Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 7923–7926

A convenient access to thermodynamically nonstabilised spiroketal isomers: the first synthesis of (*Z*)-7-methyl-1,6-dioxaspiro[4.5]decane

Jan Doubský,[a] David Šaman,[a] Jiří Zedník,[b] Soňa Vašíčková[a] and Bohumír Koutek[a,*]

[a]*Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, 166 10 Prague 6, Czech Republic*
[b]*Department of Physical and Macromolecular Chemistry, Charles University, 120 00 Prague 2, Czech Republic*

Received 15 August 2005; revised 6 September 2005; accepted 15 September 2005
Available online 29 September 2005

Abstract—Functionalised hydroxy α-alkynones were transformed to the corresponding spiroketals by a one-pot cascade consisting of palladium-catalysed hydrogenation of the triple bond, hydroxyl group deprotection and spirocyclisation under mild nonacidic conditions. The reaction does not rely upon thermodynamic control to set the configuration of the ketal stereocentre so that both the anomerically stabilised and nonstabilised isomers are similarly accessible.

The spiroketal (sub)unit forms an important structural motif of many biologically active natural products from various sources, including plants, marine organisms, fungi and insects.[1] A main strategy for its construction has been the classical acid-catalysed intramolecular cyclisation of the corresponding keto-diol precursors or their equivalents.[1,2] Consequently, control of the stereochemistry at the anomeric centre was, almost exclusively, based on the relative thermodynamic stabilities of the different isomers in the acid-catalysed spiroketalisation step. When all factors that control spirocyclisation, that is, a maximum anomeric effect and minimum steric interactions are reinforcing, a thermodynamically (anomerically) favoured isomer forms as the major or even exclusive product.

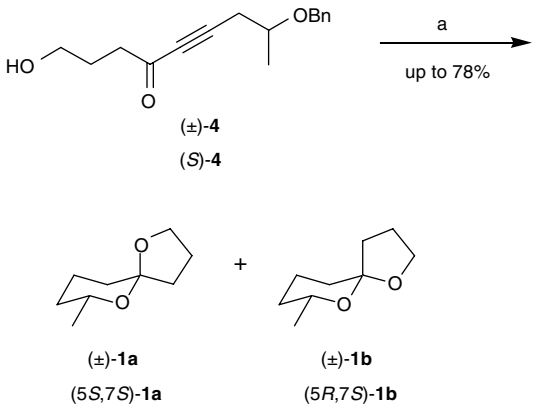
Although most of the biologically active spiroketals have the thermodynamically stabilised configuration, exceptions from this regularity have been described[1a,c,3] indicating a need for further nonstabilised spiroketal-targeted synthetic efforts. Recently, we have developed[4] a new high yielding strategy towards the construction of [4.4], [4.5], [5.5] and [5.6] spiroketal structures starting from easily available[5] benzyl protected hydroxy α-alkynones. According to our strategy, in contrast to a partly similar strategy described previously,[6] the spiroketalisation occurs under mild, nonacidic conditions. This implies that isomerisation at the spirocentre is not likely to happen, thus making our protocol well suited to the synthesis of isomeric mixtures with a unique ratio of less stable/more stable diastereoisomers.

In this letter, we describe an adaptation of our previously described strategy[4] and demonstrate its potential as a method for the preparation of stereoisomeric 7-methyl-1,6-dioxaspiro[4.5]decanes **1**, 2,7-dimethyl-1,6-dioxaspiro[4.5]decanes **2** and 2,8-dimethyl-1,7-dioxaspiro[5.5]undecanes **3**. Our intention was to construct these spiroketals in a simple fashion with particular attention to the synthesis of the intrinsically less stable diastereoisomers.

