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NEW AND EFFICIENT APPROACHES TO THE SEMISYNTHESIS OF TAXOL AND ITS C-13 SIDE CHAIN ANALOGS BY MEANS OF β–LACTAM SYNTHON METHOD

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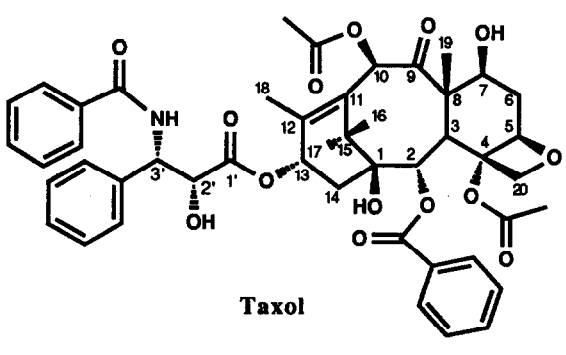
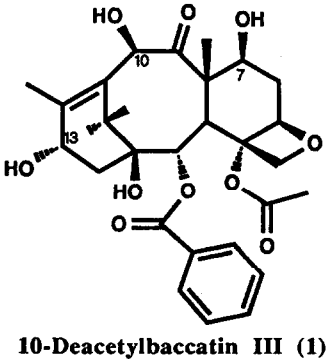
Summary: Highly efficient chiral ester enolate-imine condensation giving 3-hydroxy-4-aryl-β-lactams with excellent enantiomeric purity is successfully applied to the asymmetric synthesis of the enantiomerically pure taxol C-13 side chain, *N*-benzoyl-(2*R*,3*S*)-3-phenyl-isoserine and its analogs. (3*R*,4*S*)-*N*-benzoyl-3-(1-ethoxyethoxy)-4-phenyl-2-azetidinone readily derived from the 3-hydroxy-4-phenyl-β-lactam is coupled with protected baccatin IIIs, followed by deprotection to give optically pure taxol and 10-deacetyl-7,10-bis(Troc)-taxol in good yields. Fully assigned ^{1}H, ^{13}C, and 2D (COSY and HETCOR) NMR spectra of taxol thus synthesized are shown and discussed.

Taxol, a complex diterpene,[1] is currently considered the most exciting lead in cancer chemotherapy. Taxol possesses high cytotoxicity and strong antitumor activity against different cancers which have not been effectively treated by existing antitumor drugs. For example, taxol is currently in phase III clinical trial for advanced overian cancer, phase II for breast cancer, and phase I for lung cancers, colon cancer and acute leukemia.[2] At present, the supply of taxol is solely dependent on the extraction from the bark of *Taxus brevifolia* (Pacific yew), which is a very slowly growing tree in old growth forests in the Northwest of the United States and the total number is estimated to one million. For the set of clinical trials only, more than 25,000 trees are required because of the low concentration of taxol in the bark. The harvest of those trees endangers not only the old growth forest in the Northwest of the United States, but also the future supply of taxol.



Taxol



10-Deacetylbaccatin III (1)

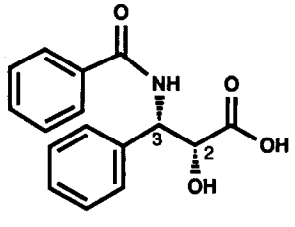
Accordingly, it is obviously an absolute necessity to develop practical cell culture or synthesis for this extremely promising anticancer drug. A couple of reports have appeared for the cell culture approach,[3] but the efficiency and practicality of those reported methods are still unknown. The total synthesis of taxol has already been attempted by a number of synthetic chemists without success so far, and requires much further elaborations.[4]

However, it has recently been found that the most complicated tetracyclic diterpene moiety of taxol, i.e., 10-deacetylbaccatin III (**1**), which is the most demanding in total synthesis, is more readily available from the leaves of *Taxus baccata* (European yew).[5] The extraction of the fresh leaves yields 10-deacetylbaccatin III in a very good yield, i.e., 1g/1Kg. The leaves are reproduced quickly, and thus it is unnecessary to cut down the trees to obtain the bark, which makes a sharp contrast to the case of taxol.

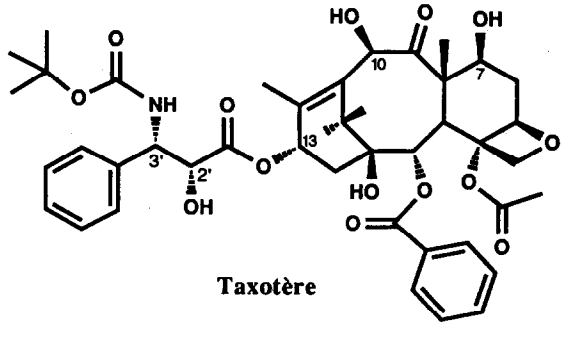
With the availability of 10-deacetylbaccatin III (**1**), it appears that sufficient supplies of taxol can now be produced in a semisynthetic fashion. Namely, if the C-13 side chain can be synthesized effectively and coupled to 10-deacetylbaccatin III (**1**) with proper protective groups, the semisynthetic process would be the most practical approach to the production of taxol and sufficient supplies of taxol may well be secured.

Although taxol is an extremely important "lead" in cancer chemotherapy, taxol has a problem in solubility in aqueous media, which may impose some serious limitation in its use. Also, it is common that better drugs can be derived from naturally occurring lead compounds. In fact, French researchers, Potier, Guéritte-Voegelein, Guénard et al. have discovered that a modification of the C-13 side chain of taxol brought about a new anticancer agent which seems to have antitumor activity superior to taxol with better bioavailability. This unnatural compound was named "taxotère", which has t-butoxycarbonyl instead of benzoyl on the amino group of (*2R,3S*)-phenylisoserine moiety at the C-13 position and a hydroxyl group instead of acetoxy group at C-10.[6] Taxotère is currently in phase II clinical trial in both United States and Europe. Taxotère has been synthesized by a semisynthetic process, including a coupling of *N*-tert-butoxycarbonyl-(2*R*,3*S*)-3-phenylisoserine (**2**) with 10-deacetylbaccatin III (**1**) with proper protecting groups.[7]

It is known that the C-13 side chain, i.e., *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine (**3**) moiety, is crucial for the strong antitumor activity of taxol.[8] Moreover, some modification of the C-13 side chain can provide a new series of taxol analogs which may have higher potency, better bioavailability and less unwanted toxicity, as exemplified by the discovery of taxotère. Accordingly, it is quite promising to investigate the structure-activity relationship (SAR) for the C-13 side chain analogs of taxol with some modification of the baccatin III moiety in order to find more effective anticancer agents with better pharmacological property.[9]



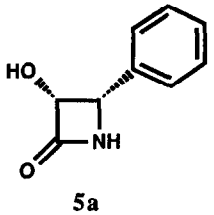
Taxol C-13 side chain (3)



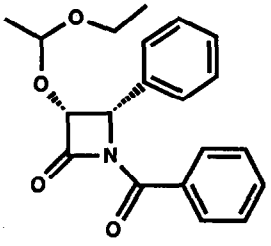
Taxotère

Accordingly, the development of an efficient method which can be applied not only to taxol, but also to taxotère and other analogs, i.e, the method having flexibility and wide applicability is extremely important and of current demand to promote the research in this area. We describe here an efficient and practical approach to the semisynthesis of the C-13 side chain analogs of taxol on the basis of the "β-Lactam Synthon Method",[10] which has the desired flexibility and wide applicability.

The first enantioselective synthesis of the important side chain **3** was obtained in 8 steps and 23% yield via a Sharpless epoxidation from cis-cinnamyl alcohol with an enantiomeric excess of 76-80%.[11] The obtained **3** was coupled with 7-triethylsilylbaccatin III (**4a**) by esterification.[12] A recent publication describes the chemo-enzymatic synthesis of a derivative of **3**, in which the racemic mixture was resolved by enzymatic hydrolysis with lipases.[13] We successfully applied lithium chiral ester enolate - imine cyclocondensation strategy[14] to the asymmetric synthesis of **3** via a (3*R*,4*S*)-3-hydroxy-4-phenylazetidin-2-one (**5a**) as the key-intermediate.[15] Based on this protocol, **3** can be obtained in 3 steps in high yield with virtually 100% e.e. Quite recently, it was found that 1-benzoyl-(3*R*,4*S*)-3-(1-ethoxyethoxy)-4-phenyl-2-azetidinone (**6a**), readily derived from the hydroxy-β-lactam (**5a**), served as the key-intermediate for the synthesis of taxol.[16] Therefore, our β-lactam intermediate **5a** serves as the key-intermediate for both coupling methods.



5a

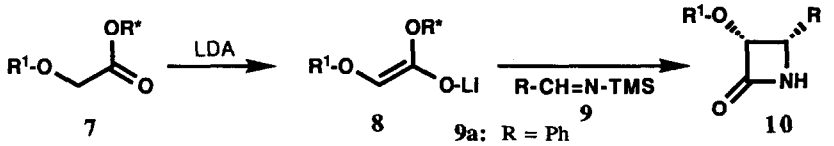


6a

RESULTS AND DISCUSSION

Synthesis of C-13 side chain of taxol and its analogs

First, we carried out the reactions of chiral lithium ester enolates (**8**) generated in situ from silyloxyacetates (**7**) (**Chart 1**) with *N*-trimethylsilylimines (**9**), which gave the corresponding chiral β-lactams **10** (eq. 1). Results are summarized in Table 1.



7 **8** **9** **10** (1)

9a: R = Ph
9b: R = 4-(MeO)C_6H_4
9c: R = 3,4-$(MeO)_2C_6H_3$

Chart 1

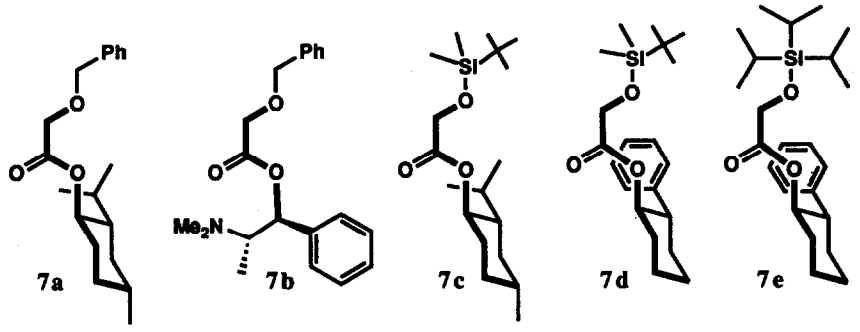


Table 1. Asymmetric synthesis of β-lactams (**10**) through chiral enolate - imine cyclocondensation

Entry	Ester	Imine	β-Lactam	Isolated Yield (%)	Configuration	Enantiomeric Purity (% e.e.)[a]
1	**7a**	**9a**	(-)**10-A**	18	3R,4S	15
2	**7b**	**9a**	(+)**10-A**	20	3S,4R	67
3	**7c**	**9a**	**10-B**	52	3R,4S	50
4	**7d**	**9a**	**10-B**	90	3R,4S	76
5	(-)**7e**	**9a**	(+)**10-C**	85	3R,4S	96
6	(+)**7e**	**9a**	(-)**10-C**	80	3S,4R	97
7	(-)**7e**	**9b**	(+)**10-D**	80	3R,4S	96
8	(-)**7e**	**9c**	(+)**10-E**	80	3R,4S	98

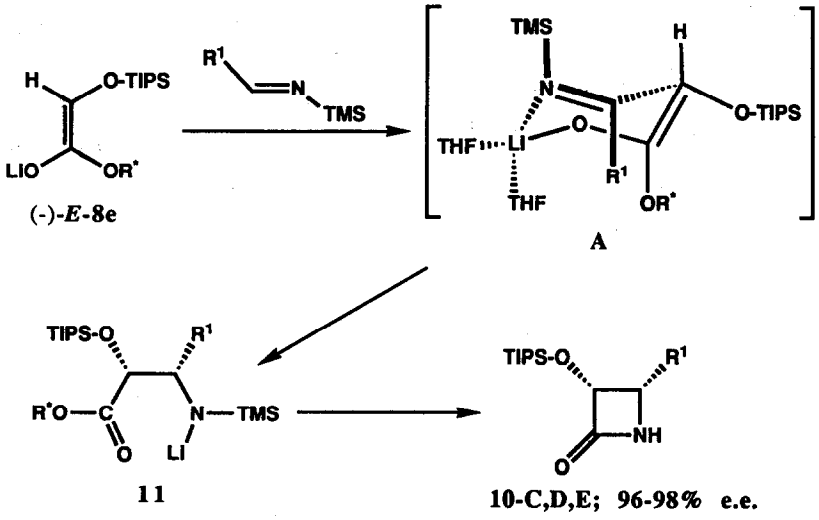
[a] Determined by ^{1}H NMR analysis using a chiral shift reagent, (+)-Eu(hfc)$_3$, (Entries 1-3) and by HPLC analysis on a chiral column - DAICEL CHIRACEL OD using n-hexane - 2-propanol as the solvent (Entries 4-8).

