## ENANTIOMERICALLY PURE, CRYSTALLINE 'ANTI'-ALDOLS FROM N-ACYLBORNANESULTAMS: ALDOLIZATION AND STRUCTURE OF INTERMEDIATE t-BUTYLDIMETHYLSILYL-N,O-KETENE ACETAL.

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<u>Abstract:</u> O-Silylation of N-propionylsultam 1 provides pure Z O-silyl-N,O-ketene acetal 2 which undergoes Lewis acid promoted addition of aromatic and aliphatic aldehydes to give diastereomerically pure, crystalline "anti" aldols 7 or their silylethers 3. Hydroperoxide-assisted hydrolysis/esterification of products 7 yields enantiomerically pure methoxycarbonyl aldols (11, 12, 13, 14).

The importance of the aldol reaction in organic synthesis has stimulated a prolific development of useful  $\pi$ -face selective versions.<sup>1,2</sup> Most of them provide 'syn' aldols <sup>1</sup> as recently exemplified by the bornanesultam directed conversions  $1 \rightarrow 8$  and  $1 \rightarrow 9$  (Scheme 1). <sup>1e</sup> We describe here the advantageous use of the <u>same</u> N-acylsultam substrate <u>1</u> to prepare 'anti' aldols <u>7</u> in a highly diastereo- and stereoface controlled manner.

Scheme 1



Treatment of N-propionylsultam  $1^{1e}$  with t-butyldimethylsilyl triflate (TBDMSOTf)/NEt<sub>3</sub> (1.2 mol-equiv., CH<sub>2</sub>Cl<sub>2</sub>, RT, 16 h), evaporation, trituration of the residue with pentane and evaporation of the pentane solution furnished crude O-silyl-N,O-ketene acetal 2 which is rapidly hydrolyzed on exposure to air. For spectral analyses, X-ray diffraction measurements, and control experiments (*vide infra*) 2 was recrystallized from dry pentane under argon. As expected, no reaction took place on treating recrystallized "O-silylenolate" 2 with benzaldehyde (entry 1). In contrast, non-isolated intermediate 2 underwent  $\pi$ -face- and 'anti' selective aldolizations in the presence of a suitable Lewis acid (Scheme 1, Table). <sup>5</sup>

	Aldehyde R	Lewis Acid	Temp. [°C]	Time [h]	Product/Ratio 3+7 / 5+9	Major Product	Yield [%] cryst.	Мр. [*C]	Purity [%]
1	Ph	none	- 30	16	no reaction	_	-		
2	Ph	TBDMSOTf	- 40	0.5	98.5 / 1.5	3 <b>a</b>	89	196-197	> 99
3	pMeOC <sub>6</sub> H <sub>4</sub>	TBDMSOTf	- 40	0.5	98 / 2ª	3b	78	178-179	> 99
4	pClC <sub>6</sub> H <sub>4</sub>	TBDMSOTf	- 40	0.5	98.5 / 1.5ª	3c	84	168-169	> 99
5	2,3-OCH2OC6H3	TBDMSOTf	- 40	0.5	97 / 3ª	3d	69	231-232	> 99
6	pO2NC6H4	TBDMSOTf	- 40	0.5	95 / 5	3e	≤20 <sup>b</sup>		_
7	Et	TBDMSOTf	- 40	0.5	95 / 5	3f	≤30 <sup>b</sup>	_	_
8	pO2NC6H4	ZnCl <sub>2</sub>	- 78	1.0	97.2 / 2.8ª	3e	80	116-117	> 99
9	iBu	ZnCl <sub>2</sub>	- 78	1.0	<b>98.9</b> / 1.1	3g	78	121-122	> 99
10	Ph	TiCl4	- 78	0.1	98.9 / 1.1	7 <b>a</b>	70	183-184	> 99
11	Me	TiCl <sub>4</sub>	- 78	0.1	>99.5 / <0.5	7h	72	125-126	> 99
12	Et	TiCl4	- 78	0.1	>99.5 / <0.5	7f	64	75-76	> 99
13	iPr	TiCl <sub>4</sub>	- 78	0.1	99.2 / 0.8	7i	76	147-148	> 99
14	iBu	TiCl <sub>4</sub>	- 78	0.1	>99.5 / <0.5	7g	78	oil	> 99

Table: Asymmetric, Lewis Acid Promoted Aldolizations  $2 \rightarrow 3$  and  $2 \rightarrow 7^{5}$ 

a) Minor stereoisomer arbitrarily assigned. b) conversion determined by GC-analysis

Most conveniently, TBDMSOTf may serve both as a silylating agent and as an aldolization catalyst (entries 2 to 5).

