Selective Intermolecular Photo-[4 + 4]-cycloaddition with 2-Pyridone Mixtures. 3. Synthetic Transformations of the Trans Cross-Product (1α,2β,5β,6α)-3-Butyl-9-methoxy-3,7-diazatricyclo[4.2.2.2^{2,5}]dodeca-9,11-diene-4,8-dione

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Transformations of the tricyclic product **3** derived from [4 + 4] photocycloaddition of *N*-butyl-2-pyridone with 4-methoxy-2-pyridone has demonstrated, for the first time, facile opening of the secondary lactam after activation of the amide nitrogen with a *tert*-butyl carboxylate (Boc) group. Methanolysis and lithium borohydride reduction both result in opening of the amide group under very mild conditions to give **21** and **24**, respectively. Concomitant reduction of a ketone derived from hydrolysis of the enol ether sets an additional stereogenic center in **24** with complete stereogenic control. These reactions illustrate the synthetic potential of the 2-pyridone photocycloaddition products, generating a cyclooctene as a single isomer, with functionality at seven carbons and five stereogenic centers.

The higher-order cycloaddition of 2-pyridones has been broadly investigated since the initial discovery of this [4 + 4] reaction in 1960.[1] Its attributes include a wide toleration of substitution, good isolated yields, and few side reactions. This cycloaddition yields a terpene-like carbon skeleton with high regioselectivity and a stereoselectivity favoring the trans isomers.[2] Nevertheless, the potential utility of this reaction for natural product synthesis suffers from the symmetry of the dimerization product. Although the effect of substituents on the relative photoreactivity has not been studied, a mixture of two 2-pyridones would be expected to yield a statistical mixture of products.

Our initial efforts to harness this cycloaddition utilized a tether to enforce a reaction between two different pyridones.[3−5] Recently we have discovered that a mixture of pyridones can yield one major product when one of the reactants is a 4-alkoxy-2-pyridone.[6] Photoreaction of the readily available 4-methoxy-2-pyridone **1** and *N*-butyl-2-pyridone **2** forms [4 + 4] cycloadduct **3** in 51% yield (see preceding paper). Product **3** is a conformationally locked cyclooctadiene with four stereogenic centers and four distinct functional groups (Figure 1).

A realization of the potential usefulness of 2-pyridone photoproducts requires that subsequent chemistry be predictably and readily accomplished. Despite many investigations of 2-pyridone photochemistry,[2] studies of 2-pyridone photoproduct transformations have been quite limited. These reactions include alkene hydrogenation and epoxidation, and the reduction of tertiary amides to tertiary amines.[5,7,8] Hydrolytic or reductive cleavage of the amides has not been reported. We report here studies of the transformations of **3**, a molecule containing four distinct functional groups. These transformations, including both hydrolytic and reductive openings of an activated amide bond, occur under mild conditions with high yields and often high stereoselectivity.

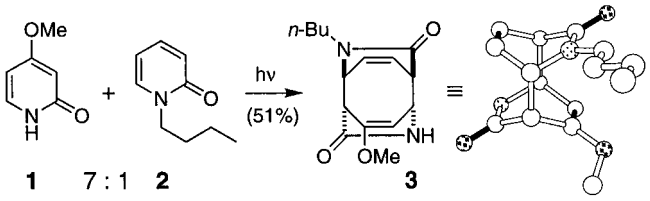

Figure 1. Selective intermolecular 2-pyridone photocycloaddition.

Results and Discussion

The simplest transformation of **3** is hydrogenation, a reaction reported in the early investigations of Paquette[7] and Taylor[8] for 2-pyridone dimers. We have reported hydrogenation of **6**, a structure similar to **3** containing both alkene and enol ether groups, during paclitaxel model studies.[5] In this paclitaxel model, reduction of only the alkene without reduction of the enol ether to give **7** was readily achieved with platinum oxide. In the simpler model system **3**, however, this catalyst reduced the alkene and the enol ether simultaneously[9] to yield **5**. The use of commercial Raney nickel catalyst, however, cleanly gave dihydro **4** in quantitative yield (Figure 2).

Formation of tetrahydro **5** as a single diastereomer provides a good demonstration of the stereoselectivity

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(9) Partially reduced reaction mixtures were complex, containing **3**, **4**, **5**, and the intermediate in which only the enol ether had been reduced.

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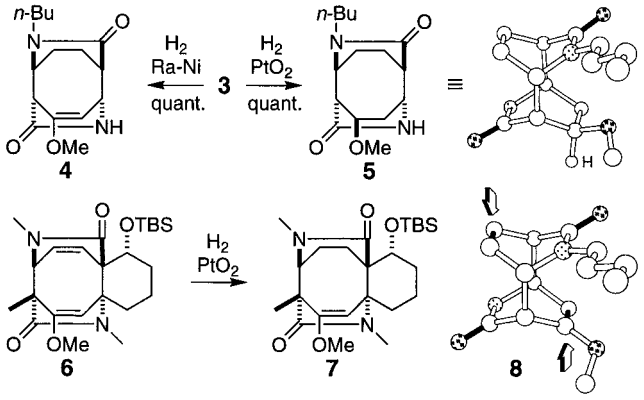

Figure 2. Hydrogenation of **3**. Platinum catalysis reduces both alkenes, unlike the reaction of **6**, and sets a stereogenic center.

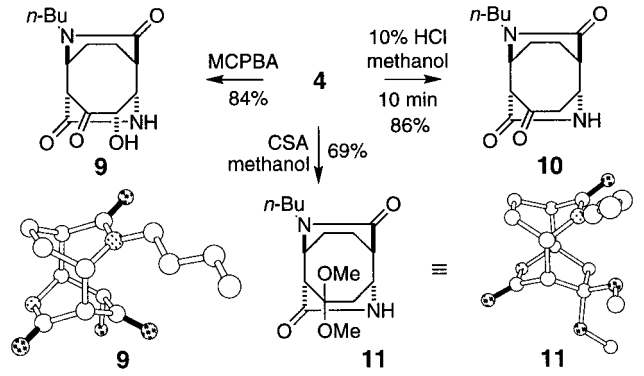

Figure 3. Epoxidation, acetylation, and hydrolysis of the enol ether of **4**.

that is expected from approach of reagents to the least hindered alkene face. In tricyclic **3** and related molecules, one face of each alkene is blocked by an amide group (see **8**). An alkene substituent such as the methoxy group is thereby forced into the more sterically encumbered position during this hydrogenation. The structure of **5** was confirmed by X-ray crystallography (see Supporting Information).

