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Synthesis and Biological Evaluation of Amide-Linked A-Norpaclitaxels

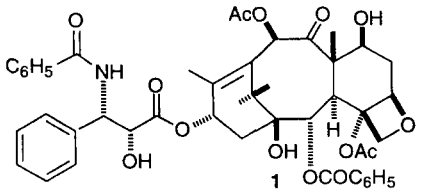
Mahendra D. Chordia and David G.I. Kingston*

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061-0212

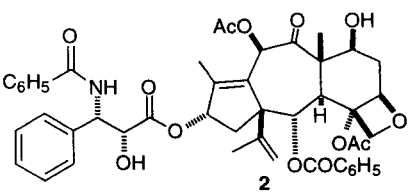
Abstract: A novel amide-linked A-*nor*paclitaxel **3a** and two 2-aroyl analogs **3b** and **3c** were prepared from 10-deacetyl baccatin III. Key steps in the synthesis were the conversion of 7-(triethylsilyl)baccatin III to its 13β-chloro-A-nor derivative **6**, reaction with sodium azide with inversion of stereochemistry to give the azide **8**, and coupling of **8** with a protected β-phenylisoserine side chain **14** to give a protected version **15** of the final product. The three analogs **3a-3c** were all less active than paclitaxel in the P-388 cytotoxicity assay, and **3c** was also less active in a tubulin-assembly assay. © 1997 Elsevier Science Ltd.

INTRODUCTION

The novel diterpenoid paclitaxel (**1**) continues to command intense chemical interest, due both to its complex and densely functionalized structure and to its potent activity as a clinically effective agent against breast and ovarian cancer.[1] In the area of structural modification, published work has included studies of the effect of changes in the side chain[2] and of various functional groups of the ring system.[3] An important finding in the latter area has been the observation that paclitaxel analogs with modified benzoyl groups at the 2-position can have significantly improved activity as compared with paclitaxel.[4] The effects of changes of the basic taxane ring system have been much less studied, but it has been shown that the A-norpaclitaxel analog **2** was less cytotoxic than paclitaxel and yet retained much of its tubulin-assembly activity.[5] In more recent work, however, it was found that compound **2** was at least ten times less effective than paclitaxel as a tubulin-assembly promoter when the assay was carried out with purified tubulin rather than microtubular protein.[6]



1



2

The lack of cytotoxicity of **2** in comparison with its relatively good tubulin-assembly activity was intriguing, since these activities normally parallel each other relatively well, at least within a series of related compounds such as 2-aroyl paclitaxels.[7] Molecular modeling studies showed that both molecules had a very similar shape (Fig. 1), and it was thus speculated that the relative lack of cytotoxicity of **2** might be due to an increased instability of the C-13 ester linkage under the conditions of the cytotoxicity assay. If this were the

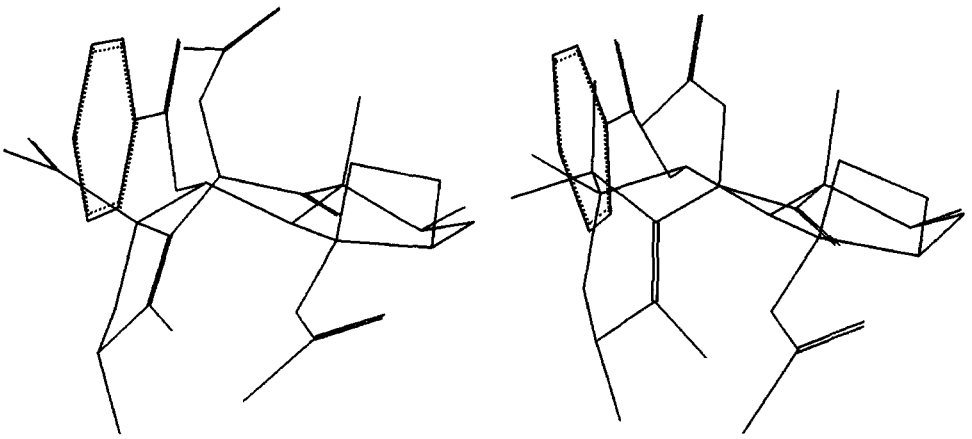
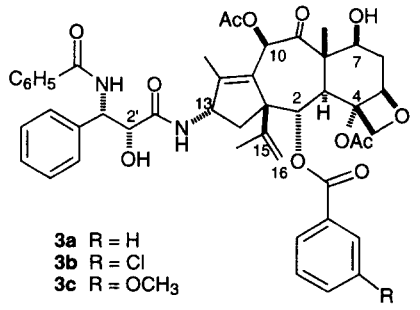


Figure 1 *Energy-minimized structures of A-norbaccatin III (left) and baccatin III (right); see Experimental Section for details.*

case, a C-13 amide-linked analog (**3**) might be more cytotoxic than **2**, since amide groups are more stable to hydrolysis than ester groups. It was of course recognized that the amide group is more rigid than an ester group, and that the NH group offers additional options for hydrogen bonding, but these effects were difficult to evaluate and could be either positive or negative. We thus initiated a study to prepare the amide-linked A-norpaclitaxel analog **3a** and the two additional derivativaes **3b** and **3c**. These analogs were selected based on the improved activity noted for the corresponding derivatives of paclitaxel.[4a] It is noteworthy that Chen and his collaborators have recently reported the preparation of an amide-linked paclitaxel analog.[8]



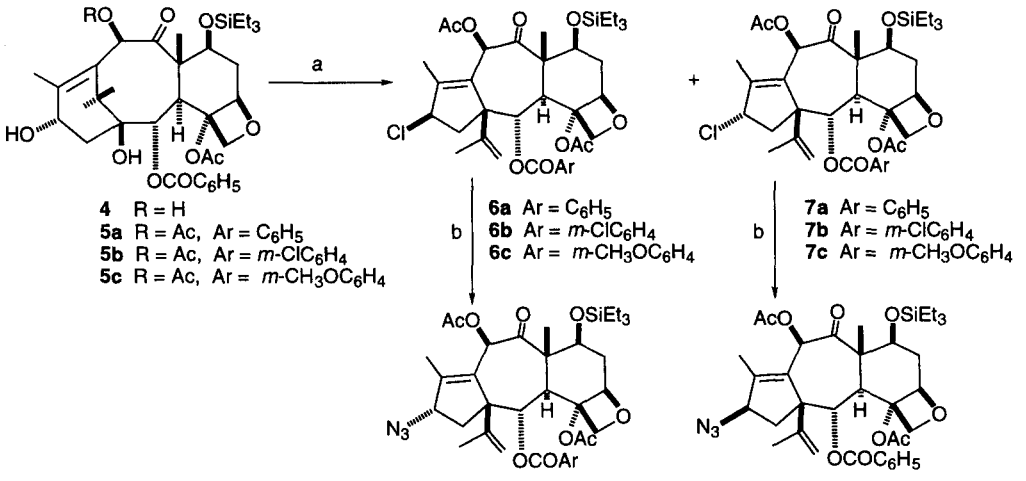
3a R = H
3b R = Cl
3c R = OCH_3

RESULTS AND DISCUSSION

Chemistry

The synthetic pathway envisaged for the preparation of **3** involved the initial formation of an A-norbaccatin III followed by transformation of the C-13 hydroxyl group to an azido group, and final coupling of a protected C-13 side chain and deprotection. The synthesis of the analogs **3b** and **3c** involved the additional steps of debenzoylation of baccatin III at the C-2 position and reacylation with the selected substituted benzoic acid. These proposed pathways were reduced to practice as described below.

