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Pyridinium Salt Photochemistry in a Concise Route for Synthesis of the Trehazolin Aminocyclitol, Trehazolamine

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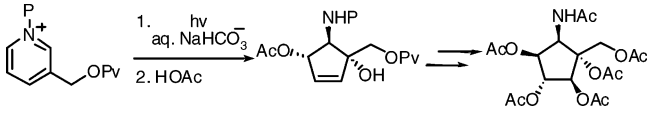

A strategy for the concise synthesis of trehazolamine, the aminocyclitol core of the potent trehalase inhibitor trehazolin, has been developed. The methodology takes advantage of photocyclization reaction of 1-methoxyethoxymethyl-3-pivaloxymethylpyridinium perchlorate to generate a bicyclic-aziridine intermediate, which is transformed under aziridine ring opening conditions to the key intermediate, 3,5-diacetoxy-3-pivaloxymethyl-4-(*N*-acetylamino)cyclopentene. In addition, the strategy is used in an enantio-divergent sequence for preparation of the natural (+)-trehazolamine and its unnatural (−)-enantiomer. In this route, the chiral auxiliary containing 1-(tetracetyl-α-D-glucosyl)-3-pivaloxymethylpyridinium perchlorate undergoes photocyclization to generate separable, diastereomeric bicyclic-aziridines, which are then independently transformed to enantiomeric 3,5-diacetoxy-3-pivaloxymethyl-4-(*N*-acetylamino)cyclopentenes.

In the early 1970s, at a time when great interest focused on photoinduced valance bond isomerization reactions of benzene and its derivatives,[1] Kaplan, Pavlik, and Wilzbach[2] reported that irradiation of *N*-methylpyridinium chloride (**1**) in aqueous base leads to production of bicyclic aziridine **3** (Scheme 1). The mechanism, proposed for this process, involves initial excited-state cyclization to form the intermediate allylic cation **2** followed by least-hindered exo-addition of hydroxide. No further exploration of this photoreaction occurred until the mid-1980s when Mariano and co-workers[3] observed that irradiation of a methanol solution of *N*-allylpyridinium perchlorate (**4**) promoted efficient formation of the aminocyclopentendiol derivative **6** (Scheme 2). Cognizant of the earlier proposal by Kaplan, Pavlik, and Wilzbach, these workers suggested that **6** arises by acid-promoted methanol ring opening of bicyclic-aziridine **5**, produced by photocyclization of **4**.

It was not until the mid-1990s that the synthetic potential of the pyridinium salt photocyclization process was recognized and explored in detail. In one effort,[4] Mariano and co-workers demonstrated the generality of the process by showing that pyridinium salts with a

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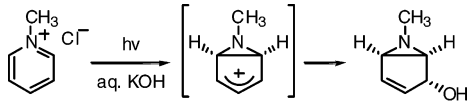

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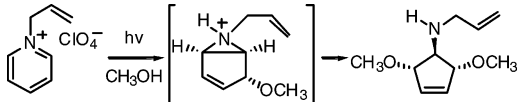

variety of N-substituents (Me, *n*-Pr, CH_2, $CONH_2$, CH_2-CH_2OH) are transformed to bicyclic-aziridines upon irradiation in aqueous or methanolic base. In addition, these workers showed that the products of these reactions undergo stereocontrolled, acid-promoted ring opening with a variety of nucleophiles (H_2O, CH_3OH, HOAc, HSAc). Since that time, a number of informative studies of these processes have been described.[5−10] Also, unique applications of the bicyclic-aziridine ring forming and opening sequence to the synthesis of aminocyclitols,[11−13]

(1) Bryce-Smith, D.; Gilbert, A. *Tetrahedron* **1976**, *32*, 1309.
(2) Kaplan, L.; Pavlik, J. W.; Wilzbach, K. E. *J. Am. Chem. Soc.* **1972**, *94*, 3283.
(3) Yoon, U. C.; Quillen, S. L.; Mariano, P. S.; Swanson, R.; Stavinoha, J. L.; Bay, E. *J. Am. Chem. Soc.* **1983**, *105*, 1204.
(4) Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 4439.
(5) Acar, E. A.; Glarner, F.; Burger, U. *Helv. Chim. Acta* **1998**, *81*, 1095.
(6) Glarner, F.; Acar, B.; Etter, I.; Damiano, T.; Acar, E. A.; Bernardinelli, G.; Burger, U. *Tetrahedron* **2000**, *56*, 4311.
(7) King, R. A.; Luthi, H. P.; Schaefer, H. F.; Glarner, F.; Burger, U. *Chem.-Eur. J.* **2001**, *7*, 1734.
(8) Penkett, C. S.; Simpson, I. D. *Synlett* **1999**, 93.

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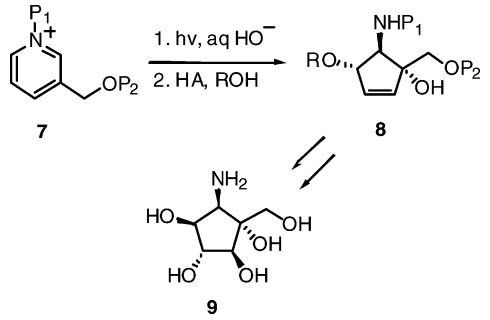
SCHEME 3



polyhydroxylated indolizidines,[14] and amino-aldopentoses[15] have been reported.

Perhaps the most remarkable feature of the photocyclization−ring opening sequence is that it enables rapid construction of functionally and stereochemically complex products from simple ("flat") starting materials. This feature can be used advantageously in the design of concise routes for the preparation of biologically interesting targets. An example of this is found in a strategy we have recently developed for the synthesis of the key aminocyclitol, trehazolamine (**9**), of the potent trehalase inhibitor, trehazolin.[16,17] The design revolves about photoconversion of an appropriately protected 3-hydroxymethylpyridinium salts **7** followed by aziridine ring opening to produce an advanced aminocyclopentene intermediate **8** (Scheme 3).