Dihydro **4** could, in turn, be transformed in several ways. Epoxidation of the enol ether with MCPBA yields, after workup, the expected α-hydroxy ketone **9** as a single isomer, presumably due to approach of the peracid to the least hindered face.[10] A model of **9** is shown in Figure 3. Hydrolysis of the enol ether of **4** was rapid in acidic aqueous methanol, yielding ketone **10**. Alternatively, the acetal of the ketone was readily prepared using methanolic camphorsulfonic acid, despite the steric congestion induced during acetal formation to form **11**.

Hydrolysis of the enol ether of **3** proved to be a more sensitive reaction than for dihydro **4**. Treatment of **3** with camphorsulfonic acid in methanol rapidly formed acetal **12**. Acidic hydrolysis of **3** to the corresponding ketone **13** occurs quickly with aqueous methanolic hydrochloric acid, giving **13** after 10 min. If, on the other hand, the hydrolysis of **3** is allowed to run for several hours, a new product is formed in high yield. This new product has the same molecular weight as **3** but has both a pyridone and a stereogenic center. The spectroscopic data is consistent with **14**, and a mechanistic pathway is shown

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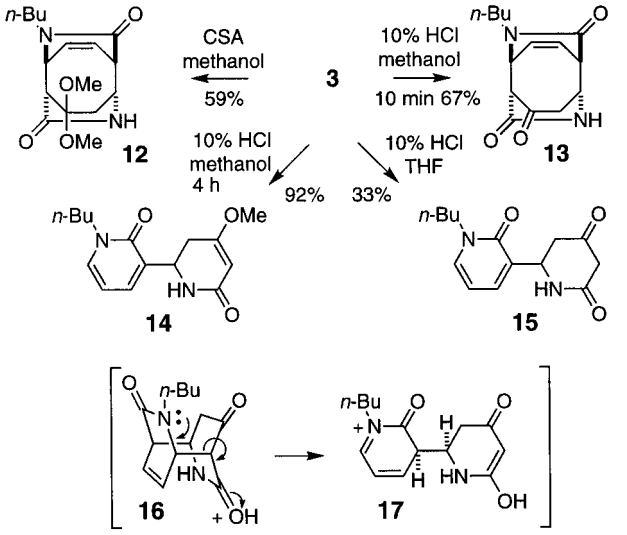

Figure 4. Enol ether hydrolysis leads to either **13** or **14** from **3** in high yield.

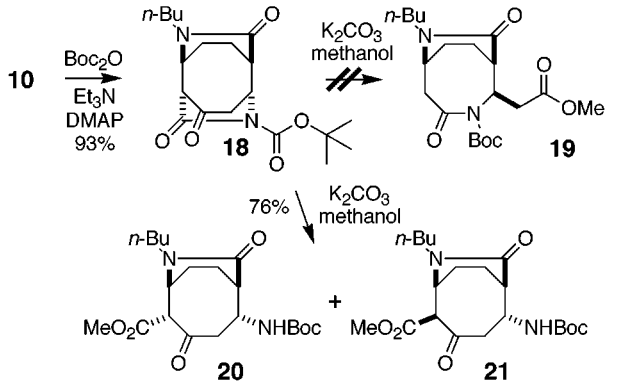

Figure 5. Activation and methanolysis of the secondary amide.

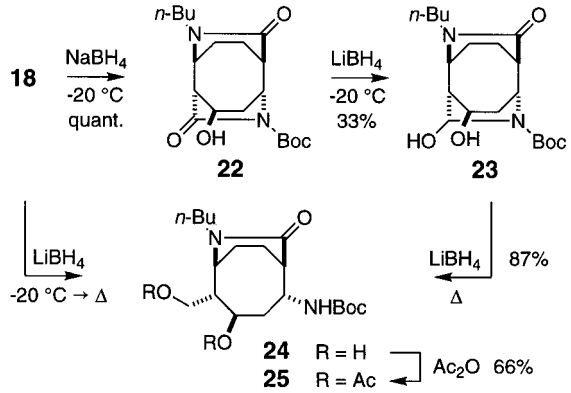

Figure 6. Stepwise reduction of **18**.

in Figure 4. Following hydrolysis to **13**, protonation of the amide (or ketone) allows for the retro-aldol-like fragmentation of **16** to yield **17**. Proton loss from **17** aromatizes the pyridone, and the acidic methanol reforms the enol ether to give **14**. Changing the reaction solvent from methanol to aqueous THF yields ketone **15**.

Whereas amides are among the most difficult carboxylic acid derivatives to hydrolyze, primary and secondary amides are readily cleaved after activation. This proved to be a productive strategy for both **10** and **13** (Figures 5 and 7, respectively). Treatment of **10** with di-*tert*-butyl

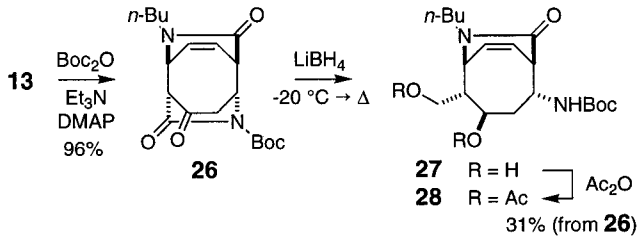

Figure 7. Activation and reductive opening of **13**.

dicarbonate in the presence of DMAP and triethylamine formed the *N*-Boc derivative **18**.[11] This compound, in turn, reacts rapidly with methanolic potassium carbonate to yield two products, each containing a methyl ester. Nonenolizable ketone **18** has the potential for a retro-Claisen condensation to yield **19**; however, the difficulty separable methanolysis products both retain the ketone functional group, as determined by ^{13}C NMR spectroscopy, ruling out formation of **19**. Crystallization of one of the product isomers led to its identification by X-ray crystallography as **21** (see Supporting Information).

