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Highly Stereocontrolled and Concise Asymmetric Synthesis of the β-Lactam Framework via a TCC Method

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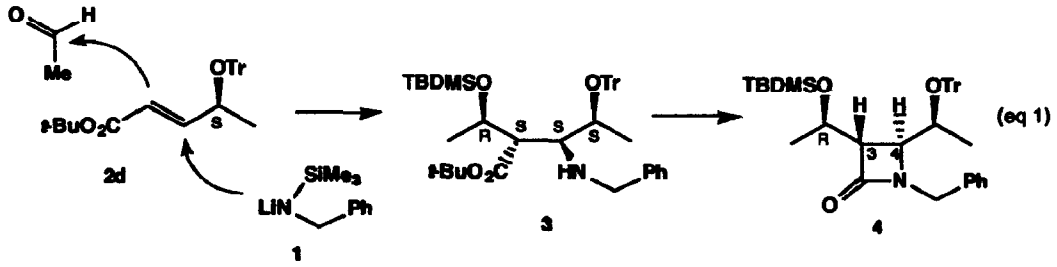
Abstract : The conjugate addition of LSA **1** to t-butyl (4S)-4-(trityl)oxy-2-pentenoate **2d** followed by aldol condensation with acetaldehyde produces a key intermediate **3** to β-lactam derivatives as a single diastereoisomer in 77 % yield.

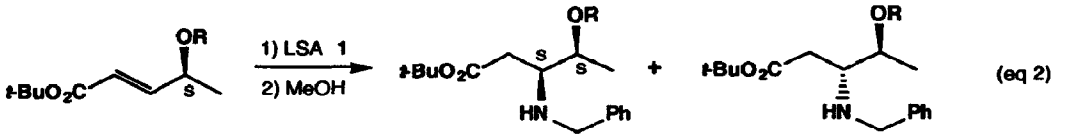
A number of excellent methods for the synthesis of β-lactams including 1β-methylcarbapenems have been developed in the past ten years.[1] We previously reported an entirely new approach to the synthesis of the β-lactam framework via a three component coupling (TCC) process using higher order amide cuprates[2]; the regioselective conjugate addition of the amide cuprate reagent of LSA (lithium N-benzyl(trimethylsilyl)amide) to 5-phenyl-2,4-pentadienoate having a sultam chiral auxiliary, followed by aldol condensation with acetaldehyde, afforded a β-lactam with high de and ee (all in one-pot). Although the absolute stereochemistry at C-3 corresponded to that of natural β-lactams, the stereochemistries at C-4 and the hydroxyethyl unit were opposite to those in the natural framework.[2] More recently, we have shown that the conjugate addition of chiral lithium amide, LiNBn(C*HMePh), to t-butyl 5-phenyl-2,4-pentadienoate provides regio- and diastereoselectively the corresponding β-amino ester in essentially quantitative yield with >99 % de, which can be converted via aldol condensation into the β-lactam having the correct absolute configuration (a modified TCC process).[3] However, the diastereoselectivity of the aldol condensation step was not 100 %; the ratio of the desired diastereoisomer to other diastereomers was 91 : 9 at best.[3]

We wish to report that the conjugate addition of LSA **1** to t-butyl (4S)-4-(trityl)oxy-2-pentenoate **2d** followed by aldol condensation with acetaldehyde produces the desired diastereoisomer **3** as a single product in 77 % yield (all in one-pot) (eq 1). Conversion of **3** to the azetidinone derivative **4** proceeded in 81 % yield.



When we started this project, little was known about the diastereoselectivity on the 1,2-asymmetric induction in the conjugate addition of lithium amides to γ-alkoxy-substituted α,β-unsaturated esters, although the

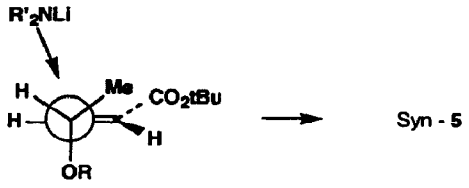
selectivities of the addition of amines,[4] alkoxides,[5] and carbon nucleophiles[6] had been reported. The syn-selectivity was previously reported for the conjugate addition of benzylamine[4a,b] and various alkoxides[5] to acyclic α,β-enoates and their derivatives. A more complex situation holds for the addition of organometallic reagents (carbon nucleophiles) to acyclic γ-alkoxy-α,β-unsaturated enoates and enones[6]; the anti-selectivity has been observed frequently with organocopper reagents, but in certain cases organolithium and copper reagents have reacted with syn-selectivity. Accordingly, we first examined the diastereoselectivity on the addition of LSA to the γ-silyloxy and alkoxy-α,β-unsaturated esters **2** (eq 2). Although the syn-selectivity



syn **5** anti **6**

2a;	R = TBDMS	91%	54	:	46
b;	R = TBDPS	99%	89	:	11
c;	R = TIPS	95%	90	:	10
d;	R = Tr	77%	100	:	0

was quite low in the case of the t-butyldimethylsilyloxy derivative **2a**, the diastereoselectivity was increased up to 100 % by using the sterically very bulky trityloxy derivative **2d**. However, the chemical yield was decreased to 77 % due to the steric bulkiness. Both t-butyldiphenylsilyl **2b** and triisopropylsilyl **2c** protected substrates gave the syn-adducts **5** in very high chemical yelds with significantly high syn diastereoselectivity.[7] The syn selectivity can be accounted for by a modified Felkin-Anh model **7**, in which RO group adopts anti,