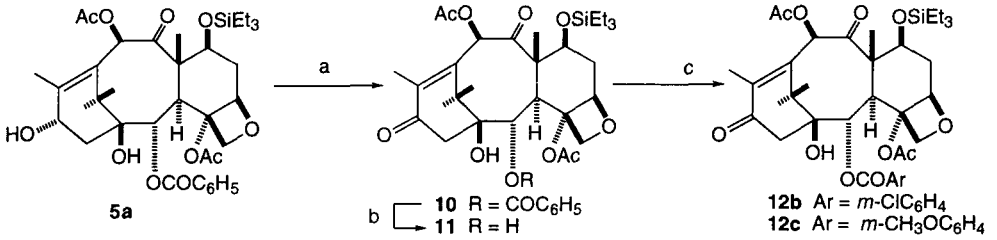
The starting material used for this study was the 10-deacetylbaccatin III, which was converted to 7-*O*-(triethylsilyl)baccatin III (**5a**) by silylation to 10-deacetyl-7-*O*-(triethylsilyl)baccatin III (**4**) followed by selective acetylation to **5a**, as previously described[9]. Treatment of **5a** with excess thionyl chloride in CH_2Cl_2 in the presence of pyridine gave two non-polar products, **6a** and **7a**, both of which showed characteristic ^{1}H-NMR signals for a terminal double bond, indicating that both had undergone ring contraction. In addition, both **6a** and **7a** showed characteristic peaks for chlorine in a 3:1 ratio *m/z* 701 and 703 in FABMS. The structures **6a** and **7a** were assigned to the major and minor products, respectively, on the basis of FABMS and NMR data. The stereochemistry at C-13 was assigned by a NOESY spectrum for each compound. The major compound **6a** showed correlations in its NOESY spectrum between H-13 and a C-2 ortho aroyl proton and between H-13 and the C-18 methyl protons. On the other hand, the minor compound **7a** showed a correlation between H-13 and an olefinic proton on C-17. The formation of both isomers **6a** and **7a** was surprising, and suggests that the mechanism of chlorination at C-13 involves a mechanism with both S_N1 and S_N2 components (Scheme 1).



Scheme 1

The major β-chloro isomer **6a** was treated with sodium azide in DMF/water at 60 °C to give the less polar α-azido product **8a**: a similar reaction with the α-chloro isomer **7a** gave the more polar β-azido isomer **9**. The presence of the azide function in **8a** and **9a** was revealed by an IR absorption at 2100 cm^{-1} for each compound. The fact that only one product was obtained from each reaction defined the reaction as an S_N2 process, and thus established the relative stereochemistry of **8a** as 13-α and that of **9** as 13-β (Scheme 1).[10]

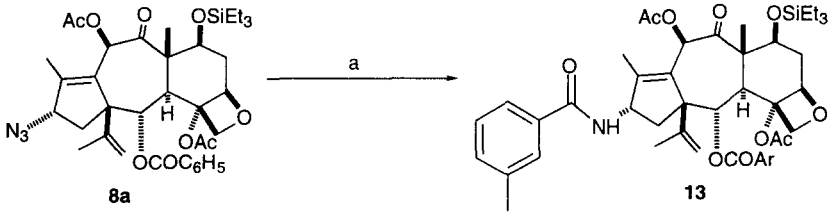
The modified 13-azido-A-norbaccatin III analogs **8b** and **8c** were prepared from the 7-(triethylsilyl)-2-debenzoyl-2-aroylbaccatin III derivatives **6b** and **6c** by the procedure outlined above. Compounds **6b** and **6c** were prepared from 7-*O*-(triethylsilyl)baccatin III (**5a**) by oxidation to the 13-oxo derivative **10**, then treatment with Triton B to give the 2-debenzoyl derivative **11**. Rebenzoylation at C-2 (ArCOOH/DCC/PP) gave the 2-aroyl analogs **12b** and **12c**, which could be reduced to the baccatin III derivatives **5b** and **5c** with sodium borohydride[4b] (Scheme 2).



Reagents: (a) MnO_2, CH_2Cl_2, 91%; (b) Triton B, MeOH/CH_2Cl_2, -78 °C, 30 min, 94%; (c) ArCOOH, DCC, PF $PhCH_3$, 60 °C, 3h, 70-80%

Scheme 2

The final stage of the synthesis required that the paclitaxel side chain be coupled to an amine function at C-13. Initially attempts were made to reduce the C-13 azide to an amine by catalytic hydrogenation or reduction with $NaBH_4$ or PPh_3/H_2O. These methods gave mixtures of products, however, and were thus deemed unsuitable for the desired synthesis. We thus elected the direct coupling of the appropriate acid with the azide group.[11] In a model reaction the azidobaccatin III **8a** was stirred with Bu_3P and *m*-toluic acid at room temperature in toluene to yield the amide **13** in a clean reaction (Scheme 3).

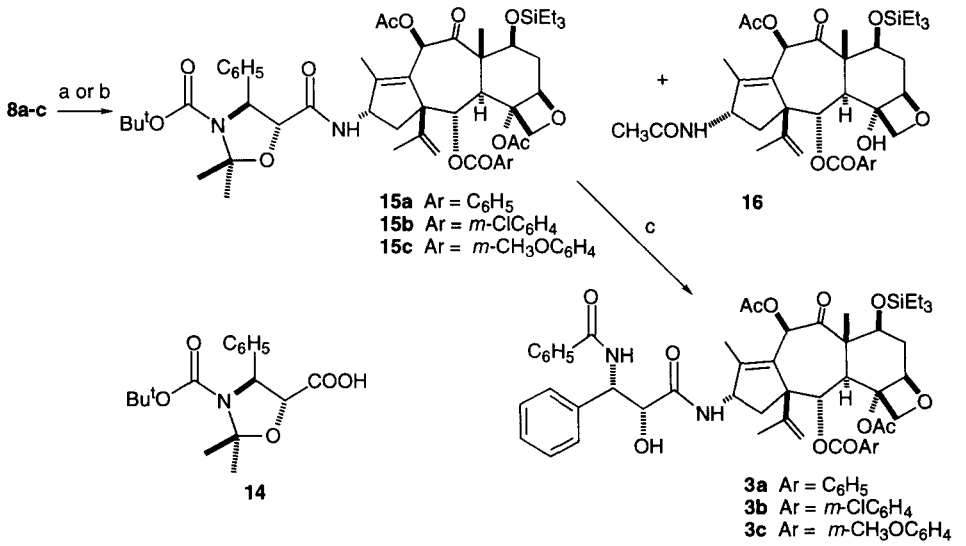


Reagents: (a) *m*-$CH_3C_6H_4COOH$, Bu_3P, $CH_3C_6H_5$, 70 °C, 16 h, 53%

Scheme 3

Repetition of this reaction with the protected side chain acid **14**[12] and the azide **8a** gave the coupled derivative **15a** together with a second product identified as the 4-deacetyl-N-acetyl product **16**. The

formation of **16** can be explained by an intramolecular transacylation reaction; the occurrence of this reaction provides a further example of the similarity of shape between the baccatin III framework and that of the A-norpaclitaxel framework, since a similar transacylation reaction is detectable in baccatin III derivatives.[13] This reaction also incidentally provides independent support for the assignment of the 13-α stereochemistry to the azide group in **8a-c.**



Reagents: (a) **14**, Bu_3P, $CH_3C_6H_5$, 70 °C, 16 h, 25% (**15a**), 22% (**16**); (b) **14**, Bu_3P, $C_6H_5SeSeC_6H_5$, CH_3C_6 25 °C, 24 h, 80-87% (**15a-c**); (c) HCOOH, 25 °C, 2 h, then C_6H_5COCl, $NaHCO_3$, 25 °C, 44-50%.

Scheme 4

In order to minimize the formation of the undesired by-product **16**, the reaction conditions were modified to include diphenyl diselenide to form the activated selenoester derivative of acid **14**.[14] Thus when the 13-α-azide **8a** was added to a previously mixed solution of the acid **14** with Bu_3P and PhSeSePh in toluene at room temperature, and the resulting solution stirred for a further 24h at room temperature, the desired amide **15a** was formed exclusively in excellent yield. The amide **15a** was characterized from its spectroscopic data, and particularly from its ^1H NMR spectrum.

Deprotection of **15a** with formic acid as previously reported[11] followed by benzoylation as described by Georg[15] gave the final product **3a**. The analogs **3b** and **3c** were then prepared by the same procedure from the azides **8b** and **8c**, prepared as described earlier.