The activated amide can also be opened reductively with lithium borohydride, and, interestingly, each reduction intermediate can be isolated. Treatment of **18** with sodium borohydride results in reduction of the ketone only. This reduction yields two products when it is conducted at 0 °C or above, tentatively identified as epimeric alcohols. When the reduction is conducted at −20 °C, however, only a single product can be detected. This product has been assigned as **22** based on an approach of the hydride from the least-hindered face.

Treatment of alcohol **22** with lithium borohydride reduces the amide bond. When this reduction is conducted at −20 °C, this reduction can be intercepted at the aldehyde oxidation level **23**. The stability of this intermediate is presumably due to the limited conformational flexibility of the polycyclic system; however, on warming the reaction to reflux, compound **23** is reduced to diol **24** in high yield. Alternatively, the reduction of **18** to **24** can be accomplished in a single step by treatment with lithium borohydride. The resulting diol, isolated in both cases as a single isomer, was further characterized as diacetate **25**.

Activation and reductive opening of the enone diamide **13** proceeds similarly. Treatment of **13** with di-*tert*-butyl dicarbonate yields activated amide **26**. Addition of this product to a cold solution of lithium borohydride results, after warming to reflux, in the formation of diol **27**. Acetylation of this diol yields **28**. Notably, the additional inflexibility imposed by the alkene in **13**, relative to the saturated system **10**,[12] does not alter the chemistry of the polycyclic system.

Conclusions

Intermolecular photoreaction of pyridone mixtures, when one carries a 4-alkoxy group, yields a complex cycloadduct from simple and readily available aromatic precursors. In the case of trans cross-product **3**, hydrolysis of the enol ether, activation of the secondary amide, and reduction with lithium borohydride produces cyclooctene **22** as a single isomer with five stereogenic centers and functionality at seven of the eight carbons. These are the first examples of amide bond cleavage for the 2-pyridone [4 + 4]-cycloaddition product. The mild conditions, high yields, and the good stereogenic control found for these reactions is encouragment for continuing studies in this area.

Experimental Section

(1α,2β,5β,6α)-3-Butyl-9-methoxy-3,7-diazatricyclo-[4.2.2.2^{2,5}]dodeca-9-ene-4,8-dione (4). To a solution of **3** (350 mg, 1.27 mmol) in methanol (15 mL) was added Raney-nickel (1 mL of a commercial slurry in H_2O). The system was flushed with hydrogen and affixed with a hydrogen balloon (1 atm). The reaction was vigorously stirred for 0.5 h and then filtered through Celite. Removal of the solvent in vacuo gave the title compound as a colorless solid (351.9 mg, 99.6%). Recrystallization from either ethyl acetate or acetonitrile gave an analytical sample. $R_f = 0.5$ (9:1 CH_2Cl_2/methanol) mp = 238−239 °C. ^1H NMR ($CDCl_3$) δ 7.38 (br, 1H), 5.23 (dd, J = 2.4, 7.3 Hz, 1H), 4.19 (ddd, J = 6.2, 7.1, 10.4 Hz, 1H), 4.06 (dd, J = 5.1, 10.5 Hz, 1H), 3.79 (dt, J = 7.6, 13.6 Hz, 1H), 3.51 (s, 3H), 3.35 (dt, J = 2.2, 10.6 Hz, 1H), 3.16 (dd, J = 4.7, 10.4 Hz, 1H), 2.59 (quintet, J = 6.8 Hz, 1H), 2.10 (d, J = 10.7, 2H), 2.1−1.8 (m, 2H), 1.42 (quintet, J = 7.4 Hz, 2H), 1.25 (sextet, J = 7.3 Hz, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 177.0, 174.0, 157.6, 96.7, 55.8, 55.6, 53.6, 49.9, 47.5, 45.9, 30.0, 25.2, 22.1, 19.9, 13.7; IR (KBr) 3471, 3252, 1651, 1672 cm^{-1}; MS (DCI/NH_3) m/z 279 (M^+, 66), 153 (54), 126 (100); exact mass (DCI/NH_3) m/z calcd for $C_{15}H_{23}N_2O_3$: 279.1709, found: 279.1705. Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H,7.97; N, 10.06, found: C, 64.70; H,8.04; N, 10.06.

(1α,2β,5β,6α,9β)-3-Butyl-9-methoxy-3,7-diazatricyclo-[4.2.2.2^{2,5}]dodeca-4,8-dione (5). To a solution of **3** (20.4 mg, 0.74 mmol) in methanol (7 mL) was added PtO_2 (4 mg). The system was flushed with hydrogen and affixed with a hydrogen balloon (1 atm). The reaction was vigorously stirred for 1 h and then filtered through Celite. Removal of the solvent in vacuo gave the title compound as a colorless solid (20.6 mg, 100%). Recrystallization from either ethyl acetate or acetonitrile gave an analytical sample. $R_f = 0.52$; mp = 222−223 °C; ^1H NMR ($CDCl_3$) δ 6.37 (d, J = 5.5, 1H), 4.07 (ddd, J = 6.7, 8.8, 14.0 Hz, 1H), 4.0−4.8 (m, 2H), 3.81 (quintet, J = 5.2, 1H), 3.31 (s, 3H), 3.22 (ddd, J = 1.8, 4.9, 10.6 Hz, 1H), 3.03 (dd, J = 4.1, 11.2, 1H), 2.68 (ddd, J = 5.1, 8.9, 14.1 Hz, 1H), 2.49 (ddd, J = 7.5, 10.8, 14.6 Hz, 1H), 2.16 (d, J = 13.4 Hz, 2H), 2.0−1.8 (m, 3H), 1.48 (m, 2H), 1.31 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172, 171, 76, 57, 55, 51, 48, 47, 46, 32, 30, 26, 22, 21, 14; MS (DCI/NH_3) m/z 281 (MH^+, 100), 249 (50), 152 (41); exact mass (DCI/NH_3) m/z calcd for $C_{15}H_{25}N_2O_3$: 281.1865, found: 281.1874. Anal. Calcd for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63; N, 9.99, found: C, 63.99; H, 8.59; N, 9.91.

