An Efficient Synthesis of the Taxane-Derived Anticancer Agent ABT-271

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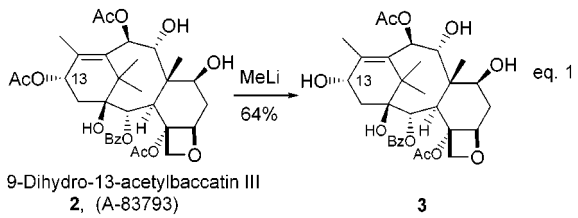
ABT-271, **1**, has been identified as a promising anticancer agent. ABT-271 is a novel taxane possessing a C9-(*R*)-hydroxyl group as opposed to a C9-ketone which is present in Taxol and Taxotere. To further evaluate ABT-271 as a potential anticancer agent, an efficient synthesis was developed which allows the large scale synthesis of ABT-271. Ketalization of the 7,9-diol of 9-DHAB-III, **2**, allows selective removal of the C13-acetate with phenyllithium. The resulting C13-hydroxyl group is then acylated using LiHMDS and *β*-lactam **22** to give ABT-271 in protected form. The protecting groups were removed first by acidic hydrolysis followed by basic hydrolysis to provide ABT-271. Application of this synthetic sequence provided over 600 g of ABT-271, **1**.

Introduction

Taxol (paclitaxel) and Taxotere (docetaxel) are two promising antitumor agents undergoing clinical trials for the treatment of a variety of cancers.[1] Taxol has been approved for the treatment of ovarian, breast, and lung cancer and in 1998 it had sales of $1.2 billion.[2] Although Taxol is currently the agent of choice for the treatment of these tumors, it suffers from low water solubility which causes problems for the formulation and the administration of the drug.[3] Taxol analogues with greater water solubility, better tolerability, and less prone to resistance would be of significant benefit for the treatment of solid tumors.

In 1992 a new taxane, 13-acetyl-9(*R*)-dihydrobaccatin III (9-DHAB-III, A-83793), **2**, was isolated from the Canadian bush *Taxus canadensis*.[4] The significant difference between this taxane and the previously isolated taxanes is at the C-9 position. The previously isolated taxanes possess a carbonyl at C-9 whereas the newly isolated taxane possesses an α-hydroxyl group at C-9. This novel baccatin compound provides a new template for the preparation of analogues with potentially greater therapeutic benefits. One such compound under study is ABT-271, **1**.[5] In our effort to further explore the biological properties of **1** we required an efficient synthesis which would allow the production of multigram quantities.

The plan for the synthesis was to begin with the commercially available 9-DHAB-III, **2**.[6] The overall required transformations were the removal of the C-10 and C-13 acetates and selective acylation of the C-13 hydroxyl with the desired side chain. These chemical transformations are not straightforward and require the development of an efficient strategy. Initial efforts followed the route published by Klein et al. attempting to selectively remove the C-13 acetate of **2**.[7]



9-Dihydro-13-acetylbaccatin III
2, (A-83793) **3**

Results and Discussion

Methyllithium was identified as the reagent which gave the highest yield and selectivity, 64% yield for **3** after chromatography (eq 1).[7] Invariably these optimized conditions were accompanied by C-10 deacylated byproducts. Of particular concern was the observation that these

(1) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem.* **1994**, *106*, 38−67; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15−44.

(2) (a) *Future Oncol.* **1999**, *5*, 1025−1039. (b) *Future Oncol.* **1997**, *4*, 614−620.

(3) (a) Weiss, R. B.; Donehower, R. C.; Wiernik, P. H.; Ohnuma, T.; Gralla, R. J.; Trump, D. L.; Baker, J. R.; Van Echo, D. A.; Von Hoff, D. D.; Leyland-Jones, B. *J. Clin. Oncol.* **1990**, *8*, 1263−1268. (b) Woodcock, D. M.; Jefferson, S.; Linsenmeyer, M. E.; Crowther, P. J.; Chojniowski, G. M.; Williams, B.; Bertoncello, I. *Cancer Res.* **1990**, *50*, 4199−4203. (c) *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I., Chen, T. C., Ojima, I., Vyas, D. M., Eds.; ACS Symposium Series No. 583; American Chemical Society: Washington, DC, 1995.

(4) (a) Gunawardana, G. P.; Premachandran, U.; Burres, N. S.; Whittern, D. N.; Henry, R.; Spanton, S.; McAlpine, J. B. *J. Nat. Prod.* **1992**, *55*, 1686−1689. (b) Zamir, L. O.; Nedea, M. E.; Belair, S.; Sauriol, F.; Mamer, O.; Jacqmain, E.; Jean, F. I.; Garneau, F. X. *Tetrahedron Lett.* **1992**, *33*, 5173−5176. (c) Zhang, S.; Chen, W. M.; Chen, Y. H. *Acta Pharm. Sinica* **1992**, *27*, 268−272.

(5) Gunawardana, G. P.; Klein, L. L.; McAlpine, J. B. US Patent 5,530,020, 1996; Gunawardana, G. P.; Klein, L. L.; McAlpine, J. B. US Patent 5,352,806, 1994.

(6) Suppliers of 9-DHAB-III, **2**, Atlantic Biochemical Research, Box 250, 1540 Plains Road, Building #397, Debert, N. S. Canada B0M 1G0; L. D. Pharmaceutical, 277 Restigouche Road, Oromocto, N. B. Canada, E2V 2H1.

(7) (a) Klein, L. L.; Li, L.; Maring, C. J.; Yeung, C. M.; Thomas, S. A.; Grampovnik, D. J.; Plattner, J. J. *J. Med. Chem.* **1995**, *38*, 1482−1492. (b) Klein, L. L.; Yeung, C. M.; Li, L.; Plattner, J. J. *Tetrahedron Lett.* **1994**, *35*, 4707−4710. (c) Klein, L. L. *Tetrahedron Lett.* **1993**, *34*, 2047−2050.

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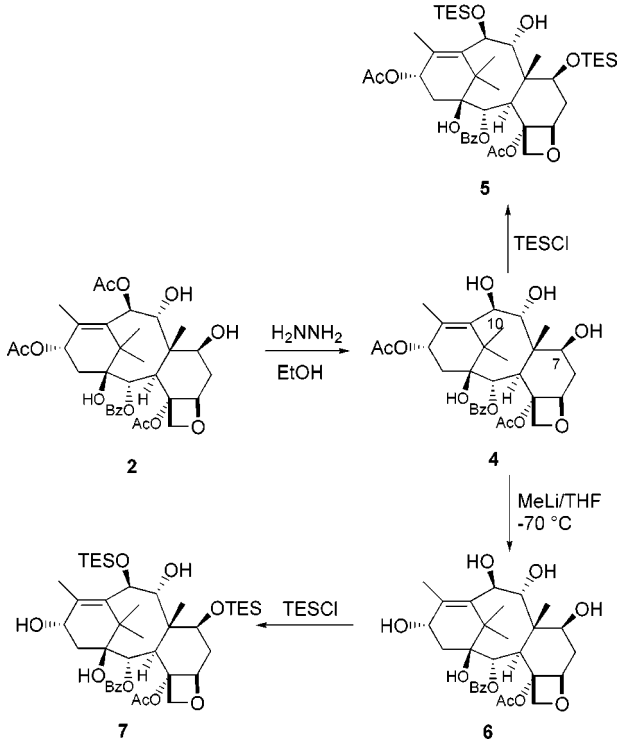
Scheme 1



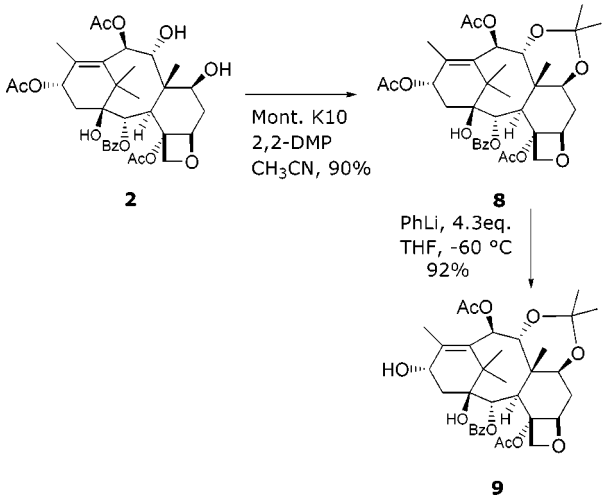
byproducts increased with elongated addition times of the methyllithium which would present a problem on scale-up. The addition of Lewis acids, variation of the solvent, and lowering the reaction temperature to −100 °C did not provide any significant benefit. Efforts to increase the efficiency of this conversion required the exploration of alternative protecting group strategies for the baccatin core.

