Pergamon

Tetrahedron 57 (2001) 2345–2347

TETRAHEDRON

Synthesis of a functionalized cyclohepten-one from erythronic acid-4-lactone

Wolfgang Pitsch,[a] Alex Russel,[a] Manfred Zabel[b] and Burkhard König[a,*]

[a]*Institut für Organische Chemie der Universität Regensburg, Universitätsstr. 31, D-93053 Regensburg, Germany*
[b]*Zentrale Analytik der NWF IV, Universität Regensburg, Universitätsstr. 31, D-93053 Regensburg, Germany*

Received 15 January 2001

Abstract—A convenient two-step synthesis of a functionalized and chiral cyclohepten-one **4**, which may serve as a useful building block in synthesis, is reported. The X-ray structure analysis of the intermediate hemiacetal **2** reveals the presence of a single anomer in the solid state, that equilibrates rapidly in solution.

Functionalized seven-membered ring systems are key structural elements of many natural products and artificial carbocyclic sugars.[1] Modern organic synthesis provides several methods for their synthesis including metal-catalyzed reactions.[2] We report here an efficient cycloheptenone formation by intramolecular Michael reaction. The cyclization is initiated by base and does not require any additional reagents, a fact which might be advantageous for large scale reactions or the development of environmental benign processes. The functionality and structure of the product cyclohepten-one of **4** render it an interesting building block for natural products or new chemical syntheses.

The synthesis starts from commercially available 2,3-*O*-isopropylidene-*D*-erythronolactone **1**.[3] Addition of the lithium acetylide of TMS acetylene following known procedures gave lactol **2** in 67% isolated yield.[4] Singh and coworkers proposed in their earlier report[4] that after recrystallization **2** is obtained as a single anomer, whose stereochemistry was not determined. We obtained suitable crystals of **2** after slow evaporation from petrol ether/diethyl ether for the X-ray analysis. Careful analyses of many crystals confirmed that the structure of **2** in the solid state indeed consisted of the single anomer shown in Fig. 1.[5] The ^{1}H NMR spectra immediately recorded after crystals were dissolved in $CDCl_3$ showed one set of signals for a single anomer. The ^{1}H NMR spectra recorded after 2 h at room temperature showed two sets of signals of equal intensity, which most likely is due to complete epimerization of the anomeric center.

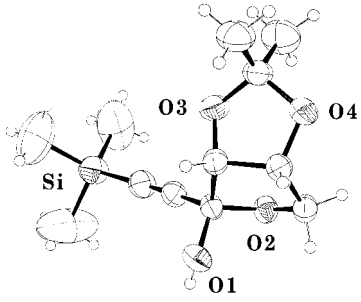


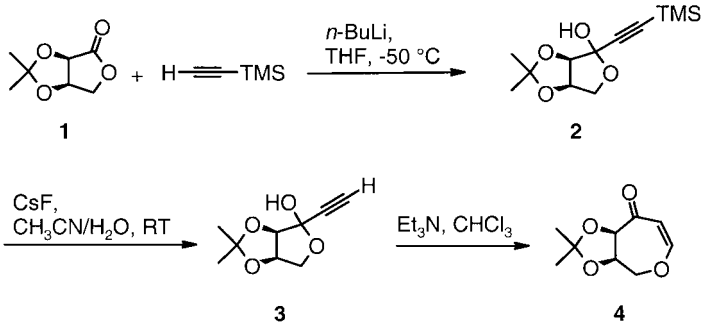
Figure 1. Structure of compound **2** in the solid state.

The TMS protecting group was removed with cesium fluoride under standard conditions to yield the cyclization precursor **3**. Attempts to deprotect the alkyne with tetrabutyl ammonium fluoride, lithium hydroxide or silver nitrate/potassium cyanate were not successful. When treated with 3 equiv. triethylamine in dichloromethane compound **3** cyclizes to give the target molecule **4** in 95% isolated yield. The reaction proceeds most likely via the open form of the lactol hemiacetal in which the hydroxy group undergoes base assisted nucleophilic attack to the terminal acetylenic carbon atom. The process can be described as a favorable 7-endo-dig cyclization[6] and subsequent protonation of the stabilized carbanion yields the cyclohepten-one structure of **4**. The *cis* geometry of the double bond is determined by the small ring size. All spectroscopic data confirm the structure of **4** (Scheme 1).

HPLC Analysis of the product **4** revealed an impurity of approx. five percent of a second diastereomer most likely caused by racemization under the reaction conditions. Optically pure **4** was obtained by HPLC separation (column Chiralcel OD, *n*-heptane/*i*-propanol, 9:1) and Fig. 2 shows the CD spectra (in the flow) of the compound **4**.

