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A NEW STEREOSELECTIVE APPROACH TO THE TRANS-PERHYDROAZULENE SKELETON

Brigitta Popp, Frank Sönnichsen and Werner Tochtermann*

Institut für Organische Chemie der Universität, Olshausenstr. 40, D-2300 Kiel, FRG

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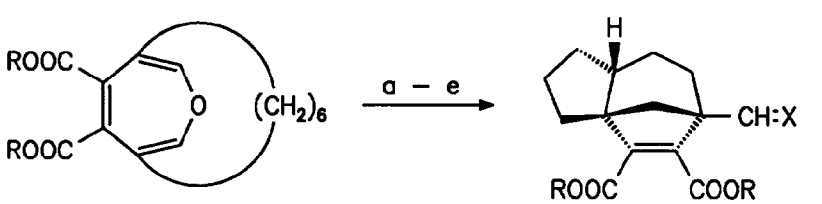
Key Words: Solid state photochemical rearrangement; Ring enlargement; Ruthenium tetroxide oxidation

Abstract: Optically active hydroazulenes have been synthesized by solid state photochemical rearrangement of the diester (–)-**1a** and subsequent ring enlargement of the tosylhydrazone (+)-**2c**. Oxidative cleavage of the double bond of (+)-**3** gives the trans-perhydroazulene (–)-**4**.

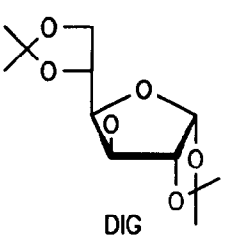
The hydroazulene skeleton occurs widely in natural products. Stereoselective syntheses for this class of compounds are therefore highly desirable[1]. We here report on a new approach to optically active trans-perhydroazulenes functionalized on C-3a and C-6.

Our synthesis starts with the solid state photochemical rearrangement of the di-*O*-isopropylidene-α-D-glucofuranosyl diester (–)-**1a**. This diester gives, by solid state photochemical rearrangement of the oxepine part in aqueous suspension, the methanohydroazulene **2a** in 58% yield with 92% *de*[2,3]. The aldehyde (+)-**2b** with (3a*S*,6*R*,8a*R*)-configuration[3] is obtained in 96% yield after removal of the chiral auxiliary.



1 **2**

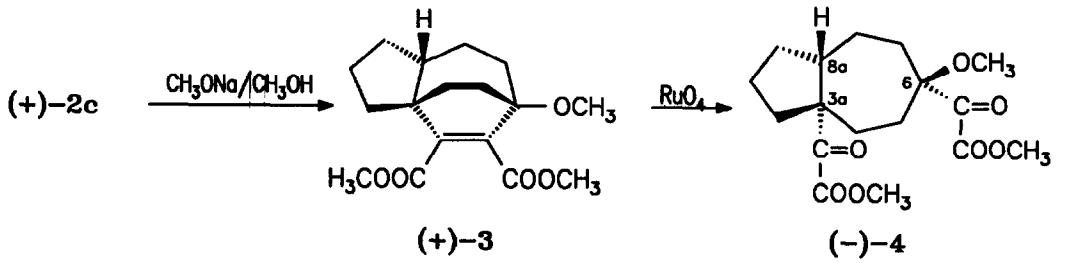
a) hν
b) CH_3ONa/CH_3OH
c) CH_2N_2/CH_2Cl_2
d) 2 N HCl, THF
e) $Ts–NH–NH_2/CH_3OH$



1,2	RO	X
a	DIG	O
b	CH_3O	O
c	CH_3O	N–NH–Ts

Decomposition of the tosylhydrazone (+)-**2c** with sodium methoxide in methanol[4] (42 hours under reflux) gives, by ring enlargement under the migration of the methano bridge, the methyl ether (+)-**3** in 35% yield. (+)-**3** can be easily separated from by-products (see below) by flash chromatography on silica gel with ether/pentane (1:1).

Ruthenium tetroxide oxidation[5] finally leads to the crystalline perhydroazulene derivative (−)-**4** in 36% - 58% yield.

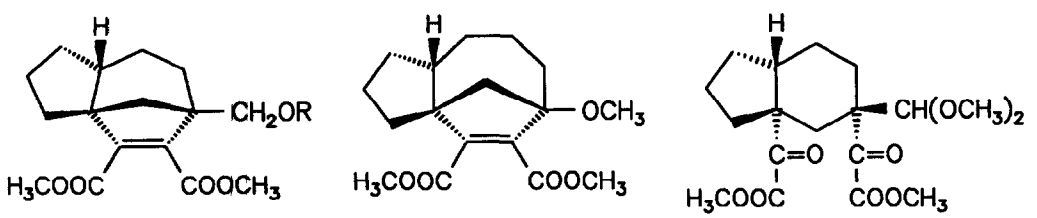


(+)−3 (−)−4

Structural assignments

Characteristic physical and spectroscopic data for all new compounds are given[6].

