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Extremely Stereoselective Alkylation of 3-Siloxy-β-lactams and Its Applications to the Asymmetric Syntheses of Novel 2-Alkylisoserines, Their Dipeptides, and Taxoids

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Abstract: New and efficient synthetic routes to 2-alkylisoserines, their dipeptides and 2'-alkyl-taxoids were synthesized from enantiopure 3-alkyl-β-lactams **3** which were obtained through extremely distereoselective alkylation of β-lactams **2.**

The significance of non-protein amino acids has been recognized in connection with the design and syntheses of enzyme inhibitors as potential pharmaceutical drugs and also for the study of enzymatic reaction mechanisms.[1] Among these non-protein amino acids, α-alkylamino acids have been attracting medicinal and biochemical interest because many of them serve as powerful substrate-based inhibitors of enzymes.[1-3] α-Alkylamino acid residues also serve as conformational modifiers of physiologically active peptides, bringing in conformational restraints.[4] The asymmetric synthesis of α-alkylamino acids with excellent enantiopurity has therefore been extensively investigated.[5]

We have been applying the "*β-Lactam Synthon Method*" to the asymmetric syntheses of the C-13 side chain of paclitaxel, norstatine and its analogs as well as isoserine-dipeptides.[6-9] Modifications of the C-13 side chain of paclitaxel has provided us with a new series of taxoids that possess stronger anticancer activity than paclitaxel, as exemplified by the discovery of the "Second Generation" taxoid anticancer agents.[10-13] We communicate here distereoselective alkylation of 3-siloxy-β-lactams, and its applications to the syntheses of novel α-alkylisoserines, their dipeptides, and taxoids.

The enantiopure (3*R*,4*S*)-1-PMP-3-TIPSO-β-lactams **1a-d** (PMP = *para*-methoxy-phenyl; TIPS = triisopropylsilyl) were readily obtained through efficient chiral ester enolate-imine cyclocondensations.[14] Although the TIPS group is essential for obtaining excellent enantioselectivity in the cyclocondensation step, it is too bulky for 3-alkylation. As Scheme 1 and Table 1 illustrate, removal of the TIPS group of **1a-d** followed by treatment with chlorodimethylphenylsilane (DMPS-Cl) or chlorotriethylsilane (TES-Cl) gave **2a-d** in 66-81% yields. Alkylations were carried out by reacting the corresponding β-lactams **2a-d** with LDA to form the enolates, followed by the addition of methyl iodide or allyl bromide as electrophiles to give 3-alkyl-β-lactams **3a-d** as the single diastereomers in 56-84% yields.

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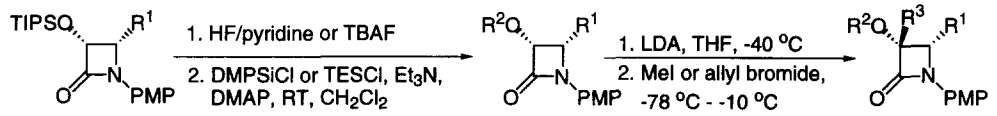
Scheme 1



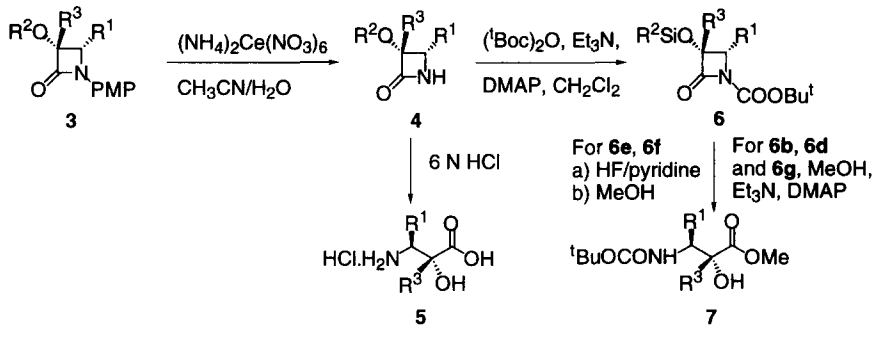
1 2 3

Table 1

R^1	R^2	R^3	2	yields (%)	3	yields (%)
isobutenyl	DMPS	Me	**2a**	81	**3a**	84
cyclohexylmethyl	DMPS	Me	**2b**	68	**3b**	81
isobutyl	DMPS	Me	**2c**	66	**3c**	84
phenyl	DMPS	Me	**2d**	68	**3d**	56
isobutenyl	TES	Me	**2e**	77	**3e**	74
isobutenyl	TES	allyl			**3f**	70
phenyl	DMPS	allyl			**3g**	72

Novel 2-alkylisoserine derivatives can be readily obtained from 3-alkyl-β-lactams **3a-g**. As Scheme 2 and Table 2 show, removal of the PMP group of **3c-g** with ceric ammonium nitrate (CAN) afforded **4c-g** (16-70%) together with desilylated products **4c'-g'**. Treatment of β-lactams **4c-d** with 6 N hydrochloric acid gave α-alkylisoserine hydrochloride **5c** and **5d**.

