Synthesis and Biological Evaluation of C-13 Amide-Linked Paclitaxel (Taxol†) Analogs

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Several C-13 amidopaclitaxel analogs have been synthesized during the course of our structure−activity relationship study at the C-13 position. These include 4-deacetyl-13-amidopaclitaxel (**4**), 13-amidopaclitaxel 4-(methyl carbonate) derivatives (**5a**,**b**), and 13-amidopaclitaxel (**6**). None of these novel C-13 amidopaclitaxel analogs retain any activity in the tubulin polymerization assay or the in vitro cytotoxicity assay.

Paclitaxel (Taxol) (**1**), the structurally unique diterpenoid[1] marketed by Bristol-Myers Squibb, is one of the most exciting antitumor drugs available today. Its current indications (refractory ovarian and metastatic breast cancer) may soon be expanded to include lung and head−neck cancers.[2] The clinical importance of this drug, coupled with its structural complexity[1] and novel mechanism of action,[3] has stimulated intensive research activities toward its total synthesis[4] and structure−activity relationship (SAR) studies.[5]

In 1990, we launched systematic SAR investigations in search of analogs possessing improved biological profiles. As a result of such efforts, we have reported on a wide variety of paclitaxel analogs modified at the C-2,[6] C-4,[7] C-6,[8] C-7,[9] and C-10[10] positions.

In addition to our core SAR modifications, we were also interested in the side-chain SAR.[11] Despite the fact that a large number of paclitaxel side-chain analogs have been prepared, including the C-13 acetic acid, crotonic acid, lactic acid derivatives,[12] and the C-13-*epi*-paclitaxel,[13] modifications of the C-13 ester linkage itself, such as replacement of the C-13 oxygen moiety with other heteroatoms, have not yet been reported. We thought that the exchange of the C-13 phenylisoserine moiety with the amide linkage could in principle alter the side-chain conformation.[14] This may in turn have considerable impact on the drug's overall performance. With these considerations in mind, we decided to embark on the syntheses of a novel series of C-13 amide-linked paclitaxel analogs. One of our goals was to devise a method for the preparation of such C-13 amido-carrying analogs, such as the C-4-deacetyl derivative **4**, the C-4 methyl carbonate **5**, and the C-13 amidopaclitaxel **6** itself, and to evaluate their biological profile. Herein we report the details of our investigations.

One obvious strategy for the synthesis of C-13 amidopaclitaxel analogs utilized the known coupling reaction between a C-13 amino-bearing baccatin III and the paclitaxel side-chain β-lactam[15] according to the method of Holton[16a] or Ojima.[16b] We further envisioned that C-13 aminobaccatin derivative might be obtained from the direct functionalization of baccatin III via either reductive

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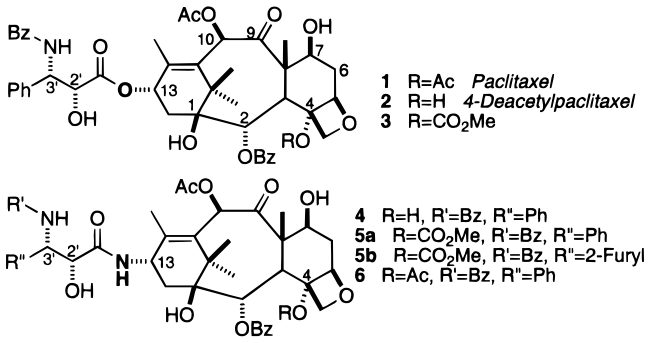

Figure 1.

amination[17] or a sequence of double Mitsunobu reactions with net retention at C-13.[18] Much to our disappointment, heating an ethanol solution of 13-keto-7-TES baccatin III and hydroxylamine only led to the removal of the acetoxy moiety at C-10. Furthermore, 7-TES-baccatin III was found to be inert under standard Mitsunobu conditions.[19] The lack of reactivity of the C-13 hydroxyl moiety in this case was possibly due to its intramolecular hydrogen bonding to the C-4 acetoxy group. More vigorous conditions were therefore tried. Attempts to brominate C-13 with CBr_4/PPh_3[20] resulted in oxetane opening. We have already shown that this opening reaction occurs with anchimeric participation of the C-4 acetoxy moiety. Bearing this in mind, it was concluded that in order to modify the C-13 position the intramolecular hydrogen bonding between the C-13 carbinol and the C-4 acetoxy moiety had to be removed.[21] Thus, an alternative strategy was devised consisting of (i) chemoselective removal of the C-4 acetoxy group in baccatin III, (ii) introduction of an amine/azide functionality at the C-13 with retention of configuration, and (iii) reacylation of the C-4 hydroxyl moiety.

Scheme 1 summarizes the synthetic route leading to the preparation of the C-13 azidobaccatin derivative **12**. Treatment of 7-TES-baccatin **7** with two silylation reagents sequentially (TMSCl, DMSCl) afforded fully silylated baccatin **8** in 87% yield. When this material was treated with 4 equiv of Red-Al in THF at 0 °C, the C-13 desilylated C-4 deacetylbaccatin **10** was isolated, after workup with sodium tartaric acid saturated solution, as the major product in 50−60% yield. Small amounts of the C-10 deacetyl product **9** were also obtained. We also noted that the trimethylsilyl group at C-13 was removed during the aqueous workup prior to the more labile C-1 dimethylsilane (DMS). We immediately recognized that compound **10** would be an ideal substrate on which to study the C-13 modification and the C-4 reacylation.

Indeed, the reactivity of the allylic hydroxyl group at C-13 in **10** was improved after the removal of the C-4 acetoxy group. For example, when compound **10** was treated with aza-Mitsunobu reagents,[19c] the C-13β azidobaccatin derivative **11** was obtained in 35% yield. The C-13 α-azidobaccatin derivative **12** was also prepared in two steps from the C-13 carbinol **10** in ~35% overall yield. In this case, the hydroxyl group in **10** was first brominated with CBr_4/PPh_3,[20] affording 2:1 (β/α) mixtures of the two C-13 bromobaccatin derivatives without oxetane opening. Gently heating of a DMF solution of the resulting C-13 bromobaccatins with sodium azide provided only the 13α-azido-bearing baccatin **12** with the desired stereochemistry at C-13.