The original studies by Kaplan, Pavlik, and Wilzbach,[2] and efforts by us[4] and later by Burger,[7] showed that irradiation of 3-substituted pyridinium salts **10** leads to formation of mixtures of bicyclic-aziridines **12** and **13**, formed presumably by indiscriminant hydroxide addition to intermediate allylic cations **11** (Scheme 4). Consequently, we expected that irradiation of **7** followed by aziridine ring opening would give rise to both the desired aminocyclopentene **8** and an undesired regioisomer. However, we felt that this shortcoming would not deter the application of this chemistry to a trehazolamine synthesis because it was difficult to envision any other

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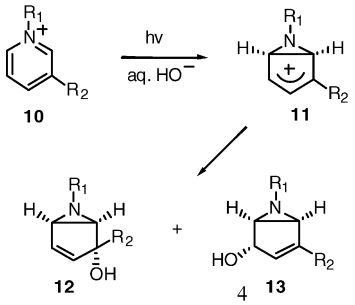

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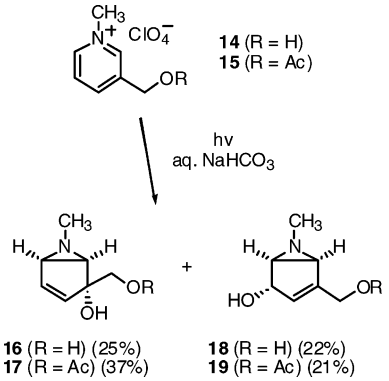


synthetic plan that would as efficiently produce such an advanced intermediate in a sequence to this target.

Results and Discussion

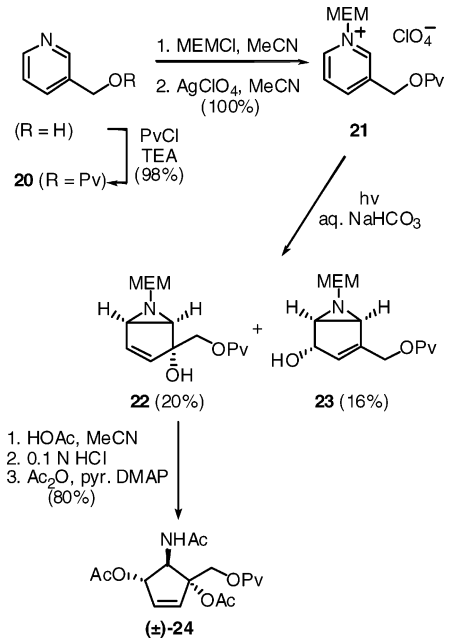
Preliminary exploratory studies were carried out to determine if hydroxyl protection would impact regiochemical preferences in photocyclization reactions of 3-hydroxymethylpyridinium salts. For this purpose, *N*-methyl-3-hydroxymethylpyridinium perchlorate **14** and its acetate ester **15** were prepared and irradiated ($\lambda >$ 225 nm, 70% conversion) in N_2-purged aqueous $NaHCO_3$ solutions. These photoreactions generate mixtures of separable regioisomeric bicyclic-aziridines (**16**−**19**) in moderately high yields and in ratios that only marginally depend on the nature of the 3-substituent (Scheme 5). The finding that the acetate group does not detrimentally alter the regioselectivity of this process helped in the identification of the MEM-protected[6] 3-pivaloxy-methylpyridinium perchlorate **21** as the starting point for the trehazolamine synthesis.

Pyridinium salt **21** was prepared by a two-step sequence from the commercially available 3-hydroxymethylpyridine (Scheme 6). As anticipated, irradiation of **21** in aq $NaHCO_3$ leads to production of the separable bicyclic-aziridines **22** (20%) and **23** (16%). Acetic acid-promoted ring opening of **22**, followed by MEM-removal and peracetylation, then provides the acetamidocyclopententriol derivative **24** (80%, three steps).

From the perspective of functionality and stereochemistry, it is clear that **24** can serve as a late-stage intermediate in a trehazolamine synthesis because all that remains to be accomplished is (1) inversion of hydroxyl stereochemistry guided by the adjacent amide group, and (2) trans-stereoselective dihydroxylation orchestrated by hydroxyl-directed epoxidation and epoxide

(9) Penkett, C. S.; Simpson, I. D. *Tetrahedron* **1999**, *55*, 6183.
(10) Clark, M. A.; Schoenfeld, R. C.; Ganem, B. *J. Am. Chem. Soc.* **2001**, *123*, 10425.
(11) Ling, R.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 6072.
(12) Cho, J. C.; Ling, R.; Kim, A.; Mariano, P. S. *J. Org. Chem.* **2000**, *65*, 1574.
(13) Lu, H.; Mariano, P. S.; Lam, Y. F. *Tetrahedron Lett.* **2001**, *42*, 4755.
(14) Song, L.; Duesler, E. N.; Mariano, P. S. *J. Org. Chem.* **2004**, *69*, 7284.
(15) Lu, H.; Su, Z.; Song, L.; Mariano, P. S. *J. Org. Chem.* **2002**, *67*, 3525.
(16) For an excellent review describing the isolation, biological properties, and pre-1998 syntheses of trehazolamine, see: (a) Berecibar, A.; Grandjean, C.; Siriwardena, A. *Chem. Rev.* **1999**, *99*, 779. (b) Kobayashi, Y. *Carbohydr. Res.* **1999**, *315*, 3.
(17) (a) Li, J.; Lang, F.; Ganeme, B. *J. Org. Chem.* **1998**, *63*, 3403. (b) Boiron, A.; Zillig, P.; Faber, D.; Giese, B. *J. Org. Chem.* **1998**, *63*, 5977. (c) de Gracia, I. S.; Dietrich, H.; Bobo, S.; Chiara, J. L. *J. Org. Chem.* **1998**, *63*, 5883. (d) de Gracia, I. S.; Bobo, S.; Martin-Ortega, M.; Chiara, J. L. *Org. Lett.* **1999**, *1*, 1705. (e) Clark, M. A.; Goering, B. K.; Li, J.; Ganem, B. *J. Org. Chem.* **2000**, *65*, 4058. (f) Seepersaud, M.; Al-Abed, Y. *Tetrahedron Lett.* **2001**, *42*, 1471. (g) Crimmins, M. T.; Tabet, E. A. *J. Org. Chem.* **2001**, *66*, 4012. (h) Sugiyama, Y.; Nagasawa, H.; Suzuki, A.; Sakuda, S. *J. Antibiot.* **2002**, *55*, 263. (i) Akiyama, M.; Awamura, T.; Kimura, K.; Hosomi, Y.; Kobayashi, A.; Tsuji, K.; Kuboki, A.; Ohira, S. *Tetrahedron Lett.* **2004**, *45*, 7133.

