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Photocyclization Reactions of Cyclohexa- and Cyclopenta-Fused Pyridinium Salts. Factors Governing Regioselectivity

Zhiming Zhao, Eileen Duesler, Canhui Wang, Hua Guo, and Patrick S. Mariano*

Department of Chemistry, University of New Mexico, Albuquerque, New Mexico 87131

mariano@unm.edu

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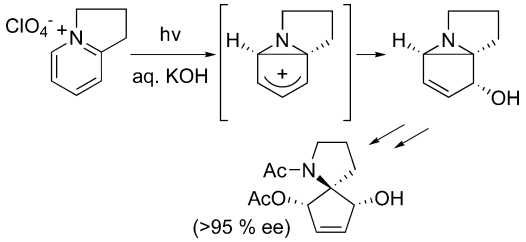
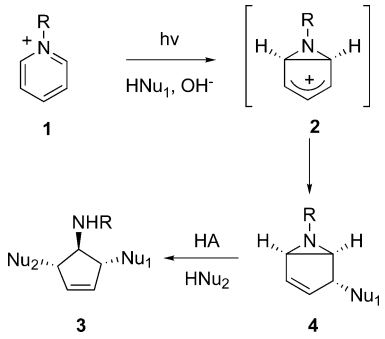


The results of studies described in this report show that irradiation of 1,2-cyclopenta-fused pyridinium perchlorate in aqueous base promotes a remarkably regioselective photocyclization reaction that results in exclusive formation of a single tricyclic allylic alcohol. Moreover, transformation of this photoproduct to a spirocyclic amido diester followed by enzymatic desymmetrization produces an enantiomerically pure monoalcohol. This chemistry comprises a highly concise sequence for the preparation of what should become a useful synthon in synthetic organic chemistry.

Introduction

Over the past decade,[1] we and others[2] have recognized the unique synthetic potential of pyridinium salt photocyclization reactions.[3] Our studies in this area during this period have demonstrated that irradiation of pyridinium salts **1** (Scheme 1) bearing a variety of N-substituents in basic media leads to efficient and stereoselective generation of bicyclic aziridines **4**. These processes take place by formation and nucleophilic capture of intermediate allylic cations **2**. In addition, we have shown that the bicyclic aziridines participate in stereoselective aziridine ring-opening reactions upon treatment with a second nucleophile in acidic media to produce 4-aminocyclopentene derivatives **3**. The remarkable increase in structural and stereochemical complexity attending these two-step transformations serves as a key element of the application of this chemistry to the design of concise strategies for preparation of members of biomedically interesting families, including aminocyclopentitols,[4] polyhydroxylated indolizidines,[5] and amino sugars.[6]

SCHEME 1



Recently, we carried out exploratory studies to probe the photochemical behavior of 1,2-fused pyridinium salts **5** (Scheme 2). We envisaged that photocyclization reactions of these substrates would generate allylic cation intermediates **6**, which are not like those formed from 2-alkyl-substituted analogues[2,3] in that they should resist

(1) Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 4439.

(2) (a) Acar, E. A.; Glarner, F.; Burger, U. *Helv. Chim. Acta* **1998**, *81*, 1095. (b) Penkett, C. S.; Simpson, I. D. *Tetrahedron* **1999**, *55*, 6183. (c) Clark, M. A.; Schoenfeld, R. C.; Ganem, B. *J. Am. Chem. Soc.* **2001**, *123*, 10425.

(3) Kaplan, L.; Pavlik, J. W.; Wilzbach, K. E. *J. Am. Chem. Soc.* **1972**, *94*, 3283.

(4) (a) Ling, R.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 6072. (b) Cho, S. J.; Ling, R.; Mariano, P. S. *J. Org. Chem.* **2000**, *65*, 1574. (c) Lu, H.; Mariano, P. S.; Lam, Y.-F *Tetrahedron Lett.* **2001**, *41*, 4755. (d) Feng, X.; Duesler, E. N.; Mariano, P. S. *J. Org. Chem.* **2005**, *70*, 5618.

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(6) Lu, H.; Su, Z.; Song, L.; Mariano, P. S. *J. Org. Chem.* **2002**, *67*, 3525.