Scheme 2



3 4 6 5 7

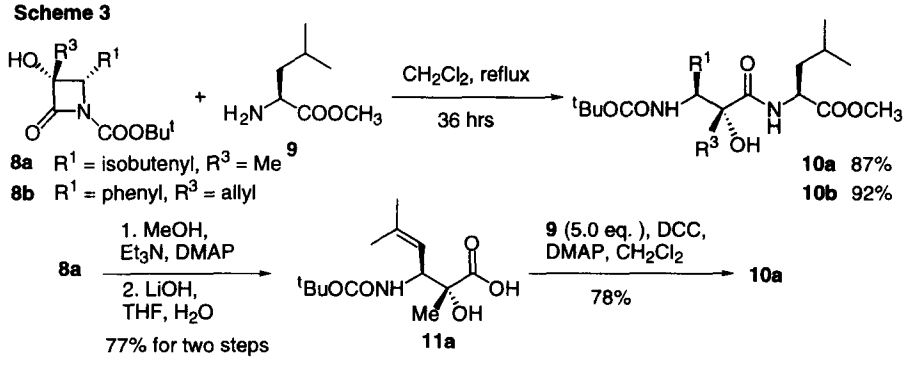
Table 2

R^1	R^2	R^3	4	4' 3-OH	5	6	7
isobutyl	DMPSi	Me	**4c** (35%)	**4c'** (36%)	**5c** (82%)	**6c** (92%)	**7c** (93%)
phenyl	DMPSi	Me	**4d** (16%)	**4d'** (53%)	**5d** (79%)	**6d** (81%)	**7d** (50%)
isobutenyl	TES	Me	**4e** (50%)	**4e'** (8%)		**6e** (88%)	**7e** (78%)
isobutenyl	TES	allyl	**4f** (62%)	**4f'** (2%)		**6f** (93%)	**7f** (70%)
phenyl	DMPSi	allyl	**4g** (70%)	**4g'** (0%)		**6g** (93%)	**7g** (63%)

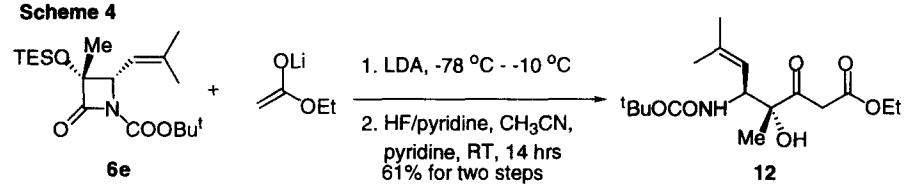
Protection of **4c-g** as their carbamates gave **6c-g**. Methanolysis of **6c-d** and **6g** gave desilylated α-alkylisoserine methyl esters **7c-d** and **7g**. For 3-TES-protected β-lactams **6e** and **6f**, treatment with HF/pyridine followed by methanolysis gave **7e** and **7f**. These N-protected α-alkylisoserines can serve as important building blocks for the synthesis of enzyme inhibitors.

Ring-opening coupling reactions of enantiopure (3*R*,4*S*)-1-*t*-Boc-3-hydroxy-3-alkyl-β-lactams with an (*S*)-amino acid ester were also investigated.[9] As Scheme 3 illustrates, the ring-opening coupling reaction with (*S*)-Leu-OMe **9** gave dipeptide **10a** and **10b** in high yields. An alternative approach is to react **8a** with methanol followed by hydrolysis to give 2-methylisoserine **11a**, first. Then, the subsequent coupling of **11a** with Leu-OMe (**9**) gave the same dipeptide **10a**. Both methods can be used to incorporate various α-methylisoserines into peptides.

Scheme 3



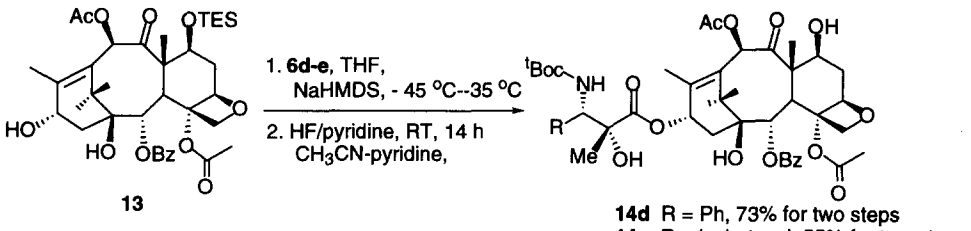
Scheme 4



The reaction of **6e** with an ester enolate[15] gave hydroxy(keto)ethylene dipeptide isostere **12** in 61% yield after deprotection (Scheme 4). The product exists predominantly in its keto form based on ^{1}H NMR analysis.

Kant et al. recently reported the distereoselective additions of Grignard reagents to azetidine-2,3-dione and its application to the syntheses of C-2' substituted taxoids.[16] These taxoids show better binding affinity to microtubules than paclitaxel. As described above, we have applied our extremely stereoselective alkylation method to the synthesis of enantiopure 3-methyl-β-lactams. Accordingly, we synthesized 2'-methyl-taxoids using these 3-methyl-β-lactams. Coupling of 1-*t*-Boc-3-methyl-β-lactam **6d-e** with 7-TES-baccatin (**13**) under the standard conditions using NaHMDS as the base, followed by deprotection, gave the corresponding 2'-methyl-taxoids **14a** and **14b** in 73% and 55% yields, respectively (Scheme 5). Our synthesis of **14a** gave a much higher yield than the reported one (44%) that used LiHMDS as the base.[16] The cytotoxicity of new taxoid **14b** is currently being assayed and will be reported elsewhere.

Scheme 5



13

14d R = Ph, 73% for two steps
14e R = isobutenyl, 55% for two steps

Further studies on the asymmetric syntheses of a variety of enzyme inhibitors and new taxoids containing 2-alkylisoserine moieties are actively underway.

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