# A [4 + 4] 2-Pyridone Approach to Taxol. 3. Stereocontrol during Elaboration of the Cyclooctane

Yong-gyun Lee,[1] Kevin F. McGee, Jr., Jianhao Chen, David Rucando, and Scott McN. Sieburth*

*Department of Chemistry, State University of New York, Stony Brook, New York 11794-3400*

*scott.sieburth@sunysb.edu*

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Intramolecular photocycloaddition of 2-pyridones connected through a four-carbon tether (6-[4-(1,2-dihydro-1-methyl-2-oxo-3-pyridinyl)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]butyl]-4-methoxy-1,3-dimethyl-2(1*H*)-pyridinone) yields a single tetracyclic product with four new stereogenic centers. The diastereoselectivity of this [4 + 4] reaction is fully controlled by a stereogenic carbon of the tether. Treatment of the photoproduct with osmium tetraoxide transforms the alkene to a diol and the enol ether to an α-hydroxy ketone, with stereocontrol dictated by nearby lactams that block one face of each alkene. Allylmagnesium bromide addition to the ketone also yields a single diastereomer, but unexpectedly this product results from approach of the nucleophile to the most-hindered face of the ketone. Study of this reaction in a model system has found the allylic nucleophile to be unique, with nonallylic reagents approaching along the expected, least-hindered path. This contrasteric addition likely results from coordination of the allylic nucleophile to the nearby amide. The amide can therefore act either as a steric shield or as a directing group. The three steps of photocycloaddition, cis-hydroxylation, and nucleophilic addition constructs both quaternary carbons of the cyclooctane and four of the five stereogenic centers found in the eight-membered ring of Taxol.

## Introduction

During the past decade, synthesis of the anticancer drug Taxol **1** and related natural products, such as taxusin **2**, has been among the most intensively researched challenges in organic chemistry.[2] These studies have culminated in extraordinary total syntheses, for which the basic skeletal disconnections[3−9] are shown in Figure 1. Our studies of 2-pyridone [4 + 4] photocycloaddition[10] include an approach to Taxol[11,12] utilizing an intramolecular reaction of 2-pyridones linked through a four-atom chain. We describe here the post-photochemistry transformations of the tetracyclic intermedate and supporting model studies, including an anomalous, highly stereoselective addition of an allylic Grignard reagent to the most-hindered face of a ketone.

## Background

An outline of our 2-pyridone route to Taxol is shown in Figure 2. Bis-2-pyridone **6** is a photosubstrate devel-

* *To whom correspondence should be addressed. Voice: 631-632-7851. FAX: 631-632-8882.

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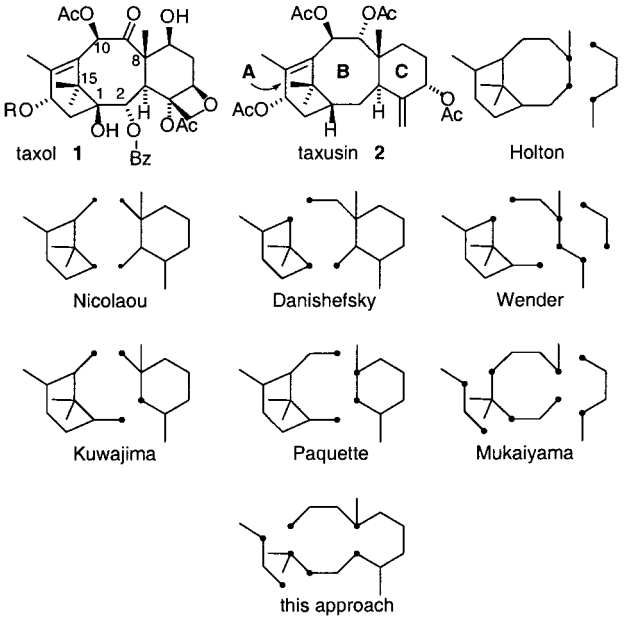


**Figure 1.** Structures of Taxol (R = (2*R*,3*S*)-2-hydroxy-3-benzoylamino-3-phenylpropionyl) and taxusin, and the skeletal disconnections embodied in the total syntheses and in the approach described here.

