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ASYMMETRIC SYNTHESIS OF trans-β-LACTAMS THROUGH $TiCl_4$-MEDIATED ADDITION TO IMINES.

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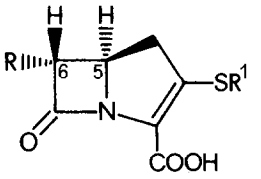
Abstract.- $TiCl_4$-mediated addition of the chiral silyl ketene acetal (2) to benzylideneaniline proceeds with high stereoselectivity to give, after cyclization, trans-β-lactam (7) in good yield and 95% e.e.

Since the discovery of thienamicin in 1976, more than 40 carbapenem and carbapenam antibiotics have been isolated from microorganisms so far.[1a]

We reasoned that an entire group of these antibiotics, e.g. (1) characterized by the 5,6-trans arrangement of the β-lactam side chains,[1b] could be easily synthesized via the stereocontrolled acid-catalyzed aldol type condensation of an ester silyl ketene acetal with an imine.



(1)

R=Et NS-5, PS-5, PS-7, OA-6129A

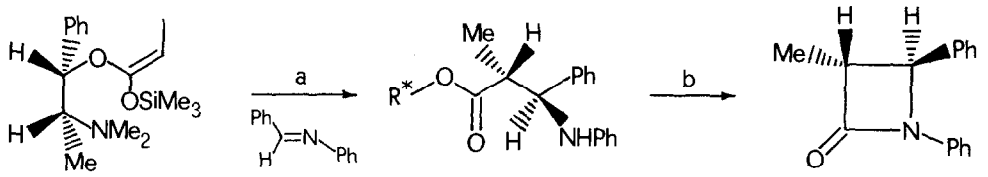
R=iPr PS-6, PS-8

Although the acid-catalyzed silyl ketene acetal additions to imine-type compounds have been studied in some detail,[2a-g] only the ZnI_2 promoted addition to N-trimethylsilyl imines was reported to proceed with a certain 5,6-trans-stereoselectivity.[2g] On the other hand quite high asymmetric induction at carbon-5 was reported in the construction of the β-lactam ring via addition to chiral optically active imines.[2b]

In this letter we wish to report our preliminary model studies in this field regarding the enantio- and diastereo-controlled synthesis of the β-lactam moiety of (1) by the use of the silyl ketene acetal derived from (1S,2R)-N-methylephedrine-O-propionate (2)[3] (Scheme 1).

This silyl ketene acetal was recently shown to be a very useful reagent for the $TiCl_4$-mediated asymmetric synthesis of anti α-methyl-β-hydroxy esters.[4] Asymmetric electrophilic formylation[5] ($TiCl_4$/ $HC(OMe)_3$) and amination[6] ($TiCl_4$/ $^tBuOOC-N=N-COOBu^t$) proved also to be quite successful.

By reaction of the silyl ketene acetal (2) with benzylideneaniline in the presence of excess $TiCl_4$ one of the possible four stereoisomers, anti-(3), was formed as the major product in 67% yield.[7]



(2) (3) (7)

Scheme 1. a) $TiCl_4$, CH_2Cl_2, -78°C (75%) b) LHDS, THF, -10°C (79%)

The minor isomer detectable by 200 MHz-^{1}H NMR spectroscopy in the crude reaction mixture was syn-(4) (anti-(3)/syn-(4) ratio $\geq$ 10:1), while anti-(5) was present only in traces (anti-(3)/anti-(5) ratio $\geq$ 38:1) and syn-(6) could not be detected (Scheme 2).

An authentic mixture of the four stereoisomers was synthesized by LDA enolization of (1S,2R)-N-methylephedrine-O-propionate (THF-HMPA, -78°C) and subsequent addition to benzylideneaniline.[8] The enolate addition in THF (without HMPA) gave low yields of the cis-β-lactam (e.e. 30%),[8,9] together with a mixture of the syn adducts (4) and (6) (ratio 5.1 : 1), and the bis-adduct (8) as a single diastereoisomer (^{1}H, ^{13}C NMR).

