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ASYMMETRIC PHOTOCYCLOADDITION BETWEEN FURAN AND OPTICALLY ACTIVE KETONES

SŁAWOMIR JAROSZ and ALEKSANDER ZAMOJSKI*
Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warszawa, Poland

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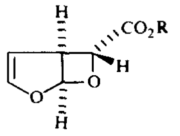
Abstract—The photochemical reaction between 3β-acetoxyandrost-5-en-17-one **4** or (−)-methone **5** and furan was preceded by isomerization of the ketones to the corresponding γδ-unsaturated aldehydes which subsequently added to furan furnishing 6-substituted 2,7-dioxabicyclo-[3.2.0]hept-3-enes, **8** and **9**. Under the same conditions 1,2:5,6-di-O-isopropylidene α-D-ribo-hexofuranos-3-ulose **12** reacted with furan without any isomerization and afforded all four stereoisomeric bicyclic photoadducts **14–17**. The ratio of the products resulting from the approach of the furan molecule to **12** from the less hindered and from the more hindered sides was 3:1. This pointed at the decisive role of steric factors in controlling the course of photochemical cycloaddition.

In the previous paper[1] we reported on the results of asymmetric synthesis of alkyl 2,7-dioxabicyclo-[3.2.0]hept-3-ene-6-carboxylates **1** by photocycloaddition between chiral alkyl glyoxylates and furan. Photoadducts **1** are precursors of chiral 3-substituted furans **2**; compounds of this type are of potential importance in the synthesis of natural products containing 3-furyl moiety.



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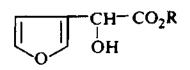

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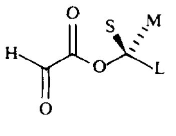
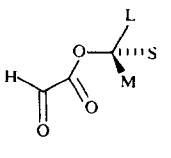
Photoadducts **1** were of low optical purity ranging from 2.3% to 7.3%. In order to explain the low asymmetric induction in this reaction we proposed[1] two hypotheses. In the first hypothesis, we assumed that the alkyl glyoxylate attacks the furan molecule in *endo* and *exo* fashion which causes partial cancellation of the inducing effects of the chiral alkoxy groups. The second explanation was based on the assumption that alkyl glyoxylate (being conformationally mobile) entered into reaction in two Prelog-type conformations: s-*trans* and s-*cis*, **3a** and **3b**.



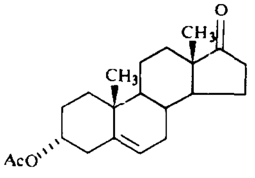
3a



3b

Here again, partial quenching of inducing effects must result. We prefer this last hypothesis in view of the similarity of our results with those observed for asymmetric diene[2] and ene[3] syntheses with the participation of chiral alkyl glyoxylates.

If this interpretation were correct, then application of chiral, conformationally rigid carbonyl compounds should decidedly enhance the yield of asymmetric induction in this photocycloaddition. Two readily available optically active cyclic ketones have been chosen for that purpose: 3β-acetoxyandrost-5-en-17-one **4** and *R*(−)-methone **5**.



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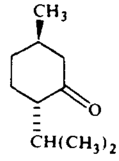

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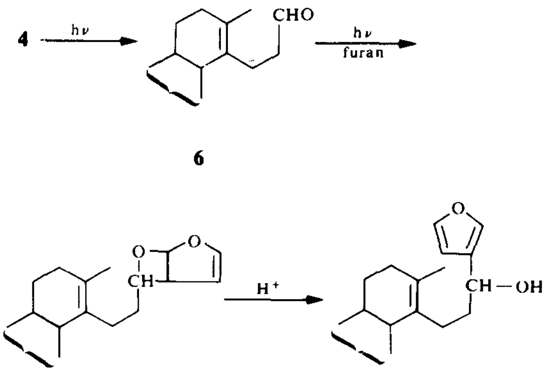
Irradiation of **4** and **5** with furan furnished in low yield photoadducts whose ^{1}H NMR spectra revealed the presence of a 2,7-dioxabicyclo-[3.2.0]hept-3-ene system. Isomerization of both photoadducts with *p*-toluenesulfonic acid gave—as expected—3-furyl derivatives. However, closer examination of the ^{1}H NMR spectral data of the photoadducts as well as their isomerization products led to the conclusion that both starting ketones **4** and **5** were photochemically isomerized to γδ-unsaturated aldehydes **6**[4] and **7**[5] (Norrish-type I photoisomerization) *before* reacting with furan. In consequence, photoadducts **8** and **9** and the derived 3-furylmethanols **10** and **11** had the following structures:



