Taxol Semisynthesis: A Highly Enantio- and Diastereoselective Synthesis of the Side Chain and a New Method for Ester Formation at C-13 Using Thioesters

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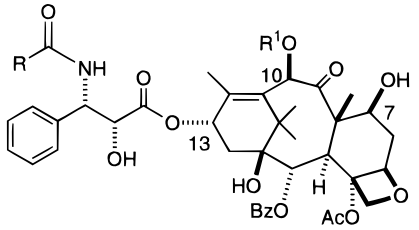
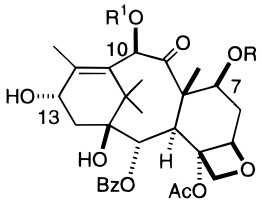
A very simple, new, and straightforward approach to the Paclitaxel (Taxol) and Docetaxel (Taxotere) side chains has been developed using the imine addition reaction of thioester-derived boron enolates bearing chiral ligands. The addition reaction was studied extensively, using a combination of different thioesters ($ROCH_2COSPh$, $ROCH_2COS$*t*-Bu), oxygen protecting groups (R = Bn, TBDMS, COPh, EE, TMS), chiral boron ligands [derived from both (−) and (+)-menthone], imines ($PhCH{=}NSiMe_3$, PhCH=NCOPh), and in the presence or in the absence of additional Lewis acids ($BF_3{-}OEt_2$, Et_2AlCl, $TiCl_4$). The side chain was assembled in a few steps with the correct relative (*syn*) and absolute stereochemistry (2*R*,3*S*). The stereochemical outcome of the boron-mediated reaction was rationalized using chair vs boat transition state structures. A new direct route for attachment of the side chains to the baccatin nucleus using thioester chemistry has also been developed. By treatment of a mixture of a thioester (**8**, **12**, or **17**) and protected baccatin III (**2b**, **2c**) with LHMDS, the 13-O acylated compounds were obtained in high yield (up to 90%). Hydrolysis of **18b** gave Paclitaxel (**1a**) in 80% yield.

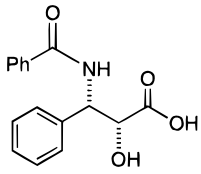
Introduction

Paclitaxel (Taxol, **1a**), isolated from the bark of the Pacific Yew *Taxus brevifolia*, is considered one of the most promising cancer chemotherapeutic agents and has recently been approved for treatment of metastatic ovarian and breast cancer.[1] It is also undergoing clinical trials in nonsmall cell lung cancer (nsclc), head and neck cancer, glioblastoma, and oesophageal cancer. The scarcity of **1a** and its highly challenging structure have stimulated interest in its synthesis. Central to all synthetic strategies is the attachment of the C-13 side chain to the baccatin III nucleus, since the presence of this side chain has proven to be essential for the biological activity of Paclitaxel.[1] Owing to the chemical complexity of Paclitaxel (**1a**), its commercial production by total synthesis is not likely to be economical. However, the naturally derived 10-deacetylbaccatin III (**2a**) is readily available in relatively high yield from the needles of the European Yew *T. baccata*. Preparation of quantities of Paclitaxel economically by a semisynthetic approach which involves the condensation of suitably protected 10-deacetylbaccatin III (**2b,c**) with suitably protected *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine (**3**) provides an alternative source of this important natural product and access to semisynthetic analogs.



1a; R = Ph; R^1 = Ac
1b; R = $OCMe_3$; R^1 = H





2a; R = R^1 = H
2b; R = -$SiEt_3$; R^1 = -$COCH_3$
2c; R = R^1 = -CO-OCH_2CCl_3

3

Therefore, the development of short and practical synthetic routes to phenylisoserine derivatives, as well as procedures for attaching the C-13 side chain to the baccatin III nucleus, which are adaptable for industrial-scale production, have become very important.

The numerous papers devoted to the preparation of enantiomerically enriched (**3**) include research on semisynthesis drawing from the chiral pool,[2] enzymatic and/or microbal processes,[3] diastereoselective reactions with covalently-bound chiral auxiliaries or with chiral sub-

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‡ Pharmacia&Upjohn.
§ New address: Pharmacia&Upjohn.
⊗ Abstract published in *Advance ACS Abstracts,* June 15, 1997.
(1) Taxol is the registered trademark of Bristol-Myers Squibb Company for Paclitaxel. For a review, see: Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem.* **1994**, *106*, 38−67; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15−44.

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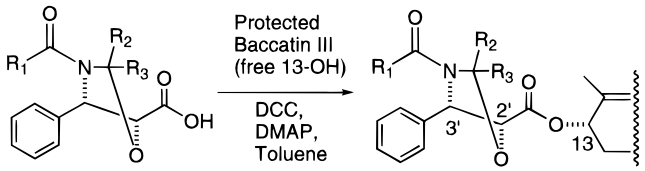
strates,[4] asymmetric catalysis,[5] and chemical resolution of racemic acids.[6]

In contrast, only a few reactions have been developed to attach the "side chain" to the free C-13 OH group of baccatin derivatives. This esterification reaction appears to be hampered by the steric hindrance around the C-13 OH group.[1] Essentially only two general methods have been developed to solve this problem: the first one relies on the DCC protocol by Rhone-Poulenc Rorer/Gif/Grenoble,[7,8] and the second one on the β-lactam protocol by Holton *et al.* and Ojima *et al.* (Scheme 1).[9,10]

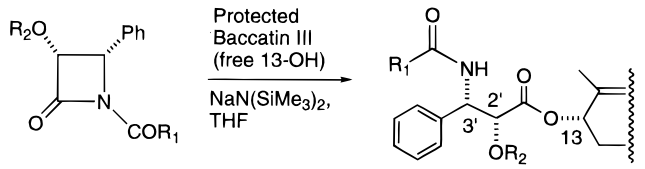
Under forcing conditions (excess of DCC, DMAP, 75 °C in toluene), coupling of (2*R*,3*S*)-*N*-benzoyl-*O*-(1-ethoxyethyl)-3-phenylisoserine with suitably protected baccatin III led to the corresponding ester; unfortunately, acylation under the above mentioned conditions led also to the 2′-epimerized compound.[7a,b] In order to prevent epimerization at carbon 2′, other esterification procedures have been developed. In particular the use of cyclic derivatives (oxazolidines) allow milder conditions and no epimerization (Scheme 1, DCC approach).[4a,7c,e,11] Following a similar route, an oxazoline acid intermediate has been synthesized and used for the DCC coupling reaction with no epimerization (Scheme 2).[8] Recently it has been shown that even substrates with the wrong stereochemistry [2(*S*)] can be transformed into the esterified compounds with the right stereochemistry [2′(*R*)], using the oxazolidine/DCC approach (Scheme 2).[7d]

Scheme 1

DCC Rhone-Poulenc Rorer/Gif/Grenoble approach



Holton *et al.* and Ojima *et al.* β-lactam approach



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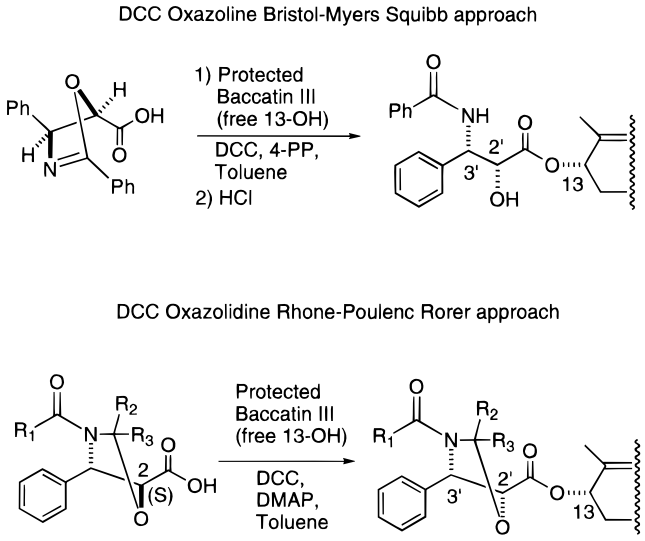
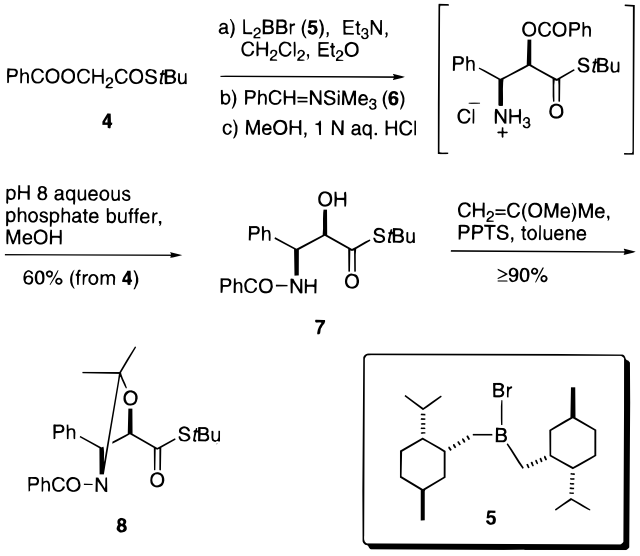
Scheme 2



Scheme 3



We have developed a very simple, new, and straightforward approach to the Paclitaxel side chain using the imine addition reaction of thioester-derived boron enolates bearing chiral ligands.[12−14] The results are described in this paper.

