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Practical Synthesis of Taxol Side Chain

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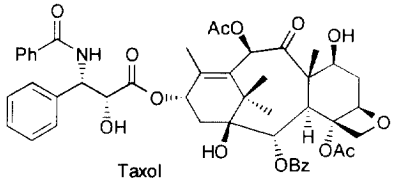
Abstract

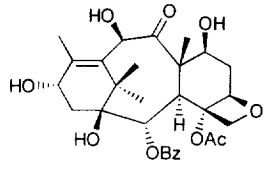
Practical large scale synthesis of *N*-benzoyl-(2*R*,3*S*)-phenylisoserine methyl ester of the Taxol side chain has been attained from the coupling of chiral imine of *N*-[(*S*)-methylbenzyl]benzaldimine with (*Z*)-α-methoxy trimethylsilyl ketene acetal followed by the sequential reactions of lactamization, demethylation, methanolysis and *N*-benzoylation.

Keywords: Taxol side chain; synthesis; imine; stereochemistry.

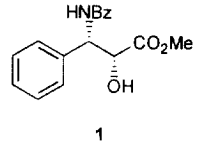
Plant derived natural Taxol[1] from the bark of *Taxux brevifolia* is the most promising anticancer agents discovered [1]. Due to the limited amounts of Taxol which can be derived from the plants, a semisynthetic route starting from the more abundant 10-deacetylbaccatin III is promising for obtaining large quantities. The side chain being attached to the main ring of baccatin III is *N*-benzoyl-(2*R*,3*S*)-phenylisoserine.



Taxol



10-Deacetylbaccatin III



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Ample approaches toward the synthesis of Taxol side chain were reported based on the methods including asymmetric induction of hydroxyamine from cinnamate [2], asymmetric cycloaddition of imine and ketene acetal to make azetidine-2-one and subsequent hydrolysis [3], utilization of chiral starting substrates [4], and microbial or enzymatic processes [5]. Additional synthetic methods from imine with α-silyloxy ketene acetal [6] or boron enolate of thioesters [7] were also emerged recently based on the aldol type reactions. However most of these are not practically applicable for large scale preparation. In this communication we would like to report a practical synthesis of Taxol side chain of *N*-benzoyl-(2*R*,3*S*)-phenylisoserine methyl ester (**1**).

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[1] Taxol is the registered trademark of Bristol-Myers Squibb Company for Paclitaxel.

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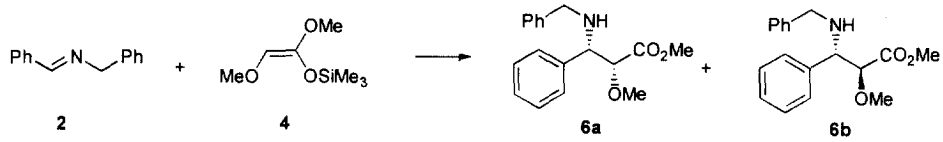
The previous study of the condensation between chiral imine with α-silyloxy ketene acetal lead to a new synthetic route to the Taxol side chain [6a,b]. In the presence of equivmolar amount of chiral boron catalysts was obtained the desired stereochemical product of 3-amino-2-hydroxy-3-phenylpropanoate that was converted directly to the target molecule by *N*-benzoylation. However, some drawbacks made this process impossible for large scale preparation. The stereoselective synthesis of starting (*Z*)-1-methoxy-1,2-di(triethylsilyloxy)ethylene required low temperature like -100 °C and the following coupling reaction with chiral imine was carried out at -78 °C with consumption of equivmolar amount of expensive chiral catalyst. Therefore a practical and inexpensive synthetic method from chiral imine with more readily available ketene acetal is required for large scale preparation of *N*-benzoyl-(2*R*,3*S*)-phenylisoserine in a practical manner.

At first the stereochemical course of the crucial coupling reaction was studied between *N*-benzylbenzaldimine (**2**) and inexpensive and readily available (*Z*)-1,2-dimethoxy-1-trimethylsilylethylene (**4**) [8], in the presence of several different Lewis acids as shown in Scheme 1 and Table 1. All of the Lewis acids lead the reaction into the *syn* fashion in moderate yields. $AlCl_3$, TMSCl and TMSTf showed the selectivity about 3:1 with the *syn* preference in good yield while $TiCl_4$, $SnCl_4$ and TiF_4 gave relatively poor stereoselectivity (entries 1-7). The best result was obtained with $MgBr_2$ resulting in the desired stereochemistry with the *syn* (**6a**) to *anti* (**6b**) ratio of 84:16 in 95% isolated yield at -25°C (entry 8). The stereochemical outcome and the reaction yield were not changed much by elevating the reaction temperature to room temp with catalytic amount of Lewis acid (entries 9-11). Thereafter the reaction was performed at room temp with 0.3 mol equivalent of $MgBr_2$.