(1α,2β,5β,6α,10α)-3-Butyl-10-hydroxy-3,7-diazatricyclo-[4.2.2.2^{2,5}]dodeca-4,8,9-trione (9). To a 0 °C solution of **4** (99.6 mg) in CH_2Cl_2 (10 mL) was added MCPBA (882 mg, 10 equiv). The solution was stirred for 3 h, quenched with 20% NaOCl, and then transferred to a separatory funnel. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 5 mL). The combined organics were extracted with 20% Na_2CO_3, (10 mL) and sat. NaCl (10 mL), respectively. The organic phase was dried over K_2CO_3, and the solvent was removed in vacuo. The isolated material was dissolved in a solution of CH_2Cl_2 and methanol (1:1 10 mL). NaOH 0.5 N (0.2 mL) was added, and the solution was stirred for 5 min. The solution was then neutralized with 0.5 N HCl (0.2 mL). Saturated NaCl was added and transferred to a separatory funnel. The aqueous phase was extracted with CH_2Cl_2 (10 × 5 mL), and the combined organics were dried over Na_2SO_4. The solvent was removed in vacuo to give hydroxy ketone **9** as a colorless solid (84.2 mg, 84%). An analytical sample was obtained by recrystallization from acetonitrile. $R_f = 0.34$ (9:1, CH_2Cl_2/methanol) mp = 231−232 °C; ^1H NMR (D_2O) δ 4.55

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(dd, J = 5.8, 11.6 Hz, 1H), 4.21 (dd, J = 2.0, 11.3 Hz, 1H), 3.97 (d, J = 1.9 Hz, 1H), 3.79 (d, J = 11.6 Hz, 1H), 3.60 (dt, J = 7.7, 13.7 Hz, 1H), 3.34 (dd, J = 5.4, 11.3 Hz, 1H), 2.83 (quintet, J = 6.8 Hz, 6.8 Hz, 1H), 2.37 (m, 1H), 2.1−2.0 (m, 3H), 1.48 (quintet, J = 7.3 Hz, 2H), 1.26 (sextet, J = 7.4 Hz, 2H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$/CD_3OD) 203.0, 172.6, 171.9, 69.8, 61.6, 54.0, 52.7, 46.4, 44.2, 28.6, 24.0, 19.9, 19.6, 13.2; IR (KBr) 3567, 3230, 1744, 1664, 1634 cm^{-1}; MS (DCI/NH_3) m/z 281 (MH^+, 34) 265 (43) 237 (19) 156 (100) 126 (18); exact mass (DCI/NH_3) m/z calcd for $C_{14}H_{21}N_2O_4$: 281.1501, found: 281.1511. Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99, found: C, 59.85; H,7.20; N, 9.95.

(1α,2*β*,5*β*,6α)-3-Butyl-3,7-diazatricyclo[4.2.2.2^{2,5}]dodeca-4,8,9-trione (10). To a 0 °C solution of **4** (212.6 mg, 0.764 mmol) in methanol (3 mL) was added dropwise HCl (0.5 N, 3 mL). The solution was stirred for 10 min, saturated with brine, and then transferred to a separatory funnel. The aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL), and the combined organics were dried over K_2CO_3. The solvent was removed in vacuo to give ketone **10** as a colorless solid (173.5 mg, 86%). An analytical sample was obtained by recrystallization from ethyl acetate. R_f = 0.56 (9:1 CH_2Cl_2/methanol). mp = 216−217 °C. ^{1}H NMR ($CDCl_3$) δ 7.01 (d, J = 5.6 Hz, 1H), 4.3−4.1 (m, 2H), 3.83 (dt, J = 7.8, 13.8 Hz, 1H), 3.61 (dd, J = 1.8, 11.5 Hz, 1H), 3.22 (dd, J = 3.7, 11.0 Hz, 1H), 2.7−2.5 (m, 3H), 2.29 (m, 1H), 2.2−2.0 (m, 3H), 1.44 (quintet, J = 7.7 Hz, 2H), 1.27 (sextet, J = 7.3 Hz, 2H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 202.2, 172.8, 172.2, 62.4, 54.5, 46.5, 46.4, 46.0, 42.0, 29.0, 24.3, 21.2, 19.9, 13.7; IR (KBr) 3196, 3090, 1671, 1650 cm^{-1}; MS (DCI/NH_3) m/z 265 (MH^+, 100), 152 (70); exact mass (DCI/NH_3) m/z calcd for $C_{14}H_{21}N_2O_3$: 265.155218, found: 265.1557. Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60, found: C, 63.54; H, 7.62; N, 10.54.

(1α,2*β*,5*β*,6α)-3-Butyl-9,9-dimethoxy-3,7-diazatricyclo-[4.2.2.2^{2,5}]dodeca-4,8-dione (11). To a solution of **4** (42.5 mg, 0.1527 mmol) in methanol (5 mL) was added camphorsulfonic acid (145 mg, 4 equiv). The solution was stirred for 2.5 h, quenched with 10% K_2CO_3 (5 mL), and then transferred to a separatory funnel. The aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL), and the combined organics were dried over K_2CO_3. The solvent was removed in vacuo to give acetal **11** as a colorless solid (32.6 mg, 69%). An analytical sample was obtained by recrystallization from ethyl acetate. R_f = 0.5 (9:1 CH_2Cl_2/methanol); mp = 219−221 °C; ^{1}H NMR ($CDCl_3$) δ 6.82 (d, J = 6.3 Hz, 1H), 4.2−3.8 (m, 2H), 3.90 (m, 1H), 3.28 (d, J = 12.3 Hz, 1H), 3.20 (s, 3H), 3.16 (s, 3H), 3.04 (dd, J = 3.8, 11.2 Hz, 1H), 2.71 (m, 1H), 2.3−2.1 (m, 4H), 1.9−1.7 (m, 3H), 1.46 (m, 2H), 1.29 (sextet, J = 7.04 Hz, 2H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) 175.3, 173.6, 103.4, 54.5, 53.7, 52.8, 48.9, 47.8, 47.2, 46.9, 36.3, 29.9, 25.6, 21.1, 20.2, 13.8; IR (KBr) 3404, 1645 cm^{-1}; MS (CI, NH_3) m/z 311 (MH^+, 34), 279 (100); exact mass (DCI/NH_3) m/z calcd for $C_{16}H_{27}N_2O_4$: 311.1970, found: 311.1965. Anal. Calcd for $C_{16}H_{26}N_2O_4$: C, 61.91; H, 8.44; N,9.03, found: C, 61.94; H, 8.44; N, 8.88.