Results and Discussion

Paclitaxel Side Chain. The side chain is assembled in one step with the correct relative (*syn*) and absolute stereochemistry (2*R*,3*S*). The easily accessible *tert*-butyl (benzoyloxy)thioacetate (**4**) was enolized with triethylamine and the chiral boron reagent **5** derived from (+)-menthone[13] and then treated with *N*-(trimethylsilyl)-benzaldimine[15a] (**6**) (Scheme 3). After quenching and extraction, the crude product was transformed into the amine hydrochloride. Salt formation freed the reaction product from the boron ate-complex and allowed easy removal of all the byproducts simply by washing the resulting white solid with ether; this workup protocol represents a major experimental improvement compared to the usual H_2O_2 oxidative workup of the boron-mediated reactions with aldehydes. Treatment of the amine hydrochloride with buffered MeOH−H_2O at pH 8.0 caused clean intramolecular COPh migration from oxygen to nitrogen[4e,8f,16] to give the desired compound **7**, which was isolated practically pure by simple solvent extraction and without the need of chromatography. The overall yield is around 60% (starting from **4**), and the stereochemical control is high (*syn:anti* ≥ 96:4; ee ≥ 96%).[17] Treatment of **7** with 2-methoxypropene and pyridinium *p*-toluenesulfonate (PPTS) in toluene smoothly furnished oxazolidine (**8**) (≥90%), and the small amount of the unwanted *anti* diastereomer was removed in this step by chromatography (the *anti* compound does not cyclize under these conditions). The absolute configuration was checked by chemical correlation to known intermediates, and the enantiomeric excess was determined by ^{1}H-NMR analysis of the Mosher ester derivative of **7** (see the Supporting Information).

Following a different approach, the easily accessible phenyl [(*tert*-butyldimethylsilyl)oxy]thioacetate (**9**) was enolized with triethylamine and the chiral boron reagent derived from (−)-menthone (*ent*-**5**)[13] and then treated with *N*-(trimethylsilyl)benzaldimine[15a] (**6**) (Scheme 4). After quenching and extraction, the crude product was transformed into the amine hydrochloride to free the reaction product from the boron ate-complex. The white solid salt was then treated in dichloromethane with PhCOCl, Et_3N, and a catalytic amount of DMAP, and the resulting crude product was purified by filtration through silica gel to give **10** (*anti*) and traces of the *syn* diastereomer.[17] The overall yield was 71% (starting from **9**), the *anti:syn* ratio is 97:3, and the major *anti* compound (**10**) is ≥95% enantiomerically pure (average over several experiments). The 97:3 mixture was then treated with aqueous HF in acetonitrile, and the resulting crude compound **11** (100%, *anti:syn* 97:3)[17] was cyclized by treatment with thionyl chloride in refluxing 1,2-dichloroethane. Oxazoline formation occurred uneventfully with complete inversion of stereochemistry at the C-2 stereocenter[8e,f] to give **12** (65% yield, average over several experiments), and the traces of the unwanted *syn* diastereomer were removed in this step by chromatography (the *syn* compound does not cyclize under these condi-

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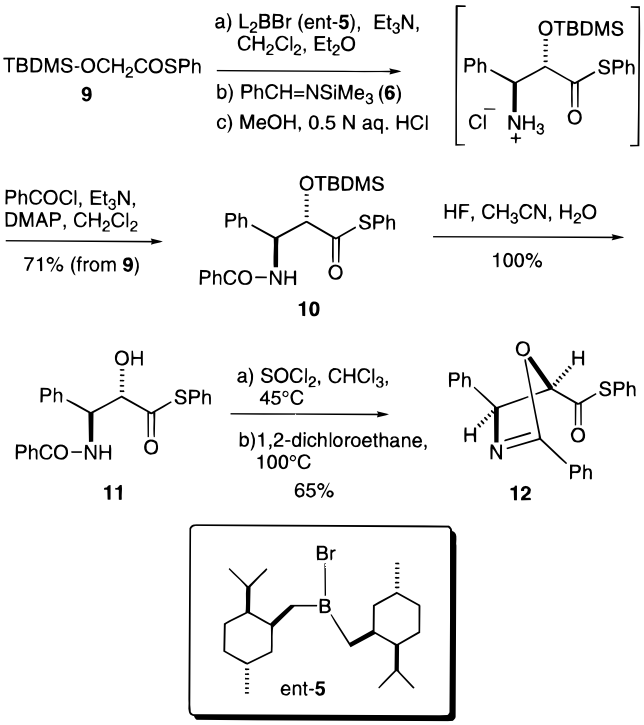
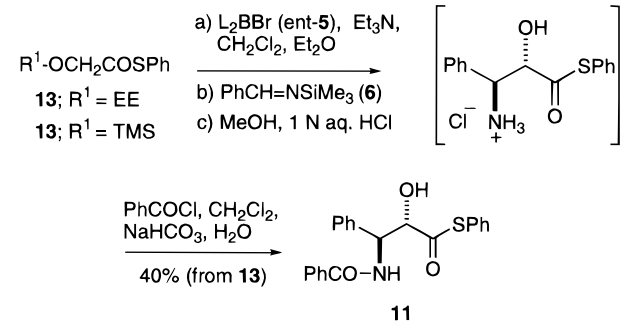
(17) The *syn:anti* mixture was used in the next synthetic step. Pure *syn* and *anti* compounds were separated and isolated only for analytical purposes.

Scheme 4



Scheme 5



tions). The absolute configuration was checked by chemical correlation with known intermediates, and the enantiomeric excess was determined by ^{1}H-NMR analysis of the Mosher ester derivative of *anti* (**11**) (see the Supporting Information). The synthesis of **12** has an overall yield of 46% (starting from **9**) and requires only two chromatographic purifications, the first one (purification of **10**) being a silica gel filtration rather than a real chromatography.

A simple variant of the above procedure makes use of more acid labile oxygen-protecting groups. Thus, glycolate thioester R^1OCH_2COSPh (**13**, R^1 = EE = 1-ethoxyethyl or R^1 = TMS = trimethylsilyl) was enolized with triethylamine and the chiral boron reagent derived from (−)-menthone (*ent*-**5**)[13] and then treated with *N*-(trimethylsilyl)benzaldimine[15a] (**6**) (Scheme 5). After quenching with pH 7 phosphate buffer and extraction, the organic phase was treated with HCl−MeOH−H_2O, with consequent removal of the protecting groups. The resulting crude β-amino alcohol [$PhCH(NH_3^+)CH(OH)COSPh\ Cl^-$] was washed several times with ethyl ether and then *N*-benzoylated in dichloromethane/water (1:1 v:v) with PhCOCl and $NaHCO_3$ under Schotten−Baumann conditions. The resulting crude mixture was purified by flash cromatography to give the *anti* compound **11**. The overall yield is about 40% (average over several experiments), the *anti:syn* ratio is >99:1 (the *syn* diastereomer is not detected by ^{1}H-NMR), and the major *anti* compound (**11**) is ca. 85−88% enantiomerically pure (85% from R^1 = EE, 88% from R^1 = TMS). This procedure has several advantages compared to the one shown in Scheme 4 (TBDMS protecting group): EE- and TMS-protection is less expensive than TBDMS-protection, EE and TMS are immediately removed on quenching the aldol reaction mixture, and the *anti:syn* ratio is excellent (>99:1). The disadvantage is that both the enantiomeric excess (ca. 85−88%) and the yield (ca. 40%) of the aldol product **11** are lower.

The boron enolate−imine reaction was carried out with a combination of different thioesters (COSPh, $COSBu^t$), oxygen protecting groups (Bn, TBDMS, COPh), chiral boron ligands [derived from both (−)- and (+)-menthone], imines ($PhCH{=}NSiMe_3$,[15a] $PhCH{=}NCOPh$[4a,15b]), and in the presence or in the absence of additional Lewis acids ($BF_3{-}OEt_2$, Et_2AlCl, $TiCl_4$). The results can be summarized as follows (Table 1):[18]

(1) In the reaction of the above described chiral boron enolates with *N*-(trimethylsilyl)benzaldimine $PhCH{=}NSiMe_3$ (**6**) a preponderance of the *syn* diastereoisomer is obtained with the $COSBu^t$ thioesters (Table 1, entries 1−3), while a preponderance of the *anti* isomer is obtained with the COSPh thioesters (entries 4−6).

(2) With the $COSBu^t$ thioesters and *N*-(trimethylsilyl)-benzaldimine (**6**), the *syn:anti* ratios vary from 70:30 (entry 1, TBDMS oxygen protecting group, see below Scheme 7) to 75:25 (entry 2, Bn oxygen protecting group) to ≥96:4 (entry 3, PhCO oxygen protecting group, see Scheme 3). The desired imine *re*-face attack, leading to the 3(*S*) stereocenter in the major *syn* isomer, was obtained in all cases with high selectivity (*re:si* ≥ 98:2; ee ≥ 96%) using the chiral boron reagent **5** derived from (+)-menthone (Scheme 6i).