Biological Activity

The amides **3a-3c** were assayed for bioactivity in the P-388 cytotoxicity assay, and in addition compound **3c** was examined in a tubulin-assembly assay. All three compounds were significantly less cytotoxic than paclitaxel itself, with compounds **3a-3c** having ED_{50} values of 2.7, 0.38, and 0.1 μg/mL, respectively; in this system paclitaxel has an ED_{50} value of 0.02-0.03 μg/mL. The most cytotoxic analog **3c** was subjected to a tubulin-assembly assay, but it was inactive and indistinguishable from control at a

concentration of 40 μM under conditions in which paclitaxel shows significant tubulin assembly at 10 μM.[16] For comparison purposes, the A-norpaclitaxel analogs corresponding to **3a** and **3c** had ED_{50} values of 0.5 and 0.03 μg/mL in the same cytotoxicity assay; they were also less active in a tubulin-assembly assay than paclitaxel.[6] These results indicate that replacing the ester function at C-13 with an amide function is deleterious to the cytotoxicity of A-norpaclitaxel analogs, at least in the P-388 assay, in spite of providing a hydrolytically more stable linkage. It should also be noted that Chen et al. found that their amide-linked paclitaxel analogs were also significantly less active than paclitaxel.[8]

EXPERIMENTAL

General methods: General methods and experimental procedures were the same as described previously.[17] The structures of Figure 1 were obtained with the MacSpartan program, Wavefunction Inc., Irvine, CA, using the SYBYL force field.

7-Triethylsilyl-13-oxobaccatin III (10).[18] 7-(Triethylsilyl)baccatin III (**5a**, 250mg, 0.0357 mmol) was dissolved in 10.0 mL CH_2Cl_2. Manganese dioxide (155 mg, 1.79 mmol, 5.0 equiv.) was added to the stirring solution, and the reaction was allowed to proceed at room temperature under argon for 1 h. The reaction mixture was filtered through Celite, and the solvent evaporated to give a crude product which was purified by preparative TLC (EtOAc:hexanes, 1:2) to give 228mg (91.5%) of 7-triethylsilyl-13-oxo-baccatin III (**10**) as a white amorphous powder. ^{1}H NMR: δ 0.59 (6H, q, J = 7.6, $SiCH_2$), 0.92 (9H, t, J = 7.6, CH_2CH_3), 1.19 (3H, s), 1.25 (3H, s), 1.27 (3H, s) 1.67 (3H, s), 1.88 (1H, m), 2.19 (3H, s), 2.23 (3H, s), 2.54 (1H, m), 2.81 (2H, ABq), 3.92 (1H, d, J = 6.7), 4.23 (2H, ABq, J = 8.4, $\Delta\nu_{AB}$ 56, H_2-20), 4.49 (1H, dd, J = 6.8, 10.4), 4.93 (1H, br d, J = 9.3), 5.70 (1H, d, J = 6.8), 6.59 (1H, s) 7.46-7.66 (3H, m), 8.08 (2H, dd, J = 1.1, 8.4). FABMS *m/z* $[M+H]^+$ 699.

2-Debenzoyl-7-(triethylsilyl)-13-oxobaccatin III (11). To a cooled (dry ice, acetone -78 °C) and stirred solution of 13-oxo-7-(triethylsilyl)baccatin III (**10**) (150 mg, 0.215 mmol) in dry CH_2Cl_2 (2.0 mL) was added Triton-B (0.1 mL, 40% v/v in methanol, 0.215 mmol) by syringe. The mixture was allowed to stir at -78° for 30 minutes; during this time the starting material was consumed to form a more polar compound as analyzed by TLC. The reaction mixture was quenched with dil. HCl and diluted with CH_2Cl_2 (10 mL). The CH_2Cl_2 layer was washed with dil. $NaHCO_3$, water, and finally with brine. The organic layer was dried over Na_2SO_4 and evaporated to give crude product which was purified by preparative TLC (silica gel, 1000μm, hexanes :EtOAc 1:1) to furnish the debenzoyl compound **12** (120mg, 94%). ^{1}H NMR: δ 0.58 (6H, q, J = 7.6, $SiCH_2$), 0.91 (9H, t, J = 7.6, CH_2CH_3), 1.16 (3H, s, 16-H), 1.19 (3H, s, 17-H), 1.65 (3H, s, 19-H), 1.88 (1H, m, 6-H), 2.04 (3H, s, 18-H), 2.13 (3H, s, 10-OAc), 2.20 (3H, s, 4-OAc), 2.52 (1H, m, 6-H), 2.56 (1H, d, J = 19.7, 14-H), 2.81 (1H, d, J = 19.1, 14-H), 3.55 (1H, d, J = 6.4, 3-H), 3.95 (1H, t, J = 6.4, 1H, 2-H), 4.43 (1H, dd, J = 6.7,10.3, 7-H), 4.7 (2H, ABd, J = 9.0, H_2-20), 4.92 (1H, d, J = 8.2, 5-H), 6.52 (1H, s, 10-H). FABMS *m/z* $[M+H]^+$ 595.

Preparation of 2-aroyl-2-debenzoyl-7-(triethylsilyl)-13-oxobaccatins III (12b and 12c). A mixture of DCC (1.0 mmol), pyrrolidinopyridine and substituted benzoic acid (1.0 mmol) in dry toluene (0.2 mL) was stirred at room temperature for 5 min. To this mixture a solution of 2-debenzoyl-13-oxo-7-(triethylsilyl)baccatin III (**11**) (0.1 mmol) in dry toluene (0.1 mL) was added and mixture was heated at 60 °C for 2-3 h. The reaction mixture was allowed to cool to room temperature and was then diluted with EtOAc (2 mL). The mixture was filtered through a pad of silica gel and Celite. The crude material obtained after evaporation was subjected to column chromatography over silica gel to yield the 2-debenzoyl-2-aroyl-13-oxo-7-(triethylsilyl)baccatin III derivatives (**12b** and **12c**) (70-80%)

2-(m-Chlorobenzoyl)-2-debenzoyl-7-(triethylsilyl)-13-oxobaccatin III (12b): ^{1}H NMR: δ 0.59 (6H, q, *J* = 7.6, $SiCH_2$), 0.94 (9H, t, *J* = 7.6, CH_2CH_3), 1.19 (3H, s, 16-H), 1.27 (3H, s, 17-H), 1.66 (3H, s, 19-H), 2.18 (3H, s, 18-H), 2.20 (3H, s, 10-OAc), 2.23 (3H, s, 4-OAc), 2.54 (1H, m, 6-H), 2.66 (1 H, d, *J* = 19.9, 14-H), 2.93 (1H, d, *J* = 19.9, 14-H), 3.91 (1H, d, *J* = 6.8, 3-H), 4.11 (1H, d, *J* = 8.3, 1H, 20-H), 4.30 (1H, d, *J* = 8.3 20-H), 4.48 (1H, dd, *J* = 6.8,10.3, 7-H), 4.93 (1H, d, *J* = 8.5, 5-H), 5.65 (1H, d, *J* = 6.8, 2-H), 6.59 (1H, s, 10-H), 7.43 (1H, t, *J* = 7.0, Ar 5'-H), 7.58 (1H, d, *J* = 7.0, Ar 4'-H), 7.95 (1H, d, *J* = 7.7, Ar 6'-H), 8.05 (1H, br s, Ar 2'-H). FABMS *m/z* $[M+H]^+$ 733.

2-Debenzoyl-7-(triethylsilyl)-2-(m-methoxybenzoyl)-13-oxobaccatin III (12c): ^{1}H NMR:δ 0.59 (6H, q, *J* = 7.6, $SiCH_2$), 0.93 (9H, t, *J* = 7.6, CH_2CH_3), 1.19 (3H, s, 16-H), 1.27 (3H, s, 17-H), 1.66 (3H, s, 19-H), 2.18 (3H, s, 18-H), 2.20 (3H, s, 10-OAc), 2.23 (3H, s, 4-OAc), 2.54 (1H, m, 6-H), 2.66 (1 H, d, *J* = 19.9, 14-H), 2.93 (1H, d, *J* = 19.9, 14-H), 3.91 (1H, d, *J* = 6.8, 3-H), 4.11 (1H, d, *J* = 8.3, 1H, 20-H), 4.30 (1H, d, *J* = 8.3 20-H), 4.48 (1H, dd, *J* = 6.8,10.3, C-7 H), 4.93 (1H, d, *J* = 8.5, 5-H), 5.65 (1H, d, *J* =6.8, 2-H), 6.59 (1H, s, 10-H), 6.70 (1H, d, *J* = 7.7, Ar 4'-H), 7.14 (1H, br d, *J* = 7.6, Ar 5'-H), 7.38 (1H, t, *J* = 8.0, Ar 6'-H), 7.62 (1H, br s, Ar 2'-H). FABMS *m/z* $[M+H]^+$ 729.3.

