the simultaneous 1,5 H migration unnecessary. The interactions of BTF with isobutenyl, methallyl, and allyl ethers (and sulfides)[2] present the second extreme; only the bond $HC(CF_3)_2$ is established in the first step, and the same allylic ion pair is reached from positional isomers. BTF reactions with 1,3-diarylpropenes and benzylic H follow the same course.[8] *Between these two extremes, BTF combines both functions in a wide range of ene reactions.*

The rate constant for the reaction of ethyl methallyl ether with BTF is only little dependent on solvent polarity;[2] some modifications to the one-step hydride transfer[3] were discussed: H atom transfer giving a radical pair or, in combination with SET, a radical ion pair as intermediate. Although we do not favor these alternatives, they cannot be ruled out on the basis of the substituent effects on the regiochemistry of ene reaction described here.

Efficient and Practical Asymmetric Synthesis of the Taxol C-13 Side Chain, *N*-Benzoyl-(2*R*,3*S*)-3-phenylisoserine, and Its Analogues via Chiral 3-Hydroxy-4-aryl-β-lactams through Chiral Ester Enolate–Imine Cyclocondensation

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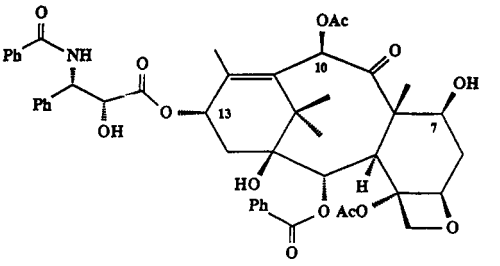
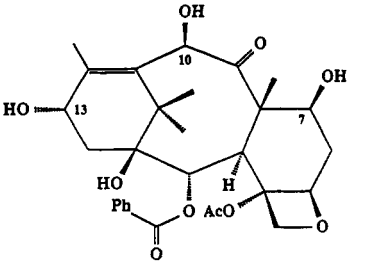
Summary: A highly efficient chiral ester enolate–imine condensation giving 3-hydroxy-4-aryl-β-lactams with >96% ee is successfully applied to the asymmetric synthesis of the enantiomerically pure taxol C-13 side chain, *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine, and its analogues.

Taxol (1), a complex diterpene[1] isolated from the bark of *Taxus brevifolia* (Western Yew), is currently considered the most exciting lead in cancer chemotherapy. Taxol (1) possesses high cytotoxicity and strong antitumor activity and is currently in phase II clinical trials in the United States.[2,3] Significant activity against cisplatin refractory advanced ovarian cancer has been established.[3b,c] A recent report has now shown that a more readily available taxol precursor can be isolated from the leaves of *Taxus baccata*.[4] Extraction of the fresh leaves yields 10-deacetyl baccatin III (2), (1 g/1 kg), which has been converted to 1.[4]

With the availability of 2, it appears that sufficient supplies of 1 can now be produced in a semisynthetic fashion. It should be noted that the C-13 side chain, i.e., the *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine (9) moiety, is crucial for the strong antitumor activity of 1.[5] The first enantioselective synthesis of the important side chain 9 was achieved in eight steps and 23% yield via a Sharpless epoxidation from *cis*-cinnamyl alcohol with an enantiomeric excess of 76–80%.[6] A recent publication describes the chemoenzymatic synthesis of a derivative of 9, in which the racemic mixture was resolved by enzymatic hydrolysis with lipases.[7]



1



2

We describe here our preliminary results on the successful application of lithium chiral ester enolate–imine cyclocondensation strategy[8,9] to the asymmetric synthesis of the C-13 side chain of taxol, 9, and its derivatives using 3-hydroxy-4-aryl-β-lactams as the key intermediates. With this approach, 9 and its derivatives can be obtained in three steps in good yields with virtually 100% ee.

First, we carried out the reactions of chiral lithium ester enolates (4), generated in situ from (silyloxy)acetates (3), with *N*-(trimethylsilyl)imines (5), which gave the corresponding chiral β-lactams 6 (eq 1). Results are summarized in Table I.

