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The Asymmetric Cyclocondensation Reaction of 1-Methoxy-3-silyloxybuta-1,3-dienes with *N*-Glyoxyloyl-(2*R*)-bornane-10,2-sultam

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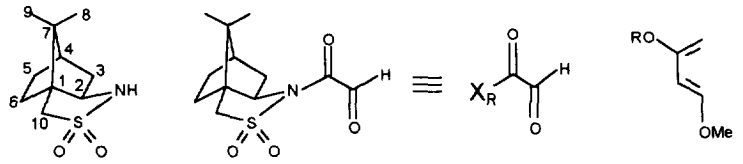
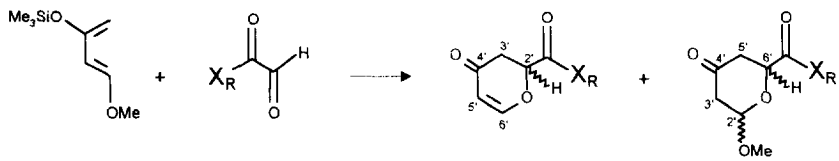
Abstract: The asymmetric cyclocondensation reaction of 1-methoxy-3-trimethylsilyloxy- **3a**, 1-methoxy-3-*t*-butyldimethylsilyloxy- **3b** or 1-methoxy-3-triisopropylsilyloxybuta-1,3-diene **3c** with *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **2** in the presence of Eu(fod)$_3$ is reported. For diene **3a** the classic Danishefsky's product **4** predominated over the desilylated [4+2] cycloadduct **5**, whereas in the case of dienes **3b** and **3c** only product **4** and the primary [4+2] cycloadduct **6b** or **6c** were formed. The absolute configuration (*via* X-ray analysis of **5** and chemical correlation) and the extent of asymmetric induction were established.

There is a growing interest in synthetic applications[1-5] of *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **2**,[1,6] readily available from Oppolzer's (2*R*)-bornane-10,2-sultam **1**[7]. Recently, we have described the successful application of compound **2** to the highly stereocontrolled hetero-Diels-Alder reaction with 1-methoxybuta-1,3-diene,[1,4] leading to the (2'*S*)-methoxy-(6'*S*)-[(2*R*)-bornane-10,2-sultam]carbonyl-5',6'-dihydro-2*H*-pyran, a convenient starting material for the synthesis of natural products.[2,5] These facts prompted us to initiate systematic studies on the Danishefsky's type cyclocondensation[8] with the use of chiron **2**. In this communication we report on cyclocondensation between compound **2** and 1,3-dioxygenated dienes **3a**, **3b**, and **3c**, in the presence of Eu(fod)$_3$ as a mild Lewis acid catalyst.[9]



1 X_RH **2** **3a** R=$SiMe_3$
3b R=$SiMe_2Bu^t$
3c R=$SiPr^i_3$

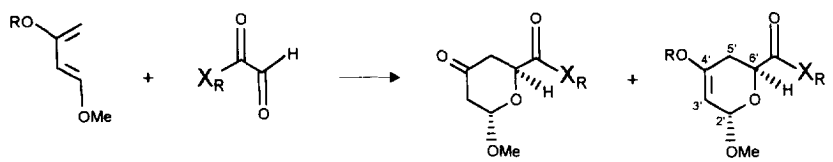
The reaction of **2** with commercially available diene **3a**, carried out in ethyl ether in the presence of a catalytic amount of $Eu(fod)_3$, afforded after usual workup a mixture of 2'-[(2*R*)-bornane-10,2-sultam]carbonyl-2',3'-dihydro-2*H*-pyrone-4 **4** and 2'-methoxy-6'-[(2*R*)-bornane-10,2-sultam]carbonyl-tetrahydropyrone-4 **5** (Scheme 1).



3 **2** **4** **5**

Scheme 1

Because of the sensitivity of the trimethylsilyl group as well as the moderate stereoselectivity of this reaction, we decided to use the more stable dienes **3b** (R=$SiBu^tMe_2$) and **3c** (R=$SiPr^i_3$), which are readily prepared according to the known literature procedures.[10,11] In the case of diene **3b**, the reaction with compound **2**, carried out under identical conditions as for diene **3a**, led to a mixture of products **5** and **6b** in a ratio of 9:1, respectively, (50% overall yield) (Scheme 2).