The C-10 acetate of **2** could selectively be removed with hydrazine in ethanol giving **4** in a 76% yield after crystallization (Scheme 1). The C-7 and C-10 hydroxyl groups of **4** were selectively protected as their TES ethers, but unfortunately, the bis-TES ether **5** was not stable to the basic conditions necessary for the removal of the acetate at C-13. Alternatively, the C-13 acetate of **4** was removed with MeLi (10 equiv) to give **6** in 75% yield. However, due to difficulties in efficient purification of **6** and poor solubility characteristics of **7** our efforts turned to a more robust approach (Scheme 2).

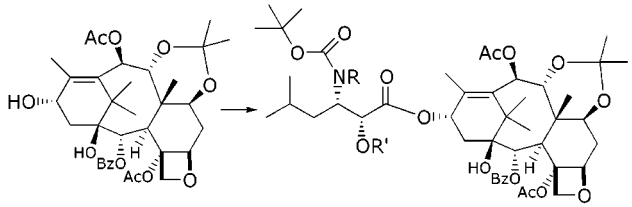
Protection of **2** as the 7,9-acetonide prevents the acidic protons of the C-7 and C-9 hydroxyl groups from reacting with the basic reagents being examined for the selective deacylation of C-13 (Scheme 2). Several conditions proved successful for the formation of the 7,9-acetonide **8**, but conditions employing Montmorillonite K10 and 2,2-dimethoxypropane in CH_3CN gave the highest yielding and most direct procedure.[8] The crude product is isolated by filtration to remove the Montmorillonite K10 and concentration of the filtrate. The acetonide **8** proved to be crystalline, allowing its isolation and purification if necessary, but it is typically used crude in the next step. The 7,9-acetonide **8** was then examined for selectivity in the deacylation at C-13.

(8) The acidity of the Montmorillonite K10 varied from lot to lot. For efficient acetonide formation, the pH of an aqueous suspension of the Montmorillonite K10 should be between pH 3 and pH 3.5. When the pH is above pH 3.5 the reaction is sluggish and does not go to completion.

Scheme 2



On the basis of our results with the previously studied substrates, our efforts focused on carbon nucleophiles for C-13 deacylation of the 7,9-acetonide **8**. From an extensive study of organometallic reagents, the C-13 deacylation is optimally carried out by reacting acetonide **8** with 4.3 equiv of PhLi in THF at −60 °C, affording carbinol **9** in 92% yield. Presumably, the steric bulk of the phenyllithium matched with the steric bulk of the 7,9-acetonide results in enhanced selectivity for the C-13 acetate. It is noteworthy that this combination yielded a reaction that was tolerant of elongated addition times and extended stir periods encountered upon scale-up. In addition to the increased yield, the product of deacylation is readily crystallized, allowing the removal of the phenyl containing byproducts of the reaction.[9] Interestingly, phenyllithium gave only a 50% yield for selective deacylation at C-13 for compound **2**. With the selective removal of the C-13 acetate the baccatin core is poised for coupling with an appropriately protected side chain precursor (eq 2).

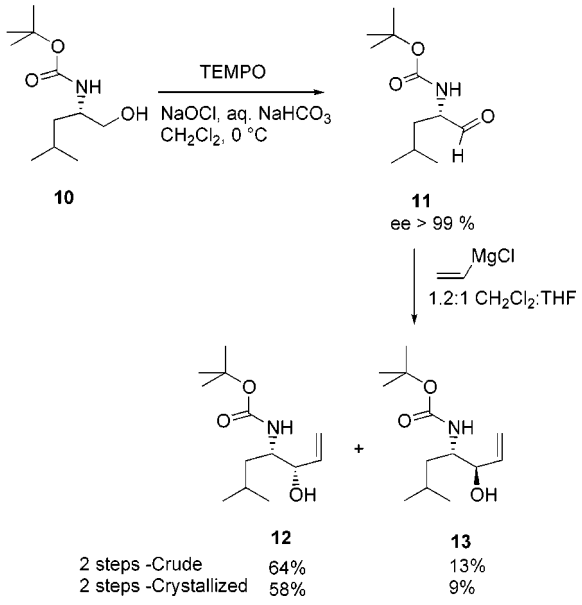


An efficient synthesis of the requisite isobutyl isoserine side chain was achieved by taking advantage of the similar structure found in *N*-Boc-L-leucinol **10**.[10] *N*-Boc-L-Leucinal **11** was prepared via a TEMPO-mediated oxidation of *N*-Boc-L-leucinol **10** (Scheme 3). The TEMPO oxidation avoids the unpleasant coproduction of dimethyl sulfide in the Swern oxidation and the requirement of

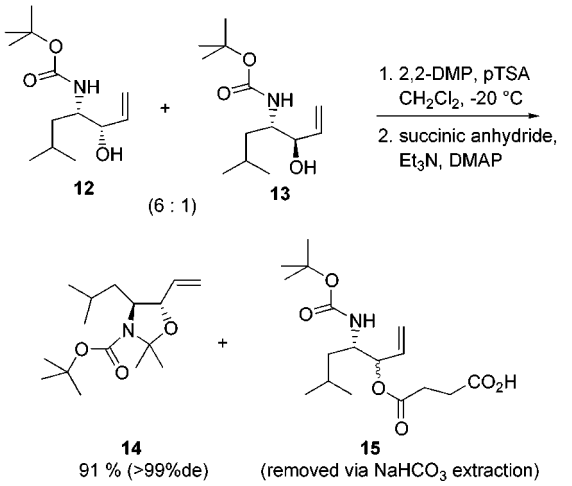
(9) (a) Investigation of other organometallics, reducing agents, amide bases, alkoxide bases, and hydroxide proved to be less selective and lower yielding. (b) The reaction will tolerate up to 90 mol % water with the only consequence that more phenyllithium is required to drive the reaction to completion. (c) The reaction may be run as warm as −40 °C without consequence.

(10) Leanna, M. R.; DeMattei, J. A.; Li, W.; Nichols, P. J.; Rasmussen, M.; Morton, H. E. *Org. Lett.* **2000**, *2*, 3627−3630.

Scheme 3



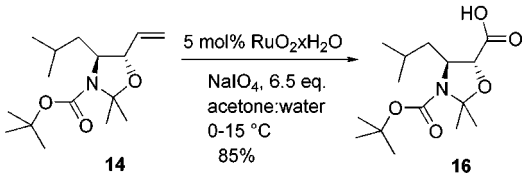
Scheme 4



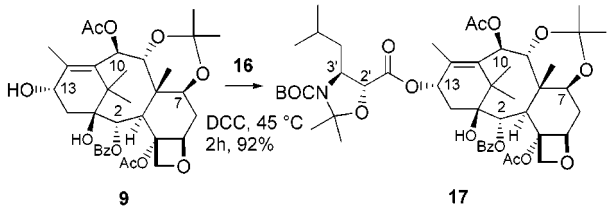
cryogenic conditions. Furthermore, it affords the aldehyde in superior chemical yield and stereochemical purity.[11] After an aqueous workup, the CH_2Cl_2 solution of the aldehyde **11** was added to 3.5 equiv of vinylmagnesium chloride in THF at 10 °C. The product was isolated by crystallization giving the desired *syn*-amino alcohol **12** in 56% yield (from **10**) contaminated with 9% of the epimeric *anti*-alcohol **13** (from **10**).[12]