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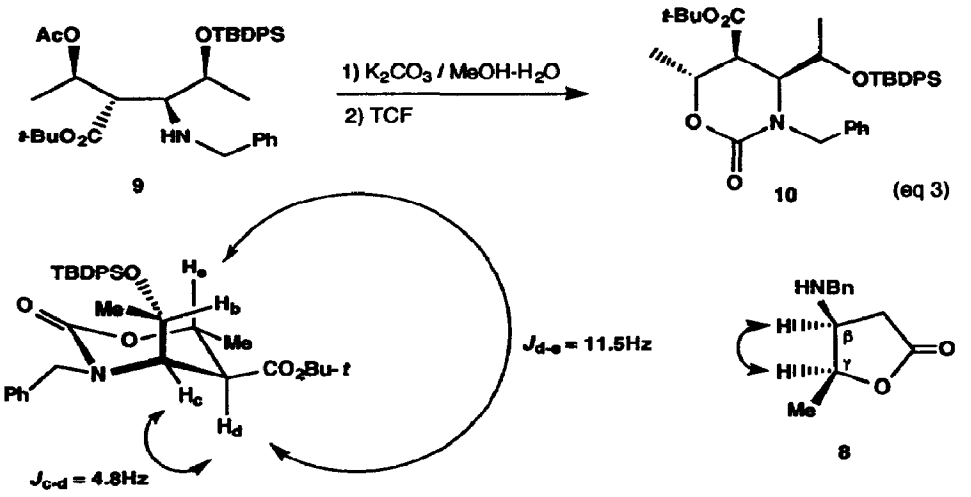
Me adopts inside, and the nucleophile attacks from the less hindered outside. It is not clear at the present time why the addition of methylcuprates to **2a** produces the anti-adduct with high diastereoselectivity[6] although the lithium amide addition to the same enoate gives the syn β-amino ester **5** predominantly.

Being encouraged by the perfect stereocontrol via **2d**, we carried out the TCC process (all in one-pot). To a THF solution (50 mL) of N-benzyl(trimethylsilyl)amine (4.1 mL, 21 mmol) at -78 °C under Ar was added dropwise a 1.76 M hexane solution of n-BuLi (11 mL, 20 mmol). The mixture was stirred for 30 min and a THF (10 mL) solution of **2d** (5.0 g, 12 mmol) was added at -78 °C. After 90 min, MeOH (0.89 mL, 22 mmol) was added and the mixture was stirred for 20 min at -78 °C. To this mixture under Ar was added slowly a THF (40 mL) solution of LDA (100 mmol) precooled at -78 °C; it took 10 min for the addition. After

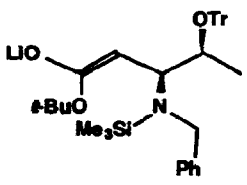
20 min, a 5M THF solution of acetaldehyde (30 mL, 150 mmol) was added slowly. The mixture was stirred for 90 min at -78 °C, and the reaction was quenched with aqueous NH_4Cl solution. After the usual work-up, a crude product was treated with TBDMSCl (3.0 g, 20 mmol) and imidazole (1.2 g, 17 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The usual work-up and purification with a silica-gel column chromatography using hexane / ethyl acetate (10 / 1) as an eluent gave **3** (6.3 g) in 77 % yield. To a THF (15 mL) solution of **3** (0.43 g, 0.63 mmol) at 0 °C under Ar was added a 0.9 M THF solution of ethylmagnesium bromide (2.1 mL, 1.9 mmol).[8] After 2 h, the reaction was quenched with aqueous NH_4Cl solution. The usual work-up and purification gave **4** (0.31 g) in 81 % yield.

The absolute configurations at C-4, C-3, and the silyloxyethyl unit of **4** were determined in the following way. Since the syn stereochemical relationship between C-3 and C-4 of **5** is established,[7] it is clear that the absolute configuration at C-3 of **3** is S. The coupling constant between H^4 and H^3 of **4** was J = 2.0 Hz, indicating that the two substituents at C-4 and C-3 of the β-lactam skeleton adopt trans-geometry and the absolute configuration at C-2 of **3** is S. The TCC product **9**, obtained from **2b**, was converted to **10** upon deprotection of an acetyl group with K_2CO_3 / MeOH – H_2O and subsequent treatment with TCF (trichloromethyl chloroformate) (eq 3). From the coupling constant ($J_{d\text{-}e}$ = 11.5 Hz), it is clear that the



stereochemical relation between methyl and t-butoxycarbonyl substituent of **10** is trans and hence the absolute configuration of silyloxyethyl unit of **3** (and **4**) is R. (3S, 4S) Configuration of **4** is also confirmed by the coupling constant Jc-d = 4.8 Hz of **10**.

Since Z-enolates are formed stereoselectively from the reaction of β-amino esters with LDA,[9] the Z-isomer **11** is presumably a key intermediate for the aldol condensation of **5d**. The electrophilic attack of acetaldehyde to **11** would take place as shown in **12**; a hydrogen atom adopts inside due to severe 1,3-allylic strain by t-BuO group. The condensation would occur via a synclinal 6-membered cyclic transition state **13**, giving **3** with essentially 100 % de. Now we are in a position to obtain concisely the β-lactam framework **4** having correct absolute configurations at the three contiguous chiral centers. We are investigating a method for converting **4** into other β-lactam derivatives.



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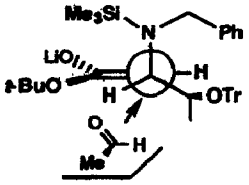

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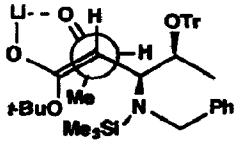

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