As Table 1 shows, the chiral auxiliary and the *O*-protecting group exert marked effects on the enantioselectivity as well as on the chemical yield of the reaction.[17] For example, the reactions of **7e**, bearing (-)- or (+)-trans-2-phenyl-1-cyclohexyl as the chiral auxiliary[19] and triisopropylsilyl (TIPS) as the *O*-protecting group, with **9a-c** give exclusively the corresponding cis-β-lactams **10** in high yields with extremely high enantiomeric purity (96-98% e.e.) (Entries 5-8). However, the reaction of **7d** bearing t-butyldimethylsilyl (TBDMS) as the *O*-protecting group with **9a** gives **10-B** in 90% yield, but with 76% e.e. (Entry 4). When (-)-menthyl is used as the chiral auxiliary and t-butyldimethylsilyl as the *O*-protecting group (**7c**), the reaction with **9a** gives **10-B** in 52% yield with only 50% enantiomeric purity (Entry 3). The use of benzyl as the *O*-protecting group and (-)-menthyl or ephedrinyl, **7a** and **7b**, gives (-)**10-A** (18% e.e.) or (+)**10-A** (67% e.e.) in low yield (15-20%) (Entries 1,2).

Absolute configurations of β-lactams (**10**) were determined by chemical correlation with authentic samples: **10-B** and (+)**10-C** were converted to (*R*)-3-phenyllactic acid via hydrogenolysis on 10% Pd-C followed by hydrolysis[10d-f] and to (2*R*,3*S*)-3-phenylisoserine by hydrolysis with 6N hydrochloric acid (*vide infra*), respectively. For (+)**10-D** and (+)**10-E**, absolute configurations were assigned by analogy with (+)**10-C** based on specific rotations and retention times on HPLC analyses on a chiral column (see Experimental Section). The absolute configuration of (-)**10-A** and (+)**10-A** were determined on the basis of the fact that **7d** bearing (-)-menthyl group gives (3*R*,4*S*)-β-lactam (**10-B**), i.e, (-)**10-A** should have (3*R*,4*S*) configuration and (+)**10-B** (3*S*,4*R*). The chiral auxiliaries, (+)- and (-)-trans-2-phenyl-1-cyclohexanol were recovered >90% yield in the Entries 5-8.

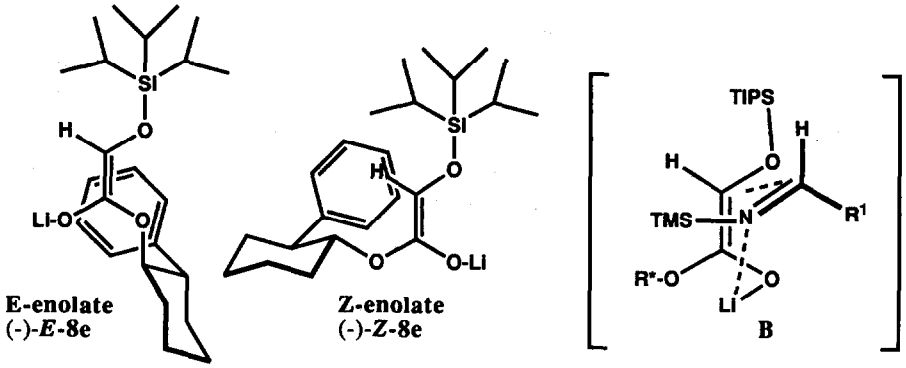
The exclusive formation of cis-β-lactams (+)**10-C,D,E** with 96-98% e.e. is rationalized by taking into account the highly selective generation of (*E*)-lithium enolates, (-)-*E*-**8e**, and the transition state A depicted in Scheme 1 on the basis of analysis discussed below.

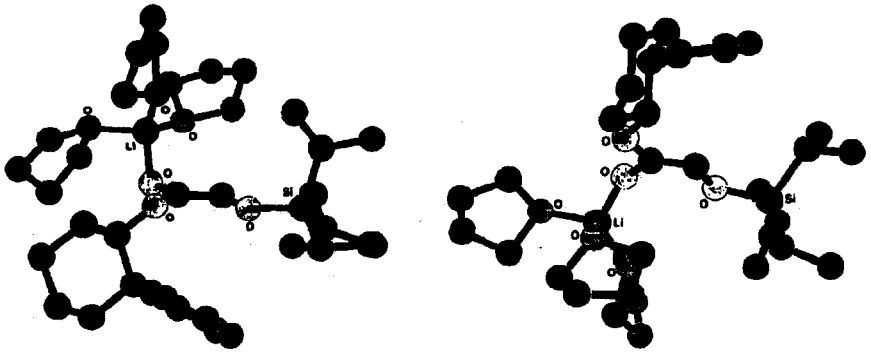
Scheme 1



There are two possible mechanistic pathways, i.e., (a) *E*-enolate formation followed by a chair-like transition state **A** and (b) *Z*-enolate formation followed by a boat-like transition state **B**, which can accommodate the observed stereochemical outcome. Since these are early transition states, the boat-like transition state **B** is not necessarily unfavorable. However, the chiral auxiliary is in an exo position in **B**, whereas it is located in an endo position in **A**. Accordingly, it is reasonable to assume that the transition state **A** would bring about much better asymmetric induction than **B**.

For the formation of *E*- or *Z*-enolate, *E*-enolate formation should be kinetically favorable.[20] In order to examine thermodynamic preference, we carried out MM2 calculations for both (-)-***E*-8e.3THF** and (-)-***Z*-8e.3THF** using MACROMODEL program. Then, it was found that (-)-***E*-8e.3THF** is more favorable than (-)-***Z*-8e.3THF** by 2.5 kcal/mol. Therefore, the formation of *E*-enolate is clearly preferred in this case.





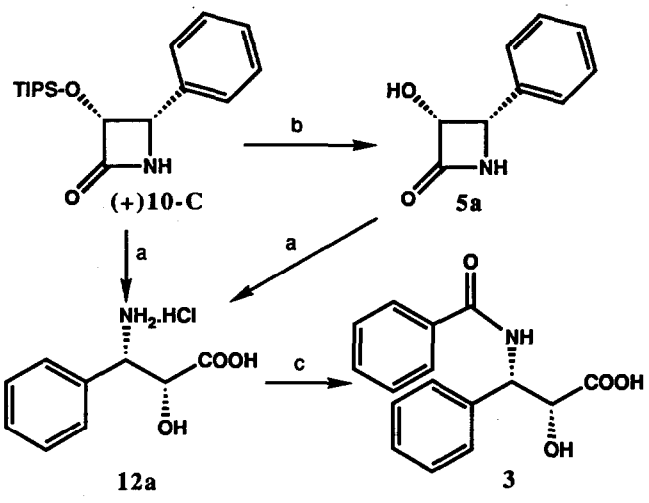
***E*-enolate, (-)-*E*-8e.3THF** **Z-enolate, (-)-Z-8e.3THF**

It is apparent that the chiral auxiliary, (-)-trans-2-phenyl-1-cyclohexyl, directs the approach of the *N*-TMS-imines (**9a-c**) extremely effectively from the *si*-face of (-)-***E*-8e** to give *N*-lithiated-β-amino esters (**11**), which then cyclize to afford the corresponding cis-β-lactams **10-C,D,E** (Scheme 1). In the same manner, the enantiomeric (-)**10-C** is yielded from (+)-***E*-8e** with 97% e.e. Until now, the asymmetric synthesis of 3-hydroxy-β-lactam has been limited by low stereoselectivity and often low chemical yield.[21] Thus, our method provides the first efficient and practical route to 3-hydroxy-β-lactams with extremely high enantiomeric purity.

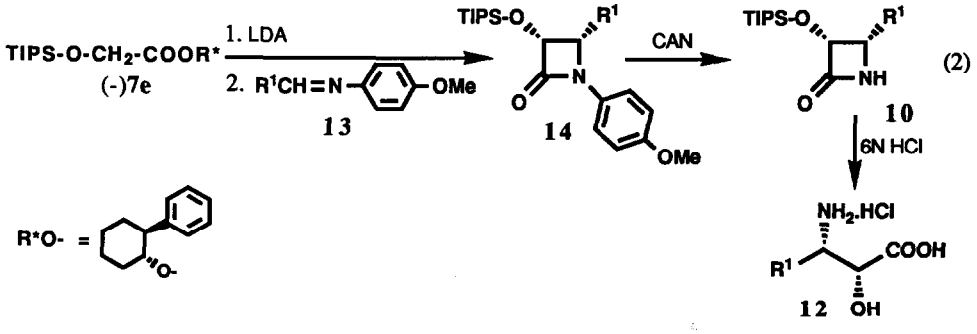
Next, (+)**10-C** thus obtained was converted to the desired *N*-benzoyl-(2*R*,3*S*)-phenylisoserine (**3**) through the procedure illustrated in Scheme 2. As Scheme 2 shows, (+)**10-C** was hydrolyzed with 6N hydrochloric acid at 25°C for 3-4 h to give (2*R*,3*S*)-phenylisoserine hydrochloride (**12a**) in quantitative yield, which was benzoylated by the usual Schotten-Baumann procedure followed by purification on a short silica gel column to give enantiomerically pure *N*-benzoyl-(2*R*,3*S*)-phenylisoserine (**3**) in 72% yield.

Alternatively, (+)**10-C** was deprotected by reacting with tetra-n-butylammonium fluoride in THF[22] at 25°C to give the (3*R*,4*S*)-3-hydroxy-β-lactam **5a** in 97% yield (Scheme 2). Then, **5a** was hydrolyzed with 6N hydrochloric acid at 25°C for 3 h to afford **12a** in quantitative yield. Other 3-silyloxy-4-aryl-β-lactams, (+)**10-D** and (+)**10-E**, can be converted to the corresponding substituted *N*-benzoylphenylisoserines in the same manner.

Scheme 2



a: 6N HCl, 25°C. b: n-Bu_4NF, THF. c: PhCOCl, $NaHCO_3$, CH_2Cl_2 - H_2O.



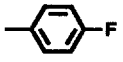
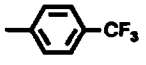
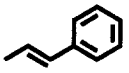
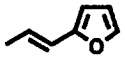
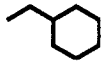
(2)

The substituent R^1 other than phenyl is important for the synthesis of taxol analogs which may possess better bioavailability as well as cytotoxicity and/or stronger binding ability to microtubles. Therefore, we synthe-

sized new β-lactams bearing aryl, heteroaryl, and alkyl substituents at C-4, which can be converted to the C-13 side chain analogs of taxol. In these syntheses, *N*-PMP-imines (PMP = 4-methoxyphenyl) (**13**) were used for the chiral enolate - imine cyclocondensation (eq. 2). These imines **13** are much more stable than *N*-TMS-imines **9**, especially for alkylaldimines. It is worthy of note that alkylaldimines can be used for this reaction in spite of the acidity of hydrogen at the α-carbon. Results are listed in Table 2. As Table 2 shows, the reactions achieve extremely high stereoselectivity (98-99% e.e.) for phenyl-, 4-fluorophenyl- and 4-(trifluoromethyl)phenylaldimine (**13a-c**) (Entries 1-3). The reactions also give excellent stereoselectivity for phenylethenyl-, 2-furylethenyl, isobutyl, and cyclohexylmethylaldimines (**13e-h**) (Entries 5-8). *To the best of our knowledge, Entries 7 and 8 provide the first examples in which aldimines of enolizable alkylaldehydes are successfully used to give the corresponding β-lactams in chiral ester - enolate condensation process.*[23]

All reactions give cis-β-lactams (**14**) with (3*R*,4*S*) configuration exclusively except for the case of furfurylaldimine (**14d**), which gives a small amount of trans-isomer (cis/trans = 91/9); Nevertheless, the stereoselectivity for the formation of cis-isomer (**14d**) is excellent (92% e.e.) (Entry 4).

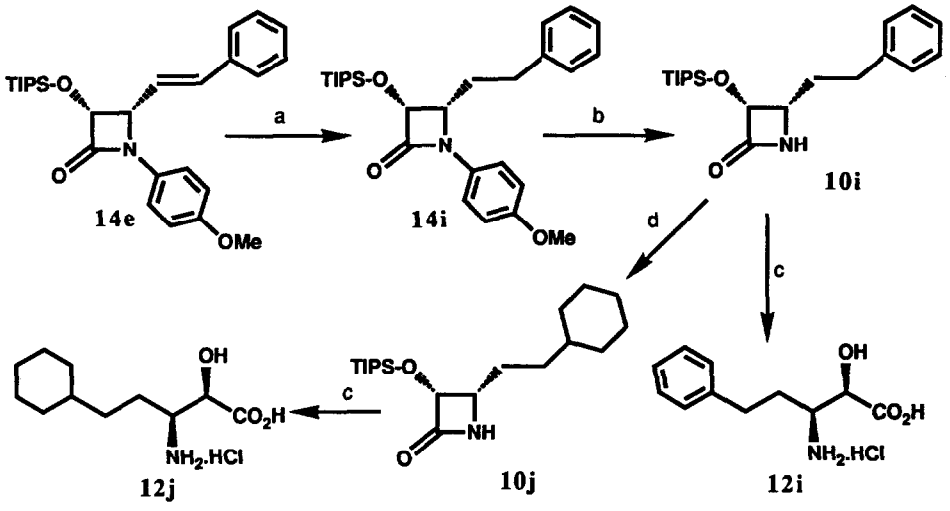
Table 2. Asymmetric synthesis of β-lactams (**14**)

Entry	R^1	β-Lactam[a]	Isolated yield(%)	%ee[b]
1		**14a**	89	98
2		**14b**	81	98
3		**14c**	84	99
4		**14d**	78[c]	92[d]
5		**14e**	85	96
6		**14f**	72	94
7		**14g**	85	92
8		**14h**	85	90

[a] All β-lactams are cis and (3*R*,4*S*) configuration unless otherwise noted. [b]Determined by chiral HPLC on a chiral column - DAICEL CHIRACEL OD using n-hexane - 2-propanol as the solvent. [c] Obtained as a mixture of cis- and trans-isomers (cis/trans = 91/9).
[d] Enantiomeric excess for the cis-isomer.