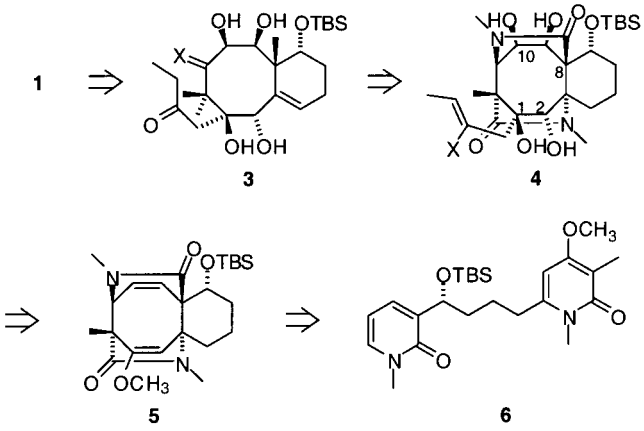


**Figure 2.** Retrosynthetic outline of the 2-pyridone approach to Taxol.

oped from studies of intramolecular 2-pyridone photoreactions with four-carbons linking the pyridones.[11−13] This substrate was anticipated to undergo [4 + 4] cycloaddition to yield tetracyclic **5**. This rigid structure constrains the conformation of the new eight-membered ring, allowing one to readily predict the stereochemistry of synthetic transformations. The lactams of **5**, each shielding one face of an alkene (see Figure 4) would direct cis-dihydroxylation to the other face, stereospecifically transforming the disubstituted alkene into a diol and the enol ether into an α-hydroxy ketone. Nucleophilic addition of the A-ring carbons to the resulting ketone, governed by the same steric approach considerations, would yield **4**. This three-step sequence from **6** to **4** would form both quaternary carbons of Taxol (C8, C15[14]) and four of the five stereogenic centers of the Taxol cyclooctane ring (C1, C2, C8, C10[14]).

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(14) Taxol numbering is used throughout the schemes. Chemical Abstracts numbering is used in the Experimental Section.

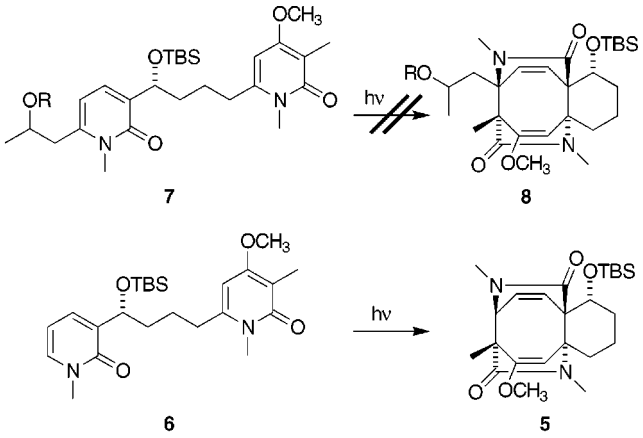


**Figure 3.** A four-carbon tether will allow photocycloaddition to give three fully substituted carbons.

This synthesis strategy was developed after testing an alternative approach to Taxol (Figure 3). Bis-2-pyridone **7** carries the A-ring carbons, but it did not undergo photocycloaddition.[13] In contrast, irradiation of **6** smoothly gave photoproduct **5** as a single isomer, characterized by X-ray crystallography of a dihydro derivative.[13] These examples demonstrated that [4 + 4] cycloaddition with this tether length could generate three, but not four, fully substituted carbons simultaneously.

## Results and Discussion

With **5** in hand, the planned cyclooctadiene elaboration commenced. As described in Figure 4, cis-hydroxylation was expected to yield a keto-triol. The anticipated stereochemistry follows from the steric bias of the alkenes, with one face substantially shielded by the nearby lactam (see arrows, intermediate **5**, Figure 4). This steric effect is observed in reactions of *N*-butyl-2-pyridone dimer **12**. Epoxidation of **12** with MCPBA yields diepoxide **13** with complete diastereoselectivity, and the crystal structure of this diepoxide is shown in Figure 4.[15] With this as precedent, it was gratifying that treatment of **5** with osmium tetroxide gave the single triol diastereomer **9** in nearly quantitative yield. Introduction of the A-ring carbons by nucleophilic addition to ketone **9** was expected to benefit from the same steric effect. Addition from the least-hindered face would result in a *trans*-1,2-diol, with the correct stereochemistry at the new C1 stereocenter, yielding **10**. Use of an excess of a basic nucleophile, especially a Grignard reagent, was expected to reinforce the stereoselectivity by coordination of the nucleophile to the adjacent alkoxide at C2. The stereochemical directing effect of alkoxides and ethers with Grignard reagents has been reported for a variety of α-hydroxy and alkoxy ketones and aldehydes.[16−18] Further, protection

(15) Compound **13** crystallizes from ethyl acetate in the monoclinic space group $P2_1/c$ with $a = 7.192(1)$ Å, $b = 10.2279(8)$ Å, $c = 11.530(2)$ Å, $\beta = 103.193(7)°$, $V = 825.7(2)$ Å$^3$, and $Z = 2$. Final least squares refinement using 1038 unique reflections with $I > 3\sigma(I)$ gave $R(R_w) = 0.037(0.031)$.