SCHEME 6



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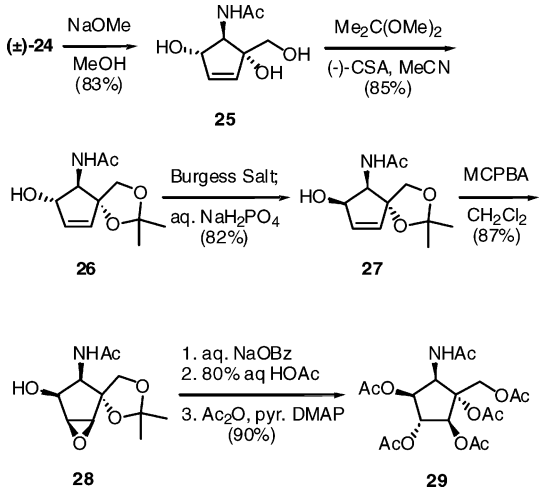
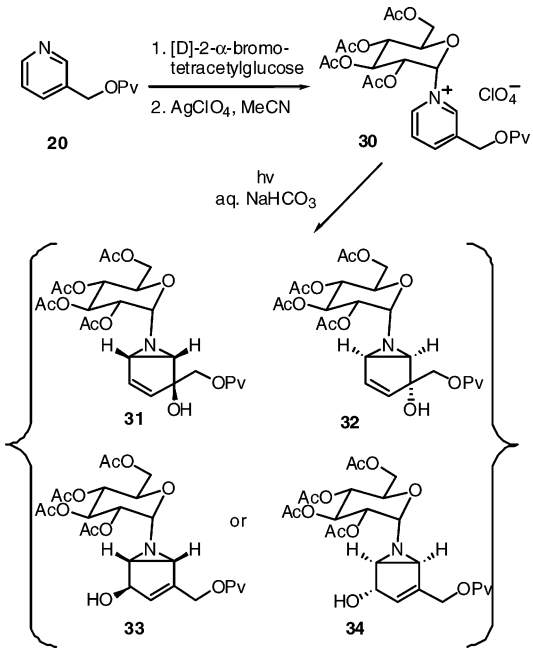


ring opening. Inversion of the C-3 hydroxyl is set up by transformation of **24** to acetonide **26** (Scheme 7). Treatment of **26** with Burgess salt followed by ring opening of the bicyclic-oxazolidine intermediate with NaH_2PO_4 in aq THF leads to clean formation of the epimeric alcohol **27**.[18] Hydroxyl directed epoxidation of **27** produces epoxide **28** (confirmed by xray crystallographic analysis), which is then transformed to the known[17g] hexacetylated (±)-trehazolamine **29** by regioselective epoxide ring opening, acetonide cleavage, and acetylation.

The strategy outlined above can be used to design an enantio-divergent sequence for the synthesis of the natural (+)-tetrazolamine derivative and its unnatural (−)-enantiomer. The route to these targets begins with preparation and photocyclization of *N*-[tetraacetyl-α-D-glucosyl]-3-pivaloxymethylpyridinium perchlorate **30** (Scheme 8). As anticipated,[6] irradiation of **30** in aq $NaHCO_3$ leads to formation of a mixture of isomeric

SCHEME 8



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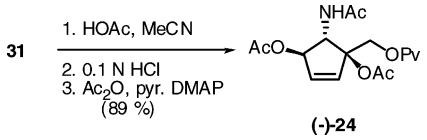

N-glucosyl-bicyclic-aziridines, which can be partially separated by silica gel chromatography to yield pure **31** (15%) and a mixture of **32** and **33** or **34** (30%). Acetic acid-promoted aziridine ring opening of **31**, followed by hydrolytic cleavage of the glycosidic C−N bond and peracetylation, then gives the (−)-enantiomer of the acetamidocyclopententriol derivative (−)-**24** (Scheme 9).

Treatment of the mixture containing **32** and **33** or **34** with acetic acid generates a separable mixture of the *N*-glucosylaminocyclopentenes **35** (46%) and **36** (47%) (Scheme 10). The stereochemistry at the three chiral centers in the cyclopentene moiety of **36** relative to that of the sugar group is not known at this time. The former substance **35** serves as the precursor of acetamidocyclopentenes (+)-**24** formed by sequential glucosyl cleavage and acetylation. The absolute stereochemistry of (+)-**24** was determined by X-ray crystallography on the Mosher ester **37**, derived by conversion of (+)-**24** to acetonide (+)-**26** and acylation with (R)-MTPACl.

The preparation of (+)-**24** and (−)-**24**, by using this modified sequence, represents a formal synthesis of the hexaacetyl derivatives of the respective (+)- and (−)-enantiomers of trehazolamine. As such, this chemistry serves as an important example of the preparative power of pyridinium salt photochemistry.

Experimental Section

1-Methyl-3-(hydroxymethyl)pyridinium Perchlorate (14). A solution of 3-(hydroxymethyl)pyridine (2.2 g, 20 mmol) and iodomethane (3.12 g, 22 mmol) was stirred at 0 °C for 3 h and concentrated in vacuo to give the crude iodide salt. A solution of this salt in 50 mL of methanol containing silver

(18) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 1575.