Having made the desired C-13 azidobaccatin **12**, we next turned our attention to the C-4 reacylation and subsequent reduction of the azido moiety at C-13. Surprisingly, the C-4 hydroxyl moiety in **12** was found to be rather resistant to various acylation conditions. For example, treating **12** with LiHMDS/AcCl afforded only small amounts (<5%) of the desired product **14**. Attempted acylation of **12** with DCC and acetic acid or acetic anhydride at room temperature also failed to provide the desired product. However, treatment of **12** with LiHMDS and methyl chloroformate in anhydrous THF provided the desired C4 methyl carbonate derivative **15** in low yield (20−45%). After many unsuccessful attempts, it was later found that heating a toluene solution of **12** with a large excess (15−20 equiv) of acetic anhydride and DMAP at 80 °C led to the formation of the desired C-4 acetylated-13-azido baccatin **18** (22%) along with similar amount of the A-ring contraction product **17** (20%). The C-1 protecting group (DMS) was lost under these harsh conditions (Scheme 2).

Surprisingly again, treatment of the C-13 azido moiety by either standard palladium-catalyzed hydrogenolysis[22] and triphenylphosphine or tributylphosphine[23] failed to effect the desired reduction. After some experimentation, it was found that gently heating a triethylamine solution of **12** and PhSeH[24] at 60 °C provided the desired 13α-amino-bearing baccatin **13** in 86% yield. The C-13 azido moieties in **15** and **18** were reduced in an analogous manner and provided the desired C-13 amino-bearing baccatins **16** (80%) and **19** (58%), respectively, as shown in Scheme 2.

The paclitaxel side chain was readily attached to the C-13 aminobaccatin **13** *via* Holton's protocol[16a] using β-lactam **20**[15] as the side-chain source and afforded a 53% yield of the adduct **21**. This intermediate was further desilylated to provide the desired 13-amido-4-deacetylpaclitaxel **4** in 71% yield (see Scheme 3).

A similar coupling reaction was attempted with the C-13-aminobaccatin **16**. Disappointingly, no desired coupling product was formed. The lack of reactivity observed here with the free amine **16** was likely due to the intramolecular hydrogen bonding between the C-13 amino moiety and the C-4 carbonate group. In view of this difficulty, we then decided to attempt an alternative method which employed oxazolines **22a**/**22b** as the side-chain sources.[25] Successful applications of the similar DCC/DMAP-mediated side-chain coupling reactions were recently reported by Kingston and by scientists from Bristol-Myers Squibb.[25b] Indeed, treatment of a toluene solution of the C-13 aminobaccatin **16** and the side-chain carboxylic acid **22a** or **22b** with DCC and DMAP resulted

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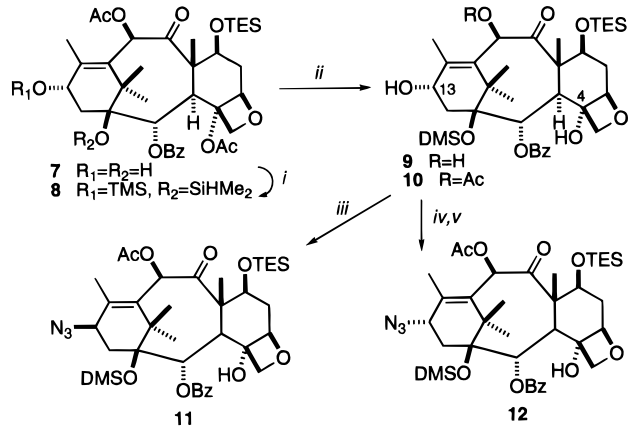
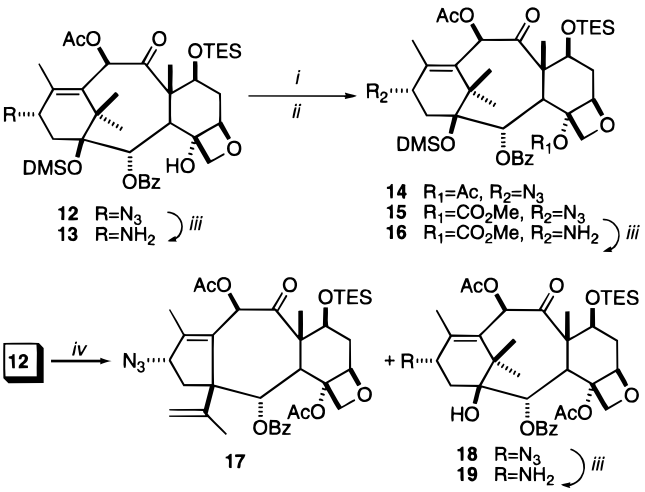
Scheme 1



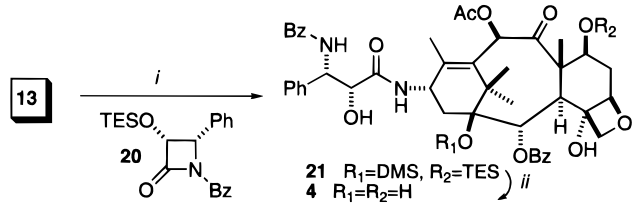
[a] Conditions: (i) TMSCl/imidazole/DMF/0 °C, then DMSCl/imidazole/0 °C, 87%; (ii) Red-Al/THF/0 °C, 15% of **9** plus 58% of **10**; (iii) DEAD/PPh_3/$(BnO)_2P(O)N_3$/THF, rt, 35%; (iv) CBr_4/PPh_3/CH_2Cl_2/0 °C, 50%; (v) NaN_3/DMF/rt to 40 °C, 63%.

Scheme 2[a]



[a] Conditions: (i) LHMDS/THF/0 °C, AcCl/0 °C, <5% of **14**; (ii) LHMDS/THF/0 °C, then MeOC(O)Cl, 28%; (iii) PhSeH/Et_3N/60 °C, 86% of **13**; 80% of **16**; 58% of **19**; (iv) Ac_2O/DMAP/toluene/80 °C, 20% of **17** plus 22% of **18**.