Scheme 1 illustrates the synthesis of 7-methyl-1,6-dioxaspiro[4.5]decane **1**. Treatment of (±)-**4** with hydrogen in the presence of 10% palladium on charcoal in EtOH or EtOAc solutions resulted in a smooth and reproducible one-pot formation of a 7:3–3:2 (by gas chromatography) separable mixture of the major (*E*)-spiroketal (±)-**1a** together with the minor (*Z*)-isomer (±)-**1b** in about 75–78% yields (Table 1). Significantly, the two isomers were successfully separated and isolated by column chromatography under carefully controlled conditions (silica gel deactivated with 6% of water, 6:1 pentane/Et_2O)

Keywords: Spiroketals; α-Alkynones; Diastereoselective synthesis; Nonstabilised isomers.
* Corresponding author. Tel.: +420 220 183 201; fax: +420 220 183 582; e-mail: koutek@uochb.cas.cz

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.09.085



Scheme 1. Reagents and conditions: (a) H_2 (1 atm), 10% Pd/C, rt (for further details see Table 1).

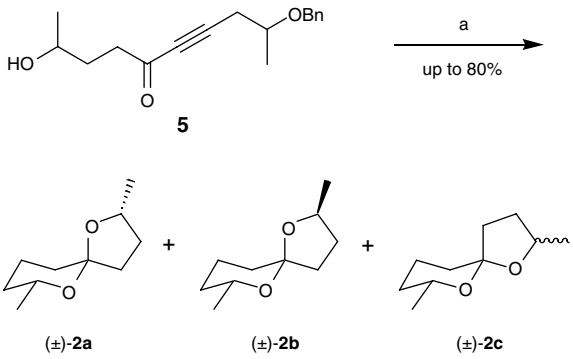
Table 1. Synthesis of spiroketals

Entry	Alkynone	Conditions[a]	Product	Yield[b] (%)
1	(±)-**4**	EtOAc, 14 h	(±)-**1a**	55 (76)[c]
			(±)-**1b**	23
2	(±)-**4**	EtOH, 11 h	(±)-**1a**	45 (61)
			(±)-**1b**	30 (11)
3	(*S*)-**4**	EtOH, 11 h	(5*S*,7*S*)-**1a**	(66)
			(5*R*,7*S*)-**1b**	(9)
4	**5**	EtOAc, 32 h	(±)-**2a**	21
			(±)-**2b**	21
			(±)-**2c**	38
5	**5**	EtOH, 15 h	(±)-**2a**	19 (27)
			(±)-**2b**	19 (25)
			(±)-**2c**	39 (21)
6	**6**	EtOAc, 24 h	(±)-**3a**	23 (30)[d]
			(±)-**3b**	38 (30)[d]
			(±)-**3c**	15
7	**6**	EtOH, 32 h	(±)-**3a**	24 (27)
			(±)-**3b**	39 (31)
			(±)-**3c**	16 (13)

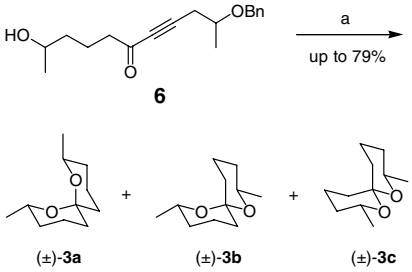
[a] Starting from 1 mmol of alkynone.
[b] GC yields. Numbers in parentheses refer to the isolated yields after liquid chromatography.
[c] After acidification of the reaction mixture and distillation. Starting from 50.8 mmol of the alkynone.
[d] After acidification of the reaction mixture and liquid chromatography.

yielding 61% of (±)-**1a** and 11% of (±)-**1b**. Both isomers were of sufficient purity to allow a full characterization by IR and NMR measurements and mass spectrometry. Analogous results were obtained when starting with the optically active (*S*)-**4**. As expected, the reaction afforded a mixture of (5*S*,7*S*)-**1a** (ee 99%) and (5*R*,7*S*)-**1b** (de 88%, ee 99%) with isolated yields of 66% and 9%, respectively. These reactions demonstrate, to the best of our knowledge, the first synthesis[7] of the very unstable contra-thermodynamic (*Z*)-isomer **1b**.