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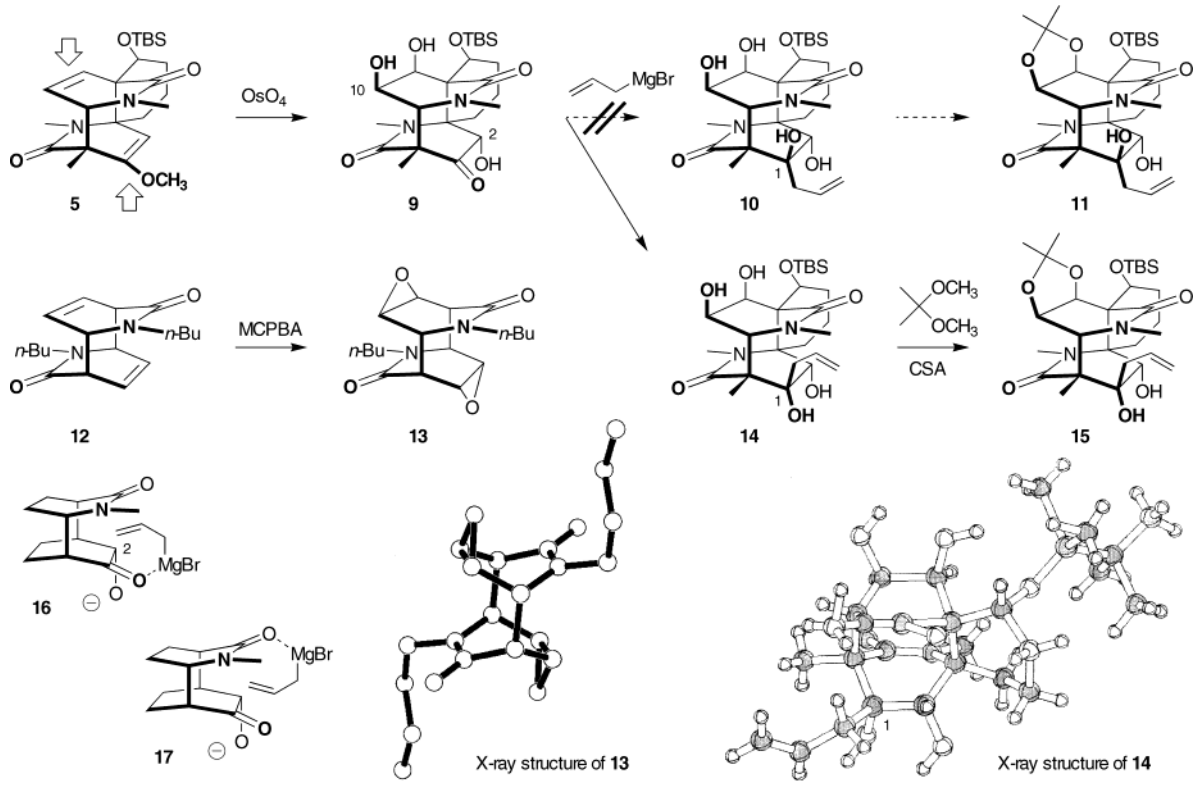


**Figure 4.** Cis-hydroxylation yields one keto-triol **9**, setting the C2 and C10 stereocenters. A similarly steric-controlled reaction is found in bis-epoxidation of **12**. In contrast, allylmagnesium bromide was found to add to the most-hindered face of the ketone.

of the alcohols would add a steric impediment to the desired addition to the ketone.[17]

As expected, addition of excess allylmagnesium bromide to the keto-triol **9** gave a single addition product. Subsequent treatment with 2,2-dimethoxypropane gave a mono acetal, assumed to be **11**. Much to our dismay, however, an X-ray crystal structure of the tetraol revealed it to be **14**,[19] the product of addition to the most-hindered face of the ketone **9**!

This very selective and anti-steric result was surprising, especially in view of the often nonselective nature of allyl Grignard reagents,[20] and was presumed to originate from the ambident nature of this nucleophile. As depicted with **16**, Figure 4, the magnesium could ligate the ketone carbonyl, with the allyl group directed to the internal face of the ketone by the steric effect of the C2 alkoxide.[21] Alternatively, the magnesium could coordinate the proximal amide carbonyl, the most Lewis basic site, effecting delivery as depicted with **17**.

To evaluate this anomalous result,[22,23] the more readily accessible substrate **21** was prepared (Figure 5), using intermolecular photocycloaddition of a 2-pyridone mixture.[24] Irradiation of a methanolic solution of *N*-butyl-2-pyridone **18** and 4-methoxy-2-pyridone **19** gave the trans-cross adduct **20**. Reduction of the alkene with Raney-

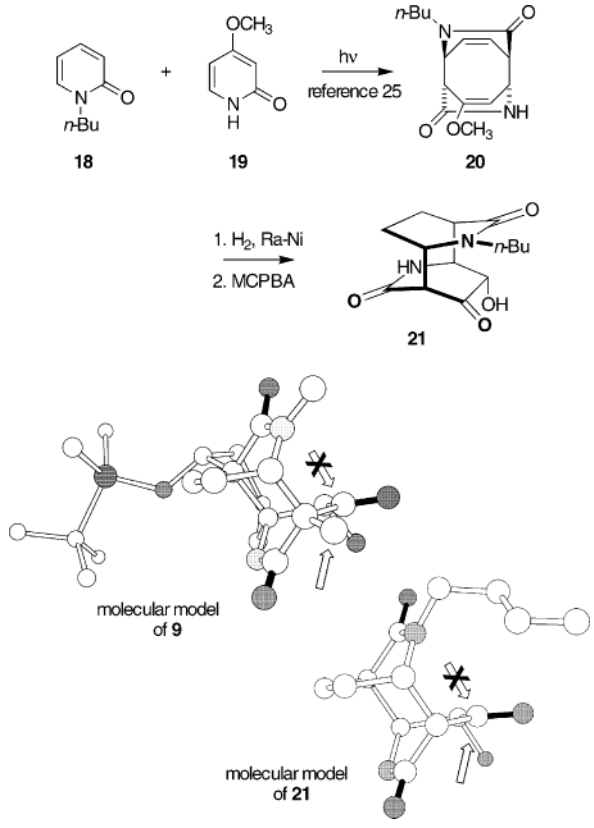


**Figure 5.** Model substrate for nucleophilic ketone additions, **21**, and Chem3D models of **9** and **21** showing approximate nucleophilic approach paths to the ketone. One approach to the ketone is blocked (X).