As Table I shows, the chiral auxiliary and the O-protecting group exert marked effects on the enantioselectivity

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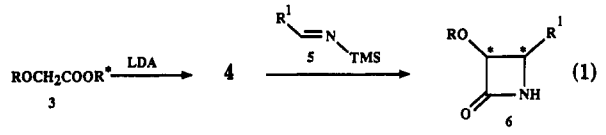


3a : R= t-BuMe$_2$Si ; R*= (-)-menthyl
3b : R= t-BuMe$_2$Si ; R*= (-)-*trans*-2-phenyl-1-cyclohexyl
3c : R= t-BuMe$_2$Si ; R*= (-)-10-dicyclohexylsulfamoyl-D-isobornyl
3d(-) : R= *i*-Pr$_3$Si ; R*= (-)-*trans*-2-phenyl-1-cyclohexyl
3d(+): R= *i*-Pr$_3$Si ; R*=(+)-*trans*-2-phenyl-1-cyclohexyl

5a : R^1 = Ph
5b : R^1 = *p*-MeOC$_6$H$_4$
5c : R^1 = 3,4-(MeO)$_2$C$_6$H$_3$

as well as on the chemical yield of the reaction.[10] For example, the reactions of **3d**, bearing (-)- or (+)-*trans*-2-phenyl-1-cyclohexyl as the chiral auxiliary[11] and triisopropylsilyl as the O-protecting group, with **5a–c** give exclusively the corresponding *cis*-β-lactams **6** in high yields with extremely high enantiomeric purity (96–98% ee) (entries 4–7). When (-)-menthyl is used as the chiral auxiliary and *tert*-butyldimethylsilyl is used as the O-protecting group (**3a**), the reaction with **5a** gives **6-A** in 52% yield with only 50% enantiomeric purity (entry 1). The reaction of **3b** (*t*-BuMe$_2$Si; (-)-*trans*-2-phenyl-1-cyclohexyl) with **5a** gives **6-A** in 90% yield with 76% ee, while with (-)-10-(dicyclohexylsulfamoyl)-D-isobornyl as the chiral auxiliary,[12] **6-A** is obtained in only 5% yield, but with 97% ee.

The exclusive formation of the *cis*-β-lactams (+)-**6-B,-C,D** with 96–98% ee is rationalized by the selective generation of the (*E*)-lithium enolates, (-)-***E*-4d**, and the transition state A depicted in Scheme I. It is apparent that the chiral auxiliary, (-)-*trans*-2-phenyl-1-cyclohexyl, very effectively directs the approach of the *N*-TMS-imines (**5a–c**) to the *si* face of (-)-***E*-4d** to give N-lithiated β-amino esters (**10**), which then cyclize to afford the corresponding *cis*-β-lactams (+)-**6-B,C,D**. In the same manner, the enantiomeric (-)-**6-B** arises from (+)-***E*-4d** with 97% ee. Until now, the asymmetric synthesis of 3-hydroxy-β-lactams has been limited by low stereoselectivity and often low chemical yield.[10,13] Our method provides the first efficient and practical route to 3-hydroxy-β-lactams with extremely high enantiomeric purity.

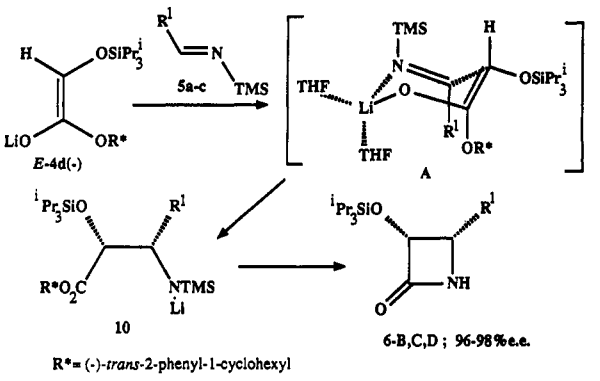
Next, (+)-**6-B** was converted to the desired *N*-benzoyl-(2*R*,3*S*)-phenylisoserine (**9**) as illustrated in Scheme II. (+)-**6-B** was deprotected with tetra-*n*-butylammonium fluoride in THF[14,15] at room temperature to give the 3-hydroxy-β-lactam **7** in 97% yield.[16] Then, **7** was hydrolyzed with refluxing 6 N HCl (12 h) to afford **8** as the hydrochloride salt, in quantitative yield.[17] The phenylisoserine **8** 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 (**9**) in 70% yield.[19] Other

Table I. Asymmetric Synthesis of β-Lactams (6) through Chiral Enolate–Imine Cyclocondensation[a]