(1α,2*β*,5*β*,6α)-3-Butyl-9,9-dimethoxy-3,7-diazatricyclo-[4.2.2.2^{2,5}]dodeca-11-ene-4,8-dione (12). To a solution of **3** (52.0 mg, 0.181 mmol) in methanol (10 mL) was added camphorsulfonic acid (232 mg, 10 equiv). The solution was stirred for 2 h, quenched with 10% K_2CO_3 (10 mL), and then transferred to a separatory funnel. The aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL), and the combined organics were dried over K_2CO_3. The solvent was removed in vacuo to give ketal **12** as a colorless solid (32.9 mg, 59%). An analytical sample was obtained by recrystallization from ethyl acetate. R_f = 0.5 (9:1, CH_2Cl_2/methanol); mp = 220−222 °C; ^{1}H NMR ($CDCl_3$) δ 6.56 (t, J = 1.4, 6.6 Hz, 1H), 6.31 (d, J = 6.3 Hz, 1H), 6.10 (t, J = 8.2 Hz, 1H), 4.14 (ddd, J = 1.1, 6.6, 10.4 Hz, 1H), 4.06 (m, 1H), 3.91 (dt, J = 7.2, 14.2 Hz, 1H), 3.58 (ddd, J = 1.4, 7.3, 10.6 Hz, 1H), 3.43 (d, J = 10.3 Hz, 1H), 3.22 (s, 3H), 3.16 (s, 3H), 2.75 (d, J = 7 Hz, 1H), 2.32 (d, J = 14.6 Hz, 1H), 2.20 (dd, J = 7.1, 14.7, 1H), 1.36 (m, 2H), 1.21 (m, 2H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.9, 173.7, 133.3, 131.3, 104.2, 55.3, 53.7, 50.9, 48.9, 48.2, 47.1, 47.0, 36.7, 29.4, 19.9, 13.8; MS (CI/NH_3) m/z 309 (MH^+, 4), 152 (100); exact mass (CI/NH_3) m/z calcd for $C_{16}H_{25}N_2O_4$: 309.1814, found: 309.1803. Anal. Calcd for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.84; N, 9.08, found: C, 62.24; H,7.79; N, 9.08.

(1α,2*β*,5*β*,6α)-3-Butyl-3,7-diazatricyclo[4.2.2.2^{2,5}]dodeca-11-ene-4,8,9-trione (13). To a 0 °C solution of **3** (79.1 mg, 0.286 mmol) in THF/H_2O (1:1, 10 mL) was added dropwise HCl (0.5 N, 2 mL). The solution was stirred for 10 min, saturated with 5% K_2CO_3, and then transferred to a separatory funnel. The aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL), and the combined organics were dried over K_2CO_3. The solvent was removed in vacuo to give ketone **13** as a colorless solid (53.1 mg, 67%). An analytical sample was obtained by recrystallization from ethyl acetate. R_f = 0.5 (9:1, CH_2Cl_2/methanol); mp = 158−159 °C; ^{1}H NMR ($CDCl_3$) δ 6.69 (bd, J = 5.2 Hz, 1H), 6.54 (td, J = 1.5, 6.6 Hz, 1H), 6.42 (td, J = 1.4, 7.2 Hz, 1H), 4.45 (ddd, J = 1.4, 6.5, 10.9 Hz, 1H), 4.2 (m, 1H), 3.8−3.7 (m, 3H), 2.65−2.60 (m, 3H), 1.39 (m, 2H), 1.23 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 201.0, 171.9, 171.8, 133.0, 131.5, 64.1, 53.9, 497, 45.6, 45.0, 40.0, 28.6, 19.8, 13.6; IR (KBr) 3238, 2933, 1726, 1644, cm^{-1}; MS (DCI/NH_3) m/z 263 (MH^+, 33), 152 (100); exact mass (DCI/NH_3) m/z calcd for $C_{14}H_{19}N_2O_3$: 263.1396, found: 263.1395. Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.11; H, 6.92; N, 10.61, found: C, 63.99; H,6.89; N, 10.61.

6-[3-(1-Butyl-2-oxo-2(1*H*)-pyridinyl)]-5,6-dihydro-4-methoxy-2(1*H*)pyridinone (14). To a solution of **3** (200 mg, 0.724 mmol) in methanol 20 mL was added HCl (0.5 N, 2 mL). The solution was stirred for 4 h, diluted with brine, and extracted with CH_2Cl_2 (4 × 20 mL). The combined organics were dried over Na_2SO_4, and the removal of solvent in vacuo gave **14** (183 mg, 92%) as a yellow solid. R_f = 0.51 (9:1, CH_2Cl_2/methanol); ^{1}H NMR ($CDCl_3$) δ 7.31 (d, J = 6 Hz, 1H), 7.23 (dd, J = 6 Hz, 1H), 6.18 (t, J = 6 Hz, 1H), 5.65 (br, 1H), 5.08 (s, 1H), 4.93 (td, J = 3.0, 4.0 Hz, 1H), 4.1−3.8 (m, 2H), 3.66 (s, 3H), 2.96 (dd, J = 6.0, 18.0 Hz, 1H), 2.54 (dd, J = 6.0, 18.0 Hz, 1H), 1.72 (m, 2H), 1.36 (m, 2H), 0.95 (t, J = 9.0 Hz, 3H); MS (DCI/NH_3) m/z 277 (MH^+, 100); exact mass (DCI/NH_3) m/z calcd for $C_{15}H_{21}N_2O_3$: 277.1552, Found: 277.1539.