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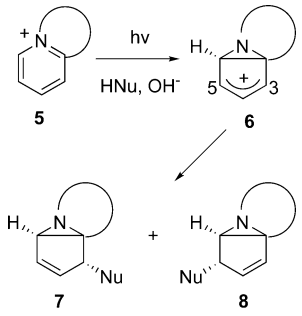
SCHEME 2



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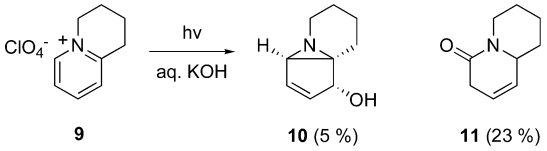
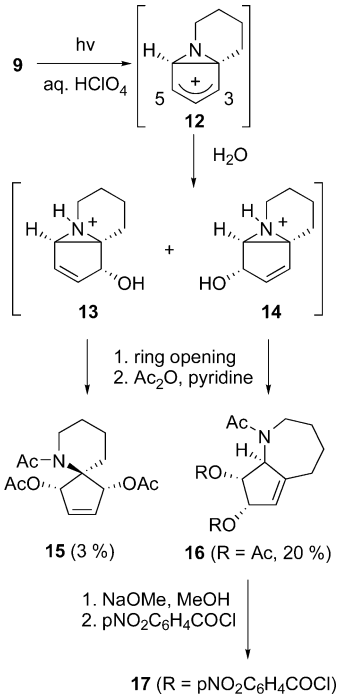


known rearrangement processes that take place via azabenzvalene cation intermediates. We recognized that addition of nucleophiles to the tricyclic allylic cations **6** could take place at either allylic position to produce the aziridine containing photoproducts **7** and **8**. Moreover, simple steric-based reasoning suggested that addition to the C-5 position in **6** would be preferred and that this would result in preferential formation of tricyclic allylic alcohols **8**. As described below, studies with the cyclohexa-fused pyridinium salt have shown that this prediction is correct. However, we have found that the photocyclization reaction of the homologous cyclopenta-fused pyridinium salt follows a completely different regiochemical course and, as a result, it can be used as a key step in a short, efficient sequence to prepare a unique spirocyclic aminocyclopentene synthon.

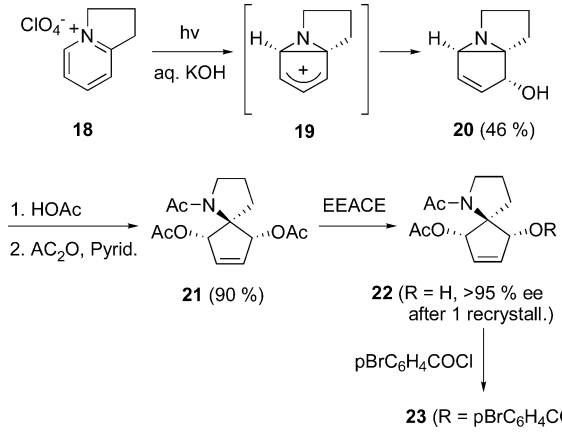
Results and Discussion

The cyclohexa-fused pyridinium perchlorate **9** was prepared by $AgClO_4$ promoted cyclization of the known 1-chloro-4-(2-pyridyl)butane, derived from the corresponding alcohol.[7] Irradiation of **9** in aq. KOH (see Supporting Information) leads to formation of a complex product mixture from which the tricyclic allylic alcohol **10** (5%) and dihydropyridone **11** (23%) can be separated (Scheme 3). This process is far more complex than those of simple alkyl-substituted pyridinium salts. In particular, reactions related to the generation of dihydropyridone **11**,[8] which likely arises by hydroxide addition to **9** followed by tautomerization, are unprecedented in this series. This undesired competitive process can be avoided by carrying out the photoreaction of **9** in an acidic medium. Accordingly, irradiation of a solution of **9** in aq. $HClO_4$, followed by treatment of the amino diol product mixture with Ac_2O in pyridine, leads to formation of the spirocyclic diester **15** (3%) and fused hydroazepine **16** (20%) (Scheme 4). Under the acidic photochemical reaction conditions, the initially formed tricyclic allylic alcohol intermediates **13** and **14** undergo acid-catalyzed ring opening to produce aminocyclopentendiols, which upon

