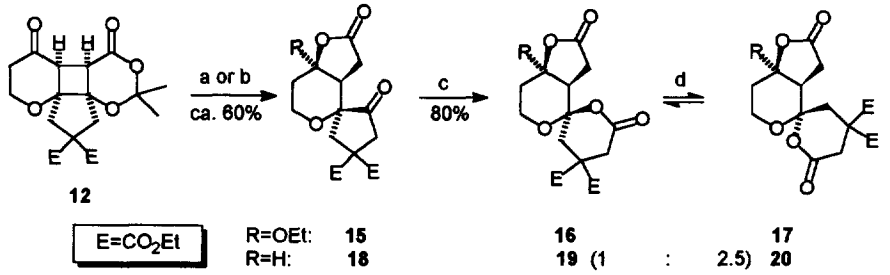
The photosubstrates **10** and **11** were prepared[6,7] as shown in scheme 2. In contrast to the intramolecular photoaddition of simple dihydropyrones[8], irradiation of these photosubstrates required a triplet sensitizer such as acetone[6] or benzophenone. Irradiation[9] of **10** afforded a single product **12** in over 90% yield[10]. A 9% NOE enhancement in each of the proton signals on the four member ring, obtained upon irradiation of its vicinal proton resonance, allows assignment of *syn* sereochemistry.



(a) Diethylmalonate, NaH, THF, r.t., 2h (70%); (b) H_2, Pd/C (10%), 1 atm, THF, Et_3N, 20 min (90%); (c) NaH, THF (70%); (d) hv /Pyrex, CH_3CN, $Ph_2C{=}O$, (90%)

Scheme 2

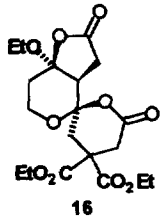
Selective cleavage of the cyclobutane ring was achieved *via* acidic hydrolysis of the dioxanone in ethanol solution[11], affording lactone **15** in a 57% yield. Baeyer-Villager oxidation[12] of **15** provided a single product **16** in 80% yield. No trace of **17**, which might be formed from isomerization at the ketal center, could be detected by ^{1}H-NMR.



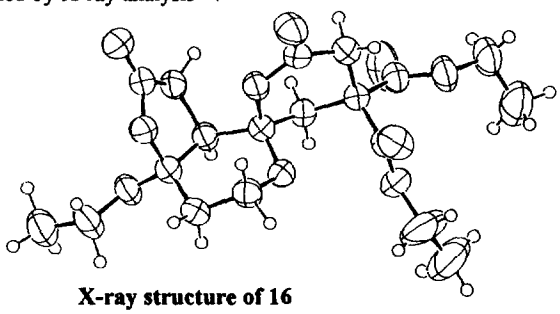
(a) p-TsOH, EtOH (57%); (b) $NaBH_4$, EtOH, THF, -70 °C, 20 min (67%); Jones oxidation, EtOAc:Ether 1:1, (80%); (c) m-CPBA, Li_2CO_3 CH_2Cl_2, r.t., 5h (80%); (d) p-TsOH, $CDCl_3$, r.t., 45 min, t-butylcyclohexanone as IS; the ratio of the epimers was determined by ^{1}H-NMR.

Scheme 3

The structure of **16** was confirmed by X-ray analysis[13].



16



X-ray structure of 16

The utility of this synthetic method in selective preparation of a less thermodynamically stable spiroisomer could be demonstrated in a stereoselective synthesis of spiroketal **19**. Epimerization of the spirocenter of **19**, will afford R_3=H at the axial position in the corresponding structure **20** instead of the axial oxygen at the lactone moity in **19**, leading into a more thermodynamically stable isomer. A highly stereoselective synthesis of the less thermodynamically stable spiroketal **19** (R_3=H) was achieved as follows: Reduction[14] of the photoproduct **12** with $NaBH_4$ took place at the cyclic ketone with high selectivity for approach from the convex face, leading to the expected[14] spontaneous formation of the corresponding lactone *via* fragmentation of the cyclobutane ring. This process introduced a ketone functionality at the cyclopentane ring which was over-reduced under the reaction conditions to the corresponding alcohol, Jones oxidation[15] of this alcohol afforded **18** in 54% total yield from **12**. Baeyer-Villager oxidation of **18** afforded a single compound **19** in 80% yield[16]. Controlled epimerization of the spiro center was performed by treatment of **19** with p-TsOH in the presence of p-*tert*-butylcyclohexanone as an internal standard (IS). This experiment shows a clean and rapid isomerization affording a mixture of **19** and **20** in a 1:2.5 ratio, respectively[16], with less than 5% increase in the IS ratio.