The strategy was similarly successful in transforming the alkynones **5** (Scheme 2) and **6** (Scheme 3) both of which are mixtures of diastereoisomeric racemic pairs due to



Scheme 2. Reagents and conditions: (a) H_2 (1 atm), 10% Pd/C, rt (for further details see Table 1).



Scheme 3. Reagents and conditions: (a) H_2 (1 atm), 10% Pd/C, rt (for further details see Table 1).

the presence of the two secondary methyl groups. Thus, the reaction of (±)-**5** afforded 2,7-dimethyl-1,6-dioxaspiro[4.5]decane **2** as a 1:1:2 mixture of (±)-**2a**, (±)-**2b** and (±)-**2c** (according to NMR analysis (±)-**2c** is an inseparable 1:1 mixture of two (7*Z*)-isomers),[8] while the reaction of (±)-**6** led to the formation of 2,8-dimethyl-1,7-dioxaspiro[5.5]undecane **3** as a mixture of (±)-**3a**, (±)-**3b** and (±)-**3c** in the ratio of 3:5:2. The results are summarised in Table 1. While no characteristic analytical data for the (7*Z*)-isomer(s) **2c** could be found in the literature, the corresponding data for (*Z*,*Z*)-isomer **3c** have been published previously[9] and agree with those obtained in this work.

The conformations of spiroketals **1** and **2** were determined on the basis of standard 1D and 2D NMR techniques (Table 2). Although, due to rather complex spectra of these mono- and disubstituted spiroketals, we were not able to detect sufficiently clear diagnostic NOESY cross-peaks to confirm the conformations

Table 2. Selected NMR data of spiroketals **1** and **2**[a]

	1a	**1b**	**2a**	**2b**	**2c**
δ_H (α-H_{ax})	4.02	3.50	4.17	4.22	3.47–3.55
δ_C (C7)	65.89	69.01	65.46	65.15	68.67
					69.19
$^3J_{aa}$	11.3	9.9	11.2	11.4	10.2
$^3J_{ae}$	2.3	2.8	2.3	2.3	2.7
δ_C (C5)	104.98	105.95	105.24	104.99	105.29
					105.76

[a] Measured in C_6D_6, at 500 MHz (for 1H) and 125 MHz (for 13C), chemical shifts are given in ppm and coupling constants in hertz.

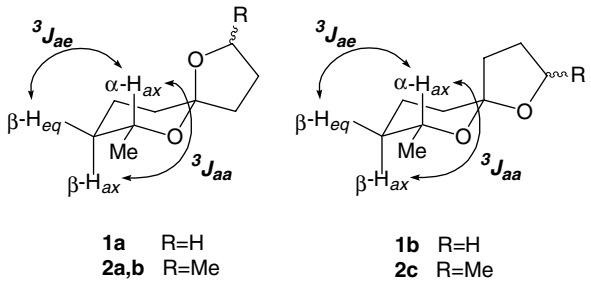
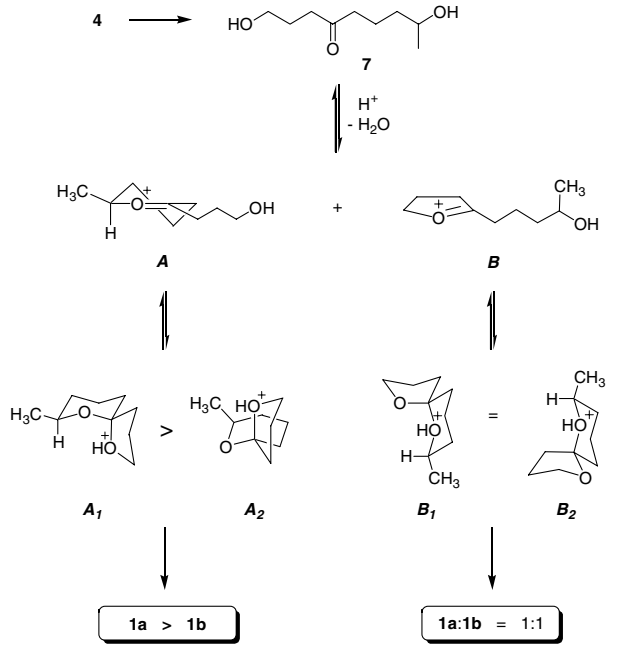