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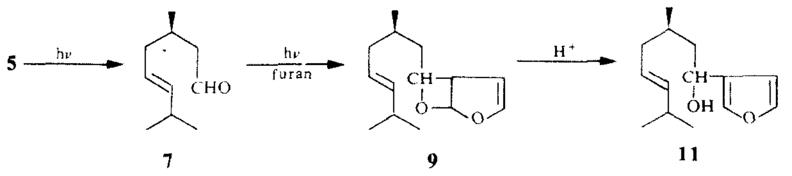
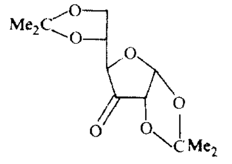
8 **10**



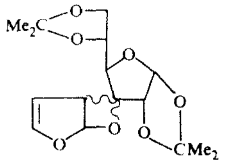
As expected, products **8**, **10** and **9**, **11** were mixtures of two diastereoisomeric species. In the case of compounds **8** and **10** we were unable to separate the mixture into its components. According to the ^{1}H NMR spectrum of **10** the proportion of both stereoisomers was close to 1:1. This proportion could have been foreseen because the closest chiral carbon atom in the $\gamma\delta$-unsaturated aldehyde **6** is four carbon atoms distant from the reacting carbonyl group. In contrast, the mixture of diastereoisomeric 3-furyl derivatives **11** could be separated by chromatography and the proportion of both components was estimated at 2:1. By means of the Horeau method,[6] it was possible to assign the 1*R*:3*R* configuration to the major diastereoisomer of **11**. This result is interesting in so far as that by application of Cram's model for 1,3-asymmetric induction[7] diastereoisomers of this configuration could be predicted for **9** and **11** as the main products. Cram's induction model is based on steric interactions which, in turn, points at the importance of steric factors in photocycloadditions between furan and aldehydes.

Although the results of both the photocycloadditions with ketones **4** and **5** were interesting and pointed indirectly at the importance of steric factors in the photochemical process, they did not furnish the answer to our problem.

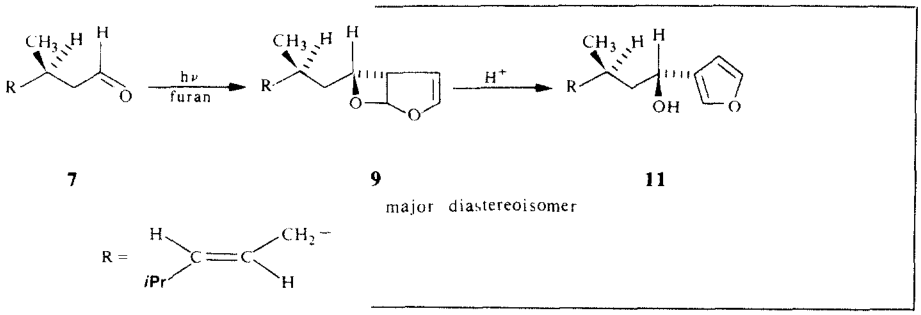
In the search for suitable, conformationally-rigid substrates for the photocycloaddition we turned our attention to the work of Tronchet and Baehler.[8] These authors reported that furan can be photochemically added to the carbonyl group of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose **12** *without* cleavage of the 5-membered ketone ring system. The photoadduct **13** was isolated in 20% yield however its configuration was not