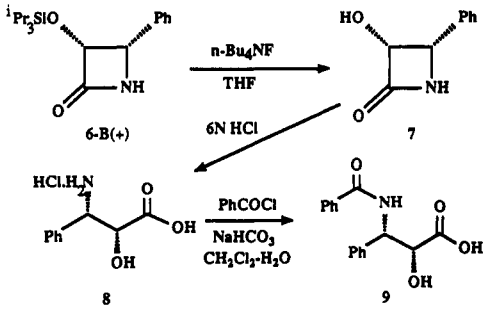
entry	ester	imine	β-lactam	isolated yield (%)[b]	config[c]	% ee[d]
1	**3a**	**5a**	**6-A**	52	3*R*,4*S*	50
2	**3b**	**5a**	**6-A**	90	3*R*,4*S*	76
3	**3c**	**5a**	**6-A**	5[e]	3*R*,4*S*	97
4	(-)-**3d**	**5a**	(+)-**6-B**	85	3*R*,4*S*	96
5	(+)-**3d**	**5a**	(-)-**6-B**	80	3*S*,4*R*	97
6	(-)-**3d**	**5b**	(+)-**6-C**	80	3*R*,4*S*	96
7	(-)-**3d**	**5c**	(+)-**6-D**	80	3*R*,4*S*	98

[a] All reactions were run with **3** (2.00 mmol), LDA (2.20 mmol), and **5** (2.00 mmol) in THF (6.0 mL) at −78 °C for 4 h, warmed gradually to ambient temperature for overnight, and quenched by saturated aqueous NH_4Cl unless otherwise noted. For details, see the supplementary material. [b] Yield of β-lactam after passing crude reaction mixture through a short column (15 cm, 10 g of silica gel) to eliminate unreacted starting materials, i.e., chiral auxiliary, aldehyde, and amine. The chiral auxiliaries, (+)- and (-)-*trans*-2-phenyl-1-cyclohexanol were recovered in >90% yield in entries 4–7. [c] Determined by chemical correlation with authentic samples: **6-A** and (+)-**6-B** were converted to (*R*)-3-phenyllactic acid and (2*R*,3*S*)-3-phenylisoserine, respectively. For (+)-**6-C** and (+)-**6-D**, absolute configurations were assigned by analogy with (+)-**6-B** based on specific rotations and retention times on HPLC analyses on a chiral column (see note *d*). [d] Determined by ^1H NMR analysis using a chiral shift reagent, (+)-Eu(hfc)$_3$, (entries 1, 2) and by HPLC analysis on a chiral column: DAICEL CHIRACEL OD (J.T. Baker) using *n*-hexane/2-propanol (32/1 for **6-A**; 13/1 for **6-B,C,D**) as the solvent. [e] Reaction was run at −78 °C for 1 h and at ambient temperature for 17 h and then quenched by adding ether and 1 N HCl. A substantial amount (55%) of **3c** was recovered through a flash chromatography on silica gel.

Scheme I



Scheme II



(10) When chiral benzyloxy- or phenoxyacetates were used, chemical yield was in the range of 15–25%, and the enantioselectivity was 15–67% ee. See ref 9.

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(15) Cumico, R. F.; Bedell, L. *J. Org. Chem.* **1980**, *45*, 4797.

(16) **7**: mp 187–188 °C (from ethyl acetate), $[\alpha]^{20}_D$ +198.8° (*c* 1.0; methanol).

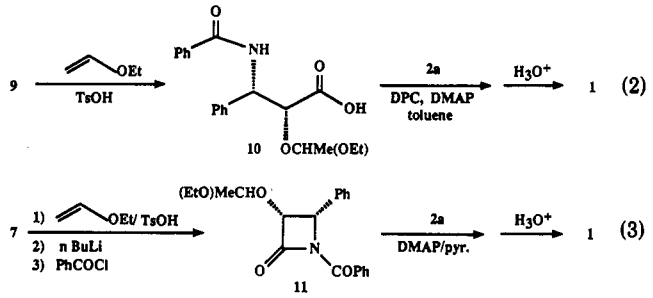
(17) **8**·HCl: mp 222–224 °C dec; $[\alpha]^{20}_D$ −14.6° (*c* 1.03, 6 N HCl); lit.[7] $[\alpha]^{20}_D$ −14.8° (6 N HCl); lit.[18] $[\alpha]^{25}_D$ +14.9° (*c* 0.737, 6 N HCl) (for 2*S*,3*R* isomer).

(18) Harada, K.; Nakajima, Y. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2911.

(19) **9**: mp 167–169 °C; $[\alpha]^{25}_D$ −37.78° (*c* 0.9, EtOH); lit.[18] $[\alpha]^{25}_D$ +36.5° (*c* 1.45, EtOH) (for 2*S*,3*R* isomer).

3-(silyloxy)-4-aryl-β-lactams, (+)-6-C and (+)-6-D, can be converted to the corresponding substituted N-benzoylphenylisoserines in the same manner.