The structural assignment of **3** and **4** is based on the NMR spectra and the comparison with the related compounds **5** and **6**. With (±)-**2c** as the starting material, 6% (±)-**5b**, 8% (±)-**6**, and 26% (±)-**5a** were separated by flash chromatography and isolated in addition to the main product (±)-**3**. Compounds **2c**, **5** and **6** show characteristic signals for the *syn* and *anti* hydrogens of the isolated methylene group belonging to the methano bridge[6]. This also holds for the trans-hydrindane (+)-**7**, described earlier[7]. These signals are no longer present in **3** and **4** hereby establishing the ring enlargement and formation of an ethano bridge in **3**.



(±)−5 (±)−6 (+)−7

(±)−5	a	b
R	H	CH_3

The chemical shifts of C-8a (**3**: 48.74 ppm (d); **4**: 48.54 ppm (d)) are typical for trans-fused bicyclic systems[8]. The absolute (3a*S*,6*R*,8a*R*)-configurations of (+)-**3** and (−)-**4** follow from the x-ray structural analysis of the dimenthylester **2** [RO = menthyl] and chemical correlations[3]. In the above reaction sequence **2a** → **2b** → **2c** → **3** the stereochemistry on C-3a and C-8a remains untouched. The stereochemistry on C-6 of compound **3** is determined by the bridgehead position. The diastereomeric purity (≥98%) of **2a** is derived from the NMR spectra[3]. In addition the relative configuration of our starting material (+)-**2b** is established by x-ray structural analysis of the oxidation product (+)-**7**[7].

Recently we have performed the rearrangement **1** → **2** with di-*O*-isopropylidene-α-L-glucofuranose as chiral auxiliary (yield 54% with 93% *de*)[3]. In consequence the enantiomers (−)-**3** and (+)-**4** can be synthesized by the same procedure.

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References and Notes

*) Dedicated with respect to the memory of Professor Günther Snatzke.

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We have been able to increase our originally reported yield of 45% **2a** with 83% de by the use of very pure di-*O*-isopropylidene-α-D- and L-glucose synthesized by the method of Schmidt, O. T. *Methods Carbohydr. Chem.* **1963**, *2*, 318-325. Ott, F. *diploma thesis*, Universität Kiel, **1992**; *Chem. Ber.* in preparation.

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6) Selected physical and spectroscopic data of new compounds:

(+)-**2c**: mp. 49 °C (from dichloromethane/pentane); $[\alpha]_D^{20}$ = + 72.5, $[\alpha]_{546}^{20}$ = + 87.1, $[\alpha]_{436}^{20}$= +156.5 (c = 0.72, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.42 ppm (d, *J* = 10.9 Hz, 1 H, *anti* 9-H), 2.41 (dd, *J* = 10.9, 2.0 Hz, 1 H, *syn* 9-H).

(+)-**3c**: Oil; $[\alpha]_D^{20}$ = + 15.0, $[\alpha]_{546}^{20}$ = + 17.7, $[\alpha]_{436}^{20}$= + 25.8 (c = 0.48, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.8 - 2.3 ppm (m, 15 H), 3.21 (s, 3 H, 6-OCH_3), 3.70, 3.73 (2 s, 6 H, $COOCH_3$).

(−)-**4**: mp. 98 °C (from ether/pentane); $[\alpha]_D^{20}$ = − 49.5, $[\alpha]_{546}^{20}$ = − 58.0, $[\alpha]_{436}^{20}$= −102.5 (c = 0.2, ether). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.60 - 2.52 ppm (m, 15 H, CH, CH_2), 3.35 (s, 3 H, 6-OCH_3), 3.85 (s, 3 H, $COOCH_3$), 3.86 (s, 3 H, $COOCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.53 ppm (t, CH_2), 25.19 (t, CH_2), 30.67 (t, CH_2), 32.28 (t, CH_2), 33.12 (t, CH_2), 33.36 (t, CH_2), 39.90 (t, CH_2), 48.54 (d, C-8a), 52.39 (q, OCH_3), 52.52 (q, OCH_3), 53.32 (q, OCH_3), 59.81 (s, C-3a), 85.48 (s, C-6), 163.67 (s, $COOCH_3$), 165.03 (s, $COOCH_3$), 200.14 (s, C=O)*, 200.44 (s, C=O)*.

(±)-**5a**: mp. 59-60 °C (from ether/pentane); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.25 ppm (d, *J* = 10 Hz, 1 H, *anti* 9-H), 2.33 (dd, *J* = 10, 1.5 Hz, 1 H, *syn* 9-H).

(±)-**5b**: Oil; ^1H NMR (90 MHz, $CDCl_3$): δ = 1.27 ppm (d, *J* = 10 Hz, 1 H, *anti* 9-H), 2.30 (dd, *J* = 10, 1-2 Hz, 1 H, *syn* 9-H), 3.27 (s, 3 H, CH_2OCH_3), 3.44 (AB, 2 H, CH_2OCH_3).

(±)-**6**: mp. 82 °C; ^1H NMR (90 MHz, $CDCl_3$): δ = 1.93 ppm (AB, *J* = 12 Hz, 1 H), 2.39 (AB, *J* = 12 Hz, 1 H), 3.14 (s, 3 H, OCH_3).

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