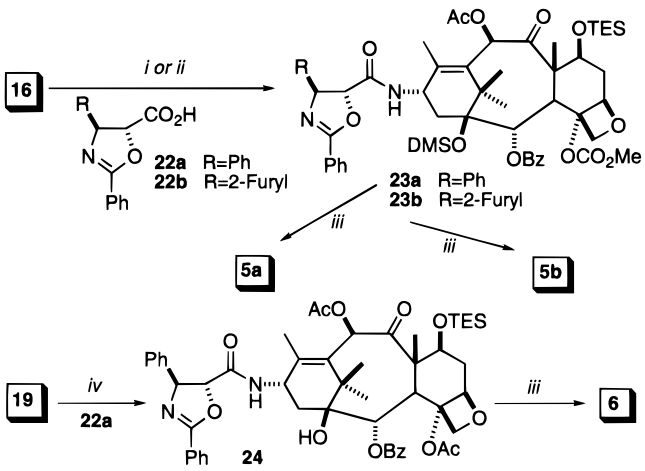
Scheme 3[a]



[a] Conditions: (i) LHMDS/THF/−40 °C, then **20**, 53%; (ii) Pyr/48% HF/CH_3CN, 71%.

in the formation of the desired adducts **23a** and **23b** in 92% and 68% yields, respectively. Finally, acidic hydrolysis of the oxazoline moiety followed by side-chain benzoyl migration (from 2′-O to 3′-N) and desilylation (at C-1 and C-7) furnished the desired products **5a** (61%) and **5b** (39%). Following the same sequence, the C-13 amidopaclitaxel **6** was obtained in 50% overall yield *via*

Scheme 4[a]



[a] Conditions: (i) DCC/DMAP/toluene/rt/**22a**, 92% of **23a**; (ii) DCC/DMAP/toluene/rt/**22b**, 68% of **23b**; (iii) 1 N HCl/THF + MeOH/5 °C, then $NaHCO_3$/rt, 61% of **5a**; or 39% of **5b**; or 50% of **6**; (iv) DCC/DMAP/toluene/rt/**22a**, 100%.

Table 1. Results of Biological Evaluation of C-13 Amidopaclitaxel Analogs 1−6

compd	tubulin polym. ratio[a]	IC_{50} (nM)[b] HCT-116
1 (Paclitaxel)	1.0	2.4
6	>200	>100
2	200	>58
4	60	>96
3	0.41	2.0
5a	>200	54
5b	>200	82

[a] This ratio indicates the potency of an analog relative to paclitaxel. [b] IC_{50} measures the drug concentration required for the inhibition of 50% cell proliferation after a 72 h incubation.

coupling of the C-13 aminobaccatin **19** and the carboxylic acid **22a** followed by subsequent oxazoline hydrolysis and deprotection at C-7 (see Scheme 4).

Compounds **4**, **5**(**a**,**b**), and **6** were evaluated in a tubulin polymerization assay[12c] and an *in vitro* cytotoxicity assay against a human colon cancer cell line (HCT-116).[26] The results are summarized in Table 1. Two C-4 paclitaxel analogs, **2** and **3**, were synthesized[7c] using the methodology disclosed recently,[7] as reference compounds for their C-13 amide counterparts **4** and **5**, respectively. As can be seen in Table 1, the two C-4 deacetyl derivatives, the C-4-deacetylpaclitaxel (**2**) and its C-13 amido congener **4**, were devoid of any activity. This observation confirms that the presence of a C-4 acyl group is essential for biological activity.[7] Surprisingly, unlike the *bioactive* C-4 methyl carbonate **3**, its C-13 amido conterpart **5a** was also found to be *inactive* in both the tubulin polymerization assay and the cytotoxicity assay. Similar results were also obtained with the 3′-furyl-bearing C-13 amido analog **5b** and with the C-13 amidopaclitaxel **6**. *These results clearly indicate that replacement of the C-13 ester linkage with the corresponding amide is detrimental to activity.*

In summary, we have succeeded in the preparation of a novel series of C-13 amido-containing paclitaxel analogs. None of these analogs (**4**, **5a**, **5b**, **6**) was found to be bioactive *in vitro*. Further study aimed at determining

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the cause(s) for the lack of activity of analogs (**4**−**6**) is in progress, and the result of this investigation will be reported in due time.

Experimental Section

Preparation of Compound (8). 7-TES-baccatin III **7** (3.00 g, 4.286 mmol) was dissolved in dry DMF (17 mL). To this solution at 0 °C was added imidazole (874.3 mg, 12.86 mmol), followed by TMSCl (1.63 mL, 12.86 mmol). After stirring at 0 °C for 1.5 h, the reaction mixture was diluted with EtOAc (300 mL) and washed with water (3 × 20 mL) and then brine (30 mL). The organic layer was dried and concd *in vacuo*. The resulting material was then dissolved in dry DMF (20 mL) and treated at 0 °C with imidazole (816 mg, 12.00 mmol), followed by chlorodimethylsilane (1.135 g, 12.00 mmol). The reaction mixture was stirred for 1 h at 0 °C and then diluted with EtOAc (200 mL). The organic layer was washed with water and brine. Upon silica gel chromatography (10% ethyl acetate in hexane), 3.197 g (90%) of the desired product **8** was obtained.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09−8.06 (m, 2H), 7.59−7.43 (m, 3H), 6.43 (s, 1H), 5.70 (d, J = 6.9 Hz, 1H), 4.92 (d, J = 7.7 Hz,1H), 4.86 (m, 1H), 4.50 (m, 1H), 4.43 (dd, J = 6.6 Hz, J' = 10.5 Hz, 1H), 4.20 (ABq, J = 8.2 Hz, 2H), 3.78 (d, J = 6.9 Hz, 1H), 2.50−0.16 (m, 46H, includes singlets at 2.26, 2.16, 2.07, 1.65, 1.18, 1.05, 3H each, 0.18, 9H), 0.05 (d, J = 2.7 Hz, 3H), −0.28 (d, J = 2.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.1, 169.8, 169.2, 165.2, 144.4, 133.1, 131.6, 130.2, 130.0, 128.3, 84.1, 81.7, 80.8, 76.4, 75.6, 75.5, 72.1, 68.3, 58.2, 46.6, 43.9, 38.8, 37.1, 27.3, 22.5, 21.7, 20.8, 14.8, 9.9, 6.6, 5.1. HRMS: calcd for $C_{42}H_{67}O_{11}Si_3$ (MH^+) 831.3991, found 831.4001.