1-Butyl-3-(6-piperidinyl-2,4-dione)-2(1*H*)-pyridinone) (15). To a solution of **3** (49.7 mg, 0.179 mmol) in THF/H_2O (1:1 10 mL) was added HCl (0.5 N, 2 mL). The solution was stirred for 4 h, diluted with brine, and extracted with CH_2Cl_2 (4 × 5 mL). The combined organics were dried over Na_2SO_4, and the removal of solvent in vacuo gave **15** (15.7 mg, 33%) as a colorless solid. R_f = 0.60 (9:1, CH_2Cl_2/methanol); ^{1}H NMR ($CDCl_3$) δ 7.25 (t, J = 17.5 Hz, 2H), 6.87 (br, 1H), 4.95 (m, 1H), 3.91 (t, J = 7.5 Hz, 2H), 3.30 (d, J = 2.5 Hz, 2H), 2.98 (dd, J = 5.0, 15.0 Hz, 1H), 2.81 (dd, J = 5.0, 15.0 Hz, 1H), 1.66 (m, 2H), 1.33 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 204, 169, 162, 137.5, 134.5, 130.6, 105.1, 49.9, 48.3, 47.0, 42.2, 31.3, 19.9, 13.7.

(1α,2*β*,5*β*,6α)-3-Butyl-7-[(1,1-dimethylethoxy)carbonyl]-9-methoxy-3,7-diazatricyclo[4.2.2.2^{2,5}]dodeca-4,8,9-trione (18). To a 0 °C solution of ketone **10** (104 mg, 0.393 mmol) in CH_2Cl_2 (10 mL) was added DMAP (48 mg, 1.1 equiv), triethylamine (0.5 mL) and di-*tert*-butyl dicarbonate (400 mg, 4.7 equiv). The solution was allowed to warm to room temperature and after 30 min the reaction was diluted with sat. NH_4Cl (10 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL), the combined organics were dried over Na_2SO_4, and the solvent was removed in vacuo. Purification by flash chromatography (1:1 ethyl acetate/hexane) gave **18** as a colorless solid (133 mg, 93%). R_f = 0.71 (9:1 CH_2Cl_2/MeOH). mp = 165−168 °C. ^{1}H NMR ($CDCl_3$) δ 5.2 (ddd, J = 11.4, 2.4, 5.1 Hz, 1H), 4.21 (dd, J = 4.6, 11.7 Hz, 1H), 3.84 (m, 1H), 3.75 (d, J = 11.6 Hz, 1H), 3.33 (d, J = 11.2 Hz, 1H), 2.8−2.6 (m, 2H), 2.59 (m, 1H), 2.1−2.0 (m, 4H), 1.55 (s, 9H), 1.42 (m, 2H), 1.27 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 201.4, 171.7, 167.9, 151.8, 84.9, 64.4, 54.1, 49.4, 46.5, 45.3, 42.0, 29.1, 27.9, 24.4, 20.9, 19.9, 13.6; IR (KBr) 1771, 1736, 1655 cm^{-1}; MS (DCI/NH_3) m/z 365 (MH^+, 31), 282 (22), 265 (100), 152 (92); exact mass (DCI/NH_3) m/z calcd for $C_{19}H_{29}N_2O_5$: 365.2085, found: 365.2076. Anal. Calcd for $C_{19}H_{28}N_2O_5$: C, 62.62; H, 7.74; N, 7.69, found: C, 62.52; H, 7.73; N, 7.74.

(1α,2α,5α,6α)-7-Butyl-2-[(1,1-dimethylethyl)carbamoyl]-

5-carbomethoxy-7-azabicyclo[4.2.2]deca-4,8-dione (20) and (1α,2α,5*β*,6α)-7-butyl-2-[(1,1-dimethylethyl)carbamoyl]-5-carbomethoxy-7-azabicyclo[4.2.2]deca-4,8-dione (21). To a 0 °C solution of **18** (47.8 mg, 0.131 mmol) in methanol (5 mL) was added K_2CO_3 (30 mg, 1.7 equiv). After 10 min the reaction was diluted with sat. NH_4Cl (5 mL), the layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4 and the ester mixture was isolated by flash chromatography (1:1 ethyl acetate/hexane) to give the products as a colorless solid (39 mg, 76%). ^{13}C NMR ($CDCl_3$) δ 207.6, 207.1, 171.0, 170.7, 168.9, 168.1, 154.4, 64.7, 64.6, 62.6, 57.5, 53.5, 54.4, 54.3, 52.9, 52.8, 52.4, 52.3, 49.5, 46.7, 44.1, 42.8, 36.4, 30.2, 29.7, 29.3, 28.3, 23.1, 20.2, 17.2, 16.7, 16.3, 13.8.

The isomer **21** crystallized from a mixture of ethyl acetate and hexane. R_f = 0.44 (1:1, ethyl acetate/hexane); mp =199−200 °C; ^1H NMR ($CDCl_3$) δ 5.28 (br, 1H), 4.32 (br, 1H), 4.27 (br, 1H), 3.94 (m, 1H), 3.77 (s, 3H), 3.45 (d, J = 2.3 Hz, 1H), 3.36 (br, 1H), 3.22 (dd, J = 12.3, 4.8 Hz, 1H), 2.80 (m, 1H), 2.42 (dd, J = 12.5, 3.6 Hz, 1H), 1.94 (m, 1H), 1.85−1.80 (m, 2H), 1.6−1.4 (m, 3H), 1.44 (s, 9H), 1.31(m, 2H), 0.93 (t, J = 7.3 Hz, 3H); MS (DCI/NH_3) m/z 397 (MH^+, 100), 341 (26), 323 (27), 297 (28), 153 (16); exact mass (DCI/NH_3) m/z calcd for $C_{20}H_{33}N_2O_6$: 397.2339, found: 397.2346.