Reduction of 2-aroyl-2-debenzoyl-7-(triethylsilyl)-13-oxobaccatins III (12b and12c) to the corresponding baccatin III analogs 5b and 5c. To a solution of 2-aroyl-2-debenzoyl-7-(triethylsilyl)-13-oxobaccatin III (0.5 mmol) in dry THF (2.0 mL) was added $NaBH_4$ (38.0 mg, 1.0 mmol) followed by MeOH (0.5 mL). The mixture was stirred at room temperature for 15 minutes, diluted with EtOAc, and quenched with dil. HCl. The organic layer was separated washed with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure to yield crude product. Column chromatography over silica gel gave pure 2-aroyl-7-(triethylsilyl)baccatin III (**5b,5c**) (80-84%).

2-(m-Chlorobenzoyl)-2-debenzoyl-7-(triethylsilyl)baccatin III (5b): ^{1}H NMR: δ 0.58 (6H, q, *J* = 7.7, $SiCH_2$), 0.92 (9H, t, *J* = 7.7, CH_2CH_3), 1.03 (3H, s, 16-H), 1.17 (3H, s, 17-H), 1.67 (3H, s, 19-H), 1.90 (1H, m, 6-H), 2.17 (6H, s, 18-H & 10-OAc), 2.29 (3H, s, 4-OAc), 2.55 (1H, m, 6-H), 3.88 (1H, d, *J* = 7.0, 3-H), 4.11 (1H, d, *J* = 7.0, 1H, 20-H), 4.28 (1H, d, *J* = 7.0 20-H), 4.67 (1H, dd, *J* = 6.8, 10.2, C-7 H), 4.81 (1H, m, 13-H), 4.97 (1H, d, *J* = 8.5, 5-H), 5.58 (1H, d, *J* = 7.0, 2-H), 6.45 (1H, s, 10-H), 7.42 (1H, t, *J* = 7.9, Ar 5'-H), 7.58 (1H, d, *J* = 8.0, Ar 4'-H), 7.97 (1H, d *J* = 7.7, Ar 6'-H), 8.11 (1H, br s, Ar 2'-H). FABMS *m/z* $[M+H]^+$ 735.

2-Debenzoyl-7-(triethylsilyl)-2-(m-methoxybenzoyl)baccatin III (5c): ^{1}H NMR: δ 0.58 (6H, q, *J* = 7.6, $SiCH_2$), 0.92 (9H, t, *J* = 7.6, CH_2CH_3), 1.03 (3H, s, 16-H), 1.19 (3H, s, 17-H), 1.67 (3H, s, 19-H), 1.91 (1H, m, 6-H), 2.17 (6H, s, 18-H & 10-OAc), 2.26 (3H, s, 4-OAc), 2.55 (1H, m, 6-H), 3.86 (3H, s, OMe), 3.89 (1H, d, *J* = 7.0, 3-H), 4.14 (1H, d, *J* = 8.2, 1H, 20-H), 4.34 (1H, d, *J* = 8.2, 20-H), 4.49 (1H, dd, *J* = 6.7, 10.2, C-7 H), 4.82 (1H, t, 13-H), 4.96 (1H, d, *J* = 8.0, 5-H), 5.62 (1H, d, *J* = 7.0, 2-H), 6.46 (1H, s, 10-H), 6.69 (1H, d, *J* = 7.7, Ar 4'-H), 7.12 (1H, br d, *J* = 7.6, Ar 5'-H), 7.37 (1H, t, *J* = 8.0, Ar 6'-H), 7.63 (1H, br s, Ar 2'-H). FABMS *m/z* $[M+H]^+$ 731.

Reaction of 7-(triethylsilyl)baccatin III derivatives (5a-c) with thionyl chloride. To a stirred solution of 7-(triethylsilyl)baccatin III derivative (**5a-c**) (0.1mmol) in dry CH_2Cl_2 (2.0 mL) was added dry pyridine (0.1 mL) followed by thionyl chloride (0.025 mL, excess) at room temperature. The mixture was stirred at room temperature for 15 minutes. TLC analysis (8:2, hexanes:EtOAc) showed that starting material was completely consumed to form two new less polar spots (Rf 0.4 for **6a** and 0.5 for **7a**). The mixture was diluted with CH_2Cl_2 (15 mL) and washed with dil $NaHCO_3$, dil. HCl, again with dil $NaHCO_3$ and finally with water and brine. The organic layer was dried over Na_2SO_4 and evaporated to give crude product as a thick pale yellow syrup. The crude product was purified by preparative TLC (silica gel, 500μm, 4:1 hexanes:EtOAc) to furnish two compounds (**6a-c**) and (**7a-c**) in 86-90% overall yield.

The major more polar compounds **6a-6c** were formed in 65-70% yield.

Compound 6a: ^{1}H NMR : δ 0.59 (6H, q, *J* = 7.6, Si-CH_2), 0.92 (9H, t, *J* = 7.6, CH_2CH_3), 1.59 (s, 3H, 19-CH_3), 1.76 (s, 3H, 18-CH_3), 1.89 (s, 3H, 16-CH_3), 1.95 (3H, s, 10-OAc), 2.18 (3H, s, 4-OAc), 2.50 (2H, m, 6-H & 14-H), 3.13 (1H, d, *J* = 9.8, 3-H), 4.27 (1H, d, *J* = 8.2, 20-H), 4.45 (2H, m, 20-H & 7-H), 4.69 (1H, t, *J* = 6.0, 13-H), 4.85 (1H, d, *J* = 8.0, 5-H), 4.96 (1H, s, olefinic H), 5.22 (1H, s, olefinic H), 5.99 (1H, d, *J* = 9.8, 2-H), 6.45 (1H, s, 10-H), 7.44-7.64 (3H, m, ArH), 8.14 (2H, d,

J = 8.3, o-ArCOH); ^{13}C NMR δ 5.23, 6.83, 10.09, 12.87, 20.47, 20.89, 21.55, 37.40, 46.02, 46.43, 54.21, 64.11, 65.07, 70.05, 71.12, 73.16, 74.40, 79.50, 84.58, 114.39, 128.72, 129.18, 129.69, 133.80, 135.48, 145.49, 145.56 165.01 169.13, 169.64, 200.13; FABMS *m/z* (rel int.) $[M+H]^+$ 701 (90), 611 (93), 429 (89), HRFAB *m/z* $[M+H]^+$ 701.2899 ($C_{37}H_{50}O_9ClSi$ requires 701.2912).

Compound 6b: ^{1}H NMR is similar to that of **6a** except for aromatic signals as follows: 7.46 (1H, t, *J* = 7.9, Ar 5'-H), 7.62 (1H, d, *J* = 8.0, Ar 4'-H), 7.88 (1H, d, *J* = 7,7, Ar 6'-H), 7.95 (1H, br s, Ar 2'-H); FABMS *m/z* $[M+H]^+$ 735.

Compound 6c: ^{1}H NMR is similar to that of **6a** except for an additional signal at 3.83 (3H, s, OMe), and aromatic signals; 7.20 (1H, t, *J* = 7.9, Ar 5'-H), 7.41 (1H, d, *J* = 8.0, Ar 4'-H), 7.56 (1H, d, *J* = 7,7, Ar 6'-H). FABMS *m/z* $[M+Na]^+$ 753

The less polar compounds **7a-7c** were formed in 28-30% yield.