Preparation of Compounds 9 and 10. To a THF solution (8.8 mL) of **8** (439 mg, 0.529 mmol) was added at 0 °C Red-Al (0.514 mL, 60%, 2.645 mmol). The reaction was stirred vigorously for 40 min. At this time, a saturated sodium tartrate solution (4 mL) was slowly added. After 5−10 min, the reaction mixture was extracted with EtOAc (2 × 50 mL). The organic layer was washed with brine and then dried and concd *in vacuo*. The residue was chromatographed (40% ethyl acetate in hexanes) to afford 53 mg (15%) of **9** along with 220 mg (58%) of the desired product **10**.

^{1}H NMR (300 MHz, CDCl3) of **9**: δ 8.04−8.01 (m, 2H), 7.54−7.34 (m, 3H), 5.54 (d, J = 5.6 Hz, 1H), 5.16 (s, 1H), 4.70 (m, 2H), 4.54 (m, 2H), 4.35 (d, J = 8.3 Hz, 1H), 4.29 (s, 1H), 4.06 (d, J = 8.1 Hz, 1H), 4.00 (d, J = 8.7 Hz, 1H), 3.91 (dd, J = 5.6 Hz, J' = 11.6 Hz, 1H), 3.66 (d, J = 5.6 Hz, 1H), 2.72−0.32 (m, 31H, includes singlets at 2.05, 1.58, 1.03, 0.97, 3H each), −0.01 (d, J = 1.8 Hz, 3H), −0.35 (d, J = 1.9 Hz, 3H). MS: calcd for $C_{35}H_{54}O_9Si_2$ (M^+) 674, found 674.

^{1}H NMR (300 MHz, $CDCl_3$) of **10**: δ 8.05−8.02 (m, 2H), 7.56−7.37 (m, 3H), 6.43 (s, 1H), 5.62 (d, J = 5.8 Hz, 1H), 4.70 (dd, J = 4.5 Hz, J' = 9.7 Hz, 1H), 4.58 (m, 1H), 4.22 (ABq, J = 8.5 Hz, 2H), 4.05 (m, 1H), 3.64 (m, 2H), 2.80−0.50 (m, 34H, includes singlets at 2.18, 6H, 1.55, 1.16, 0.95, 3H each), 0.03 (d, J = 2.7 Hz,3H), −0.31 (d, J = 2.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.7, 169.3, 164.9, 142.5, 135.2, 133.3, 130.0, 129.8, 128.4, 88.3, 80.5, 80.2, 75.9, 73.7, 72.0, 68.9, 58.8, 50.2, 43.0, 37.3, 37.1, 29.7, 20.8, 18.9, 16.8, 9.8, 6.6, 5.1. HRMS: calcd for $C_{37}H_{57}O_{10}Si_2$ (MH^+) 717.3490, found 717.3505.

Preparation of Compound 11. To a THF solution (1.2 mL) of **10** (50 mg, 0.070 mmol) were added DEAD (0.013 mL, 0.084 mmol) and triphenylphosphine (22.0 mg, 0.084 mmol) followed by diphenylphosphoryl azide (0.018 mL, 0.084 mmol). The reaction was stirred at room temperature for 1.5 h. The solvent was removed, and the residue was chromatographed (10−20% EtOAc/hexanes) to afford 18 mg (35%) of C-13 β-azido-bearing baccatin **11**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02−7.98 (m, 2H), 7.58−7.43 (m, 3H), 6.38 (s, 1H), 5.65 (d, J = 5.5 Hz, 1H), 4.66 (m, 2H), 4.19 (ABq, J = 8.4 Hz, 2H), 4.16 (dd, J = 4.8 Hz, J' = 9.8 Hz, 1H), 3.93 (m, 1H), 3.06 (dd, J = 9.8 Hz, J' = 14.5 Hz, 1H), 3.00 (d, J = 6.4 Hz, 1H), 2.40−0.48 (m, 33H, includes singlets at 2.18, 2.12, 1.54, 1.13, 1.09, 3H each), 0.05 (d, J = 2.8 Hz, 3H), −0.29 (d, J = 2.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.2, 169.2, 164.6, 139.4, 137.4, 133.5, 129.8, 129.6, 128.6, 87.0, 84.8, 80.9, 75.7, 74.4, 73.7, 72.2, 62.4, 58.3, 50.0, 42.7, 37.0, 33.9, 31.5, 20.8, 19.1, 19.0, 9.7, 6.6, 5.1, 1.1, 0.1. HRMS: calcd for $C_{37}H_{56}N_3O_9Si_2$ (MH^+) 742.3555, found 742.3515.

Preparation of Compound 12. A dichloromethane solution of **10** (219 mg, 0.306 mmol) was treated at 0 °C with triphenylphosphine (96.2 mg, 0.367 mmol), followed by carbon tetrachloride (121.6 mg, 0.367 mmol). The reaction mixture was stirred at 0 °C for 1 h. The solvent was then removed, and the residue was chromatographed (20−40% EtOAc/hexane) to afford 120 mg (50%) of a mixture of the two (**a** and **b**) C-13 bromobaccatin derivatives along with 44 mg (20%) of starting material **10**. These two intermediates were dissolved in dry DMF (1.5 mL) and treated with sodium azide (100 mg, 1.54 mmol). The reaction mixture was stirred at 40 °C for 2 h. The reaction mixture was then diluted with EtOAc (50 mL) and washed with water (3 × 5 mL). The organic layer was dried and concd *in vacuo*. The residue was chromatographed (20% EtOAc/hexane) to afford 60 mg (63%) of the desired C-13 azido-bearing baccatin derivative **12**.