Removal of the undesired C-2 epimer **13** was accomplished via a kinetically controlled ketalization (Scheme 4). The syn diasteromer **12** readily cyclizes in CH_2Cl_2 at −20 °C with cat. pTSA to form the desired *trans*-oxazolidine **14**, whereas the anti-diastereomer **13** proceeds to the sterically congested *cis*-oxazolidine very slowly. The reaction was quenched by addition of triethylamine and succinic anhydride to form the succinate

Scheme 5



Scheme 6



esters of the unreacted alcohols (∼1.8:1 anti/syn). The reaction mixture was then washed with aqueous $NaHCO_3$ to remove the undesired succinate esters **15**. The desired oxazolidine **14** is isolated as an oil in 91% yield (based on the amount of **12** in the starting material mixture) and 99% purity.[13]

The vinyl oxazolidine **14** was oxidized to the corresponding carboxylic acid with catalytic RuO_2 and $NaIO_4$ as the oxidant in a 1:1 ratio of acetone:water using modified Sharpless conditions (Scheme 5).[14] The active catalyst, RuO_4, is generated by mixing $RuO_2 \cdot xH_2O$ (7 mol %) and $NaIO_4$ (33 mol %) prior to adding the acetone/olefin mixture to minimize an exotherm that occurrs in this oxidation. Control of this exotherm was necessary for the reaction to be safely conducted on large scale. An aqueous solution of the oxidant (6.2 equiv of $NaIO_4$) was then added to the olefin and catalyst over 3 h at 15 °C. Following an alcohol quench, an extractive base/acid purification gave the desired acid **16** in 85% yield with 98% purity.[15]

Following the approach of Commercon et al., the oxazolidine acid **16** was coupled to the baccatin core **9** with DCC and DMAP in EtOAc at 45 °C in 2 h to provide the coupled product **17** in 92% yield after chromatography (Scheme 6).[16] Interestingly this acylation is faster, and it is conducted at a lower temperature than other couplings with baccatin III that have been reported in the literature.[16,17] Unfortunately, attempts to remove the 2′,3′-*N*,*O*-acetal resulted in competitive decomposition of the baccatin core as well as hydrolysis of the *N*-*tert*-butyl carbamate. Because of the difficulty in removing the *N*,*O*-ketal a more labile 2′ protecting group was necessary.

The Holton/Ojima *β*-lactam coupling method allows a direct method of coupling and obviates the need for additional protecting groups.[18] The requisite *β*-lactam

(11) Leanna, M. R.; Sowin, T. J.; Morton, H. E. *Tetrahedron Lett.* **1992**, *33*, 5029−5032. The aldehyde **11** was reduced to the primary alcohol with LAH and acylated with DNBCl. The DNB ester was analyzed by chiral HPLC, >95% ee (see Supporting Information).

(12) By conducting the reaction in CH_2Cl_2, the crude ratio of **12:13** (prior to crystallization) is lowered to 3:1 as opposed to 4.5:1 for 1.2:1 CH_2Cl_2:THF. When the reaction temperature was lowered to −10 °C for the 1.2:1 CH_2Cl_2:THF conditions, the crude ratio of **12:13** was lowered to 2.8:1.

(13) Purity determined by HPLC analysis relative to a pure standard.

(14) (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (b) Weber, A. E.; Halgren, T. A.; Doyle, J. J.; Lynch, R. J.; Siegl, P. K. S.; Parsons, W. H.; Greenlee, W. J.; Patchett, A. A. *J. Med. Chem.* **1991**, *34*, 2692−2701.

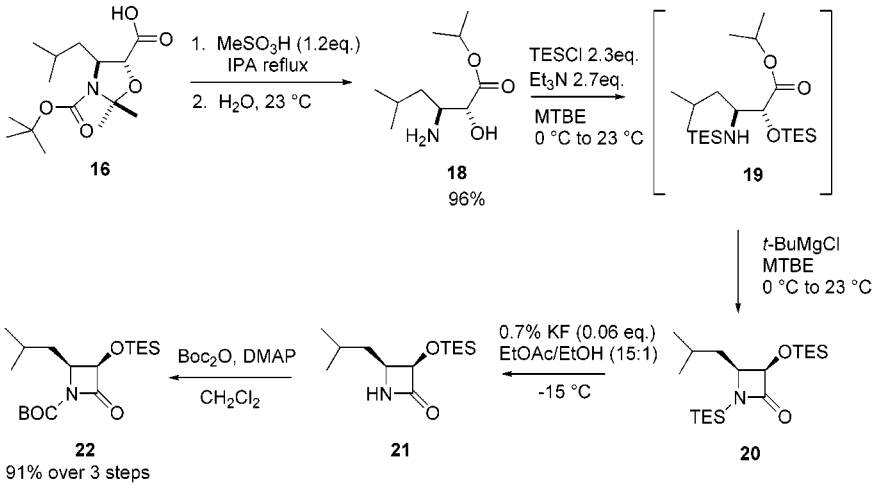
(15) The acid **16** could be further purified by preparation of the dicyclohexylamine (DCHA) salt in acetonitrile.

(16) Commercon, A.; Bezard, D.; Bernard, F.; Bourzat, J. D. *Tetrahedron Lett.* **1992**, *33*, 5185−5188.

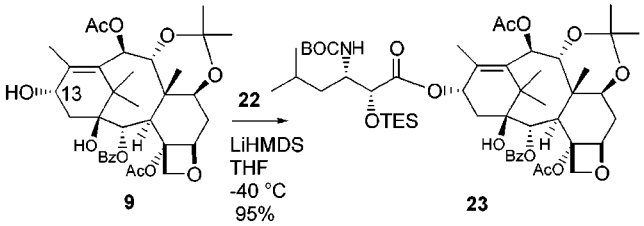
(17) Denis, J.-N.; Greene, A. E.; Guenard, D.; Gueritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917−5919.

(18) (a) Holton, R. A. US Patent 5,539,103, 1996. (b) Ojima, I.; Sun, C. M.; Zucco, M.; Park, Y. H.; Duclos, O.; Kudud, S. *Tetrahedron Lett.* **1993**, *34*, 4149−4152. (c) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985−7012.

Scheme 7



Scheme 8



was prepared by treating the *trans*-oxazolidine acid **16** with 1.2 equiv of methanesulfonic acid in refluxing IPA followed by the addition of H_2O to provide the isopropyl ester **18** in 96% yield (Scheme 7). Although this solvolysis works very well using a variety of alcohols, the isopropyl ester was chosen because of its ease of extraction from water mixtures and for its stability. Preparation of straight-chain esters invariably afforded mixtures of dimeric byproducts.

Preparation of the bis-silyl lactam **20** was accomplished by in situ formation of the bis-triethylsilyl intermediate **19** followed by the addition of 4 equiv of *tert*-butylmagnesium chloride.[19] Selective mono-hydrolysis of the *N*,*O*-triethylsilyl lactam to the required *O*-triethylsilyl lactam was achieved with 15:1 ethyl acetate:0.7% KF (0.06 equiv) solution in EtOH at −15 °C. The *β*-lactam nitrogen was then protected as the *tert*-butyl carbamate in 91% overall yield from **18**. This protection of nitrogen also activates the *β*-lactam for acylation of the baccatin core.

Acylation using the *β*-lactam strategy requires the generation of a metal alkoxide at C-13 which opens the *β*-lactam, providing the appropriately protected coupled side chain. This was accomplished by adding lithium bis-(trimethylsilyl)amide to a mixture of **9** and **22** in THF at −40 °C which provided the coupled product **23** (Scheme 8). This approach is procedurally very simple, and the desired product **23** is isolated by crystallization in 95% yield with a purity of 97%.[20,21] The high purity that is obtained from this crystallization is remarkable considering that the purity of the *β*-lactam **22** is 72%[22a] and the purity of **9** is only 86%.[22b]

The product of the side chain coupling provides ABT-271 in protected form. A two-step deprotection of the triethylsilyl group, the acetonide, and the C10 acetate is required to yield ABT-271. First the triethylsilyl group and the acetonide were removed under acidic conditions to give the penultimate compound **24** which was hydrolyzed under basic conditions to give **1**, ABT-271 (Scheme 9). Careful attention must be given to these final two deprotections because of the lability of the oxetane ring, the lability of the newly incorporated side chain, the presence of an acetate and a benzoate, and the presence of a tertiary alcohol at C-1 which is prone to ionization leading to skeletal rearrangements. The acid-catalyzed deprotection was achieved using 0.1 N HCl in methanol at 40 °C for 13 h. The penultimate compound was isolated by extractive workup to give a 90% yield for the acid hydrolysis. The remaining 10% was comprised of several impurities, but no impurity exceeded 2%. Other acids, solvents, and concentrations were examined, but the described conditions gave the best results. The penultimate **24** could not be crystallized and was used crude in the final step.