The β-lactams **14a**, **14e**, **14g**, and **14h** thus obtained were treated with cerium ammonium nitrate (CAN) in water at 0°C for 1 h to give β-lactams (+)**10-C**, **10e**, **10g**, and **10h**, respectively, in 75-85% yields (eq. 2). The hydrolysis of **10e**, **10g**, and **10h** with 6N hydrochloric acid at 25°C for 3-4 h gave the corresponding (2*R*,3*S*)-isoserines in quantitative yields (see Experimental Section). The β-lactam **14e** was further hydrogenated on 10% Pd-C to give the 4-phenylethyl-β-lactam **14i** (96% yield), followed by reacting with CAN at 0°C in water to afford the β-lactam **10i** in 85% yield. The β-lactam **10i** was further hydrogenated on 5% Rh-C at 50°C and 800 psi of hydrogen to give the 4-cyclohexylethyl-β-lactam **10j** in 93% yield. The β-lactams **10i** and **10j** were hydrolyzed with 6N hydrochloric acid in the same manner to that described above to afford the corresponding isoserine hydrochlorides, **12i** and **12j**, respectively, in quantitative yields. These transformations are illustrated in Scheme 3.

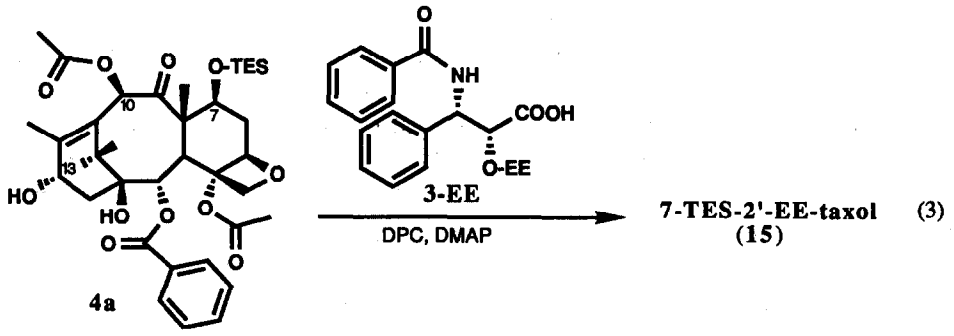
Scheme 3



a: H_2/Pd-C, MeOH-AcOEt, 25°C. b: CAN, CH_3CN-H_2O. c: 6N HCl, 25°C. d: H_2/Rh-C (800 psi), MeOH, 50°C.

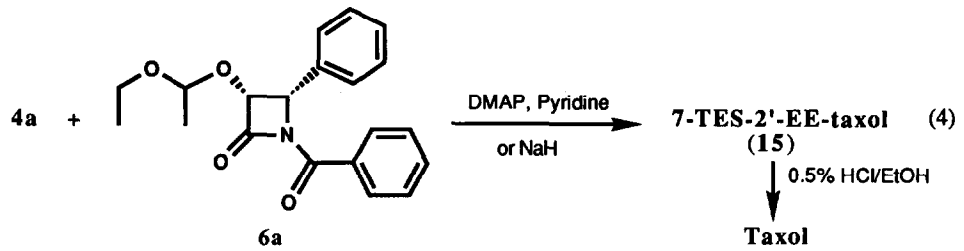
Coupling of the C-13 side chain precursors with baccatin III derivatives - semisynthesis of taxol

The *N*-benzoylphenylisoserine (**3**) with *O*-(1-ethoxyethyl) (*O*-EE) protecting group has already been coupled with 7-TES-baccatin III (**4a**) (TES = triethylsilyl) in the presence of dipyridylcarbonate (DPC) and 4-dimethylaminopyridine (DMAP) by Greene et al. (eq. 3).[12a] The best result so far reported for the synthesis of 7-TES-2'-EE-taxol (**15**) is 80% yield at 50% conversion by using ca. 6 equiv. of *O*-EE-*N*-benzoyl-phenylisoserine (**3-EE**) at 73°C in toluene.[12a]



Recently, Holton developed a newer coupling method (eq. 4),[16] directly from 1-benzoyl-(3*R*,4*S*)-3-(1-ethoxy)ethoxy-4-phenyl-2-azetidinone (**6a**), which was derived from (3*R*,4*S*)-3-hydroxy-β-lactam **5a**. The required **5a** was obtained through tedious optical resolution of racemic cis-3-hydroxy-β–lactam.[16] As shown in Scheme 2, **5a** can be obtained in two steps in excellent yield through our method. According to Holton's procedure in his patent application,[16] the coupling of **6a** (5 equiv.) with **4a** proceeds at 25°C in the presence of DMAP and pyridine for 12 h to give 7-TES-2'-EE-taxol (**15**) in 92% yield, which was deprotected with 0.5% hydrochloric acid in ethanol at 0°C to afford taxol in ca.90% yield. We carried out the coupling following the Holton procedure and found that the reported result was reproducible except for the reaction time, i.e., the reaction proceeded much slower than reported and thus 24-36 h were necessary for completion.

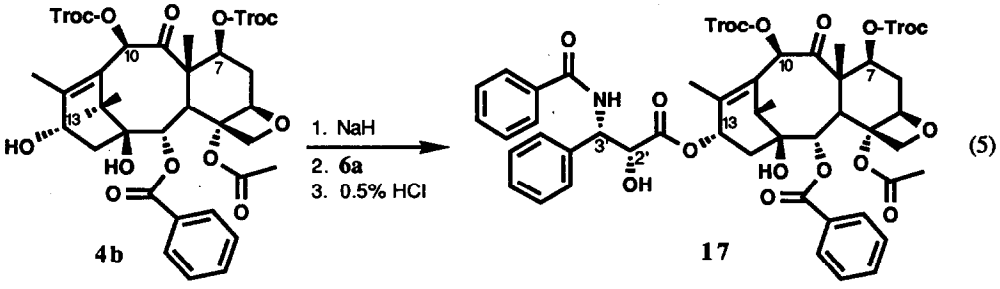
Since Holton's protocol requires 5 equiv. of **6a** and the reaction is very slow even under almost neat conditions, we looked for a better coupling procedure. Thus, we investigated the coupling of the sodium salt of **4a**, which should have higher nucleophilicity than neutral **4a**, with **6a** in THF. The sodium salt of **4a** was generated by reacting **4a** with NaH in THF (eq. 4). Although the reaction conditions have not been optimized yet, some encouraging result has been obtained.



A mixture of 7-TES-baccatin III (**4a**) (0.10 mmol) and **6a** (0.15 mmol, 1.5 equiv.) in THF was added to NaH (large excess) in THF suspension at 0°C. The suspension was stirred at 35°C for 3 h and quenched with brine at 0°C. Conversion was 50% on the basis of ^{1}H NMR analysis. After column chromatography on silica gel, 7-TES-2'-EE-taxol (**15**) was isolated in 40% yield (80% yield based on **4a** reacted) and unreacted **4a** was recovered (37%). The 7-TES-2'-EE-taxol (**15**) thus obtained was a 1:1 mixture of diastereomers due to the chiral center at 2'-EE (*Note*: Holton reported in his patent application[16] that a 2:1 diastereomer mixture of **15** was obtained. It is possible to assume that one of the two diastereomers was enriched through kinetic resolution since

5 equiv. of β-lactam (**rac-6a**) were employed.). In order to examine the stereochemical integrity during the coupling, **15** was deprotected by 0.5% hydrochloric acid in ethanol at 0°C, following Greene's procedure,[12a] to give taxol in 88% yield after column chromatography on silica gel. It was then confirmed by ^1H and ^{13}C NMR analyses that no racemization took place during the coupling process and optically pure taxol was obtained.

We also carried out the coupling of **6a** with 7,10-bis(Troc)-baccatin III (**4b**)[12b] (Troc = trichloroethoxycarbonyl) in the same manner as that described above. In this coupling, the sodium salt of **4b** was generated first at -15°C, followed by the addition of **6a** at the same temperature. The suspension was stirred for 1 h and quenched with brine. 10-Deacetyl-7,10-bis(Troc)-2'-EE-taxol (**16**) was obtained in 88% yield based on **4b** reacted (43% conversion). It is noteworthy that **4b** showed substantially higher reactivity than **4a** in this coupling process in spite of the fact that the substituents at C-7 and C-10 do not seem to be in a proximity of C-13 hydroxyl group. After deprotecting 2'-EE with 0.5% hydrochloric acid in THF, 10-deacetyl-7,10-bis(Troc)-taxol (**17**)[12b] was obtained in 90% yield after column chromatography on silica gel (eq. 5). No racemization was observed during the coupling on the basis of ^1H and ^{13}C NMR analyses of **17**.



(5)

While our NMR study was in progress, complete assignments for the ^1H and ^{13}C NMR of taxol with the aid of 2D NMR experiments were reported by Falzone,[24a] Chmurny,[24b] Baker[24c] and their coworkers which prompts us to report here ^1H and ^{13}C NMR, HETCOR and COSY spectra of taxol thus synthesized. The ^1H (600.139 MHz) and ^{13}C (150.925 MHz) NMR spectra are shown in Figure 1, and Figures 2 and 3 illustrate the HETCOR and COSY spectra, respectively. The ^1H and ^{13}C NMR data perfectly match with those reported for naturally occurring taxol.[24]

On the basis of ^1H, ^{13}C, DEPT, COSY and ^1H - ^{13}C HETCOR (CSCM) NMR spectra of taxol as well as ^1H and ^{13}C NMR spectra of 10-deacetylbaccatin III (**1**), 7-TES-baccatin III (**4a**) and 10-deacetyl-7,10-bis(Troc)-baccatin III (**4b**), all protons and all carbons were unambiguously assigned. The assignments of protons and carbons of three phenyl groups are not shown for simplicity.

Our COSY and HETCOR analyses disclosed that the previously reported[25] assignment of the methylene protons at C14 (C14-H_2) was incorrect, i.e., the C14-H_2 protons were reported to appear at 2.5 ppm in $CDCl_3$ as a multiplet, and the C6-H_2 methylene protons were not assigned. Although C-6 virtually overlaps with C-14 at 35.64 ppm, the expanded HETCOR spectrum at the C-14 and C-6 region (Figure 2) clearly indicates the existence of diastereotopic protons. The COSY spectrum shows a cross peak due to the geminal coupling between the C6-H_2 methylene protons. These protons also show two cross peaks arising from the vicinal couplings with the C7-H methine proton.(4.40 ppm). A cross peak due to the vicinal coupling of C14-H_2 with C13-CH (6.23 ppm) is