(17) Chen, X. N.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778−1784.

(18) For an example of allyl Grignard addition to an α-hydroxy ketone to yield a *cis*-diol in a structurally unrelated bicyclic system, see: La Clair, J. J.; Lansbury, P. T.; Zhi, B.-x.; Hoogsteen, K. *J. Org. Chem.* **1995**, *60*, 4822−4833.

(19) Compound **14** crystallizes from ethanol/water in the monoclinic space group $\mathbf{P2_1/c}$ with $a = 7.126$ Å, $b = 8.183(18)$ Å, $c = 25.972(15)$ Å, $\alpha = 81.317°$, $\beta = 89.496°$, $\gamma = 66.646°$, $V = 1372(2)$ Å$^3$, and $Z = 2$. Final least squares refinement using 2543 unique reflections with $I > 3\sigma(I)$ gave $R(R_w) = 0.140(0.127)$.

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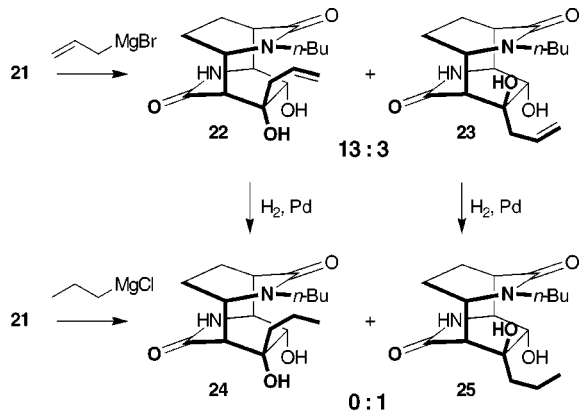


**Figure 6.** Allyl Grignard yields two products, but *n*-propyl Grignard only one, correlated to the minor allyl adduct **23**.

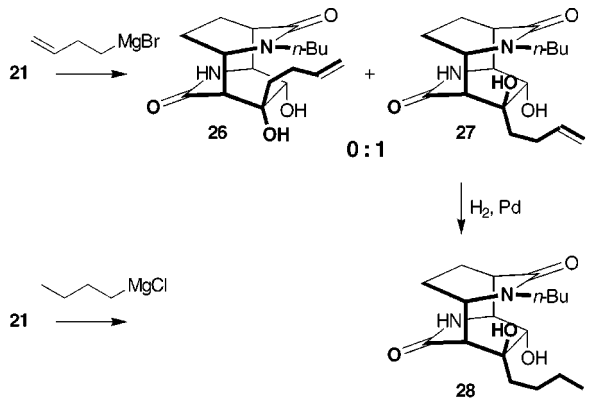


**Figure 7.** Addition of butenyl and butyl Grignard reagents.

nickel, followed by epoxidation of the enol ether, gave hydroxy ketone **21**.[25]

The periphery of the ketone in **21**, relative to ketone **9**, lacks the adjacent methyl group and has an *N*-butyl amide in place of the *N*-methyl amide. In the context of nucleophile approach to the carbonyl,[26] the *N*-alkyl group is an impediment whereas the adjacent methyl group in **9** is orthogonal to the nucleophile approach and presumably irrelevant. The ketone of **21**, with an *N*-butyl group over one face, was therefore expected to have an even greater steric bias toward nucleophiles than *N*-methyl **9**.

Consistent with an increased steric shielding of ketone **21** relative to **9**, addition of allylmagnesium bromide gave a mixture of two products, **22** and **23**, isolated in yields of 64% and 15%, Figure 6. In contrast, *n*-propylmagnesium chloride gave only one isomer, **25**. Hydrogenation of the two allyl addition products correlated **23**, the minor allyl diastereomer, with the *n*-propyl Grignard adduct **25**. X-ray crystallography of major allyl adduct **22** confirmed the stereochemical assignments[27] (see Supporting Information).

As an additional test of the unique reactivity of the allyl Grignard reagent,[22,23] ketone **21** was treated with the homologous nucleophiles 3-buten-1-ylmagnesium bromide and butylmagnesium chloride. In each case, only addition to the least-hindered face of the ketone was observed. Adducts **27** and **28** were readily correlated by hydrogenation of **27**. The clean addition of the butenyl nucleophile to give **27** is particularly useful in view of the recent work of Mukaiyama in which the Taxol A-ring was constructed from a butenyl group attached at C1.[9]

## Conclusions

Photocycloaddition of 2-pyridones yields a polycyclic product comprised of a cyclooctadiene bridged and conformationally locked by two lactams. Each lactam sterically hinders approach to one face of the cyclooctadiene alkenes, leading to stereochemistry that is very selective and readily predicted. The studies described here have generated several new examples of this stereocontrol and have also uncovered the potential of these lactams to direct reagents along the alternative, more-hindered pathway. Combining the three steps of photocycloaddition, alkene dihydroxylation, and nucleophilic addition, bis-2-pyridone **6** forms the B and C rings of the taxane system, including both quaternary carbons and four of the five stereogenic centers of Taxol, with all stereochemistry derived from the single tether stereocenter. Completion of the taxane ring B is predicated on successful lactam openings in related polycyclic systems[25,28] and will be reported in due course.