(1α,2*β*,5*β*,6α,9*β*)-3-Butyl-7-[(1,1-dimethylethoxy)carbonyl]-9-hydroxy-3,7-diazatricyclo[4.2.2.2^{2,5}]dodeca-4,8-dione (22). To a −20 °C solution of ketone **18** (30.5 mg, 0.0834 mmol) in methanol (5 mL) was added $NaBH_4$ (31 mg, 10 equiv). After 5 min the reaction was quenched with sat. NH_4Cl (10 mL). The resulting mixture was extracted with CH_2Cl_2 (4 × 10 mL). The combined organics were dried over Na_2SO_4, and the solvent was removed in vacuo to give **22** as a colorless solid (30.4 mg, >99%). R_f = 0.51 (9:1 CH_2Cl_2/MeOH). mp = 171−174 °C. ^1H NMR ($CDCl_3$) δ 4.89 (dd, J = 7.0, 12.0 Hz, 1H), 4.36 (q, J = 5 Hz, 1H), 4.09 (ddd, J = 2.3 Hz, 1H), 3.98 (dd, J = 5.0, 11.0 Hz, 1H), 3.28 (dd, J = 5.5, 10.5 Hz, 1H), 3.15 (dd, J = 5.0, 12.0 Hz, 1H), 2.83 (m, 1H), 2.57 (m, 1H), 2.07 (m, 1H), 2.0−1.8 (m, 4H), 1.6−1.4 (m, 11H), 1.27 (m, 2H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.5, 172.4, 151.8, 84.1, 66.5, 55.7, 54.2, 51.4, 48.0, 45.7, 34.2, 30.1, 27.9, 25.8, 20.8, 20.2, 13.8; IR (KBr) 3406 1703, 1724, 1638 cm^{-1}; MS (DCI/NH_3) m/z 367(MH^+, 50), 267 (100), 249 (9), 152 (39); exact mass (DCI/NH_3) m/z calcd for $C_{19}H_{31}N_2O_5$: 367.2233, Found: 367.2227. Anal. Calcd for $C_{19}H_{30}N_2O_5 \cdot H_2O$: C, 59.36; H, 8.39; N, 7.29, found: C, 59.42; H, 7.92; N, 7.30.

(1α,2*β*,5*β*,6α,9*β*)-3-Butyl-7-(1,1-dimethylethoxycarbonyl)-8,9-dihydroxy-3,7-diazatricyclo[4.2.2.2^{2,5}]dodeca-4-one (23). To a −20 °C solution of **22** (60.8 mg) in THF (10 mL) was added dropwise a THF solution (1.3 mL) containing $LiBH_4$ (0.55 M, 10 equiv) and water (0.55 M). The resulting solution was warmed to 0 °C and stirred for 0.5 h, quenched with sat. NH_4Cl (10 mL), and then transferred to a separatory funnel. The aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL), and the combined organics were concentrated to give aminal **23** as a colorless solid (20.0 mg, 33%). R_f = 0.44 (9:1, CH_2Cl_2/methanol); ^1H NMR ($CDCl_3$) δ 5.14 (d, J = 3.4 Hz, 1H), 4.52 (dd, J = 7.1, 11.4 Hz, 1H), 4.10 (m, 1H), 4.02 (m, 1H), 3.89 (dd, J = 4.5, 9.5 Hz, 1H), 3.1 (d, J = 12.0 Hz, 1H), 3.04 (dd, J = 6.3, 11.4 Hz, 1H), 2.89 (m, 1H), 2.82 (m, 1H) 2.35 (m, 1H), 1.99 (m, 1H), 1.9−1.7 (m, 5H), 1.63 (m, 2H) 1.47 (s, 9H), 1.32 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H); MS (FAB) m/z 369 (MH^+, 100), 313 (49), 233 (20), 154 (94).

(1α,2α,4*β*,5α,6α)-7-Butyl-2-[(1,1-dimethylethyl)carbamoyl]-4-hydroxy-5-(hydroxymethyl)-7-azabicyclo[4.2.2]deca-8-one 24. To a −20 °C solution of alcohol **23** (22.5 mg, 0.0614 mmol) in THF (5 mL) was added dropwise a THF solution (1.3 mL) containing $LiBH_4$ (0.55 M, 10 equiv) and water (0.55 M). The resulting solution heated to reflux and was stirred for 0.5 h and then quenched by dropwise addition of NaOH (1 N, 2 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL), and the combined organics were concentrated to give diol **24** as a colorless solid (19.5 mg, 87%). An analytical sample was obtained by crystallization from ethyl acetete/hexane. R_f = 0.44 (9:1; CH_2Cl_2/MeOH), mp = 188−190 °C; ^1H NMR (D_2O) δ 3.9−3.7 (m, 4H), 3.63 (dt, J = 7.5, 14.0 Hz, 1H), 3.46 (dd, J = 8.7, 11.1 Hz, 1H), 2.85 (m, 2H), 2.0−1.8 (m, 3H), 1.8−1.7 (m, 3H), 1.45 (m, 2H), 1.31 (s, 9H), 1.19 (sextet, J = 7.4 Hz, 2H), 0.79 (t, J = 6.8 Hz, 3H) (D_2O overlaps one peak); ^{13}C NMR ($CDCl_3$) δ 78.4, 74.6, 61.2, 56.8, 51.3, 46.0, 41.6, 38.0, 33.9, 24.0, 22.9, 15.1, 8.6 (carbonyl peaks not observed); IR (KBr) 3421, 1702 cm^{-1}; MS (DCI/NH_3) m/z 371(MH^+, 59), 315 (100), 253 (19); exact mass (ESI+) m/z calcd for $C_{19}H_{35}N_2O_5$: 371.2546, found: 371.2542.

(1α,2α,4*β*,5α,6α)-4-Acetoxy-5-(acetoxymethyl)-7-butyl-2-[(1,1-dimethylethyl)carbamoyl]-7-azabicyclo[4.2.2]deca-8-one (25). To a 0 °C solution of diol **24** (66 mg, 0.179 mmol) in CH_2Cl_2 (5 mL) were added triethylamine (0.05 mL), acetic anhydride (0.05 mL), and a catalytic amount of DMAP. The mixture was stirred for 10 min and then diluted with sat. NH_4Cl (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organics were dried over Na_2SO_4. Purification by flash chromatography (2:98 methanol/CH_2Cl_2) gave diacetate **25** as a colorless oil (54 mg, 66%). R_f = 0.53 (9:1, CH_2Cl_2/methanol); ^1H NMR ($CDCl_3$) δ 5.77 (br, 1H), 4.89 (t, J = 10.1 Hz, 1H), 4.14 (dd, J = 3.5, 11.4 Hz, 1H), 4.04 (d, J = 8.3 Hz, 1H), 4.01 (d, J = 8.0 Hz, 1H), 3.82 (ddd, J = 6.5, 8.9, 13.9 Hz, 1H), 3.70 (t, J = 2.7 Hz, 1H), 3.35 (br, 1H), 2.81 (ddd, J = 6.0, 8.7, 13.44 Hz, 1H), 2.34 (m, 1H), 2.10 (m, 1H), 2.06 (s, 3H), 2.04 (s, 3H), 2.0−1.8 (m, 4H), 1.70 (dd, J = 3.6, 30.8 Hz, 1H), 1.55 (m, 2H), 1.43 (s, 9H), 1.31 (sextet, J = 7.4 Hz, 2H), 0.92 (t, 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.4, 170.6, 155.3, 68.6, 63.3, 56.0, 49.9, 46.3, 45.8, 41.4, 37.8, 29.6, 28.2, 21.1, 21.0, 20.7, 20.1, 20.0, 17.3, 13.6 (one peak overlaps); IR (neat) 3382, 1740, 1714, 1642 cm^{-1}; MS (DCI/NH_3) m/z 455 (MH^+, 100), 399 (22), 381 (28); exact mass (DCI/NH_3) m/z calcd for $C_{23}H_{39}N_2O_7$: 455.2757, found: 455.2745.