SCHEME 4



SCHEME 5



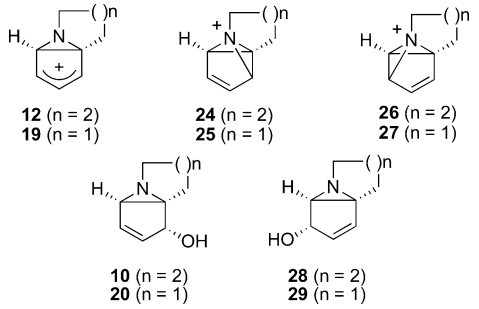
peracetylation are transformed into the respective amido diester products **15** and **16**. The structure and stereochemistry of **16** were established by X-ray crystallographic analysis (see Supporting Information) of its bis-*p*-nitrobenzoate derivative **17**, prepared from **16** by sequential treatment with NaOMe and $pNO_2C_6H_4COCl$.

In the above process, the tricyclic allylic cation **12**, formed by photocyclization of the cyclohexa-fused salt **9**, undergoes preferential addition of water at the C-5 position, accounting for formation of the alcohols **13** and **14** in an approximate 1:7 ratio. Selective formation of **14** in this process shows that steric effects govern the preferred addition of the nucleophile water to the exo-face at C-5 of the intermediate cyclohexa-fused allylic cation **12**. Finally, in this reaction in situ, acid-catalyzed ring opening of the tricyclic aziridine intermediate **13** takes place by a direct S_N2 process whereas S_N2' ring opening of **14** predominates.

Analysis of the stereostructure of the tricyclic allylic cation **19**, produced by excited-state cyclization of the cyclopenta-fused salt **18**, indicates that here also steri-

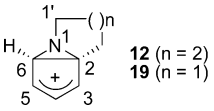
(7) Mayer, J. M.; Testa, B. *Helv. Chim. Acta* **1982**, *65*, 1868.
(8) Lim, H.; Ma, S.; Beak, P. *J. Org. Chem.* **2001**, *66*, 9056.

TABLE 1. Results of DFT Energy Calculations (see Supporting Information for Atomic Coordinates)



structure	relative energies (kcal/mol) B3LYP/6-31++G(d,p)	B3LYP/6-31++G(d,p)+ZPE	B3LYP/6-3G(d)
	Cyclohexa-Fused Series		
12	0	0	0
24	−2.7	−1.7	−2.3
26	−1.2	−0.2	−0.7
10	0	0	–
28	−0.7	−0.8	–
	Cyclopenta-Fused Series		
19	0	0	0
25	+1.6	+2.5	+1.3
27	+7.4	+8.4	+7.4
20	0	0	–
29	−0.3	−0.3	–

TABLE 2. Dihedral Angles and Natural Charges in Tricyclic Allylic Cations 12 and 19 Obtained at the B3LYP/6-31++G(d,p) Level of Theory



cation	dihedral angle C1′,N1′, C6′,C5	dihedral angle C1′,N1′, C2,C3	natural charges C-3	H-3	C-5	H-5
12	−157.3	+153.2	+0.047	+0.281	+0.034	+0.280
19	−166.9	+153.2	+0.102	+0.282	+0.079	+0.283

cally controlled nucleophilic addition should take place at the C-5 position (Scheme 5).

As a result of this prediction, we were surprised by the observations that irradiation of **18**, prepared by $AgClO_4$-promoted cyclization of the known 1-chloro-3-(2-pyridyl) propane that is derived from the corresponding alcohol,[9] in aq. KOH leads to selective production of the tricyclic allylic alcohol **20** (46%). Acetic acid ring opening of **20** followed by peracetylation results in clean formation of the spirocyclic amido diester **21** (90%). This two-step procedure serves as a highly effective method to construct **21**, a meso-diester that is readily desymmetrized by enantioselective enzymatic hydrolysis with electric eel acetyl cholinesterase[10] to yield monoalcohol **22** (65%, 83% ee; 46%, >95% ee after one recrystallization, by ^{1}H NMR analysis of (*R*)- and (*S*)-Mosher esters). The absolute configuration of **22** was established by using X-ray crystallographic analysis (direct methods, see Supporting Information) of its corresponding *p*-bromobenzoate ester derivative **23**.