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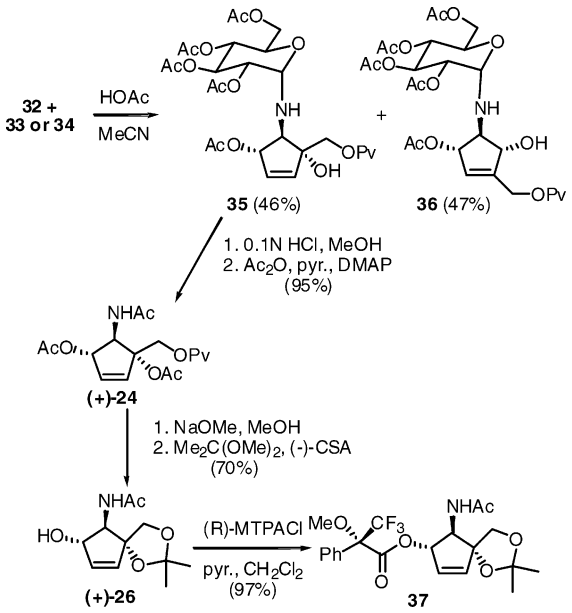

perchlorate (4.14 g, 20 mmol) was stirred at 0 °C for 1 h and filtered. Concentration of the filtrate in vacuo gave 4.42 g (99%) of the perchlorate salt **14**. ^{1}H NMR (D_2O): 9.18 (s, 1H), 9.10 (d, J = 6.1 Hz, 1H), 8.87 (d, J = 8.0 Hz, 1H), 8.43 (t, 1H), 5.27 (s, 2H), 4.80 (s, 3H). ^{13}C NMR (D_2O): 144.4, 143.8, 143.4, 140.1, 128.1, 60.7, 48.8. HRMS (*m/z*, M) 124.0760, calculated for $C_7H_{10}NO$ 124.0762.

1-Methyl-3-(acetoxymethyl)pyridinium Perchlorate (15). A procedure similar to that used to prepare **14** (starting with 3-(acetoxymethyl)pyridine in place of 3-(hydroxymethyl)-pyridine) was used to generate **15**. ^{1}H NMR (d_6-acetone): 9.08 (s, 1H), 8.97 (d, J = 6.1 Hz, 1H), 8.65 (d, J = 8.0 Hz, 1H), 8.19 (t, J = 6.5 Hz, 7.6 Hz, 1H), 5.36 (s, 2H), 4.57 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (d_6-acetone): 171.0, 146.0, 145.6, 145.2, 139.1, 128.8, 62.5, 49.4, 20.7. HRMS (*m/z*, M) 166.0867, calculated for $C_9H_{12}NO_2$ 166.0868.

Irradiation of 1-Methyl-3-(hydroxymethyl)pyridinium Perchlorate (14) in Aqueous $NaHCO_3$. A N_2-purged solution of **14** (453 mg, 2.0 mmol) and sodium bicarbonate (201 mg, 2.4 mmol) in 150 mL of deionized H_2O was irradiated in a preparative apparatus for 2 h. The residue obtained by concentration of the photolyzate was subjected to column chromatography (1:8 hexane−acetone, then 1:1 acetone−methanol) to yield 50 mg (25% at 70% conversion) of 4-hydroxy-4-(hydroxymethyl)-6-methyl-6-azabicyclo[3.1.0]hex-2-ene (**16**) and 54 mg (27% yield at 70% conversion) of 4-hydroxy-2-(hydroxymethyl)-6-methyl-6-azabicyclo[3,1,0]hex-2-ene (**18**).

16. ^{1}H NMR (d_6-acetone): 6.10 (d, J = 5.65 Hz, 1H), 5.60 (d, J = 5.65 Hz, 1H), 4.27 (br, 1H), 4.08 (br, 1H), 3.61−3.68 (ABq, J = 10.3 Hz, 2H), 2.41 (d, J = 4.5 Hz, 1H), 2.28 (d, J = 4.5 Hz, 1H), 2.23 (s, 3H). ^{13}C NMR (d_6-acetone): 140.0, 134.8, 82.5, 66.9, 53.1, 48.1, 44.7. HRMS (*m/z*, M) 141.0786, calculated for $C_7H_{11}NO_2$ 141.0790.

18. ^{1}H NMR (d_4-methanol): 5.64 (s, 1H), 4.39 (s, 1H), 4.27 (s, 2H), 2.61 (s, 1H), 2.52 (s, 1H), 2.33 (s, 3H). ^{13}C NMR (d_4-methanol): 150.9, 131.0, 75.2, 60.8, 53.7, 49.4, 44.6. HRMS (*m/z*, M + 1) 142.0862, calculated for $C_7H_{12}NO_2$ 142.0868.

Irradiation of 1-Methyl-3-(acetoxymethyl)pyridinium Perchlorate (15) in Aqueous $NaHCO_3$. A N_2-purged solution of **15** (320 mg, 1.2 mmol) and sodium bicarbonate (120 mg, 1.4 mmol) in 150 mL of deionized H_2O was irradiated in a preparative apparatus for 1 h. The residue obtained by concentration of the photolyzate was subjected to column chromatography (1:8 hexane−acetone, then 1:1 acetone−methanol) to yield 57 mg (37% yield at 70% conversion) of 4-hydroxy-4-(acetoxymethyl)-6-methyl-6-azabicyclo[3,1,0]hex-2-ene (**17**) and 32 mg (21% yield at 70% conversion) of 4-hydroxy-2-(acetoxymethyl)-6-methyl-6-azabicyclo[3,1,0]hex-2-ene (**19**).

17. ^{1}H NMR (d_6-acetone): 6.12−6.09 (m, 1H), 5.63−5.60 (m, 1H), 4.26−4.07 (ABq, J = 11.3 Hz, 2H), 2.38 (d, J = 4.5 Hz, 1H), 2.23−2.22 (m, 1H), 2.20 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (d_6-acetone): 171.1, 137.9, 135.6, 82.1, 68.7, 52.4, 48.5, 45.0, 20.9. HRMS (*m/z*, M − 1) 182.0827, calculated for $C_9H_{12}NO_3$ 182.0817.