Compound 7a: ^{1}H NMR : δ 0.61 (6H, q, *J* = 7.6, Si-CH_2), 0.94 (9H, t, *J* = 7.6, CH_2CH_3), 1.67 (3H, s, 19-CH_3), 1.72 (3H, s, 18-CH_3), 1.85 (3H, s, 16-CH_3), 1.87 (1H, br t, *J* = 12.7, 1H, 14-H), 2.15 (3H, s, 10-OAc), 2.27 (3H, s, 4-OAc), 2.57 (1H, m, 6-H), 2.69 (1H, dd, *J* = 6.5, 13.9, 14-H), 3.51 (1H, d, *J* = 8.0, 3-H), 4.23 (2H, br s, 20-H), 4.53 (1H, dd, *J* = 7.2,9.5, 1H, 7-H), 4.78 (2H, m, 13-H & olefinic H), 4.95 (1H, s, olefinic H), 5.01 (1H, d, *J* = 8.0, 5-H), 5.67 (1H, d, *J* = 8.0, 2-H), 6.35 (1H, s, 10-H), 7.44-7.64 (3H, m, ArH), 8.03 (2H, d, *J* = 7.1, o-ArCOH); ^{13}C NMR δ 5.21, 6.86, 9.22, 12.29, 20.39, 20.62, 22.07, 38.13, 43.62, 44.36, 56.52, 64.04, 64.52, 70.66, 70.78, 72.21, 74.50, 78.89, 84.73, 113.08, 128.61, 129.13, 129.82, 133.62, 136.50, 144.45, 145.97, 165.17, 168.78, 170.03, 201.36; FABMS *m/z* (rel int.) $[M+H]^+$ 701; HRFAB *m/z* $[M+H]^+$ 701.2938 ($C_{37}H_{50}O_9ClSi$ requires 701.2912)

Compound 7b: ^{1}H NMR: similar to that of **7a** except for the aromatic signals; 7.42 (1H, t, *J* = 7.8, Ar 5'-H), 7.56 (1H, dd, *J* = 1.1, 5.8, Ar 4'-H), 7.92 (1H, d, *J* = 7.7, Ar 6'-H), 8.06 (1H, dd, *J* = 1.7,3.6, Ar 2'-H). FABMS *m/z* (rel int.) $[M+H]^+$ 735.

Compound 7c: ^{1}H NMR: similar to that of **7a** except for an additional signal at 3.85 (3H, s, OMe) and aromatic signals; 7.16 (1H, dd, *J* = 7.8, Ar 5'-H), 7.37 (1H, t, *J* = 7.9, Ar 4'-H), 7.56 (1H, br s, Ar 2'-H), 7.62 (1H, d, *J* = 7.6, Ar 6'-H). FABMS *m/z* (rel int.) $[M+H]^+$ 731.

Preparation of 13-α-azido-7-(triethylsilyl)-A-nor-baccatin III derivatives (8a-8c). A 13-β-chloro-7-(triethylsilyl)-A-nor-baccatin III derivative (**6a-c**) (0.05mmol) was dissolved in DMF (0.5 mL) and two drops of water. To this solution NaN_3 (30 mg, excess) was added and the mixture was heated on an oil bath at 70 °C for one hour and the reaction mixture cooled to room temperature. The mixture was then diluted with EtOAc (10 mL) and washed with water and brine. The organic layer was dried over Na_2SO_4 and evaporated to yield crude compound. The crude compound was further purified by preparative TLC (silica gel, 500μm, 4:1 hexanes:EtOAc) to furnish pure **8a-8c** (95-98%).

Compound 8a:: IR(nujol) 2100, 1720 br cm^{-1}; ^{1}H NMR: δ 0.61 (6H, q, *J* = 7.7, Si-CH_2), 0.93 (9H, t, *J* = 7.7, CH_2CH_3), 1.68 (3H, s, 19-CH_3), 1.72 (3H, s, 18-CH_3), 1.82 (3H, s, 16-CH_3), 2.15 (3H, s, 10-OAc), 2.27 (3H, s, 4-OAc), 2.47 (1H, dd, *J* = 6.7,13.5, 14-H), 2.60 (1H, m, 6-H), 3.46 (1H, d, *J* = 7.8, 3-H), 4.23 (2H, br s, 20-H), 4.36 (1H, t, *J* = 6.9, 13-H), 4.50 (1H, dd, *J* = 7.4, 9.5, 7-H), 4.77 (1H, s, olefinic H), 4.92 (1H, s, olefinic H), 5.00 (1H, d, *J* = 8.9, 5-H), 5.64 (1H, d, *J* = 7.8, 2-H), 6.35 (1H, s, 1H, 10-H), 7.44-7.64 (3H, m, ArH), 8.0.1 (2H, d, *J* = 8.3, o-ArCOH); ^{13}C NMR δ 5.21, 6.86, 9.17, 11.95, 20.41, 20.67, 21.87, 38.16, 39.21, 44.10, 56.61, 63.92, 67.19, 70.62, 70.71, 72.24, 74.48, 78.88, 84.73, 112.94, 128.66 , 129.21, 129.75, 133.62, 136.39, 144.46, 145.50 165.16 168.83, 170.04, 201.47; FABMS *m/z* (rel int.) $[M+H]^+$ 708.4 (90), 408 (95), HRFAB *m/z* $[M+H]^+$ 708.3303 ($C_{37}H_{50}O_9N_3Si$ requires 708.3316).

Compound 8b: ^{1}H NMR is similar to that of **8a** except for aromatic signals: δ 7.43 (1H, t, *J* = 7.8, Ar 5'-H), 7.58 (1H, br d, *J* = 8.1, Ar 4'-H), 7.91 (1H, d, *J* = 7.7, Ar 6'-H), 8.0.4 (1H, s, Ar 2'-H). FABMS: *m/z* (rel int.) $[M+H]^+$ 742 (60), 744 (21).

Compound 8c: ^{1}H NMR is similar to that of **8a** except for an additional signal at 3.86 (3H, s, OMe) and aromatic signals: 7.16 (1H, dd, *J* = 2.6,8.1, Ar 4'-H), 7.38 (1H, t, *J* = 8.1, Ar 5'-H), 7.55 (1H, br s, Ar 2'-H), 7.60 (1H, d, *J* = 7.6, Ar 6'-H). FABMS *m/z* $[M+H]^+$ 738.

Preparation of 13-β-azido-7-(triethylsilyl)-A-nor-baccatin III (9). Reaction of 13–α–chloro-7-(triethylsilyl)-A-nor-baccatin III (**7a**, 45.0mg, 0.064 mmole) under similar conditions to those described above for the β-isomer gave compound **9** (42 mg, 94%). ^{1}H NMR: δ 0.58 (6H, q, *J* = 7.5, Si-CH_2), 0.93 (9H, t, *J* = 7.5, CH_2CH_3), 1.58 (3H, s, 19-CH_3), 1.77 (3H, s, 18-CH_3), 1.87 (3H, s, 16-CH_3), 1.94 (3H, s, 10-OAc), 2.18 (3H, s, 4-OAc), 2.27 (1H, dd, *J* = 7.4, 14.3, 14-H), 2.49 (1H, m, 6-H), 2.69 (1H, dd, *J* = 6.5, 13.9, 14-H), 3.11 (1H, d, *J* = 10.0, 3-H), 4.13 (1H t, *J* = 6.8, 13-H), 4.30 (1H, d, *J* = 8.2, 20-H), 4.44 (1H, dd, *J* = 7.1,9.8, 7-H), 4.50 (1H, d, *J* = 8.2, 20-H), 4.84 (1H, d, *J* = 7.8, 5-H), 4.97 (1H, s, olefinic H), 5.22 (1H, s, olefinic H), 6.04 (1H, d, *J* = 10.0, 2-H), 6.39 (1H, s, 10-H), 7.44-7.64 (3H, m, ArH), 7.97 (2H, d, *J* = 7.0, o-ArCOH). FABMS: *m/z* (rel int.) $[M+H]^+$ 708.3 (26); HRFAB: *m/z* $[M+H]^+$ 708.3319 ($C_{37}H_{50}O_9N_3Si$ requires 708.3316).