In an attempt to understand the source of the unpredicted remarkable regioselectivity associated with photochemical conversion of the cyclopenta-fused pyridinium salt **18** to the tricyclic allylic alcohol **20**, we have performed density functional theory calculations on the possible intermediates in and products from this photoreaction as well as that of the cyclohexa-fused homologue **9**. The results of these calculations, summarized in Tables 1 and 2, point out several interesting features. First, the allylic alcohols **28** and **29** arising by addition of hydroxide ion to the C-5 carbons of the respective tricyclic allylic cations **12** and **19** are lower in energy than those (**10** and **20**) arising from addition to C-3. These results support the prediction that exo-approach of hydroxide to the C-5 positions in **12** and **19** is less sterically hindered. Second, as with intermediates generated by photocyclization of *N*-methylpyridinium salts,[11] DFT calculations show that the tricyclic allyl cation **19** formed from the cyclopenta-fused substrate is lower in energy than the corresponding azabenzvalene cations **25** and **27**. Consequently, the unexpected regioselectivity seen in conversion of the cyclopenta-fused pyridinium salt **18** to the tricyclic allylic alcohol **20** is not due to preferences in formation and S_N2'-type ring-opening reactions of azabenzvalene cation intermediates.[12] Third, a significant difference is observed in the geometries of the bicyclic aziridine units in allylic cations **12** and **19**. Analysis of these structures shows that ring strain distorts the cyclopenta-fused cation **19** to create a non-pseudo-symmetric orientation of the nitrogen lone pair relative to the allylic cation π-orbital array. This distortion is best seen by viewing the C1′,-

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(10) (a) Deardorff, D. R.; Windham, C. Q.; Craney, C. L. *Org. Synth*. **1995**, *73*, 25. (b) Deardorff, D. R.; Matthews, A. J.; McMeekin, D. S.; Craney, C. L. *Tetrahedron Lett*. **1986**, *27*, 1255.
(11) King, R. A.; Luthi, H. P.; Schaefer, H. F.; Glarner, F.; Burger, U. *Chem.−Eur. J.* **2001**, *7*, 1734.
(12) Surprisingly, the DFT calculations suggest that the tricyclic allylic cation **12** formed by photocyclization of the cyclohexa-fused pyridinium salt is higher in energy than the corresponding azabenzvalene cations **24** and **26**. The reason for this energy reversal is unknown.

N1,C6,C5- versus C1′,N1,C2,C3-dihedral angles in the calculated structure of **19** (Table 2). Importantly, this distortion is not present in the cyclohexa-fused tricyclic allylic cation **12**. It is difficult to assess the importance of the nitrogen lone pair orientation in governing the regiochemical course of hydroxide addition to **19**. It is interesting and perhaps relevant that the calculated natural charges (Table 2) at the C-3 allylic carbon and attached hydrogen H-3 in **19** are higher than those at C-5 and H-5, a difference not seen in the homologous cyclohexa-fused allylic cation **12**. Although the differences in the positive charge densities are small, they might be sufficiently large to drive counter-steric nucleophilic addition to C-3 in **19**.

Summary

The results described in the previous section demonstrate that the photocyclization reaction of cyclopenta-fused pyridinium perchlorate **18** is remarkably regioselective, forming the tricyclic allylic alcohol **20** exclusively. Moreover, the transformation of **20** to the spirocyclic amido diester **21**, followed by enzymatic desymmetrization, produces enantiomerically pure monoalcohol **22**. This chemistry comprises a highly concise sequence for the preparation of what should become a useful synthon in synthetic organic chemistry.