Figure 1. Structure of spiroketals **1** and **2**.

depicted in Figure 1, the observed coupling constants for H7 (Table 2) unambiguously indicate that this proton is predominantly axial (7-Me equatorial) in all isomers, thus supporting the presented structures. The lower values of $^{3}J_{aa}$ for the (7*Z*)-isomers **1b** and **2c** can be explained by a small distortion of the chair geometry. Furthermore, there are several characteristic trends in the ^{1}H and ^{13}C NMR spectra (Table 2) that mirror earlier findings.[3c,9–11] The chemical shifts of the axially-oriented H7 are one of the most distinctive features. When the H7 is in a 1,3-diaxial relationship with the C–O bond, the resonance is shifted downfield for the (7*E*)-isomers compared to the (7*Z*)-isomers. Also the differences in chemical shifts of C7 caused by the well known γ-effect are significant and argue for the suggested structures. Somewhat controversially, although mentioned in the literature,[3c,10] trends in the chemical shifts of the spirocarbon C5, where (*E*)-isomers of spiroketals usually show resonances shifted to a slightly lower frequency (upfield), are consistent with our observations, especially for **1a** and **1b**.

Importantly, the (*E*)/(*Z*) isomer ratio was found to remain unchanged under our mild conditions, while the mixture of **1a** and **1b** was very rapidly (<5 min) equilibrated upon treatment with hydrochloric acid to give the spiroketal **1a** as sole product. To a certain extent, isomer **1b** also undergoes conversion to **1a** during the isolation work-up; this explains the discrepancy between the initial and isolated diastereoisomer ratio (Table 1). The same **1b** → **1a** conversion was observed during storage both neat and as solutions in nonpolar solvents. On the other hand, **1b** is relatively stable in polar solvents (EtOH or EtOAc) where it may be stored without significant changes for at least several weeks. The anomerically nonstabilised isomers **2c** and **3c** displayed nearly the same chemical behaviour.

It can be inferred from the above results that the spiroketalisation under prescribed conditions proceeds in a way similar to that described by Deslongchamps for the formation of [5.5] spiroketals by kinetically controlled cyclisation of dihydroxyketones or hydroxyenolethers.[11] Additional observations, namely that no unsaturated spiroketals were detected during the whole course of these transformations and that the ratio of isomers **3a**:**3b**:**3c** = 3:5:2 formed under our conditions (Table 1) was essentially identical with that formed by kinetically controlled cyclisation,[11b] lend further support to the kinetically controlled process.



Scheme 4. Proposed mechanism of the kinetically controlled formation of spiroketal **1**.

Accordingly, the formation of, for example, [4.5] spiroketal isomers **1** from **4** is assumed to occur via intramolecular dehydrative ketalisation of the pre-formed dihydroxyketone **7**, whose protonation[12] promotes the formation of two oxocarbenium ion intermediates **A** and **B** (Scheme 4). Although the oxocarbenium ion **A** can actually exist in two conformations (both conformations leading to energetically equivalent protonated spiroketals) that (showed in Scheme 4) with the methyl group in an equatorial position should be, due to steric reasons, explicitly favoured. The formation of oxocarbenium ions **A** and **B** would then be followed by a stereoelectronically controlled antiperiplanar attack by the hydroxyl group either from the lower or upper side affording the respective chair-like ($\mathbf{A_1}$) and twist-boat-like ($\mathbf{A_2}$) transition states. Assuming an early transition state,[11b] the $\mathbf{A} \rightarrow \mathbf{A_1}$ conversion benefits from steric interactions and would be slightly favoured over the $\mathbf{A} \rightarrow \mathbf{A_2}$ conversion. On the other hand, in the case of **B**, both pathways leading to transition states $\mathbf{B_1}$ and $\mathbf{B_2}$ are stereoelectronically nearly equivalent. This reasoning would explain the observed excess (~20% de even at the beginning of the reaction) of isomer **1a** over **1b** (see Table 1). We suppose that the formation of spiroketal **2** proceeds similarly furnishing the **2a**:**2b**:**2c** isomer ratio of about 1:1:2. This ratio may indicate that the energetic differences in possible pathways are less after introduction of the second methyl group.