The absolute configuration was proven by hydrogenolysis (H_2, $PdCl_2$, CH_3CO_2H) of the product mixture derived from the $TiCl_4$-mediated reaction (see Scheme 2) to give the known acid (9).[10]

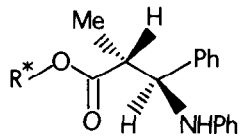
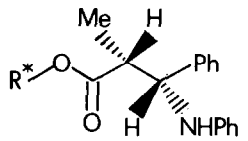
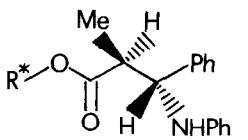
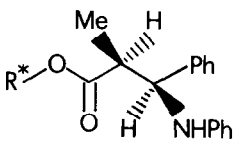
The same mixture was cyclized with $LiN(TMS)_2$ in THF to give, after flash-chromatography, trans-β-lactam (7) in 79% yield and 95% e.e.($\geq$ 38:1, ^{1}H NMR-Eu(hfc)$_3$).

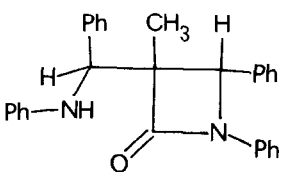
A brief experimental procedure is given below.

A solution of benzylideneaniline (15.6 mmol) and of silyl ketene acetal (2) (15.6 mmol) in CH_2Cl_2 (62.8 ml) was slowly added (during 1 h) to a solution of $TiCl_4$ (31.2 mmol) in CH_2Cl_2 (31.2 ml) at -78°C, under nitrogen, with stirring. After 1 h at -78°C, the mixture was slowly warmed up to -40°C (during 2 h), then quenched with 1.5 N NaOH/ sat. $NaHCO_3$ aq. sol., and filtered through celite. The aq. phase was extracted with CH_2Cl_2, and the combined organic extracts were dried (Na_2SO_4) and evaporated. The crude

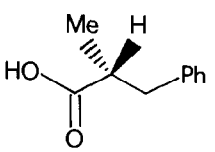
product was filtered through silica gel (CH_2Cl_2, then 97:3 CH_2Cl_2-MeOH) to give the stereoisomeric mixture described in the main text in 75% yield. This mixture (11.7 mmol) was dissolved in dry THF (19.5 ml) and then slowly added to a solution of $LiN(TMS)_2$ (12.8 mmol) in THF (32 ml) at -10°C under nitrogen, with stirring. After 45 min at -10°C the mixture was quenched (NH_4Cl sat.sol.) and worked up as usual. Flash chromatography (n-hexane-EtOAc 9:1) gave pure trans- β-lactam (7) in 79% yield and 95% e.e.. Recrystallization (n-hexane/EtOAc) gave optically pure (7) as white crystals, m.p. = 136°C, $[\alpha]_D^{25}$ = -64.8° (c 1.0, $CHCl_3$).

Scheme 2.

	-CH(NHPh) Ph δ (ppm)	J (Hz)	(TiCl$_4$-mediated react.) %ratio
	anti-(3) 4.47	7.00	89.2
	syn-(4) 4.83	4.66	8.5
	anti-(5) 4.51	7.56	2.3
	syn-(6) 4.75	5.12	0.0



(8)



(9)

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1b) For recent efforts in the enantioselective synthesis of (+) PS-5, see : D.A.Evans, E.B.Sjogren, Tetrahedron Letters, 1986, 3119; D.J.Hart, C.S. Lee, W.H. Pirkle, M.H. Hyon, A. Tsipouras, J.Am.Chem.Soc., 1986, 108, 6054.

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g) E.W. Colvin, D.G. McGarry, J.Chem.Soc.Chem.Commun., 1985, 539.

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6) C. Gennari, L.Colombo, G.Bertolini, J.Am.Chem.Soc., 1986, 108, 6394.

7) Both the imine and the ephedrine $-NMe_2$ group are expected to bind to $TiCl_4$, which usually ligates two electron-donating molecules to form cis-octahedral, six-coordinate complexes. Therefore the conformational freedom of the system is likely to be dramatically reduced, and the C-C bond formation occurs on the six-coordinate metal in a highly stereoselective way. Mechanistic aspects will be discussed more rigorously in a forthcoming full paper.

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9) C. Gluchowski, L. Cooper, D.E. Bergbreiter, M. Newcomb, J.Org.Chem., 1980, 45, 3413.

10) Found $[\alpha]_D^{25} = -23.0°$ (neat), absolute conf.: R ; G. Helmchen, et al., Angew.Chem.Int.Ed.Engl., 1979, 18, 63, $[\alpha]_D^{22} = -25.4°$ (neat), R; A.W. Schrecker, J.Org.Chem., 1957, 22, 33, $[\alpha]_D^{22} = -24.6°$ (neat), R.

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