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Efficient Synthesis of *N*-Glyoxyloyl-(2*R*)-bornane-10,2-sultam

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Abstract: Starting from (2*R*)-bornane-10,2-sultam **1**, the useful chiron *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **5** is prepared *via* its crystalline precursor **4**. The hemiacetal **4** whose structure was proved by the X-ray analysis is formed in diastereomerically pure form.

Chiral glyoxylates are important starting materials for syntheses of sugars[1] and other natural products.[3,4] They have been shown to undergo asymmetric ene reactions,[5,6] [4+2][7,8] and [2+2] cycloadditions,[9,10] various organometallic additions,[11-13] Friedel-Crafts[14,15] and Henry[16] reactions.

Recently, we have found that *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **5**, obtained in a moderate yield *via* ozonolysis of *N,N'*-fumaroyl-di-[(2*R*)-bornane-10,2-sultam],[17] is an efficient heterodienophile that can serve as an extremely useful chiron in the total syntheses of various natural products, *e.g.* compactin.[18] A recent report[19] illustrating increasing interest in compound **5**, prompted us to present our large-scale method of the synthesis of its crystalline precursor **4** (Scheme 1).

Several approaches to the synthesis of the crystalline hemiacetal **4** were made. All concepts were based on the cleavage of the double bond in an appropriate enoyl derivative either by ozonolysis or *via* stereoselective *cis*-dihydroxylation, followed by a cleavage of the resulting diol with sodium periodate or lead tetraacetate.[20]

Finally, we found that the best method is the ozonolysis of *N*-crotonoyl-(2*R*)-bornane-10,2-sultam **3**,[21] performed in a 1:1 (v/v) mixture of methylene chloride and methanol, at -78°C.[22] Reduction of the ozonide with dimethyl sulfide afforded, after evaporation and trituration of the residue with methanol, the crude hemiacetal **4** in 90% yield. Recrystallization of **4** from methanol gave a single diastereoisomer in

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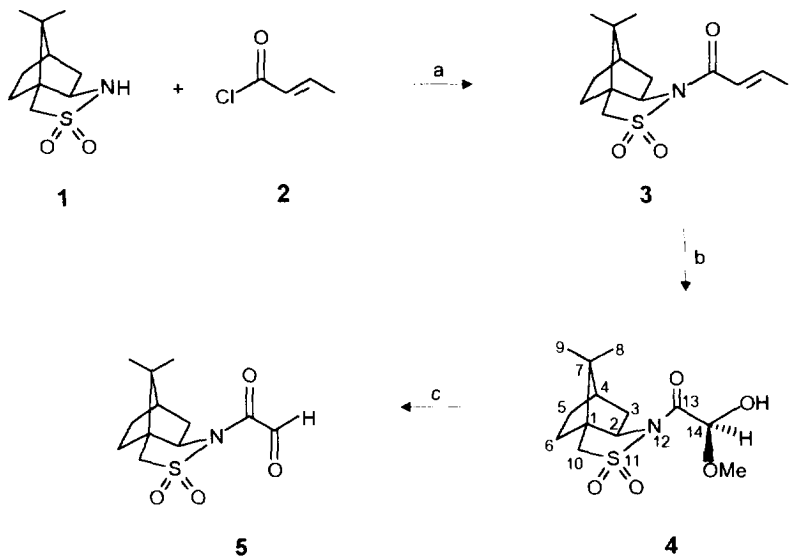
crude hemiacetal **4** in 90% yield. Recrystallization of **4** from methanol gave a single diastereoisomer in 85% yield, without any traces of dimer reported by Bernauer *et al.*[19] X-ray analysis allowed the (14*S*) absolute configuration for the hemiacetal center of the major diastereoisomer **4** (Figure 1) to be established.



Scheme 1. Reagents and reaction conditions: (a) 1.2 eq NaH, toluene, -5°C→RT, 2 h; (b) *i.* O_3, CH_2Cl_2-MeOH 1:1 -78°C, ~0.5 h, *ii.* Me_2S, -78°C→RT, 15 h; (c) 110°C, 0.1mmHg, 2 h.

The minor diastereoisomer of the (2*R*,14*R*) absolute configuration can also be distinguished by differential ^1H and ^{13}C NMR analysis. Its ^1H NMR spectrum exhibits all the characteristic signals, but they are shifted upfield by *ca.* 0.05 ppm.

The final liberation of the formyl functionality, leading to the title compound **5**, was carried out by heating the single diastereoisomer **4** or the crude mixture of diastereoisomers at 100-110°C/0.1 mmHg.

The successful asymmetric [4+2] cycloadditions, cyclocondensations, ene reactions, and various organometallic additions, that we carried out with this extremely reactive and potent chiron, are reported in the following papers.

