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Highly Stereoselective Addition of 2-Trimethylsilyloxyfuran to *N*-Glyoxyloyl-(2*R*)-bornane-10,2-sultam

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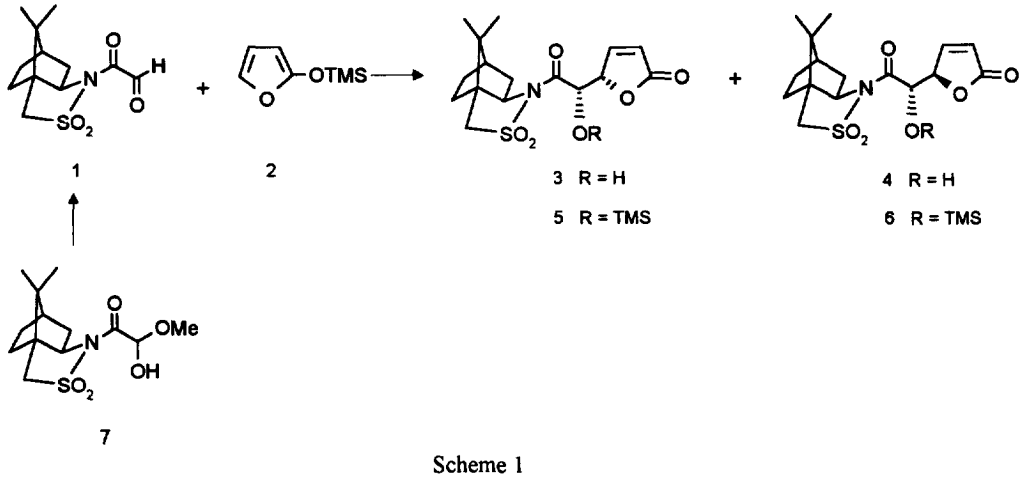
Abstract: $Eu(fod)_3$-catalyzed stereoselective nucleophilic addition of 2-trimethylsilyloxyfuran to *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam yields g-substituted butenolides with high diastereoselectivity.

Recently, we have developed a new chiral derivative of glyoxylic acid - *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **1**[1], using highly potent chiral auxiliary - Oppolzer's sultam[2]. This new aldehyde derivative shows an excellent diastereoselectivity in the [4+2] cycloaddition to both nonactivated[3,4] and activated dienes[5], yielding adducts which are versatile starting materials for the synthesis of natural products, for example compactin lactone[4, 6] and purpurosamine C[7]. These results prompted us to evaluate the applicability of **1** in another stereoselective process - nucleophilic addition to its formyl group. For this purpose we have selected 2-trimethylsilyloxyfuran (TMSOF) **2**, an excellent nucleophile, earlier successfully applied in the stereoselective synthesis of higher carbohydrates[8, 9].

Now we report on a new application of *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **1** leading to g-substituted butenolides. Enantiomerically pure g-substituted butenolides are versatile starting materials for the synthesis of natural products, so the development of new methods for their stereoselective synthesis is still challenging. The addition of 2-trimethylsilyloxyfuran **2** to aldehyde **1** was investigated under various conditions in order to establish optimal set of parameters giving high chemical yield and enantiomeric purity of the product (Scheme 1).

First, we carried out this reaction under noncatalytic conditions. 2-Trimethylsilyloxyfuran **2** was reacted with aldehyde **1** in CH_2Cl_2 in the absence of any catalyst. The trimethylsilyl group liberated during the course of the reaction was only partially trapped by the newly generated hydroxy group, which resulted in the presence of both nonsilylated (**3**, **4**) and silylated (**5**, **6**) products. Moreover, the silyl ether is cleaved to some extent during flash chromatography, which excludes this method for assessing the ratio of diastereoisomers. In order to find out the diastereoisomeric ratio, a crude post-reaction mixture was silylated with TMSCl/pyridine, followed by

work-up with aqueous $CuSO_4$ and ^1H NMR spectroscopic analysis spectra. A 59:41 ratio of diastereoisomers was found. Subsequently, the reaction was carried out in the presence of a mild Lewis acid - $Eu(fod)_3$[10]. Additions catalyzed by 2 or 3 mol% of $Eu(fod)_3$, after silylation and ^1H NMR analysis (*vide supra)*, gave a **5**:**6** ratio of 94:6 or 95:5, respectively.



Scheme 1

After examination of a broad spectrum of desilylation methods, including citric acid in methanol[11] we were unable to cleave the trimethylsilyl ether; all attempts led to decomposition of the starting material. This problem was overcome when we used for the addition reaction the methyl hemiacetal **7** of *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **1** (a crystalline, stable derivative from which we liberate free aldehyde[1]). The ratio of silylated to nonsilylated products was strongly shifted in favour of the latter. Evidently, the trimethylsilyl group was trapped by methanol originating from the hemiacetal cleaved. Having this in mind, we carried out the addition of 2-trimethylsilyloxyfuran **2** to hemiacetal **7** in the presence of 3 mol% of $Eu(fod)_3$ in a 99:1 methylene chloride - methanol mixture as solvent. Thin-layer chromatography showed only traces of **5** and **6**, and flash chromatography afforded products **3** and **4** (646 mg, 86.6% yield and 23 mg, 3.1% yield, respectively)[12]. ^1H NMR analysis of the silylated crude post-reaction mixture gave a 95:5 ratio of **5** and **6**[13].