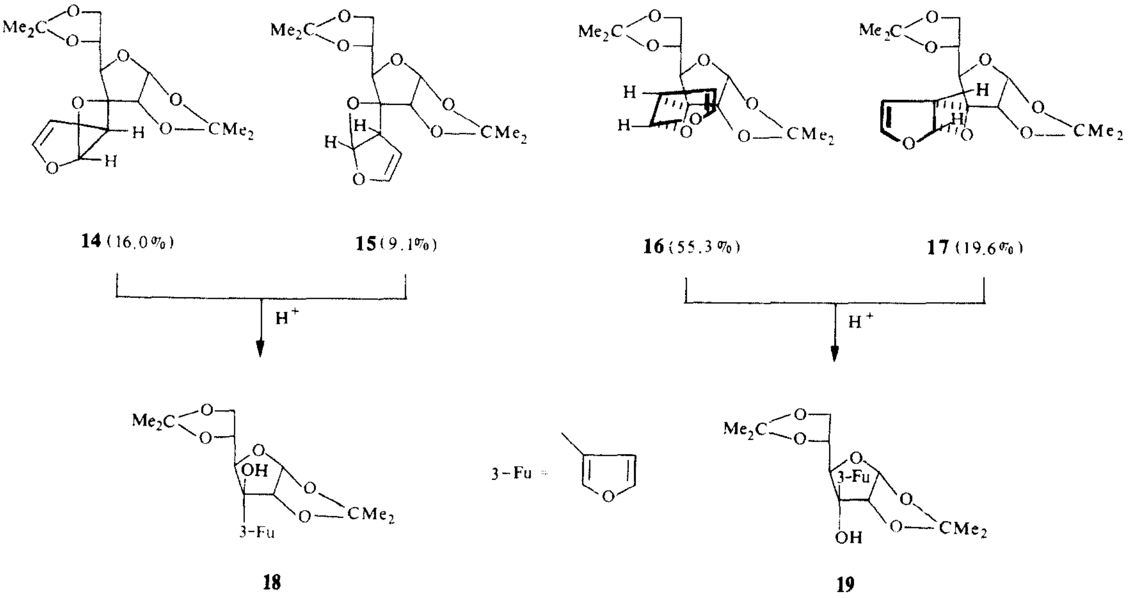


12



13





Scheme 1. The configuration of the bicyclic hept-3-ene system in pairs **14**–**15** and **16**–**17** is tentative.

determined.[8] We repeated the experiment of Tronchet and Baehler and found that irradiation of a solution of **12** in furan by a high-pressure mercury lamp gave a mixture of four, chromatographically-separable products **14–17** in *ca.* 60% overall yield. Elemental analysis confirmed that all products were adducts of **12** and furan. The ^{1}H NMR spectra of **14–17** were almost identical; they all displayed signals for H-1 and H-2 of the furanose ring which indicated that the five-membered ketone ring was not opened under the conditions of the photochemical reaction. Signals at δ:6.6 (multiplet), 6.3 (d, J = 4.0 Hz), and 5.3 (t, J = 3.0 Hz) pointed at the presence of a 2,7-dioxabicyclo-[3.2.0]hept-3-ene skeleton. It was clear therefore that the cycloaddition reaction resulted in *all* four possible diastereoisomeric adducts. The ratio of products **14–17**—in order of their appearance from the chromatographic column—was approximately 16:9:55:20. The main product **16** had physical constants identical with those reported in the literature.[8] Isomerization of **14** and **15** with *p*-toluenesulfonic acid afforded the same 3-furyl derivative: 1,2:5,6-*O*-isopropylidene-3-C-(3′-furyl)-α-D-*gluco*furanose **18**. Similarly, isomerization of **16** and **17** under the same conditions gave 1,2:5,6-di-*O*-isopropylidene-3-C-(3′furyl) α-D-*allo*furanose **19** (Scheme 1).

The configuration of stereoisomeric furanoses **18** and **19** could be unequivocally assigned by means of Eu(fod)$_3$-shifted ^{1}H NMR spectra. Armitage and Hall[9] reported a large downfield shift of H-5 signal in the spectrum of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose on addition of the europium shift reagent, whereas under analogous conditions the shift of H-5 in 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose was negligible. After addition of Eu(fod)$_3$ we did observe distinct downfield shift of H-5 signal in the spectrum of **18** and almost no shift of this signal in the spectrum of **19**.

The conclusion derived from this experiment is that photoadducts resulting from the attack of the furan molecule on the less hindered "upper" side of **12** constituted *ca.* 75% of the product mixture, contrasting with only 25% of photoproducts formed from the less accessible side of ketone **12**.