19. ^{1}H NMR: 5.60−5.57 (m, 1H), 4.69 (s, 2H), 4.10−4.08 (m, 1H), 2.37−2.31 (m, 1H), 2.30 (s, 1H), 2.20 (s, 3H), 2.02 (s, 3H). ^{13}C NMR: 170.7, 145.0, 133.8, 75.1, 62.2, 53.6, 48.7, 45.2, 20.8. HRMS (*m/z*, M + 1) 184.0978, calculated for $C_9H_{14}NO_3$ 184.0974.

3-(Pivaloxymethyl)pyridine (20). To a solution of 3-(hydroxymethyl)pyridine (2.2 g, 20 mmol) in ethyl ether (20 mL) at 0 °C was added TEA (5 mL), and pivaloyl chloride (2.5 mL, 22 mmol) was added dropwise. The resulting mixture was stirred for 3 h at 0 °C, diluted with water, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with water, dried, and concentrated in vacuo to give 3.79 g (98%) of 3-(pivaloxymethyl)pyridine (**20**). ^{1}H NMR: 8.48 (s, 1H), 8.43 (d, J = 6.1 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.16 (dd, J = 6.7 Hz, 7.6 Hz, 1H), 4.98 (s, 2H), 1.07 (s, 9H). ^{13}C NMR: 177.7, 148.8, 148.7, 135.5, 131.9, 123.2, 63.2, 38.5, 26.8. HRMS (*m/z*, M + 1) 194.1180, calculated for $C_{11}H_{15}NO_2$ 194.1176.

1-(Methoxyethoxymethyl)-3-(pivaloxymethyl)pyridinium Perchlorate (21). A solution of 3-(pivaloxymethyl)-pyridine (**20**) (1.93 g, 10 mmol) and 2-methoxyethyoxymethyl chloride (MEMCl) (1.25 g, 10 mmol) in 20 mL of CH_3CN was stirred at 0 °C for 20 min. Silver perchlorate (2.07 g, 10 mmol) was added, and the solution was stirred at 0 °C for 1 h and filtered. Concentration of the filtrate in vacuo gave 3.81 g of the 1-(methoxyethoxymethyl)-3-(pivaloxymethyl)pyridinium perchlorate (**21**). ^{1}H NMR (d_3-acetonitrile): 8.84 (s, 1H), 8.81 (d, J = 6.0 Hz, 1H), 8.55 (d, J = 8.0 Hz, 1H), 8.10 (t, J = 7.4 Hz, 1H), 5.87 (s, 2H), 5.27 (s, 2H), 3.81−3.79 (m, 2H), 3.47−3.45 (m, 2H), 1.19 (s, 3H). ^{13}C NMR (d_3-acetonitrile): 177.7, 145.9, 141.9, 141.2, 138.0, 127.9, 89.4, 70.9, 70.8, 61.7, 57.9, 38.5, 26.3. HRMS (*m/z*, M) 282.1704, calculated for $C_{15}H_{24}NO_4$ 282.1699.

Irradiation of 1-(2-Methoxyethoxymethyl)-3-(pivaloxymethyl)pyridinium Perchlorate (8) in Aqueous $NaHCO_3$. A solution of **8** (380 mg, 1 mmol) and sodium bicarbonate (126 mg, 1.5 mmol) in H_2O (160 mL) was irradiated for 2 h and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated in vacuo to give a residue, which was subjected to column chromatography (1:1 hexane−acetone) to yield 60 mg (20%) of 4-hydroxy-4-(pivaloxymethyl)-6-(2-methoxyethoxymethyl)-6-azabicyclo[3,1,0]hex-2-ene (**22**) and 50 mg (16%) of 4-hydroxy-2-(pivaloxymethyl)-6-(2-methoxyethoxymethyl)-6-azabicyclo[3,1,0]hex-2-ene (**23**).

22. ^{1}H NMR: 6.22 (d, J = 5.4 Hz, 1H), 5.69 (d, J = 5.7 Hz, 1H), 4.39−4.16 (ABq, J = 11.3 Hz, 2H), 3.92−3.85 (ABq, J = 8.8 Hz, 2H), 3.72−3.70 (m, 2H), 3.50−3.48 (m, 2H), 3.33 (s, 3H), 2.74 (m, 1H), 2.54 (s, 1H), 1.20 (s, 9H). ^{13}C NMR: 178.7, 136.7, 135.5, 86.9, 82.2, 71.7, 68.5, 67.8, 58.9, 46.4, 44.3, 38.8, 27.1. HRMS (*m/z*, M + Na) 322.1619, calculated for $C_{15}H_{25}NO_5Na$ 322.1625.

23. ^{1}H NMR: 5.71 (s, 1H), 4.72 (s, 2H), 4.47 (s, 1H), 3.98 (d, J = 8.3 Hz, 1H), 3.87 (d, J = 8.3 Hz, 1H), 3.70 (s, 2H), 3.50 (m, 2H), 3.32 (s, 3H), 2.70 (s, 2H), 1.18 (s, 9H). ^{13}C NMR: 177.8, 144.1, 132.5, 86.7, 73.9, 71.6, 68.4, 61.4, 58.6, 47.4, 44.2, 38.5, 26.9. HRMS (*m/z*, M + Na) 322.1626, calculated for $C_{15}H_{25}NO_5Na$ 322.1625.

Conversion of 22 to 3-Acetoxy-4-*N*-acetylamino-5-(pivaloxymethyl)cyclopent-1-en-5-ol (24). A solution of bicyclic-aziridine **22** (30 mg, 0.1 mmol) in 2 mL of glacial acetic acid was stirred at 25 °C for 5 h, diluted with aq $NaHCO_3$ (pH 7), and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated in vacuo to give a residue. A solution of the residue in 5 mL of MeOH and 0.5 mL of 1 N HCl was stirred

at 25 °C for 12 h, and concentrated in vacuo giving a residue. A solution of the residue in 2 mL of pyridine, 1 mL of acetic anhydride, and 5 mg of DMAP was stirred at 25 °C for 12 h, diluted with aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated in vacuo to give a residue which was subjected to column chromatography (1:1 hexane−acetone) to yield 28 mg (80%) of amidocyclopentene **24.** ^{1}H NMR: 6.22 (d, J = 6.3 Hz, 1H), 6.16 (d, J = 9.2 Hz, 1H), 5.92 (d, J = 4.6 Hz, 1H), 5.48 (d, J = 6.2 Hz, 1H), 5.02−4.98 (m, 1H), 4.51−4.09 (ABq, J = 11.3 Hz, 2H), 2.05 (s, 3H), 2.02 (s, 3H), 1.96 (s, 3H), 1.14 (s, 9H). ^{13}C NMR: 177.5, 171.0, 170.4, 170.0, 134.0, 132.5, 88.4, 78.8, 62.3, 61.5, 38.7, 27.1, 23.4, 21.6, 20.9. HRMS (*m/z*, M + Na): 378.1536, calculated for $C_{17}H_{25}NO_7Na$ 378.1523.