^{1}H NMR (300 MHz, $CDCl_3$) of **12**: δ 8.08−8.05 (m, 2H), 7.58−7.41 (m, 3H), 6.37 (s, 1H), 5.61 (d, J = 6.0 Hz, 1H), 4.75 (dd, J = 3.7 Hz, J' = 9.7 Hz, 1H), 4.58 (m, 2H), 4.19 (ABq, J = 8.0 Hz, 2H), 3.98 (dd, J = 6.1 Hz, J' = 11.5 Hz, 1H), 3.11 (d, J = 6.0 Hz, 1H), 2.94 (dd, J = 4.7 Hz, J' = 15.5 Hz, 1H), 2.57 (dd, J = 10.4 Hz, J' = 15.2 Hz, 1H), 2.38 (m, 1H), 2.21 (s, 3H), 2.17 (s, 3H), 1.94 (m, 1H), 1.56 (s, 3H), 1.18 (s, 3H), 0.99 (s, 3H), 0.88 (m, 9H), 0.53 (m, 6H), 0.04 (d, J = 2.7 Hz, 3H), −0.31 (d, J = 2.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.5, 169.5, 165.1, 138.5, 136.9, 133.4, 130.2, 129.9, 128.5, 87.8, 80.7, 80.0, 75.5, 75.1, 74.1, 72.6, 61.9, 58.9, 51.7, 43.5, 37.4, 34.7, 28.7, 20.9, 19.5, 17.4, 9.8, 6.7, 5.2, 0.7, 0.1. HRMS: calcd for $C_{37}H_{56}N_3O_9Si_2$ (MH^+) 742.3555, found 742.2383.

Preparation of Compound 14. A THF solution (2.5 mL) of **12** (95 mg, 0.128 mmol) was treated at 0 °C with LHMDS (0.166 mL, 1 M, 0.166 mmol) for 30 min. At this time, acetyl chloride (0.014 mL, 0.192 mmol) was added, and the resulting reaction mixture was stirred at 0 °C for 1 h. After the reaction was quenched with NH_4Cl saturated solution (2 mL), the reaction mixture was extracted with EtOAc (50 mL). The organic layer was washed with water and brine and then dried and concd *in vacuo*. The residue was chromatographed (10−20% EtOAc/hexane) to provide only a trace amount (<5%) of the desired product **14**. Large amounts of the starting material **12** (71 mg, 75%) were recovered.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11−8.08 (m, 2H), 7.63−7.46 (m, 3H), 6.42 (s, 1H), 5.70 (d, J = 7.0 Hz, 1H), 4.92 (d, J = 7.8 Hz, 1H), 4.76 (m, 1H), 4.57 (m, 1H), 4.43 (dd, J = 6.7 Hz, J' = 10.5 Hz, 1H), 4.21 (ABq, J = 8.2 Hz, 2H), 3.69 (d, J = 6.9 Hz, 1H), 2.58−0.50 (m, 37H, includes singlets at 2.34, 2.22, 2.19, 1.67, 1.20, 1.07, 3H each), 0.08 (d, J = 2.7 Hz, 3H), −0.26 (d, J = 2.7 Hz, 3H). MS: calcd for $C_{39}H_{57}N_3O_{10}Si_2$ (M^+) 783, found 783.

Preparation of Compound 15. A THF solution (4.7 mL) of **12** (209.5 mg, 0.283 mmol) was treated at 0 °C with LHMDS (0.368 mL, 1 M, 0.368 mmol). After 30 min at that temperature, methyl chloroformate (0.033 mL, 0.425 mmol) was added. After stirring for 1 h at 0 °C, the reaction was quenched with an NH_4Cl-saturated solution (2 mL), and then the solution was extracted with EtOAc (75 mL). The organic layer was washed with water and brine and then dried and concd *in vacuo*. The resulting residue was chromatographed (10−20% EtOAc/hexane) to afford 62.6 mg (28%) of the desired product **15** along with 100 mg (48%) of the recovered starting material **12**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12−8.09 (m, 2H), 7.59−7.45 (m, 3H), 6.42 (s, 1H), 5.71 (d, J = 6.8 Hz, 1H), 4.96 (d, J = 9.4 Hz, 1H), 4.78 (m, 1H), 4.56 (m, 1H), 4.39 (dd, J = 6.5 Hz, J' = 10.4 Hz, 1H), 4.20 (ABq, J = 8.4 Hz, 2H), 3.93 (s, 3H), 3.69 (d, J = 6.8 Hz, 1H), 2.56−0.52 (m, 34H, includes singlets at 2.21, 2.18, 1.66, 1.20, 1.06, 3H each), 0.07 (d, J = 2.7 Hz, 3H), −0.28 (d, J = 2.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.4, 169.2, 165.2, 153.7, 139.5, 134.6, 133.3, 130.1, 129.9, 128.5, 83.7, 82.2, 81.7, 76.0, 75.3, 74.7, 72.1, 60.5, 58.3,

54.4, 47.0, 43.7, 37.0, 35.2, 27.2, 20.9, 20.8, 16.1, 9.8, 6.6, 5.1. HRMS: calcd for $C_{39}H_{58}N_3O_{11}Si_2$ (MH^+) 800.3610, found 800.3601.

Preparation of Compound 13. Compound **12** (60.0 mg, 0.081 mmol) was dissolved in triethylamine (1 mL). To this solution at room temperature was added PhSeH (0.034 mL, 0.324 mmol). The reaction mixture was then heated at 60 °C for 3 h. The reaction mixture was then cooled to room temperature and chromatographed (30−100% EtOAc/hexane) to provide 49.8 mg (86%) of the desired product **13**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15−8.12 (m, 2H), 7.55−7.40 (m, 3H), 6.40 (s, 1H), 5.63 (d, J = 5.8 Hz, 1H), 4.75 (dd, J = 3.7 Hz, J' = 9.7 Hz, 1H), 4.57 (m, 1H), 4.22 (ABq, J = 7.7 Hz, 2H), 4.05 (m, 2H), 3.65 (d, J = 5.8 Hz, 1H), 2.60−0.50 (m, 34H, includes singlets at 2.19, 6H, 1.57, 1.13, 0.98, 3H each), 0.03 (d, J = 2.7 Hz, 3H), −0.30 (d, J = 2.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.8, 169.6, 165.2, 139.0, 136.2, 133.0, 130.2, 130.1, 128.3, 88.8, 81.1, 79.8, 76.0, 74.6, 73.5, 72.7, 59.2, 51.2, 49.7, 43.0, 37.4, 36.1, 29.4, 20.9, 18.8, 16.7, 9.5, 6.6, 5.1. HRMS: calcd for $C_{37}H_{58}NO_9Si_2$ (MH^+) 716.3650, found 716.3635.