This result certainly confirms the importance of steric factors in the photochemical cycloaddition of the type discussed here. At the same time it provides answer to the problem of the low optical yields achieved with chiral alkyl glyoxylates: the exclusion of conformational liability of substrate visibly turns the reaction in one direction. We regard, therefore, the result of this experiment as a good confirmation of the second hypothesis put forward in the previous paper.

On the other hand, it is interesting to note that in the photochemical reaction of **12** up to 15% of less-favored products **14** and **15** were formed. It must be remembered that reactions of **12** in the ground state (e.g. reduction with NaBH$_4$[10]) occur almost exclusively from the "upper", readily accessible side of the ketone grouping.

EXPERIMENTAL

B.ps refer to air-bath temperature. M.ps are not corrected. The ^{1}H NMR spectra were recorded in CDCl$_3$ solutions on a Jeol JNM-4H-100 spectrometer. Rotations were measured using a Perkin–Elmer PE-141 automatic spectropolarimeter. All photochemical reactions were carried out in a Pyrex photochemical reactor[11] using a high pressure mercury lamp (250W) and were monitored by tlc (ligroine–ethyl acetate 4:1).

Photochemical reaction between 3β-acetoxyandrost-5-en-17-one **4** *and furan.* Ketone **4** (1 g) was dissolved in 150 ml of furan and irradiated for 16h. Furan was distilled off and 50 ml of ether was added causing the precipitation of furan polymers. Polymers were filtered off and the filtrate was evaporated to dryness. The oily residue was an inseparable (by tlc) mixture of several compounds which contained approximately 20% of product with 2,7-dioxabicyclo-[3.2.0]hept-3-ene skeleton [^{1}H NMR δ: 6.58 (*m*), 6.25 (d, J = 4.0 Hz); and 5.25 (t, J = 2.8 Hz)]. This mixture was dissolved in 5 ml of dry ether and kept overnight with 50 mg of *p*-toluenesulfonic acid monohydrate. After neutralization with triethylamine (0.1 ml) the product was isolated by chromatography (ligroine-ethyl acetate 9:1). 3-Furylmethanol **10**; yield, 102 mg, IR (film): 3550, 2900, 1740, 1510, and 880 cm^{-1}. ^{1}H NMR δ: 7.38 (m, 2H), 6.41 (m, 1H), 4.62 (m, 2H), 1.68 (s, 3H), and 1.00 (s, 3H). After addition of Eu(fod)$_3$ to the sample of alcohol **10** the signal at δ 1.68 (CH$_3$ on double bond) was split into two peaks of about equal intensity, which could be associated with both diastereoisomers **10**.

Alcohol **10** was acetylated (pyridine, acetic anhydride). ^{1}H NMR spectrum of the acetate showed two different signals for the methyl group at δ: 1.58 and 1.42 of equal intensity. Mass spectrum, *m/e*: 440 (M$^+$), 380, and 320.

Photochemical reaction between R($-$)*-methone* **5** *and furan.* Ketone **5** (1.54 g) in 150 ml of furan was irradiated for 23 hr. The residue, after evaporation of the furan, was distilled (b.p. 95°/0.3 Torr). The distillate—according to the ^{1}H NMR spectrum—was a mixture of several compounds containing *ca.* 25% of the photoadduct **9** [^{1}H NMR δ: 6.64 (m), 6.30 (d, J = 4.0 Hz), and 5.34 (t, J = 4.0 Hz)]. This mixture was dissolved in 10 ml of dry ether and kept for 4 hr at room temperature with 50 mg of *p*-toluenesulfonic acid monohydrate. After neutralization with *triethylamine (0.1 ml) the products were separated by chromatography* (ligroine–ethyl acetate 4:1). Three fractions were collected:

(1) A compound which did not contain a 3-furylmethanol grouping in the molecule–yield 1.0 g (^{1}H NMR spectrum showed no signals above δ 6 ppm).