2 4 6a 6b

Scheme 1

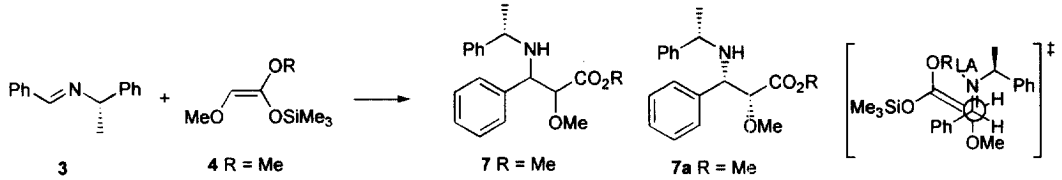
Table 1. Reaction of imine (**2**) and ketene acetal (**4**) in the presence of Lewis acids.

Entry	Lewis acid	mole equiv.	Temp (°C)	Time (h)	Yield[a] (%)	*Syn* (**6a**) / *Anti* (**6b**)[b]
1	$TiCl_4$	1.0	rt	1	56	52 : 48
2	$SnCl_4$	1.0	rt	1	61	58 : 42
3	TiF_4	1.0	-78	3	78	54 : 46
4	$AlCl_3$	1.0	-78	2	87	71 : 29
5	$AlCl_3$	1.0	rt	1	92	76 : 24
6	TMSCl	1.0	rt	1.5	83	74 : 26
7	TMSTf	1.0	0	2	68	75 : 25
8	$MgBr_2$	1.0	-25	3	95	84 : 16
9	$MgBr_2$	1.0	rt	1	89	80 : 20
10	$MgBr_2$	0.5	rt	2	91	81 : 19
11	$MgBr_2$	0.3	rt	4	93	83 : 17

a. Isolated yield. b. Ratio was determined by either HPLC or ^{1}H NMR.

Once the reaction condition was established we carried the reaction with chiral imine of *N*-[(*S*)-methylbenzyl]benzaldimine (**3**) considering additional factor of diastereofacial selectivity. We could obtained the expected product of (2*R*,3*S*)-2-methoxy-3-phenyl-3-[(*S*)-methylbenzylamino]propanoate (**7a**) as a major among all four possible stereoisomers (**7**) in 59% of isolated yield after flash column chromatography. (*syn*:*anti* = 78:22, diastereofacial

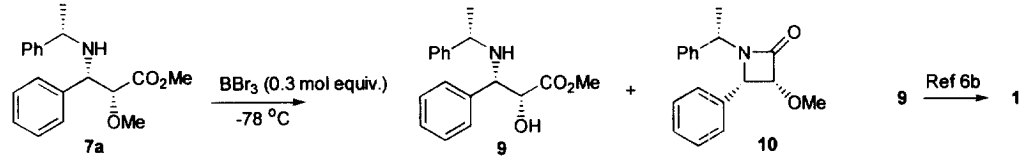
ratio = 92:8). The same reaction with (*Z*)-1-*t*-butoxy-2-methoxy-1-trimethylsilyloxyethylene (**5**) gave the product of *t*-butylester (**8a**) in 61% isolated yield (*syn*:*anti* = 81:19, diastereofacial ratio = 94:6).[2] The diastereoselectivity was not quite much improved by changing methyl (**4**) to *t*-butyl (**5**) in the ketene acetal. The transition state of the reaction can be drawn as in the bracket of the Scheme 2 with *synclinal* orientation of imine activated by Lewis acid and ketene acetal approaching to the less hindered face of the chiral imine [9].



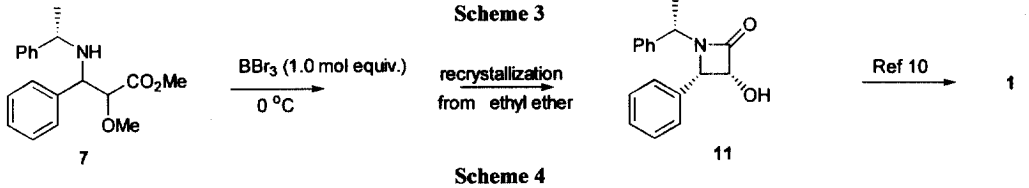
3 **4** R = Me; **5** R = *t*-Bu **7** R = Me; **8** R = t-Bu **7a** R = Me; **8a** R = t-Bu

Scheme 2

The coupled product of (2*R*,3*S*)-2-methoxy-3-phenyl-3-[(*S*)-methylbenzylamino]propanoate (**7a**) was further treated for demethylation with 0.3 mol equiv. of BBr_3 at -78 °C to give free hydroxy compound (**9**) with the minor product of (3*R*,4*S*)-3-methoxy-4-phenyl-1-[(*S*)-methylbenzyl]azetidin-2-one (**10**) in 75% and 15% of isolated yields respectively[3]. **10** was also obtained from lactamization of either **7a** or **8a** with MeMgBr in CH_2Cl_2 in quantitative yield.[4] The known literature procedure of debenzylation and benzoylation from **9** afforded the target molecule of *N*-benzoyl-(2*R*,3*S*)-phenylisoserine methyl ester (**1**) [6a,b]. Further treatment of **10** with 0.3 mol equiv. of BBr_3 at 0 °C gave (3*R*,4*S*)-3-hydroxy-4-phenyl-1-[(*S*)-methylbenzyl]azetidin-2-one (**11**).