Reaction of 13-α-azido-7-(triethylsilyl)-A-nor-baccatin III (8a) with Bu3P and *m*-toluic acid. To a stirred solution of compound **8a** (5.0 mg, 0.007 mmol) in dry toluene was added Bu_3P (10.0 μL) under nitrogen at room temperature. After stirring for 1h *m*-toluic acid (6.0 mg, 0.04 mmol) was added to the reaction mixture which was then heated with stirring at 70 °C on an oil bath for 16 h. After cooling to room temperature the mixture was diluted with EtOAc and washed with dil. $NaHCO_3$, water, and brine. The organic layer was dried over Na_2SO_4 and evaporated to yield crude product. Purification of crude product by preparative TLC (silica gel, 500 μm, 3:1; hexanes:EtOAc) gave compound **13** (3.0 mg, 53%). ^{1}H NMR: δ 0.63 (6H, q, *J* = 7.4, Si-CH_2), 0.95 (9H, t, *J* = 7.4, CH_2CH_3), 1.70 (3H, s, 19-CH_3), 1.79 (3H, s, 18-CH_3), 1.83 (3H, s, 16-CH_3), 1.95 (1H, m, 14-H), 2.00 (3H, s, 10-OAc), 2.15 (3H, s, 4-OAc), 2.44 (3H, s, ArCH_3), 2.64 (2H, m, 6-H & 14-H), 3.76 (1H, d, *J* = 7.5, 3-H), 4.16 (1H, d, *J* = 8.2, 20-H), 4.38 (1H, d, *J* = 8.2, 20-H), 4.47 (1H, br t, *J* = 7.4, 7-H), 4.79 (1H, br s, olefinic H), 4.92 (1H, br s, olefinic H), 4.94 (1H, d, *J* = 8.4, 5-H), 5.20 (1H, m, 13-H), 5.63 (1H, d, *J* = 7.5, 2-H), 6.19 (1H, d, *J* = 8.2, C-13NH), 6.37 (1H, s, 10-H), 7.35-7.56 (5H, m, ArH), 7.71 (1H, br s, ArH), 7.91 (2H, m, o-ArCOH & ArH). FABMS: *m/z* $[M+H]^+$ 800.3.

Reaction of 13–α–azido-7-(triethylsilyl)-A-nor-baccatin III (8a) with Bu3P and acid 14. To a stirred solution of compound **8a** (8.5 mg, 0.012 mmol) in dry toluene was added Bu3P (15.0 μL) under nitrogen at room temperature. After stirring for 1h at room temperature the reaction mixture was transferred to an oil bath (70 °C), and acid **14** (17.0 mg, 0.051mmol) was added. Heating with stirring was continued for 16 h, after which the mixture was cooled to room temperature, diluted with EtOAc, and washed with dil. $NaHCO_3$, water and brine. The organic layer was dried over Na_2SO_4 and evaporated to obtained crude product, which was purified by preparative TLC (silica gel, 500 μm, 3:1; hexanes:EtOAc) to yield two compounds.

The major non-polar (R_f 0.5) compound was **15a** (3.0 mg, 25%). ^{1}NMR: δ 0.63 (6H, q, *J* = 7.5, Si-CH_2), 0.94 (9H, t, *J* = 7.5, CH_2CH_3), 1.18 (9H, br s, t-BOC), 1.58 (1H, dd, *J* = 8.8, 13.4, H-14), 1.68 (3H, s, 19-H), 1.76 (3H, s, CH_3), 1.78 (3H, s, CH_3), 1.81 (3H, s, 18-H), 1.83 (3H, s, 16-H), 2.16 (3H, s, 10-OAc), 2.24 (3H, s, 4-OAc), 2.52 (2H, m, 6-H & 14-H), 3.68 (1H, d, *J* = 7.6, 3-H), 4.18 (1H, d, *J* = 8.0, 20-H), 4.32 (1H, d, *J* = 8.0, 20-H), 4.36 (1H, d, *J* = 6.1, 2'-H), 4.48 (1H, t, 7-H), 4.76 (1H, s, olefinic H), 4.90 (1H, s, olefinic H), 4.94 (2H, m, 5-H & 13-H), 5.09 (1H, m, 3-H'), 5.61 (1H, d, *J* = 7.6, 2-H), 6.36 (1H, s, 10-H), 6.51 (1H,d, *J* = 9.3, 13-NH), 7.22-7.57 (8H, m, ArH), 7.94 (2H, d, *J* = 7.1, o-ArCOH). FABMS *m/z* (rel int.) $[M+H]^+$ 985 (100), HRFAB *m/z* $[M+H]^+$ 985.4902 ($C_{54}H_{73}O_{13}N_2Si$ requires 985.4881).

The minor polar (R_f 0.3) compound was **16** (1.8 mg, 22%). ^{1}H NMR : δ 0.63 (6H, q, *J* = 7.9, Si-CH_2), 0.95 (9H, t, *J* = 7.9, CH_2CH_3), 1.62 (1H, m, 14-H), 1.68 (3H, s, 19-CH_3), 1.76 (3H, s, 18-CH_3), 1.79 (3H, s, 16-CH_3), 1.96 (1H, m, 6-H), 2.15 (3H, s, 10-OAc), 2.29 (3H, s, NH-Ac), 2.70 (2H, m, 6-H & 14-H), 3.68 (1H, d, *J* = 7.5, 3-H), 4.19 (1H, d, *J* = 8.2, 20-H), 4.38 (1H, d, *J* = 8.2, 20-H), 4.45 (1H, br t, *J* = 7.7, 7-H), 4.62 (1H, d, *J* = 9.2, 13-NH), 4.76 (1H, s, olefinic H), 4.89 (2H, m, 13-H & olefinic H), 4.97 (1H, d, *J* = 8.2, 5-H), 5.63 (1H, d, *J* = 7.5, 2-H), 6.33 (1H, s, 10-H), 7.44-7.63 (3H, m, ArH), 7.97 (2H, dd, *J* = 7.1, 1.4, o-ArCOH).

Reaction of 13-α-azido-7-(triethylsilyl)-A-nor-baccatins III 8a-8c with Bu_3P, PhSeSePh and acid 14. To a solution of acid **14** (32.6 mg, 0.1 mmol) in dry toluene (0.2 mL) was added diphenyldiselenide (31.2 mg, 0.1 mmol) and tributyl phosphine (25.0 μL, 0.11 mmol). The mixture was stirred at room temperature for 30 min, and to this mixture a 13-azido-A-nor-baccatin derivative (**8a**, **8b**, or **8c**) (0.041 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, after which TLC analysis showed the absence of starting material and the presence of a new polar spot (Rf 0.4, 3:1 hexanes:EtOAc). The reaction mixture was diluted with EtOAc (10 mL) and washed with water and brine. The organic layer was separated, dried over Na_2SO_4, and evaporated. The crude product thus obtained was purified by preparative TLC (silica gel, 500μm, 3:1 hexanes:EtOAc) to furnish the coupled compound **15a-c** (80-87%).

*Compound **15a*** was identical in all respect with the compound obtained from the previous reaction.

*Compound **15b***: ^{1}NMR: δ 0.62 (6H, q, *J* = 7.7, Si-CH_2), 0.94 (9H, t, *J* = 7.7, CH_2CH_3), 1.17 (9H, br s, t-boc), 1.54 (1H, dd, *J* =6.5, 13.5, 14-H), 1.68 (3H, s, 19-CH_3), 1.73 (3H, s, CH_3), 1.77 (3H, s, CH_3), 1.80 (3H, s, 18-CH_3), 1.83 (3H, s, 16-CH_3), 1.91 (1H, m, 6-H), 2.15 (3H, s, 10-OAc), 2.26 (3H, s, 4-OAc), 2.52 (1H, dd, *J* = 7.1, 13.5, 14-H), 2.60 (1H, m, 6-H), 3.68 (1H, d, *J* = 7.7, 3-H), 4.19 (1H, d, *J* = 8.0, 20-H), 4.27 (1H, d, *J* = 8.0, 20-H), 4.33 (1H, d, *J* = 6.0, 2'-H), 4.49 (1H, br t, *J* = 7.5, 7-H), 4.77 (1H, s, olefinic H), 4.90 (1H, s, olefinic H), 5.00 (2H, m, 5-H & 13-H), 5.05 (1H, dd, *J* = 6.0, 9.2 , 3-H'), 5.59 (1H, d, *J* = 7.7, 2-H), 6.35 (1H, s, 10-H), 6.49 (1H, d, *J* = 9.2, 13-NH), 7.22-7.40 (6H, m, ArH), 7.50 (1H, d, *J* = 7.1, 2-Ar 4'-H), 7.81 (1H, d, *J* = 7.7, 2-Ar 6'-H), 7.93 (1H, s, 2-Ar 2'-H). ^{13}C NMR δ 5.20, 6.84, 9.24, 11.70, 20.42, 20.55, 22.06, 26.84, 27.98, 38.46, 40.20, 43.60, 54.37, 57.04, 63.59, 64.16, 70.80, 71.30, 72.32, 74.73, 79.89, 81.71, 84.85, 112.96, 126.15, 127.46, 127.78, 128.47, 129.70, 129.99, 130.98, 133.56, 134.75, 136.08, 144.06, 145.72, 151.56, 163.95, 169.00, 170.10, 170.39, 201.29. FABMS *m/z* (rel int.) $[M+H]^+$ 1019.4 (65), HRFAB *m/z* $[M+H]^+$ 1019.4519 ($C_{54}H_{71}O_{13}N_2SiCl$ requires 1019.4492)