The penultimate compound **24** was hydrolyzed with 0.1 N KOH in methanol at −10 °C for 9 h to provide **1**, ABT-271. It was critical to use 0.5 equiv of 0.1 N KOH and maintain the reaction temperature below −10 °C to minimize the amount of side chain hydrolysis while maintaining an acceptable rate of hydrolysis. The product was isolated by crystallization from acetone/hexane in 86% yield (93% yield of crude product with a purity of 93%).[23] The major impurity is the C13-OH compound **25** which is formed in 3−5% during the base hydrolysis. The crystalline product is an acetone solvate and was determined not to be the most stable crystal form.[24] When this acetone solvate was slurried in 10% EtOH in H_2O and warmed to 45 °C it underwent a change in crystal form

(19) Lynch, J. K.; Holladay, M. W.; Ryther, K. B.; Bai, H.; Hsiao, C.-N.; Morton, H. E.; Dickman, D. A.; Arnold, W.; King, S. A. *Tetrahedron: Asymmetry* **1998**, *9*, 2791−2794.

(20) The reaction functions equally well at −25 °C, and the reaction will tolerate water levels up to 60 mol %.

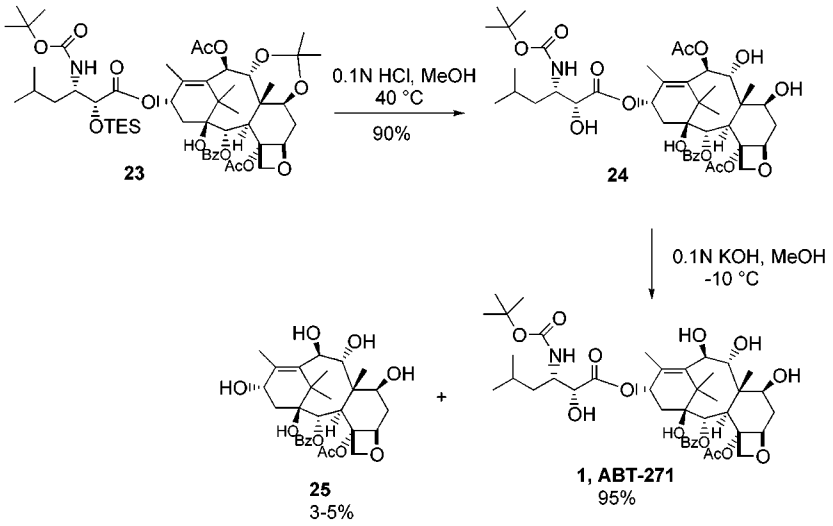
(21) Purity determined by HPLC analysis relative to a pure standard.

(22) (a) The *β*-lactam **22** is contaminated with 23% ethoxytriethylsilane. (b) The crystalline alcohol **9** is contaminated with 1,1-diphenylethanol and other phenyl impurities from the phenyllithium addition reaction.

(23) Purity determined by HPLC analysis relative to a pure standard.

(24) X-ray diffraction studies were conducted by Geoff G. Z. Zhang Ph.D., Research Scientist, Pharmaceutical Products Division and John Quick, Research Investigator, Pharmaceutical Analytical Research Division, Abbott Laboratories.

Scheme 9



as determined by X-ray diffraction.[24] This crystal form conversion removes the side chain hydrolysis impurity **25** giving a 97% recovery of **1**, ABT-271, in a purity of >99%.

Conclusion

The potential anticancer agent ABT-271, **1**, was efficiently prepared beginning with the commercially available 9-DHAB-III, **2**. Protection of the 7,9-diol of **2** as the acetonide allows the selective removal of the C-13 acetate. The resulting C-13 hydroxyl group was acylated with the β-lactam **22** to incorporate the desired side chain. The β-lacam **22** was prepared from *N*-Boc-L-leucinol in eight steps and 40% overall yield. Coupling of the baccatin core with the side chain provides ABT-271, **1**, in protected form. Deprotection is accomplished by acidic hydrolysis followed by basic hydrolysis to reveal ABT-271, **1**. Final purification is achieved by heating in 10% EtOH in H_2O which also converts ABT-271 to its most stable crystal form. This optimzed synthesis provides ABT-271 in five steps and 67% overall yield (54% with no chromatographic purifications) from 9-DHAB-III, **2**. The efficiency of this synthesis allowed the preparation of over 600 g of ABT-271, **1**.

Experimental Section

(3*S*,4*S*)-4-[(*tert*-Butyloxycarbonyl)amino]-6-methyl-1-hepten-3-ol (12). To a solution of *N*-Boc-L-leucinol, **10** (2.00 kg, 9.126 mol), and 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (14.5 g, 92.7 mmol) in CH_2Cl_2 (36.6 kg) and H_2O (5.54 kg) at 0 °C were added 7% $NaHCO_3$ solution (28.9 kg) and 12.6% NaOCl solution (6.62 kg) over 2 h with vigorous stirring. The biphasic mixture was stirred for 20 min, and then the layers were separated. The organic layer was washed sequentially with 10% $NaHSO_4$ solution (25.7 kg) containing NaI (151 g), 10% $Na_2S_2O_3$ (28.7 kg), 7% $NaHCO_3$ (28.5 kg), and brine (21.7 kg). The organic layer was dried over Na_2SO_4, filtered, and concentrated to 3.80 kg of **11** in CH_2Cl_2 (a small portion was concentrated to dryness for characterization $[\alpha]^{25}_D$ −32.4 (*c* 1.0, MeOH); IR (neat) 3346, 2955, 1731, 1713, 1694, 1515, 1363, 1249, 1166, 1054, 1017 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.43 (s, 1H), 7.22 (d, J = 7.8 Hz, 1H), 3.86 (ddd, J = 11.0, J = 7.8, J = 4.7 Hz, 1H), 1.65 (sept., J = 6.8 Hz, 1H), 1.34−1.48 (m, 2H), 1.39 (s, 9H), 0.89 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.0, 155.7, 78.2, 57.8, 36.5, 28.1, 24.0, 22.9, 21.3. Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.16; H, 9.77; N, 6.43. The ee of **11** was determined; see below in supplementary addendum.

To a solution of vinylmagnesium chloride in THF (17.5 wt %, 13.8 kg, 27.9 mol) was added CH_2Cl_2 (18.8 kg). The resulting solution was cooled to 10 °C and treated with *N*-Boc-L-leucinal **11**/CH_2Cl_2 (3.80 kg) while maintaining an internal temperature <30 °C. The reaction was stirred for 25 min, poured into a stirring solution of 15% NH_4Cl (51.9 kg), and diluted with MTBE (25.6 kg). Layers were separated, and the organic layer was washed with brine (26.9 kg). The organic layer was concentrated to approximately 6 L, whereupon heptane 20 kg was added and concentrated to 3.65 kg, cooled to −20 °C (overnight), filtered, and washed with cold heptane (1.2 kg) to afford 1.48 kg of off-white solid as a mixture of **12** (1.28 kg assay 58% overall) and the undesired isomer **13** (0.20 kg, 9.0%). **(3*S*,4*S*)-4-[(*tert*-Butyloxycarbonyl)amino]-6-methyl-1-hepten-3-ol (12).** TLC: 2:1 heptane:EtOAc; R_f = 0.42; $[\alpha]^{25}_D$ −54.8° (*C* = 0.81, $CDCl_3$); IR (neat) 3383, 2955, 2868, 1688, 1506, 1367, 1169, 919 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.89 (ddd, J = 17.3, 10.7, 5.9 Hz, 1H), 5.29 (ddd, J = 17.3, 1.5, 1.5 Hz, 1 H), 5.18 (ddd, J = 10.7, 1.5, 1.5 Hz, 1H), 4.68 (br d, 1H), 4.06 (br s, 1H), 3.66 (br m, 1H), 2.60 (br s, 1H), 1.68 (hept, J = 6.6 Hz, 1H), 1.43 (s, 9H), 1.71−1.35 (m, 2H), 0.92 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.3, 138.2, 116.1, 75.1, 52.9, 40.7, 28.3, 24.8, 23.3, 21.9; MS $C_{13}H_{25}NO_3$ *m*/*z* 243, DCI/NH_3^+ [M + 1] 244, ESI$^+$ [M + 1] 244, ESI$^-$ [M − 1] 242. Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76 Found: C, 64.00; H, 10.25; N, 5.65.