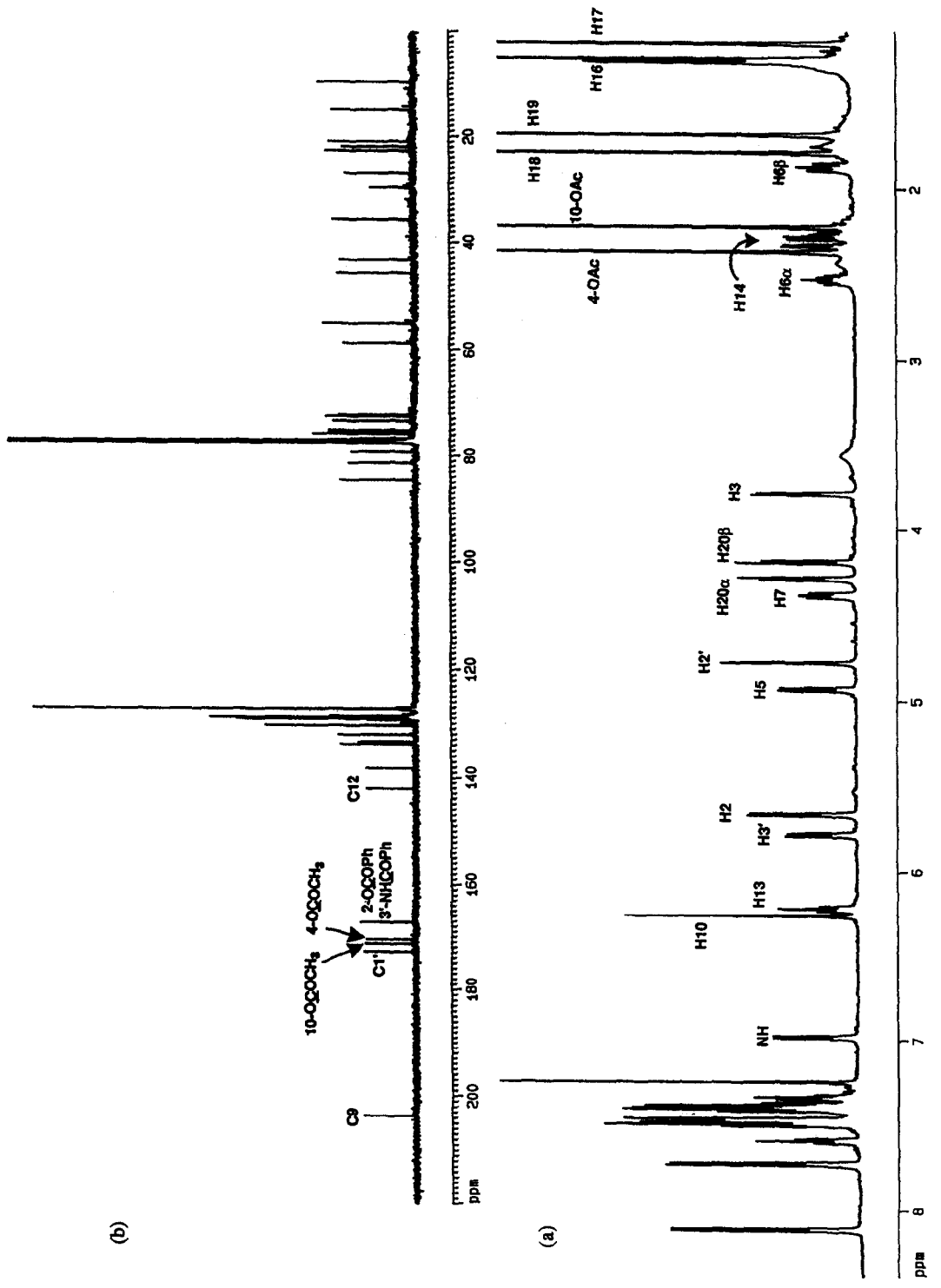


Figure 1. (a) ^{1}H NMR (600 MHz) and (b) ^{13}C NMR (150 MHz) spectra of taxol in $CDCl_3$

Figure 2. ^{1}H-^{13}C HETCOR spectra (250 MHz) of taxol in $CDCl_3$

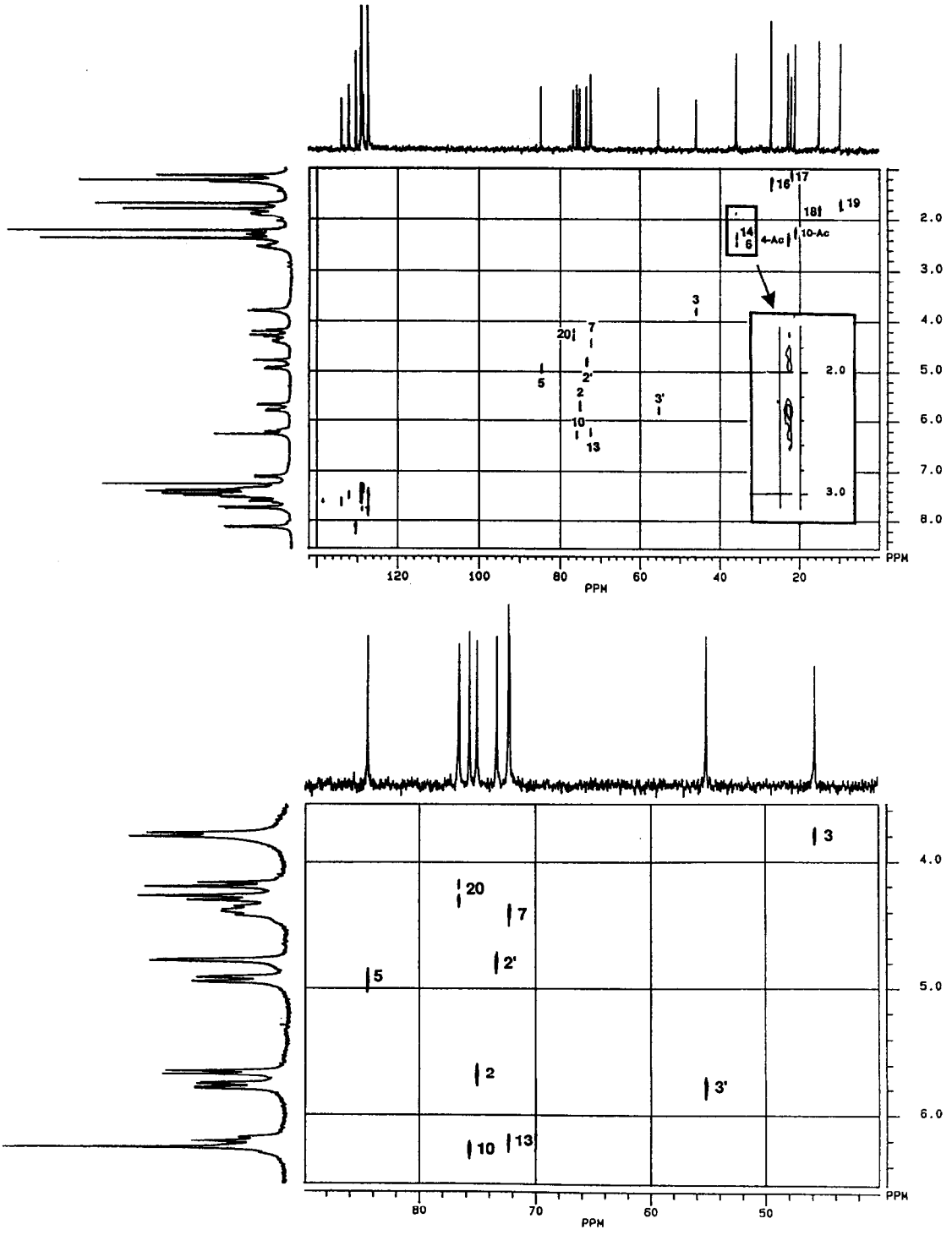
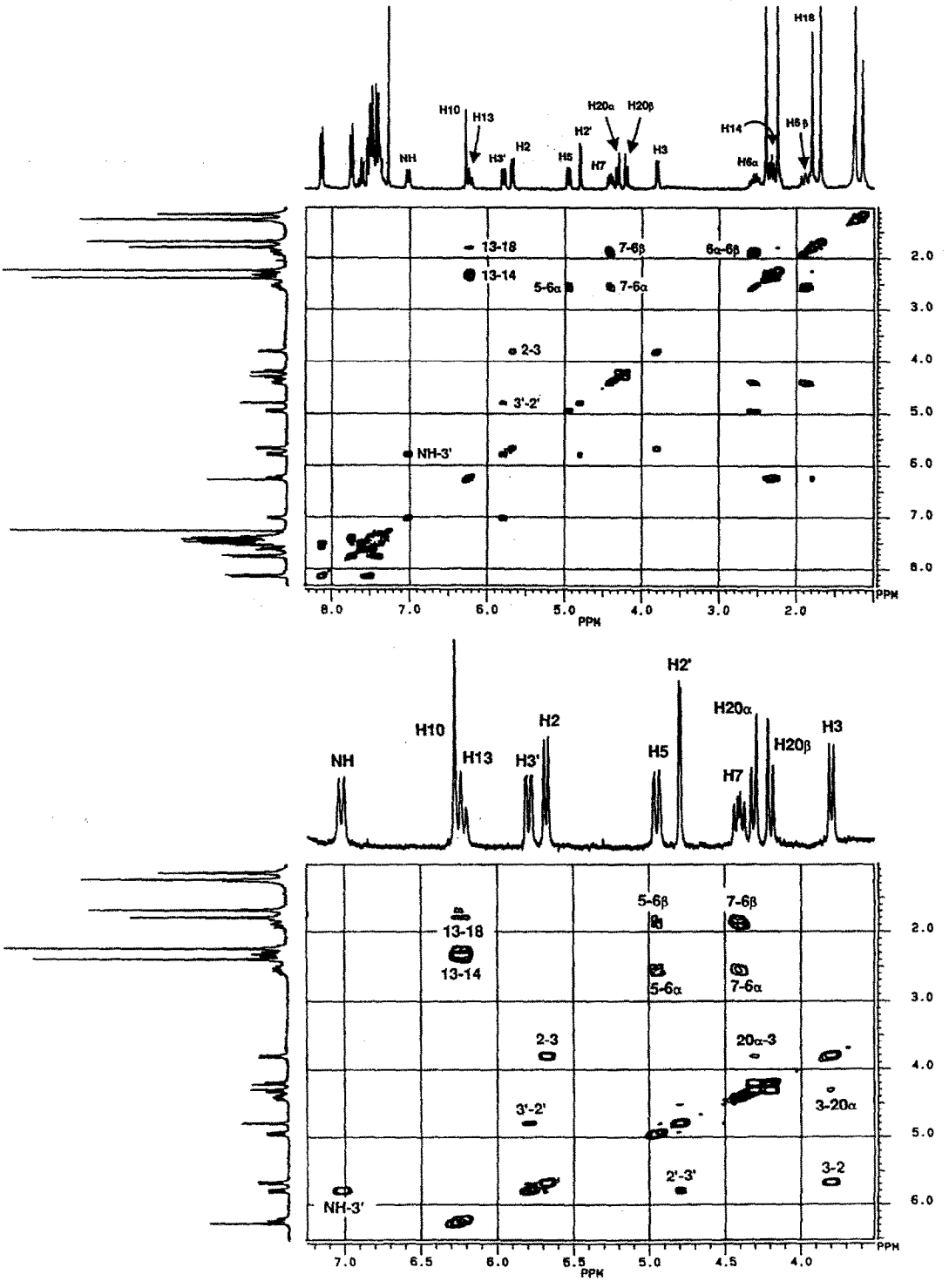


Figure 3. COSY spectra (250 MHz) of taxol in $CDCl_3$



observed as well. Therefore, the signals at 1.86 (m) ppm and 2.53 (ddd) ppm in the ^1H NMR spectrum are unambiguously assigned to C6-H_2 and the signals at 2.26 (dd) ppm and 2.34 (dd) ppm to C14-H_2. Our assignments are consistent with those reported by Falzone et al.[24a] as well as Chmurny et al.[24b]

In conclusion, it is demonstrated that 3-hydroxy-4-substituted-β–lactams serve as the key-intermediates for the asymmetric synthesis of the taxol C-13 side chain and its analogs, which are readily obtained through highly efficient chiral ester enolate - imine cyclocondensations with extremely high enantiomeric purity. These 3-hydroxy-4-substituted-β-lactams are readily converted to the corresponding 1-acyl-3-EEO-β-lactams in high yields, which can directly be coupled with protected baccatin IIIs to give taxol and its analogs after deprotection. The most efficient and crucial chiral auxiliary, (-)-trans-2-phenylcyclohexanol can readily be obtained in 100 g scale using the lipase-catalyzed kinetic resolution of its racemic acetate developed by Whitesell et al.,[19] which is fully recyclable after the reaction. Triisopropylsilyl protecting group (TIPS) can also be recycled and its recovery process is currently in active investigation. This synthetic method provides efficient and practical routes to a variety of new taxol C-13 side chain analogs which may have better bioavailability and cytotoxicity with lower undesired toxicity as well as various photoaffinity and radio-labeled taxol analogs which would play a key-role in biochemical study of taxol.

EXPERIMENTAL SECTION

General Method. Melting points were measured with a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer FTIR 1600 series spectrophotometer. ^1H, ^{13}C, and 2D NMR spectra were measured with a Bruker AMX 600, a Bruker AC 250 or a General Electric QE-300 spectrometer for solutions using tetramethylsilane as the internal standard. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. Thin Layer chromatography was performed on Merck DC-alufolien with Kieselgel 60F-254. Column chromatography was carried out on silica gel (Silica gel 60, 230-400 mesh ASTM, Merck). Chiral HPLC analysis for the determination of enantiomeric excess, was carried out with a Waters HPLC assembly consisting of a Waters M45 solvent delivery system, a Waters Model 680 gradient controller, and a Waters M440 detector (at 254 nm), equipped with a Spectra Physics Model SP4270 integrator using a chiral column J. T. Baker DAICEL - CHIRACEL OD employing hexane/2-propanol (13/1) as the solvent system with a flow rate of 0.2mL/min. MACROMODEL program was run on a Vax Station 3100 (digital).

Materials. 10-Deacetylbaccatin III (**1**) was a gift from Indena, SpA. 10-Deacetyl-7,10-bis(trichloroethoxycarbonyl)baccatin III (**4b**) was a gift from Rhone-Poulenc Rorer. 7-Triethylsilylbaccatin III (**4a**) was prepared from 10-deacetylbaccatin III (**1**) by the literature method.[12a] (-)- and (+)-trans-2-Phenylcyclohexanol were prepared by the literature method.[19] Triisopropylsilyl chloride was obtained from Aldrich Chemical Co.