## Experimental Section

**(3α,4*β*,6a*β*,7*β*,10aα,11*S**,13*S**,14*R**)-7-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]hexahydro-11,13,14-trihydroxy-1,3,5-trimethyl-3,10a:4,6a-diethano-1,5-benzodiazocine-2,6,12(1*H*,3*H*)-trione, 9.** To a solution of photoproduct **5**[25] (423 mg, 0.95 mmol) in ether (10 mL) and pyridine (1.7 mL) was added dropwise a solution of $OsO_4$ (530 mg, 2.1 mmol) in ether (7 mL). The resulting suspension was stirred for 17 h at ambient temperature. A solution of $NaHSO_3$ was added and, after it was stirred at room temperature for 3 h, was heated to reflux overnight. The colorless precipitate was filtered, and the filtrate was extracted with methylene chloride (6 × 10 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated to give **9** as a colorless solid (423 mg, 97%). $^1$H NMR ($CDCl_3$/$CD_3OD$) $\delta$ 4.53 (bs, 1H), 4.31 (d, $J$ = 7.3 Hz, 1H), 3.91 (d, $J$ = 7.3, 1H), 3.72 (s, 1H), 3.30 (s, 1H), 3.2 (m, 1H), 3.04 (s, 3H), 2.77 (s, 3H), 2.4 (m, 1H), 2.1 (m, 1H), 2.0−1.6 (m, 3H), 1.45 (s, 3H), 0.93 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H).

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(22) For examples of nucleophilic addition to α-hydroxy and alkoxy carbonyls in which allylic and aliphatic Grignards give similar stereoselectivity, see: Mülzer, J.; Angermann, A. *Tetrahedron Lett.* **1983**, *24*, 2843−2846. Charette, A. B.; Benslimane, A. F.; Mellon, C. *Tetrahedron Lett.* **1995**, *36*, 8557−8560. Charette, A. B.; Mellon, C.; Motamedi, M. *Tetrahedron Lett.* **1995**, *36*, 8561−8564. Mulzer, J.; Pietschmann, C.; Buschmann, J.; Luger, P. *J. Org. Chem.* **1997**, *62*, 3938−3943.

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(26) Bürgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153−161.

(27) Compound **22** crystallizes from methanol/ether in the monoclinic space group *C*2/*c* with $a$ = 34.1748(58) Å, $b$ = 10.8159(18) Å, $c$ = 9.1783(15) Å, $\beta$ = 99.157(4)°, $V$ = 3349(2) Å$^3$, and $Z$ = 8. Final least squares refinement using 3837 unique reflections with $I > 3\sigma(I)$ gave $R(R_w)$ = 0.090(0.177).

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**(3α,4*β*,6a*β*,7*β*,10aα,11*S**,12*R**,13*S**,14*R**)-7-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]hexahydro-11,12,13,14-tetrahydroxy-12-(1-prop-2-enyl)-1,3,5-trimethyl-3,10a:4,-6a-diethano-1,5-benzodiazocine-2,6,12(1*H*,3*H*)-trione, 14.** To a 0 °C solution of **9** (285 mg, 0.59 mmol) in THF (90 mL) was added dropwise a solution of allyl maganesium bromide (8.2 mL of a 1 M solution in ether). After 5 h, saturated $NH_4Cl$ (60 mL) was added, and the aqueous phase was extracted with methylene chloride (3 × 60 mL). The organic phases were dried over $Na_2SO_4$ and concentrated in vacuo to give a yellow solid. Flash chromatography (97:3 methylene chloride/methanol) gave **14** (173 mg, 56%) as a colorless solid. $^1$H NMR ($CDCl_3$) $\delta$ 5.92 (m, 1H), 5.10 (m, 2H), 4.60 (bs, 1H), 4.11 (m, 1H), 4.04 (d, $J$ = 7.3 Hz, 1H), 3.86 (d, $J$ = 7.3 Hz, 1H), 3.77 (s, 1H), 3.38 (s, 1H), 3.07 (s, 3H), 2.98 (s, 3H), 2.53 (dd, $J$ = 13.9, 5.9 Hz, 1H), 2.41 (m, 1H), 2.24 (dd, $J$ = 13.9, 7.8 Hz, 1H), 2.06 (bs, 1H), 2.01 (s, 1H), 1.78 (m, 1H), 1.70 (m, 2H), 1.46 (s, 3H), 1.25 (d, $J$ = 7.1 Hz, 1H), 0.92 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H). $^{13}$C NMR ($CDCl_3$/$CD_3OD$) $\delta$ 175.3, 174.4, 132.3, 117.5, 75.6, 72.8, 72.5, 70.8, 67.4, 66.3, 65.6, 61.7, 54.6, 41.0, 39.6, 29.3, 26.7, 25.1, 23.9, 22.1, 18.0, 12.4, −5.8, −6.0;

