157. Preparation of Enantiomerically Pure β-Silylcarboxyl Derivatives by Asymmetric 1,4-Addition to *N*-Enoyl-sultams

Preliminary Communication[1])

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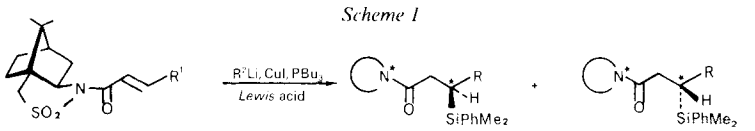
$EtAlCl_2$-promoted additions of organocopper reagents to camphor-derived, conjugated *N*-enoyl-sultams gave saturated and olefinic β-silylcarboxyl derivatives with high diastereodifferentiation. Nondestructive removal of the chiral auxiliary followed by oxidative Si-C bond cleavage furnished enantiomerically pure acetate-derived aldols and propionate-derived *'anti'*-aldols (*via* silyl-directed α-methylation).

β-Silylcarbonyl compounds show significant promise in organic synthesis. Two features of the β-$SiPhMe_2$ substituent are particularly interesting: 1) its topological bias on α-enolate protonation and methylation [1] as well as 2) its convertibility into a OH group with retention of configuration [2].

In continuation of previous work on asymmetric *Diels-Alder* [3] and hydride additions [4] to conjugated *N*-acyl-sultams, we report here the first asymmetric synthesis of β-silylcarboxylates and their transformation into enantiomerically pure acetate-derived aldols and propionate-derived *'anti'*-aldols. Furthermore, we describe the analogous π-face-selective preparation of γ,δ-alkenyl-β-silylcarboxyl derivatives which offer additional synthetic possibilities *via* S_E2'-type allylsilane substitutions[2]).

For reasons of versatility, it was advantageous to incorporate the silyl group into the prochiral substrate. The starting *N*-[β-(silyl)enoyl]sultam **1** (R^1=$SiPhMe_2$, (*Scheme 1*)[3]) was readily prepared by successive treatment of (*E*)-3(dimethylphenylsilyl)acrylic acid[3][4])

Scheme 1



1 R^1 = $SiPhMe_2$, R^1 = Ph **2** **3**

[1]) Presented at the IASOC-II-Meeting, Ischia, May 1986.

[2]) For an alternative approach to racemic and to enantiomerically pure γ,δ-alkenyl-β-silylcarbonyl derivatives by *Claisen* rearrangements see [5]; for asymmetric syntheses of non-functionalized allylsilanes, see [6]; for reviews on stereospecific S_E2'-type substitutions of allylsilanes, see [7].

[3]) All new compounds were characterized by IR, ^{1}H-NMR (360 MHz), and mass spectra.

[4]) This acid (m.p. 89–91°) was prepared in analogy to 3-(trimethylsilyl)acrylic acid [8] by successive treatment of (*E*)-1,2-bis(tributylstannyl)ethylene [9] at −78° with BuLi, $ClSiPhMe_2$, BuLi, and CO_2.

Table 1. *Asymmetric Conjugate Additions* **1** + $R^2Cu \rightarrow$ **2** + **3**

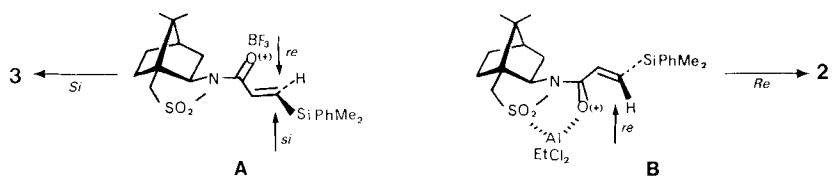
Entry [a])	R^1	R^2	*Lewis* acid	Ratio of crude **2/3**	Ratio of crystallized **2/3**	Yield of crystallized **2** + **3** [%]
1	$SiPhMe_2$	Vinyl	$BF_3 \cdot OEt_2$	27:73	3:97	60
2	$SiPhMe_2$	Vinyl	$EtAlCl_2$	95:5	98:2	57
3	$SiPhMe_2$	(*Z*)-Prop-1-enyl	$EtAlCl_2$	98:2	99:1	65
4	$SiPhMe_2$	(*E*)-prop-1-enyl	$EtAlCl_2$	98:2	98:2	67
5	$SiPhMe_2$	Me	$EtAlCl_2$	93:7	96.7:3.3	61
6	$SiPhMe_2$	Et	$EtAlCl_2$	93:7	96:4	62
7	$SiPhMe_2$	Pr	$EtAlCl_2$	94:6	98:2	57
8	$SiPhMe_2$	i Pr	$EtAlCl_2$	93:7	97:3	64
9	$SiPhMe_2$	Bu	$EtAlCl_2$	95.7:4.3	98.4:1.6	61
10	$SiPhMe_2$	Ph	$EtAlCl_2$	97.4:2.6	100:0	86
11	Ph	$SiPhMe_2$	$EtAlCl_2$	10.6:90.4	1.5:98.5	43