(2) ($-$)-1-(3′-furyl)-3*R*, 7-dimethyl-oct-5-en-1*S*-ol[($-$)-**11**], yield 71.2 mg, b.p. 110°/0.3 Torr, $[\alpha]_D^{20} - 16.3°$ (c 1.0, CHCl$_3$). Analysis. (Found: C, 75.3; H, 10.3 calc. for C$_{14}$H$_{22}$O$_2$: C, 75.6; H 10.0%). IR (film): 3400, 2950, 1510, and 880 cm^{-1}. ^{1}H NMR δ: 7.41 (m, 2H), 6.43 (m, 1H), 5.36 (m, 2H), and 4.76 (t, 1H, J = 8.0 Hz). The absolute configuration of this alcohol was determined by the Horeau method:[6] 121.5 mg of racemic α-phenylbutyric anhydride was dissolved in 1 ml of dry pyridine, 43.3 mg of ($-$)-**11** was added, and the mixture was kept at room temperature overnight. Excess of anhydride was decomposed with 0.5 ml of water and 0.6 ml of 10% NaOH. After addition of 5 ml of water the alkaline solution was extracted twice with ether *(in order to remove chiral alkyl α-phenylbutyrates) and acidified* to pH 1 with conc. HCl. α-Phenylbutyric acid was extracted thrice with ether; its rotation $[\alpha]_D^{20} - 4.0°$ (c 1.1, benzene).

(3) (+)-1-(3′-furyl)3*R*, 7-dimethyl-oct-5-en-1*R*-ol[(+)-**11**], yield 128.8 mg, b.p. 110°/0.3 Torr, $[\alpha]_D^{20} + 7.0°$ (c 1.0, CHCl$_3$), IR (film): 3400, 2950, 1510, and 880 cm^{-1}. ^{1}H NMR δ: 7.40 (m, 2H), 6.41 (m, 1H), 5.38 (m, 2H), and 4.75 (dd, J = 9.0, J = 4.5 Hz). Absolute configuration of this alcohol was determined as described above as 1*R*, 3*R*.

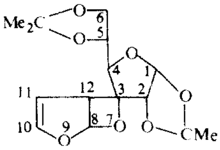
Mass spectrum of the mixture of both diastereoisomers **11**, *m/e*: 222 (M$^+$) and 97.

The position of the double bond in **11** was determined by ozonolysis of the diastereoisomeric mixture of **11**. The ozonide was decomposed with H$_2$O and zinc, and the resulting isobutyric aldehyde was characterized as its 2,4-dinitrophenylhydrazone, m.p. 182–184° (lit.[12] 185–187°).

Photochemical reaction between 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose **12** *and furan.* Ketone **12**[13] (4.8 g) in 180 ml of furan was irradiated for 25 hr. The residue after evaporation of furan was chromatographed (ligroine–ethyl acetate 7:3). Four fractions were collected:

(1) Oxetane **14** (577 mg), $[\alpha]_D^{18} + 39.0°$ (c 1.6, CHCl$_3$). Analysis. (Found: C, 59.0; H, 7.1 calc. for C$_{16}$H$_{22}$O$_7$: C, 58.9; H, 6.8%). IR (film): 3000 and 1605 cm^{-1}.

Table 1. ^1H NMR spectra of photoadducts **14–17**



Photoadducts \ ^1H NMR δ:	H-1 ($J_{1,2}$ Hz)	H-2	H-8 ($J_{8,12}$ Hz)	H-10	H-11 ($J_{10,11}$ and $J_{11,12}$ Hz)
14	5.74 (d, 3.5)	4.56 (d)	6.30 (d, 4.1)	6.67 (m)	5.45 (t, 3.0)
15	5.92 (d, 3.5)	4.60 (d)	6.28 (d, 4.25)	6.65 (m)	5.29 (dd, 2.8 and 4.0)
16	5.63 (d, 3.5)	4.54 (d)	6.44 (d, 4.0)	6.71 (m)	5.20 (t, 3.0)
17	5.78 (d, 3.25)	4.67 (d)	6.42 (d, 4.25)	6.62 (m)	5.28 (dd, 3.0 and 3.25)

(2) Oxetane **15** (531 mg); this product was contaminated with unidentified compounds. Purity of this material—estimated from ^1H NMR spectrum— was *ca.* 60%.