4-*N*-Acetylamino-5-(hydroxymethyl)cyclopenten-3,5-diol (25). A solution of the triester (**24**) (28 mg, 0.8 mmol), and sodium methoxide (5 mg) in methanol (2 mL) was stirred at 25 °C for 3 h and concentrated in vacuo and filtered. Concentration of the filtrate in vacuo gave 12 mg (83%) of amidocyclopententriol **25**. ^{1}H NMR: 5.90 (d, J = 6.1 Hz, 1H), 5.72 (d, J = 6.1 Hz, 1H), 4.53 (d, J = 6.6 Hz, 1H), 4.11 (d, J = 6.6 Hz, 1H), 3.40 (s, 2H), 2.03 (s, 3H). ^{13}C NMR: 173.6, 134.9, 134.3, 83.2, 77.6, 68.9, 64.0, 21.1. HRMS (*m/z*, M + Na) 210.0729, calculated for $C_8H_{13}NO_4Na$ 210.0737.

4-*N*-Acetylamino-5-(hydroxymethyl)cyclopenten-3,5-diol Acetonide 26. A solution of triol **25** (24 mg, 0.13 mmol), 2,2-dimethoxypropane (3 mL), and (−)-CSA (5 mg) in 3 mL of CH_3CN was stirred at 25 °C for 30 min, diluted with water, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated in vacuo to give a residue, which was subjected to column chromatography (1:2 hexane−acetone) to afford the acetonide **26** (25 mg, 85%). ^{1}H NMR: 6.70 (1H), 5.86 (d, J = 6.1 Hz, 1H), 5.62 (d, J = 6.1 Hz, 1H), 4.34−4.32 (m, 1H), 3.93−3.60 (ABq, J = 9.8 Hz, 2H), 3.76−3.74 (m, 1H), 1.98 (s, 3H), 1.35 (s, 3H), 1.27 (s, 3H). ^{13}C NMR: 173.2, 135.9, 131.5, 109.7, 88.8, 78.0, 70.0, 67.1, 27.3, 25.0, 23.0. HRMS (*m/z*, M + Na) 250.1046, calculated for $C_{11}H_{17}NO_4Na$ 250.1050.

4-*N*-Acetylamino-5-(hydroxymethyl)cyclopenten-3,5-diol Acetonide 27. To a solution of monoalcohol **26** (80 mg, 0.35 mmol) in 10 mL of THF at 70 °C was added a solution of Burgess reagent (90 mg, 0.38 mmol). The resulting solution was stirred for 2 h at 70 °C, diluted by addition of 10 mL of NaH_2PO_4 buffer (pH 4.9), stirred for 24 h at 25 °C, and concentrated to give a residue, which was triturated with CH_2Cl_2. The CH_2Cl_2 triturates were dried and concentrated in vacuo to give a residue that was subjected to column chromatography (1:3 hexane−acetone) to afford hydroxyl inversion product **27** (66 mg, 82%) as a crystalline solid, mp 132−134 °C. ^{1}H NMR: 6.30 (d, J = 7.5, 1H), 6.03−6.01 (m, 1H), 5.92 (d, J = 7.9 Hz, 1H), 4.72−4.70 (m, 1H), 4.28−4.25 (m, 1H), 4.04−3.74 (ABq, J = 9.6 Hz, 2H), 2.03 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H). ^{13}C NMR: 171.0, 138.2, 134.2, 109.5, 90.2, 72.2, 69.1, 58.9, 26.5, 25.6, 23.3. HRMS (*m/z*, M + Na) 250.1043, calculated for $C_{11}H_{17}NO_4Na$ 250.1050.

Acetonide-Epoxide 28. A solution of allylic alcohol **27** (40 mg, 0.17 mmol) and MCPBA (recrystallized) (100 mg, 0.44 mmol) in 4 mL of CH_2Cl_2 was stirred at 25 °C for 48h, diluted with 5% $NaHCO_3$, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated in vacuo to give a residue, which was subjected to column chromatography (1:3 hexane−acetone) to give epoxide **28** (37 mg, 87%), mp 162−164 °C (hexane−acetone). ^{1}H NMR: 5.95 (d, J = 10.3 Hz, 1H), 4.59 (d, J = 7.3 Hz, 1H), 4.33 (dd, J = 10.2 Hz, 7.5 Hz, 1H), 4.14 and 3.97 (ABq, J = 9.5 Hz, 2H), 3.65 (d, J = 2.3 Hz, 1H), 3.40 (d, J = 2.3 Hz, 1H), 1.98 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H). ^{13}C NMR: 171.5, 111.2, 86.3, 71.7, 67.4, 58.6, 57.2, 54.0, 27.1, 24.9, 23.1. HRMS (*m/z*, M + Na) 266.1008, calculated for $C_{11}H_{17}NO_5Na$ 266.1000.