In conclusion, we have developed a new scalable kinetically controlled approach towards simple spiroketals, which could be applied to the synthesis of different spiroketal isomers, including those lacking anomeric stabilisation. The approach is capable of providing the nonstabilised isomers in relatively large amounts thus making biological tests of some less-stable spiroketal insect pheromone components (e.g., **1b**) possible for

the first time (cf. Refs. 1c,3b). Moreover, we believe the approach holds considerable potential for further syntheses of more elaborated spiroketal targets.

Acknowledgements

Financial support from the research projects Z4-055-905 and MSM 113100001 is gratefully acknowledged. We also thank Ms. Jana Mašková for performing chromatographic analyses.

Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.09.085. A general procedure and analytical data for spiroketals **1**, **2** and **3** are included.

References and notes

1. For reviews of spiroketals, see: (a) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617–1661; (b) Jacobs, M. F.; Kitching, W. *Curr. Org. Chem.* **1998**, *2*, 395–436; (c) Francke, W.; Kitching, W. *Curr. Org. Chem.* **2001**, *5*, 233–251; (d) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227–256.
2. Ghosh, S. K.; Hsung, R. P.; Liu, J. *J. Am. Chem. Soc.* **2005**, *127*, 8260–8261.
3. (a) Chen, J.; Fletcher, M. T.; Kitching, W. *Tetrahedron: Asymmetry* **1995**, *6*, 967–972; (b) Zhang, Q.-H.; Tolasch, T.; Schlyter, F.; Francke, W. *J. Chem. Ecol.* **2002**, *28*, 1839–1852; (c) Pihko, P. M.; Aho, J. E. *Org. Lett.* **2004**, *6*, 3849–3852.
4. Doubský, J.; Streinz, L.; Šaman, D.; Zedník, J.; Koutek, B. *Org. Lett.* **2004**, *6*, 4909–4911.
5. Doubský, J.; Streinz, L.; Lešetický, L.; Koutek, B. *Synlett* **2003**, 937–942.
6. Jacobson, R.; Taylor, R. J.; Williams, H. J.; Smith, L. R. *J. Org. Chem.* **1982**, *47*, 3140–3142.
7. Selected analytical data. Compound (±)-**1b**: ^{1}H NMR (500 MHz, C_6D_6): $\delta = 1.15$–1.20 (m, H8, 1H), 1.29–1.34 (m, H8, 1H), 1.30 (d, Me, $J = 6.2$ Hz, 3H), 1.32–1.36 (m, H9, 1H), 1.33–1.38 (m, H4, 1H), 1.58–1.61 (m, H3, 1H), 1.63–1.67 (m, $H10_{eq}$, 1H), 1.69–1.71 (m, H9, 1H), 1.91 (ddq, H3, $J = 6.1$, 8.3 and 11.8 Hz, 1H), 1.94 (dt, $H10_{ax}$, $J = 4.1$ and 12.5 Hz, 1H), 2.07 (ddd, H4, $J = 3.9$, 8.2 and 12.5 Hz, 1H), 