*Compound **15c***: ^{1}NMR: δ 0.62 (6H, q, *J* = 7.6, Si-CH_2), 0.94 (9H, t, *J* = 7.6, CH_2CH_3), 1.18 (9H, br s, t-boc), 1.54 (1H, dd, *J* =6.5, 13.4, 14-H), 1.68 (3H, s, 19-CH_3), 1.75 (3H, s, CH_3), 1.77 (3H, s, CH_3), 1.80 (3H, s, 18-CH_3), 1.82 (3H, s, 16-CH_3), 1.91 (1H, m, 6-H), 2.15 (3H, s, 10-OAc), 2.24 (3H, s, 4-OAc), 2.51 (1H, dd, *J* =7.0, 13.5, 14-H), 2.60 (1H, m, 6-H), 3.67 (1H, d, *J* = 7.6, 3-H), 3.81 (3H, s, OMe), 4.21 (1H, d, *J* = 8.0, 20-H), 4.31 (1H, d, *J* = 8.0, 20-H), 4.34 (1H, d, *J* = 6.0, 2'-H), 4.49 (1H, br t, *J* =7.5, 7-H), 4.76 (1H, s, olefinic H), 4.90 (1H, s, olefinic H), 4.99 (2H, m, 5-H & 13-H), 5.07 (1H, dd, *J* = 6.0, 9.4, 3-H'), 5.59 (1H, d, *J* = 7.6, 2-H), 6.36 (1H, s, 10-H), 6.48 (1H, d, *J* = 9.4, 13-NH), 7.08 (1H, dd, *J* = 2.4, 8.0, 2-Ar 4'-H), 7.22-7.35 (6H, m, ArH), 7.47 (1H, br s, 2-Ar 2'-H), 7.51 (1H, d, *J* = 8.0, 2-Ar 6'-H). ^{13}C NMR δ 5.22, 6.84, 9.25, 11.67, 20.41, 20.58, 22.09, 26.85, 27.98, 38.49, 40.23, 43.62, 54.40, 55.38, 57.11, 63.68, 64.18, 70.86, 70.98, 72.33, 74.86, 79.92, 81.73, 84.87, 112.93, 114.67, 119.59, 121.83, 126.17, 127.45, 128.46, 129.60, 130.53, 136.28, 144.16, 145.58, 151.57, 159.67, 165.13, 169.00, 170.06, 170.41, 201.39. FABMS *m/z* (rel int.) $[M+H]^+$ 1015.4 (35), HRFAB *m/z* $[M+H]^+$ 1015.4981 ($C_{55}H_{74}O_{14}N_2Si$ requires 1015.4988)

Reaction of amides 15a-15c with formic acid followed by PhCOCl/$NaHCO_3$: preparation of amido-A-norpaclitaxels 3a-3c. The coupled compound **15a-c** (0.015 mmol) was dissolved in formic acid (50.0 mL, 97%), and the solution was stirred at room temperature for 2 h. The solution was then diluted with EtOAc (10 mL), and washed with dil $NaHCO_3$ solution followed by water and brine. The organic layer was separated, dried and evaporated to get crude amine. This crude amine was then treated with benzoyl chloride (2.8 μL, 0.02 mmol) and $NaHCO_3$ (2.1 mg, 0.25 mmol) under biphasic conditions in EtOAc:water (1.0 mL, 1:1). After stirring for 1 h at room temperature the reaction mixture was diluted with EtOAc (10 mL) and washed with water and brine. The organic layer was dried and evaporated to give crude product. Further purification with preparative TLC (silica gel, 500μm, 3:7 hexanes:EtOAc) gave the pure product **3a-3c** (44-50%).

*Compound **3a***: ^{1}H NMR : δ 1.16 (3H, s, C-19 CH_3), 1.61 (3H, s, 18-CH_3), 1.66 (3H, s, C-16CH_3), 1.93 (1H, m, 6-H), 2.16 (3H, s, 10-OAc), 2.18 (3H, s, 4-OAc), 2.30 (1H, dd, 14-H), 2.60 (1H, m, 6-H), 3.41 (1H, d, *J* = 8.7, 3-H), 4.29 (1H, d, *J* = 8.1, 20-H), 4.32 (1H, d, *J* = 8.1, 20-H), 4.55 (2H, m, 7-H & 2'-H), 4.70 (1H, m, 13-H), 4.79 (1H, s, olefinic H), 4.94 (1H, s, olefinic H), 5.00 (1H, d,

J = 9.1, 5-H), 5.59 (1H, d, *J* = 8.8, 2-H), 5.78 (1H, m, 3'-H), 6.15 (1H, s, 10-H), 6.62 (1H, d, *J* = 9.9, 13-NH), 7.30-7.60 (11H, m, ArH), 7.86 (2H, d, *J* = 7.0, 3'-ArCO ortho H), 8.00 (2H, d, *J* = 7.5, 2-ArCO ortho H), 8.63 (1H, d, *J* = 9.1, C-3' NH). FABMS: *m/z* (rel int.) $[M+H]^+$ 835.3; HRFAB *m/z* $[M+H]^+$ 835.3428 ($C_{47}H_{50}O_{12}N_2$ requires 835.3442).

Compound 3b: ^1H NMR : δ 1.17 (3H, s, 19-H), 1.61 (3H, s, 18-H), 1.64 (3H, s, 16-H), 1.85 (1H, m, 6-H), 2.16 (3H, s, 10-OAc), 2.25 (3H, s, 4-OAc), 2.32 (1H, dd, *J* =7.2, 12.8, 14-H), 2.45 (1H, d, *J* =4.4, 7-OH), 2.58 (1H, m, 6-H), 3.39 (1H, d, *J* = 8.4, 3-H), 4.18 (1H, d, *J* = 8.8, 20-H), 4.25 (1H, d, *J* = 8.8, 20-H), 4.54 (2H, m, 7-H & 2'-H), 4.70 (1H,, br s, OH), 4.80 (1H, s, olefinic H), 4.96 (1H, s, olefinic H), 5.00 (1H, d, *J* = 7.8, 5-H), 5.30 (1H, m, 13-H), 5.58 (1H, d, *J* = 8.8, 2-H), 5.74 (1H, dd, *J* = 4.8, 8.8, 3-H'), 6.15 (1H, s, 10-H), 6.60 (1H, d, *J* = 9.6, 13-NH), 7.26-7.60 (11H, m, ArH), 7.85 (2H, d, *J* = 7.6, Ar ortho-CONH), 7.89 (1H, d, *J* = 7.6, 2-ArCO 6'-H), 7.99 (1H, br s, 2-ArCO 2'-H), 8.43 (1H, d, *J* = 8.8 , C-3' NH). FABMS: *m/z* (rel int.) $[M+H]^+$ 869.4; HRFAB *m/z* $[M+H]^+$ 869.3605 ($C_{47}H_{49}O_{12}N_2Cl$ requires 869.3652).