Experimental Section

1,2-Cyclohexa-Fused Pyridinium Perchlorate 9. A solution of 4-(2-pyridyl) butanol (13 g, 86 mmol) and thionyl chloride (31 g, 0.26 mol) in $CHCl_3$ (100 mL) was stirred at 25 °C for 12 h and diluted with 10% aq. NaOH to adjust the pH to 13−14. Extraction with $CHCl_3$ gave extracts that were dried and concentrated in vacuo to yield the crude chloride as an oil that was heated at 80 °C for 3 h, then recooled to 25 °C and mixed with CH_3CN (100 mL) and $AgClO_4$ (12 g, 58 mmol). The resulting mixture was stirred at 25 °C for 12 h and filtered. The filtrate was concentrated in vacuo to yield the pyridinium salt **9** (15 g, 100%) as a solid. mp 105−107 °C. ^{1}H NMR 1.91−1.97 (m, 2H), 2.07−2.12 (m, 2H), 3.20 (t, J = 6.7 Hz, 2H), 4.50 (t, J = 6.2 Hz, 2H), 7.73−7.80 (m, 2H), 8.27−8.30 (m, 1H), 8.47 (d, J = 6.2 Hz, 1H); ^{13}C NMR 18.9, 22.4, 29.9, 57.6, 126.7, 130.7, 146.1, 146.3, 158.8. HRMS (ES) *m/z* 134.0968 (M^+), calcd for $C_9H_{12}N$ 134.0964.

Photoreaction of 9 in Aqueous KOH. Formation of 10 and 11. A solution of pyridinium salt **9** (2.0 g, 8.6 mmol, UV: γ_{max} 266 nm) and KOH (0.51 g, 9.1 mmol) in water (500 mL) was irradiated (RPR-2537Å reactor lamps, Rayonet company) at 25 °C for 36 h (70% conversion) and concentrated in vacuo to give a residue that was subjected to column chromatography (1:1 acetone/hexane) to give the tricyclic allylic alcohol **10** as a colorless oil (0.05 g, 5%) and the known[9] dihydropyridone **11** as a red oil (0.2 g, 23%).

10: ^{1}H NMR 1.25−1.28 (m, 1H), 1.33−1.38 (m, 2H), 1.58−1.62 (m, 1H), 2.18−2.28 (m, 2H), 2.47 (s, 1H), 2.61−2.64 (m, 1H), 3.32−3.35 (m, 1H), 4.26 (s, 1H), 5.75−5.77 (m, 1H), 6.26 (d, J = 5 Hz, 1H); ^{13}C NMR 18.5, 19.2, 21.5, 49.6, 51.3, 51.8, 78.0, 136.0, 136.1. HRMS (ES) *m/z* 152.1075 (M^+ + 1), calcd for $C_9H_{14}N$ 152.1075.

11: ^{1}H NMR 1.10−1.13 (m, 1H), 1.25 (m, 1H), 1.33−1.36 (m, 1H), 1.48−1.55 (m, 1H), 1.68−1.75 (m, 1H), 2.27−2.37 (m, 1H), 2.78 (s, 2H), 3.65−3.68 (m, 1H), 4.69 (dd, J = 1.9, 13.1 Hz, 1H), 5.44 (d, J = 10.2 Hz, 1H), 5.50 (dd, J = 1.6, 10.2 Hz, 1H), 5.70 (d, J = 9.8 Hz, 1H); ^{13}C NMR 24.3, 25.0, 31.4, 33.7, 41.8, 57.9, 120.6, 125.4, 165.4.

Photoreaction of 9 in Aqueous Perchloric Acid. Formation of 15 and 16. A solution of pyridinium salt **9** (2.0 g, 8.6 mmol UV: γ_{max} 266 nm) and $HClO_4$ (5 mL, 70%) in water (500 mL) was irradiated (RPR-2537Å reactor lamps, Rayonet company) at 25 °C for 28 h (76% conversion) and concentrated in vacuo, giving a residue. A solution of the residue, DMAP (0.1 g), pyridine (10 mL), and Ac_2O (5 mL) in CH_2Cl_2 (30 mL) was stirred at 25 °C for 12 h, diluted with saturated $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and concentrated in a vacuum to give a residue that was subjected to column chromatography (2:3 acetone/hexane) to yield the spirocyclic amido diester **15** (58 mg, 3%) as a colorless oil and fused hydroazepine **16** (0.38 g, 20%) also as a colorless oil.