3.50 (ddq, $H7_{ax}$, $J = 2.8$, 6.2 and 9.9 Hz, 1H), 3.86 (dt, H2, $J = 6.1$ and 7.9 Hz, 1H), 4.14 (dt, H2, $J = 5.8$ and 8.1 Hz, 1H). ^{13}C NMR (125 MHz, C_6D_6): $\delta = 20.59$ (C9), 21.32 (Me), 23.44 (C3), 31.61 (C8), 32.20 (C4), 33.31 (C10), 66.29 (C2), 69.01 (C7), 105.95 (C5). GC–IR: 2980, 2948, 2889, 1456, 1376, 1214, 1073, 1010 cm^{-1}. Compound (5*R*,7*S*)-**1b**: $[\alpha]_D^{20}$ +25.4 (*c* 0.156, Et_2O).
8. Selected analytical data. Compound (±)-**2c**: ^{1}H NMR (500 MHz, C_6D_6): $\delta = 1.14$–1.26 (m, H8, 2H), 1.25 (d, *Z*,*Z*-7-Me, $J = 6.1$ Hz, 3H), 1.28 (d, *E*,*Z*-7-Me, $J = 6.2$ Hz, 3H), 1.30 (d, *E*-2-Me, $J = 6.2$ Hz, 3H), 1.30–1.35 (m, *E*-H3, 1H), 1.32–1.36 (m, H10, 1H), 1.32–1.37 (m, $2 \times$ H8 + $2 \times$ H9, 4H),1.45 (d, *Z*-2-Me, $J = 6.1$ Hz, 3H), 1.55–1.60 (m, H10, 1H), 1.62–1.66 (m, H4, 2H), 1.65–1.76 (m, H9, 2H), 1.70–1.82 (m, *Z*-H3, 1H), 1.89–1.96 (m, H4, 2H), 1.99–2.05 (m, H3, 2H), 2.03–2.06 (m, H10, 1H), 2.20 (ddd, H10, $J = 1.9$, 7.1 and 12.4 Hz, 1H), 3.47–3.55 (m, $H7_{ax}$, $J = 2.7$, 6.2 and 10.2 Hz, 2H), 4.20 (m, *Z*-H2, 1H), 4.52 (m, *E*-H2, 1H). ^{13}C NMR (125 MHz, C_6D_6): $\delta =$ 20.39 (*Z*,*Z*-7-Me), 20.56 (C9), 20.69 (C9), 21.36 (*E*-2-Me), 21.70 (*E*,*Z*-7-Me), 22.31 (*Z*-2-Me), 31.26 (C3), 31.29 (C3), 31.66 (C8), 31.79 (C8), 32.61 (C10), 32.84 (C10), 33.91 (C4), 33.93 (C4), 68.67 (C7), 69.19 (C7), 73.22 (*E*-C2), 75.24 (*Z*-C2), 105.29 (C5), 105.76 (C5). GC–IR: 2979, 2946, 2878, 1459, 1379, 1220, 1076, 1012 cm^{-1}.
9. Kitching, W.; Lewis, J. A.; Perkins, M. V.; Drew, R.; Moore, Ch. J.; Schurig, V.; König, W. A.; Francke, W. *J. Org. Chem.* **1989**, *54*, 3893–3902.
10. Francke, W.; Reith, W.; Sinnwell, V. *Chem. Ber.* **1980**, *113*, 2686–2693.
11. (a) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauvé, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105–1121; (b) Pothier, N.; Goldstein, S.; Deslongchamps, P. *Helv. Chim. Acta* **1992**, *75*, 604–620.
12. The origin of acid catalysis (H^+ or Lewis acid) essential for the acetal formation still remains unclear. Some plausible explanations are: trace amounts of acetic acid present as impurity in the solvents, acidic nature of the glassware used or small traces of HCl present in the palladium catalyst (cf. Ref. 13).
13. Brimble, M. A.; Park, J. H.; Taylor, C. M. *Tetrahedron* **2003**, *59*, 5861–5868.