Preparation of (-)-(1*R*,2*S*)-2-phenyl-1-cyclohexyl triisopropylsilyloxyacetate (7e): A solution of (-)-(*1R,2S*)-2-phenyl-1-cyclohexyl hydroxyacetate (851 mg, 3.63 mmol) was prepared through esterification of benzyloxyacetyl chloride with (-)-(*1R,2S*)-2-phenyl-1-cyclohexanol followed by hydrogenolysis. Then, triiso-

propylsilyl chloride (840 mg, 4.36 mmol) and imidazole (618 mg, 9.08 mmol) in dimethylformamide (DMF) (1.7 mL) was stirred at room temperature for 12-20 hours. The mixture was poured into pentane (25 mL), and washed with water and brine. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was subjected to a purification on a short silica gel column using hexane/chloroform (3/1) as the eluant to give pure (-)**7e** (1.35 g, 95% yield) as a colorless oil.

(-)**7e:** $[\alpha]_D^{20}$ -17.1° (c 3.15, $CHCl_3$); IR (neat) 1759, 1730 (νCO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93-0.99 (m, 21H), 1.30-1.62 (m, 4H), 1.72-2.0 (m, 3H), 2.10-2.19 (m, 1H), 2.66 (dt, J = 11.5, 4.0 Hz, 1H), 3.90 (d, J = 16.6 Hz, 1H), 4.07 (d, J = 16.6Hz, 1H), 5.07 (dt, J = 10.6, 4.0 Hz, 1H), 7.16-7.30 (m, 5H). Anal. Calcd for $C_{23}H_{38}O_3Si$: C, 70.72; H, 9.81. Found: C, 70.79; H, 9.85.

In the same manner, **7c**, **7d**, and (+)**7e** were prepared by the combinations of (-)-menthyl hydroxyacetate with tert-butyldimethylsilyl chloride, (-)-(*1R,2S*)-2-phenyl-1-cyclohexyl hydroxyacetate with tert-butyldimethylsilyl chloride, and (+)-(*1S,2R*)-2-phenyl-1-cyclohexyl hydroxyacetate with triisopropylsilyl chloride, respectively, in 90-95% yields. In a similar manner, **7a** and **7b** were prepared by the reactions of benzyloxyacetyl chloride with (-)-menthol and (*1R,2S*)-*N*-methylephedrine, respectively, in 92-95% yields.

(-)Menthyl benzyloxyacetate (7a): Colorless oil; $[\alpha]_D^{20}$ -59.2° (c 0.85, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.77 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.3 Hz, 3H), 0.92-1.14 (m, 3H), 1.34-1.56 (m, 2H), 1.64-1.73 (m, 2H), 1.84 (m, 1H), 2.02 (m, 1H), 4.07 (s, 2H), 4.64 (s, 2H), 4.80 (dt, J = 10.9, 4.4 Hz, 1H), 7.30-7.45 (m, 5H).

(*1R,2S*)-*N*-Methylephedrinyl benzyloxyacetate (7b): Pale yellow oil; $[\alpha]_D^{20}$ -25.78° (c 1.28, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.05 (d, J = 6.7 Hz, 3H), 2.28 (s, 6H), 2.91 (m, 1H), 4.15 (s, 2H), 4.62 (s, 2H), 6.04 (d, J = 5.4 Hz, 1H), 7.25-7.35 (m, 10 H).

(-)Menthyl t-butyldimethylsilyloxyacetate (7c): Colorless oil; $[\alpha]_D^{20}$ -59.3° (c 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.11 (s, 6H), 0.76 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H), 0.92 (s, 9H), 0.90-1.13 (m, 3H), 1.32-1.43 (m, 1H), 1.40-1.56 (m, 1H), 1.63-1.72 (m, 2H), 1.80-1.91 (m, 1H), 1.98-2.05 (m, 1H), 4.22 (s, 2H), 4.75 (ddd, J = 10.9, 10.9, 4.4 Hz, 1H). HRMS Calcd for $C_{18}H_{36}O_3Si$: C, 65.80; H, 11.05. Found: C, 65.60; H, 10.96.

(*1R,2S*)-2-Phenyl-1-cyclohexyl t-butyldimethylsilyloxyacetate (7d): Colorless oil; $[\alpha]_D^{20}$ -18.7° (c 1.03, $CHCl_3$); ^1H NMR ($CDCl_3$) δ -0.08 (s, 3H), -0.06 (s, 3H), 0.83 (s, 9H), 1.25-1.62 (m, 4H), 1.76-1.98 (m, 3H), 2.10-2.17 (m, 1H), 2.66 (dt, J = 3.7, 11.5 Hz, 1H), 3.83 (d, J = 16.8 Hz, 1H), 3.99 (d, J = 16.8 Hz, 1H), 5.06 (dt, J = 4.4, 10.5 Hz, 1H), 7.18-7.31 (m, 5H). Anal. Calcd for $C_{20}H_{32}O_3Si$: C, 68.92; H, 9.25. Found: C, 68.83; H, 9.18.

(+)**7e:** Colorless oil; $[\alpha]_D^{20}$ +17.07° (c 3.29, $CHCl_3$); ^1H NMR spectrum is identical to that of (-)**7e**.

Preparation of N-trimethylsilylimines (9): *N*-Trimethylsilylaldimines used in these syntheses can readily be obtained by the reaction of lithium hexamethyldisilazide with aldehydes. Typical procedure is described for the preparation of *N*-trimethylsilylbenzaldimine (**9a**): In 75 mL of anhydrous THF were added 17.29 mL (75 mmol) of hexamethyldisilazane and 30 mL (75 mmol) of n-butyllithium (2.5 M in hexane) at 0°C under nitrogen. After stirring for 1h, 7.65 mL (75 mmol) of benzaldehyde was added at room temperature, and the mixture was refluxed for 3h. Then, 9.52 mL (75 mmol) of freshly distilled trimethylsilyl chloride was added via a syringe. The mixture was refluxed for 2h. White precipitate came out during this process. The reaction mixture was then cooled to room temperature and the liquid layer was transferred to a distillation flask under nitrogen via a syringe. The solvent was evaporated in vacuo, and the oily residue was distilled under reduced pressure (68°C/1mm Hg) to give pure **9a** as a pale yellow oil (10.6 g, 80%): ^{1}H NMR ($CDCl_3$) δ 0.18 (s, 9 H), 7.33-7.36 (m, 3H), 7.72-7.75 (m, 2H), 8.89 (s, 1H); ^{13}C NMR ($CDCl_3$) δ -1.25, 128.34, 128.39, 131.96, 138.70, 168.32

In the same manner, **9b** and **9c** were prepared from 4-methoxybenzaldehyde and 3,4-dimethoxybenzaldehyde, respectively, in 78-82% yields.

9b: Pale yellow oil; bp 105°C/0.4 mmHg; ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 9H), 3.60 (s, 3H), 6.69 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 8.66 (s, 1H).

9c: Colorless oil; bp 140°C/0.2 mmHg; ^{1}H NMR δ 0.00 (s, 9H), 3.67 (s, 3H), 3.71 (s, 3H), 6.65 (d, J = 8.2 Hz, 1H), 7.01 (dd, J = 8.2, 1.8 Hz, 1H), 7.22 (d, J = 1.8 Hz, 1H), 8.63 (s, 1H).

Asymmetric synthesis of 3-triisopropylsilyloxy-4-arylazetidin-2-ones (10-C,D,E): To a solution of diisopropylamine (223 mg, 2.20 mmol) in THF (2.0 mL) was added 2.5 M solution of n-butyllithium (2.20 mmol) in THF (1.0 mL) at 0°C. The solution was stirred for 30 min. at 0°C and then cooled to 78°C. To the mixture was added a solution of (-)**7e** or (+)**7e** (781 mg, 2.0 mmol) in THF (2.0 mL). The solution was stirred for 2 h followed by addition of a solution of *N*-trimethylsilylaldimine (**9a-c**) (2.0 mmol) in THF (2.0 mL). The mixture was stirred at -78°C for 4 h, and then slowly allowed to warm to room temperature, and further stirred overnight. The reaction was quenched with saturated aqueous solution of NH_4Cl (50 mL), and the reaction mixture was extracted with chloroform (25 mL x 3). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was submitted to a short column chromatography on silica gel using hexane/EtOAc (6/1) as the eluant to give the corresponding β-lactam (**10- C,D,E**) in 80-85% isolated yield.

In the same manner, 3-(tert-butyldimethylsilyloxy)-4-phenylazetidin-2-one (**10-B**) was synthesized in 52% yield by the reaction of **7c** with **9a** or that of **7d** with **9a** in 90% yield. In a similar manner, (-)- and (+)-3-benzyloxy-4-phenylazetidin-2-one ((-)**10-A** and (+)**10-A**) were obtained in 18% and 20% yields by the reaction of **7a** with **9a** and **7b** with **9a**, respectively.

(3*R*,4*S*)-3-Benzyloxy-4-phenylazetidin-2-one ((-)10-A): Coloriess crystals; mp 195-196°C; $[\alpha]_D^{20}$ -10.66° (c 1.03, DMSO); ^{1}H NMR ($CDCl_3$) δ 4.28 (d, J = 11.3 Hz, 1H), 4.32 (d, J = 11.3 Hz, 1H), 4.86 (d, J = 4.5 Hz, 1H), 4.95 (dd, J = 4.5, 2.6 Hz, 1H), 6.15 (bs, 1H), 6.93-7.46 (m, 10H). The enantiomeric purity of this sample was determined to be 15% e.e. by ^{1}H NMR analysis using $Eu(hfc)_3$.

(3*S*,4*R*)-3-Benzyloxy-4-phenylazetidin-2-one ((+)10-A): Mp 195-197°C; $[\alpha]_D^{20}$ +32.04° (c 1.03, DMSO); ^{1}H NMR spectrum was identical with that of (-)**10-A**. The enantiomeric purity of this sample was determined to be 67% e.e. by ^{1}H NMR analysis using Eu(hfc)$_3$.

(3*R*,4*S*)-3-tert-Butyldimethylsilyloxy-4-phenylazetidin-2-one (10-B) (obtained from the reaction of **7d** with **9a**, Entry 4): Colorless solid; $[\alpha]_D^{20}$ -59.3° (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ -0.18 (s, 3H), -0.04 (s, 3H), 0.64 (s, 9H), 4.80 (d, J = 4.7 Hz, 1H), 5.05 (dd, J = 4.7, 2.7 Hz, 1H), 6.30 (bs, 1H), 7.30-7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ -5.46, -4.95, 17.78, 25.23, 59.13, 79.57, 127.97, 128.04, 136.25, 169.73. HRMS Calcd for $C_{15}H_{23}NO_2Si$: 277.1497. Found: 277.1509. The enantiomeric purity of this sample was determined to be 76% e.e. by the chiral HPLC analysis.

(3*R*,4*S*)-3-Triisopropylsilyloxy-4-phenylazetidin-2-one ((+)10-C): Colorless solid; 85% yield; mp 78-79°C; $[\alpha]_D^{20}$ +56.82° (c 1.10, $CHCl_3$); IR (KBr disk) 3264 (νNH), 1766 (νCO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86-0.91 (m, 21H), 4.81 (d, J = 4.7 Hz, 1H), 5.17 (dd, J = 4.7, 2.6 Hz, 1H), 6.22 (bs, 1H), 7.30-7.40 (m, 5H). HRMS Calcd for $C_{18}H_{29}NO_2Si$: 319.1967. Found: 319.1969. Anal. Calcd for $C_{18}H_{29}NO_2Si$: C, 67.66; H, 9.15; N, 4.38. Found: C, 67.64; H, 9.25; N, 4.44. The enantiomeric purity of this sample was determined to be 96% e.e. by the chiral HPLC analysis.

(3*S*,4*R*)-3-Triisopropylsilyloxy-4-phenylazetidin-2-one ((-)10-C): Colorless solid; mp 77-79°C; $[\alpha]_D^{20}$ -55.83° (c 1.20, $CHCl_3$). The enantiomeric purity of sample was determined to be 97% e.e. by the chiral HPLC analysis.

(3*R*,4*S*)-3-Triisopropylsilyloxy-4-(4-methoxyphenyl)-2-azetidinone ((+)10-D): Colorless solid; $[\alpha]_D^{20}$ +34.26° (c 1.08, $CHCl_3$); IR (KBr disk) 3276 (νNH), 1770 (νCO), 1514 (δNH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80-0.89 (m, 21H), 3.73 (s, 3H), 4.68 (d, J = 4.6 Hz, 1H), 5.05 (dd, J= 4.6, 2.5 Hz, 1H), 6.35 (bs, 1H), 6.80 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H). HRMS Calcd for $C_{19}H_{31}NO_3Si$: 349.2073. Found: 349.2075. The enantiomeric purity of this sample was determined to be 96% e.e. by the chiral HPLC analysis.