For the determination of the ee% of **12**, see the Supporting Information . Optical rotation of **12** is larger in magnitude to previously published report by Franciotti et al. (*Tetrahedron Lett*. **1991**, *32*, 6783−6786) where $[\alpha]^{25}_D$ −27° (*c* = 0.8, $CDCl_3$).

(3*R*,4*S*)-4-[(*tert*-Butyloxycarbonyl)amino]-6-methyl-1-hepten-3-ol (13). TLC: 2:1 heptane:EtOAc; R_f = 0.33; $[\alpha]^{25}_D$ −41.3 (*c* 1.01, $CHCl_3$); IR (neat) 3358, 2949, 1682, 1527 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.82 (ddd, J = 17.3, 10.6, 5.5 Hz, 1H), 5.31 (ddd, J = 17.3, 1.5,1.5 Hz, 1 H), 5.21 (ddd, J = 10.6, 1.5, 1.5 Hz, 1H), 4.53−4.58 (br m, 1H), 4.17 (br s, 1H), 3.85−3.74 (br m, 1H), 3.14 (br s, 1H), 1.70−1.60 (m, 1H), 1.43 (s, 9H), 1.27−1.21 (m, 2H), 0.91 (d, J = 5.5 Hz, 3H), 0.89 (d, J = 5.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.8, 136.7, 116.5, 75.9, 53.5, 39.1, 28.3, 24.7, 23.4, 21.7; MS (APCI$^+$) $C_{13}H_{25}NO_3$ *m*/*z* 243 (relative intensity), 244 (M + 1, 85) 244, (100) 188, (47) 170, 144 (90). Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76. Found: C, 63.91; H, 10.36; N, 5.85.

(4*S*,5*S*)-3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-5-ethenyl-4-(2-methylpropyl)oxazolidine (14). To a solution of allylic alcohols **12** and **13** (20.5 g, 84.4 mmol, **12:13**, 6:1; assay for **12**, 17.6 g, 72.3 mmol) in CH_2Cl_2 (200 mL) was added pTSA (0.64 g, 3.4 mmol). The resulting mixture was cooled to −20

°C, and then 2,2-dimethoxypropane (35.4 g, 340 mmol) was added. The reaction was stirred at −20 °C for 4 h. While maintaining temperature at −20 °C, Et_3N (30.4 g, 300 mmol), succinic anhydride (25.1 g, 251 mmol), and DMAP (15.8 g, 129 mmol) were added to the reaction mixture. The reaction was then allowed to warm to ambient temperature. The reaction was quenched with MeOH (10.8 mL) and stirred for 30 min. The volatiles were removed by concentration and then diluted with heptane (210 mL), MTBE (55 mL), and a 5% NaH_2PO_4 solution (500 mL). The layers were separated, and the organic layer was washed with a mixture of 5% $NaHCO_3$ solution (450 mL) and methanol (75 mL). The layers were separated, and the remaining organic layer was washed with brine (50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give **14** (18.6 g, 91% yield based on starting alcohol **12**) as a viscous oil. TLC: 2:1 heptane:EtOAc; **14**, R_f = 0.56; $[\alpha]^{25}_D$ +17.8 (*c* 0.609, MeOH); IR (neat) 2950, 1702, 1460, 1385, 1178 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 5.97 (ddd, J = 17.3, 10.3, 7.4 Hz, 1H), 5.32 (dt, J = 17.3, 1.1 Hz, 1H), 5.19 (dt, J = 10.3, 1.1 Hz, 1H), 4.29 (dd, J = 7.4, 3.6 Hz, 1H), 3.66 (br d, J = 8.5 Hz, 1H), 1.68−1.53 (m, 2H), 1.50 (s, 3H), 1.42 (s, 3H), 1.41 (s, 9H), 1.40−1.35 (m, 1H), 0.88 (dd, J = 9.7, 6.1 Hz, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 150.8, 138.8, 117.2, 93.7, 81.2, 79.3, 59.8, 28.3, 27.5, 24.8, 23.9, 21.4; MS (APCI$^+$) $C_{16}H_{29}NO_3$ *m/z* (relative intensity) 284 (M + 1, 11), 184 (100). Anal. Calcd for $C_{16}H_{29}NO_3$: C, 67.90; H, 10.33; N, 4.95. Found: C, 67.66; H, 10.33; N, 4.83.

(4*S*,5*R*)-3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-4-(2-methylpropyl)oxazolidine-5-carboxylic Acid (16). To a suspension of $RuO_2{\cdot}xH_2O$ (0.42 g, 3.1 mmol), acetone (17 mL), and water (17 mL) at 0 °C was added $NaIO_4$ (2.90 g, 13.6 mmol) in H_2O (20 mL). After 5 min the vinyl oxazolidine **14** (12.0 g, 41.6 mmol) in acetone (375 mL) was added. Next, $NaIO_4$ (55.2 g, 256 mmol) in H_2O (355 mL) was added dropwise over 3 h, keeping the temperature below 15 °C. After 1 h of additional stirring, the reaction was cautiously quenched with 2-propanol (21 mL) and stirred for 30 min while the reaction warmed to ambient temperature. The reaction was then filtered though Celite and the resulting filter cake washed with a 1:1 acetone:water solution (300 mL). NaCl (20 g, 342 mmol) was added to the combined filtrates and then extracted with MTBE (500 mL). The organic extract was washed with a 1:1 mixture of 1 M $NaHSO_4$ and 1 M $NaHSO_3$ (190 mL total). The organic layer was then extracted with 0.5 M K_2CO_3 aq solution (380 mL). The alkaline aqueous layer was pH adjusted to pH 5 with portionwise addition of a concentrated citric acid solution (47 g in 100 mL of H_2O). The acidic aqueous layer was extracted with MTBE (360 mL), and the organic layer was washed with brine (90 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give **16** (10.6 g, 85%). TLC: 2:1 heptane:EtOAc; R_f = 0. 12; mp 91−93.5 °C, $[\alpha]^{25}_D$ −7.4 (*c* 1.061, $CHCl_3$); IR (neat) 3500 (br), 1704, 1381 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 13.0 (br s, 1H), 4.35 (d, J = 1.5 Hz, 1H), 4.22−4.06 (br m, 1H), 1.80−1.55 (m, 2H), 1.51 (s, 3H), 1.47 (s, 3H), 1.41 (s, 9H), 1.40−1.32 (m, 1H), 0.96 (d, J = 6.7 Hz, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 172.9, 150.3, 94.8, 79.2, 77.9, 58.2, 43.4, 28.1, 25.9, 25.0, 23.6, 21.1; MS (ESI$^-$) $C_{15}H_{27}NO_5$ *m/z* 301 (relative intensity) 301 (M, 15), 300 (M − 1, 100). Anal. Calcd for $C_{15}H_{27}NO_5$: C, 59.77; H, 9.03; N, 4.65. Found: C, 59.46; H, 8.99; N, 4.66.