15: ^{1}H NMR 1.69−1.71 (m, 6H), 2.08 (s, 6H), 2.09 (s, 3H), 3.38 (d, J = 5.7 Hz, 2H), 5.87 (s, 2H), 6.36 (s, 2H); ^{13}C NMR 16.7, 21.0(2), 22.4, 22.9, 24.1, 42.9, 71.0, 82.0(2), 132.0(2), 170.2, 171.2 (2); HRMS (ES) *m/z* 318.1303 (M + Na), calcd for $C_{15}H_{21}NO_5Na$ 318.1312.

16: ^{1}H NMR mixture of two rotamers (1:1) 5.91 (d, J = 6.5 Hz, 1H), 5.75 (d, J = 16.5 Hz, 2H), 5,62−5.64 (m, 2H), 5.05 (t, J = 6.0 Hz, 2H), 4.9 (t, J = 5.5 Hz, 1H), 4.21 (d, J = 134.0 Hz, 1H), 3.63 (d, J = 12.5 Hz, 1H), 2.80 (dd, J = 12.0, 15.3 Hz, 1H), 2.61 (∼t, J = 14.0 Hz, 2H), 2.36 (∼t, J = 13.0 Hz, 1H), 2.22 (s, 3H), 2.17 (s, 3H), 2.15 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 1.81−1.95 (m, 7H), 1.42−1.53 (m, 2H), 1.22−1.27 (m, 1H); ^{13}C NMR 20.4, 20.7, 20.7, 20.8, 21.5, 21.7, 28.7, 29.4, 29.5, 29.8, 30.1, 30.8, 41.6, 44.3, 61.8, 66.2, 73.0, 73.4, 73.6, 74.6, 123.8, 124.0, 152.1, 152.7, 169.8, 170.1, 170.4, 170.6, 170.7, 171.2; HRMS (FAB) *m/z* 318.1325 (M + Na), calcd for $C_{15}H_{21}NO_5Na$ 318.1312.

Bis-*p*-Nitrobenzoate Diester 17. A solution of hydroazepine diester **16** (0.2 g, 0.68 mmol) and NaOMe (36.6 mg, 0.68 mmol) in MeOH (10 mL) was stirred at 25 °C for 12 h, diluted with water, and concentrated in vacuo to yield the crude diol. A solution of the diol, Et_3N (0.5 mL), and *p*-nitrobenzoyl chloride (0.5 g, 2.7 mmol) in CH_2Cl_2 (10 mL) was stirred at 25 °C for 12 h, diluted with saturated $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and concentrated in vacuo, giving a residue that was subjected to column chromatography (1:2 acetone/hexane) to give bis-ester **17** (0.30 g, 85%) as a white solid. mp 211−213 °C (CH_2Cl_2/hexane); ^{1}H NMR (major rotamer) 8.18−8.27 (m, 4H), 8.10−8.13 (m, 4H), 6.25−6.26 (m, 1H), 6.05−6.07 (m, 1H), 5.96 (m, 1H), 5.31−5.36 (m, 1H), 3.73 (d, J = 15.4 Hz, 1H), 2.91 (dd, J = 11.8, 15.4 Hz, 1H), 2.70−2.72 (m, 1H), 2.17 (s, 3H), 1.97−2.06 (m, 3H), 1.54−1.56 (m, 1H), 1.30−1.38 (m, 1H); ^{13}C NMR 21.6, 29.5, 29.8, 30.2, 44.6, 62.0, 75.1, 75.6, 123.6, 123.7, 123.8, 130.5, 130.7, 130.8, 134.7, 134.9, 150.6, 153.8, 164.2, 164.4, 171.3. HRMS (ES) *m/z* 510.1522 (M + 1), calcd for $C_{25}H_{24}N_3O_9$ 510.1513