(3*R*,4*S*)-3-Triisopropylsilyloxy-4-(3,4-dimethoxyphenyl)-2-azetidinone ((+)10-E): Colorless solid; mp 99-101°C; $[\alpha]_D^{20}$ +23.11° (c 1.32, $CHCl_3$); IR (KBr disk) 3309 (νNH), 1758sh, 1735 (νCO), 1517 (δNH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89-0.98 (m, 21H), 3.87 (s, 3H), 3.88 (s, 3H), 4.76 (d, J = 4.7 Hz, 1H), 5.14 (dd, J = 4.7, 2.7 Hz, 1H), 6.22 (bs, 1H), 6.82-7.00 (m, 3H). HRMS Calcd for $C_{20}H_{33}NO_4Si$: 379.2179. Found: 379.2177. The enantiomeric purity of this sample was determined to be 98% e.e. by the chiral HPLC analysis.

(3*R*,4*S*)-3-Hydroxy-4-phenyl-2-azetidinone (5a): A solution of (+)**10-C** (169 mg, 0.53 mmol; 96% e.e.) in THF (3 mL) was treated with tetra-n-butylammonium fluoride (1.0 mL of 1M solution in THF) at room temperature for 25 min under nitrogen. The reaction mixture was poured into water and extracted with ethyl acetate (10 mL x 3). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated in

vacuo. The residue was submitted to a short column chromatography on silica gel using ethyl acetate as the eluant to give **5a** (84 mg, 97%), which was used for the subsequent reaction. Recrystallization from ethyl acetate afforded enantiomerically pure **5a** (69 mg, 81%).

5a: Colorless crystals; mp 189-190°C; $[\alpha]_D^{20}$ +198.8° (c 1.0, MeOH); IR (KBr disk) 3370 (νOH), 3252 (νNH), 1743 (νCO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32 (bs, 1H), 4.95 (d, J = 5.0 Hz, 1H), 5.12 (dd, J = 5.0, 2.3 Hz, 1H), 6.27 (bs, 1H), 7.30-7.47 (m, 5H); ^1H NMR (DMSO-d_6) δ 4.70 (d, J = 4.9 Hz, 1H), 4.94 (ddd, J = 2.3, 4.9, 7.2 Hz, 1H), 5.82 (bs, 1H), 7.32-7.42 (m, 5H), 8.47 (bs, 1H). Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.42; H, 5.74; N, 8.62.

(2*R*,3*S*)-3-Phenylisoserine hydrochloride (12a): A mixture of (+)**10-C** (640 mg, 2.00 mmol) in 0.1 mL of $CHCl_3$ and 6N hydrochloric acid (8.0 mL) was stirred at 25°C for 3 h. The reaction mixture was concentrated in vacuo to dryness, giving **12a** (437 mg, 100%) as a white solid. The hydrolysis of **5a** in 6N hydrochloric acid at 25°C for 3 h also gave **12a** in virtually quantitative yield.

12a: mp 222-224°C (dec.); $[\alpha]_D^{20}$ -14.6° (c 1.03, 6N HCl) [lit.[26,13] $[\alpha]_D^{20}$ -14.6° (6N HCl)]; IR (KBr disk) 3456 (νOH), 3300-2200 (νOH, νNH), 1732 (νCO), 1589 (δNH) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.30-4.50 (m, 2H), 6.65 (bs, 1H), 7.38-7.45 (m, 3H), 7.50-7.55 (m, 2H), 8.65 (bs, 3H), 12.99 (bs, 1H).

(2*R*,3*S*)-N-Benzoyl-3-phenylisoserine (3): To a solution of **12a** (219 mg, 1.00 mmol) in water (10 mL) containing sodium bicarbonate (500 mg, 5.95 mmol) was added a solution of benzoyl chloride (0.14 mL, 1.20 mmol) in dichloromethane (5.0 mL). The mixture was vigorously stirred for 16 h at room temperature. The reaction mixture was acidified with 0.1N HCl and the crude product was extracted with ethyl acetate (40 mL x 3). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo to dryness. The residue was purified on a short silica gel column using $CHCl_3$/MeOH (2/1) as the eluant to give **3** (205 mg, 72%) as a white solid.

3: mp 167-169°C [lit.[26] 168-169°C]; $[\alpha]_D^{25}$ -37.8° (c 0.9, EtOH) [lit.[26] $[\alpha]_D^{25}$ +36.5° (c 1.45, EtOH) for (2*S*,3*R*)-isomer]; IR (KBr disk) 3600-2200 (νOH, νNH), 1710 (νCO), 1624 (νCO), 1523 (δNH) cm^{-1}; ^1H NMR (D_2O) δ 4.43 (bs, 1H), 5.45 (bs, 1H), 7.30-7.43 (m, 5H), 7.50-7.75 (m, 5H). ^1H-NMR (DMSO-d_6) δ 3.38 (bs, 1H), 3.84 (bs, 1H), 5.14 (bs, 1H), 7.10-7.40 (m, 5H), 7.52 (m, 3H), 7.82 (m, 2H), 9.76 (bs, 1H).

***N*-(4-Methoxyphenyl)aldimines (13a-h):** A typical procedure is described for the preparation of *N*-(4-methoxyphenyl)-(4-fluoro)benzaldimine (**13b**): To a solution of 4.81 g (39 mmol) of p-anisidine in 60 mL of dichloromethane was added 4.85 g (39 mmol) of 4-fluorobenzaldehyde. The mixture was stirred over anhydrous magnesium sulfate at room temperature for 15 h. The dehydration agent was filtered off and the filtrate was concentrated in vacuo to give the crude imine. The crude imine was recrystallized from hexane/dichloromethane to give 7.69 g (86%) of pure **13b** as white needles: Mp 99°C; ^{1}NMR ($CDCl_3$) δ 3.82 (s, 3H), 6.92 (d, J = 8.7 Hz, 2H), 7.13 (t, J = 8.6 Hz, 2H), 7.21 (d, J = 8.7 Hz, 2H), 7.88 (dd, J = 8.6, 5.7 Hz, 2H), 8.39 (s ,1H).

In the same manner, other *N*-(4-methoxylphenyl)aldimines (**13**) were prepared in high yields.

***N*-(4-Methoxyphenyl)benzaldimine (13a):** White solid; mp 71-72°C; ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 6.93 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 7.46 (m, 3H), 7.87 (m, 2H), 8.48 (s, 1H).

***N*-(4-Methoxyphenyl)-(4-trifluoromethyl)benzaldimine (13c):** White needles; mp 124°C; ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 6.91 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 7.75 (d, J = 8.6 Hz, 2H), 8.10 (d, J = 8.6 Hz, 2H), 8.39 (s ,1H).

***N*-(4-Methoxyphenyl)furfuraldimine (13d):** Yellow pellets; mp 68-70°C; ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H), 6.54 (dd, J = 3.5, 1.8 Hz, 1H), 6.90 (d, J = 3.5 Hz, 1H), 6.92 (d, J = 8.9 Hz, 2H), 7.26 (d, J = 8.9 Hz, 2H), 7.59 (d, J = 1.8 Hz, 1 H), 8.31 (s, 1 H).

***N*-(4-Methoxyphenyl)-3-phenylpropenaldimine (13e):** Yellow leaves; mp 119-121°C; ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 6.90-7.60 (m, 7H), 8.28 (m, 1H) (ca. 1 : 1 mixture of stereoisomers).

***N*-(4-Methoxyphenyl)-3-(2-furyl)propenaldimine (13f):** Yellow needles; mp 71-73°C; ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3H), 6.45 (dd, J= 3.4, 1.6 Hz, 1H), 6.52 (d, J= 3.4 Hz, 1H), 6.87 (d, J= 15.8 Hz, 1H), 6.90 (d, J= 8.9 Hz, 2H), 6.98 (dd, J= 15.8, 8.7 Hz, 1H), 7.18 (d, J= 8.9 Hz, 2H), 7.46 (d, J= 1.6 Hz, 1H), 8.20 (d, J= 8.7 Hz, 1H).

***N*-(4-Methoxyphenyl)-3-methylbutanaldimine (13g):** Yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.02 (d, J = 6.7 Hz, 6H), 2.03 (m, 1H), 2.33 (dd, J = 6.9, 5.3 Hz, 2H), 3.78 (s, 3H), 6.86 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 8.8 Hz, 2H), 7.86 (t, J = 5.3 Hz, 1H).

***N*-(4-Methoxyphenyl)cyclohexylacetaldimine (13h):** Yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.00-1.80 (m, 11H), 2.34 (dd, J = 6.7, 5.4 Hz, 2H), 3.79 (s, 3H), 6.86 (d, J = 8.9 Hz, 2H), 7.02 (d, J = 8.9 Hz, 2H), 7.86 (t, J = 5.4 Hz, 1H); IR (neat) 3033-2849, 1505, 1244, 1038, 803 cm^{-1}.

Asymmetric synthesis of 1-(4-methoxyphenyl)-3-triisopropylsilyloxy-2-azetidinones (14): The chiral ester enotate - imine condensation of (-)**7e** with **13** was carried out in the same manner to that described for the synthesis of β-lactams **10**. Enantiomeric purity was determined by HPLC analysis on a chiral column, DIACEL CHIRACEL OD using n-hexane/2-propanol as the solvent. The absolute configurations of **14a-h** were determined by chemical correlation with authentic samples as follows: **14a** was converted to (+)**10-C**; **14g** and **14h** were converted to norstatine hydrochloride (**12g**) and (2*R*,3*S*)-3-amino-2-hydroxy-4-cyclohexylbutanoic acid hydrochloride (**12h**), respectively (*vide infra*). For **14b-f**, absolute configurations were assessed by analogy with **14a**, **14g**, and **14h** based on retention times on the chiral HPLC analyses described above.

1-(4-Methoxyphenyl)-3-triisopropylsilyloxy-4-phenyl-2-azetidinone (14a): ^{1}H NMR ($CDCl_3$) δ 0.88-1.02 (m, 21H), 3.73 (s, 3H), 5.14 (d, J = 5.0 Hz, 1H), 5.23 (d, J = 5.0 Hz, 1H), 6.77 (d, J = 9.0 Hz,

2H), 7.28 (d, J = 9.0 Hz, 2H), 7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 11.72, 17.42, 17.48, 55.36, 63.27, 77.79, 114.25, 118.65, 128.16, 128.24, 128.30, 130.96, 134.04, 156.10, 165.66. Anal. Calcd. For $C_{25}H_{35}NO_3Si$: C, 70.54; H, 8.29;, N 3.29. Found: C, 70.38; H, 8.36; N, 3.22.

1-(4-Methoxyphenyl)-3-triisopropylsilyloxy-4-(4-fluorophenyl)-2-azetidinone (14b): White solid; mp 121-122°C; $[\alpha]_D^{20}$ +82.5° (c 0.724, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.82-0.84 (m, 18H), 0.86-1.01 (m, 3H), 3.62 (s, 3H), 5.02 (d, J = 4.9 Hz, 1H), 5.11 (d, J = 4.9 Hz, 1H), 6.68 (d, J= 6.9 Hz, 2H), 6.96-7.25 (m, 6H); IR ($CHCl_3$) 3050, 2974, 2868, 1748 cm^{-1}. Anal. Calcd for $C_{25}H_{34}NO_3FSi$: C, 67.69; H, 7.72; N, 3.16. Found: C, 67.77; H, 7.83; N, 3.19.

1-(4-Methoxyphenyl)-3-triisopropylsilyloxy-4-(4-trifluoromethylphenyl)-2-azetidinone (14c): White solid; mp 132-133°C; $[\alpha]_D^{20}$ +89.7° (c 0.925, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.87-1.15 (m, 21H), 3.74 (s, 3H), 5.21 (d, J = 4.9 Hz, 1H), 5.27 (d, J = 4.9 Hz, 1H), 6.79 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2 H); IR ($CHCl_3$) 3050, 2975, 2868, 1750, 878 cm^{-1}. Anal. Calcd for $C_{26}H_{34}NO_3F_3Si$: C, 63.26; H, 6.94; N, 2.84. Found: C, 63.36; H, 7.13; N, 2.88.

1-(4-Methoxyphenyl)-3-triisopropylsilyloxy-4-(2-furyl)-2-azetidinone (14d): White solid; mp 109-110°C; $[\alpha]_D^{20}$ -86.2° (c 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.98-1.10 (m, 21H), 3.75 (s, 3H), 5.20 (d, J = 4.9 Hz, 1H), 5.24 (d, J = 4.9 Hz, 1H), 6.35-6.40 (m, 2H), 6.81 (d, J = 9.0 Hz, 2H), 7.30 (d, J = 9.0 Hz, 2H), 7.42 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 11.96, 17.52, 17.57, 55.43, 57.19, 78.13, 110.23, 110.63, 114.44, 118.55, 131.08, 142.80, 148.51, 156.45, 165.27. Anal. Calcd for $C_{23}H_{33}NO_4Si$: C, 66.47; H, 8.00; N, 3.37. Found: C, 66.56; H, 8.13; N, 3.30.