(3) With the COSPh thioesters and *N*-(trimethylsilyl)-benzaldimine (**6**), the *anti:syn* ratios vary from ≥90:10 (entry 6, PhCO oxygen protecting group) to 97:3 (entry 4, TBDMS oxygen protecting group, see Scheme 4) to ≥98:2 (entry 5, Bn oxygen protecting group). The desired imine *re*-face attack, leading to the 3(*S*) stereocenter in the major *anti* isomer, was obtained in all cases with high selectivity (*re:si* ≥ 97.5:2.5; ee ≥ 95%) using the chiral boron reagent *ent*-**5** derived from (−)-menthone. The minor *syn* isomer had the opposite and undesired configuration at C-3 (*R*) (Scheme 6ii).

The practical use of the aldol product with PhCO oxygen protecting group was hampered by failure to give clean intramolecular COPh migration from oxygen to nitrogen by treatment of the amine hydrochloride with buffered MeOH−H_2O (pH 7.0−8.0) because of competitive thiophenyl ester hydrolysis.

(4) The reaction of the above described chiral boron enolates with imine $PhCH{=}NCOPh$ needs the presence of additional Lewis acid in order to give high yields. With the $COSBu^t$ thioesters, the *syn:anti* ratios vary from 87:13 [(a) entry 9, Bn oxygen protecting group, $BF_3{-}OEt_2$ Lewis acid] to 57:43 [for both (b) entry 8, Bn oxygen

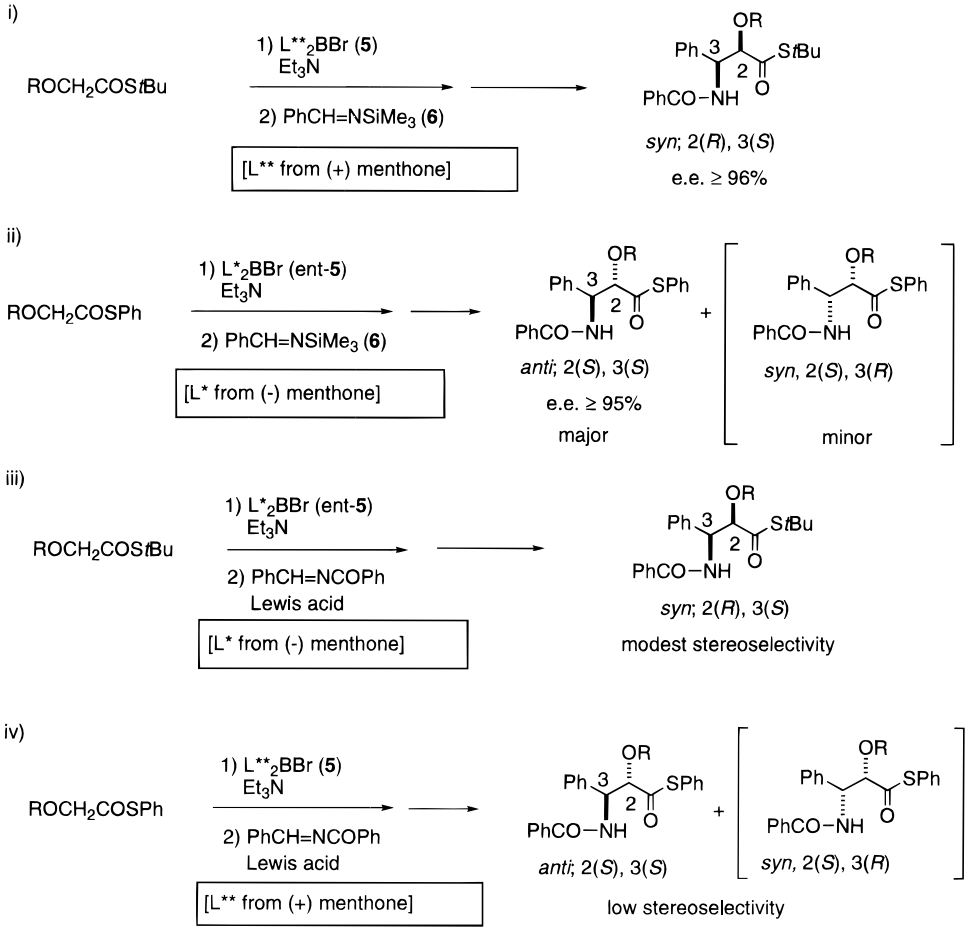
(18) *Syn−anti* ratios were determined by observing the ^{1}H-NMR C(2)H−C(3)H coupling constant values of the *N*-benzoyl compounds (J_{syn} = 2.1−2.5 Hz; J_{anti} = 5.0−5.7 Hz). Enantiomeric excesses were determined via Eu(hfc)$_3$ ^{1}H-NMR analysis of the *N*-benzoyl compounds and/or ^{1}H-NMR analysis of the Mosher derivatives (esters with the C-2 OH group). The absolute configurations were determined via chemical correlation with known compounds (see the Supporting Information, and Mukai, C.; Kim, I. J.; Hanaoka, M. *Tetrahedron: Asymmetry* **1992**, *3*, 1007−1010).

Table 1. [a] **Boron Enolate−Imine Reactions with a Combination of Different Thioesters, Oxygen Protecting Groups (R), Chiral Boron Ligands, Imines, Additional Lewis Acids (Scheme 6)**

entry	R	thioester	L_2BBr	imine	additional Lewis acid	syn:anti ratio	absolute config (major isomer)	% ee
1	TBDMS	S*t*-Bu	**5**	**6**	−	70:30	2(*R*),3(*S*)	≥96
2	Bn	S*t*-Bu	**5**	**6**	−	75:25	2(*R*),3(*S*)	≥96
3	PhCO	S*t*-Bu	**5**	**6**	−	≥96:4	2(*R*),3(*S*)	≥96
4	TBDMS	SPh	*ent*-**5**	**6**	−	3:97	2(*S*),3(*S*)	≥95
5	Bn	SPh	*ent*-**5**	**6**	−	≤2:98	2(*S*),3(*S*)	≥95
6	PhCO	SPh	*ent*-**5**	**6**	−	≤10:90	2(*S*),3(*S*)	≥95
7	TBDMS	S*t*-Bu	*ent*-**5**	PhCH=NCOPh	BF_3−OEt_2	57:43	2(*R*),3(*S*)	62
8	Bn	S*t*-Bu	*ent*-**5**	PhCH=NCOPh	$TiCl_4$	57:43	2(*R*),3(*S*)	46
9	Bn	S*t*-Bu	*ent*-**5**	PhCH=NCOPh	BF_3−OEt_2	87:13	2(*R*),3(*S*)	82
10	TBDMS	SPh	**5**	PhCH=NCOPh	Et_2AlCl	15:85	2(*S*),3(*S*)	40
11	Bn	SPh	**5**	PhCH=NCOPh	BF_3−OEt_2	20:80	2(*S*),3(*S*)	60
12	TBDMS	SPh	**5**	PhCH=NCOPh	BF_3−OEt_2	48:52	2(*S*),3(*S*)	20

[a] For determination of the *syn:anti* ratios, of the enantiomeric excesses (ee), and of the absolute configurations, see footnote 18, the Experimental Section, and the Supporting Information.

Scheme 6

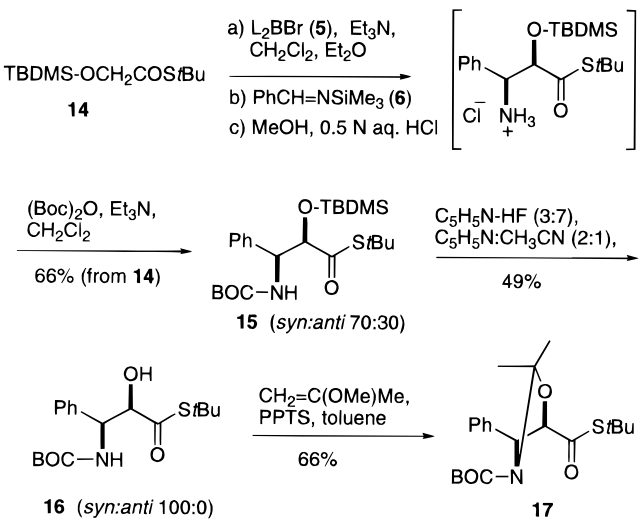


protecting group, $TiCl_4$ Lewis acid and (c) entry 7, TBDMS oxygen protecting group, BF_3−OEt_2 Lewis acid]. The desired imine *re*-face attack, leading to the 3(*S*) stereocenter in the major *syn* isomer, was obtained in all cases with modest selectivity [*re:si* 91:9 (a), 73:27 (b), 81:19 (c)] using the chiral boron reagent *ent*-**5** derived from (−)-menthone (Scheme 6iii).