Isopropyl (2*R*,3*S*)-3-Amino-2-hydroxy-5-methylhexanoate (18). To a solution of the oxazolidine acid **16** (16.0 g, 53 mmol) in 2-propanol (95 mL) was added $MeSO_3H$ (6.5 g, 68 mmol), and the resulting solution was heated to 73 °C for 4 h. The reaction was then cooled to ambient temperature and stirred for 1 h. Water (27 mL) was added to the reaction, which was stirred for an additional 3 h. The reaction mixture was concentrated to a low volume and then diluted with isopropyl acetate (350 mL). The isopropyl acetate solution was washed with 2 M K_2CO_3 solution (45 mL). The organic extract was dried over Na_2SO_4, filtered, and concentrated to give **18** (10.3 g, 96%). mp 54.6−55.8 °C; $[\alpha]^{25}_D$ −13.6 (*c* 0.527, $CHCl_3$); IR (neat) 3085 (br), 1731, 1592, 1462, 1378, 1208; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.20 (hept, J = 6.3 Hz, 1H), 4.07 (d, J = 2.6 Hz, 1H), 3.22 (td, J = 7.0, 2.6 Hz, 1H), 2.33 (br s, 3H), 1.81 (hept, J = 6.6 Hz, 1H), 1.46 (t, J = 7.0 Hz, 2H), 1.37 (s, 3H), 1.35 (s, 3H), 1.02 (d, J = 6.6 Hz, 3H), 0.99 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.3, 75.1, 70.8, 52.9, 44.9, 26.1, 24.5, 23.5, 23.2; MS (APCI$^+$) $C_{10}H_{21}NO_5$ *m/z* 245 (M + 42, 32) 204 (M + 1, 100). Anal. Calcd for $C_{10}H_{21}NO_5$: C, 59.08; H, 10.41; N, 6.89. Found: C, 58.70; H, 10.32; N, 6.80.

(3*R*,4*S*)-Bis-*N*,*O*-triethylsilyl-4-(2-methylpropyl)-3-hydroxy-azetidin-2-one (20). To a solution of isopropyl (2*R*,3*S*)-3-amino-2-hydroxy-5-methylhexanoate (**5**) (10.0 g, 49.3 mmol) in MTBE (200 mL) was added NEt_3 (13.3 g, 131 mmol). The mixture then was cooled to 0 °C and treated with TESCl (17.1 g, 113 mmol). The resulting white slurry was stirred at 23 °C for 1.5 h. The mixture was cooled to 0 °C and treated dropwise with *tert*-butylmagnesium chloride (197 mL, 1 M solution in THF, 197 mmol). The reaction was stirred at 23 °C for 1 h during which it became thick slurry. The reaction mixture was poured into 15% NH_4Cl solution (735 mL) and diluted with MTBE (375 mL). The layers were separated, and the organic layer was washed with brine (212 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford the crude bis-TES lactam **20** as a brown oil (23.4 g, 78% pure by HPLC which indicates 18.3 g, 49.3 mmol). The crude **20** was used directly in the next step. TLC: EtOAc/hexane (1:4), R_f = 0.82; $[\alpha]^{25}_D$ +83.14 (*c* 1.002, $CHCl_3$); IR (neat) 2956, 1749, 1194, 1017 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.82 (d, J = 5.1 Hz, 1H), 3.62 (ddd, J = 10.5, 5.3, 3.3 Hz, 1 H), 1.77 (ddd, J = 13.2, 10.2, 4.5 Hz, 1H), 1.67−1.57 (m, 1H), 1.28 (ddd, J = 13.2, 9.0, 3.0 Hz, 1H), 0.98−0.91 (m, 18 H), 0.90 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H), 0.76−0.61 (m, 12 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.8, 79.0, 57.1, 41.8, 27.2, 25.6, 23.9, 8.64, 8.56, 6.7, 5.6; MS (ESI$^+$) $C_{19}H_{41}NO_2Si_2$ *m/z* (relative intensity) 372 (MH$^+$, 100), 342 (5). Anal. Calcd for $C_{19}H_{41}NO_2Si_2$: C, 61.39, H, 11.12. Found: C, 61.27, H, 11.28.

(3*R*,4*S*)-3-Triethylsilyloxy-4-(2-methylpropyl)azetidin-2-one (21). To a solution of crude bis-TES lactam **20** (23.4 g crude at 78% purity gives 18.3 g, 49.3 mmol) in EtOAc (250 mL) at −10 °C was added 0.7% KF in EtOH (16 mL), and then the reaction mixture was stirred at −10 °C for 4 h. The reaction mixture was diluted with 2% NaCl solution (100 mL), and the layers were separated. The organic layer was diluted with hexane (130 mL) and washed sequentially with 5% NaH_2PO_4 (50 mL), 7% $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford 21.0 g of the crude mono-TES lactam **21** (21.0 g, 60% pure by HPLC which indicates 12.7 g, 49.3 mmol). The crude **21** was used directly in the next step. TLC EtOAc/hexane (1:4), R_f = 0.15; $[\alpha]^{25}_D$ +33.60 (*c* 1.093, $CHCl_3$); IR (neat) 3228, 2957, 1760, 1182 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.77 (bs, 1H), 4.81 (dd, J = 4.8, 2.7 Hz, 1H), 3.71 (ddd, J = 7.6, 5.7, 5.0 Hz, 1H), 1.70−1.57 (m, 1H), 1.37−1.34 (m, 2H), 0.95 (t, J = 7.8 Hz, 9H), 0.92 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H), 0.68−0.59 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 77.2, 54.1, 38.7, 25.3, 23.0, 22.3, 6.5, 4.6; MS (ESI$^-$) $C_{13}H_{27}NO_2Si$ *m/z* (relative intensity) 256 (M$^+$ − H, 100). Anal. Calcd for $C_{13}H_{27}NO_2Si$: C, 60.65, H, 10.57. Found: C, 60.45, H, 10.59.

(3*R*,4*S*)-1-(*tert*-Butyloxycarbonyl)-3-triethylsilyloxy-4-(2-methylpropyl)azetidin-2-one (22). To a solution of mono-TES lactam **21** (21.0 g, 60% pure by HPLC indicates 12.7 g, 49.3 mmol) in CH_2Cl_2 (80 mL) at 23 °C were added NEt_3 (14.6 g, 144 mmol), a solution of di-*tert*-butyl dicarbonate (16.1 g, 73.9 mmol) in CH_2Cl_2 (15 mL), and DMAP (3.31 g, 27.1 mmol). The reaction mixture was stirred at 23 °C for 1.5 h. The reaction was diluted with hexane (90 mL) and washed sequentially with 5% NaH_2PO_4 (3 × 255 mL), 7% $NaHCO_3$ (120 mL), and brine (180 mL). The organic layer was dried over Na_2SO_4 and concentrated to give the crude Boc lactam **22** (22.0 g crude oil, 74% pure by HPLC indicates 16.3 g, 91% yield over three steps). The major impurity (∼20 wt %) is the byproduct ethoxytriethylsilane carried over from the previous desilylation step. TLC EtOAc/hexane (1:4), R_f = 0.67; $[\alpha]^{25}_D$ +79.19 (*c* 1.007, $CHCl_3$); IR (neat) 2957, 1805, 1731, 1330 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.83 (d, J = 5.7 Hz, 1H), 4.05 (q, J = 6.1 Hz, 1H), 1.78−1.64 (m, 3H), 1.49 (s, 9H), 0.96 (t, J = 7.8 Hz, 9H), 0.94 (d, J = 6.3 Hz, 3H), 0.93 (d, J = 5.9 Hz, 3H), 0.70−0.62 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.4, 148.4,

83.1, 75.7, 57.0, 36.5, 28.3, 28.0, 25.1, 23.0, 6.5, 4.6; MS (ESI$^+$) $C_{18}H_{35}NO_4Si$ *m/z* (relative intensity) 375 ($M^+ + NH_4$, 100). Anal. Calcd for $C_{18}H_{35}NO_4Si$: C, 60.46, H, 9.87. Found: C, 60.57, H, 10.10.