**Acetal 15**. To a solution of **14** (55 mg, 0.105 mmol) in DMF (2 mL) was added camphorsulfonic acid (5.5 mg) and 2,2′-dimethoxypropane ((0.19 mL, 1.6 mmol). After 24 h, $K_2CO_3$ (4 mg) was added and stirred for 0.5 h. The mixture was filtered, and the filtrate was concentrated in vacuo. Flash chromatography (98:2 methylene chloride/methanol) gave **15** as a colorless solid (41 mg, 69%). $^1$H NMR ($CDCl_3$/$CD_3OD$) $\delta$ 6.0 (m, 1H), 5.2 (m, 2H), 4.46 (bs, 1H), 4.45 (m, 1H), 4.37 (d, $J$ = 7.5 Hz, 1H), 3.92 (d, $J$ = 10 Hz, 1H), 3.22 (d, $J$ = 8 Hz, 1H), 3.08 (s, 3H), 3.05 (s, 3H), 2.5 (m, 2H), 2.4 (m, 1H), 2.0 (m, 1H), 1.9−1.6 (m, 4H), 1.51 (s, 3H), 1.31 (s, 3H), 1.24 (s, 3H), 0.92 (s, 9H), 0.14 (s, 3H), 0.05 (s, 3H).

**Diepoxide 13.** To a solution of **12**[29] (1.02 g, 3.3 mmol) in methylene chloride (20 mL) was added MCPBA (8.16 g, 10 equiv). The solution was heated to reflux for 24 h, cooled to 0 °C, and filtered. The filtrate was washed with 12% sodium bisulfite (15 mL), 10% sodium bicarbonate (3 × 10 mL), and saturated NaCl (25 mL). The organic phase was dried over $Na_2SO_4$, and the solvent was removed in vacuo. Recrystalization from ethyl acetate gave diepoxide **13** (520 mg, 47%) as colorless prisms. $R_f$ = 0.54 (5:1 ethyl acetate/hexane); mp = 238 °C; $^1$H NMR ($CDCl_3$) $\delta$ 4.14 (ddd, $J$ = 1.3, 3.8, 10.1 Hz, 2H), 3.79 (dq, $J$ = 6.8, 8.4 Hz, 2H), 3.60−3.55 (m, 4H), 3.28 (td, $J$ = 1.3, 4.2 Hz, 2H), 2.70 (ddd, $J$ = 5.9, 8.3, 13.7 Hz, 2H), 1.57−1.42 (m, 4H), 1.39−1.23 (m, 4H), 0.92 (t, $J$ = 7.2 Hz, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 167.5, 52.4, 50.3, 49.7, 47.7, 46.4, 29.7, 19.9, 13.8; IR (KBr) 1662 cm$^{-1}$; MS (DCI/$NH_3$) $m/z$ 335 ($M^+$, 100); exact mass (DCI/$NH_3$) Calcd for $C_{18}H_{27}N_2O_4$: 335.1971. Found: 335.1974. Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found C, 64.72; H, 7.87; N, 8.32.

**(1α,2*β*,5*β*,6α,9α,10α)-3-Butyl-9,10-dihydroxy-9-(1-prop-2enyl)-3,7-diazatricyclo[4.2.2.2$^{2,5}$]dodeca-4,8-dione 22 and (1α,2*β*,5*β*,6α,9*β*,10α)-3-Butyl-9,10-dihydroxy-9-(1-prop-2enyl)-3,7-diazatricyclo[4.2.2.2$^{2,5}$]dodeca-4,8-dione 23.** To a 0 °C solution of ketone **21**[25] (75 mg, 0.26 mmol) in THF (5 mL) was added allylmagnesium bromide (0.9 mL of a 1 M solution in THF). After 5 min, the ice bath was removed, and the solution was stirred at room temperature for 4 h and then diluted with saturated $NH_4Cl$ (10 mL). The aqueous phase was extracted with ethyl acetate (5 × 10 mL), and the combined organic phases were dried over $Na_2SO_4$ and then concentrated in vacuo. Purification by flash chromatography (95:5 methylene chloride/methanol) gave **22** (55 mg, 64%) and **23** (13 mg, 15%) as colorless solids.