The stereochemical results with imine PhCH=NCOPh and *N*-(trimethylsilyl)benzaldimine are quite different, in particular the absolute configuration is opposite: cf. Scheme 6i with 6iii. This can be rationalized by a change in the reaction mechanism, i.e. the usual cyclic transition structures involving *N*-(trimethylsilyl) benzaldimine (see the stereochemical analysis in the relevant paragraph below and Scheme 8) are replaced in the case of imine PhCH=NCOPh by open transition structures, due to the presence of the additional Lewis acid.

(5) With the COSPh thioesters and imine PhCH=NCOPh, the *anti:syn* ratios vary from 85:15 [(a) entry 10, TBDMS oxygen protecting group, Et_2AlCl Lewis acid] to 80:20 [(b) entry 11, Bn oxygen protecting group, BF_3−OEt_2 Lewis acid] to 52:48 [(c) entry 12, TBDMS oxygen protecting group, BF_3−OEt_2 Lewis acid]. The desired imine *re*-face attack, leading to the 3(*S*) stereocenter in the major *anti* isomer, was obtained in all cases with low selectivity (*re:si* 60:40−80:20) using the chiral boron reagent **5** derived from (+)-menthone. The minor *syn* isomer had the opposite and undesired configuration at C-3 (*R*) (Scheme 6iv).

Scheme 7



Docetaxel Side Chain. Docetaxel (Taxotere, **1b**)[19] side chain was assembled using an approach similar to the ones discussed for Paclitaxel (see above). The easily accessible *tert*-butyl [(*tert*-butyldimethylsilyl)oxy]thioacetate (**14**) was enolized with triethylamine and the chiral boron reagent **5** derived from (+)-menthone[13] and then treated with *N*-(trimethylsilyl)benzaldimine[15a] (**6**) (Scheme 7). After quenching and extraction, the crude product was transformed into the amine hydrochloride to free the reaction product from the boron ate-complex. The white solid salt was then treated in dichloromethane with Et_3N and di-*tert*-butyl dicarbonate, and the resulting crude product was purified by silica gel filtration to give **15** (*syn:anti* 70:30)[17] with an overall yield of 66% (starting from **14**). Compound **15** was then treated with HF−pyridine (7:3) in pyridine−acetonitrile (2:1) at 50 °C,[19d] and the resulting compound was purified by flash chromatography to give the major *syn* alcohol (**16**) (49%; *re:si* ≥ 98:2; ee ≥ 96%) together with the minor *anti* diastereomer (21%). Oxazolidine formation occurred using 2-methoxypropene and PPTS in toluene to give (**17**) (66%).[7c,19c] The absolute configuration was checked by chemical correlation to known intermediates, and the enantiomeric excess was determined by ^{1}H-NMR analysis of the Mosher esters derived from **16** (see the Supporting Information).

Stereochemical Analysis of the Enolate Additions. From a mechanistic standpoint, the stereochemical divergence of the reactions of *E*(OB) boron enolates with aldehydes (*anti* products)[13c] and imines (*syn* products)[13f] was reasonably expected based on the different coordination of aldehydes and *trans* imines to the boron atom in the chairlike cyclic transition states (cf. the two chair transition state structures in Scheme 8).[13i] On the contrary, the stereodivergence caused by the different type of thioester in the addition to imines (COS*t*Bu: *syn* products vs COSPh :*anti* products) is quite surprising. The stereochemical outcome can be rationalized by using chair vs boat transition structures, as shown in Scheme 8.[20] However, there is no obvious explanation why this strong stereocontrol is operating as a function of R^2 (*t*Bu vs Ph), while the role of the oxygen protecting group R^1 is relatively minor (see results above).

Semisynthesis of Paclitaxel and Docetaxel. Thioester oxazoline **12** and oxazolidine **8** were attached directly to the baccatin nucleus. By treatment of a mixture of protected baccatin III (7-TES, **2b**)[7a] or protected 10-deacetylbaccatin III (7,10-di-Troc, **2c**)[21] and oxazoline (**12**) or oxazolidine (**8**) in THF at 0 °C with lithium bis(trimethylsilyl)amide (LHMDS), the 13-O acylated compounds **18** and **19** were obtained with high conversion and yield (89−90% for **18** and 74−75% for **19**, Scheme 9).[12]

The enantiomeric excess of oxazoline **12** was also confirmed in the reaction with 7-TES-protected baccatin III (**2b**) by isolating, besides the desired compound **18b** (89%), trace amounts (about 2%) of the "wrong" Taxol derivative 7-(triethylsilyl)-13-*O*-[[(4*R*,5*S*)-2,4-diphenyl-4,5-dihydrooxazol-5-yl]carbonyl]baccatin (see the Experimental Section).

The use of lithium amides for C-13 OH metalation of protected baccatin III is well described in the literature.[9a,c,d] The most surprising yet gratifying aspect of this new coupling reaction is the high reactivity of the thioester derivatives, given the scarcity of methods for this important transformation and its difficulty. Thioesters have attracted the interest of organic chemists since the discovery that they are used by Nature in enzymatic acylation processes.[22] The resonance overlap of the lone-pair electrons with the carbonyl group is much weaker for the sulfur atom than for the oxygen atom; thus a thioester carbonyl group is much less stabilized by resonance than the carbonyl group of an ester and is therefore much more reactive.[22] In addition, thioesters **8** and **12** are particularly electrophilic due to the presence of electron-withdrawing substituents in both the α and β position. Replacement of the amide group in the β position (PhCON in **8**) with a carbamate group (BocN in **17**) makes the thioester carbonyl group less reactive toward C-13 OH nucleophilic addition. In fact, the yield of the Docetaxel precursor **20c** under the above conditions is somewhat lower (ca. 60%) (Scheme 9).

Various attempts were made to promote the coupling reaction between 10-deacetylbaccatin III (7,10-di-Troc, **2c**)[21] and thioester oxazolidine **8** or oxazoline **12** without the use of lithium amides. The ester formation was attempted using different Lewis acids as promoters [Ag(OCOCF$_3$), Ag(OSO$_2$CF$_3$), Cu(OSO$_2$CF$_3$)$_2$, Cu(OSO$_2$CF$_3$)−PhH, Hg(OCOCF$_3$)$_2$] in different solvents (CH_2Cl_2, CH_3CN, THF).[23] In most cases no formation of the desired compound was observed, while the use of Ag(OCOCF$_3$) in dichloromethane or benzene at room temperature promoted the coupling reaction between **2c** and thioester oxazoline (**12**) to give **18c** only in poor yields (30%).

Both **18**[8] and **19**-type[7c,d,e] compounds have been depro-

(19) Taxotere is the registered trademark of Rhone-Poulenc Rorer Company for Docetaxel. For recent references on Docetaxel semisynthesis, see: (a) Didier, E.; Fouque, E.; Commercon, A. *Tetrahedron Lett.* **1994**, *35*, 3063−3064. (b) Didier, E.; Fouque, E.; Taillepied, I.; Commercon, A. *Tetrahedron Lett.* **1994**, *35*, 2349−2352. (c) Bourzat, J. D.; Commercon, A. *Tetrahedron Lett.* **1993**, *34*, 6049−6052. (d) Ojima, I.; Kuduk, S. D.; Slater, J. C.; Gimi, R. H.; Sun, C. M. *Tetrahedron* **1996**, *52*, 209−224.

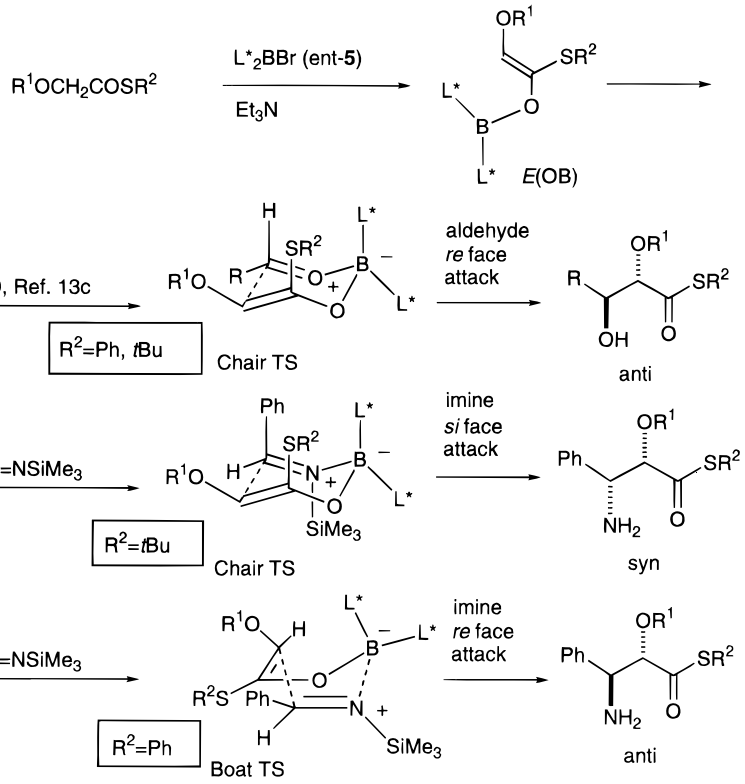
(20) *Ab initio* MO calculations (3-21G basis set) featuring the addition of the BH_2 enol borinate derived from acetaldehyde to formaldehyde-imine have recently shown that two competing cyclic transition structures are important: the chair and the boat. Bernardi, A.; Gennari, C.; Raimondi, L.; Villa, M. B. *Tetrahedron* **1997**, *53*, 7705−7714.