1,2-Cyclopenta-Fused Pyridinium Perchlorate 18. A solution of 3-(2-pyridyl)propanol (6.85 g, 0.05 mol) and thionyl chloride (9 mL) was stirred at 25 °C for 5 h and then cooled to 0 °C, and aq. NaOH was added to bring the pH to 12−14. The solution was extracted by $CHCl_3$. The $CHCl_3$ extracts were concentrated in vacuo to yield the crude chloride as an oil that was heated at 80 °C for 2 h, recooled to 25 °C, and mixed with CH_3CN (50 mL) and $AgClO_4$ (9 g, 0.043 mol). The mixture was stirred for 12 h at 25 °C and filtered. The filtrate was concentrated in a vacuum at room temperature to yield the pyridinium salt **18** (9.2 g, 85%) as a solid. mp 112−113 °C. ^{1}H NMR (CD_3CN) 2.46 (m, 2H), 3.48 (t, J = 7.6 Hz, 2H), 4.79 (t, J = 7.6 Hz, 2H), 7.82 (t, J = 6.6 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 8.36 (t, J = 7.8 Hz, 1H), 8.66 (d, J = 6.1 Hz, 1H); ^{13}C NMR 22.1, 33.2, 60.2, 125.8, 126.5, 142.0, 146.1, 160.4. HRMS (ES) *m/z* 120.0809 (M), calcd for $C_8H_{10}N$ 120.0808.

Photoreaction of 18 in Aqueous KOH. Formation of Tricyclic Allylic Alcohol 20. A solution of **18** (2.14 g, 0.01 mol, UV: γ_{max} 266 nm) in H_2O (500 mL) containing KOH (0.6 g, 0.01 mol) was irradiated (RPR-2537Å reactor lamps, Rayonet company) for 24 h (70% conversion). Concentration in a vacuum was followed by extraction with $CHCl_3$. The extracts were filtered and concentrated in a vacuum, giving a residue

that was subjected to column chromatography (silica gel, 1:1 ethyl acetate/MeOH) to yield the allylic alcohol **20** (0.63 g, 46%) as a red oil. ^{1}H NMR (acetone-d_6) 1.50−1.54 (m, 1H), 1.66−1.69 (m, 1H), 2.08−2.10 (m, 1H), 2.26−2.30 (m, 1H), 2.55 (s, 1H), 2.78−2.86 (m, 1H), 2.87−2.90 (m, 1H), 4.28 (s, 1H), 5.72 (d, J = 5.0 Hz, 1H), 6.02 (d, J = 5.3 Hz, 1H), 8.05 (s, 1H). ^{13}C NMR 21.9, 23.5, 46.0, 52.9, 62.8, 75.0, 133.4, 138.0; HRMS (ES) *m/z* 138.0916 (M + 1), cald for $C_8H_{12}NO$ 138.0919.

Spirocyclic Amido Diester 21. A solution of the allylic alcohol **20** (0.63 g, 0.03 mol) and CH_3COOH (1 mL) in CH_2Cl_2 (30 mL) was stirred at 25 °C for 12 h. Pyridine (1.5 mL), DMAP (0.1 g), and Ac_2O (2 mL) were added, and the resulting solution was stirred for another 12 h at 25 °C, diluted with saturated $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and concentrated in vacuo to yield a residue that was subjected to column chromatography (1:2 acetone/hexane) to give amido diester **21** (1.17 g, 90%) as a white solid. mp 98−100 °C (acetone/hexane); ^{1}H NMR 1.63−1.68 (m, 2H), 1.87−1.90 (m, 2H), 1.95 (s, 3H), 1.96 (s, 6H), 3.28 (t, J = 6.6 Hz, 2H), 5.78 (s, 2H), 6.27 (s, 2H). ^{13}C NMR 20.8 (2), 23.5, 23.8, 27.4, 48.5, 77.0, 78.4 (2), 132.4 (2), 169.7, 170.0 (2); HRMS (ES) *m/z* 304.1143 (M + Na), calcd for $C_{14}H_{19}NO_5Na$ 304.1155.