3b R=$SiMe_2Bu^t$ **2** **5** **6b** R=$SiMe_2Bu^t$
3c R=$SiPr^i_3$ **6c** R=$SiPr^i_3$

Scheme 2

The $Eu(fod)_3$-mediated reaction of compound **2** with the most stable diene **3c** afforded also a mixture of products **5** and **6c** in a ratio of 5:95, respectively (63% overall yield) (Scheme 2). Compounds **6b** and **6c** were readily transformed into product **5** upon treatment with tetrabutylammonium fluoride. Compound **5** formed single crystals suitable for X-ray analysis which was used for determination of absolute configuration on the C-6' stereogenic center (Figure 1).

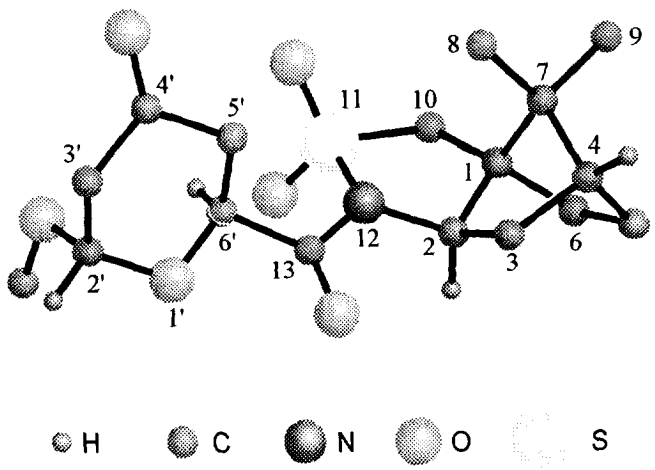


Figure 1. Molecular structure of compound (2'*S*, 6'*S*)-**5**

The present results, featuring very high chemo- and stereoselectivity, open an alternative efficient route to the enantiomerically pure compounds **4**, **5**, **6b** and **6c**, and consequently to the synthesis of enantiomerically pure sugars and sugar-like natural products from noncarbohydrate precursors.

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) specrtometer, 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 a Syntex $P2_1$ diffractometer. Flash column chromatography was undertaken according to Still *et al.*[12] on silica gel (Kieselgel-60, Merck, 200-400 mesh). Dienes **3b** and **3c** were prepared according to the literature procedures,[10,11] and sultam **2** was obtained according to our own methodology.[6]

Preparation of (2'*S*)-methoxy-(6'*S*)-[(2*R*)-bornane-10,2-sultam]carbonyltetrahydropyrone-4 **5.**

To a solution of dienophile **2** (313 mg, 1.15 mmol) in Et_2O (25 mL) was added $Eu(fod)_3$ (30 mg), and after stirring for 1h at room temperature, diene **3b** (420 mg, 1.96 mmol) was added dropwise. The stirring was continued for 48h at room temperature, and then the reaction mixture was washed with saturated $NaHCO_3$ aq (20 mL), extracted with Et_2O (3×30 mL), the combined organic layers were dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (hexanes-ethyl acetate 9:1→6:4) to afford the crystalline, analytically pure compound **5** (192.8 mg) and contaminated by **5** cycloadduct **6b** (27.4 mg) (88:12, total yield 50%). Analytical and spectral data for **5**: mp 208-209°C (from $CHCl_3$-EtOH); $[\alpha]_D^{20}$=-44.1 (*c* 0.54, CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 1730, 1704, 1409, 1334, 1282, 1224, 1193, 1111, 950, 865, 702; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.28(dd, J_1=11.1 Hz, J_2=3.6 Hz, 1H), 5.26 (dd, J_1=4.4 Hz, J_2=1.6 Hz, 1H), 3.96 (dd, J_1=7.8 Hz, J_2=4.8 Hz, 1H), 3.5 (ABq, J=13.8 Hz, 2H), 3.42 (s, 3H), 2.75 (ddd, J_1=15.0 Hz, J_2=3.5 Hz, J_3=1.7 Hz, 1H), 2.74 (ddd, J_1=15.0 Hz, J_2=4.5 Hz, J_3=0.7 Hz, 1H), 2.56-2.51 (m, 2H), 2.30 (dd, J_1=14.0 Hz, J_2=7.7 Hz, 1H), 2.02 (dd, J_1=14.0 Hz, J_2=3.4 Hz, 1H), 1.98-1.86 (m, 3H), 1.48-1.34 (m, 2H), 1.11 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 201.6, 168.8, 99.9, 67.6, 65.0, 55.4, 53.0, 48.8, 47.9, 46.2, 44.5, 43.4, 38.0, 32.8, 26.4, 20.8, 19.8; (EIHR) calculated for $C_{17}H_{25}NO_6S$ $(M)^+$ 371.1403, found 371.1398.