(21) Guéritte-Voegelein, F.; Sénilh, V.; David, B.; Guénard, D.; Potier, P. *Tetrahedron* **1986**, *42*, 4451−4460.

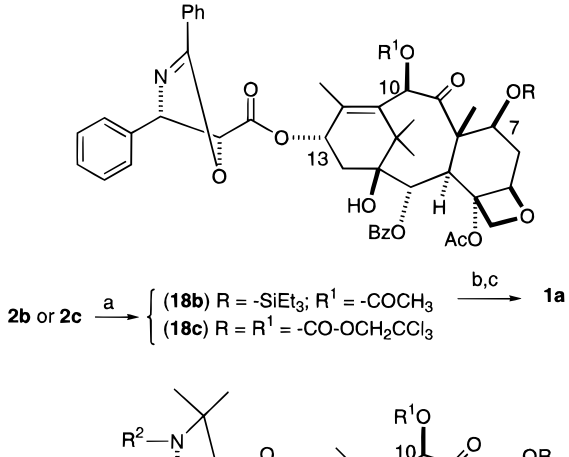
(22) Bruice, T. C.; Benkovic, S. J. *Bioorganic Mechanisms*; W. A. Benjamin Inc.: New York, 1966; Vol. 1, Chapter 3.

(23) (a) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756−6758. (b) Booth, P. M.; Fox, C. M. J.; Ley, S. V. *J. Chem., Soc. Perkin Trans. 1* **1987**, 121−129.

Scheme 8



Scheme 9[a]



[a]Reagents and conditions: (a) **12** (3.5 mol.eq.), $LiN(SiMe_3)_2$ (4.5 mol.eq.), THF, 15 min at 0°C, 89-90%; (b) from **18b**: 0.04 N HCl in MeOH : H_2O (1.5 : 1 v:v), 60-80°C; (c) $NaHCO_3$, H_2O, pH 7.5, 16 h, RT, (80% yield over steps b,c); (d) **8** (3.5 mol.eq.), $LiN(SiMe_3)_2$ (2.0 mol. eq.), THF, 24 h at 0°C, 74-75%; (e) **17** (3.5 mol.eq.), $LiN(SiMe_3)_2$ (4.5 mol.eq.), THF, 24 h at 0°C, 60%

tected to give Paclitaxel in high yields. Docetaxel precursor **20c** has been transformed into both Docetaxel and Paclitaxel via known routes.[7c,19b] Our preferred route involves the hydrolysis of **18b** to give Paclitaxel (**1a**) in 80% yield (Scheme 9). This represents the third original approach (after the two described in the introduction)[4a,7–11] for the attachment of the Paclitaxel side chain.

Experimental Section

General. Chromatographic purification of products was carried out by "flash chromatography"[24] using Merck silica gel 60 (230–400 mesh). Thin layer chromatography was carried out on Merck silica gel 60F plates. Organic solutions were dried over sodium sulfate (Na_2SO_4). ^1H NMR spectra were obtained at 200 MHz and ^{13}C NMR at 50.28 MHz at 25 °C (unless otherwise stated). Chemical shifts are reported in parts per million (ppm), δ, from TMS = 0.00 ppm. *J* values are given in Hz.

***tert*-Butyl (Benzoyloxy)thioacetate (4).** A solution of $AlMe_3$ (2.0 M in hexanes, 30.4 mL, 60.8 mmol) in CH_2Cl_2 (65 mL) was treated at 0 °C with *t*-BuSH (6.85 mL, 60.8 mmol). After 20 min at 0 °C, a solution of methyl glycolate ($HOCH_2$-COOMe, 0.786 mL, 10.1 mmol) in CH_2Cl_2 (15.2 mL) was added at −10 °C. The mixture was stirred at 0 °C for 48 h, quenched with NH_4Cl saturated aqueous solution (30 mL), and filtered through Celite, washing the Celite cake with CH_2Cl_2. The organic phase was dried and evaporated to give a crude mixture which was purified by flash chromatography (hexanes−Et_2O 7:3) to afford pure *tert*-butyl (hydroxy)thioacetate (*t*-BuSCOCH$_2$OH, 0.795 g, 53%). A solution of the latter compound (0.72 g, 4.88 mmol) in CH_2Cl_2 (32.5 mL) was treated with DMAP (0.06 g, 0.488 mmol), Et_3N (1.0 mL, 7.318 mmol), and PhCOCl (0.736 mL, 6.342 mmol) at 0 °C, under stirring. After 30 min at 0 °C, a saturated aqueous NH_4Cl solution (10 mL) was added, and the organic phase was separated, dried, and evaporated to give a crude compound, which was purified by flash chromatography (hexanes−Et_2O 94:6) to afford pure **4** (1.09 g, 89%): ^1H NMR ($CDCl_3$): δ = 1.52 (9H, s), 4.89 (2H, s), 7.45−7.65 (4H, m), 8.10−8.18 (2H, m). Anal. Calcd for $C_{13}H_{16}O_3S$ (252.3): C 61.88, H 6.39, S 12.71. Found: C 61.76; H 6.40; S 12.68.

(24) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

Aldol Reaction To Give *tert*-Butyl (2*R*,3*S*)-3-(Benzoylamino)-2-hydroxy-3-phenylthiopropionate (7). To a stirred solution of **4** (0.184 g, 0.730 mmol) in Et_2O (3.2 mL) at −25 °C, under argon atmosphere, were added a solution of reagent **5** in CH_2Cl_2 (0.4 M; 3.2 mL, 1.28 mmol) and then Et_3N (0.188 mL, 1.350 mmol) dropwise. Enol borinate was generated with concurrent formation and precipitation of Et_3N−HBr. After 7.0 h at −25 °C, the mixture was cooled to −78 °C, and imine **6** (1.460 mmol, preparation of the imine in ref 15a) was added dropwise. The resulting mixture was stirred at −78 °C for 0.5 h and then slowly warmed to −5 °C during 2 h and stirred at −5 °C overnight. The mixture was then quenched with pH 6 phosphate buffer and extracted several times with CH_2Cl_2. The organic phase was evaporated to give a residue which was dissolved in MeOH:1 N aqueous HCl (1:1 v:v, 24.0 mL) and stirred at rt for 1 h. The resulting solution was evaporated to dryness and pumped (0.1 mmHg). The white solid residue was washed with dry Et_2O (3 × 10 mL), removing the ether phase by centrifugation and decantation. The white solid residue was then dissolved in MeOH (10.0 mL) and pH 8 phosphate buffer (10.0 mL) and stirred at rt for 1 h. The pH was adjusted to 7 with dil (0.1 M) aqueous HCl, the mixture was concentrated in order to remove most of the MeOH, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried and evaporated to give practically pure **7** (0.139 g, 53%). In addition, 19.7 mg (7.5%) of **7** was obtained via flash chromatography (hexanes−acetone 70:30) of the crude mixture contained in the Et_2O phase, used to wash the white solid residue (see above). Total yield = 60.5%. The product was flash chromatographed (pentanes−Et_2O 50:50) to give analytically pure **7**: $[\alpha]^{25}_D = -12.2°$ ($c = 1.69$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 1.45 (9H, s), 3.85 (1H, br, OH), 4.57 (1H, br d), 5.70 (1H, dd, J = 2.5, 8.7), 7.14 (1H, d, J = 8.7), 7.20−7.60 (8H, m), 7.70−7.90 (2H, m); ^{13}C NMR ($CDCl_3$): δ = 29.60, 38.79, 56.42, 79.62, 126.87, 127.02, 127.77, 128.57, 131.61, 138.27, 166.94, 202.16; MS (70 eV, EI): m/z 358 (M + 1), 268, 250, 240, 222, 210, 193, 122, 105, 91, 77. Anal. Calcd for $C_{20}H_{23}NO_3S$ (357.5): C 67.20, H 6.49, N 3.92, S 8.97. Found: C 67.07; H 6.50; N 3.93, S 8.95.

Synthesis of *tert*-Butyl (4*S*,5*R*)-*N*-Benzoyl-2,2-dimethyl-4-phenyl-1,3-oxazolidine-5-thiocarboxylate (8). A solution of compound **7** (not chromatographed, containing ≤4% of the *anti* isomer) (186 mg, 0.5203 mmol) in toluene (5.2 mL) was treated with PPTS (13 mg) and freshly distilled 2-methoxypropene (0.98 mL). The mixture was stirred at rt for 5 min and at 80 °C for 75 min. After dilution with EtOAc (15 mL), the organic phase was washed with aqueous $NaHCO_3$ saturated solution (5 mL) and brine (2 × 5 mL), dried, and evaporated to give a crude mixture. Purification via flash chromatography (hexanes−acetone 90:10) gave pure oxazolidine **8** (186 mg, 90%): $[\alpha]^{25}_D = +39.4°$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 1.52 (9H, s), 1.91 (3H, s), 1.96 (3H, s), 4.50 (1H, d, J = 5.65), 5.20 (1H, d, J = 5.65), 6.90−7.30 (10H, m); ^{13}C NMR ($CDCl_3$): δ = 25.73, 26.27, 29.59, 48.13, 56.37, 87.35, 126.10, 126.66, 127.58, 127.98, 128.23, 128.38, 129.25, 131.57, 137.47, 138.89, 168.00, 198.72; MS (70 eV, EI): m/z 398 (M + 1, 44%), 382, 340, 292, 280 (100%), 250, 210, 162, 146, 105, 91, 77. Anal. Calcd for $C_{23}H_{27}NO_3S$ (397.5): C 69.49, H 6.85, N 3.52, S 8.06. Found: C 69.35; H 6.86; N 3.51, S 8.04.