**22:** $R_f$ = 0.33 (9:1 methylene chloride/methanol); mp = 199−201 °C; $^1$H NMR ($CD_3OD$) $\delta$ 5.95 (m, 1H), 5.12 (dd, $J$ = 2.1, 13.2 Hz, 2H), 4.03 (m, 2H), 3.72 (s, 1H), 3.70 (d, $J$ = 12.0 Hz, 1H), 3.05 (dd, $J$ = 3.9, 12.0 Hz, 1H), 2.97 (d, $J$ = 11.7 Hz, 1H), 2.71 (quin, $J$ = 6.8 Hz, 1H), 2.40 (dd, $J$ = 6.9, 14.7 Hz, 1H), 2.25 (dd, $J$ = 6.9, 14.7 Hz, 1H), 1.96−2.20 (m, 2H), 1.64−1.90 (m, 2H), 1.46 (m, 2H), 1.26 (m, 2H), 0.90 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CD_3OD$) $\delta$ 178.8, 176.8, 134.2, 118.9, 76.4, 72.7, 58.1, 58.0, 55.1, 50.3, 47.0, 44.7, 30.9, 27.4, 21.6, 21.1, 14.1; MS (DCI/$NH_3$) $m/z$: 323 (M + 1, 100%). Exact mass (DCI/$NH_3$) calcd for $C_{17}H_{27}N_2O_4$ (M + 1) 323.1970, found 323.1955.

**23:** $R_f$ = 0.30 (9:1 methylene chloride/methanol); mp = 228−230 °C; $^1$H NMR ($CD_3OD$) $\delta$ 5.90 (m, 1H), 5.15 (d, $J$ = 9.6 Hz, 1H), 5.03 (d, $J$ = 17.4 Hz, 1H), 4.13 (s, 1H), 3.95 (m, 2H), 3.69 (d, $J$ = 11.4 Hz, 1H), 3.07 (d, $J$ = 11.1 Hz, 1H), 3.04 (dd, $J$ = 4.8, 11.4 Hz, 1H), 2.91 (quin, $J$ = 6.8 Hz, 1H), 2.60 (dd, $J$ = 5.7, 14.7 Hz, 1H), 2.02−2.20 (m, 3H), 1.80 (m, 2H), 1.50 (m, 2H), 1.35 (m, 2H), 0.90 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CD_3OD$) $\delta$ 178.8, 176.0, 134.9, 119.8, 79.3, 78.4, 59.2, 57.2, 56.3, 49.8, 46.6, 43.1, 30.9, 26.9, 21.4 (2C), 14.2; MS (DCI/NH3) $m/z$: 323 ($MH^+$, 100%). Exact mass (DCI/$NH_3$) calcd for $C_{17}H_{27}N_2O_4$ (M + 1) 323.1970, found 323.1958.

**(1α,2*β*,5*β*,6α,9α,10α)-3-Butyl-9,10-dihydroxy-9-(1-propyl)-3,7-diazatricyclo[4.2.2.2$^{2,5}$]dodeca-4,8-dione, 24.** To a solution of **22** (42 mg, 0.13 mmol) in ethanol (4.5 mL) was added 10% Pd/C (8 mg). The system was flushed with hydrogen and affixed with a hydrogen balloon (1 atm). The reaction was vigorously stirred for 1 h, filtered through Celite, and concentrated in vacuo to give **24** as a colorless solid (41 mg, 97%). $R_f$ = 0.65 (85:15 methylene chloride/methanol); mp = 230−233 °C; $^1$H NMR ($CD_3OD$) $\delta$ 4.10 (dd, $J$ = 5.1, 11.4 Hz, 1H), 4.03 (m, 1H), 3.73 (d, $J$ = 12.0 Hz, 1H), 3.67 (s, 1H), 3.09 (dd, $J$ = 4.2, 12.0 Hz, 1H), 3.03 (d, $J$ = 11.4 Hz, 1H), 2.60 (quin, $J$ = 6.4 Hz, 1H), 2.20 (dt, $J$ = 2.7, 7.5 Hz, 1H), 2.07 (dt, $J$ = 2.7, 7.5 Hz, 1H), 1.25−1.90 (m, 10H), 0.90 (m, 6H); $^{13}$C NMR ($CD_3OD$) $\delta$ 179.0, 176.7, 76.7, 73.6, 58.1, 57.7, 54.8, 49.8, 47.0, 43.1, 30.9, 27.3, 21.6, 21.1, 17.4, 14.5, 14.0; MS (DCI/$NH_3$) $m/z$: 325 ($MH^+$, 100%). exact mass (DCI/$NH_3$) $m/z$ calcd for $C_{17}H_{29}N_2O_4$ 325.2127, found 325.2125.

**(1α,2*β*,5*β*,6α,9*β*,10α)-3-Butyl-9,10-dihydroxy-9-(1-propyl)-3,7-diazatricyclo[4.2.2.2$^{2,5}$]dodeca-4,8-dione, 25, by Hydrogenation of 23.** Following the procedure used to prepare **24**, compound **23** (12 mg, 0.037 mmol) gave **25** (12 mg, 99% yield) as colorless solid. $R_f$ = 0.62 (85:15 methylene chloride/methanol); mp = 227−230 °C; $^1$H NMR ($CD_3OD$) $\delta$ 4.11 (s, 1H), 3.95−4.07 (m, 2H), 3.68 (d, $J$ = 11.7 Hz, 1H), 3.07 (d, $J$ = 10.5 Hz, 1H), 3.05 (dd, $J$ = 3.9, 10.5 Hz, 1H), 2.92 (quin, $J$ = 6.6 Hz, 1H), 2.05 (dt, $J$ = 2.7, 7.5 Hz, 1H),), 1.17 (dt, $J$ = 2.7, 7.5 Hz, 1H), 1.65−1.95 (m, 4H), 1.22−1.58 (m, 6H), 0.90 (m, 6H); $^{13}$C NMR ($CD_3OD$) $\delta$ 179.1, 176.1, 79.7, 78.6, 59.3, 57.4, 56.4, 49.8, 46.7, 40.8, 30.9, 26.9, 21.4, 21.3, 17.1, 15.0, 14.2; MS (DCI/$NH_3$) $m/z$: 325 ($MH^+$, 100%). Exact mass (DCI/$NH_3$) calcd for $C_{17}H_{29}N_2O_4$ 325.2127, found 325.2125.