1-(4-Methoxyphenyl)-3-triisopropylsilyloxy-4-(2-phenylethenyl)-2-azetidinone (14e): White solid; mp 127-129°C; $[\alpha]_D^{25}$ -76.2° (c 1.04, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.02-1.18 (m, 21H), 3.75 (s, 3H), 4.74 (dd, J = 4.9, 8.9 Hz, 1H), 5.16 (d, J = 4.9 Hz, 1H), 6.35 (dd, J = 16.0, 8.9 Hz, 1H), 6.76-6.84 (m, 3H), 7.26-7.48 (m, 7H); IR (KBr) 2944, 2865, 1879, 1743, 1654, 1647, 1513, 1460, 1389, 1366 cm^{-1}. Anal. Calcd for $C_{27}H_{37}NO_3Si$: C, 71.80; H, 8.26; N, 3.10. Found: C, 71.91; H, 8.31; N, 3.07.

1-(4-Methoxyphenyl)-3-triisopropylsilyloxy-4-{2-(2-furyl)ethenyl}-2-azetidinone (14f): White solid; mp 103.5-105.5°C; $[\alpha]_D^{20}$ -128.4° (c 2.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.05-1.09 (m, 21H), 3.76 (s, 3H), 4.69 (dd, J = 4.9, 8.6 Hz, 1H), 5.15 (d, J = 4.9 Hz, 1H), 6.25 (dd, J = 8.6, 16.0 Hz, 1H), 6.29 (d, J = 3.3 Hz, 1H), 6.37 (dd, J = 1.8, 3.3 Hz, 1H), 6.57 (d, J = 16.0 Hz, 1H), 6.83 (m, 2H), 7.34-7.41 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 12.11, 17.70, 17.74, 55.54, 61.94, 77.18, 78.45, 107.88, 108.42, 111.26, 114.54, 118.70, 123.46, 123.82, 142.46, 190.99; IR (KBr) 2948, 2866, 1743, 1513, 1389, 1246, 1181, 1120 cm^{-1}. Anal. Calcd for $C_{25}H_{35}NO_4Si$: C, 67.99; H, 7.99; N, 3.17. Found: C, 68.07; H, 7.94; N, 3.10.

1-(4-Methoxyphenyl)-3-triisopropylsilyloxy-4-(2-methylpropyl)-2-azetidinone (14g): Pale yellow solid; mp 59-60 °C; $[\alpha]_D^{20}$ -60.46° (c 1.26, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.96 (d, J = 6.4 Hz, 3H), 1.03 (d, J = 6.4 Hz, 3H), 1.10-1.30 (m, 21H), 1.60-1.68 (m, 1H), 1.70-1.92 (m, 2H), 3.75 (s, 3H), 4.16-4.22 (m,

1H), 5.06 (d, J = 5.1 Hz, 1H), 6.86 (d, J = 9.0 Hz, 2H), 7.32 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.34, 17.82, 17.91, 22.18, 23.37, 25.34, 35.89, 55.50, 57.33, 76.34, 114.52, 118.73, 131.00, 156.29, 165.58; IR (KBr) 2946, 1742, 1513, 1458, 1249 cm^{-1}. Anal. Calcd for $C_{23}H_{39}O_3NSi$: C, 68.10; H, 9.70; N, 3.45. Found: C, 68.26; H, 9.85; N, 3.35.

1-(4-Methoxyphenyl)-3-triisopropylsilyloxy-4-(2-cyclohexylmethyl)-2-azetidinone (14h): Low melting point solid; $[\alpha]_D^{20}$ -43.7° (c 0.92, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.85-1.95 (m, 34H), 3.78 (s, 3H), 4.19-4.25 (m, 1H), 5.05 (d, J = 5.1 Hz, 1H), 6.86 (d, J = 9.0 Hz, 2H), 7.32 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.15, 17.76, 17.83, 26.12, 26.22, 26.47, 32.84, 34.22, 34.51, 55.36, 56.41, 76.13, 114.30, 118.45, 130.81, 155.99, 165.55; IR (neat) 2925-2865, 1749, 1513, 1464, 1448, 1389, 1246, 1174, 1145, 1128, 939, 882, 828, 684 cm^{-1}. Anal. Calcd for $C_{26}H_{43}NO_3Si$: C, 70.06; H, 9.72; N, 3.14. Found: C, 69.91; H, 9.71; N, 3.02.

(3*R*,4*S*)-1-(4-Methoxyphenyl)-3-triisopropylsilyloxy-4-(2-phenylethyl)-2-azetidinone (14i): A mixture of **14e** (436 mg, 0.97 mmol) in ethanol/ethyl acetate (2/1) and 10% Pd-C (100 mg) was stirred in a standard hydrogenation apparatus at 25°C and atmospheric pressure of hydrogen for 10 h. Removal of the catalyst by filtration, followed by evaporation of the solvent afforded 420 mg (96% yield) of **14i** as a white solid; mp 78-79°C; $[\alpha]_D^{20}$ -85.7° (c 1.1, $CHCl_3$); ^{1}H ($CDCl_3$) δ 1.03-1.20 (m, 21H), 2.15-2.35 (m, 2H), 2.70-2.82 (m, 2H), 3.75 (s, 3H), 4.14-4.20 (m, 1H), 5.09 (d, J= 5.1 Hz, 1H), 6.82-6.86 (m, 2H), 7.16-7.31 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 11.99, 17.71, 17.79, 28.61, 31.55, 55.22, 57.73, 75.95, 114.24, 118.27, 125.87, 128.09, 128.30, 130.80, 141.25, 155.99, 165.33; IR (KBr disk) 3012, 2944, 2893, 1761, 1496, 1384 cm^{-1}. Anal. Calcd for $C_{27}H_{39}NO_3Si$: C, 71.48; H, 8.66; N, 3.09. Found: C, 71.35; H, 8.66; N, 3.01.

(3*R*,4*S*)-3-Triisopropylsilyloxy-4-(2-phenylethyl)-2-azetidinone (10i): To a solution of **14i** (92 mg, 0.20 mmol) in acetonitrile (2 mL) was added slowly a solution of cerium ammonium nitrate (334 mg, 0.61 mmol) in water (3 mL) at 0°C. The mixture was stirred at 0°C for 1 h and diluted with 15 mL of water. The mixture was then extracted with ethyl acetate (15 mL x 3). The organic extracts were washed with 5% sodium bicarbonate (10 mL) and the aqueous extracts were washed with ethyl acetate (15 mL). The combined organic extracts were washed with 10% sodium sulfite (until the aqueous layer remained colorless), 5% sodium bicarbonate (10 mL), and brine. The combined extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified on a short silica gel column using hexane/ethyl acetate (5/1) as the eluant to give 60 mg (85% yield) of **10i** as a colorless oil; $[\alpha]_D^{20}$ -90.8° (c 0.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.02-1.18 (m, 21H), 1.91-2.06 (m, 2H), 2.68-2.76 (m, 2H), 3.68-3.74 (m, 1H), 4.96 (dd, J= 4.8, 2.4 Hz, 1H), 6.07 (bs, 1H), 7.17-7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 11.94, 17.72, 17.79, 31.62, 32.32, 55.60, 77.80, 126.04, 128.29, 128.49, 141.23, 169.91; IR (neat) 3248 (b, NH), 3062, 3027, 2944, 2893, 2867, 1761 (νC=O), 1603, 1496, 1463, 1384, 1350, 1245 cm^{-1}. Anal. Calcd for $C_{20}H_{33}NO_2Si$: C, 69.11; H, 9.57; N, 4.03. Found: C, 69.10; H, 9.55; N, 3.85.

Transformation of *N*-(4-methoxyphenyl)-β-lactam 7 to β-lactam 10: In the same manner to that described for the synthesis of **14i**, other β-lactams **14** can be converted to the corresponding deprotected β-lactams **10**. Selected examples are shown below:

(3*R*,4*S*)-3-Triisopropylsilyloxy-4-(2-phenylethenyl)-2-azetidinone (10e): Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.02-1.06 (m, 21H), 4.34 (dd, J = 4.7, 8.2 Hz, 1H), 5.07 (dd, 4.7, 2.3 Hz, 1H), 6.28 (dd, J = 8.2, 16.0 Hz, 1H), 6.58 (d, J = 16.0 Hz, 1H), 7.00 (bs, 1H), 7.23-7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 11.80, 17.54, 17.59, 58.22, 79.82, 126.11, 126.40, 127.75, 128.45, 134.45, 136.35, 169.76; IR (neat) 3274, 30834, 3062, 3028, 2945, 2867, 1760 (νCO), 1654, 1495, 1464, 1450, 1368, 1247, 1183, 1147, 1015, 965, 904, 842 cm^{-1}.

(3*R*,4*S*)-3-Triisopropylsilyloxy-4-(2-methylpropyl)-2-azetidinone (10g): Yellow oil; $[\alpha]_D^{20}$ -35.45° (c 1.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.93 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 1.05-1.25 (m, 22H), 1.52 (m, 1H), 1.67 (m, 1H), 3.78 (m, 1H), 4.96 (dd, J = 4.8, 2.4 Hz, 1H), 6.02 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 12.12, 17.72, 17.80, 22.29, 23.08, 25.35, 39.08, 54.45, 78.04, 170.00; IR (neat) 3238, 1759, 1465, 1184 cm^{-1}. Anal. Calcd for $C_{16}H_{33}O_2NSi$: C, 64.16; H,11.1; N, 4.68. Found: C, 64.17; H, 10.96; N, 4.47.

(3*R*,4*S*)-3-Triisopropylsilyloxy-4-(cyclohexylmethyl)-2-azetidinone (10h): Yellow oil; $[\alpha]_D^{20}$ -12.44 (c=1.46, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0,97–1.25 (m, 32H), 1.40-1.70 (m, 2H), 3.80 (dt, J=8.4, 4.8 Hz, 1H), 4.95 (dd, J = 4.8, 2.4 Hz, 1H), 6.05 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 12.06, 17.77, 17.82, 26.16, 26.25, 26.46, 33.15, 33.82, 34.85, 37.72, 53.89, 77.98, 169.98; IR (neat) 3238, 1759, 1465, 1184 cm^{-1}. Anal. Calcd for $C_{19}H_{37}O_2NSi$: C, 67.20; H, 10.98; N, 4.12. Found: C, 67.40; H, 10.79; N, 3.98.

(3*R*,4*S*)-3-Triisopropylsilyloxy-4-(2-cyclohexylethyl)-2-azetidinone (10j): A mixture of **10i** (100 mg, 0.29 mmol) in methanol (10 mL) and 5% Rh-C catalyst (10 mg) was hydrogenated at 50°C and 800 psi of hydrogen for 20 h. After the catalyst was filtered out and the solvents evaporated in vacuo, the residue was purified on a short silica gel column using hexane/ethyl acetate (5/1) as the eluant to give 95 mg (93% yield) of **10j** as a colorless liquid: $[\alpha]_D^{20}$ -162.3° (c 1.46, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.07-1.72 (m, 36H), 3.61-3.67 (m, 1H), 4.94 (dd, J= 2.4, 4.8 Hz, 1H), 6.42 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 12.02, 17.79, 26.31, 26.60, 27.54, 33.19, 33.39, 33.54, 37.71, 56.44, 77.74, 170.15; IR (neat) 3236 (νNH), 2925, 2866, 1760 (νCO), 1464, 1451, 1384, 1348, 1244 cm^{-1}. Anal. Calcd for $C_{27}H_{39}NO_3Si$: C, 71.48; H, 8.66; N, 3.09. Found: C, 71.35; H, 8.66; N, 3.01.

Synthesis of (2*R*,3*S*)-3-substituted-isoserines (12): In the same manner to that described for the synthesis of **12a**, **10e**, **10g-j** were hydrolyzed with 6N hydrochloric acid to give the corresponding hydrochloric acid salts of (2*R*,3*S*)-3-substituted-isoserines (**12**) in nearly quantitative yields.

(2*R*,3*S*)-3-Amino-2-hydroxy-5-phenyl-4-*trans*-pentenoic acid hydrochloride (12e): White solid; mp 202-204°C (dec.); $[\alpha]_D^{20}$ +41.7° (c 1.08, MeOH); ^{1}H NMR (DMSO-d_6) δ 3.35 (bs, 2H), 3.99 (m, 1H),

4.20 (d, J = 6.6 Hz, 1H), 6.20 (dd, J = 8.4, 16.1 Hz, 1H), 6.78 (d, J = 16.1 Hz, 1H), 7.32-7.44 (m, 5H), 8.29 (bs, 3H); ^{13}C NMR (DMSO-d_6) δ 55.01, 70.90, 121.89, 126.37, 128.30, 128.62, 135.15, 135.38, 171.77; IR (KBr disk) 3500-2500, 1708 (νCO), 1485 cm^{-1}. Anal. Calcd for $C_{11}H_{14}NO_3Cl$: C, 54.22; H, 5.79; N, 5.75. Found: C, 54.48; H, 5.56; N, 5.61.

(2*R*,3*S*)-3-Amino-2-hydroxy-5-methylhexanoic acid hydrochloride (12g): White solid; m.p. 200°C (dec.); $[\alpha]_D^{20}$ +7.21(c 2.08, 1N HCl); ^{1}H NMR (CD_3OD) δ 0.93 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H), 1.33 (dt, J =13.7, 6.9 Hz, 1H), 1.47 (dt, J =13.7, 6.9 Hz, 1H), 1.75 (m, 1H), 3.19 (m, 1H), 3.83 (d, J =2.3 Hz, 1H); ^{13}C NMR δ 22.79, 23.28, 25.71, 42.66, 52.94, 74.71, 179.19; IR (KBr) 1757 (νCO) cm^{-1}. Anal. Calcd for $C_7H_{16}NO_3Cl$: C, 42.54; H, 8.16; N, 7.09. Found: C, 42.39 ; H, 7.99 : N, 6.88.