(3) Oxetane **16** (2.0 g), m.p. 178–179° (from ethanol, lit.[8] 175.5–177°), $[\alpha]^{18}_{D}+57.1°$ (c 1.0, $CHCl_3$, lit.[8] $[\alpha]_D+50.0°$, $CHCl_3$). Analysis. (Found: C, 58.8; H, 6.9 calc. for $C_{16}H_{22}O_7$: C, 58.9; H, 6.8%). IR (KBr): 3030, 2990, and 1610 cm^{-1}.

(4) Oxetane **17** (710 mg), m.p. 188–190° (from ethanol), $[\alpha]^{18}_{D}+101.8$ (c 1.4, $CHCl_3$). Analysis. (Found: C, 58.8; H, 7.0 calc. for $C_{16}H_{22}O_7$: C, 58.9; H, 6.8%). IR (KBr): 3050, 3030, and 1610 cm^{-1}.

^1H NMR spectral data of all four photoadducts are collected in Table 1.

Isomerization of photoadducts **14–17** *to* 3-*furylderivatives* **18** *and* **19**. Compound **14** (200 mg) in 6 ml of dry ether was kept for 3 hr at room temperature with 25 mg of *p*-toluenesulfonic acid monohydrate. After neutralization with triethylamine (0.1 ml) 1,2:5,6-di-*O*-isopropylidene-3-*C*-(3′-furyl)-α-D-*gluco*furanose **18** was isolated by chromatography (ligroine-ethyl acetate 7:3), yield 105 mg (syrup), $[\alpha]^{18}_{D}+75.3$ (c 1.6, $CHCl_3$). Analysis. (Found: C, 58.7; H, 6.9 calc. for $C_{16}H_{22}O_7$: C, 58.9; H, 6.8%). IR (film): 3500, 3000, and 865 cm^{-1}. ^1H NMR δ: 7.55 (m, 1H), 7.44 (m, 1H), 6.49 (m, 1H), 6.02 (d, 1H, J = 3.6 Hz, H-1 of the furanose ring), and (4.37 (d, 1H, H-2 of furanose)).

Isomerization of impure oxetane **15** under the same conditions yielded also the *gluco* isomer **18** (tlc).

Compound **16** (280 mg) in 10 ml of dry THF was kept at room temperature with 30 mg of *p*-toluenesulfonic acid monohydrate. Neutralization with triethylamine (0.1 ml) followed by chromatography (ligroine–ethyl acetate 7:3) afforded 140 mg of 1,2:5,6-di-*O*-isopropylidene-3-*C*-(3′-furyl)-α-D-*allo*furanose **19**, m.p. 91–93° (from ethanol), $[\alpha]^{18}_{D}+33.4$ (c 0.9, $CHCl_3$). Analysis. (Found: C, 58.7; H, 7.0 calc. for $C_{16}H_{22}O_7$: C, 58.9; H, 6.8%). IR (KBr): 3600, 3020, and 875 cm^{-1}. ^1H NMR δ: 7.48 (m, 2H), 6.39 (m, 1H), 5.92 (d, 1H, J = 3.75 Hz, H-1 of furanose ring), and 4.43 (d, 1H, H-2 of furanose).

Oxetane **17** under the same conditions afforded also the *allo* isomer **19** (m.p. 92–93° from ethanol).

It is likely that partial removal of one isopropylidene group (presumably from the 5,6-position) was observed during isomerization of all oxetanes **14–17**. Tlc (ligroine–ethyl acetate 3:2) showed formation of two compounds: alcohol **18** (or **19**) and some quantity of more polar product. This last compound was not isolated in pure state.

Determination of configuration of **18** *and* **19**. The ^1H NMR spectra of both epimeric sugars **18** and **19** (50 mg) were recorded in the presence of Eu(fod)$_3$ (20 mg). A large downfield shift of the H-5 signal was observed in the spectrum of the *gluco* isomer **18** (δ4.4→5.6). The shift of H-5 in the spectrum of the *allo* derivative **19** was not significant (δ4.0→4.5). In contrast, a large downfield shift of H-4 was observed in the spectrum of **19** (δ4.0→5.75). The shift of the H-4 signal in the spectrum of **18** was distinctly smaller (δ4.3→4.9).

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