(1α,2*β*,5*β*,6α)-3-Butyl-7-[(1,1-dimethylethoxy)carbonyl]-9-methoxy-3,7-diazatricyclo[4.2.2.2^{2,5}]dodeca-11-ene-4,8,9-trione (26). To a 0 °C solution of ketone **13** (41.0 mg, 0.1563 mmol) in CH_2Cl_2 (10 mL) were added DMAP (19 mg, 1.1 equiv), triethylamine (0.5 mL), and di-*tert*-butyl dicarbonate (136 mg, 4.7 equiv). The solution was allowed to warm to room temperature, and after 30 min the reaction was diluted with sat. NH_4Cl (10 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL), the combined organics were dried over Na_2SO_4, and the solvent was removed in vacuo. Purification by flash chromatography (1:1 ethyl acetate/hexane) gave **26** as a colorless solid (56.6 mg, 96%). R_f = 0.43 (1:1, ethyl acetate/hexane); mp = 157−159 °C; ^1H NMR ($CDCl_3$) δ 6.50 (td, J = 1.3, 6.6 Hz, 1H), 6.36 (td, J = 1.0, 7.7 Hz, 1H), 5.10 (ddd, J = 3.2, 4.3, 10.9 Hz, 1H), 4.48 (ddd, J = 1.0, 6.5, 10.0 Hz, 1H), 3.88 (ddd, J = 1.4, 7.2, 11.0 Hz, 1H), 3.85 (d, J = 11.1 Hz, 1H), 3.75 (dt, J = 7.7, 14.0 Hz, 1H), 2.7−2.5 (m, 3H), 1.54 (s, 9H), 1.38 (m, 2H), 1.21 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 201.1, 171.5, 167.0, 151.9, 132.7, 131.1, 84.8, 65.1, 53.5, 48.7, 48.3, 45.7, 39.8, 28.6, 27.9, 19.8, 13.6; IR (KBr) 1775, 1736, 1661 cm^{-1}; MS (DCI/NH_3) m/z 380 (MNH_4^+, 3), 363 (MH^+, 5), 152 (100); exact mass (DCI/NH_3) m/z calcd for $C_{19}H_{30}N_3O_5$: 380.2185, found: 380.2189. Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.97; H, 7.23; N, 7.73, found: C, 62.61; H, 7.23; N, 7.41.

(1α,2α,4*β*,5α,6α)-7-Butyl-2-[(1,1-dimethylethyl)carbamoyl]-4-hydroxy-5-(hydroxymethyl)-7-azabicyclo[4.2.2]deca-9-en-8-one (27). To a −20 °C solution of **26** (55.5 mg, 0.153 mmol) in THF (5 mL) was added dropwise a THF solution (2.7 mL) containing $LiBH_4$ (0.55 M, 10 equiv) and water (0.55 M). The resulting solution heated to reflux and was stirred for 0.5 h and then quenched by dropwise addition of NaOH (1 N, 2 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL), and the combined organics were concentrated to give diol **27** as a colorless solid. The product was used without purification in the next step.

(1α,2α,4*β*,5α,6α)-4-Acetoxy-5-(acetoxymethyl)-7-butyl-2-[(1,1-dimethylethyl)carbamoyl]-7-azabicyclo[4.2.2]deca-9-en-8-one (28). To a 0 °C solution of diol **27** in CH_2Cl_2 (5 mL) were added triethylamine (0.05 mL), acetic anhydride (0.05 mL), and a catalytic amount of DMAP. The mixture was stirred for 10 min and then diluted with sat. NH_4Cl (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organics were dried over Na_2SO_4. Purifica-

tion by flash chromatography (2:98 methanol/CH_2Cl_2) gave diacetate **28** as a colorless oil (21 mg, 31% two steps). R_f = 0.66 (9:1, CH_2Cl_2/methanol); ^{1}H NMR ($CDCl_3$) δ 6.1−6.0 (m, 2H), 5.46 (m, 1H), 4.95 (t, J = 9.7 Hz, 1H), 4.2−3.8 (m, 6H), 3.78 (br, 1H), 2.8 (quintet, J = 7.0 Hz, 1H), 2.42 (m, 1H), 2.10 (s, 3H), 2.03 (s, 3H), 1.77 (dd, J = 4.5, 15.4 Hz, 1H), 1.55 (septet, J = 8.0 Hz, 2H) 1.46 (s, 9H), 1.31 (sextet, J = 7.3 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.0, 171.0, 157.6, 129.8, 125.9, 67.8, 62.7, 56.8, 48.5, 44.9, 29.5, 28.4, 21.1, 20.1, 13.8; IR (neat) 3375, 1741, 1711, 1645 cm^{-1}; MS (DCI, NH_3) m/z 453 (MH^+, 100), 397 (23), 379 (16); exact mass (DCI/NH_3) m/z calcd for $C_{23}H_{37}N_2O_7$: 453.2601, found: 453.2584.

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Supporting Information Available: ^{1}H NMR spectra of **3**−**5**, **9**−**15**, **18**, **20**−**26**, **28**, and X-ray structures of **5** and **21** (21 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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