Hexaacetyl Derivative 29 of Trehazolamine. A solution of the epoxide **28** (10 mg, 0.04 mmol) and sodium benzoate (3 mg) in 1 mL of H_2O was stirred at 110 °C for 32 h and concentrated in vacuo. A solution of the residue in 2 mL of 80% aqueous acetic acid was stirred at 80 °C for 24 h and concentrated in vacuo, giving a residue. A solution of the residue, 2 mL of pyridine, 1 mL of acetic anhydride, and 5 mg of DMAP, was stirred at 25 °C for 24 h, diluted with aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated in vacuo to give a residue, which was subjected to column chromatography (2:1 hexane−acetone) to yield 16 mg (90%) of the hexacetyl-trehazolamine **29**. The ^{1}H and ^{13}C NMR data recorded for this substance (see below) match those previously reported.[17g] ^{1}H NMR: 5.89 (d, J = 9.6 Hz, 1H), 5.77 (d, J = 5.6 Hz, 1H), 5.34 (dd, J = 7.6, 4.8 Hz, 1H), 5.29 (dd, J = 9.2, 8.2 Hz, 1H), 5.21 (t, J = 5.2 Hz, 1H), 4.58 and 4.52 (ABq, J = 12 Hz, 2H), 2.10 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H). ^{13}C NMR: 170.4, 169.9, 169.7, 169.5, 168.9, 86.6, 78.9, 76.4, 73.3, 59.5, 52.7, 23.1, 21.6, 20.9, 20.7, 20.6, 20.5.

1-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)-3-(pivaloxymethyl)pyridinium Perchlorate (30). A solution of 3-(pivaloxymethyl)pyridine (**20**) (1.93 g, 10 mmol) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (4.11 g, 10 mmol) in 50 mL of CH_3CN was stirred at 60 °C for 24 h. Silver perchlorate (2.07 g, 10 mmol) was added to the solution, and the mixture was stirred at 0 °C for 1 h and filtered. Concentration of the filtrate in vacuo gave a residue mixture, which was dissolved in ethyl acetate and hexane. 1-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)-3-(pivaloxymethyl)pyridinium perchlorate (**30**) (2.68 g, 42%) crystallized from this solution, mp 162−163 °C (EtOAc). ^{1}H NMR (d_3-acetonitrile): 8.97 (s, 1H), 8.93 (d, J = 6.1 Hz, 1H), 8.64 (d, J = 8.0 Hz, 1H), 8.15 (dd, J = 6.5, 7.8 Hz, 1H), 6.08 (d, J = 9.0 Hz, 1H), 5.53 (t, J = 9.7 Hz, 1H), 5.29−5.26 (m, 3H), 4.29−4.26 (m, 2H), 4.23−4.21 (m, 1H), 2.01 (s, 3H), 1.95 (s, 3H), 1.86 (s, 3H), 1.19 (s, 9H). ^{13}C NMR (d_3-acetonitrile): 178.8, 171.7, 171.1, 170.9, 170.6, 149.3, 143.0, 142.1, 140.0, 129.7, 93.5, 76.3, 72.9, 72.4, 68.2, 62.7, 62.4, 39.6, 27.3, 21.02, 21.01, 20.9, 20.5. HRMS (*m/z*, M) 524.2128, calculated for $C_{25}H_{34}NO_{11}$ 524.2126.

Irradiation of 1-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)-3-(pivaloxy-methyl)pyridinium Perchlorate (30) in Aqueous $NaHCO_3$. A solution of **30** (623 mg, 1 mmol) and sodium bicarbonate (120 mg, 1.4 mmol) in H_2O (160 mL) was irradiated for 2 h and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated in vacuo to give a residue, which was subjected to column chromatography (2:1 hexane−acetone) to yield the glucosyl-azabicyclohexenol **31** (81 mg, 15%) and an inseparable mixture (160 mg, 30%) of **32** and **33** or **34**.

31. ^{1}H NMR: 6.16 (d, J = 5.7 Hz, 1H), 5.64 (d, J = 5.1 Hz, 1H), 5.19 (t, J = 9.5 Hz, 1H), 4.97−4.93 (m, 3H), 4.37 (d, J = 11.2 Hz, 1H), 4.14−4.04 (m, 6H), 3.58−3.57 (m, 1H), 3.14 (d, J = 4.5 Hz, 1H), 2.97 (d, J = 4.5 Hz, 1H), 2.04 (s, 3H), 2.00(s, 3H), 1.99 (s, 3H), 1.98 (s, 3H), 1.21 (s, 9H). ^{13}C NMR: 178.7, 170.5, 170.1, 169.5, 169.4, 136.3, 135.9, 87.1, 82.5, 73.4, 72.8, 71.1, 68.6, 67.7, 62.0, 44.8, 40.6, 38.9, 27.2, 20.7, 20.5. HRMS (*m/z*, M) 564.2037, calculated for $C_{25}H_{35}NO_{12}Na$ 564.2051.

Conversion of 31 to (−)-3,5-Diacetoxy-4-acetylamino-3-(pivaloxymethyl)-cyclopentene ((−)-24). A solution of **31** (81 mg) in 2 mL of glacial acetic acid was stirred at 25 °C for 12 h, diluted with aq $NaHCO_3$ (pH 7), and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated in vacuo, giving a residue that was dissolved in 5 mL of MeOH and 0.5 mL of 1 N HCl. The solution was stirred at 25 °C for 12 h and concentrated in vacuo, giving a residue that was dissolved in 2 mL of pyridine, 1 mL of acetic anhydride, and 5 mg of DMAP. The mixture was stirred at 25 °C for 12 h, diluted with aq $NaHCO_3$, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated in vacuo to give a residue that was subjected to column chromatography (2:1 hexane−acetone) to yield 47 mg (89%) of 3,5-diacetoxy-4-acetyllamino-3-(pivaloxymethyl)cyclopentene (−)-**24**, $[\alpha]^{24}_D = -67°$ (c = 0.45, $CHCl_3$).

Conversion of the Mixture of 32 and 33 or 34 to 5-Acetoxy-4-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-

amino-3-(pivaloxymethyl)cyclopent-1-en-3-ol (35) and 1-(Pivaloxymethyl)-3-acetoxy-4-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-amino-cyclopent-1-en-5-ol (36). A solution of the mixture of **32** and **33** or **34** (160 mg) in 4 mL of glacial acetic acid was stirred at 25 °C for 12 h, diluted with aqueous $NaHCO_3$ to (pH 7), and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated in vacuo to give a residue that was subjected to column chromatography (2:1 hexane−acetone) to afford 82 mg (46%) of 5-acetoxy-4-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)amino-3-(pivaloxymethyl)-cyclopent-1-en-3-ol (**35**) and 84 mg (47%) of 1-(pivaloxymethyl)-3-acetoxy-4-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-amino-cyclopent-1-en-5-ol (**36**).