Thus, adding TBDMSOTf (1.5 mol-equiv.) and NEt<sub>3</sub> (1.2 mol-equiv.) to propionylsultam 1 in CH<sub>2</sub>Cl<sub>2</sub>, stirring the mixture at r.t. for 16 h, cooling to -40°C, addition of the (aromatic) aldehyde, stirring at -40°C for 30 min and quenching with sat. aq. NH<sub>4</sub>Cl provided the corresponding *O*-silylated '*anti*' aldol 3 in high stereochemical purity. Only 1.5 to 3% of '*syn*' isomer 5 (and none of isomers 4 and 6) was found by GC analysis. Pure silylethers 3a to 3d were easily obtained by crystallization. However, with (the weaker Lewis bases) *p*-nitrobenzaldehyde or propionaldehyde only partial conversions  $2 \rightarrow 3$  were observed (entries 6, 7).

This limitation was readily overcome by using a stronger Lewis acid.

For example,  $ZnCl_2$  induced addition of *p*-nitrobenzaldehyde or isovaleraldehyde to "*O*-silylketene acetal" <u>2</u> proceeded smoothly at -78°C to give *O*-silylated products <u>3</u> together with small amounts of the corresponding free aldols <u>7</u>. Silylation of the crude product mixtures followed by crystallization furnished pure silyl ethers <u>3e</u> and <u>3g</u> in good yields (entries 8, 9).

TiCl<sub>4</sub> promoted aldolizations of <u>2</u> with benzaldehyde and various aliphatic aldehydes provided mainly free aldols <u>7</u> in a particularly stereoselective manner (entries 10 to 14).

Adding a solution of 2 (1.1 mol-equiv. in  $CH_2Cl_2$ ) to a 1:1-mixture of TiCl<sub>4</sub> and an aldehyde in  $CH_2Cl_2$  at -78°C, stirring at -78°C for 5 min. and quenching with sat, aq. NH<sub>4</sub>Cl furnished free aldols <u>7</u> accompanied by minor amounts of their O-silyl derivatives <u>3</u>. Desilylation of the product mixture (CH<sub>3</sub>CN/40% aq. HF, 10:1, 1 h) gave corresponding 'anti' aldol <u>7</u>. No stereoisomers (entries 11, 12, 14) or just a trace of 'syn' isomer <u>9</u> (entries 10, 13) were found by HPLC- and GC analysis. <sup>5</sup> Direct crystallization (except entry 15) afforded pure aldols <u>7</u>.

HPLC- and GC comparison <sup>5</sup> with the "syn" isomers § and 2 as well as with mixtures 7+8+9+10 provided evidence for the "anti" configuration of aldols 7. This was confirmed more easily by examination of the vicinal coupling constants J(2,3) = 7 Hz.

Final proof for the relative and absolute configuration of aldols  $\underline{7}$  was obtained via removal of the auxiliary group. Mild, hydrogenperoxide-assisted saponification of  $\underline{7}$  gave recovered auxiliary (82 - 94%) and, after treatment of the resulting carboxylic acids with CH<sub>2</sub>N<sub>2</sub>, the corresponding enantiomerically pure "anti" methoxycarbonylaldols (49 - 88%). The optical rotations of resulting hydroxyesters <u>11</u>, <u>12</u> and <u>13</u> (Figure 1) were compared with published reference values. <sup>5</sup>

Figure 1: Methoxycarbonylaldols by Hydrolysis/Esterification of 7



This surprisingly selective formation of 2S products indicates that intermediate 2 is stereochemically pure. Indeed, the <sup>1</sup>H-NMR spectrum of crude 2 shows the presence of a single stereoisomer ((C $\alpha$ )CH<sub>3</sub> doublet at  $\delta = 1.62$  ppm, J = 7 Hz). Its Z configuration was established *via* an X-ray diffraction analysis of crystals obtained from pentane (Figure 2).<sup>6</sup>



The nitrogen atom is pyramidal (calculated height = 0.223 Å). An angle of  $52.5^{\circ}$  is observed between the lone electron pair on the N-atom (defined by a line perpendicular to the C(2), C(11), S plane) and the olefinic p orbital (defined by a line perpendicular to the N, O(3), C(12) plane). Hence interaction of the N lone pair and the olefinic bond in 2 seems to be very weak.