X-ray structure determination of compound **5.** 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.[13] The structure was solved by the SHELXS86[14] and refined with the SHELXL93[15] programs.

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

Table 1. Crystal data and measurement conditions for compound (2'*S*,6'*S*)-**5**

Formula	$C_{17}H_{25}NO_6S$
Molecular weight	371.14
Crystal system	triclinic
a [Å]	7.164(1)
b [Å]	7.753(1)
c [Å]	18.891(4)
α [deg]	89.66(2)
β [deg]	79.80(2)
γ [deg]	63.15(1)
v [Å^3]	918.1(3)
Molecular multiplicity	*Z*=2
Calculated density [g cm^{-3}]	1.34
Space group	*P1*
Radiation (graphite monochromated)	Mo K_α
Wavelenght [Å]	0.71069
Linear absorption coeff. μ [cm^{-1}]	1.65
Number of electrons *F* (000)	396
Crystal size [mm]	0.32×0.45×0.25
Temperature [°C]	22±1
Scan mode	ω/2θ
Scan range (2θ) [deg]	0-50
Number of collected data:	
total measured	3263
unique [with *I* >2σ]	2737
R	0.0567
R_w	0.0372
w	$1.084/\sigma^2_F$

Preparation of (2'*S*)-methoxy-4'-triisopropylsilyloxy-(6'*S*)-[(2*R*)-bornane-10,2-sultam]carbonyl-5',6'-dihydro-2*H*-pyran **6c**. The reaction of dienophile **2** (346.1 mg, 1.27 mmol) with diene **3c** (556.1 mg, 2.17 mmol) in the presence of Eu(fod)$_3$ (30mg) in Et_2O (30 mL) was carried out under identical conditions as in the former case. After similar workup, the residue was purified by flash chromatography (hexanes-ethyl acetate 9:1→6:4) to afford the crystalline, analytically pure compounds **6c** (402.1 mg) and **5** (15.5 mg) (96:4, total yield 63%). Analytical and spectral data for **6c**: mp 170-171°C (from MeOH); $[\alpha]_D^{20}$=-59.7 (*c* 0.96, CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 1704, 1674, 1463, 1335, 1274, 1216, 1190, 1134, 1055, 962, 905, 779, 740, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.18 (t, J=7.7 Hz, 1H), 5.12 (d, J=3.2 Hz, 1H), 4.92 (dd, J_1=3.8 Hz, J_2=2.1 Hz, 1H), 4.02 (dd, J_1 =7.6 Hz, J_2=4.9 Hz, 1H), 3.48 (ABq, J=13.8 Hz, 2H), 3.39 (s, 3H), 2.35 (d, J=7.7 Hz, 2H), 2.14-2.01 (m, 2H), 1.94-1.86 (m, 3H), 1.46-1.34 (m, 2H), 1.13 (s, 3H), 1.11-1.02 (m, 2H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.0, 151.5, 101.6, 97.3, 67.1, 64.9, 55.3, 53.1, 48.8, 47.9, 44.6, 38.2, 33.1, 32.8, 26.5, 20.7, 19.9, 17.9, 12.5.; (EIHR) calculated for $C_{26}H_{45}NO_6SSi$ $(M)^+$ 527.2735, found 527.2739.

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