Keywords: cyclohepten-one; cyclization; TMS.
* Corresponding author. Tel.: +49-941-943-4576; fax: +49-941-943-1717; e-mail: burkhard.koenig@chemie.uni-regensburg.de

0040–4020/01/$ - see front matter
PII: S0040-4020(01)00106-5



Scheme 1.

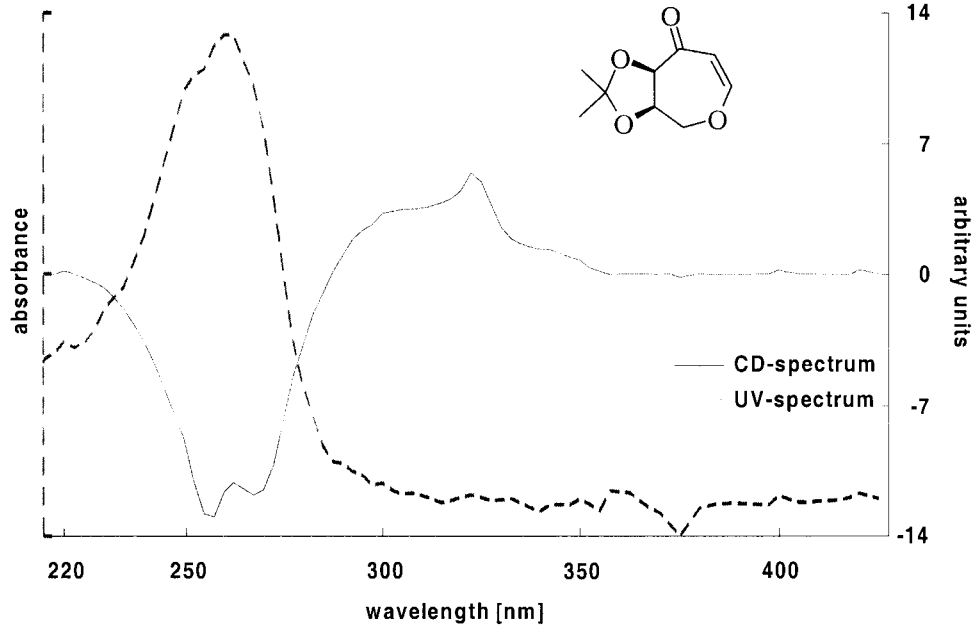


Figure 2. CD spectrum of compound **4** in *n*-heptane/*i*-propanol, 9:1.

1. Experimental

All ^{1}H NMR spectra were recorded at 200 MHz, all ^{13}C NMR spectra at 50 MHz in $CDCl_3$. The multiplicity of the ^{13}C signals was determined with the DEPT technique and quoted as: (+) for CH_3 or CH, (−) for CH_2 and (C_{quat}) for quaternary carbons. CC means column chromatography on silica gel. PE means petrol ether with a boiling range of 60–70°C. EE means ethyl acetate.

1.1. General

Crystal data[5] $C_{12}H_{20}O_4Si$, M=256.37, orthorhombic, space group $P2_12_12_1$, a=597.35 (4), b=1038.36 (8), c=2390.29 (18) pm, V=1.4826 nm^3, Z=4, D_x=1.149 Mg m^{-3}, μ(MoKα)=0.16 mm^{-1}, T=297 K. *Data collection*. A colourless plate like crystal 0.60×0.24×0.16 mm^3 was used to collect 20957 data (2865 unique) to $2\Theta_{max}$ 51.8° on a STOE Imaging Plate Diffraction System. *Structure refinement*. Structure solution by direct methods (SIR97),[7] structure refinement by SHELXL 97[8] with anisotropical thermal parameters for all non H atoms, hydrogen atoms attached to C atoms were included using a riding model, the hydrogen attached to O1 was found in the difference Fourier synthesis and refined isotropically. The correct absolute structure was proved by Flack parameter[9] x=0.0(2). For all data the final $wR2$ was 0.1494 for 158 parameters, $R1$=0.060, S=0.988, max. $\Delta\rho$=395 e nm^{-3}

1.1.1. 1-Trimethylsilylethynyl-2,3-*O*-isopropylidene-D-erythrofuranosyl acetate (2)[4]. To a solution of TMS acetylene (0.78 g, 7.94 mmol) in 30 mL of THF was added under nitrogen at −30°C *n*-BuLi (6.4 mL, 9.5 mmol, 1.5 mol/L), the reaction mixture was allowed to warm up to room temperature for 15 min and was then cooled to −80°C. A solution of **1** (1.51 g, 9.5 mmol) in 25 mL of THF was added dropwise, the reaction mixture was allowed to warm up to room temperature over 2 h and quenched with aqueous sat. NH_4Cl (30 mL). The aqueous phase was extracted with diethyl ether (3×50 mL), the combined organic phases were dried over Na_2SO_4, the solvent was removed in vacuo and the crude product was purified by CC (PE/EE 3:1) to yield 1.37 g (67%) **2**, as a white solid, mp=92°C. IR (neat): $\tilde{\nu}$=3352 cm^{-1}, 2963, 2181, 1461, 1381. ^{1}H NMR: δ=0.19 (s, 9H), 1.34 (s, 3H), 1.51 (s, 3H), 4.02 (m, 2H), 4.52 (m, 1H), 4.70 (m, 1H).