Considering the Z configuration of N,O-ketene acetal 2 and the 2S configuration of products 3, 7 it follows that 2 undergoes electrophilic attack from its  $C\alpha$ -Re face. The thus observed  $C\alpha$ -Re/"anti" topicity is consistent with an "open" transition state A<sup># 3</sup> featuring attack of a Lewis-acid-coordinated aldehyde opposite to the SO<sub>2</sub> group (Figure 3).

We believe that this approach to "anti" aldols compares very favorably with existing methods and exemplifies once more the versatility and practical utility of bornanesultam-directed reactions in asymmetric synthesis.<sup>7</sup>

Acknowledgements: Financial support of this work by the Swiss National Science Foundation, Sandoz Ltd., Basel and Givaudan SA, Vernier, is gratefully acknowledged. We thank Mr O. Nyanguile for his technical assistance and are grateful to Mr. J.P. Saulnier, Mr. A. Pinto and Mrs. C. Clément for NMR and MS measurements.

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- 3) Achiral <sup>4</sup> and chiral <sup>2c,d,f,g</sup> O-silylenolates are known to undergo "anti" selective aldolizations in the presence of a Lewis acid. This topicity has been ascribed to "open" transition states. <sup>2d,g,4</sup>
- 4) C. H. Heathcock, K. T. Hug, L. A. Flippin, Tetrahedron Lett. 1984, 25, 5973.
- All new compounds were characterized by IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and MS. Stereoisomer ratios were 5) determined by comparison (HPLC of free aldols or GC of TBDMS derivatives) with "syn" aldols § and 9 and with mixtures 7+8+9+10. 1e [a]D values, (20°C, CHCl3, g/100ml): 3g: +44.0° (0.75); 3b: +44.1° (1.3); 3c: +46.9° (0.9);  $\underline{3d}$ : +46.9° (1.15);  $\underline{3c}$ : +36.4° (1.3);  $\underline{3c}$ : -49.4° (1.05),  $\underline{7a}$ : +7.4° (1.25);  $\underline{7c}$ : -64.4° (1.65);  $\underline{7a}$ : -63.0° (0.76);  $\underline{7h}$ : -62.2° (0.2);  $\underline{7i}$ : -67.2° (1.9);  $\underline{11}$ : +53.1° (1.05), Lit. <sup>1f</sup>: +58.9° (1.88);  $\underline{12}$ : +7.2° (0.9), Lit. <sup>2g</sup> antipode: -7.9° (0.52, 23°C);  $\underline{13}$ : +11.1° (0.85), Lit. <sup>2a</sup> antipode: -12.5° (1.04). The following procedures are representative: TBDMSOT f-mediated O-silylation/aldolization: A mixture of TBDMSOT f (0.38 ml, 1.66 mmol), NEt3 (0.185 ml, 1.32 mmol) and propionylsultam 1 (300 mg, 1.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 ml) was stirred at r.t. for 16 h. Adding a soln. of benzaldehyde (0.133 ml, 1.32 mmol) in  $CH_2Cl_2$  ( $\overline{l}$  ml) at -40°C, stirring for 0.5 h at -40°C, quenching with sat. aq. NH<sub>4</sub>Cl, workup and crystallization (hexane/Et<sub>2</sub>O) gave silulether <u>3a</u>, m.p. 196-197°C (485 mg, 89%). Desilylation of <u>3a</u> (100 mg, 0.2 mmol) via stirring with MeCN/40% aq. HF (20:1, 3 ml) at r.t. for 2 h, workup and crystallization (EtOH) furnished aldol 7a (67 mg, 89%). O-Silylation of 1: t-Butyldimethylsilyl triflate (0.348 ml, 1.5 mmol), then NEt<sub>3</sub> (0.209 ml, 1.5 mmol) were added at r.t. to a soln. of propionylsultam 1 (374 mg, 1.