**(1α,2*β*,5*β*,6α,9*β*,10α)-3-Butyl-9,10-dihydroxy-9-(1-propyl)-3,7-diaza-tricyclo[4.2.2.2$^{2,5}$]dodeca-4,8-dione, 25, from Propylmagnesium Chloride.** To an ambient temperature solution of **21** (45 mg, 0.16 mmol) in THF (5 mL) was added 1-propylmagnesium chloride (0.5 mL of a 1 M solution in THF). The solution was stirred for 4.5 h, diluted with saturated $NH_4Cl$ (10 mL), and extracted with ethyl acetate (4 × 10 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated in vacuo. Purification was by flash chromatography (95:5 methylene chloride/methanol) to give **25** (23 mg, 44%).

**(1α,2*β*,5*β*,6α,9*β*,10α)-3-Butyl-9,10-dihydroxy-9-(1-but-3-enyl)-3,7-diazatricyclo[4.2.2.2$^{2,5}$]dodeca-4,8-dione, 27.** Following a procedure identical to the preparation of **25**, substituting 3-buten-1-ylmagnesium bromide for propylmagnesium chloride, gave **27** (45% after flash chromatography). $R_f$ = 0.65 (9:1 methylene chloride/methanol); $^1$H NMR ($CD_3OD$) $\delta$ 5.80 (m, 1H), 5.03 (dd, $J$ = 1.8, 17.1 Hz, 1H), 4.90 (dd, $J$ = 1.8, 9.4 Hz, 1H), 4.12 (s, 1H), 3.97 (m, 2H), 3.68 (d, $J$ = 12.0 Hz, 1H), 3.05 (d, $J$ = 10.8 Hz, 1H), 3.04 (m, 1H), 2.92 (quin, $J$ = 6.4 Hz, 1H), 1.92−2.19 (m, 3H), 1.77−1.90 (m, 3H), 1.23−1.51 (m, 6H), 0.91 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR ($CD_3OD$) $\delta$ 179.0, 176.1, 140.2, 114.7, 79.5, 78.6, 59.4, 57.6, 56.4, 49.8, 46.7, 38.0, 30.9, 28.6, 26.9, 21.4(2C), 14.2; MS (DCI/$NH_3$) $m/z$: 337 ($MH^+$, 100%). exact mass (DCI/$NH_3$) calcd for $C_{18}H_{29}N_2O_4$ 337.2127, found 337.2117

**(1α,2*β*,5*β*,6α,9*β*,10α)-3,9-Di-*n*-butyl-9,10-dihydroxy-3,7-diazatricyclo[4.2.2.2$^{2,5}$]dodeca-4,8-dione, 28.** Following a procedure identical to the preparation of **25**, substituting butylmagnesium chloride for propylmagnesium chloride, gave **28** (56% after flash chromatography). $Rf$ = 0.64 (85:15 methylene chloride/methanol); $^1$H NMR ($CD_3OD$) $\delta$ 4.11 (s,1H), 3.97

(m, 2H), 3.68 (d, $J$ = 11.7 Hz, 1H), 3.08 (d, $J$ = 10.5 Hz, 1H), 3.03 (dd, $J$ = 4.5, 11.7 Hz, 1H), 2.92 (quin, $J$ = 6.9 Hz, 1H), 1.7−2.20 (m, 5H), 1.26−1.48 (m, 9H), 0.93 (m, 6H); $^{13}$C NMR ($CD_3OD$) $\delta$ 179.1, 176.1, 79.7, 78.7, 59.3, 57.3, 56.4, 49.7, 46.7, 38.2, 30.9, 26.9, 26.1, 24.4, 21.4 (2C), 14.4, 14.2; MS (DCI/$NH_3$) $m/z$: 339 ($MH^+$, 100%). exact mass (DCI/$NH_3$) calcd for $C_{18}H_{31}N_2O_4$ 339.2284, found 339.2281.

**(1α,2*β*,5*β*,6α,9*β*,10α)-3,9-Di-*n*-butyl-9,10-dihydroxy-3,7-diazatricyclo[4.2.2.2$^{2,5}$]dodeca-4,8-dione, 28, by Hydrogenation of 27**. Following the procedure used to prepare **24**, compound **27** gave **28** in quantitative yield.

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**Supporting Information Available:** Proton NMR spectra for compounds **9**, **14**, **15**, **21**−**25**, **26**−**28**, COSY spectra for **22**, **23**, and X-ray structure of **13**, **14**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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