1.1.2. (*R*,*R*)-2,2-Dimethyl-3a,8a-dihydro-4H-[1,3]dioxolo-[4,5-c]oxepin-8-one (4). A solution of **2** (280 mg, 1.1 mmol) and CsF (200 mg, 1.3 mmol) in 1 mL of water and 30 mL of acetonitrile was stirred at room temperature for 4 h. Water (50 mL) and diethyl ether (200 mL) were added, the organic phase was separated and dried over Na_2SO_4, and the solvent was removed in vacuo to yield 200 mg (99%) of **3**, as a slightly yellow oil. ^{1}H NMR: δ=1.34 (s, 3H), 1.51 (s, 3H), 2.65 (s, 1H) 4.02 (m, 2H), 4.52 (m, 1H), 4.70 (m, 1H). MS (70 eV); *m*/*z* (%): 183 (5) [M^+-H], 169 (70), 59 (100).

Compound **3** (200 mg, 1.1 mmol) was dissolved in 50 mL of $CHCl_3$, triethylamine (0.33 mL, 210 mg, 2.3 mmol) was added and the reaction mixture was stirred for 30 min at room temperature. The solvent and base were removed in vacuo and the crude product was purified by CC (PE/Et_2O 1:1) to yield 199 mg (95%) of **4**, as an oil. IR (neat): $\tilde{\nu}$=3060 cm^{-1}, 2989, 1765, 1681, 1679, 1667. UV (CH_2Cl_2): λ_{max} (lg ϵ)=254 nm (3.643), 224 (3.198), 314 (1.942). ^{1}H NMR: δ=1.30 (s, 3H, CH_3); 1.41 (s, 3H, CH_3); 3.83 (m, 1H, CH_2^A); 4.30 (m, 1H, CH_2^B); 4.62 (m, 2H, CH); 5.13 (d, 1H, CH, ^3J=7.3 Hz); 6.93 (d, 1H, CH, ^3J=7.3 Hz). ^{13}C NMR: δ=24.5 (+), 26.5 (+), 73.0 (−), 75.5 (+), 83.8 (+), 105.4 (+), 110.2 (C_{quat}), 158.9 (+), 194.7 (C_{quat}). MS (70 eV); *m*/*z* (%): 185 (18) [M^++H], 170 (72) [M^++H−CH_3]. HRMS: $C_9H_{12}O_4$ Calcd 184.073559; found 184.07354±1.26 ppm.

References

1. For recent examples, see: Wagner, C.; Heidrun, A.; Sterner, O. *J. Nat. Prod.* **1998**, *61*, 501–502. Mulholland, D. A.; Iourine, S. *Phytochemistry* **1998**, 1357–1362.
2. For a recent review of the use of metathesis for ring synthesis, see: Maier, M. E. *Angew. Chem.* **2000**, *112*, 2153–2157. Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073–2077.
3. (a) Csuk, R.; Schaade, M. *Tetrahedron Lett.* **1993**, *34*, 7907–7910. (b) Heitz, M.-P.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 2591–2596. (c) Csuk, R.; Schaade, M. *Tetrahedron* **1994**, *50*, 3333–3348. (d) Perri, S. T.; Dyke, H. J.; Moore, H. W. *J. Org. Chem.* **1989**, *54*, 2032–2034. (e) Glaenzer, B. I.; Csuk, R. *Carbohydr. Res.* **1991**, *220*, 79–92.
4. Jiang, S.; Singh, G.; Wightman, R. H. *Chem. Lett.* **1996**, 67–68.
5. Full details of the X-ray structure analysis have been deposited with the Cambridge Crystallographic Data Centre, No.: CCDC 153054.
6. Johnson, C. D. *Acc. Chem. Res.* **1993**, *26*, 476–482.
7. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A. *J. Appl. Crystalogr.* **1993**, *26*, 343–350.
8. Sheldrick, G. M. SHELXL 97: *Program for crystal structure refinement*; University of Göttingen: Germany, 1997.
9. Flack, H. D. *Acta Crystalogr.* **1983**, *A39*, 876–881.