Monoalcohol 22 by Enzymatic Desymmetrization. A solution of 50 mg of sodium azide, 500 units lypholized electric eel acetyl cholinesterase (EEACE), and amido diacetate **21** (2.0 g, 7.1 mmol) in 0.58 M sodium dihydrogen phosphate buffer (100 mL, pH 6.9) at 25 °C was gently stirred. The progress of the hydrolysis was monitored by TLC, and the reaction was stopped at ca. 60% of conversion at which time the aqueous solution was extracted with $CHCl_3$. The extracts were dried and concentrated in vacuo to give a residue that was subjected to column chromatography (silica gel, 1:1 acetone/hexane) to yield the monoalcohol **22** ($[\alpha]_D^{23}$ +3.8 (*c* 0.71, $CHCl_3$); 1.1 g, 65%, 83%ee, by ^{1}H NMR analysis of (*R*)- and (*S*)-Mosher esters; 88% based on recovered starting material), a diol (0.1 g, 5%), and recovered starting material (0.53 g). One recrystallization from 1:1 acetone/hexane provides 0.77 g (46%) (>95% ee). $[\alpha]_D^{23}$ +4.7 (*c* 0.68, $CHCl_3$). mp 154.7−155.1 °C (acetone/hexane); ^{1}H NMR 1.65−1.1.75 (m, 1H), 1.80−1.90 (m, 2H), 2.06 (s, 3H), 2.08 (s, 3H), 2, 2.18−2.30 (m, 1H), 3.39−3.41 (m, 1H), 3.46−3.48 (m, 1H), 4.26−4.30 (m, 1H), 5.43 (d, J = 4.9 Hz, 1H), 5.75−5.77 (m, 1H), 5.92−5.93 (m, 1H), 6.36 (d, J = 1.7 Hz, 1H, OH). ^{13}C NMR 21.0, 23.5, 24.1, 26.5, 49.3, 75.2, 78.4, 79.2, 130.1, 136.7, 169.9, 170.4; HRMS (ES) *m/z* 262.1054 (M + Na), Calcd for $C_{12}H_{17}NO_4Na$ 262.1050.

***p*-Bromobenzoate Ester 23.** A solution of Et_3N (0.38 mL), *p*-BrC_6H_4COCl (0.37 g, 1.7 mmol), and monoalcohol **22** (0.2 g, 0.84 mmol) in CH_2Cl_2 (5 mL) was stirred at 25 °C for 12 h, poured into saturated $NaHCO_3$ (30 mL), and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and concentrated in vacuo to give a residue that was subjected to column chromatography (1:3 acetone/hexane) to yield ester **23** (0.29 g, 80%) as a solid. $[\alpha]_D^{23}$ −122.4° (*c* 0.23, $CHCl_3$). mp 177−179 °C (CH_2Cl_2/hexane). ^{1}H NMR 1.75−1.81 (m, 2H), 2.05−2.15 (m, 2H), 2.11 (s, 3H), 2.12 (s, 3H), 3.43 (t, J = 6.8 Hz, 2H), 6.00 (dd, J = 5.3, 16.1 Hz, 2H), 6.46 (d, J = 1.4 Hz, 1H), 6.66 (d, J = 1.4 Hz, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.89 (d, J = 8.5 Hz, 2H); ^{13}CNMR 20.9, 23.6, 23.9, 27.6, 48.5, 77.3, 78.6, 79.4, 128.2, 128.7, 131.0, 131.7, 132.2, 132.9, 164.9, 169.7, 170.1. HRMS (ES) *m/z* 422.0604 (M + 1), calcd for $C_{19}H_{21}NO_5Br$ 422.0603.

Density Functional Theory Calculations. All density functional theory calculations were carried out by using the Becke3−Lee−Yang−Parr (B3LPY) exchange-correlation functional,[13,14] as implemented in Gaussian 03.[15] Energy minima were determined by geometry optimization with the 6-31G(d) and 6-31++G((d,p) basis sets. Frequency calculations were performed to confirm these stationary points and to provide zero-point energy (ZPE) corrections to the energy. The natural charges of the atoms were obtained using the natural population analysis.[16]

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Supporting Information Available: (1) General experimental information, (2) ^{1}H and ^{13}C NMR spectra of **9**−**11**, **15**−**18**, **20**−**23**, (3) summaries of crystallographic parameters for **17** and **23**, and (4) tables of atomic coordinates for the DFT-derived structures found in Tables 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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