(2*R*,3*S*)-3-Amino-2-hydroxy-4-cyclohexylbutanoic acid hydrochloride (12h): White solid; m.p. 192°C (dec.); $[\alpha]_D^{20}$ -11.01° (c 3.18, 1N HCl) [lit.[27] mp 190°C (dec.); $[\alpha]_D^{20}$ -12.4° (c 0.482, 1N HCl)]; ^{1}H NMR (D_2O) δ 0.89–1.68 (m, 13H), 3.72 (m, 1H), 4.42 (d, J = 3.2 Hz, 1H).; ^{1}H NMR (CD_3OD) δ 0.43-1.26 (m, 13H), 2.95 (m, 1H), 3.72 (d, J = 3.5 Hz, 1H); ^{13}C NMR (CD_3OD) δ 26.67, 26.75, 27.10, 33.89, 34.35, 37,99, 51.89, 70.21, 174.07; IR (KBr) 1727 (νCO) cm^{-1}. Anal. Calcd. for $C_{10}H_{20}O_3NCl$: C, 50.50; H, 8.48; N, 5.89. Found: C, 50.30; H, 8.59; N, 5.66.

(2*R*,3*S*)-3-Amino-2-hydroxy-5-phenylpentanoic acid hydrochloride (12i): White solid; mp 198-200°C; $[\alpha]_D^{20}$ -1.72° (c= 1.2, MeOH); ^{1}H NMR (CD_3OD) δ 1.82-2.09 (m, 2H), 2.69 (t, J= 8.1 Hz, 2H), 3.46 (m, 1H), 4.26 (d, J= 3.1 Hz, 1H), 7.10-7.24 (m, 5H); ^{13}C NMR (CD_3OD) δ 30.92, 31.48, 52.78, 63.25 125.99, 127.89, 128.21, 140.12; IR (KBr disk) 1746 (νCO) cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_3NCl$: C, 53.77; H, 6.56; N, 5.70. Found: C, 53.85; H, 6.44; N, 5.51.

(2*R*,3*S*)-3-Amino-2-hydroxy-5-cyclohexylpentanoic acid hydrochloride (12j): White solid; mp 198-202°C; $[\alpha]_D^{20}$ -3.4° (c 1.2, 1N-HCl); ^{1}H NMR (CD_3OD) δ 0.89-1.79 (m, 15H), 3.48 (m, 1H), 4.27 (d, J = 3.6 Hz, 1H); ^{13}C NMR (CD_3OD) δ 27.31, 27.65, 28.41, 33.88, 34.23, 38.80, 55.17, 93.26; IR (KBr disk) 1728 (νCO) cm^{-1}. Anal. Calcd for $C_{11}H_{22}NO_3Cl$: C, 52.48; H, 8.81; N, 5.56. Found: C, 52.38, H, 8.52, N, 5.57.

(3*R*,4*S*)-1-Benzoyl-3-(1-ethoxyethoxy)-4-phenyl-2-azetidinone (6a): A mixture of 3-hydroxy-4-phenyl-2-azetidinone (**5a**) (320 mg, 1.9 mmol) and ethyl vinyl ether (375 μL, 3.9 mmol) in THF (20 mL) was stirred for 2 h at 0°C. Then, the reaction mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$, and extracted with dichloromethane. The combined extracts were dried over anhydrous Na_2CO_3 and concentrated in vacuo to yield 3-(1-ethoxyethoxy)-4-phenylazetidin-2-one (**5a-EE**) (465 mg, 100%) as a white solid: mp 78-80 °C; ^{1}H NMR ($CDCl_3$) δ [0.98 (d, J = 5.4 Hz), 1.05 (d, J = 5.4 Hz)] (3H), [1.11 (t, J = 7.1 Hz), 1.12 (t, J = 7.1 Hz)] (3H), [3.16-3.26 (m), 3.31-3.42 (m), 3.59-3.69 (m)] (2H), [4.47 (q, J = 5.4 Hz), 4.68 (q, J = 5.4 Hz)] (1H), [4.82 (d, J = 4 .7 Hz), 4.85 (d, J = 4.7 Hz)] (1H), 5.17-5.21 (m, 1H), 6.42 (bd, 1H), 7.35 (m, 5H); IR (KBr disk) 3214, 2983, 2933, 1753, 1718, 1456 cm^{-1}.

To a solution of **5a-EE** (460 mg, 1.9 mmol), DMAP (5 mg), and triethylamine (542 μL, 3.9 mmol) in 20 mL of dichloromethane, was added dropwise benzoyl chloride (340 μL, 2.9 mmol) at 0°C with stirring. The cooling bath was removed and the mixture was stirred at 25°C for 2 h. The reaction mixture was washed with saturated aqueous NH_4Cl and brine, dried over anhydrous Na_2CO_3 and concentrated in vacuo to give the oily crude product. The crude product was purified through a short silica gel column (eluant: EtOAc/hexanes = 1/5) to afford pure **6a** (611 mg, 92%) as a colorless oil: IR (neat) 3064–2933, 1798, 1682, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ [1.04 (d, J = 5.4 Hz), 1.14 (d, J = 5.4 Hz)] (3H), 1.11-1.17 (m, 3H), 3.23-3.74 (m, 2H), [4.57 (q, J = 5.4 Hz), 4.76 (q, J = 5.4 Hz)] (1H), 5.28 (d, J = 6.2 Hz, 1H), [5.43 (d, J = 6.2 Hz), 5.46 (d, J = 6.2 Hz)] (1H), 7.30-7.65 (m, 8H).

2'-(1-Ethoxyethoxy)-7-triethylsilyl-taxol (15): To a solution of 7-TES-baccatin III (**4a**) (105 mg, 0.15 mmol) and of 3-EEO-1-benzoyl-β-lactam (**6a**) (75 mg, 0.22 mmol) in 3.0 mL of THF, was added portion by portion a suspension of NaH (200 mg in 3.0 mL of THF) at 0°C over the period of 30 min. Then, the mixture was warmed to 35°C and stirred for 3 h. The reaction was quenched by addition of brine at 0°C. The reaction mixture was extracted with dichloromethane, and the combined extracts were washed with brine, dried over anhydrous Na_2CO_3 and concentrated to give the oily residue. The ^1H NMR analysis of the crude product revealed that 50% of **4a** was consumed. The crude product was purified by column chromatography on silica gel using EtOAc/hexanes (1/2) to give **15** (62 mg, 40%; 80% conversion yield) as a white solid and unreacted **4a** (38 mg, 37%) was recovered.

15: mp 135-139°C; $[\alpha]_D^{23}$ -32.4° (c 0.4, CH_3OH) [lit.[12a] $[\alpha]_D^{23}$ -34° (c 0.4, CH_3OH)].

Taxol: To a solution of 2'-EE-7-TES-taxol (**15**) (55 mg, 0.054 mmol) in 1.0 mL of EtOH was added 0.5% hydrochloric acid (1.5 mL) at 0°C, and the mixture was stirred for 48 h at 0°C. TLC analysis of the reaction mixture revealed that **15** was almost consumed. Thus, the reaction mixture was diluted with 20 mL of EtOAc and washed with saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The extract was dried over anhydrous $MgSO_4$, and concentrated to give the crude product, which was purified through a short silica gel column (eluant: EtOAc/hexanes = 1/1) to afford taxol (39.5 mg, 88%) as a white solid: $[\alpha]_D^{22}$ -44.1° (c 0.27, MeOH) [lit.[1b] $[\alpha]_D^{20}$ -49°(MeOH); lit.[28] $[\alpha]_D^{20}$ -42° (c 0.37, MeOH)]; mp 192-194°C; ^1H NMR ($CDCl_3$) δ 1.12 (s,3H), 1.22 (s,3H), 1.67 (s,3H), 1.77 (s,3H), 1.86 (m, 1H), 2.21 (s,3H), 2.26 (dd, J = 15.4, 8.9 Hz, 1H), 2.34 (dd, J = 15.4, 8.9 Hz, 1H), 2.36 (s,3H), 2.43 (bs, 1H), 2.53 (ddd, J = 15.5, 9.6, 6.0 Hz, 1H), 3.55 (bs, 1H), 3.78 (d, J = 7.0 Hz, 1H), 4.18 (d, J = 8.4 Hz, 1H), 4.28 (d, J = 8.4 Hz, 1H), 4.38 (dd, J = 10.6, 6.8 Hz, 1H), 4.77 (d, J = 2.1 Hz, 1H), 4.92 (bd, J = 8.9 Hz, 1H), 5.65 (d, J = 7.0 Hz, 1H), 5.77 (dd, J = 8.8, 2.6 Hz, 1H), 6.21 (bt, J = 9.0 Hz, 1H), 6.25 (s, 1H), 6.97 (d, J = 8.8 Hz, 1H), 7.33 (m, 5H), 7.54 (m, 5H), 7.59 (t, J = 7.1 Hz, 1H), 7.71 (d, J = 7.9 Hz, 2H), 8.11 (d, J = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.59, 14.83, 20.87, 21.81, 22.62, 26.84, 35.65, 43.16, 45.66, 55.11, 58.56, 72.23, 73.24, 74.93, 75.58, 76.54, 79.00, 81.11, 84.40, 127.05, 128.33, 128.68, 128.99, 130.20, 131.95, 133.13, 133.73, 137.98, 141.98, 167.09, 166.97, 170.39, 171.25, 172.70, 203.64.

10-Deacetyl-7,10-bis(Troc)-taxol (17): To a suspension of NaH (15 mg, 60% in oil) in THF (3.0 mL), was added 10-deacetyl-7,10-bis(Troc)-baccatin (**4b**) (133 mg, 0.15 mmol) in THF (2.0 mL) at -10°C. After stirring the suspension for 30 min, **6a** (75 mg, 0.22 mmol) in THF (2.0 mL) was added, then the mixture was stirred for 1 h at -10°C. The reaction mixture was warmed to 0°C and quenched with brine. The reaction mixture was extracted with dichloromethane and the combined extracts were washed several times with brine, dried over anhydrous Na_2CO_3, and concentrated in vacuo to give the crude product. The ^1H NMR analysis of the crude product revealed that 43% of **4b** was consumed. The crude product was subjected to column chromatography on silica gel (eluant: EtOAc /hexanes =1/2) to give 2'-EE-10-deacetyl-7,10-bis(Troc)-taxol (**16**) (69 mg, 37%; 88% conversion yield) as a white solid (mp 136-140°C) and unreacted of **4b** (57 mg, 43%) was recovered.

A mixture of **16** (64 mg, 0.050 mmol) in THF (1.0 mL) and 0.5% hydrochloric acid (2.0 mL) was stirred for 6 h at 0°C. TLC analysis of the reaction mixture revealed that virtually all **16** was consumed. The reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$ and concentrated to give the crude product. The crude product was purified through a short silica gel column (eluant: EtOAc /hexanes = 1/2) to give 10-Deacetyl-7,10-bis(Troc)-taxol (**17**) (54 mg, 90%) as a white solid.

17:[12b] $[\alpha]_D^{23}$ -21° (c 0.28, CH_3OH); mp 144-146°C; ^1H NMR ($CDCl_3$) δ 1.23 (s,3H), 1.26 (s,3H), 1.86 (s,3H), 1.88 (s,3H), 2.06 (m, 1H), 2.34 (m, 2H), 2.39 (s, 3H), 2.62 (m, 1H), 2.66 (bs, 1H), 3.89 (d, J = 6.6 Hz, 1H), 4.19 (d, J = 8.5 Hz, 1H), 4.32 (d, J = 8.5 Hz, 1H), 4.60 (d, J = 11.5 Hz, 1H), 4.77 (bs, 2H), 4.79 (bs, 1H), 4.91 (d, J = 11.5 Hz, 1H), 4.95 (bd, J = 8.3 Hz, 1H), 5.53 (dd, J = 10.5, 7.3 Hz, 1H), 5.69 (d, J = 6.9 Hz, 1H), 5.79 (dd, J = 8.8, 2.1 Hz, 1H), 6.19 (bt, J = 8.6 Hz, 1H), 6.22 (s, 1H), 7.07 (d, J = 8.8 Hz, 1H), 7.30-7.65 (m, 11H), 7.75 (d, J = 7.3 Hz, 2H), 8.12 (d, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 10.72, 14.68, 20.89, 26.42, 33.29, 35.48, 43.09, 46.88, 55.04, 56.26, 72.15, 73.17, 74.11, 76.41, 77.12, 77.39, 78.57, 79.12, 80.79, 83.66, 94.17, 127.07, 128.40, 128.71, 128.75, 128.98, 129.04, 130.19, 131.98, 132.16, 133.61, 133.85, 137.89, 142.19, 153.18, 166.82, 167.12, 170.55, 172.58, 200.67; IR (KBr disk) 3550, 3425, 3011, 1757, 1725, 1661, 1375 cm^{-1}.

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