Preparation of Compound 16. To a triethylamine solution (2 mL) of **15** (84.0 mg, 0.105 mmol) was added PhSeH (0.033 mL, 0.315 mmol) at room temperature. The reaction mixture was heated at 60 °C for 3 h. The reaction mixture was then directly chromatographed (30−60% EtOAc/hexane) to provide 65 mg (80%) of the desired product **16**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12−8.09 (m, 2H), 7.58−7.42 (m, 3H), 6.44 (s, 1H), 5.71 (d, J = 6.9 Hz, 1H), 4.95 (d, J = 8.2 Hz, 1H), 4.52 (m, 1H), 4.38 (dd, J = 6.6 Hz, J' = 10.6 Hz, 1H), 4.22 (ABq, J = 8.2 Hz, 2H), 4.15 (m, 1H), 3.87 (s, 3H), 3.82 (d, J = 6.9 Hz, 1H), 2.50−0.50 (m, 34H, includes singlets at 2.19, 2.17, 1.67, 1.19, 1.06, 3H each), 0.04 (d, J = 2.7 Hz, 3H), −0.30 (d, J = 2.7 Hz, 3H). HRMS: calcd for $C_{39}H_{60}NO_{11}Si_2$ (MH^+) 774.3705, found 774.3729.

Preparation of Compounds 17 and 18. C-4 carbinol **12** (281 mg, 0.379 mmol) was dissolved in toluene (3.8 mL). To this solution were added Ac_2O (0.72 mL, 7.584 mmol) and DMAP (92.7 mg, 0.758 mmol). The reaction mixture was heated at 80 °C for 13 h and then cooled to room temperature and diluted with dichloromethane (75 mL). The resulting mixture was washed with an $NaHCO_3$-saturated solution (2 × 15 mL) and brine (15 mL). The organic layer was dried and filtered. The filtrates were concd *in vacuo*, and the resulting residue was perified by silica gel chromatography (20−25% EtOAc/hexanes) to provide 54 mg (20%) of the A-ring contraction product **17** along with 61 mg (22%) of the desired product **18**.

^{1}H NMR of **17** (300 MHz, $CDCl_3$): δ 8.02−8.00 (m, 2H), 7.61−7.45 (m, 3H), 6.35 (s, 1H), 5.62 (d, J = 7.9 Hz, 1H), 5.00 (d, J = 8.5 Hz, 1H), 4.92 (s, 1H), 4.77 (s, 1H), 4.50 (dd, J = 7.3 Hz, J' = 9.4 Hz, 1H), 4.36 (t, 1H), 4.23 (s, 2H), 3.46 (d, J = 7.8 Hz, 1H), 2.59−1.66 (m, 19H, includes singlets at 2.25, 2.17, 1.81, 1.72, 1.68, 3H each), 0.93 (m, 9H), 0.63 (m, 6H). ^{1}H NMR of **18** (300 MHz, $CDCl_3$): δ 8.10−8.07 (m, 2H), 7.62−7.46 (m, 3H), 6.43 (s, 1H), 5.62 (d, J = 7.1 Hz, 1H), 4.93 (d, J = 8.8 Hz, 1H), 4.74 (t, J = 8.4 Hz, 1H), 4.46 (dd, J = 6.7 Hz, J' = 10.5 Hz, 1H), 4.20 (ABq, J = 8.3 Hz, 2H), 3.71 (d, J = 7.0 Hz, 1H), 2.53−0.52 (m, 31H, includes singlets at 2.33, 2.18, 2.18, 1.66, 1.20, 1.10, 3H each).

Preparation of C-13 Amine 19. C-13 azidobaccatin **18** (102 mg, 0.141 mmol) was dissolved in triethylamine (2 mL), and the resulting solution was degassed with dry N_2. To this solution was added PhSeH (59 uL, 0.563 mmol), and the resulting suspension was heated at 60 °C for 3 h. At this point, the reaction mixture was allowed to cool to room temperature. After usual silica gel chromatography, 57 mg (58%) of the correponding C-13 free amine **19** was obtained.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10−8.07 (m, 2H), 7.59−7.43 (m, 3H), 6.46 (s, 1H), 5.63 (d, J = 7.1 Hz, 1H), 4.91 (d, J = 8.0 Hz, 1H), 4.45 (dd, J = 6.8 Hz, J' = 10.5 Hz, 1H), 4.21 (ABq, J = 8.3 Hz, 2H), 4.13 (m, 1H), 3.86 (d, J = 7.0 Hz, 1H), 2.60−0.53 (m, 37 H, includes singlets at 2.33, 2.17, 2.15, 1.68, 1.20, 1.12, 3H each). HRMS: calcd for $C_{37}H_{54}NO_{10}Si$ (MH^+) 700.3517, found 700.3520.

Preparation of Compound 4 *via* 21. A THF solution (1.2 mL) of **13** (47 mg, 0.0657 mmol) was treated at −40 °C with LHMDS (0.079 mL, 1M, 0.079 mmol), followed by a THF solution (0.5 mL) of β-lactam **20** (27.5 mg, 0.0723 mmol). The reaction mixture was stirred at 0 °C for 1 h, and the reaction was quenched with an NH_4Cl-saturated solution (1 mL). The reaction mixture was extracted with EtOAc (2 × 25 mL), and the combined organic layers were washed with brine and then dried and concd *in vacuo*. The residue was chromatographed (20−30% EtOAc/hexane) to afford 34 mg (53%) of **21**. A part of this material (26.6 mg, 0.027 mmol) was dissolved in CH_3-CN (0.7 mL) and treated at 0 °C with pyridine (0.08 mL), followed by 48% HF (0.24 mL). The reaction mixture was kept at 5 °C for 12 h. The reaction mixture was then diluted with EtOAc (25 mL) and washed with 1N HCl (3 mL), an $NaHCO_3$-saturated solution (3 × 5 mL), and brine. The resulting organic layer was dried and concd *in vacuo*. The residue was chromatographed (60−80% EtOAc/hexane) to provide 15.6 mg (71%) of the desired product **4**.