Phenyl [(*tert*-Butyldimethylsilyl)oxy]thioacetate (9). Methyl glycolate (1.90 mL, 2.20 g, 24.5 mmol) was added to a suspension of TBDMS-Cl (4.43 g, 29.4 mmol) and imidazole (4.17 g, 61.25 mmol) in dry DMF (4.9 mL) at 0 °C, under stirring. After 90 min stirring at rt, water (60 mL) was added, and the resulting mixture was extracted with Et_2O (3 × 35 mL). The organic phases were combined, washed with water (3 × 35 mL), dried, and evaporated to give TBDMS-OCH_2CO_2-Me (5.0 g, 100%): ^{1}H NMR ($CDCl_3$): δ = 0.12 (6H, s), 0.93 (9H, s), 3.75 (3H, s), 4.26 (2H, s). A solution of $AlMe_3$ (2.0 M in hexanes, 12.25 mL, 24.5 mmol) in CH_2Cl_2 (49 mL) was treated at 0 °C with PhSH (2.5 mL, 24.5 mmol). After 20 min at 0 °C, a solution of TBDMS-OCH_2COOMe (2.5 g, 12.25 mmol) in CH_2Cl_2 (6.125 ml) was added at 0 °C. The mixture was stirred at rt for 0.5 h, quenched with NH_4Cl saturated aqueous solution (12 mL), and filtered through Celite, washing the Celite cake with CH_2Cl_2. The organic phase was washed with 5% aqueous NaOH and saturated brine, dried, and evaporated to give a crude mixture which was purified by flash chromatography (hexanes−Et_2O 95:5) to afford pure **9** (2.74 g, 79%): ^{1}H NMR ($CDCl_3$): δ = 0.20 (6H, s), 1.01 (9H, s), 4.38 (2H, s), 7.43 (5H, m). Anal. Calcd for $C_{14}H_{22}O_2SSi$ (282.5): C 59.53, H 7.85, S 11.35. Found: C 59.65; H 7.83; S 11.37.

Aldol Reaction To Give Phenyl (2*S*,3*S*)-3-(Benzoylamino)-2-[(*tert*-butyldimethylsilyl)oxy]-3-phenylthiopropionate (10). To a stirred solution of **9** (1.572 g, 5.56 mmol) in Et_2O (25 mL) at 0 °C, under argon atmosphere, were added a solution of reagent *ent*-**5** in CH_2Cl_2 (0.4 M; 25 mL, 10.0 mmol) and then Et_3N (1.47 mL, 10.56 mmol) dropwise. Enol borinate was generated with concurrent formation and precipitation of Et_3N−HBr. After stirring for 0.5 h at 0 °C and 5 h at +15 °C, the mixture was cooled to −78 °C, and a solution of imine **6** (1.36 g, 7.67 mmol) (for the preparation, see ref 15a) in a minimum volume of CH_2Cl_2 (1 mL), cooled to −78 °C, was added dropwise via cannula. The resulting mixture was stirred at −78 °C for 0.5 h and then slowly warmed to −5 °C during 2 h and stirred at −5 °C overnight. The mixture was then quenched with pH 7 phosphate buffer (23 mL), and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried and evaporated. The crude product was dissolved in MeOH:0.5 N aqueous HCl (1:1 v:v, 40.0 mL). The mixture was diluted with CH_2Cl_2 (3.0 mL), and the resulting solution was stirred at rt for 3 h and then evaporated to dryness under reduced pressure. The resulting crude product was pumped in vacuo (0.1 mmHg) in a desiccator overnight over P_2O_5. The white solid residue (2.35 g, 5.56 mmol) was then dissolved in CH_2Cl_2 (9.26 mL) and treated at 0 °C with DMAP (0.068 g, 0.556 mmol), Et_3N (5.57 mL, 40.0 mmol), and, after further 10 min, with PhCOCl (freshly distilled) (2.26 mL, 19.44 mmol). The mixture was stirred at 0 °C for 30 min and then diluted with EtOAc (72 mL) and quenched at 0 °C with water and ice. The organic phase was washed with saturated $NaHCO_3$ aqueous solution and saturated brine, dried, and evaporated. The crude reaction product was flash chromatographed (hexanes−Et_2O 65:35) to give pure compound **10** (*anti*) + traces of *syn* (71% yield). Chromatography can be used in this case with a low silica gel product ratio (filtration), just to remove the major byproducts [the subsequent reaction can be performed even if the product is not entirely pure (purity ≥80%)]. The *anti*−*syn* ratio of the product was determined by ^{1}H NMR analysis, by integration of the relevant peaks of the *anti* and *syn* isomers (97:3). The 97:3 mixture was flash chromatographed (hexanes−*i*-Pr_2O 50:50) to give pure **10** (*anti*) and *syn* compounds only for analytical purposes.

10 (*anti*): $[\alpha]^{25}_D = -166.6°$ ($c = 1.29$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = −0.05 (3H, s), 0.20 (3H, s), 1.02 (9H, s), 4.78 (1H, d, J = 5.5), 5.52 (1H, dd, J = 5.5, 7.8), 6.89 (1H, d, J = 7.8), 7.10−7.60 (13H, m), 7.70−7.90 (2H, m); ^{13}C NMR ($CDCl_3$): selected peaks δ = 25.74, 38.69, 57.53, 80.17, 126.92, 128.18, 128.28, 128.43, 128.53, 129.03, 129.29, 131.62, 134.65, 137.23, 166.53, 200.83. Anal. Calcd for $C_{28}H_{33}NO_3SSi$ (491.7): C 68.39, H 6.76, N 2.85, S 6.00. Found: C 68.53; H 6.75; N 2.86, S 5.99.

Phenyl (2*S*,3*R*)-3-(benzoylamino)-2-[(*tert*-butyldimethylsilyl)oxy]-3-phenylthiopropionate (*syn*): $[\alpha]^{25}_D = -29.4°$ ($c = 1.98$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = −0.21 (3H, s), 0.14 (3H, s), 1.00 (9H, s), 4.60 (1H, d, J = 2.4), 5.62 (1H, dd, J = 2.4, 8.8), 7.20−7.60 (13H, m), 7.80−8.00 (2H, m); ^{13}C NMR ($CDCl_3$): selected peaks δ = 56.52, 81.03, 166.23.

Synthesis of Phenyl (2*S*,3*S*)-3-(Benzoylamino)-2-hydroxy-3-phenylthiopropionate (11). In a round bottom Pyrex-glass flask the mixture containing **10** (*anti*) + traces of *syn* (97:3) (1.92 g, 3.91 mmol) was treated with a 0.5 M solution of HF in CH_3CN−H_2O (66:1) (62.51 mL), at 0 °C, under stirring. The mixture was stirred at rt for 24 h. The solvent was removed under reduced pressure, and the resulting crude product was pumped *in vacuo* (0.1 mmHg) in a desiccator overnight over P_2O_5. The crude product **11** (*anti*) + traces of *syn* (97:3) was washed with Et_2O to give a white amorphous solid (1.52 g, 103.4%; the crude compound contains impurities from the glass-HF: yields are typically >100%) and used without purification for the subsequent reaction. The 97:3

mixture was flash chromatographed (*i*-Pr_2O−EtOAc 95:5) to give pure **11** (*anti*) and *syn* compounds only for analytical purposes.

11 (*anti*): $[\alpha]^{25}_D = -140.23°$ ($c = 0.8$ in acetone); ^{1}H NMR (CD_3COCD_3): $\delta = 4.90$ (1H, dd, $J = 5.6, 6.3$), 5.65 (1H, dd, $J = 5.6, 8.6$), 5.94 (1H, d, $J = 6.3$), 7.10−7.70 (13H, m), 7.80−7.90 (2H, m), 8.05 (1H, d, $J = 8.6$); ^{13}C NMR (CD_3COCD_3): selected peaks $\delta = 56.53, 79.10, 127.41, 127.61, 128.00, 128.28, 128.90, 129.32, 131.30, 134.69, 138.15, 139.89, 166.24, 200.39$; MS (70 eV, EI): m/z 378 ($M + 1$, 57%), 360, 268, 240, 222, 210, 193, 105 (100%), 91, 77. Anal. Calcd for $C_{22}H_{19}NO_3S$ (377.5): C 70.01, H 5.07, N 3.71, S 8.49. Found: C 69.87; H 5.06; N 3.72, S 8.47.