Compound 3c: ^1H NMR : δ 1.17 (3H, s, 19 -H), 1.61 (3H, s, 18-H), 1.66 (3H, s, 16-H), 1.93 (1H, m, 6-H), 2.16 (3H, s, 10-OAc), 2.18 (3H, s, 4-OAc), 2.30 (1H, dd, 14-H), 2.60 (1H, m, 6-H), 3.38 (1H, d, *J* = 7.4, 3-H), 3.83 (3H, s, OMe), 4.10 (2H, ABd, 20-H), 4.58 (2H, m, 7-H & 2'-H), 4.78 (1H, s, olefinic H), 4.94 (1H, s, olefinic H), 4.98 (1H, d, *J* = 7.8, 5-H), 5.43 (1H, d, *J* = 7.4, 2-H), 5.74 (1H, dd, *J* = 3.6, 8.4, 3-H'), 6.30 (1H, s, 10-H), 6.95 (1H, d, *J* = 9.2 C-13-NH), 7.12 (1H, dd, *J* = 1.6, 7.2, 2-ArCO 4' H), 7.30-7.60 (11H, m,ArH), 7.91 (2H, d, *J* = 7.5, Ar ortho CONH), 8.30 (1H, d, *J* = 8.8, C-3' NH). FABMS: *m/z* (rel int.) $[M+H]^+$ 864

Biological Evaluation. Compounds **3a** - **3c** were evaluated in a cytotoxicity assay against the P-388 lymphocytic leukemia cell line,[19] and had ED_{50} values of 2.7, 0.38, and 0.1 μg/mL, respectively. Compound **3c** was subjected to a tubulin-assembly assay as previously described;[15] it was inactive and indistinguishable from control at a concentration of 40 μM under conditions in which paclitaxel shows significant tubulin assembly at 10 μM. The A-norpaclitaxel analogs corresponding to **3a** and **3c** were also evaluated in the P-388 cytotoxicity assay, and had ED_{50} values of 0.5 and 0.03 μg/mL, respectively.

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REFERENCES

1. For recent reviews see: a) McGuire, W. P.; Rowinsky, E. K., Eds. *Paclitaxel in Cancer Treatment;* M. Dekker, Inc: New York, 1995; pp 1-349. b) Georg, G. I.; Chen, T. T.; Ojima, I.; Vyas, D. M., Eds. *Taxane Anticancer Agents. Basic Science and Current Status.* ACS Symposium Series 583, American Chemical Society: Washington DC, 1995; pp 1-353. c) Suffness, M., Ed. *Taxol: Science and Applications*: CRC Press: Boca Raton, Florida, 1995; pp 1-426. d) Farina, V., Ed. *The Chemistry and Pharmacology of Taxol and its Derivatives.* Elsevier: Amsterdam, 1995; pp 1-336.. e) K. C. Nicolaou, W. M. Dai and R. K. Guy, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*15-44. f) D. G. I. Kingston, *Trends Biotech.* **1994**, *12*, 222-227.
2. a) Georg, G. I.; Boge, T. C.; Cheruvallath Z. S.; Clowers, J. S., Harriman, G. C. B.; Hepperle, M.; Park, H. The Medicinal Chemistry of Taxol. In *Taxol: Science and applications;* Suffness M. Ed.;. CRC Press: Boca Raton. 1995; pp 317-375. b) Kant, J. The Chemistry of the Taxol Side Chain: Synthesis Modifications and Conformational Studies. In *The Chemistry and Pharmacology of Taxol and its Derivatives*; Farina, V., Ed.; Elsevier Science B. V.: Amsterdam. 1995; pp 255-300. c) Ojima, I.; Park,

Y. H.; Fenoglio, I.; Duclos, O.; Sun, C.-M.; Kuduk, S. D.; Zucco, M.; Appendino, G.; Pera, P.; Veith, J. M.; Bernacki, R. J.; Bissery, M.-C.; Combeau, C.; Vrignaud, P.; Riou, J. G.; Lavelle, F. Syntheses and Structure-Activity Relationships of New Taxoids. In *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I.; Chen, T. T.; Ojima, I.; Vyas, D. M., Ed.; American Chemical Society: Washington, DC, 1995; Vol. ACS Symposium Series 583; pp 262-275. d) Ojima, I.; Slater, J. C.; Michaud, E.; Kuduk, S. C.; Bounaud, P.-Y.; Vrignaud, P.; Bissery, M.-C.; Veith, J. M.; Pera, P.; Bernacki, R. J. *J. Med. Chem.* **1996**, *39*, 3889-3896.

3. See, e.g.a) D. G. I. Kingston in *Taxane Anticancer Agents. Basic Science and Current Status.* ACS Symposium Series 583, American Chemical Society, Washington, DC, 1995, pp 203-216. b) Chen S. H.; Farina, V. Paclitaxel (Taxol) Chemistry and Structure-Activity Relationships. In *The Chemistry and Pharmacology of Taxol and its Derivatives*; Farina, V., Ed.; Elsevier Science B. V.: Amsterdam. 1995; pp 165-253.
4. a) Chaudhary, A. G.; Gharpure, M. M.; Rimoldi, J. M.; Chordia, M. D.; Gunatilaka, A. A. L.; Kingston, D. G. I.; Grover, S.; Lin, L. M.; Hamel, E. *J. Am. Chem. Soc.* **1994,** *116,* 4097-4098. b) Nicolaou, K. C.; Renaud, J.; Nantermet, P. G.; Couladouros, E. A.; Guy, R. K.; Wrasidlo, W. *J. Am. Chem. Soc.* **1995**, *117*, 2409-2410. c) Georg, G. I.; Ali, S. M.; Boge, T. C.; Datta, A.; Falborg, L.; Park, H.; Mejillano, M.; Himes, R. H. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 259-264.
5. Samaranayake, G.; Magri, N. F.; Jitrangsri, C.; Kingston, D. G. I. *J. Org. Chem.* **1991**, *56*, 5114-5119.
6. Chordia, M. D.; Kingston, D. G. I.; Hamel, E.; Lin, C. M.; Long, B. H.; Fairchild. C.; Johnston, K. A.; Rose, W. C. *Bioorg. Med. Chem.*, in press (1997).
7. Hamel, E. Personal communication.
8. Chen, S.-H.; Farina, V.; Vyas, D. M.; Doyle, T. W.; Long, B. H.; Fairchild. C. *J. Org. Chem.*, **1996**, 61, 2065-2070.
9. Denis, J.-N.; Greene, A. E.; Guenard, D.; Gueritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917-5919.
10. This compound has recently been prepared independently by another route (reference 8).
11. Zaloom, J.; Calandra, M.; Roberts, D. C. *J. Org. Chem.* **1985**, *50*, 2601-2603.
12. Commercon, A.; Bezard, D.; Bernard, F.; Bourzat, J. D. *Tetrahedron Lett.* **1992**, *33*, 5185-5188.
13. Samaranayake, G.; Neidigh, K. A.; Kingston, D. G. I. *J. Nat. Prod.* **1993**, *56*, 884-898.
14. Ghosh, S. K.; Singh, U.; Mamdapur, V. R. *Tetrahedron Lett.*, **1992**, *33*, 805-808.
15. Georg, G. I.; Boge, T. C.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperle, M.; Park, H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 335-338.
16. a) Neidigh, K. A.; Gharpure, M. M.; Rimoldi, J. M.; Kingston, D. G. I.; Jiang, Y. Q.; Hamel, E. *Tetrahedron Lett.* **1994**, *35*, 6839-6842; b) Grover, S.; Rimoldi, J. M.; Molinero, A. A.; Chaudhary, A. G.; Kingston, D. G. I.; Hamel, E. *Biochemistry* **1995**, *34*, 3927-3934.
17. Chordia, M. D.; Kingston, D. G. I. *J. Org. Chem.* **1996**, *61*, 799-801.
18. Neidigh, K. A.*Chemical Studies of the C-4 Position of Baccatin III and Taxol*, Virginia Polytechnic Institute and State University 1996.
19. Cytotoxicities were determined by Dr. W. Lichter, University of Miami School of Medicine, using standard NCI protocols.

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