35. ^{1}H NMR: 5.74 (s, 1H), 5.40 (d, J = 6.4 Hz, 1H), 5.13 (t, J = 9.5 Hz, 1H), 4.80−4.73 (m, 2H), 4.46 (d, J = 14.2 Hz, 1H), 4.21−4.17 (m, 2H), 4.17 (d, J = 8.7 Hz, 1H), 3.83−3.80 (m, 1H), 3.70−3.65 (m, 1H), 2.96 (s, 1H), 1.96 (s, 3H), 1.95 (s, 3H), 1.94 (s, 3H), 1.92 (s, 3H), 1.90 (s, 3H), 1.06 (s, 9H). ^{13}C NMR: 177.7, 170.4, 170.4, 170.2, 170.0, 135.9, 131.7, 90.3, 79.8, 80.4, 75.2, 72.4, 72.3, 70.4, 69.3, 65.5, 63.0, 38.7, 27.1, 20.9, 20.5, 20.4. HRMS (*m/z*, M + Na) 624.2233, calculated for $C_{27}H_{39}NO_{14}Na$ 624.2263.

36. ^{1}H NMR: 5.84 (s, 2H), 5.48 (d, J = 7.0 Hz, 1H), 5.26 (t, J = 9.5 Hz, 1H), 4.91−4.86 (m, 2H), 4.34 (d, J = 11.9 Hz, 1H), 4.28 (d, J = 11 Hz, 1H), 4.13 (s, 1H), 3.90−3.85 (m, 2H), 3.75−3.73 (m, 1H), 3.65 (s, 1H), 3.23 (s, 1H), 2.07 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H), 1.18 (s, 9H). ^{13}C NMR: 177.6, 170.3, 170.0, 169.8, 169.4, 137.8, 131.4, 89.7, 78.8, 78.6, 72.5, 72.4, 70.5, 69.1, 62.9, 59.7, 38.6, 26.9, 20.6, 20.4, 20.3. HRMS (*m/z*, M + NA) 624.2235, calculated for $C_{27}H_{39}NO_{14}Na$ 624.2263.

Conversion of 35 to (+)-3,5-Diacetoxy-4-acetylamino-3-(pivaloxymethyl)cyclopentene ((+)-24). A solution of 5-acetoxy-4-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)amino-3-(pivaloxy-methy l)cyclopent-1-en-3-ol (**35**) (82 mg) in 5 mL of MeOH and 0.5 mL of 1 N HCl was stirred at 25 °C for 12 h and concentrated in vacuo, giving a residue which was dissolved in 2 mL of pyridine, 1 mL of acetic anhydride, and 5 mg of DMAP. The mixture was stirred at 25 °C for 12 h, diluted with aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated in vacuo to give a residue that was subjected to column chromatography (2:1 hexane−acetone) to yield 46 mg (95%) of (+)-**24**, [α] = +60° (c = 0.46, $CHCl_3$). The spectroscopic data for this substance matched those recorded for the racemic material (see above).

Conversion of (+)-24 to the Acetonide (+)-26 of (+)-4-Acetylamino-3-(hydroxymethyl)cyclopenten-3,5-diol. A solution of the ester (+)-**24** (40 mg, 1.1 mmol) and sodium methoxide (8 mg) in methanol (2 mL) was stirred at 25 °C for 3 h, concentrated in vacuo, and filtered. Concentration of the filtrate in vacuo gave 18 mg (85%) of the (+)-enantiomer of triol **25**. A solution of (+)-**25** (18 mg, 0.11 mmol), 2,2-dimethoxypropane (3 mL), and (−)-CSA (5 mg) in 3 mL of CH_3CN was stirred at 25 °C for 30 min, diluted with water, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated in vacuo to give a residue, which was subjected to column chromatography (1:2 hexane−acetone) to afford 18 mg (83%) of (+)-**26**. The spectroscopic data for this substance matched those recorded for the racemic material (see above).

Mosher Ester 37. A solution of (+)-**26** (11 mg, 0.05 mmol), DMAP (2 mg, 0.02 mmol), 1 mL of pyridine, and *R*-(−)-α-methoxy-α-trifluoromethylphenylacetyl chloride (19 mg, 0.075 mmol) in CH_2Cl_2 (0.5 mL) was stirred for 12 h at 25 °C, diluted with water, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated in vacuo to give a residue that was subjected to column chromatography (1:2 hexane−acetone) to afford 21 mg (97%) of the crystalline Mosher ester **37**, [α] = +75° (c = 0.06, $CHCl_3$), mp 185−187 °C (hexane−acetone). ^{1}H NMR: 7.50 (t, J = 3.4 Hz, 2H), 7.38 (t, J = 3.4 Hz, 3H), 5.96 (d, J = 5.1 Hz, 1H), 5.84−5.78 (m, 2H), 4.57 (dd, J = 8.7, 6.1 Hz, 1H), 3.98 and 3.75 (ABq, J = 9.6 Hz, 2H), 3.55 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H). ^{13}C NMR: 170.4, 166.7, 137.8, 132.0, 130.3, 129.6, 128.5, 127.3, 124.9, 110.1, 88.9, 80.2, 67.6, 63.4, 55.6, 26.5, 25.8, 23.4. HRMS (*m/z*, M + Na) 466.1463, calculated for $C_{21}H_{24}F_3NO_6Na$ 466.1448.

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Supporting Information Available: (1) General experimental information, (2) ^{1}H and ^{13}C NMR spectra of **14**−**31**, **35**−**37**, and (3) summaries of crystallographic parameters for **28** and **37**. This material is available free of charge via the Internet at http://pubs.acs.org.

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