^{1}H NMR of **21** (300 MHz, $CDCl_3$): δ 8.33−7.99 (m, 5H), 7.61−7.22 (m, 11H), 6.26 (s, 1H), 5.59 (m, 2H), 4.95 (m, 1H), 4.61 (m, 2H), 4.53 (m, 1H), 4.24 (ABq, J = 8.4 Hz, 2H), 3.77 (dd, J = 5.5 Hz, J' = 11.6 Hz, 1H), 3.31 (d, J = 5.9 Hz, 1H), 2.60−0.50 (m, 34H, includes singlets at 2.15, 1.53, 1.46, 1.12, 1.00, 3H each), 0.02 (d, J = 2.6 Hz, 3H), −0.33 (d, J = 2.6 Hz, 3H).

^{1}H NMR of **4** (300 MHz, $CDCl_3$): δ 8.15−7.26 (m, 15H), 6.16 (s, 1H), 5.79 (d, J = 9.1 Hz, 1H), 5.58 (d, J = 5.3 Hz, 1H), 5.29 (m, 1H), 5.15 (m, 1H), 4.63 (bs, 2H), 4.23 (ABq, J = 8.4 Hz, 2H), 3.83 (m, 1H), 3.76 (d, J = 5.3 Hz, 1H), 2.64−0.86 (m, 19H, includes singlets at 2.20, 1.53, 1.51, 1.09, 1.05, 3H each). ^{13}C NMR of **4** (75 MHz, $CDCl_3$): δ 204.1, 171.4, 171.2, 167.6, 166.8, 142.5, 137.8, 134.9, 133.5, 133.3, 132.3, 130.0, 128.9, 128.8, 128.5, 128.0, 127.1, 126.9, 88.0, 80.5, 77.5, 75.3, 74.0, 73.5, 72.2, 58.7, 55.1, 50.0, 47.6, 42.2, 35.4, 34.3, 27.3, 20.8, 18.9, 17.2, 9.3. HRMS: calcd for $C_{45}H_{51}N_2O_{12}$(MH^+) 811.3442, found 811.3422.

Preparation of Compound 23a. To a toluene solution (0.5 mL) of amine **16** (25 mg, 0.032 mmol) and acid **22a** (13.9 mg, 0.052 mmol) were added DCC (10.7 mg, 0.052 mmol) and DMAP (6.3 mg, 0.052 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was then subjected to direct silica gel chromatography (30% EtOAc/hexane) to afford 31 mg (92%) of the desired product **23a**.

^{1}H NMR of **23a** (300 MHz, $CDCl_3$): δ 8.22−8.03 (m, 4H), 7.59−7.25 (m, 11H), 7.12 (d, J = 8.8 Hz, 1H), 6.34 (s, 1H), 5.72 (d, J = 5.3 Hz, 1H), 5.36 (m, 1H), 4.98 (d, J = 9.4 Hz, 1H), 4.92 (d, J = 5.1 Hz, 1H), 4.57 (m, 1H), 4.30 (ABq, J = 8.6 Hz, 2H), 4.20 (m, 1H), 4.06 (s, 3H), 3.76 (d, J = 4.6 Hz, 1H), 2.70−0.47 (m, 34H, includes singlets at 2.15, 1.91, 1.68, 1.23, 1.16, 3H each), 0.11 (d, J = 2.7 Hz, 3H), −0.28 (d, J = 2.7 Hz, 3H). ^{13}C NMR of **23a** (75 MHz, $CDCl_3$): δ 201.3, 170.2, 169.2, 165.0, 162.4, 153.7, 141.2, 139.1, 135.1, 133.4, 132.1, 130.0, 129.7, 128.7, 128.6, 128.4, 128.3, 127.8, 126.5, 84.1, 84.0, 83.4, 81.4, 76.1, 65.4, 74.5, 74.0, 72.3, 58.4, 55.4, 47.5, 46.9, 44.0, 37.1, 35.4, 26.8, 20.8, 20.7, 15.5, 9.8, 6.6, 5.1, 2.4, 1.4. HRMS: calcd for $C_{55}H_{71}N_2O_{13}Si_2$ (MH^+) 1023.4495, found 1023.4494.

Preparation of Compound 5a via 23a. Compound **23a** (29 mg, 0.028 mmol) was dissolved in THF (0.3 mL) and MeOH (0.3 mL) and treated at 0 °C with 1 N HCl (0.142 mL). The reaction mixture was stirred at 0 °C for 30 min and then kept at 5 °C for 12 h. The reaction mixture was then treated at room temperature with a saturated solution of $NaHCO_3$ (0.71 mL) for 4 h. The reaction mixture was poured into water (2 mL) and extracted with EtOAc (5 × 10 mL). The combined organic layers were dried and concd *in vacuo*. The residue was chromatographed (50−60−70% EtOAc/hexane) to provide 15 mg (61%) of the desired product **5a**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.99−8.96 (m, 1H), 8.06−7.26 (m, 14H), 6.66 (d, J = 8.6 Hz, 1H), 6.13 (s, 1H), 5.93 (dd, J = 5.0 Hz, J' = 9.6 Hz, 1H), 5.66 (d, J = 7.0 Hz, 1H), 5.34 (m, 1H), 4.95 (d, J = 9.1 Hz, 1H), 4.70 (m, 1H), 4.26 (m, 1H), 4.21 (ABq, J = 8.5 Hz, 2H), 3.70 (s, 3H), 3.59 (d, J = 6.9 Hz, 1H), 2.50−1.00 (m, 19H, includes singlets at 2.23, 1.62, 1.34, 1.29, 1.12, 3H each). HRMS: calcd for $C_{47}H_{53}N_2O_{14}$ (MH^+) 869.3497, found 869.3487.

Preparation of Compound 5b from 23b. These two compounds were prepared in the exact same way as their

conterparts **23a** and derivative **5a**. The physical data of **23b** and **5b** are listed below.