Scheme 3



Scheme 4

This implicates the possible direct route to **11** from the coupled product **7a**. Treatment of (2*R*,3*S*)-2-methoxy-3-phenyl-3-[(*S*)-methylbenzylamino]propanoate (**7a**) with one mol

[2] The similar stereochemical outcome like *syn*/*anti* ratio of 89:11 and diastereofacial ratio of 92:8 was reported in the same reaction with the nucleophile of α-silyloxy ketene acetal at -78 °C in the presence of equivmolar amount of boron catalysts.[6a,b]

[3] More amount of (3*R*,4*S*)-3-methoxy-4-phenyl-1-[(*S*)-methylbenzyl]azetidin-2-one (**10**) could be obtained from the same reaction at 0 °C in 45% yield.

[4] All new compounds exhibited ^{1}H-NMR, ^{13}C-NMR, and mass spectra, and combustion data in agreement with the structure indicated. **7a**: $[\alpha]_D$ +0.91 (c= 0.93, $CHCl_3$), ^{1}H-NMR (200 MHz; $CDCl_3$); δ 1.17 (d, 3H), 2.20 (brs, 1H), 3.22 (s, 3H), 3.51 (q, 1H), 3.54 (s, 3H), 3.78 (d, 1H), 4.11 (d, 1H), 7.09-7.24 (m, 10H); ^{13}C-NMR (50.3 MHz; $CDCl_3$); δ 21.7, 51.6, 54.1, 58.8, 61.9, 85.3, 126.6, 126.7, 127.5, 127.9, 128.2, 139.4, 145.9, 171.6. **8a**: $[\alpha]_D$ +3.22 (c= 0.87, $CHCl_3$), ^{1}H-NMR (200 MHz; $CDCl_3$); δ 1.19 (d, 3H), 1.28 (s, 9H), 2.18 (brs, 1H), 3.25 (s, 3H), 3.51 (q, 1H), 3.67 (d, 1H), 4.10 (d, 1H), 7.11-7.39 (m, 10H); ^{13}C-NMR (50.3 MHz; $CDCl_3$); δ 21.6, 27.7, 54.1, 58.4, 62.1, 81.2, 85.5, 126.6, 127.4, 128.1, 128.2, 128.4, 139.4, 146.1, 170.0. **10**: $[\alpha]_D$ +68.9 (c= 0.48, $CHCl_3$), ^{1}H-NMR (200 MHz; $CDCl_3$); δ 1.24 (d, 3H), 2.90 (s, 3H), 4.37 (d, 1H), 4.45 (d, 1H), 5.01 (q, 1H), 7.18-7.39 (m, 10H); ^{13}C-NMR (50.3 MHz; $CDCl_3$); δ 19.0, 51.7, 58.0, 60.9, 84.8, 127.4, 127.9, 128.1, 128.5, 128.7, 128.8, 135.2, 139.5, 166.8.

equivalent of BBr_3 at O °C gave (3*R*,4*S*)-3-hydroxy-4-phenyl-1-[(*S*)-methylbenzyl]azetidin-2-one (**11**) which could be obtained as a crystalline solid after recrystallization in ethyl ether. Once the reaction sequence was established we could succeeded to get (3*R*,4*S*)-3-hydroxy-4-phenyl-1-[(*S*)-methylbenzyl]azetidin-2-one (**11**) as optically pure form after two times of recrystallization starting from the mixture of four stereoisomers (**7**) without chromatographic separation of a single isomer **7a** as shown in Scheme 4. Methanolysis and *N*-benzoylation of azetidine-2-one (**11**) gave Taxol side chain of *N*-benzoyl-(2*R*,3*S*)-phenylisoserine methyl ester (**1**) [10]. This reaction sequence starting from chiral imine and ketene acetal was applied for multi-gram scale preparation of *N*-benzoyl-(2*R*,3*S*)-phenylisoserine methyl ester (**1**) with about 25-30% of consistent overall yield.

In conclusion we have found that the reaction of chiral imine of *N*-[(*S*)-methylbenzyl]benzaldimine with (*Z*)-α-methoxy trimethylsilyl ketene acetal in the presence of catalytic amount of $MgBr_2$ yielded (2*R*,3*S*)-2-methoxy-3-phenyl-3-[(*S*)-methylbenzylamino]propanoate as a major among all four possible stereoisomers. Lactamization and demethylation with BBr_3 from the coupled products without isolation of the major isomer were successfully achieved to afford (3*R*,4*S*)-3-hydroxy-4-phenyl-1-[(*S*)-methylbenzyl]azetidin-2-one as an optically active form after recrystallization The subsequent reactions of methanolysis and *N*-benzoylation gave Taxol side chain of *N*-benzoyl-(2*R*,3*S*)-phenylisoserine methyl ester.

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