[a]) *Entries 1–10*: R = R^2; *Entry 11*: R = R^1. *Entries 1–4*: Et_2O/THF 8:1; *Entries 5–11*: Et_2O.

with oxalyl chloride and then with the bornane sultam **5** (after deprotonation with NaH) [3]. Tributylphosphine-stabilized organocopper reagents R^2Cu added smoothly to **1** at low temperatures in the presence of a *Lewis* acid to give a mixture **2**/**3** of isomers (*Scheme 1, Table 1*)[5]). Comparison of *Entries 1* and *2* reveals how significantly the stereodifferentiation depends on the nature of the *Lewis* acid: Conjugate addition of vinylcopper to **1**. (R^1=$SiPhMe_2$) proceeded with moderate (46% diastereoisomeric excess (d.e.)) C(*β*)-*Si*-face selection when promoted by $BF_3 \cdot OEt_2$ (*Entry 1*), but with 90% C(*β*)-*Re*-face preference on coordination of **1** with $EtAlCl_2$ (*Entry 2*). In practice, either the (*R*)-isomer **2** (*Entry 1*) or its (*S*)-epimer **3** (*Entry 2*) were obtained from the same precursor in *ca.* 60% yield and > 94% d.e. after crystallization of the crude products.

Mechanistically, we attribute (*Scheme 2*) this striking difference in sense and extent of induction to a BF_3-monocoordinated transition state **A** with anti-disposed SO_2/C=O groups (*Entry 1*) and, alternatively, to the Al-chelated transition state **B** (*Entry 2*). Shielding of the olefinic top face is less pronounced in **A** than in **B** consistent with the higher stereoface differentiation (favoring bottom-side attack) observed in *Entry 2*. A

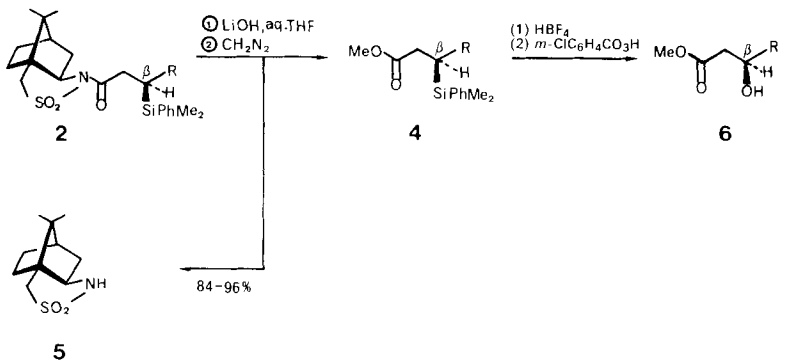
Scheme 2



[5]) For asymmetric conjugate additions of RCu · BF_3 · Bu_3P to sulfonamide-shielded enoates, see [10]. The starting organolithium reagents were prepared by metalation of the corresponding bromides (for (*E*)- and (*Z*)-prop-1-enyl bromides, see [11]) with Li [10]. Usually, sultam **1** was added slowly to a 1:1:1 mixture of RLi, CuI · Bu_3P, and $EtAlCl_2$ (10 equiv.) at −78°. In *Entry 3*, RLi, CuI · Bu_3P (1:1-mixture; 5 equiv.) was transferred by Ar pressure into a stirred solution of **1**/$EtAlCl_2$ 1:10 at −78°. Stirring 2 h at −78°, quenching with aq. NH_4Cl solution at −60°, GC of the crude mixture followed by removal of Bu_3P by chromatography, and crystallization (hexane) gave adducts **2** or **3**.