9(*R*)-Dihydro-7,9-isopropylidene-13-acetylbaccatin-III (8). To a suspension of 9-DHAB-III, **2** (14.6 g, 23.1 mmol), in CH_3CN (150 mL) and 2,2-dimethoxypropane (54 mL, 439 mmol) at 20 °C was added Montmorillonite K10 (2.92 g, 20 wt %). After 5 h the reaction mixture was filtered through Celite and rinsed with CH_3CN (2 × 20 mL). The filtrate was concentrated to give the desired product (13.96 g, 90% yield). TLC: 15% acetone in 85% CH_2Cl_2; 9-DHAB-III, **2**, R_f = 0.2 and acetonide product, **8**, R_f = 0.85; $[\alpha]^{25}_D$ +11.14 (*c* 1.01, MeOH); IR (KBr) 3476, 2991, 2942, 2878, 1712, 1372, 1249, 1080, 1018, 711 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.12 (d, *J* = 7.2 Hz, 2H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 6.48 (d, *J* = 10.8 Hz, 1H), 6.12 (t, *J* = 8.4 Hz, 1H), 5.84 (d, *J* = 6.4 Hz, 1H), 4.92 (d, *J* = 7.6 Hz, 1H), 4.55 (d, *J* = 11.2 Hz, 1H), 4.25 (t, *J* = 8.4 Hz, 1H), 4.21 (s, 2H), 3.14 (d, *J* = 6.4 Hz, 1H), 2.47 (ddd, *J* = 14.0, *J* = 8.4, *J* = 8.4 Hz, 1H), 2.36−2.20 (m, 2H), 2.31 (s, 3H), 2.19 (s, 3H), 2.09 (s, 3H), 1.99 (d, *J* = 1.2 Hz, 3H), 1.77 (s, 3H), 1.71 (ddd, *J* = 15.0, *J* = 8.8, *J* = 1.5 Hz, 1H), 1.57 (s, 3H), 1.51 (s, 3H), 1.41 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.6, 172.0, 171.9, 168.0, 136.0, 134.7, 131.6, 131.4, 129.9, 129.8, 98.6, 85.4, 83.0, 80.5, 78.7, 77.8, 75.9, 74.9, 71.2, 69.8, 45.7, 43.8, 42.0, 36.8, 35.6, 31.9, 27.6, 25.0, 23.0, 22.8, 21.2, 20.9, 14.9, 14.6; MS $C_{36}H_{46}O_{12}$ *m/z* 670 APCI$^+$ [M + 18] 688, APCI$^-$ [M + 35] 705, ESI$^+$ [M + 18] 688, ESI$^-$ [M − 1] 669. Anal. Calcd for $C_{36}H_{46}O_{12}$: C 64.46, H 6.91, O 28.62. Found: C 64.32, H 7.12, O 28.41.

9(*R*)-Dihydro-7,9-isopropylidene-baccatin-III (9). A solution of the acetonide **8** (14.9 g, 22.3 mmol) in THF (500 mL) was cooled to −60 °C, and then 1.8 M PhLi (54.0 mL, 97.2 mmol) was added over a period of 1 h. The opaque yellow solution was stirred an additional 15 min, and then the reaction was quenched by adding the reaction mixture to 20 wt % NH_4Cl (1 L). The layers were separated, and the aqueous layer was extracted with *i*-PrOAc (2 × 200 mL). The layers were separated, and the combined organic layers were washed with 5% NaCl solution (1 L). The organic layer was dried over Na_2SO_4, filtered, and concentrated. Analysis of the crude product by HPLC indicated a yield of 92%. The product, **9**, was purified by crystallization from di-*n*-butyl ether (10.5 g, 75% yield). TLC: 40% ethyl acetate in 60% hexane; acetonide,**8**, R_f = 0.3 and de-acylated product,**9**, R_f = 0.15; $[\alpha]^{25}_D$ +28.3 (*c* 1.05, MeOH); IR (KBr) 3499, 2998, 2944, 2894, 1734, 1718, 1376, 1247, 1072, 1018, 712 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.14 (d, *J* = 8.0 Hz, 2H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 6.50 (d, *J* = 10.8 Hz, 1H), 5.80 (d, *J* = 6.4 Hz, 1H), 4.91 (d, *J* = 8.4 Hz, 1H), 4.71 (t, *J* = 8.4 Hz, 1H), 4.51 (d, *J* = 11.2 Hz, 1H), 4.27 (t, *J* = 8.8 Hz, 1H), 4.23−4.17 (m, 2H), 3.20 (d, *J* = 6.4 Hz, 1H), 2.50−2.18 (m, 3H), 2.22 (s, 3H), 2.11 (d, *J* = 1.2 Hz, 3H), 2.08 (s, 3H), 1.75 (s, 3H), 1.69 (ddd, *J* = 15.0, 8.5, 1.5, 1H), 1.52 (s, 3H), 1.51 (s, 3H), 1.40 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.4, 172.1, 168.2, 145.7, 134.7, 133.9, 131.8, 131.4, 129.8, 98.5, 85.4, 82.7, 80.4, 79.1, 77.8, 76.0, 75.5, 69.8, 68.3, 46.0, 43.2, 41.9, 40.2, 35.6, 31.9, 27.9, 25.0, 22.9, 22.3, 21.1, 15.0, 14.8; MS $C_{34}H_{44}O_{11}$ *m/z* 628 APCI$^+$ [M + 1] 629, APCI$^-$ [M + 35] 663. Anal. Calcd for $C_{34}H_{44}O_{11}$: C 64.95, H 7.05, O 27.99. Found: C 64.85, H 7.09, O 27.66.

13-[(2′*R*,3′*S*)-3′-(*N*-*tert*-butoxycarbonyl)amino-2′-triethylsilyloxy-5′-methylhexanoate]-9(*R*)-dihydro-7,9-isoproylidene-baccatin-III (23). To a solution of **9** (13.8 g, 21.9 mmol) and the *β*-lactam **22** (10.2 g, 28.5 mmol) in THF (500 mL) at −40 °C was added 1.0 M LiHMDS in THF (48.3 mL, 48.3 mmol) over 1 h. The yellow solution was stirred an additional 30 min, and then the reaction was quenched by adding the reaction mixture to pH 7 buffer (1 L) and MTBE (500 mL). The layers were separated the yellow organic layer was washed with 23 wt % aqueous NaCl solution (500 mL). The layers were separated, and the organic layer was dried over Na_2SO_4, filtered, and concentrated. Analysis of the crude product by HPLC indicated a yield of 21.4 g, 99%. The product was purified by crystallization from 12% MTBE in hexane to give **23** (20.6 g, 95%). TLC: 20% ethyl acetate in 80% hexane; C13−OH, **9**, R_f = 0.3 and acylated product, **23**, R_f = 0.7; $[\alpha]^{25}_D$ −3.75 (*c* 1.02, MeOH); IR (KBr) 3447, 2958, 1738, 1715, 1496, 1368, 1245, 1168, 1111, 1016 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.15 (d, *J* = 8.0 Hz, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 2H), 6.49 (d, *J* = 10.8 Hz, 1H), 6.02 (t, *J* = 8.0 Hz, 1H), 5.85 (d, *J* = 6.0 Hz, 1H), 4.92 (d, *J* = 8.8 Hz, 1H), 4.56 (d, *J* = 10.8 Hz, 1H), 4.28−4.19 (m, 4H), 4.08 (ddd, *J* = 10.8, 3.2, 3.2 Hz, 1H), 3.14 (d, *J* = 6.0 Hz, 1H), 2.48 (ddd, *J* = 15.6, *J* = 8.2, *J* = 8.2 Hz, 1H), 2.45−2.35 (m, 2H), 2.37 (s, 3H), 2.10 (s, 3H), 1.98 (s, 3H), 1.77 (s, 3H), 1.77−1.63 (m, 3H), 1.58 (s, 3H), 1.50 (s, 3H), 1.41 (s, 3H), 1.38 (s, 9H), 1.23−1.16 (m, 1H), 1.17 (s, 3H), 1.04 (t, *J* = 8.0 Hz, 9H), 0.98 (d, *J* = 3.6 Hz, 3H), 0.97 (d, *J* = 4.0 Hz, 3H), 0.70 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (CD_3OD, 100 MHz) δ 174.5, 172.1, 171.6, 168.0, 158.3, 140.6, 136.0, 134.7, 131.7, 131.5, 129.8, 98.6, 85.4, 83.1, 80.5, 80.3, 78.7, 77.9, 76.1, 75.9, 74.8, 73.3, 69.7, 53.2, 45.6, 44.0, 42.1, 41.9, 36.4, 35.6, 31.9, 28.7, 27.7, 25.9, 25.1, 23.9, 23.5, 23.1, 22.0, 21.0, 14.9, 14.8, 7.1, 5.5; MS $C_{52}H_{79}NO_{15}Si$ *m/z* 985 ESI$^+$ [M + 1] 986, ESI$^-$ [M − 1] 984. Anal. Calcd for $C_{52}H_{79}NO_{15}Si$: C 63.33, H 8.07, N 1.42. Found: C 63.25, H 8.07.