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 ml) under argon. Stirring at r.t. for 16 h, evaporation, trituration of the residue with dry pentane under argon, decantation of the clear pentane soln. under argon and evaporation yielded crude O-silyl-NO-keteneacetal 2 which was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub>. Aliquots of this soln. were subjected to the following aldol reactions. ZnCl2-mediated aldolization: p-Nitrobenzaldehyde (0.55 ml of a 1 M soln. in CH<sub>2</sub>Cl<sub>2</sub>) was added to a soln. of anhydrous ZnCl<sub>2</sub> (by evaporation of 0.55 ml of 1 M soln. in Et<sub>2</sub>O) in CH<sub>2</sub>Cl<sub>2</sub> (0.3 ml) at r.t.. The soln. became homogeneous after several min. Subsequent addition of crude 2 (0.5 ml of a 1 M soln. in CH<sub>2</sub>Cl<sub>2</sub>) at -78°, stirring of the mixture at -78° for 1 h, addition of sat. aq NH<sub>4</sub>Cl and work up gave silylether  $\frac{3e}{1e}$  together with a small amount of free aldol <u>7e</u>. Silylation of the product mixture (TBDMSOTf/2,6-lutidine) <sup>le</sup> followed by crystallization (hexane/Et<sub>2</sub>O) provided O-silylated aldol <u>3e</u>, m.p. 116-117° (214 mg, 80%). TiCl<sub>4</sub>-mediated aldolizations: A 0.75 M soln. of crude 2 (0.48 ml, 0.36 mmol) was added at -78°C to a mixture of TiCl<sub>4</sub> (0.8 ml of 1 M soln. in CH<sub>2</sub>Cl<sub>2</sub>) and isobutyraldehyde (0.8 ml of 1 M soln. in CH<sub>2</sub>Cl<sub>2</sub>). Stirring of the mixture at -78° for 5 min, addition of sat aq. NH<sub>4</sub>Cl, extraction with Et<sub>2</sub>O, evaporation, stirring of the residue in MeCN/40% aq HF (10:1, 1ml) for 1 h at r.t., addition of sat. aq. NaHCO<sub>3</sub>, workup and crystallization (EtOH) provided free aldol <u>7i</u>, m.p. 147-148<sup>°</sup> (93 mg, 76%). Saponification/Esterification: Aq. (30%) H<sub>2</sub>O<sub>2</sub> (0.17 ml, 1.46 mmol) and LiOH.H<sub>2</sub>O (16 mg, 0.36 mmol) were added at 0°C to 7a (110 mg, 0.29 mmol) in THF/H2O (3:1, 3 ml). Stirring at 0°C for 2 h, addition of sat. aq. Na2SO3 (1 ml), basification to pH = 12 (NH4OH), extraction (CH2Cl2), drying and evaporation of the extracts and crystallization of the residue gave sultam auxiliary (51 mg, 82%). Acidification of the aq. phase to pH = 1 (HCl), extraction (Et<sub>2</sub>O), drying of the extracts, addition of CH<sub>2</sub>N<sub>2</sub> (excess), evaporation and bulb-to-bulb distillation (150-170°C / 2 Torr) furnished hydroxyester 11 (51 mg, 91%).
- 6) Crystallographic data have been deposited at the Cambridge Data Centre. Structure factors may be obtained from one of us (G.B.). Philips PW 1100 diffractometer (MoKα). The structure was solved by a direct method (Multan-87) and refined by least square analyses. The crystals of O-sily1-N,O-ketene acetal 2 (pentane, m.p. 88-90°C) are orthorhombic, a = 10.867 (2), b = 11.044 (1), c = 19.120 (2) Å; P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>, Z = 4; d<sub>c</sub> = 1.12 g. cm<sup>-8</sup>; F(000) = 840. R = 0.073 (ωR = 0.043; ω = 1/σ<sup>2</sup> (Fo)) for 1159 observed reflections [[Fo] ≥ 4σ (Fo)].
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(Received in Germany 29 October 1990)