Enantioselective synthesis of a spirosystem was achieved upon irradiation of a chiral photosubstrate. Irradiation of **11** under the usual conditions[9] at -70 °C afforded an easily separable isomeric mixture of **13** and **14** in a 1.8:1 ratio respectively. Stereoselective synthesis of **19** or its enantiomer could be achieved from enantiomerically pure **13** or **14**, respectively, following the sequence described for the conversion of **12**.

These results demonstrate the utility of this sequence in the preparation of spiroketals and more importantly, the method permits stereoselective synthesis of a less thermodynamically stable spiroketal as demonstrated in the preparation of **19**. Enantioselective synthesis of spiroketals is possible following our proposed method on the irradiation of chiral dioxinones.

Acknowledgment. This research was supported by the Israel Science Foundation administered by the Israel Academy of Sciences and Humanities. The Mass Spectrometry Center at the Technion, Haifa is acknowledged.

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13. X-ray analysis of **16**: Empirical formula $C_{19}H_{26}O_{10}$, F.W. 414.4, T = 293K, lattice triclinical, space group P1, a = 10.019(5), b = 12.326(6), c = 9.769(5) Å, α = 108.45(5), β = 93.95(5), τ = 108.56(5)°, V = 1065.2Å^3, Z = 2, F(000) = 440, Dx = 1.292 g.cm^{-3}, radiation Cu Kα, λ = 1.5418Å, μ = 0.895 mm^{-1}, θ range for data collection 4-60°, index ranges $-11 \le h \le 11$, $-13 \le k \le 13$, $0 \le l \le 10$, no. of unique reflections 3123, structure solved by SHELXS86[(a)], and refined by SHELXL93[(b)] programs, refinement method full matrix least squares on F^2, 2823 reflections for which $Fo \ge 4\sigma(Fo)$, no. of parameters 351, R = 0.042, wR2 = 0.144, largest diff. peak 0.221 eÅ^{-3}. (a) Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467; (b) Sheldrick, G. M. *J. Appl. Cryst.* in preparation. ^{1}H-NMR ($CDCl_3$) δ 4.20 (q, 4H), 3.90 (dt, *J*=1.7, 13.2 Hz, 1H), 3.72 (dd, *J*= 8.9, 8.8 Hz, 1H), 3.65 (m, 1H), 3.59 (m, 1H), 3.36 (d, *J*=16.9 Hz, 1H), 2.93 (dd, *J*=8.8, 17.0 Hz, 1H), 2.66 (d, *J*=17.0 Hz, 1H), 2.55 (d, *J*=14.9 Hz, 1H), 2.41 (dd, *J*=6.4, 9.9 Hz, 2H), 2.38 (d, *J*=14.9 Hz, 1H), 1.93 (m, 1H), 1.23 (t, 3H), 1.22 (t, 3H), 1.14 (t, 3H).
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16. ^{1}H-NMR(C_6D_6) of: **19:** δ 3.95 (q, 2H), 3.85 (m, 2H), 3.74 (t, *J*=11.6 Hz, 1H), 3.60 (bs, 1H), 3.40 (d, *J*=16.6 Hz, 1H), 2.93 (dd, *J*=5.8, 11.6 Hz, 1H), 2.46 (d, *J*=16.8 Hz, 1H), 2.40 (d, J_{ab}=16.7 Hz, 1H), 2.22 (d, J_{ab}=14.7 Hz, 1H), 2.19 (d, *J*=16.9 Hz, 1H), 1.82 (dd, *J*=8.6, 16.7 Hz, 1H), 1.43 (bd, *J*=14.5 Hz, 1H), 1.33 (dd, *J*=5.7, 8.6 Hz, 1H), 1.08 (m, 1H), 0.87 (t, 3H), 0.83 (t, 3H); **20:** δ 4.22 (dt, *J*=6.7, 10.6 Hz,1H), 3.92 (q, 2H), 3.84 (q, 2H), 3.36 (d, *J*=16.8 Hz, 1H), 3.27 (t, *J*=11.5 Hz, 1H), 2.91 (q, *J*=5.2, 11.6 Hz, 1H), 2.43 (d, *J*=16.8 Hz, 1H), 2.31 (d, *J*=14.6 Hz, 1H), 1.90 (d, *J*=14.7 Hz, 1H), 1.85 (t, *J*=7.3 Hz, 1H), 1.74 (t, *J*=13.2 Hz, 1H), 1.65 (dd, *J*=8.6, 16.4 Hz, 1H), 1.23 (m, 2H), 0.89 (t, 3H), 0.84 (t, 3H).

(*Received in UK* 8 *February* 1996; *revised* 25 *March* 1996; *accepted* 29 *March* 1996)