variety of alkenyl- and alkylcopper reagents (*Table 1, Entries 3–10*) underwent conjugate additions to **1** (R^1=$SiPhMe_2$) with 86 to 96% C(β)-*Re*-face predominance in agreement with the proposed transition state **B**; after crystallization, the adducts **2** were obtained in 92 to *ca.* 100% d.e. *Entries 10* and *11* illustrate the possibility to direct the developing configuration at C(β) by alternation of R^1 and R^2. Whereas PhCu addition to the *N*-[(silyl)enoyl]sultam **1** (R^1 =$SiPhMe_2$) afforded **2** (R=Ph), its epimer **3** (R=Ph) was formed on addition of $SiPhMe_2Cu$[6]) to the *N*-[(phenyl)enoyl]sultam **1** (R^1 =Ph). In the latter case, the diastereoisomeric excess (80% d.e.) was less prominent but could be raised to 97% d.e. by subsequent crystallization.

Scheme 3



2 **4** **6** **5**

Table 2. *Oxidative C, Si-Bond Cleavage* **2**→**4**→**6**

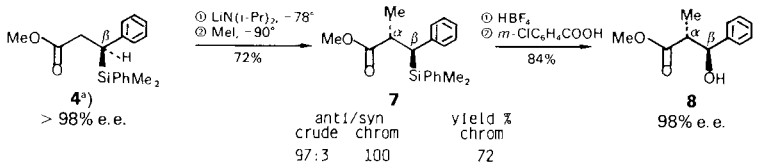
Entry	R	Yield [%] **2**→**4**	Yield [%] **4**→**6**	e.e. of aldol **6** [%]
1	Et	84	30	> 98
2	Pr	81	83	92
3	Bu	66	71	94
4	Ph	91	84	> 98

The depicted extent and direction of diastereoface differentiation was assigned by direct GC analyses of the 1,4-adducts **2** and **3**[7]) and by comparing relevant properties *(vide infra)* of the aldols **6** derived from **2** *(Scheme 3)*. Prior to transforming the $SiPhMe_2$ group into a OH function, the sultam auxiliary **5** was non-destructively removed (84 to 96% yield) from **2** mild hydrolysis (LiOH, aq. THF, 25°); esterification of the resulting carboxylic acids with diazomethane furnished methyl esters **4**[3]). Following the procedure of *Kumada et al.* [2a] the silyl-substituted esters **4** were converted into aldols **6**[3]) by successive protodesilylation (HBF_4) and oxidation (*m*-chloroperbenzoic acid, KF, DMF). Comparing aldols **6** with their racemates by means of ^{1}H-NMR measurements in the presence of the chiral shift reagent Eu(hfc)$_3$ [13] revealed enantiomeric purities above 92% e.e. All aldols **6** showed a predominance of the high-field over the low-field CH_3O signal in accord

[6]) Analogous addition of **1** (R^1 = PH) to 10 equiv. of $PhMe_2SiLi$ [12], CuI · Bu_3P, and $EtAlCl_2$ in Et_2O at −120°.

[7]) The olefinic adducts **2** of *Entry 2* and *3* were identified *via* hydrogenation to the products of *Entry 6* (*Wilkinsons*'s catalyst) and 7 (Pd/C), respectively.

Scheme 4



[a]) See *Entry 4* of *Table 2*.

with the depicted absolute configuration which is also consistent with the $[\alpha]_D^{23.4°}$ value for **6** (R=Ph) of −18.4° (EtOH, c=2.09; [14]: −17.9°). The thus assigned configurations of **6** correlate to those of **2** accounting for stereochemical retention in the oxidative Si–C-bond cleavage **4**→**6**.

Having generated enantioselectively a β-silylated center in **4**, it was interesting to exploit its inductive effect on α-alkylation, previously described by *Fleming et al.* [1].

Treatment of **4** (R=Ph) with $LiN(i\text{-}Pr)_2$ at −78°, then with MeI at −90°, and chromatographic removal of the very minor (3%) *'syn'*-isomer afforded the expected α-methylated *'anti'*-isomer **7** in 72% yield. Oxidative Si–C-bond cleavage of **7** furnished pure (GC) *'anti'*-aldol **8** in more than 98% e.e. (^{1}H-NMR in the presence of Eu(hfc)$_3$) [13].

Extensions of this new route to enantiomerically pure β-silylcarboxyl derivatives, involving stereospecific allylic substitutions of the silyl group, are presently under investigation.

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