The absolute stereochemistry of the newly created stereogenic centers was established by X-ray analysis as (4*S*,5*S*) for **3** (Figure 1)[14,15] and (4*R*,5*S*) for **4**. The stereochemical outcome of the addition confirms the powerful directing effect of the sultam moiety in *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam. From four possible diastereoisomers only two were obtained, both with complete selectivity at the C5 stereogenic center originating from the formyl group.

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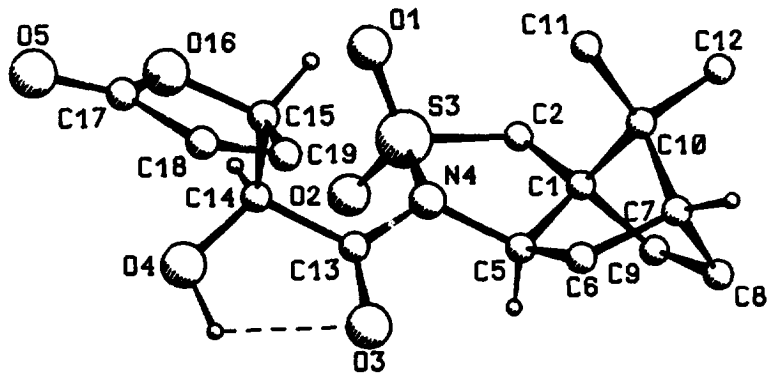

Figure 1. X-ray structure of (4*S*,5*S*)-**3**

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12. Typical procedure for the addition of TMSOF **2** to aldehyde **1**:

    To the solution of 636 mg (2.1 mmol) of methyl hemiacetal **7** of *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **1** in 10 mL of a mixture of CH_2Cl_2-MeOH (99:1) 30 mg (0.029 mmol) of $Eu(fod)_3$ were added, followed by slow addition of 0.5 mL (3.04 mmol) of TMSOF **2**. The solution was stirred at room temperature overnight, then solvent were evaporated using a rotary evaporator. The residue was

subjected to flash chromatography (hexane - ethyl acetate as eluent) yielding 20 mg of **6**, 23 mg of **4** and 646 mg of **3**. Overall yield - 92%, de 88%.

13. Selected data for compounds **3-6**:

3: ^{1}H NMR: 7.50 (1H, dd, J_{23}=4.54), 6.21 (1H, dd), 5.24 (1H, dt), 4.94 (1H, dd), 3.96 (1H, t), 3.52 (2H, q), 3.19 (1H, d), 1.3-2.2 (7H, m), 1.17 (3H, s), 0.99 (3H, s).

^{13}C NMR: 19.87, 20.74, 26.42, 32.84, 38.05, 44.58, 47.96, 49.09, 52.92, 65.20, 70.64, 83.20, 123.72, 151.95, 169.95, 171.60.

HR-MS: $C_{16}H_{19}NO_5S$ (M - H_2O) calc.: 337.09839; found: 337.09838.

$[\alpha]_D^{22}$ -82.77 (c=2.38, $CHCl_3$).

4: ^{1}H NMR: 7.48 (1H, dd), 6.19 (1H, dd), 5.58 (1H, dd), 4.95 (1H, dd), 3.53 (2H, s), 3.43 (1H, d), 1.3 - 2.2 (7H, m), 1.26 (3H, s), 0.98 (3H, s).

^{13}C NMR: 19.75, 20.40, 26.43, 32.41, 37.59, 44.25, 47.94, 49.36, 52.82, 65.06, 69.81, 83.23, 122.81, 152.43, 169.97, 172.52.

HR-MS: $C_{16}H_{19}NO_5S$ (M - H_2O) calc.: 337.09839; found: 337.09705.

$[\alpha]_D^{22}$ -140.97 (c=1.7, $CHCl_3$).

5: ^{1}H NMR: 7.35 (1H, dd, J_{23}=5.75, J_{34}=1.45), 6.20 (1H, dd, J_{24}=1.83), 5.20 (1H, m), 5.11 (1H, d, J_{45}=4.57), 3.95 (1H, q), 1.3-2.2 (7H, m), 1.17 (3H, s), 0.98 (3H, s), 0.14 (9H, s).

6: ^{1}H NMR: 7.62 (1H, dd, J_{23}=5.73, J_{34}=1.5), 6.20 (1H, dd, J_{24}=1.91), 5.25 (1H, m), 5.15 (1H, d, J_{45}=3.3). 3.95 (1H, t), 3.53 (2H, q), 1.3-2.2(7H, m), 1.15 (3H, s), 0.98 (3H, s), 0.11 (9H, s).

14. Selected crystal data for compund **3**: orthorhombic space group $P2_12_12_1$, a = 6.9343 (4), b = 11.633 (1), c = 20.457 (2) Å, V = 1650.2 (3) Å^3, Z = 4, F(000) = 752, D_x = 1.43 g cm^{-3}, m (CuKa) = 1.92 mm^{-1}. The final *R* was 0.0490 (unit weights).

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