13-[(2′*R*,3′*S*)-3′-(*N*-*tert*-butoxycarbonyl)amino-2′-hydroxy-5′-methylhexanoate]-9(*R*)-dihydro-baccatin-III (24). To a solution of the coupled product **23** (15.3 g, 15.5 mmol) in MeOH (475 mL) was added 0.1 N HCl (155 mL, 15.5 mmol) over 40 min, and the reaction was warmed to 40 °C. After 13 h the reaction was cooled and quenched into pH 7 buffer (300 mL) and MTBE (600 mL). The layers were separated, and the organic layer was washed with 23% aqueous NaCl solution (200 mL). The combined aqueous layers were extracted with MTBE (100 mL). The combined organic layers were washed with 23% aqueous NaCl solution (200 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give the desired product **24** (11.6 g, 90%). TLC: 70% ethyl acetate in 30% hexane; **23** R_f = 0.6 and hydrolyzed product, **24**, R_f = 0.5; $[\alpha]^{25}_D$ −11.5 (*c* 1.01, MeOH); IR (KBr) 3403, 2959, 1714, 1498, 1369, 1249, 1167, 1070, 1048 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.15 (d, *J* = 8.0 Hz, 2H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 6.22 (d, *J* = 11.2 Hz, 1H), 6.08 (t, *J* = 8.4 Hz, 1H), 5.78 (d, *J* = 6.0 Hz, 1H), 4.96 (d, *J* = 8.4 Hz, 1H), 4.50 (d, *J* = 10.8 Hz, 1H), 4.39 (dd, *J* = 9.6, *J* = 8.0 Hz, 1H), 4.24−4.07 (m, 4H), 3.07 (d, *J* = 5.6 Hz, 1H), 2.47 (ddd, *J* = 15.6, *J* = 8.4, *J* = 8.4 Hz, 1H), 2.37 (d, *J* = 10.5 Hz, 1H), 2.35 (s, 3H), 2.11 (s, 3H), 1.94 (s, 3H), 1.78 (s, 3H), 1.67 (s, 3H), 1.87−1.63 (m, 4H), 1.38 (s, 9H), 1.29−1.22 (m, 1H), 1.23 (s, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 175.4, 172.4, 171.7, 167.9, 158.3, 140.4, 136.9, 134.7, 131.5, 135.5, 129.8, 85.7, 83.4, 80.4, 78.8, 78.2, 77.7, 75.0, 74.9, 74.7, 74.5, 73.1, 52.8, 48.0, 45.8, 44.9, 41.8, 38.6, 36.3, 28.6, 28.5, 25.9, 23.8, 23.7, 23.4, 22.1, 21.1, 14.9, 13.1; MS $C_{43}H_{61}NO_{15}$ *m/z* 831 ESI$^+$ [M + 18] 849, ESI$^-$ [M − 1] 830. Anal. Calcd for $C_{43}H_{61}NO_{15}$: C 62.08, H 7.39, N 1.68. Found: C 62.07, H 7.20, N 1.61.

ABT-271 (1). To a solution of the penultimate **24** (12.9 g, 15.5 mmol) in MeOH (380 mL) at −10 °C was added 0.1 N KOH (80.0 mL, 8.0 mmol). The temperature was kept below −7 °C, and after 9.5 h the reaction was quenched by adding it to a stirred solution of pH 7 buffer (200 mL), 27% aqueous NaCl solution (200 mL), H_2O (200 mL), and MTBE (200 mL). The layers were separated and the aqueous layer was extracted with MTBE (2 × 50 mL). The combined organic layers were washed with 27% aqueous NaCl solution (200 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give the desired product **1**. Analysis of the crude product by HPLC indicated a yield of 11.6 g, 95%. The product was purified by crystallization from acetone in hexane to give **1** (10.5 g, 86%). TLC: 10% MeOH in 90% CH_2Cl_2; **24** R_f = 0.5 and **1**, ABT-271 R_f = 0.4; $[\alpha]^{25}_D$ −8.60 (*c* 0.997, MeOH); IR (KBr) 3481, 2960, 2937, 2897, 2872, 1748, 1722, 1712, 1688, 1495, 1370, 1244, 1177, 1052, 980, 717 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.14 (d, *J* = 8.0 Hz, 2H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 6.13 (t, *J* = 10.0 Hz, 1H), 5.78 (d, *J* = 5.8 Hz, 1H), 4.95 (d, *J* = 8.9 Hz, 1H), 4.91 (d, *J* = 10.4 Hz, 1H), 4.38 (d, *J* = 10.4,1H), 4.32 (dd, *J* = 9.7, *J* = 7.6 Hz, 1H), 4.38 (d, *J* = 10.0 Hz, 1H), 4.19 (d, *J* = 3.5 Hz, 1H), 4.17

(d, $J = 10.0$ Hz, 1H), 4.10 (ddd, $J = 12.0$, $J = 4.5$, $J = 3.5$ Hz, 1H), 3.08 (d, $J = 5.8$ Hz, 1H), 2.44 (ddd, $J = 14.5$, $J = 9.0$, $J = 9.0$ Hz, 1H), 2.35 (d, $J = 10.0$ Hz, 1H), 2.35 (s, 3H), 1.87−1.63 (m, 4H), 1.84 (s, 3H), 1.76 (s, 3H), 1.68 (s, 3H), 1.39 (s, 9H), 1.29 (s, 3H), 1.26 (ddd, $J = 14.0$, $J = 9.5$, $J = 4.5$ Hz, 1H), 0.98 (d, $J = 6.4$ Hz, 3H), 0.96 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 175.4, 171.7, 167.9, 158.3, 139.9, 137.7, 134.7, 131.6, 131.5, 129.7, 85.8, 83.5, 80.3, 79.7, 79.1, 77.8, 75.5, 74.9 (C7), 74.5, 73.4, 71.9, 52.8, 47.9, 45.4, 44.6, 41.8, 38.5, 36.4, 28.8, 28.6, 25.9, 23.8, 23.7, 23.4, 22.1, 14.7, 13.0; MS $C_{41}H_{59}NO_{14}$ *m/z* 789 ESI^+ [M + 1] 790, ESI^- [M − 1] 788, $APCI^-$ [M + 35] 824. Anal. Calcd for $C_{41}H_{59}NO_{14}$: C 62.34, H 7.53, N 1.77. Found: C 62.27, H 7.36, N 1.73.

Crystallization from Aqueous Ethanol. ABT-271, **1** (5.0 g, acetone crystalline solvate containing 3−5% 25), was slurried in 10% EtOH in H_2O (210 mL), and the slurry was warmed to 45 °C. After 5 h the slurry was cooled to 23 °C, and then the product was isolated by filtration to give pure ABT-271, **1** (4.85 g, 97% recovery). New crystal form melting point: 166 °C.

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Supporting Information Available: General methods and experimental details for the enantiomeric assay of compound **11** and **12**, a list of IR absorbances, MS, ^{1}H NMR, ^{13}C NMR, and elemental analysis for **23b** and **23c**. ^{1}H NMR spectra of compounds **1**, **8**, **9**, **11**−**14**, **16**, **18**, **20**−**23**, **23b**, **23c**, **24** and ^{1}H and ^{13}C spectra for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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