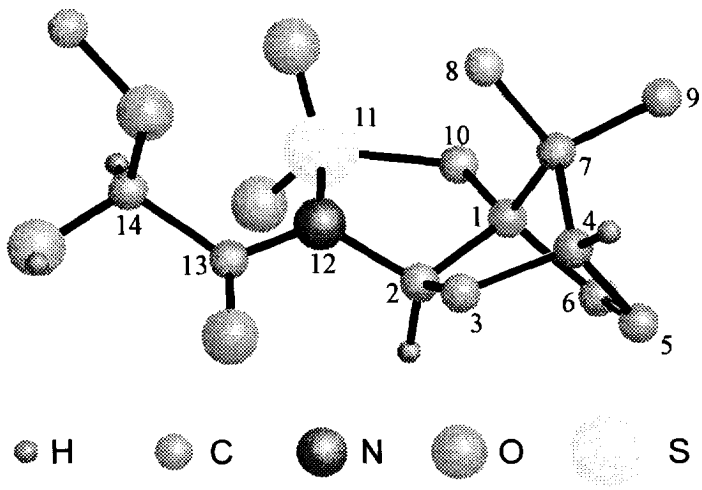


Figure 1. Molecular structure of compound (2*R*,14*S*)-**4**.

EXPERIMENTAL

General. Melting points were determined using a Kofler hot stage apparatus and are not corrected. Rotations were recorded using a JASCO DIP-360 polarimeter with a thermally jacketed 10 cm cell. IR spectra were obtained with a Perkin-Elmer 1640 FTIR spectrometer in films (for liquids) or KBr pellets (for solids). ^{1}H NMR spectra were recorded using a Varian Gemini (200 MHz) spectrometer, and ^{13}C NMR spectra were recorded with DEPT editing as necessary, using also a Varian Gemini (50 MHz) spectrometer. All chemical shifts are quoted in parts per milion relative to tetramethylsilane (δ, 0.00 ppm) and coupling constants (J) are measured in Hertz. Mass spectra were recorded on an AMD-604 Intectra instrument using the electron impact (EI) technique. Single-crystal X-ray diffraction analysis was performed on an Enraf-Nonius CAD-4 diffractometer.

Preparation of N-glyoxyloyl-(2*R*)-bornane-10,2-sultam **5** *via* its hemiacetal **4**. A solution of ester **3** (25g, 88.4 mmol) in a 1:1 mixture of CH_2Cl_2/MeOH (250 mL) was treated with ozone at -78 °C over a period of 0.5 h. The ozonide was decomposed with dimethyl sulfide (DMS, 410 mmol), which was added at -78°C, and then the mixture was stirred at room temperature over a period of 15 h. After a careful evaporation of solvents and an excess of DMS, the residue was recrystallized from MeOH to afford the analytically pure product **4** (23.0 g, 85%): mp 131-134°C (decomp. at 139°C); $[\alpha]_D^{20}$ = -103.6 (*c* 1.14, CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3486, 2966, 2889, 1699, 1457, 1406, 1367, 1342, 1274, 1241, 1169, 1137, 1102, 1061, 1029, 829, 765; ^{1}H NMR (500 MHz, $CDCl_3$) δ, 5.29 (d, J=11.0 Hz, 1H), 4.01 (d, J=9.0 Hz, 1H), 3.93 (dd, J_1=7.7 Hz, J_2=4.9 Hz, 1H), 3.51 (s, 3H), 3.49 (ABq, J=13.3 Hz, 2H), 2.16 (dd, J_1=8.1 Hz, J_2=3.5 Hz, 1H),

2.13 (dd, J_1=8.1 Hz, J_2=3.5 Hz, 1H), 1.99-1.86 (m, 3H), 1.47-1.33 (m, 2H), 1.16 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ, 168.4, 92.3, 65.0, 55.8, 52.8, 49.2, 47.8, 44.8, 37.9, 32.9, 26.3, 20.8, 19.9; elemental analysis : found C, 51.4; H, 7.1; N, 4.6; S, 10.6; $C_{13}H_{21}NO_5S$ requires C, 51.5; H, 7.0; N, 4.6; S, 10.6. Mother liquors contained also practically pure compound **4**, which after evaporation of MeOH was used for further work. Finally, a small portion (1-2 g) of the hemiacetal **4** was heated at 100-110°C/0.1 mmHg over a period of 2h to afford free aldehyde **5** which was immediatelly subjected to the respective reaction.

X-ray structure determination of hemiacetal **4**. Crystal data and measurement conditions are given in Table 1. In the final steps of least-squares procedure all but methyl group H atoms were kept fixed at their calculated positions. The known configuration of the asymmetric centers of the sultam unit has been confirmed by the Flack parameter refinement.[23] The structure was solved by the SHELXS86[24] and refined with the SHELXL93[25] programs.

Table 1. Crystal data and measurement conditions for hemiacetal **4**

Formula	$C_{13}H_{21}NO_5S$
Molecular weight	303.37
Crystal system	monoclinic
a [Å]	9.186(1)
b [Å]	6.772(1)
c [Å]	12.721(2)
β [deg]	110.55(1)
V [Å^3]	740.9(3)
Molecular multiplicity	*Z*=2
Calculated density [g cm^{-3}]	1.36
Space group	*P*2
Radiation (graphite monochromated)	Cu K_α
Wavelenght [Å]	1.54178
Linear absorption coeff. μ [cm^{-1}]	1.99
Number of electrons *F* (000)	324
Crystal size [mm]	0.28×0.35×0.40
Temperature [°C]	22±1
Scan mode	ω/2θ
Scan range (2θ) [deg]	0-150
Number of collected data:	
total measured	1826
unique [with $I > 2\sigma$]	1585
R	0.0534

Lists of the fractional atomic coordinates, isotropic thermal parameters, bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre.

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