Phenyl (2*S*,3*R*)-3-(benzoylamino)-2-hydroxy-3-phenylthiopropionate (*syn*): $[\alpha]^{25}_D = -67.0°$ ($c = 1.04$ in acetone); ^{1}H NMR (CD_3COCD_3): $\delta = 4.80$ (1H, d, $J = 3.4$), 5.70 (1H, dd, $J = 3.4, 8.2$), 7.120−7.60 (13H, m), 7.90−8.01 (2H, m); ^{13}C NMR (CD_3COCD_3): selected peaks $\delta = 56.28, 79.92$.

Synthesis of Phenyl (4*S*,5*R*)-2,4-Diphenyl-4,5-dihydrooxazole-5-thiocarboxylate (12). A solution of **11** (*anti*) + traces of *syn* (97:3, crude, without chromatography) (1.520 g, 3.89 mmol) in $CHCl_3$ (40.20 mL) was treated with $SOCl_2$ (1.47 mL, 20.13 mmol) and stirred at 45 °C for 3−4 h. The solvent was removed *in vacuo*, and the crude product was pumped (0.1 mmHg) and then dissolved in 1,2-dichloroethane (20 mL) in the presence of 3 Å molecular sieves. The resulting mixture was refluxed (100 °C) for 5 h. The solution was then filtered, dried, and evaporated to give a crude product, which was purified by flash chromatography (CH_2Cl_2:hexanes 88:12). The compound tends to trap CH_2Cl_2, giving rise to a viscous oil. Pure **12** was obtained as a white/pale-yellow amorphous solid by treating the oil with hexane:Et_2O (99:1 v:v) and collecting the product by filtration (0.909 g, 65% yield): $[\alpha]^{25}_D = +91.28°$ ($c = 0.8$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 5.06$ (1H, d, $J = 5.61$), 5.55 (1H, d, $J = 5.61$), 7.20−7.60 (13H, m), 8.10−8.30 (2H, m); ^{13}C NMR ($CDCl_3$): selected peaks $\delta = 75.48, 89.10, 126.41, 128.01, 128.60, 128.86, 129.31, 129.72, 132.15, 134.65$; MS (70 eV, EI): m/z 360 ($M + 1$, 57%), 250, 222, 193, 119, 109, 91 (100%), 77, 65. Anal. Calcd for $C_{22}H_{17}NO_2S$ (359.4): C 73.51, H 4.77, N 3.90, S 8.92. Found: C 73.36; H 4.76; N 3.91, S 8.90.

***tert*-Butyl [(*tert*-Butyldimethylsilyl)oxy]thioacetate (14).** Methyl glycolate (0.776 mL, 0.905 g, 10.0 mmol) was added to a suspension of TBDMS-Cl (1.81 g, 12.0 mmol) and imidazole (1.7 g, 25.0 mmol) in dry DMF (2.0 mL) at 0 °C, under stirring. After 90 min stirring at rt, water (25 mL) was added, and the resulting mixture was extracted with Et_2O (3 × 15 mL). The organic phases were combined, washed with water (3 × 15 mL), dried, and evaporated to give methyl [(*tert*-butylmethylsilyl)oxy]acetate (TBDMSOCH$_2$CO$_2$Me, 2.0 g, 100%): ^{1}H NMR ($CDCl_3$): $\delta = 0.12$ (6H, s), 0.93 (9H, s), 3.75 (3H, s), 4.26 (2H, s). A solution of $AlMe_3$ (2.0 M in hexanes, 8.82 mL, 17.64 mmol) in CH_2Cl_2 (35.28 mL) was treated at 0 °C with *t*-BuSH (1.99 mL, 17.64 mmol). After 20 min at 0 °C, a solution of methyl [(*tert*-butyldimethylsilyl)oxy]acetate (1.8 g, 8.82 mmol) in CH_2Cl_2 (4.41 mL) was added at −20 °C. The mixture was stirred at −20 °C for 2 h and then diluted with Et_2O and quenched with 1.0 N aqueous HCl (10 mL). The organic phase was washed with 5% aqueous NaOH and saturated brine, dried, and evaporated to give a crude mixture which was purified by flash chromatography (hexanes−CH_2Cl_2 80:20) to afford pure **14** (1.81 g, 78%): ^{1}H NMR ($CDCl_3$): $\delta = 0.10$ (6H, s), 0.94 (9H, s), 1.47 (9H, s), 4.16 (2H, s). Anal. Calcd for $C_{12}H_{26}O_2SSi$ (262.5): C 54.91, H 9.98, S 12.21. Found: C 55.02; H 9.96; S 12.19.

Aldol Reaction To Give *tert*-Butyl (2*R*,3*S*)-3-[(*tert*-Butoxycarbonyl)amino]-2-[(*tert*-butyldimethylsilyl)oxy]-3-phenylthiopropionate (15). To a stirred solution of **14** (0.701 g, 2.67 mmol) in Et_2O (12.0 mL) at 0 °C, under argon atmosphere, were added a solution of boron reagent **5** in CH_2Cl_2 (0.4 M; 12.0 ml, 4.8 mmol) and then Et_3N (0.706 mL, 5.07 mmol) dropwise. Enol borinate was generated with concurrent formation and precipitation of Et_3N−HBr. After 5 h at rt, the mixture was cooled to −78 °C, and imine **6** (0.710 g, 4.0 mmol) was added dropwise. The resulting mixture was stirred at −78 °C for 0.5 h and then slowly warmed to −5 °C during 2 h and stirred at −5 °C overnight. The mixture was then quenched with pH 7 phosphate buffer (12 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried and evaporated. The crude product was dissolved in MeOH: 0.5 N aqueous HCl (1:1 v:v, 24.0 mL) and stirred at rt for 3 h. The resulting solution was evaporated to dryness and pumped in vacuo (0.1 mmHg) in a desiccator overnight over P_2O_5. The solid residue (1.074 g, 2.66 mmol) was then dissolved in CH_2Cl_2 (4.44 mL) and treated at 0 °C with Et_3N (1.48 mL, 10.64 mmol) and, after further 10 min, with Boc_2O (1.32 g, 6.03 mmol). The mixture was stirred at rt for 4 h and then quenched with NH_4Cl and extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was washed with saturated brine, dried, and evaporated. The crude reaction product was flash chromatographed (hexanes−Et_2O 8:2) to give *tert*-butyl 3-[(*tert*-butoxycarbonyl)amino]-2-[(*tert*-butyldimethylsilyl)oxy]-3-phenylthiopropionate (0.818 mg, 66% yield). The *syn*−*anti* ratio of the mixture was determined by ^{1}H NMR analysis, by integration of the relevant peaks of the *syn* and *anti* isomers (70:30).

15 (*syn*, 70% of the mixture): ^{1}H NMR ($CDCl_3$): $\delta = -0.47$ (3H, s), −0.1 (3H, s), 0.85 (9H, s), 1.43 (9H, s), 1.54 (9H, s), 4.22 (1H, br s), 5.14 (1H, d, $J = 9.0$), 5.59 (1H, d, $J = 9.0$), 7.19−7.33 (5H, m).

tert-Butyl (2*R*,3*R*)-3-[(*tert*-Butoxycarbonyl)amino]-2-[(*tert*-butyldimethylsilyl)oxy]-3-phenylthiopropionate (*anti*, 30% of the mixture): ^{1}H NMR ($CDCl_3$): selected peaks $\delta = -0.03$ (3H, s), 0.06 (3H, s), 0.94 (9H, s), 4.35 (1H, d, $J = 4.6$), 4.95 (1H, m).

Synthesis of *tert*-Butyl (2*R*,3*S*)-3-[(*tert*-Butoxycarbonyl)amino]-2-hydroxy-3-phenylthiopropionate (16). A solution of *tert*-butyl 3-[(*tert*-butoxycarbonyl)amino]-2-[(*tert*-butyldimethylsilyl)oxy]-3-phenylthiopropionate (*syn:anti* 70:30) (0.460 g, 0.985 mmol) in pyridine (49.8 mL) and CH_3CN (24.9 mL), under argon atmosphere, was treated with a solution of Py (30%)−HF (70%) (Aldrich reagent) (11.7 mL) at rt. The mixture was warmed at 50 °C and stirred for 5 h. The solution was diluted with H_2O and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with $NaHCO_3$ (3 × 25 mL) to reach pH 7, dried, and evaporated. The mixture (*syn:anti* 70:30) was flash chromatographed (hexanes:Et_2O 65:35) to give the analytically pure **16** (*syn*) (0.170 mg) and *anti* (0.073 mg) diastereoisomers (yield 70%).