N-Benzoylphenylisoserine (9) has already been coupled with 7-(trimethylsilyl)-2 (2a) by Greene et al. (eq 2).[4] Quite recently, Holton et al. developed a more efficient coupling method, directly from 7 (eq 3).[20] Our method, described herein, provides the most efficient route to taxol (1) to date.



In summary, we have demonstrated that 3-hydroxy-4-aryl-β-lactams are efficient key intermediates for the asymmetric synthesis of the taxol C-13 side chain and its analogues, which are readily obtained via chiral ester enolate–imine cyclocondensations with extremely high enantiomeric purity. The most efficient and crucial chiral auxiliary, (−)-*trans*-2-phenylcyclohexanol, can be readily obtained in 100-g quantities using the lipase-catalyzed kinetic resolution of its racemic chloroacetate, as developed by Whitesell et al.,[11c] and is fully recyclable after the reaction. This synthetic method provides efficient and practical routes to a variety of modified taxol C-13 side chains, which are essential for the antitumor activity and the solubility of taxol (1).

Acknowledgment. This research was supported by grants from National Institute of Health (GM33665 and GM42798), the Center for Biotechnology, SUNY at Stony Brook, which is sponsored by the New York Science & Technology Foundation (for I.O., I.H., and M.Z.), American Cancer Society, and National Institute of Health (GM42260) and Biomedical Research Grant (RR 5606) (for G.I.G.). Generous support from Ajinomoto Co., Inc. (for I.O.) and Oread Laboratories, Inc. (for G.I.G. and L.R.J.) are also gratefully ackowledged. The authors are grateful to Dr. Alan Schwartz, Hoffmann-La Roche, Inc., for his generous gift of (−)-*trans*-2-phenyl-1-cyclohexanol and (+)-*trans*-2-phenyl-1-cyclohexyl chloroacetate at the beginning of this project.

Supplementary Material Available: Typical procedures and identification data for all new compounds (4 pages). Ordering information is given on any current masthead page.

(20) Holton, R. A.; Liu, J. H.; Gentile, L. Submitted for publication. We thank Professor Holton for informing us of their results prior to publication.

Remote Aromatic Metalation. An Anionic Friedel–Crafts Equivalent for the Regioselective Synthesis of Condensed Fluorenones from Biaryl and *m*-Teraryl 2-Amides

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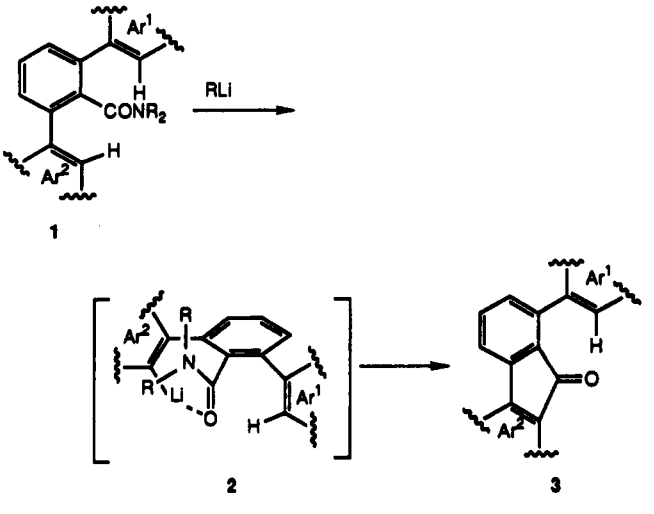
Summary: Remote metalation (*t*-BuLi, LDA) of *m*-teraryl and biaryl amides (Scheme I) constitutes a short and convenient route to a variety of substituted and condensed fluorenones, including aza analogues (Table I) and the natural product, dengibsinin (**6a**, Scheme II).

As part of expanding studies aimed to establish synthetic links between the directed ortho metalation strategy[1] and transition metal catalyzed cross coupling reactions,[2] we have developed a general route to functionalized biaryls, *m*-teraryls, and polyaryl systems.[3] Contemplation of X-ray crystal structure data of a *m*-teraryl[4] in context with the complex induced proximity effect (CIPE) concept,[5] suggested the prospect of remote metalation of teraryl amides[6] (Scheme I). Following initial amide–strong base

Scheme I



coordination, 1 may be induced to undergo remote deprotonation as a function of Ar^1/Ar^2 hydrogen relative acidities to give species 2 that could cyclize to 3 in an intramolecular version of the classical amide–RLi condensation reaction. Herein we report the affirmation of this hypothesis on *m*-teraryls and biaryls and thereby provide a general, short, and regioselective new method for the construction of simple and condensed fluorenones and azafluorenones, including the Orchid natural product, dengibsinin (**6a**).[7,8] This anionic equivalent of the Frie-

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