^{1}H NMR of **23b** (300 MHz, $CDCl_3$): δ 8.15−8.03 (m, 4H), 7.58−7.25 (m, 7H), 7.10 (d, J = 8.9 Hz, 1H), 6.41−6.35 (m, 2H), 6.33 (s, 1H), 5.73 (m, 2H), 5.33 (m, 1H), 5.17 (d, J = 4.9 Hz, 1H), 4.99 (d, J = 7.8 Hz, 1H), 4.55 (m, 1H), 4.31 (ABq, J = 8.5 Hz, 2H), 4.19 (dd, J = 6.7 Hz, J' = 10.7 Hz, 1H), 4.12 (s, 3H), 3.76 (d, J = 6.3 Hz, 1H), 2.70−0.46 (m, 34H, includes singlets at 2.14, 1.90, 1.67, 1.22, 1.14, 3H each), 0.10 (d, J = 2.8 Hz, 3H), −0.28 (d, J = 2.7 Hz, 3H). HRMS: calcd for $C_{53}H_{69}N_2O_{14}Si_2$ (MH^+) 1013.4287, found 1013.4265.

^{1}H NMR of **5b** (300 MHz, $CDCl_3$): δ 8.45−8.42 (d, 1H), 8.07−7.85 (m, 4H), 7.58−7.37 (m, 6H), 6.88 (d, J = 8.5 Hz, 1H), 6.41−6.36 (m, 2H), 6.21 (s, 1H), 6.14 (d, J = 5.0 Hz, 1H), 5.79 (dd, J = 4.1 Hz, J' = 8.7 Hz, 1H), 5.68 (d, J = 6.9 Hz, 1H), 5.40 (m, 1H), 5.99 (d, J = 9.1 Hz, 1H), 4.64 (m, 1H), 4.32 (m, 2H), 4.14 (d, J = 8.7 Hz, 1H), 3.85 (s, 1H), 3.69 (d, J = 6.8 Hz, 1H), 2.57−1.12 (m, 19H, includes singlets at 2.21, 1.69, 1.64, 1.34, 1.13, 3H each). HRMS: calcd for $C_{45}H_{51}N_2O_{15}$ (MH^+) 859.3290, found 859.3312.

Preparation of Compound 24. To a toluene solution (1 mL) of the C-13 amine **19** (26 mg, 0.037 mmol) was added the carboxylic acid **22a** (19.8 mg, 0.074 mmol) followed by DCC (15.1 mg, 0.074 mmol) and DMAP (4.5 mg, 0.037 mmol). The reaction mixture was stirred vigorously at room temperature for 16 h. The reaction mixture was then purified by silica gel chromatography (10−20−30% EtOAc/hexanes) to provide 36 mg (100%) of the desired coupling product **24**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32−8.29 (m, 2H), 8.05−8.02 (m, 2H), 7.62−7.22 (m, 12H), 6.36 (s, 1H), 5.67 (m, 2H), 5.31 (q, 1H), 4.91 (m, 2H), 4.38 (dd, J = 6.8 Hz, J' = 10.3 Hz, 1H), 4.27 (ABq, J = 8.4 Hz, 2H), 4.07 (d, J = 7.9 Hz, 1H), 3.94 (d, J = 6.7 Hz, 1H), 3.47 (m, 1H), 2.60−0.47 (m, 37H, includes singlets at 2.42, 2.15, 1.94, 1.70, 1.24, 1.20, 3H each). HRMS: calcd for $C_{53}H_{64}N_2O_{12}SiNa$ (MNa^+) 971.4126, found 971.4128.

Preparation of C-13 Amidopaclitaxel 6 via 24. Compound **24** (34 mg, 0.036 mmol) was dissolved in THF (0.4 mL) and MeOH (0.4 mL). This solution was treated at 0 °C with 1 N HCl (0.18 mL, 0.180 mmol) for 30 min. The reaction mixture was kept at 5 °C for 18 h. At this point, the reaction mixture was treated with an $NaHCO_3$-saturated solution (4 mL) at room temperature for 4 h. The reaction mixture was then diluted with water (1 mL) and extracted with EtOAc (5 × 10 mL). The extracts were combined, dried, and concd *in vacuo*. The resulting residue was chromatographed (60−80% EtOAc/hexanes) to afford 15.3 mg (50%) of the desired C-13 amidopaclitaxel **6**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.82 (d, J = 8.9 Hz, 1H), 8.02 (d, J = 7.8 Hz, 2H), 7.91 (d, J = 7.6 Hz, 2H), 7.61−7.30 (m, 11H), 7.07 (d, J = 9.4 Hz, 1H), 6.40 (d, J = 4.2 Hz, 1H), 6.15 (s, 1H), 5.90 (dd, J = 3.9 Hz, J' = 8.8 Hz, 1H), 5.60 (d, J = 6.8 Hz, 1H), 5.28 (dd, J = 9.2 Hz, J' = 22.8 Hz, 1H), 4.84 (d, J = 8.6 Hz, 1H), 4.69 (m, 1H), 4.28 (m, 1H), 4.21 (ABq, J = 8.4 Hz, 2H), 3.82 (d, J = 6.8 Hz, 1H), 2.55−1.11 (m, 22H, includes singlets at 2.35, 2.22, 1.65, 1.27, 1.23, 1.11, 3H each). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.7, 172.0, 171.4, 167.3, 166.9, 143.0, 136.5, 133.6, 133.2, 132.8, 132.2, 129.9, 129.1, 128.7, 128.5, 128.3, 128.0, 127.5, 127.1, 84.6, 81.8, 79.2, 76.7, 76.0, 74.7, 73.2, 72.2, 58.7, 56.1, 46.7, 45.0, 42.9, 37.2, 35.7, 26.1, 22.2, 21.3, 20.8, 15.0, 9.3. HRMS: calcd for $C_{47}H_{53}N_2O_{13}$ (MH^+) 853.3548, found 853.3560.

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Supporting Information Available: ^{1}H NMR (300 MHz) spectra for compounds **4**, **5a**, **5b**, **6**, **8**, **10**, **11**, **12**, **13**, **14**, **15**, **16**, **17**, **18**, **19**, **21**, **23b**, and **24** and ^{13}C (75 MHz) spectra for compounds **8**, **12**, **13**, and **15** (22 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 ACS; see any current masthead page for ordering information.

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