16 (*syn*): $[\alpha]^{25}_D = -8.7°$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 1.44$ (9H, s), 1.56 (9H, s), 3.56 (1H, br s), 4.43 (1H, br s), 5.21 (1H, d, $J = 8.33$), 5.43 (1H, d, $J = 8.33$), 7.25−7.46 (5H, m); ^{13}C NMR ($CDCl_3$): selected peaks $\delta = 28.20, 29.66, 57.18, 79.88, 126.704, 127.440, 128.390, 139.154, 155.23, 201.97$. Anal. Calcd for $C_{18}H_{27}NO_4S$ (353.5): C 61.16, H 7.70, N 3.96, S 9.07. Found: C 61.28; H 7.68; N 3.95, S 9.09.

tert-Butyl (2*R*,3*R*)-3-[(*tert*-butoxycarbonyl)amino]-2-hydroxy-3-phenylthiopropionate (*anti*): ^{1}H NMR ($CDCl_3$): $\delta = 1.42$ (9H, s), 1.44 (9H, s), 3.26 (1H, d, $J = 7.55$), 4.57 (1H, dd, $J = 3.2, 7.55$), 5.15 (1H, dd, $J = 3.2, 8.0$), 5.55 (1H, d, $J = 8.0$), 7.20−7.40 (5H, m); ^{13}C NMR ($CDCl_3$): selected peaks $\delta = 28.23, 29.6, 48.7, 79.29, 79.89, 155.07, 200.48$.

Synthesis of *tert*-Butyl (4*S*,5*R*)-*N*-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-phenyl-1,3-oxazolidine-5-thiocarboxylate (17). A solution of **16** (0.060 g, 0.17 mmol) in toluene (8.0 mL) was treated with PPTS (2.14 mg) and freshly distilled 2-methoxypropene (0.384 mL). The mixture was stirred at rt for 5 min, and at 80 °C for 4 h. After dilution with EtOAc (8 mL), the organic phase was washed with aqueous $NaHCO_3$ saturated solution (3 mL) and brine (2 × 3 mL), dried, and evaporated to give a crude mixture. Purification via flash chromatography (hexanes−Et_2O 95:5) gave pure **17** (42.5 mg, 65.6%): $[\alpha]^{25}_D = -7.8°$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 50 °C): $\delta = 1.19$ (9H, s), 1.51 (9H, s), 1.73 (3H, s), 1.79 (3H, s), 4.37 (1H, d, $J = 5.0$), 5.0 (1H, d, $J = 5.0$), 7.2−7.4 (5H, m); ^{13}C NMR ($CDCl_3$): selected peaks $\delta = 26.147, 26.601, 27.918, 29.600, 47.764, 63.934, 87.156, 126.137, 127.361, 128.393, 151.472, 199.685$; IR ($CHCl_3$): selected peaks $\nu = 1702.84$ cm^{-1} (C═O, *t*-BuSCO), 1672.00 cm^{-1} [C═O, *t*-BuO(CO)N]. Anal. Calcd for $C_{21}H_{31}NO_4S$ (393.5): C 64.09, H 7.94, N 3.56, S 8.15. Found: C 63.96; H 7.96; N 3.57, S 8.17.

Synthesis of 7-(Triethylsilyl)-13-*O*-[[(4*S*,5*R*)-2,4-diphenyl-4,5-dihydrooxazol-5-yl]carbonyl]baccatin (18b). A solution of 7-TES-baccatin III (**2b**, for preparation see ref 7a) (199 mg, 0.284 mmol) and compound **12** (357 mg, 0.994 mmol) in THF (5.68 mL) at 0 °C under argon, with stirring, was treated with a freshly prepared 0.6 M solution of LHMDS in THF−hexanes 62:38 (2.13 mL, 1.28 mmol). After 15 min stirring at 0 °C, the mixture was quenched with a saturated NH_4Cl aqueous solution (14 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL), and the combined organic extracts were dried and evaporated. The crude product was purified by flash chromatography (pentanes−Et_2O 44:56) to give pure **18b** (R_f = 0.275) (241 mg, 89%): $[\alpha]^{25}_D = -54.8°$ (c = 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 0.60 (6H, q, J = 7.29), 0.94 (9H, t, J = 7.29), 1.21 (3H, s), 1.25 (3H, s), 1.71 (3H, s), 2.01 (3H, s), 2.08 (3H, s), 2.18 (3H, s), 1.95−2.2 (1H, m), 2.22−2.45 (2H, m), 2.55 (1H, m), 3.85 (1H, d, J = 6.99), 4.15 (1H, d, J = 8.34), 4.31 (1H, d, J = 8.34), 4.51 (1H, dd, J = 6.59, 10.29), 4.96 (1H, d, J = 6.51), 4.96 (1H, d), 5.62 (1H, d, J = 6.51), 5.70 (1H, d, J = 6.99), 6.21 (1H, br t, J = 8.80), 6.44 (1H, s), 7.30−7.70 (11H, m), 8.09 (2H, d, J = 7.24), 8.25 (2H, d, J = 7.79); ^{13}C NMR ($CDCl_3$): selected peaks δ = 5.17, 6.66, 9.93, 14.43, 20.74, 21.60, 26.45, 29.58, 35.48, 37.05, 43.07, 46.90, 58.34, 71.79, 72.19, 74.67, 74.87, 78.90, 80.77, 83.24, 84.10, 126.31, 126.60, 128.17, 128.51, 128.88, 129.97, 132.05, 133.64, 133.93, 139.75, 140.68, 166.91, 169.05, 169.77, 170.09, 201.60; MS (FAB$^+$): m/z 950 (M + H$^+$, 71%), 951 (M + 2, 43%), 952 (M + 3, 21%), 972 (M + Na$^+$, 100%), 973 (M + 24, 64%), 974 (M + 25, 28%). Anal. Calcd for $C_{53}H_{63}NO_{13}Si$ (949.4): C 66.99, H 6.69, N 1.47. Found: C 67.12; H 6.68; N 1.47.

The enantiomeric excess of **12** (≥95%) was also confirmed by isolating the "wrong" Taxol derivative **7-(triethylsilyl)-13-*O*-[[(4*R*,5*S*)-2,4-diphenyl-4,5-dihydrooxazol-5-yl]carbonyl]baccatin** (5.4 mg, 2%) via flash cromatography (pentane: Et_2O 44:56) (R_f = 0.35): ^{1}H NMR ($CDCl_3$): δ = 0.60 (6H, q, J = 8.0), 0.94 (9H, t, J = 8.0), 1.25 (3H, s), 1.27 (3H, s), 1.70 (3H, s), 1.97 (3H, s), 2.17 (3H, s), 2.22 (3H, s), 1.75−1.95 (1H, m), 2.24−2.40 (2H, m), 2.55 (1H, m), 3.85 (1H, d, J = 7.03), 4.16 (1H, d, J = 8.21), 4.30 (1H, d, J = 8.21), 4.51 (1H, dd, J = 6.46, 10.41), 4.91 (1H, d, J = 8.5), 4.98 (1H, d, J = 6.4), 5.57 (1H, d, J = 6.4), 5.70 (1H, d, J = 7.03), 6.27 (1H, m), 6.47 (1H, s), 7.30−7.70 (11H, m), 8.16 (4H, m).

Paclitaxel (1a). A solution of **18b** (360 mg, 0.378 mmol) in 0.04 N HCl in MeOH:water [1.5:1 (v:v)] (40 mL) was stirred at 60 °C for 1 h and at 80 °C for 2.5 h. The mixture was cooled to rt, and a saturated $NaHCO_3$ aqueous solution (8 mL) was added (final pH = 7.5). The resulting mixture was stirred at rt for 16 h. MeOH (ca. 24 mL) was evaporated under vacuum (0.1 mmHg) at rt; the resulting aqueous mixture was then extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were dried and evaporated. The crude product was flash chromatographed (hexanes:EtOAc 1:1) to give pure Paclitaxel (**1a**) (259 mg, 80%). ^{1}H NMR ($CDCl_3$): δ = 1.14 (3H, s), 1.25 (3H, s), 1.68 (3H, s), 1.79 (3H, s), 2.23 (3H, s), 2.38 (3H, se), 2.35−2.40 (2H, m), 2.40−2.60 (2H, m), 3.67 (1H, br s), 3.79 (1H, d, J = 6.96), 4.26 (1H, A part of an AB system, J = 8.42), 4.34 (1H, B part of an AB system, J = 8.42), 4.13−4.40 (1H, m), 4.79 (1H, br s), 4.94 (1H, dd, J = 7.98, 1.5), 5.67 (1H, d, J = 6.96), 5.78 (1H, dd, J = 8.89, 2.45), 6.23 (1H, br t, J = 9.0), 6.27 (1H, s), 7.03 (1H, d, J = 8.89), 7.30−7.60 (11H, m), 7.74 (2H, d, J= 7.0), 8.13 (2H, d, J = 7.0). Anal. Calcd for $C_{47}H_{51}NO_{14}$ (853.3): C 66.09, H 6.02, N 1.64. Found: C 65.96; H 6.03; N 1.64.

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Supporting Information Available: Experimental procedure and spectroscopic characterization for boron reagents **5** and *ent*-**5**; determination of the *syn*−*anti* ratios, absolute configurations, and enantiomeric excesses for compounds **7**, **11**, and **16**; experimental procedures and spectroscopic characterization for compounds **13** and the aldol reactions described in Scheme 5; experimental procedures and spectroscopic characterization for compounds **18c**, **19b**, **19c**, **20c** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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